Functional and Structural Connectivity of Limbic and Interpersonally Relevant Regions in Non-Suicidal Self-Injury

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Abstract

Non-suicidal self-injury (NSSI) commonly begins in adolescence and is associated with an array of negative outcomes including suicide. Research has only begun to explore the neurobiological mechanisms associated with this behavior, most often among adults with borderline personality disorder. However, research is urgently needed to study NSSI among adolescents in order to understand potential neurobiological correlates. Applications of this knowledge would potentially be used to identify neurobiologically informed intervention strategies targeting these deficits and restore healthy neurodevelopmental trajectories. The present study implemented a multi-modal approach to understanding neural functioning by examining structural and functional connectivity in adolescents with versus without NSSI. Given previous clinical findings on NSSI, this study focused on brain regions implicated in negative affect and interpersonal sensitivity, the amygdala and dorsal anterior cingulate (dACC) respectively. Overall, the NSSI group showed widespread differences in both functional and structural connectivity compared to controls. These patterns were suggestive of possible influence of negative affect on emotional memory, planning of motor movements, and interpersonal relationships. Additionally, the NSSI group showed impairments in structural connectivity consistent with those seen in major depressive disorder and anxiety disorders. Given the paucity of neurobiological research on NSSI, this study represents an important first step in furthering the understanding of this behavior in adolescents and will aid in generating hypotheses for future work.

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1. Introduction to Non-Suicidal Self-Injury: An Overview of Background and Theory

The course of adolescence is often a tumultuous and exciting time full of change and exploration. During this critical developmental period, one finds him or herself navigating through a variety of transitions including the biological process of puberty, the shift toward greater independence, and an increase in responsibility. In addition, adolescents may find themselves having to navigate new relationships and interests while also exploring their self-identities. However, all of these challenges taking place within a relatively short period of time can result in the taxing of an adolescent's cognitive and emotional resources. Indeed, while most adolescents are able to successfully employ adaptive coping strategies, such as problem solving, seeking support, or rationalizing, others may struggle with maladaptive coping strategies, including rumination, self-blame, and avoidance, which may lead to or exacerbate psychopathology (Horwitz, Hill, & King, 2011; Mikolajczak, Petrides, & Hurry, 2009; Piko, 2001).

Adolescence can be conceptualized as a time in which there is increased vulnerability to the development of psychiatric disorders as well as related maladaptive behaviors. In particular, non-suicidal self-injury (NSSI) has been a growing cause for alarm among parents, teachers, clinicians, and researchers since the turn of the century. As a reflection of these concerns, there has been a recent surge in research investigating non-suicidal self-injury in adolescents since the early 2000's. This research has led to the awareness that NSSI may predict negative outcomes such as persistent psychopathology and suicide (Horwitz, Czyz, & King, 2014; Tang et al., 2011; Victor & Klonsky, 2014).

NSSI is the act of intentionally harming one's own body tissue without the intent of suicide (Winchel & Stanley, 1991) and is often repetitive with varying degrees of severity (Tuisku et al., 2009). To date, there has been ongoing research investigating the characteristics of NSSI such as its prevalence, risk factors, and even how to best define the behavior. However, studies investigating the neurobiology associated with NSSI is nascent and the utility of such information is underscored by the dearth of effective treatment options, particularly with regard to pharmacotherapy. As we have entered the era of computational psychiatry, there is significant optimism that by understanding the brain and its mechanisms we may be better equipped to employ treatment options that are both effective as well as efficient.

Developing an understanding of how neural circuits go awry in NSSI represents an important starting point for identifying ways to best address these disruptions. Given the complexity of the brain and the abundance of its circuitry, findings regarding the characteristics of NSSI provide assistance in the selection of circuits that may be particularly fruitful. In particular, previous research has identified the regulation of negative affect as being a primary function for NSSI (Dahlström, Zetterqvist, Lundh, & Svedin, 2015; Klonsky, 2009; Klonsky, Glenn, Styer, Olino, & Washburn, 2015; Lloyd-Richardson, Perrine, Dierker, & Kelley, 2007) with interpersonal relationships likely being a particularly salient context in which negative affect may occur. Provided with this information, the present study examines the neural circuitry implicated in negative affect and interpersonal relationships by investigating both functional and structural

connectivity of the amygdala (negative affect) and the dorsal anterior cingulate cortex (dACC; interpersonal relationships).

1. 1. Clinical Presentation of NSSI.

NSSI has been referred to as many different terms over the course of the past 1-2 decades, including "deliberate self-harm," "non-suicidal self-harm," "deliberate self-injury," "self-injurious behavior," and "self-mutilation." With these different terms there have also been varying definitions of self-injury as earlier studies (which often used broader terms such as "deliberate self-harm") included socially sanctioned behaviors and indirect forms of self-injury such as piercing, tattoos, and drug use within their definitions (Favazza, 1998; Hawton, Rodham, Evans, & Weatherall, 2002; Rodham, Hawton, & Evans, 2004). Fortunately, there has been growing consensus among researchers with the use of "non-suicidal self-injury" and with the definition of NSSI as being a purposeful and direct physical and harmful behavior toward the self without suicidal intent (American Psychiatric Association, 2013; Lloyd-Richardson et al., 2007; Selby, Bender, Gordon, Nock, & Joiner, 2012; Wilkinson & Goodyer, 2011).

NSSI typically begins in early-mid adolescence with an age of onset of 12-14 years of age (Glenn et al., 2017) and persists into young-adulthood (Andover, 2014; Andrews, Martin, Hasking, & Page, 2014). While there have been some inconsistencies with regard to sex differences, a recent meta-analysis found that NSSI appears to be more prevalent among females (Bresin & Schoenleber, 2015). Examples of NSSI behaviors include "minor" NSSI, such as hitting self, biting self, or skin picking; or "moderate/severe" NSSI, which includes cutting, burning, scraping, or erasing skin

(Lloyd-Richardson et al., 2007). Cutting has been identified as the most common form of NSSI (Brunner et al., 2014; Nock, 2010).

Some studies have attempted to classify different groups of NSSI. As described above, Lloyd-Richardson and colleagues demonstrate the possibility of two subgroups of individuals with NSSI, which are classified according to their severity level ("minor" versus "moderate/severe"). In contrast, another study used a data-driven approach by using a latent class analysis to identify NSSI subgroups (Klonsky & Olino, 2008). They identified four distinct subgroups of NSSI within their sample of young adults. The "experimental NSSI" group is characterized by fewer NSSI behaviors and psychiatric symptoms. The "mild NSSI" group is characterized by early age of onset and more NSSI behaviors, but fewer psychiatric symptoms. The "multiple functions/anxious" group is characterized by early age of onset, more symptoms of anxiety, and endorsement of both social and emotion regulation functions of NSSI (i.e. "automatic" functions). Finally, the "automatic functions/suicidal" group is characterized by greater symptoms of depression, anxiety, and borderline personality disorder (BPD), histories of suicide attempts, and use of NSSI for primarily emotion regulation reasons (Klonsky & Olino, 2008).

The studies reviewed above provide some insight into the clinical characteristics that accompany NSSI. At first, the clinical characteristics of NSSI seem particularly unclear when including information regarding highly transient or "experimental" NSSI, which may be reflective of normative adolescent behavior Lloyd-Richardson et al. (2007). However, when pooling together the most recent literature, a more cohesive syndrome emerges in which NSSI is characterized by high levels of negative affect and

psychopathology (including anxiety, depression, BPD symptoms and overall distress). To further characterize this behavior, it is useful to consider what risks lead to NSSI, what risks follow NSSI, and finally, what is the purpose or function of NSSI.

1.1.1. Risk factors for NSSI. Risk factors for the development of NSSI are similar to those for suicide (Maciejewski et al., 2014). However, a recent meta-analysis of 34 potential NSSI risk factors (examples of which include abuse, ethnicity, explicit affect toward unpleasant or NSSI stimuli, or social factors) found that many of these risk factors were weak and of limited clinical utility due to their relatively small increase in absolute odds (K. R. Fox et al., 2015). The risk factors that did show significant relationships with NSSI included having a previous history of NSSI, cluster B personality traits, and hopelessness (K. R. Fox et al., 2015).

Cluster B personality traits arise from Cluster B personality disorders, which were once described as "dramatic, emotional or erratic" in previous versions of the DSM (American Psychiatric Association, 2000). Further, Borderline Personality Disorder (BPD) falls within Cluster B and includes symptoms such as affective instability, identity disturbance, impulsivity, and, most notably, suicidal behavior and NSSI (American Psychiatric Association, 2013). Thus, possessing traits consistent with a threshold or even subthreshold symptoms of BPD may be an important precursor to later development of NSSI. While clinicians may be resistant to applying a diagnosis of BPD to an adolescent, assessing for the presence of these symptoms in the early stages of mental health struggles can be important in applying appropriate interventions to target these symptoms and hopefully alleviate them before an individual begins to engage in NSSI.

Hopelessness is a significant shared risk factor between NSSI and suicide and has been found to be one of the strongest predictors of suicidality including death by suicide (Asarnow et al., 2011; Courtet, Gottesman, Jollant, & Gould, 2011; K. R. Fox et al., 2015; Wilkinson, Kelvin, Roberts, Dubicka, & Goodyer, 2011). Considering the overlap of hopelessness in both NSSI and suicide, additional research is needed to better understand if hopelessness is an independent predictor of both of these behaviors, or if this relationship is obscured due to NSSI being a significant predictor of suicide (K. R. Fox et al., 2015).

While Fox and colleagues found few significant risk factors for NSSI, their results are largely limited by the quality of NSSI studies to date. In particular, studies vary in their measurement of NSSI as they differ in whether they account for frequency of the behavior (one-time NSSI episode versus recurrent NSSI) and definitions of the behavior (cutting, scab picking, trichotillomania, etc.). Additionally, most studies have examined risk factors for continued NSSI rather than NSSI onset, which would be more helpful in enabling early identification and prevention of this behavior.

As highlighted in a recent review, a likely distal risk factor for NSSI is childhood maltreatment (Serafini et al., 2017). This is particularly the case for childhood sexual abuse, especially among females (Gratz, Conrad, & Roemer, 2002; Maniglio, 2011; Romans, Martin, Anderson, Herbison, & Mullen, 1995; Ystgaard, Hestetun, Loeb, & Mehlum, 2004). From a developmental standpoint, Yates (2004) suggests that the progression from childhood maltreatment to NSSI is due to disruptions in several important areas of development including expectations of self and other, self-soothing

strategies, capacity for meaningful relationships, and the ability to regulate arousal. These disruptions create a vulnerability in which NSSI becomes a seemingly adaptive compensatory response for regulation and relational purposes (Yates, 2004).

While these previous studies are limited in their use of cross-sectional designs, a study by Hankin and Abela examined NSSI risk factors in adolescents over a 2.5-year period. Risk factors that predicted the onset of NSSI during this period included recent adolescent depression symptoms, negative cognitive style, lack of support, and onset of maternal depression (Hankin & Abela, 2011).

Overall, research understanding factors that may predispose individuals to NSSI has been mixed and is limited due to varying definitions of NSSI and cross-sectional designs. Future longitudinal work, such as that by Hankin and Abela, is essential for providing an understanding of the trajectory that leads to and maintains NSSI. Further, these studies would benefit from examining neurodevelopmental trajectories in addition to psychosocial factors as this will provide information regarding the temporal relationship between these factors and brain functioning.

1.1.2. Risk factors of NSSI. In addition to considering the risk factors that precede NSSI, it is also important to consider the problems that NSSI may lead to in the future. The importance of identifying and treating NSSI early is made evident by its strong relationship with suicide. Approximately 70% of those who engage in NSSI attempt suicide in their lifetime, with 55% reporting multiple attempts (Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006). Further, adolescents who report a greater number of "moderate/severe" episodes (such as cutting or burning) and engage in multiple forms of

NSSI are more likely to have suicidal ideation and histories of psychiatric hospitalizations and suicide attempts (Lloyd-Richardson et al., 2007). Another study found that overall, those who engage in NSSI tend to have a greater number of suicide attempts that are also more likely to require medical intervention (Ward-Ciesielski, Schumacher, & Bagge, 2016), suggesting a greater likelihood of more lethal attempts.

Although closely related, non-suicidal and suicidal self-injury have been conceptualized as overlapping, but distinct, clinical phenomena (Wichstrøm, 2009). To better understand the taxonomy of self-injurious behavior more broadly (both suicidal and non-suicidal self-injury), a study of over 1,500 female undergraduate students found that rather than being two categorically distinct behaviors, NSSI and suicide appeared to fall on a continuum of self-injury (Orlando, Broman-Fulks, Whitlock, Curtin, & Michael, 2015). While further research to validate this finding is needed, it does provide an illustration as to why NSSI presents as a significant risk for suicide.

1.1.2.1. NSSI and suicide: Theoretical connection. In addition to the possibility of the close link between suicide and NSSI being due to their existence on the same data-driven continuum, there is also a theoretical rationale as to how NSSI may progress to suicide. In particular, Joiner's interpersonal theory of suicide has three factors that when present, indicate substantial suicide risk (Joiner, 2007). The first two factors rely heavily on the quality and perception of interpersonal relationships, which may be disrupted in NSSI. *Perceived burdensomeness* is the belief that one is an encumbrance to others and/or society and can also be described as the idea that others will be "better off" if the individual were dead and *thwarted belongingness* is the lack of feeling socially connected

or accepted by others. However, the third factor of Joiner's theory, *acquired capability for suicide*, is a particularly compelling when considering the link between NSSI and suicide.

The act of suicide is in direct opposition to our innate drive for self-preservation and fear of death. The *acquired capability for suicide* explains that an individual may overcome this instinct by repeated exposure and habituation to pain in addition to increased fearlessness (Joiner, 2007). This often takes the form of direct or indirect harm to the individual such as abuse/trauma, substance use, or NSSI, which can be a particularly concerning behavior as it is a very direct act of harming oneself. Altogether, the evidence for the progression from NSSI to suicide highlights NSSI as a critical behavior in need of further investigation.

1.1.3. Functions of NSSI and role of negative affect. Several functions of NSSI have been examined including punishing self, sensation-seeking, influencing others, establishing boundaries between self and others, as an alternative to suicide, alleviating feelings of dissociation, or regulating negative affect, which is the most commonly endorsed function of NSSI (Klonsky, 2007). These functions can all be considered to fall within the four-factor model by Nock and Prinstein (2004). The four-factors include: 1. *Automatic-negative reinforcement*, in which NSSI is used to reduce unpleasant affect; 2. *Automatic-positive reinforcement*, in which NSSI is used to induce positive or more desirable affect; 3. *Social-negative reinforcement,* in which NSSI is used to escape demands or requests from others; and 4. *Social-positive reinforcement*, in which NSSI is used to gain something from others (attention or manipulation) (Nock & Prinstein, 2004).

Despite the influence of the four-factor model, more recent work using larger samples and more measures of NSSI have found more evidence for either a three- or two-factor model. In particular, the three-factor model breaks down the functions of NSSI into 1. *Social influence/Interpersonal influence and communication*; 2. *Automatic functions* (regulate negative emotions); and 3. *Nonconformist peer identification/Peer avoidance-attraction* (to "fit in" more or less in a particular group) (Dahlström et al., 2015; Young, Sproeber, Groschwitz, Preiss, & Plener, 2014). The two-factor model further simplifies the functions of NSSI into *Social functions* and *Intrapersonal functions* (Klonsky et al., 2015).

While the number of factors vary among these studies, the general consensus among these different theories is that NSSI serves either to provide some sort of intrapersonal relief through reducing negative affect/inducing a more positive feeling state, or to provide interpersonal benefits through receiving attention from others/being able to avoid undesired social responsibilities. However, both cross-sectional studies and studies using ecological momentary assessment have supported that the intrapersonal relief through regulation of affect appears to be the most common function of NSSI (Klonsky, 2007, 2009; Vansteelandt et al., 2017). Unfortunately, this regulation function appears to be highly time-limited as another momentary assessment study found that negative emotions increased again within hours of NSSI, thereby contributing to the repetitive nature of this behavior (Houben et al., 2017).

Recognizing that NSSI appears to primarily serve as a means of emotion regulation, it is important to consider the potential antecedents to the experience of negative affect that may prompt an episode of NSSI. During adolescence, it is normative

for individuals to begin exploring their identities, interests, and relationships. Adolescence is also characterized by an increase in negative affect, the reason for which has been broadly described as the realization that what one expects or wants in life is not consistent with reality (Larson & Asmussen, 1991). With this broad description, the negative affect that follow these realizations can be conceptualized as threat reactions, as these individuals are encountering disruptions to their inner representations of reality. In addition to this increase in negative affect, adolescence is also a time of increased reliance on peer relationships (Laible, Carlo, & Raffaelli, 2000), suggesting that interpersonal relationships may be a significant source of threat.

1.1.3.1. Interpersonal relationships and rejection sensitivity. Rejection sensitivity is the tendency to expect, perceive, and react more readily to interpersonal rejection and has been found to weaken intimate relationships (G. Downey & Feldman, 1996), and may represent a brain-based risk factor for maladaptive behaviors such as NSSI. Difficulties in interpersonal relationships may be a source of negative affect for those with NSSI. Indeed, heightened sensitivity to rejection and other relationship difficulties are common to those who engage in NSSI (McMahon, Reulbach, Keeley, Perry, & Arensman, 2010) and adolescents who self-report interpersonal difficulties have been found to be at higher risk for NSSI (Wang, You, Lin, Xu, & Leung, 2017).

Because adolescence is a time in which individuals are more susceptible to peer influences (Steinberg & Morris, 2001), perceived rejection by peers may be a particularly salient precipitant to engaging in NSSI among youth. Further, it is important to highlight the overlap NSSI has with suicide and consider relevant theories. As described

previously, Joiner's interpersonal theory of suicide incorporates two components, perceived burdensomeness and thwarted belongingness, that rely on the perception of some level of interpersonal rejection (Joiner, 2007).

1.1.3.1.1. Interpersonal relationships, rejection sensitivity, and NSSI. As children move through the course of development into adolescence, the attachment relationships with their parents are often similar to those they later establish with their peers (Bowlby, 1973). Thus, it is not surprising that studies have found interpersonal and attachment difficulties with parents among those with NSSI. In a recent study examining the role of parental and peer attachment, self-compassion, and NSSI, those without NSSI showed greater levels of trust, communication, and closeness with their parents while lower levels of these qualities were associated with greater likelihood of NSSI (Jiang, You, Zheng, & Lin, 2017).

Interestingly, Jiang and colleagues (2017) found that qualities of peer attachment did not differ between NSSI and non-NSSI groups. While this finding regarding peer attachment is inconsistent with previous literature (Gandhi et al., 2016), this discrepancy may be due to the measurement of past year versus lifetime NSSI. Given that Jiang et al. (2017) classified their NSSI group as those who engaged in the behavior in the past year, and those with NSSI often join peer groups who also engage in the behavior (Jarvi, Jackson, Swenson, & Crawford, 2013), there is possibly an increased likelihood of peer group cohesion similar to what was found in the non-NSSI group. Additionally, Jiang and colleagues had a relatively young sample with an average age of 13.58 years. Thus, another explanation for their lack of differentiation between NSSI and non-NSSI groups

with regard to peer attachment could be that their sample consisted of individuals who are just beginning to engage in NSSI or who are "experimenting" with NSSI.

When examining older adolescents with a mean age of around 15 years, researchers have found that those with NSSI report significantly lower levels of positive attachment and higher levels of interpersonal instability with both their mother and peers (Glazebrook, Townsend, & Sayal, 2015; Santangelo et al., 2017). While these studies provide some insight regarding the relationship between NSSI and attachment, future research is needed to determine whether those with NSSI show a clear progression of parental interpersonal difficulties in childhood, that lead to interpersonal difficulties with peers during adolescence. For instance, the presence of parental interpersonal difficulties may contribute to the onset of NSSI, while peer interpersonal difficulties may contribute to its maintenance.

The studies reviewed thus far provide evidence for anomalies regarding negative affect and interpersonal sensitivity in NSSI. However, our understanding regarding the neurobiology associated NSSI is highly limited. This information may allow for a better understanding of when, where, and how neural circuitry becomes disrupted over the course of development, which may aid in the advancement of neurobiologically-informed prevention and intervention strategies. Given previous research implicating threat and interpersonal sensitivity in NSSI, neural circuitry relevant to these constructs may be a particularly fruitful area of inquiry.

2. Neurobiology of NSSI

2.1. Rationale and Framework for Advancing Neurobiological Research on NSSI

As reviewed in previous work (Westlund Schreiner, Klimes-Dougan, Begnel, & Cullen, 2015), NSSI is a clinical problem that may be best conceptualized from the perspective of the Research Domain Criteria (RDoC) initiative. Briefly, RDoC aims to encourage researchers to strive for a better understanding of discrete behaviors using measurable constructs (negative valence systems, cognitive control, systems for social processes, etc.) across multiple units of analysis (physiology, circuits, self-reports, etc.), rather than confining research to traditional diagnostic categories (Sanislow et al., 2010). Although the previous review identifies several areas in need of further study, the present study identifies two constructs that may be of particular interest to NSSI given existing research and theory: negative valence systems (negative affect) and systems for social processes (interpersonal sensitivity). The rationale of these particular constructs is that the presence of negative affect, particularly within the context of interpersonal relationships, can be a salient affective experience that may lead to onset of an NSSI episode. The present study will focus on multiple units of analysis including neural circuits, self-report, and paradigms. The combination of circuits with other units of analysis holds promise in identifying potential anomalies in neural development that may be targets for early interventions. Thus, an important next step is to characterize neural networks associated with NSSI, which can be done using methods that assess functional and structural connectivity.

Functional and structural connectivity are useful approaches that can be employed to investigate the neural circuitry associated with NSSI. While studies have demonstrated that brain structure influences function, the extent to which is still in question as there is

still variability between these measures (Damoiseaux & Greicius, 2009; Honey, Thivierge, & Sporns, 2010). Given this, the use of both functional and structural assessments of neural circuity allow for a more holistic picture of the internal workings of the brain in NSSI. Further, it allows for the examination of the relationship or coherence between these two measures, which may differ between NSSI and controls.

2.2. Measures of Neurobiology

2.2.1. Functional connectivity: Resting-state and task fMRI. Functional connectivity within neural networks is measured by the correlation between brain regions in the pattern of spontaneous blood oxygen level dependent (BOLD) signal over time. "Positive" functional connectivity (positive correlations) within a network is believed to signify that the brain regions are serving similar goals, while "negative" functional connectivity (negative correlations) signifies that the brain regions are serving opposing goals (M. D. Fox et al., 2005). Functional connectivity can be measured at rest (resting state functional connectivity; RSFC) and during the duration of a task (task functional connectivity; TFC). Further, functional connectivity may increase or decrease during specific task conditions; this can be measured using psychophysiological interactions (PPI). While overall TFC provides longer (duration of the entire task) time scale information, PPI provides shorter (during specific task blocks) time scale information. Both approaches are important for understanding the dynamics of functional connectivity in the context of specific tasks in adolescents with NSSI.

2.2.2. Structural connectivity: Diffusion weighted imaging. In addition to functional connectivity, research may also benefit from examining structural connectivity

via the use of diffusion imaging techniques. Diffusion imaging, or dMRI, provides information about white matter organization, which is important for the efficient transmission of neural signals. One commonly used metric that reflects white matter organization is fractional anisotropy (FA). FA produces a value between zero and one in which zero reflects complete isotropy (diffusion is not at all restricted or is restricted equally in all directions) and one reflects anisotropy (diffusion is confined to a particular direction). The assumption is that higher FA values reflect more optimal white matter organization. Examining dMRI in conjunction with functional connectivity will provide a more holistic understanding of the neural circuitry associated with NSSI.

2.3. Brief Overview of Typical Adolescent Neurodevelopment

It is important to recognize that the brain undergoes substantial refinement during adolescence. Developmentally, white matter increases linearly between the ages of 4 and 20 while gray matter increases in preadolescence and is followed by a decrease in post adolescence (Giedd et al., 1999). Specifically, gray matter peaks first in the frontal lobe at around age 12 and gray matter in the occipital lobe is the last to reach its peak as it continues to develop by 20 years of age. These changes are a reflection of synaptic pruning and increased myelination, which increases speed and efficiency of neuronal communication. The continuing maturation of gray and white matter during adolescence may implicate this period as a time of a greater predisposition to the development of abnormal brain structure and function (Giedd et al., 1999). Understanding how these systems begin to go awry in the context of maladaptive thoughts and behaviors, such as

NSSI, is of great utility as interventions may be tailored to these deficits and restore healthy neurodevelopmental trajectories.

2.4. Limbic system Introduction: The Amygdala

2.4.1 Amygdala activation. The neurobiology of negative affect is relatively well-understood and is comprised of cortico-limbic neurocircuitry (LeDoux, 2000; Phillips, Drevets, Rauch, & Lane, 2003). Specifically, the amygdala is a key limbic region that initiates the threat response, while frontal regions monitor and regulate emotional responses (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Ghashghaei & Barbas, 2002). Meta-analyses of both positron emission tomography (PET) and fMRI studies using healthy controls have found that the amygdala is activated during fear stimuli (Phan, Wager, Taylor, & Liberzon, 2002), with the left amygdala in particular being activated during emotion processing studies (Baas, Aleman, & Kahn, 2004).

To date, several studies have investigated the role of amygdala activation in NSSI with an emphasis on its activation in response to emotional stimuli. Niedtfeld and colleagues used a relatively small sample of 20 participants with BPD and histories of self-injury versus healthy controls and found that those with BPD had stronger activation that generalized to both negative and neutral pictures in the amygdala, insula, and anterior cingulate cortex (Niedtfeld et al., 2010). Additionally, they found that greater amygdala activation was associated with greater self-reported emotion regulation deficits (Niedtfeld et al., 2010). A similar study of 18 adolescents with versus without NSSI found that, in response to NSSI-related pictures, those with NSSI rated them as more arousing and also had increased activity in the middle orbitofrontal cortex and inferior

and middle cortex (Plener, Bubalo, Fladung, Ludolph, & Lulé, 2012). Further, when shown emotional pictures, the NSSI group had greater amygdala, hippocampus, and ACC response compared to controls (Plener et al., 2012). These studies highlight anomalous cortico-limbic activation in response to emotional stimuli, most notably within the amygdala, among those with NSSI.

To further elaborate on the association between the amygdala and NSSI, one study examined how NSSI may serve an emotion regulation function as indexed by amygdala activation prior to and following NSSI paradigms. This is in line with the existing theories of the functions of NSSI, particularly that the majority of those with NSSI engage in the behavior as a means to regulate emotion (Klonsky, 2007). In the study by Reitz and colleagues (2015), 21 females with BPD and NSSI and 17 healthy adults completed a stress induction paradigm followed by either a small incision on the forearm or a sham (Reitz et al., 2015). Researchers also assessed participants' level of stress/tension at several time points during the scan including immediately after the stress induction and following the incision or sham. Compared to controls, those with BPD and NSSI showed significantly greater decreases in self-reported stress/tension following incision as well as decreased amygdala activation (Reitz et al., 2015). Given that studies have found that those with NSSI show increased amygdala activation in response to negative stimuli, this decreased amygdala activation seen in response to incision among those with BPD and NSSI suggests a potential "normalization" effect of NSSI on possibly maladaptive amygdala hyperactivation. These studies have contributed important knowledge regarding the neural mechanisms associated with NSSI and also

support existing theories of NSSI function. Future research may benefit from expanding upon amygdala activation work by exploring the more global neural circuitry of this region and thereby increase our understanding of how these brain areas work in concert.

2.4.2. Amygdala functional connectivity. Unlike studies examining amygdala activation, there are very few studies examining amygdala TFC, RSFC, or PPI in NSSI. Thus, studies in healthy controls are briefly reviewed to provide some background with regards to the amygdala connectivity patterns that are presumed to be typical. These studies can then highlight the transactional processes that occur between the amygdala and other brain regions implicated in functions that are highly relevant to NSSI, such as emotion processing and regulation of negative affect. Additionally, studies using healthy controls can provide an illustration of the similarities and differences of amygdala RSFC and TFC, laying the groundwork for hypotheses for future NSSI research.

In a study of amygdala RSFC in 65 healthy adults, Roy et al. (2009) found that the amygdala showed positive RSFC with the medial frontal gyrus, rostral ACC, part of the dACC, insula, thalamus, and striatum. In contrast, the amygdala showed negative RSFC with the superior frontal gyrus, middle frontal gyrus, posterior cingulate cortex, precuneus, and parietal and occipital lobes (Roy et al., 2009). With regard to amygdala TFC, a study of 83 healthy adults examined amygdala connectivity during a negative emotion task with a focus on regions found to be anatomically connected within animal models (Stein et al., 2007). During this task, Stein and colleagues found that the amygdala had positive connectivity with the parahippocampal gyrus, subgenual ACC, insula, and orbitofrontal cortex, and negative connectivity with the posterior cingulate

and supragenual cingulate (Stein et al., 2007). When compared to the RSFC findings, there are a couple overlaps suggesting similar connectivity patterns during both rest and task. In particular, the amygdala shows positive connectivity with the insula and negative connectivity with the posterior cingulate cortex during both rest and task. The similarities and differences found in these two contexts highlights the importance of examining both RSFC and TFC with regard to NSSI.

To date, only two studies have examined TFC among those with NSSI. In addition to exploring the association between brain activation and pain in NSSI as reviewed above, Reitz et al. found that the NSSI group showed impaired amygdala-frontal connectivity that normalized (or increased) several minutes following a small incision on the forearm (Reitz et al., 2015). Second, Niedtfeld et al. found enhanced amygdala-frontal TFC following a painfully cold stimulus and presentation of negative scenes (Niedtfeld et al., 2012). Thus, not only does it appear that NSSI may restore amygdala activation to normative levels, but also appears to normalize amygdala-based neural circuitry.

While there is currently no published research examining the relationship between NSSI and RSFC other than the present study (Westlund Schreiner et al., 2017), some work has emerged with regard to RSFC associated with suicide. A study comparing 19 participants with MDD and suicide attempts and 19 without suicide attempts found that those with suicide attempts showed increased amygdala RSFC with the insula, superior orbitofrontal cortex, and middle temporal area (Kang et al., 2017). Further, Kang and colleagues also used a continuous approach to suicidal thoughts and behavior by

examining the correlation of amygdala RSFC with scores on a suicide ideation scale. They found that those with suicide attempts and higher levels of suicide ideation also had greater amygdala RSFC with the parahippocampal gyrus (Kang et al., 2017).

2.4.3. Amygdala-related structural connectivity. In regard to structural connectivity, only one study to date has examined dMRI associated with NSSI. Although, it is unclear whether this study considered self-injury that was suicidal or non-suicidal, a small sample of patients with BPD and self-injury (n = 9) versus healthy controls (n = 7) found that the BPD with self-injury had decreased FA within a region of interest placed in the inferior frontal lobe (Grant et al., 2007). This finding suggests white matter disorganization involving frontal regulatory regions among those with BPD and self-injury. This study is further limited, as it is unclear as to where within the frontal lobe this white matter disorganization was found.

A promising white matter tract of interest for dMRI research that corresponds to amygdala-centered networks, particular amygdala-frontal networks, is the uncinate fasciculus. The uncinate is a bundle of white matter fibers that serve as a structural connection between fronto-limbic areas, including the amygdala. Because of the areas it serves, abnormalities within this tract may underlie difficulties in emotion regulation as well as correspond with potential functional connectivity anomalies between the amygdala and frontal regulatory regions. Although research has been mixed regarding the directionality of FA among adolescents with and without MDD, research on adults with MDD has been fairly consistent (see Bracht, Linden, & Keedwell, 2015 for review). Discrepancies of adolescent MDD literature may be explained in part to heterogeneous

groups. It is possible that by focusing on a discrete behavior, such as NSSI, results may be more consistent. Another demographic of interest to NSSI is BPD, as NSSI is considered a symptom of this disorder (American Psychiatric Association, 2013). Decreased FA has been found among both adults and adolescents with BPD (Lischke et al., 2015; New et al., 2013). Also related to the proposed study, decreased FA of the uncinate fasciculus has been found among youth with emotion dysregulation disorder (Versace et al., 2015) and is inversely correlated with levels of self-reported trauma in childhood and internalizing problems (Hanson, Knodt, Brigidi, & Hariri, 2015).

Finally, since brain connectivity within fronto-limbic networks matures between adolescence and adulthood (Cunningham, Bhattacharyya, & Benes, 2002), it is important to examine neural connectivity of NSSI among adolescents and young adults. The uncinate fasciculus is one of the latest white matter tracts to mature, reaching its peak well into adulthood (Lebel et al., 2012; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Because of its slower course of development, this particular white matter tract may be more amenable to intervention and thus, understanding its association with NSSI may be highly beneficial to the development of early identification and treatment strategies.

2.5. Interpersonal Relationships and Rejection Sensitivity: Dorsal Anterior Cingulate Cortex (dACC)

Negative affect that occurs in the context of interpersonal relationships, such as when there is perceived rejection, may be critically implicated in NSSI. Studies examining interpersonal sensitivity and rejection using functional magnetic resonance

imaging (fMRI) have highlighted brain regions included in the "salience network", a system known to be involved in self-awareness and social behavior through the integration of emotional, cognitive, and sensory information (Menon, 2015). The salience network can also be described as being involved in assessing the meaning or value of internal and external stimuli (Seeley et al., 2007). Although often attributed as being part of the "cognitive" division of the ACC (Bush, Luu, & Posner, 2000), one region of the salience network, the dorsal anterior cingulate cortex (dACC), has been implicated in several other functions including pain, reward valuation, and saliency of social information (Beckmann, Johansen-Berg, & Rushworth, 2009; Behrens, Hunt, Woolrich, & Rushworth, 2008).

2.5.1. dACC activation and functional connectivity.

Several studies have examined the neurobiology of rejection sensitivity within non-NSSI samples. A study of healthy adults found that higher levels of rejection sensitivity was associated with greater dACC activation in response to disapproving facial expressions (Burklund, Eisenberger, & Lieberman, 2007). Further, Burklund et al. found negative TFC between the dACC and subgenual ACC/ventromedial prefrontal cortex (vmPFC), thus suggesting higher dACC activation and lower activation of prefrontal regulatory regions among those with high levels of rejection sensitivity. Similarly, another study found that healthy adults with low self-esteem exhibited greater dACC activation and reported greater social pain in response to a social exclusion task (Onoda et al., 2010). However, an opposite pattern was found with regard to connectivity compared to Burklund et al. as dACC showed positive TFC with ventrolateral prefrontal

cortex (vlPFC) and vmPFC among those with low self-esteem. However, these differing TFC findings between Onoda et al. (2010) and Burklund et al. (2007) may be a reflection of the use of different clinical measures (rejection sensitivity versus low self-esteem) and/or fMRI paradigms (disapproving facial stimuli versus social exclusion).

While the above studies suggest that the relationship between rejection sensitivity and dACC connectivity remains unclear, these as well as other studies provide a consensus as to the implication of the dACC in instances of interpersonal threat and rejection sensitivity (Eisenberger, Lieberman, & Williams, 2003; Eisenberger, Way, Taylor, Welch, & Lieberman, 2007; Masten et al., 2009). Taken together, these studies of the dACC in healthy samples suggest that exploration of dACC functional connectivity may provide insight into how interpersonally-relevant networks may go awry in NSSI.

2.5.2. dACC-related structural connectivity. In regard to structural connectivity involving the dACC, perhaps the most relevant white matter tract is the cingulum. The cingulum serves to connect the ACC more broadly to other regions of the default mode network (DMN), which comprises a network of regions that are more active at rest than during task (Raichle et al., 2001). Interestingly, many of the regions that the cingulum serves, such as the dACC, tend to overlap with the "social brain" (Amft et al., 2015; Mars et al., 2012). Although some studies have reported null findings regarding differences in FA of the cingulum between psychiatric samples and controls (LeWinn et al., 2014; Lischke et al., 2015), a meta-analysis of adolescents with MDD found that overall, those with depression had decreased FA within this region (Lichenstein, Verstynen, & Forbes,

2016). However, no studies to date have investigated the role of the cingulum in adolescents with NSSI.

3. Present Study: Functional and Structural Connectivity of Limbic and Interpersonally Relevant Regions in Non-Suicidal Self-Injury

The proposed study will investigate the association of NSSI with structural and functional connectivity of two different circuits: 1. amygdala-centered circuitry, due to its role in negative affect and emotion regulation; and 2. circuitry involving the dorsal anterior cingulate cortex (dACC) due to its involvement in interpersonal sensitivity as well as with the salience network. Ideally, results from these two different indices (structural and functional connectivity) will be complementary to each other. However, because these techniques use different metrics (one relying on gray matter and the other on white matter) and because they also follow slightly different developmental trajectories (with white matter showing a linear while gray matter shows a curvilinear (Giedd et al., 1999) course of development), it is possible for disparate findings. In either case, given the paucity of research using these techniques to study NSSI, the proposed work will provide valuable information using multiple methods to further our understanding of this behavior.

3.1. Innovation

The present study takes an integrated approach using multiple neuroimaging methods in order to advance our understanding of NSSI. Specifically, this study examines functional connectivity of two neural circuits likely implicated in NSSI (negative affect-amygdala and interpersonal relationships-dACC) in the context of both rest and task.

Additionally, it will add to what is currently only one study on NSSI-related structural connectivity while also using a more robust approach.

3.1.1. Functional connectivity.

The present study will address the dearth of literature examining functional connectivity associated with NSSI by integrating functional connectivity both during rest and task. In recent years, it has become increasingly clear that functional connectivity within neural networks is not static, but changes across time and across contexts (Chang & Glover, 2010; Cole et al., 2013). Therefore, a combined approach using RSFC, TFC, and PPI to understand adolescent NSSI holds potential to reveal a deeper understanding of neural networks underlying this behavior by characterizing network aberrations both at rest and during task conditions. The proposed study also uses anatomically based ROIs located within the amygdala and dACC. The advantage of this approach over others (such as independent component analysis or spherical ROIs) is that the ROIs account for individual differences in anatomy and may also present additional information that is not constrained to the functioning of an entire "component", which is a pre-defined set of brain regions that are identified using independent component analysis. In other words, using an anatomically based ROI as a "seed" region allows for the examination of significant functional connectivity patterns across the whole brain.

The present study also uses highly conservative methods to reduce spurious results due to artifacts such as physiological noise and motion. Such artifacts are a common issue in functional connectivity literature and may be at least partly responsible for the lack of replicability across studies. These methods include deweighting

components likely representing movement or physiological noise, regression of cerebral spinal fluid (CSF), white matter (WM), and the six motion parameters, and also deweighting whole volumes that exceed a certain threshold of motion based on previous literature (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).

3.1.2. Structural connectivity. With only one study examining the relationship between structural connectivity and self-injury, further research investigating white matter microstructure associated with NSSI is warranted. The present study will provide a necessary step forward in the understanding of structural connectivity associated with NSSI. Further, the proposed study uses data that were collected in such a way that allows for High Angular Resolution Diffusion Imaging (HARDI) reconstruction. This is of significance as it allows for the use of analysis strategies that depart from the traditional tensor model. Although widely used, the tensor model is limited as it does not account for crossing or "kissing" white matter fibers. This results in inaccurate FA values attributed to individual voxels in which the directionality of fibers is heterogeneous (Pierpaoli et al., 2001; Wiegell, Larsson, & Wedeen, 2000).

By using analysis methods afforded by HARDI acquisition, strategies can be used to resolve multiple fiber directions in a voxel (Descoteaux, Angelino, Fitzgibbons, & Deriche, 2007; Tuch, 2004). This can be accomplished by using spherical harmonization to calculate the Orientation Distribution Function (ODF), which is then used to estimate Generalized Fractional Anisotropy (Assemlal, Tschumperle, & Brun, 2007). Thus, by using these methods, the proposed study will not only address a gap in the literature, but also do so in a manner that allows for more reliable results.

3.2. Hypotheses

To examine structural and functional connectivity of the threat network in adolescent females with NSSI by measuring amygdala functional connectivity during rest and during a negative emotion task and amygdala-related structural connectivity. *Hypothesis 1a.* Adolescents with NSSI will show lower amygdala-cortical functional connectivity compared to controls both during rest and during a negative emotion task, particularly involving frontal regulatory regions. *Hypothesis 1b.* Adolescents with NSSI will show compromised structural connectivity of the uncinate fasciculus, a frontolimbic white matter tract, compared to controls. *Hypothesis 1c.* Functional and structural connectivity will be associated with clinical measures implicating behavioral and emotional regulation.

To examine functional and structural connectivity of brain regions implicated in interpersonal sensitivity in adolescent females with NSSI compared to healthy controls using functional (resting-state and task fMRI) and structural connectivity. *Hypothesis 2a.* Adolescents with NSSI will show greater connectivity between the dorsal anterior cingulate cortex (dACC) and other regions involved in the salience network. *Hypothesis 2b.* Compared to healthy controls, adolescents with NSSI will show compromised structural connectivity of the cingulum, a white matter tract serving the dACC and other salience network regions. *Hypothesis 2c.* Functional and structural connectivity of these brain regions will be associated measures of interpersonal sensitivity.

4. Method

4.1. Participants

To investigate these aims, data were used from a recently completed study at the University of Minnesota (Cullen: 1R21MH094558). In this cross-sectional study, females aged 13-21 years with NSSI and age-matched HC were recruited. The rationale for this large age range was to capture the timeframe in which NSSI is typically at its peak. Recruitment strategies included community postings and referrals from local mental health services. Inclusion criteria for the NSSI group included a history of engaging in NSSI at least 4 times, with at least 1 episode occurring in the last month. Exclusion criteria for both groups was a history of bipolar, pervasive developmental, or psychotic disorders, current pregnancy or breastfeeding, unstable medical illnesses, active suicidal intent, presence of MRI-incompatible features, a positive urine drug screen, and intelligence quotient (IQ) of less than 80 as measured by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Additional exclusion criteria for HC included any history of self-injurious behavior (suicidal or non-suicidal) and any current or past DSM-IV psychiatric diagnoses.

4.2. Measures

4.2.1. Assessment. All participants completed legal written consent and assent as appropriate. Participants 18 years and older provided consent while participants under 18 provided assent with a legal parent or guardian completing consent. Following informed consent and assent (as appropriate), all participants completed a comprehensive diagnostic assessment, which were conducted by trained clinicians or graduate students under the supervision of a licensed psychologist. Interviews were conducted separately with adolescents and parents, and included Kiddie Schedule for Affective Disorders and

Schizophrenia- Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) for participants under 18 years and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First, Spitzer, Gibbon, & Williams, 2002a, 2002b) for participants 18 or older. Participants were also asked to provide general demographic information such as sex, age, and race/ethnicity. Participant handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971)

4.2.1.1. NSSI. NSSI was measured using the self-report Inventory of Statements About Self-Injury (ISAS; Glenn & Klonsky, 2011) and the clinician-administered Deliberate Self-Harm Inventory (DSHI; Gratz, 2001). These two measures were used to provide a consensus on frequency and type of self-injury for each participant in the NSSI group. The ISAS has demonstrated good stability for measurement of NSSI behaviors with a test-retest correlation of .68 (Glenn & Klonsky, 2011). Further, the DSHI showed high internal consistency ($\alpha = .82$) and a test-retest correlation of .92 (Gratz, 2001).

4.2.1.2. Other self-report measures. Additional self-report measures included the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004), Barratt Impulsiveness Scale (BIS; Patton, Stanford, & Barratt, 1995), Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996), Symptom Checklist 90 Revised (SCL-90-R; Derogatis & Savitz, 2000), and Personality Assessment Inventory (PAI) or Personality Assessment Inventory-Adolescent (PAI-A) for those under 18 (Morey, 2007b, 2007a). The PAI and PAI-A are complementary scales as the PAI has been standardized for use with 18-89 year-olds while the PAI-A has been standardized for use with 12-18 year-olds. Both of these measures include the same scales with the PAI-A

containing fewer items. The present study only considered the T-scores to allow for comparability between the two measures.

Difficulties in Emotion Regulation Scale. The DERS is a self-report measure of one's ability to successfully regulate emotions consisting of 36 items in which the participant rates each one on a scale of 1 (almost never or 0-10%) to 5 (almost always or 91-100%). In addition to a total score, the DERS provides scores for six factors: 1. Nonacceptance of Emotional Responses (NONACCEPTANCE; tendency to reject one's reactions to an emotion or experience negative secondary emotional responses); 2. Difficulties Engaging in Goal-Directed Behavior (GOALS; inability to effectively accomplish tasks in the context of negative emotions); 3. Impulse Control Difficulties (IMPULSE; inability to successfully control one's behavior in response to negative emotions); 4. Lack of Emotional Awareness (AWARENESS; inattention or lack of understanding of one's negative emotions); 5. Limited Access to Emotion Regulation Strategies (STRATEGIES; belief that one is unable to effectively handle their emotions); and 6. Lack of Emotional Clarity (CLARITY; inability to identify and/or understand one's own emotions). While this factor structure was initially found among adults (Gratz & Roemer, 2004), it has also been replicated among adolescents (Neumann, van Lier, Gratz, & Koot, 2010). These studies have also found that the DERS has acceptable to high internal consistency across factors in both adolescents (average $\alpha = .81$) and adults (average $\alpha = .85$). The DERS total score and scores from its 6 subscales (factors) were used for examining correlations with significant amygdala FC clusters and GFA of the uncinate fasciculus.

Barratt Impulsiveness Scale. The BIS is a self-report measure of impulsivity consisting of 30 items to which participants respond on a scale of 1 (Rarely/Never) to 5 (Almost Always/Always). In addition to a total score, provides scores for three second-order factors of 1. Attentional Impulsiveness (being unable to concentrate on a given task); 2. Motor Impulsiveness (behaving without thinking); and 3. Nonplanning Impulsiveness (combination of lack of self-control and cognitive complexity). The BIS total score has been found to have high internal consistency (α ranging from .79 in substance-abuse patients and .83 in general psychiatric patients)(Patton et al., 1995). The BIS total score and scores from its 3 subscales were used to calculate correlations with significant amygdala FC clusters and uncinate fasciculus GFA.

Symptom Checklist 90-Revised. The SCL-90-R is a self-report measure of nine different symptom dimensions consisting of 90 "problems". Participants are asked to respond to each problem based on how it bothers them using a scale of 0 (Not at All) to 4 (Extremely). Although there are nine symptom scales that address a range of dimensions of psychopathology and functioning, only the Interpersonal Sensitivity (I-S) scale is used for the present study. The I-S scale, consisting of the average score for 9 items, was used to calculate correlations with significant dACC FC clusters and GFA of the cingulum. It is worth noting, however, that many studies have failed to support the factor structure of these 9 symptom dimensions, thus posing a possible limitation to any of our findings involving this measure (Ardakani et al., 2016; McGough & Curry, 1992; Paap et al., 2011, 2012; Rytilä-Manninen et al., 2016).

Personality Assessment Inventory. The PAI and PAI-A are self-report psychopathology measures containing 22 scales measuring psychopathological constructs, response styles, and validity. Because the PAI has been validated for use with adults aged 18-29 years and the PAI-A has been validated for use with adolescents aged 12-18 years, both versions were used for our study due to our large age range (with participants under 18 completing the PAI-A). The items from the PAI and PAI-A require the participant to select one of the four responses: False, Not at all True; Slightly True; Mainly True; and Very True. While the PAI and PAI-A differ in length (PAI has 344 items and PAI-A has 242 items), the conversion of raw scores for each scale to t-scores allows for the two measures to be comparable. Both measures have shown high test-retest reliability with correlations of .80 or higher for all subscales of the PAI and an average correlation of .78 for the PAI-A. Additionally, both measures have demonstrated high internal consistency for the scales with a median α of .88 and average α of .80 for the PAI and PAI-A respectively. For the purposes of the present study, the variable of interest included the clinical subscale of Borderline Features-Negative Relationships (BOR-N), which assesses ambivalent and intense relationships. This scale was used to calculate correlations with significant dACC FC clusters and GFA of the cingulum.

Rejection Sensitivity Questionnaire-Adolescent. The RSQ-A is a modified version of the original RSQ and the Children's Rejection Sensitivity Questionnaire (CRSQ; G Downey & Feldman, 1996; Geraldine Downey, Lebolt, Rincón, & Freitas, 1998). Based on these previous questionnaires, items were modified to be more appropriate for adolescents as the adult version had items that were only appropriate for adults (e.g. items

involving serious romantic relationships) and the child version had items that were only appropriate for children (e.g. items involving play dates/toys). The RSQ-A includes 12 situations in which the participant must respond to two questions: 1. How concerned/anxious the participant would be that the situation would resolve favorably; and 2. How much the participant would expect the situation to resolve favorably. Participants selected their response on a scale of 1 (very unconcerned) to 6 (very concerned) for the first item and a scale of 1 (very unlikely) to 6 (very likely) for the second item.

A total of 12 different situations were presented with the focus of parent, friend, and stranger/acquaintance relationships each having four situations. Higher scores for the first question indicates greater concern/anxiety surrounding potential rejection. Answers for the second question regarding expectation were reverse scored (with the exception of one item) so that higher scores indicate greater levels of expecting a negative outcome (rejection). This measure results in a total score, total anxiety (sum of scores pertaining to participants' concern/anxious for each situation), and total expectation (sum of scores pertaining to participants' expectation of a negative outcome). Additional scales explored items related to parent, friend, and stranger/acquaintance relationships separately (total, anxiety, and expectation scores for each). The purpose of these exploratory scales was to allow for the ability to examine rejection sensitivity in the context of specific relationships, particularly parent versus friends.

Initial psychometric data on 36 participants (most of which are included in the present study) showed excellent internal consistency for total score, total anxiety, and

total expectation (Cronbach's α = .95, .91, .91 respectively). The total score from the RSQ-A was used to calculate correlations with significant dACC FC clusters and GFA of the cingulum. Given the novelty of this measure, additional information including a copy of the measure can be found in Appendix A.

4.3. Neuroimaging Acquisition.

Data were acquired at the Center for Magnetic Resonance Research at the University of Minnesota using a Siemens 3T TIM Trio scanner and a 32-channel receive-only head coil. A five-minute structural scan was acquired using a T1-weighted high-resolution magnetization prepared gradient echo (MPRAGE) sequence: TR = 2530ms; TE = 3.63ms; TI = 1100ms; 1mm slices, FOV = 256, flip angle = 7 degrees.

4.3.1. Resting-state fMRI. Resting-state fMRI data were obtained using the WU-Minn Human Connectome Project consortium (http://www.humanconnectome.org/) multi-band EPI sequence with: 64 oblique axial slices; 2mm isotropic voxel; TR = 1320ms; TE = 30ms; flip angle = 90°, FOV = 212mm; multiband factor = 4. Participants were instructed to remain awake with their eyes closed during the resting-state scan. The scan acquired 260 volumes, which lasted approximately 6 minutes. To minimize effects of task-based fMRI on resting-state fMRI, the resting state scan was acquired prior to the task.

4.3.2. Emotion Face-Matching Task. Task fMRI data were obtained using the same parameters as the resting-state scan [using WU-Minn Human Connectome Project consortium (http://www.humanconnectome.org/) multi-band EPI sequence with: 64 oblique axial slices; 2mm isotropic voxel; TR = 1320ms; TE = 30ms; flip angle = 90°,

FOV = 212mm; multiband factor = 4]. For the task, a negative emotion face-matching task was selected, which has been shown to activate the amygdala (Hariri et al., 2002). Adolescents with NSSI versus HC were compared on amygdala RSFC, amygdala TFC, and changes in amygdala TFC with task conditions (PPI).

The emotion face-matching task (Hariri et al., 2002) was projected onto a screen inside the bore of the scanner. This task used two affective stimuli, which were Ekman faces (Ekman & Friesen, 1975) depicting anger and fear, and control stimuli, which consisted of horizontal and vertical ellipses. Participants were instructed to look at the picture in the top row and use a response box to select one of the two pictures in the bottom row that matched. Participants were asked to match the shapes for the control stimuli and the emotions for the affective stimuli. The task consisted of thirteen, 24-second blocks (3 fixation, 5 shape, and 5 emotion). The task acquisition included 294 volumes, which took approximately 6.5 minutes. The present study examined the emotion blocks relative to fixation and emotion blocks relative to shape.

4.3.3. Diffusion MRI. Diffusion scans were acquired in reverse phase encode directions (right to left and left to right) to estimate and correct for distortions. These scans were acquired using a multi-band EPI sequence with: 66 oblique axial slices; 2mm isotropic voxel; 128 diffusion-weighted directions; TR = 3097ms; TE = 90.2ms; flip angle = 90°, FOV = 212mm; multiband factor = 3; b-value = 1500s/mm.

4.4. Procedure

This study was approved by the University of Minnesota Institutional Review Board. Healthy controls and participants with NSSI were recruited using primarily

community postings, clinic referrals, and online advertisements around the Minneapolis/Saint Paul area. Interested participants contacted the research team via email or phone, which was followed by a phone screen to assess for basic inclusion and exclusion criteria.

Participants who appeared eligible via the phone screen were invited to participate in the initial screening visit. At this visit, NSSI participants were offered three different options for study participation: (1) Participation in MRI study only; (2) Participation in treatment study only; or (3) Participation in both MRI and treatment study (MRI conducted both pre- and post-treatment). The treatment offered was an open label pilot study for the dietary supplement N-acetylcysteine. Further description of this trial and its clinical results have been previously published (Cullen et al., 2018). HC participants were only offered the option to participate in the MRI study. The present study only uses data from participants who elected to complete either the MRI-only study or the MRI and treatment study (using only the pre-treatment MRI data). After all questions were answered and participants selected their desired study option, informed consent and assent (where applicable) was obtained. Following consent, participants completed a thorough assessment including a diagnostic interview and several self-report measures described above. NSSI participants who selected the MRI and treatment option also completed a brief physical exam. This visit lasted approximately 1-6 hours depending on the complexity of psychopathology. Participants received monetary compensation for their time at the end of this visit.

Provided that participants still met eligibility criteria following the initial screening visit, they were invited to the Center for Magnetic Resonance Research (CMRR) for their MRI scan. Upon arrival to the CMRR, participants completed a safety screen form to ensure there were no MRI contraindications. Participants then completed a pregnancy test and urine toxicology screen to assess for illicit drug use. If pregnancy or illicit drug use were indicated, the participant could not complete the scan. Participants with negative pregnancy and drug screens proceeded to the MRI scanner where they completed an anatomical scan, spectroscopy, dMRI, resting-state fMRI, and two neuroimaging tasks. The neuroimaging tasks included the one of interest in this study, which is described above, as well as a passive face viewing task. The entire MRI protocol took approximately 1.5 hours. At the completion of the visit, participants received monetary compensation.

4.5. Statistical Analysis.

4.5.1. Demographics and clinical data. Demographic and clinical data were analyzed using the software package SPSS Version 24. Descriptive variables of interest included age, IQ, handedness, scores on clinical measures of psychopathology, and current psychiatric diagnoses and medications.

4.5.2. Anatomical imaging preprocessing. T1 data were processed through FreeSurfer Version 5.3 (surfer.nmr.mgh.harvard.edu); output have been visually inspected and manually corrected as necessary. No corrections were required in the vicinity of the amygdala.

4.5.3. Resting-state and task fMRI preprocessing and analysis. Tools from the FMRIB software library (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and custom tools developed in MATLAB were used. Initial processing included brain extraction, motion correction and correction for magnetic field inhomogeneity-induced geometric distortion using Topup. To further reduce correlation induced by subject motion, the DVARS and framewise displacement metrics introduced by Power and colleagues (Power et al., 2012) were computed. Any volume with a DVARS value exceeding 8 and/or a framewise displacement value exceeding 0.5, along with the previous volume and the two following volumes were noted for exclusion via de-weighting during the first-level FEAT analysis. Participants were excluded from analyses if >33% of all volumes were noted for de-weighting.

FSL's MELODIC was used to conduct an exploratory independent component analysis on each individual's processed data. Components were inspected with regard to spatial clusters, time series, and power spectra, as described previously (Cullen et al., 2009). FSL regfilt was used to remove components that most likely represented noise, including heart rate, respiration, or movement, as well as components in white matter (WM) or cerebrospinal fluid (CSF) according to guidelines published by Kelly et al. (Kelly et al., 2010). Using methods described previously (Cullen et al., 2014), FreeSurfer-generated regions of interest (ROIs) for CSF and WM were registered to the rsfMRI using BBRegister. Mean BOLD time series within these ROIs were extracted using *fslmeants*.

First-level RSFC analysis. To examine RSFC of the ROIs of interest [left and right amygdala (Specific Aim 1) and left and right pACC (Specific Aim 2)], the present study implemented a seed-based, whole-brain approach using methods previously described (Cullen et al., 2014). FreeSurfer was used to create anatomically based ROIs, which were registered to the preprocessed rsfMRI data. The average BOLD time series across voxels in these regions were extracted and used as primary regressors in separate (right and left) general linear model (GLM) analyses of each voxel's time series. Additional steps included spatial smoothing (5mm Gaussian kernel), prewhitening, and registration to anatomical data and MNI standard space for later group analysis. Nuisance regressors included in each voxel's analysis using nine different time series: WM, CSF, indicators of volumes of excess motion (as described above), and the six motion parameters. This resulted in whole-brain RSFC maps for each ROI.

First-level task fMRI analysis. FSL's FEAT was used to conduct TFC and PPI analyses. TFC analyses included examination of overall connectivity of the amygdala during the task, while PPI analyses are designed to assess whether specific circuits increase in synchrony specifically during task blocks (Friston et al., 1997; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). Linear regression analyses were conducted in FEAT to examine TFC and PPI individually for each participant. Analyses were completed separately for each ROI. TFC analyses included mean ROI time series as the primary regressor of interest, with the Emotion and Shape task explanatory variables included as regressors of no interest. PPI analyses included the following regressors: Emotion, Shape, mean ROI time series, and interaction terms (the result of multiplying

the mean ROI time series with each of the emotion and the shape regressors). Nuisance regressors included: WM, CSF, volumes of excess motion, and the six motion parameters. This resulted in whole-brain RSFC maps for each ROI. Data from the resulting beta contrast maps of these analyses were used for group comparisons.

Rest and task higher level analyses. To examine RSFC, TFC, and PPI group differences, whole-brain, voxel-wise group comparisons of the right and left amygdala RSFC maps were completed separately, controlling for age, using Gaussian Random Field Theory to correct for multiple testing across voxels, specifying a cluster z-threshold of 2.3 and $p < 0.025$ (the latter parameter selected to correct for the two analyses for each ROI [right and left amygdala and right and left pACC]).

4.5.4. Diffusion MRI analyses. Topup was performed on the two dMRI scans (one in the right to left and the other in the left to right phase encode direction) to estimate off-resonance field induced susceptibility. The two different scans were then concatenated using *fslmerge* for the next steps. Eddy-current and susceptibility-induced distortion corrections were completed using the Gaussian Process approach applied by FSL's *eddy* tool (Andersson & Sotiropoulos, 2016). Brain extraction was performed on the resulting data using FSL's Brain Extraction Tool (BET). Custom built tools created in MATLAB as developed by Aganj et al. (2010) based on the method presented by Assemlal, Tschumperlé, and Brun (2007) were used to calculate ODF and create GFA maps for each individual (See Appendix B for ODF examples). While the present study has specific hypotheses with regard to the specific tracts that may show anomalies

between NSSI and HC groups, a more exploratory whole-brain white matter skeleton approach was used given the significant absence of dMRI studies on NSSI.

Group comparisons examining differences between NSSI and healthy controls were then completed using the GFA maps and Tract-Based Spatial Statistics (TBSS; Smith et al., 2006). TBSS included using a nonlinear registration to convert the GFA maps into standard space, creating mean GFA images and skeleton for each individual, and then projecting the GFA data from all subjects onto the mean GFA skeleton. Finally, comparisons were conducted using GLM modeling and the Threshold-Free Cluster Enhancement (TFCE) option with a *p*-value of $< .01$, which is more robust and is comparable to cluster-based thresholding. Age was used as a covariate for these analyses.

Following group comparisons, significant regions of tracts were used as a mask to extract average GFA values from each participant. These values were used to conduct correlations between GFA values and clinical measures of interest, with clusters including the uncinate fasciculus being associated with emotion regulation and impulsivity and cingulum with measures of rejection sensitivity. These values were also used to examine their relationship with significant FC clusters.

4.5.5. Clinical correlations. To test whether there was an association between connectivity and clinical measures within the NSSI group, a series of follow-up analyses were conducted using the significant clusters from the above group analyses as individual masks to extract average z-scores from each participant's un-thresholded connectivity maps.

Measures of behavioral and emotional regulation (from DERS and BIS) and their relationships with 1. connectivity levels in significant amygdala RSFC clusters; and 2. GFA values in clusters including the uncinate fasciculus were examined within the NSSI group. A Bonferroni correction was used to correct for multiple comparisons across the 11 different behavioral and emotion regulation subscales and number of significant clusters from the neuroimaging results.

Within the NSSI group, correlations were performed to assess the relationships between measures of interpersonal sensitivity and: (1) connectivity levels in significant dACC clusters; and (2) GFA values in clusters including the cingulum. As described above, interpersonal sensitivity measures included the Interpersonal Sensitivity subscale of the SCL-90-R (Derogatis & Savitz, 2000), the BOR-N subscale of the PAI/PAI-A, and the total score from the RSQ-A, with exploratory analyses using the other RSQ-A scales. A Bonferonni correction will be used to correct for multiple comparisons using the three different clinical scales and the number of significant neuroimaging clusters.

To explore whether there was any association between frequency of NSSI episodes and significant connectivity findings, the extracted connectivity z-scores and GFA values, as described above, were correlated with average weekly cutting episodes. These data were collected using a consensus between the ISAS and DSHI. Average weekly cutting episodes was calculated by taking the consensus of lifetime cutting episodes and dividing them by the estimated number of weeks the participant engaged in NSSI. Outliers on this variable were Winsorized to three standard deviations above the mean. Focus was on cutting episodes for these analyses, as cutting was the primary

method of NSSI among all the NSSI participants. To correct for multiple comparisons across the different significant neuroimaging clusters, a Bonferroni correction was applied.

4.5.6. Exploration of the relationship between functional and structural connectivity. To provide information about how the coherence between functional and structural connectivity may vary between HC and NSSI, a GLM was used to investigate whether NSSI and HC differed with regard to their relationships between GFA values and FC values. This entailed examining the relationship between: (1) GFA values from significant group difference clusters that include the uncinate fasciculus and amygdala FC clusters; and (2) GFA values from significant group difference clusters that include the cingulum and dACC FC clusters.

5. Results

5.1. Demographic and Clinical Characteristics

Overall, 29 NSSI and 22 HC completed all study procedures. However, total usable numbers between the different scan acquisition methods of resting-state and task fMRI and dMRI varied due to factors such as motion and acquisition errors. Demographic and clinical characteristics for each acquisition method are detailed below. A CONSORT diagram of participants can be found in Figure 1.

5.1.1 RSFC. Of the initial data collected from 29 NSSI and 22 HC participants, data from 1 HC was excluded due to unusable FreeSurfer parcellation of T1 data (problematic due to use of individualized anatomical ROIs) and data from 4 NSSI and 1 HC participants were excluded due to exceeding our threshold of motion during the

"scrubbing" step. Specifically, these participants' data had over 33% of the resting-state scan's 260 volumes (87 volumes) that were noted for de-weighting during the first-level FEAT analysis. Data from a total of 25 NSSI and 20 HC participants were included for the final RSFC analyses. Further demographic and clinical characteristics for the RSFC sample can be found in Table 1.

5.1.2. TFC. Similar to the RSFC sample, data from 1 HC were excluded due to unusable FreeSurfer parcellation of T1 data. In addition, data from 1 HC were excluded due to errors in task acquisition and 1 NSSI participant did not complete the task fMRI due to time. Data from 4 NSSI and 3 HC participants were also excluded from further analyses due to having over 33% of the task fMRI's 294 volumes (98 volumes) noted for de-weighting during the first-level FEAT analysis. Data from 24 NSSI and 17 HC participants were included in the TFC and PPI analyses. Further demographic and clinical characteristics for the TFC/PPI sample can be found in Table 2.

5.1.3. dMRI. After one subject was excluded due to poor dMRI data quality, data from 28 NSSI and 22 HC participants were used for dMRI analyses. Further demographic and clinical characteristics for the dMRI sample can be found in Table 3.

5.2. Resting-State Functional Connectivity

5.2.1. Amygdala RSFC. For right amygdala, NSSI had negative RSFC but HC had positive RSFC in a cluster encompassing the left angular gyrus and lateral occipital cortex. NSSI showed positive, while HC showed negative, RSFC in a cluster involving the bilateral dorsal anterior cingulate and supplementary motor area (SMA) (see Figure 2; and Table 4). For left amygdala, significant group differences were found in the

following clusters: (1) right lateral occipital cortex and angular gyrus; (2) right frontal pole; (3) right inferior temporal gyrus, middle temporal gyrus, and temporal pole; (4) left middle temporal gyrus and superior temporal gyrus; and (5) left angular gyrus and lateral occipital cortex. In these regions, NSSI had negative RSFC but HC had positive RSFC with the left amygdala. Additionally, NSSI had positive, while HC had negative, RSFC between left amygdala and bilateral dorsal anterior cingulate and supplementary motor area (see Figure 2 and Table 4).

5.2.2. dACC RSFC. There were no significant group differences between NSSI and HC for either right or left dACC RSFC. However, it should be noted that there were two amygdala RSFC clusters that included portions of the dACC. Values from these clusters were used to compute correlations with interpersonal measures within the NSSI group.

5.3. Task fMRI

5.3.1. Amygdala TFC and PPI. When examining TFC during the entirety of the task (i.e., in the absence of a PPI with a specific task contrast), NSSI had positive, while HC had negative, connectivity between right amygdala clusters encompassing: (1) right lingual gyrus, occipital pole, and occipital and temporal fusiform; and (2) right lateral occipital cortex and superior parietal lobule. Additionally, NSSI had positive, and HC had negative, connectivity between the left amygdala clusters encompassing bilateral lateral occipital cortex and superior parietal lobule. In contrast, NSSI had negative, while HC had positive, connectivity between the left amygdala and bilateral frontal pole, medial frontal cortex, and paracingulate (see Figure 3 and Table 5).

For PPI analyses, there were no significant group differences between the left or right amygdala time series and Emotion condition.

5.3.2. dACC TFC and PPI. There were no significant differences between NSSI and HC when examining TFC for either the right or left dACC.

PPI analyses indicated significant group differences between the right dACC time series and Emotion condition. Specifically, HC showed high negative connectivity while NSSI showed positive connectivity during the Emotion condition between the right dACC and two clusters encompassing: (1) left temporal occipital fusiform gyrus, temporal fusiform gyrus, and cerebellum; and (2) right occipital pole and lateral occipital cortex. Further information can be found in Figure 4 Table 6.

5.4. dMRI

There were four clusters within white matter that showed significant differences between NSSI and HC in GFA at $p < .01$. Specifically, those with NSSI showed significantly lower GFA than HC in: (1) right inferior longitudinal fasciculus; (2) right callosal body, forceps major, superior longitudinal fasciculus, and cingulum (hippocampus); (3) bilateral callosal body, forceps minor, cingulum (cingulate gyrus), and right superior longitudinal fasciculus; and (4) bilateral anterior thalamic radiation, inferior and superior longitudinal fasciculus, uncinate fasciculus, and corticospinal tract. Further information can be found in Figure 5 and Table 7.

5.5. Clinical Correlations

5.5.1. Associations between impulsivity and emotion regulation and amygdala clusters. Given the comparison of 11 different clinical scales and 8 significant

amygdala RSFC clusters and 5 amygdala TFC clusters, comparisons were considered significant at $p < .0006$ and $p < .0009$ respectively, which was calculated using a Bonferroni correction. No significant associations were found between significant group difference clusters and clinical measures of impulsivity (BIS total score and its subscales of Attentional, Motor, and Nonplanning Impulsiveness) and emotion regulation (DERS total score and its subscales of NONACCEPTANCE, GOALS, IMPULSE, AWARENESS, STRATEGIES, and CLARITY) within the NSSI group that survived the correction for multiple comparisons.

5.5.2. Associations between interpersonal sensitivity and dACC clusters. Using a Bonferroni correction, comparisons were considered significant at $p < .008$ given the 3 interpersonal sensitivity scales and 2 significant dACC clusters. No significant association were found between significant group difference clusters of the dACC and clinical measures of interpersonal sensitivity within the NSSI group (SCL-90 Interpersonal Sensitivity, PAI/PAI-A BOR-N, and RSQ-A total score). Further, given that there were two amygdala RSFC clusters that included a portion of the dACC, correlations using these cluster values were performed with interpersonal measures, but yielded no significant results.

5.5.3. Associations between impulsivity, emotion regulation, and interpersonal sensitivity and GFA. Comparisons examining the association between measures of impulsivity and emotion regulation and GFA values including the uncinate fasciculus, findings were considered significant at $p < .005$ given the use of 11 clinical scales and one significant GFA cluster. No significant associations were found between

GFA of the uncinate fasciculus and scores on measures of impulsivity and emotion regulation within the NSSI group (BIS total score and its subscales of Attentional, Motor, and Nonplanning Impulsiveness, and DERS total score and its subscales of NONACCEPTANCE, GOALS, IMPULSE, AWARENESS, STRATEGIES, and CLARITY). For the correlations involving interpersonal sensitivity scales, a corrected p-value of $p < .008$ was applied for these comparisons given the use of 3 clinical scales and 2 GFA clusters including the cingulum. No significant associations were found between GFA of the cingulum and measures of interpersonal sensitivity within the NSSI group (SCL-90 Interpersonal Sensitivity, PAI/PAI-A BOR-N, and RSQ-A total score).

5.5.4. Exploratory associations between NSSI characteristics and imaging clusters. A separate Bonferroni correction was applied for each neuroimaging modality. Given that there were 8 significant RSFC clusters, 7 significant TFC/PPI clusters, and 4 significant GFA clusters, comparisons were considered significant at $p < .007$, $p < .007$, and $p < .01$ respectively. Within the NSSI group, average weekly cutting episodes was positively associated with left amygdala TFC with bilateral frontal pole, medial frontal cortex, and paracingulate $r(22) = .598$, $p = .002$. There were no significant associations between average weekly cutting episodes and RSFC or GFA values.

5.5.5. Exploratory associations between functional and structural connectivity metrics. With one GFA cluster including the uncinate fasciculus and a total of 8 amygdala RSFC, comparisons using these variables were considered significant at $p < .006$. Additionally, with 5 significant amygdala TFC clusters, comparisons with these variables and the relevant GFA cluster were considered significant at $p < .01$.

There were no significant group-by-GFA interactions for any of amygdala RSFC or TFC clusters.

A total of two significant GFA clusters included regions of the cingulum and two significant dACC PPI clusters. Using a Bonferroni corrected *p*-value of .0125, there were no significant group-by-GFA interactions for dACC PPI clusters.

6. Discussion

Overall, this study found aberrant functional and structural connectivity among adolescents and young adults with NSSI compared to HC. In particular, the amygdala shows widespread anomalous FC during both rest and task and the dACC shows anomalous FC during emotion blocks of the task. Further, there were extensive group differences in structural connectivity, with the NSSI group showing lower GFA than controls, indicating potential disruptions in the organization of white matter that may impact the efficiency of neural signaling. Together, these findings provide evidence for neurobiologically-based disruptions in circuits involved in negative affect and interpersonal sensitivity.

6.1. Functional Connectivity Findings

6.1.1. Amygdala-frontal RSFC and TFC. Amygdala-frontal connectivity findings support previous research suggesting amygdala-frontal network deficits, namely that adults with BPD and NSSI show decreased frontal activation and "normalization" (or increase) of amygdala-frontal connectivity in response to pain stimuli as well as compromised white matter microstructure in the frontal lobe (Grant et al., 2007; Niedtfeld et al., 2010; Reitz et al., 2015). This has also been found in depression (Cullen

et al., 2010; Musgrove et al., 2015). RSFC results suggest that disrupted amygdala-frontal connectivity persists in the absence of emotional stimuli and may become more prominent in emotionally salient contexts, as suggested by the TFC results. Because this finding transcends both resting and task conditions, amygdala-frontal hypoconnectivity appears to be a pervasive deficit among those with NSSI that may represent difficulty in regulation of negative affect, and the possible reliance upon self-injury as a self-soothing strategy. Taken together, the findings of this study support the evidence of aberrant amygdala-frontal RSFC and TFC, which may largely reflect neural mechanisms underlying both NSSI and related depression symptoms in these adolescents.

6.1.2. Amygdala-SMA RSFC. Adolescents with NSSI also demonstrated greater amygdala RSFC than HC in some regions including the SMA and bilateral dorsal anterior cingulate. The SMA is involved in the planning of complex movements, and therefore is likely invoked in the moments before and during the act of NSSI. Hyperconnectivity in this circuit could lead to (or result from) an excessive influence of negative affect upon the planning of movements, potentially increasing the likelihood of engaging in NSSI. It is possible that impaired connectivity between fronto-limbic regions coupled with hyperconnectivity between amygdala and SMA could underlie the entrenchment of NSSI behaviors and represent a potential treatment target. Longitudinal research may assist with determining whether this neurobiological profile serves to maintain NSSI.

6.1.3. Amygdala-temporal and occipital lobe RSFC. The NSSI group showed lower amygdala RSFC than HC in the temporal lobe, a region involved in processing explicit emotional memories (LeDoux, 2000). Group differences were also found

between the amygdala and angular gyrus and occipital cortex (NSSI showed negative, while HC showed positive, RSFC). Interestingly, these HC results are inconsistent with previous work in healthy adults (Roy et al., 2009), showing negative RSFC between the amygdala and angular gyrus and occipital cortex. This discrepancy could be explained by developmental differences between the studies as the present study consists of a younger sample. However, longitudinal studies with uniform methods are needed to clarify this question.

6.1.4. Amygdala-dACC RSFC. Adolescents with NSSI showed positive RSFC while the HC group showed negative RSFC between the amygdala and dACC. The RSFC findings in the HC group are consistent with previous work in healthy adults (Roy et al., 2009). As discussed previously, the dACC is part of the salience network, which is responsible for integrating and monitoring the importance of internal and external stimuli. Additionally, it has been consistently implicated in studies of interpersonal sensitivity (Burklund et al., 2007; Eisenberger et al., 2003, 2007; Masten et al., 2009). Increased functional connectivity between amygdala and dACC has been found during fear memory consolidation (Feng, Feng, Chen, & Lei, 2014). Additionally, increased connectivity between the amygdala and dACC has been found in patients with interpersonal trauma-related post-traumatic stress disorder (PTSD) in response to viewing trauma-related versus neutral images when compared to healthy adults (Neumeister et al., 2016).

It is possible that the positive RSFC seen in this circuit in the sample of adolescents with NSSI could reflect spontaneous processing of negative emotional

memories or thoughts about self-injury during the resting period. Further, hyperconnectivity between the amygdala and dACC is consistent with the hypothesis that those with NSSI have greater influence of the limbic system on areas involved with social processing. This may increase the likelihood of these individuals perceiving interpersonal interactions as negative. However, measures of interpersonal sensitivity were not associated with RSFC of this circuit when correcting for multiple comparisons. Additional research is needed to explore this hypothesis using validated, multi-method tools to further explore the role of this potential circuit abnormality in adolescents with NSSI, particularly with larger sample sizes.

It is also worth noting that while the amygdala seed showed significant connectivity with the dACC, the dACC seed did not show significant connectivity with the amygdala. This discrepancy is likely due to both the amygdala and dACC being large regions of interest consisting of subregions with heterogeneous functions. Thus, when using such a large region such as the dACC as a seed for whole-brain comparisons, the lack of specificity for a subregion of the dACC creates an opportunity for correlations with other brain areas to diminish. Future work may benefit from parcellating these seeds into smaller subregions. The present study can also be expanded by using the significant dACC cluster from the amygdala whole-brain results and using that specific region of the as a seed, as opposed to using the entire dACC for whole-brain comparisons.

6.1.5. Differential amygdala-occipital functional connectivity: TFC versus RSFC. The NSSI group showed greater overall TFC between left amygdala and regions of the occipital cortex, including the fusiform, which is a key region in the processing of

facial stimuli. This contrasts with the finding of lower amygdala-occipital connectivity during rest. However, it should be noted that the locations of these occipital clusters differ across the two sets of results. The finding of increased amygdala-occipital TFC adds to prior work showing increased amygdala-fusiform TFC while viewing fearful faces in adults with social anxiety disorder (Frick, Howner, Fischer, Kristiansson, & Furmark, 2013). Elevated amygdala-occipital TFC while processing negative facial emotion information could underlie a heightened tendency to perceive facial information as negative; speculatively, this could have relevance to adolescents with NSSI, who often have difficulties with interpersonal relationships (McMahon et al., 2010). Taken together, further research is warranted to better characterize amygdala-occipital connectivity across psychiatric disorders and contexts, and to explore whether this circuit could represent a candidate treatment target for patients with NSSI.

6.1.6. PPI with dACC connectivity and emotion. While there were no significant PPI findings for the amygdala, the dACC showed connectivity differences between groups during the emotion blocks of the task. Specifically, the HC group showed high negative connectivity while the NSSI group showed positive connectivity between the right dACC and left temporal and occipital fusiform gyri, and cerebellum, and right occipital pole and lateral occipital cortex.

While there are no studies examining dACC PPI in NSSI, a study of healthy adults examined this region in the context of an associative learning and memory task (Ravishankar et al., 2017). During this task, participants were asked to learn the associations between object-location pairs. Of relevance to our findings, Ravishankar and

colleagues found increased connectivity between the dACC and fusiform gyrus during the early learning phases of their paradigm. Ravishankar et al. defines early learning as being characterized by lower levels of proficiency and consolidation, which is also considered to be more effortful. While the present study used a task that did not require a memory component, the positive dACC-fusiform gyrus connectivity during the emotion blocks in the NSSI sample suggests these individuals may be expending more effort and using less efficient cognitive strategies during the completion of the task.

Additionally, greater negative dACC-fusiform RSFC has been associated with healthy individuals who show high levels of resilience following childhood maltreatment compared to healthy individuals who were vulnerable to developing psychopathology following childhood maltreatment and healthy individuals with no childhood maltreatment (van der Werff et al., 2013). van der Werff and colleagues suggest that those with higher levels of resilience are able to more effectively identify and encode their negative experiences in verbal declarative memory. Given previous research on post-traumatic stress disorder, positive dACC-fusiform connectivity during emotion blocks in this study may reflect a deficit of verbal declarative memory (see Samuelson, 2011 for review). However, the present study lacks measures of verbal memory performance in NSSI, thus limiting the interpretation of these findings.

Aside from previous research in predominately healthy samples, increased TFC between the dACC and temporal-occipital cortex was found among adults with past suicidal ideation during the completion of a conflict monitoring task using letter stimuli (Minzenberg, Lesh, Niendam, Cheng, & Carter, 2016). Further, greater TFC between

these regions was positively associated with the intensity of suicidal ideation. These findings are consistent with those of the present study given the substantial link between suicide and NSSI.

6.2. Structural Connectivity Findings

Consistent with hypotheses, group differences indicated that those with NSSI had significantly lower GFA than HC in the uncinate fasciculus and both hippocampal and cingulate gyrus areas of the cingulum. In addition, those with NSSI showed lower GFA in several other areas including the inferior and superior longitudinal fasciculi, callosal body, forceps major and minor, anterior thalamic radiation, and corticospinal tract. Only one known study has examined differences in structural connectivity between those with and without self-injury and found compromised white matter microstructure within the frontal lobe (Grant et al., 2007). The present study differs from this previous study as it examines adolescents, uses a larger sample size, employs methods that result in a potentially more accurate scalar measure of white matter integrity (via GFA), and also investigates NSSI more explicitly as it is unclear whether the previous study included suicidal self-injury.

Relying on FA as opposed to GFA, studies examining dMRI have found compromised white matter microstructure associated with psychopathology within these tracts including adults with MDD (Dillon, Gonenc, Belleau, & Pizzagalli, 2018) and PTSD (Olson et al., 2017), childhood adversity (McCarthy-Jones et al., 2018), and adolescents with BPD (New et al., 2013). Additionally, a meta-analysis of FA in emotional disorders (MDD, bipolar disorder, social anxiety disorder, obsessive-

compulsive disorder, and PTSD) found that those with emotional disorders had significantly lower FA compared to healthy controls in forceps minor, uncinate fasciculus, anterior thalamic radiation, and superior longitudinal fasciculus (Jenkins et al., 2016). Given that most individuals in the NSSI group in the present study had a current diagnosis of emotional disorders such as those included in the meta-analysis by Jenkins and colleagues, the widespread findings of lower GFA in this group may be a reflection of the overall psychopathology present in this sample. With this in mind, in the future it will be important to compare GFA between those with NSSI and a psychiatric control group, which will allow for greater specificity for the aberrations that are unique to NSSI.

6.3. Discussion on Lack of Findings of Functional and Structural Connectivity Associations with Clinical Measures

Overall, the present study did not find significant associations between neuroimaging findings and clinical measures. The absence of findings may largely be explained by the use of highly conservative p-thresholds, as several of these comparisons yielded results of $p < .05$ and some of $p < .01$. While the sample size is relatively large when compared to previous neuroimaging studies on NSSI, it is still small when considering the sample size needed to conduct a large number of clinical comparisons.

6.4. Strengths and Limitations

This study represents a significant advancement of existing NSSI work as it used a dynamic approach to understanding this behavior by examining neural networks in three different contexts. Given the susceptibility that fMRI has to spurious findings due to noise, the present study employed methods such as denoising and conservative motion

correction methods for both rest and task fMRI data sets. Further, this study used an approach to the dMRI data that lessens the impact of crossing fibers when compared to older dMRI methods.

Unlike many previous studies of NSSI, which investigate the behavior in the context of a specific diagnosis, the present study examines the neural circuitry of NSSI across diagnoses, which is both a strength and limitation. As a strength, the presence of varying types and levels of psychopathology seen in this study sample is consistent with what has been found in larger studies of NSSI (In-Albon, Ruf, & Schmid, 2013; Jacobson, Muehlenkamp, Miller, & Turner, 2008). Thus, these results give a broader view of the aberrations of neural circuitry that may be present in individuals with NSSI and hopefully generate hypotheses for future work aimed to understand the neurobiology of this behavior. However, as a limitation, it is important to note that it is highly possible for many of these findings to be the result of the myriad of psychiatric difficulties present within this sample. While it can be argued that the present study could increase the specificity of findings to NSSI by controlling for psychopathology variables such as depression, this creates an issue of co-linearity in which correcting for depression results in the removal of substantial meaningful variance between groups. To address this issue, future research should incorporate a psychiatric control group that is matched to the NSSI group on diagnosis and severity level/level of impairment.

An additional limitation of this study includes its cross-sectional design. Longitudinal designs are needed to more thoroughly understand the neural mechanisms associated with the predisposition, onset, and maintenance of this behavior. In doing so,

we may understand the neural processes that unfold in individuals at high risk and thus develop prevention strategies that are tailored to these individuals.

The present study is also limited by its small sample size, the presence of psychiatric medication use in nearly half of the NSSI sample, and the option provided to NSSI participants to participate in a treatment study. Larger samples are needed to provide increased power to detect associations between neurobiological and clinical measures, while the use of psychiatric medication may obscure findings. The treatment option provided to the NSSI group increases the likelihood that this sample may differ from the general NSSI population due to their motivation to reduce NSSI. Further limitations to the ability to generalize findings include that parents/guardians of minors with NSSI had to be aware of their child's behavior prior to enrolling and overall lack of ethnic diversity.

Finally, during the course of this study difficulties defining and measuring the frequency and severity of NSSI highlighted the need for the development of more thorough and valid measures of NSSI. With regard to severity in particular, it is difficult to define as it is not only important to consider the frequency of NSSI, but also the extent of the injuries that take place. Additionally, neuroimaging studies would benefit from including not only self-report measures, but also cognitive assessments, stress paradigms, and other physiological measures such as cortisol. Hopefully, the findings generated by this study will serve as a guide for selection of behavioral, self-report, and physiological measurements to further understand the role of these aberrant neural circuits in the pathophysiology of NSSI.

6.5. Conclusion

NSSI is a clinically significant behavior that raises concern given its association with persistent psychopathology and other undesirable outcomes such as suicide (Horwitz et al., 2014; Tang et al., 2011; Victor & Klonsky, 2014). While NSSI has often been examined in the context of existing psychiatric disorders, such as major depressive disorder (MDD; Hintikka et al., 2009) or borderline personality disorder (BPD; Cerutti, Manca, Presaghi, & Gratz, 2011). NSSI occurs across diagnoses and even in the absence of psychiatric diagnoses (Stanford & Jones, 2009). Thus, some have supported NSSI as a disorder in its own right, which is being more seriously considered as demonstrated by the inclusion of this behavior in the "Disorders for Further Study" section of the DSM-5 (American Psychiatric Association, 2013).

While there has been ongoing research investigating the clinical characteristics of NSSI and whether it warrants its own diagnosis, research aimed to understand the neurobiology associated with this behavior has only recently begun to emerge. The present study represents a first step toward identifying how neural circuits go awry among individuals with NSSI. The clinical characteristics of NSSI demonstrate deficits in regulation of negative affect, with interpersonal relationships being a particularly salient context for negative affect to occur. Thus, the present study identified neural circuits stemming from the amygdala and dACC as being fruitful starting points given the roles these regions play in negative affect and interpersonal sensitivity.

Findings from the present study suggest widespread disruptions in both functional and structural connectivity of neural circuits implicated in negative affect and

interpersonal sensitivity. The NSSI group showed aberrant functional and structural connectivity suggestive of a potentially problematic influence of the amygdala on areas involved in the planning of movement, regulatory control, emotional memories, and social processing. dACC findings within the NSSI group are suggestive of possibly inefficient cognitive processing and verbal memory. Finally, the NSSI group shows widespread inefficient neural signaling among brain regions, which is consistent with other forms of psychopathology including suicide.

This study provides preliminary evidence for a neurobiological basis for the difficulties in affect regulation and interpersonal relationships that have been previously documented in NSSI research. Additional research with larger sample sizes and more comprehensive measurements are necessary to replicate these findings and further elaborate how these circuits relate to the key psychological and neurobiological system abnormalities underlying NSSI. Such research is necessary to pave the way for development and selection of neurobiologically-informed interventions for adolescents with NSSI.

When considering psychopathology more broadly, the utility of investigating its neurobiology is underscored by the need to understand how to best treat these disorders and their associated maladaptive thoughts and behaviors. This is further supported by findings that treatment of psychopathology, whether it be psychotherapy or pharmacotherapy, appears to "normalize" brain functioning (Quidé, Witteveen, El-Hage, Veltman, & Olff, 2012). Thus, by understanding (1) how neural circuitry goes awry in psychopathology, such as among those with NSSI and (2) how different treatment

options and even different components of treatment options impact neural circuitry, the selection of treatment options for a given disorder may be more efficient and effective.

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Table 1. Participant Demographics: RSFC Data

	RSFC Data	
Demographic Characteristics	**NSSI (n = 25)**	**Controls (n = 20)**
Age (mean years ± SD)	17.57 ± 2.49	18.01 ± 2.08
IQ (mean ± SD)	106.29 ± 11.25 (n = 24)	110.28 ± 9.65 (n = 18)
Right Handed – n (%)[a]	21 (88%; n = 24)	17 (100%; n = 17)
Ethnicity **– n (%)**[b]		
Caucasian	23 (92%)	17 (85%)
African American	1 (4%)	1 (5%)
Hispanic	3 (12%)	0
Asian	0	2 (10%)
Other	1 (4%)	0
Clinical Characteristics		
Age of first NSSI (mean age ± SD)	11.58 ± 3.89 (n = 24)	
Lifetime Cutting Episodes (mean ± SD)	127.04 ± 190.88	
Estimated Cutting Episodes per Week (mean ± SD)[c]	0.63 ± 1.08	
Total BDI Score (mean ± SD)	26.72 ± 13.25	
Current Diagnoses **– n (%)**[d]		
Major Depressive Disorder	13 (52%)	
Depressive Disorder NOS	5 (20%)	
Generalized Anxiety Disorder	6 (24%)	
Anxiety Disorder NOS	1 (4%)	
Social Phobia	1 (4%)	
Specific Phobia	3 (12%)	
Panic Disorder	2 (8%)	
Post-Traumatic Stress Disorder	3 (12%)	
Obsessive Compulsive Disorder	2 (8%)	
Eating Disorder NOS	1 (4%)	
ADHD	1 (4%)	
Alcohol Dependence	2 (8%)	
No Current Disorder	5 (20%)	
Medications		
Currently Medicated	10 (42%; n = 24)	
Antidepressants	7 (29%; n = 24)	
Stimulants	1 (4%; n = 24)	
Antipsychotics	1 (4%; n = 24)	
Antianxiety/Benzodiazapines	3 (13%; n = 24)	
Other Psychotropics	1 (4%; n = 24)	

[a] Post-hoc analyses indicated that differing handedness did not affect study findings

[b] Participants were able to endorse more than one option for ethnicity

[c] Consensus between ISAS and DSHI was calculated to determine average number of cutting episodes per week. These are pre-Winsorized scores.

[d] Diagnoses include both primary and comorbid disorders

Table 2. Participant Demographics: TFC Data

	Task Data	
Demographic Characteristics	**NSSI (n = 24)**	**Controls (n = 17)**
Age (mean years ± SD)	17.34 ± 2.44	17.98 ± 2.00
IQ (mean ± SD)	104.68 ± 11.18 (n = 22)	109.13 ± 9.82 (n = 15)
Right Handed – n (%)[a]	19 (86%; n = 22)	14 (100%; n = 14)
Ethnicity **– n (%)**[b]		
Caucasian	23 (96%)	16 (94%)
African American	1 (4%)	1 (6%)
Hispanic	2 (8%)	0
Asian	0	0
Other	0	0
Clinical Characteristics		
Age of first NSSI (mean age ± SD)	12.30 ± 2.58 (n = 23)	
Lifetime Cutting Episodes (mean ± SD)	132.13 ± 196.98	
Estimated Cutting Episodes per Week (mean ± SD)[c]	0.74 ± 1.23	
Total BDI Score (mean ± SD)	28.96 ± 11.91	
Current Diagnoses **– n (%)**[d]		
Major Depressive Disorder	14 (58%)	
Depressive Disorder NOS	3 (13%)	
Generalized Anxiety Disorder	5 (21%)	
Anxiety Disorder NOS	2 (8%)	
Social Phobia	2 (8%)	
Specific Phobia	2 (8%)	
Panic Disorder	2 (8%)	
Post-Traumatic Stress Disorder	3 (13%)	
Obsessive Compulsive Disorder	1 (4%)	
Eating Disorder NOS	1 (4%)	
ADHD	1 (4%)	
Alcohol Dependence	1 (4%)	
No Current Disorder	5 (21%)	
Medications		
Currently Medicated	10 (44%; n = 23)	
Antidepressants	8 (35%; n = 23)	
Stimulants	1 (4%; n = 23)	
Antipsychotics	1 (4%; n = 23)	
Antianxiety/Benzodiazapines	3 (13%; n = 23)	
Other Psychotropics	1 (4%; n = 23)	

[a] Post-hoc analyses indicated that differing handedness did not affect study findings

[b] Participants were able to endorse more than one option for ethnicity

[c] Consensus between ISAS and DSHI was calculated to determine average number of cutting episodes per week. These are pre-Winsorized scores.

[d] Diagnoses include both primary and comorbid disorders

Table 3. Participant Demographics: dMRI Data

	dMRI Data	
Demographic Characteristics	**NSSI (n = 28)**	**Controls (n = 22)**
Age (mean years ± SD)	17.53 ± 2.36	17.69 ± 2.26
IQ (mean ± SD)	105.78 ± 10.68 (n = 27)	110.05 ± 9.43 (n = 20)
Right Handed – n (%)[a]	24 (89%; n = 27)	19 (100%; n = 19)
Ethnicity **– n (%)**[b]		
Caucasian	26 (93%)	19 (86%)
African American	1 (4%)	1 (5%)
Hispanic	3 (11%)	0
Asian	0	2 (7%)
Other	1 (4%)	0
Clinical Characteristics		
Age of first NSSI (mean age ± SD)	11.96 ± 3.03 (n = 27)	
Lifetime Cutting Episodes (mean ± SD)	131.11 ± 195.43	
Estimated Cutting Episodes per Week (mean ± SD)[c]	0.75 ± 1.16	
Total BDI Score (mean ± SD)	26.79 ± 12.63	
Current Diagnoses **– n (%)**[d]		
Major Depressive Disorder	16 (57%)	
Depressive Disorder NOS	5 (18%)	
Generalized Anxiety Disorder	8 (29%)	
Anxiety Disorder NOS	2 (7%)	
Social Phobia	1 (4%)	
Specific Phobia	3 (11%)	
Panic Disorder	3 (11%)	
Post-Traumatic Stress Disorder	5 (18%)	
Obsessive Compulsive Disorder	2 (7%)	
Eating Disorder NOS	1 (4%)	
ADHD	2 (7%)	
Alcohol Dependence	2 (7%)	
No Current Disorder	5 (18%)	
Medications		
Currently Medicated	12 (43%)	
Antidepressants	9 (32%)	
Stimulants	2 (7%)	
Antipsychotics	1 (4%)	
Antianxiety/Benzodiazapines	4 (14%)	
Other Psychotropics	1 (4%)	

[a] Post-hoc analyses indicated that differing handedness did not affect study findings

[b] Participants were able to endorse more than one option for ethnicity

[c] Consensus between ISAS and DSHI was calculated to determine average number of cutting episodes per week. These are pre-Winsorized scores.

[d] Diagnoses include both primary and comorbid disorders

Table 4. Location, size, peak z-values, and effect sizes of the significant clusters in the RSFC group analyses

Seed Region	Contrast	Brain Regions	Control Mean z-stat	NSSI Mean z-stat	# of Voxels	MNI Coordinates of Peak Voxel (x, y, z)	Peak z-value	Cohen's *d* [Confidence Interval]
Right Amygdala	NSSI > HC	*Bilateral* anterior cingulate cortex and supplementary motor area	-.64 ± 1.01	.39 ± .94	313	2, 10, 34	3.71	1.07 [.43-1.69]
	HC > NSSI	*Left* angular gyrus and occipital cortex	.79 ± 1.10	-.46 ± 1.11	313	-44, -56, 34	3.41	1.12 [.48-1.75]
Left Amygdala	NSSI > HC	*Bilateral* anterior cingulate cortex and supplementary motor area	-.95 ± 1.03	.28 ± .88	879	2, 10, 32	4.38	1.29 [.63-1.93]
	HC > NSSI	*Left* angular gyrus and occipital cortex	.87 ± .88	-.33 ± .79	1225	-46, -58, 34	4.19	1.45 [.78-2.11]
		Left middle temporal gyrus and superior temporal gyrus	.60 ± .58	-.49 ± .70	799	-58, -26, -8	4.33	1.68 [.99-2.36]
		Right frontal pole	.62 ± .73	-.36 ± .60	396	24, 66, 14	4.90	1.49 [.82-2.15]
		Right inferior temporal gyrus, middle temporal gyrus, temporal pole	.80 ± .81	-.33 ± .72	492	50, -8, -36	4.38	1.47 [.80-2.13]
		Right angular gyrus and occipital cortex	.98 ± 1.02	-.20 ± .78	370	40, -68, 28	4.20	1.32 [.66-1.96]

Table 5. Location, size, peak z-values, and effect sizes of the significant clusters in the TFC group analysis

Seed Region	Contrast	Brain Regions	Control Mean z-stat	NSSI Mean z-stat	# of Voxels	MNI Coordinates of Peak Voxel (x, y, z)	Peak z-value	Cohen's *d* [Confidence Interval]
Right Amygdala	NSSI > HC Overall Task	*Right* lingual gyrus, occipital pole, occipital fusiform, temporal fusiform	-.55 ± .68	.52 ± .73	699	26, -66, -18	4.16	1.51 [.80-2.21]
		Right lateral occipital cortex and superior parietal lobule	-.39 ± .84	.65 ± .87	822	32, -66, 52	3.58	1.21 [.53-1.88]
Left Amygdala	NSSI > HC Overall Task	*Right* lateral occipital cortex and superior parietal lobule	-.36 ± .81	.74 ± .82	828	32, -60, 62	4.20	1.34 [.65-2.02]
		Left lateral occipital cortex and superior parietal lobule	-.41 ± .71	.64 ± .69	874	-34, -42, 38	3.38	1.50 [.79-2.20]
	HC > NSSI Overall Task	*Bilateral* frontal pole, medial frontal cortex, and paracingulate	.73 ± .98	-.35 ± .87	663	0, 56, -4	4.04	1.18 [.50-1.85]

Table 6. Location, size, peak z-values, and effect sizes of the significant clusters in the PPI group analysis

Seed Region	Contrast	Brain Regions	Control Mean z-stat	NSSI Mean z-stat	# of Voxels	MNI Coordinates of Peak Voxel (x, y, z)	Peak z-value	Cohen's *d* [Confidence Interval]
Right dACC	NSSI > HC Emotion Blocks	*Left* temporal occipital fusiform gyrus, temporal fusiform gyrus, and cerebellum	-.70 ± .83	.35 ± .45	571	-40, -52, -26	4.15	1.70 [1.51-1.89]
		Right occipital pole and lateral occipital cortex	-.61 ± 1.09	.38 ± .83	591	26, -96, 20	3.71	1.07 [.79-1.36]

Table 7. Location, group means, and effect sizes of significant GFA clusters

Brain Regions	**Control Mean GFA**	**NSSI Mean GFA**	**Cohen's *d* [Confidence Interval]**
Right inferior longitudinal fasciculus	.38 ± .03	.34 ± .03	1.36 [1.35-1.37]
Right callosal body, forceps major, superior longitudinal fasciculus, and cingulum (hippocampus)	.63 ± .02	.60 ± .02	1.53 [1.53-1.54]
Bilateral callosal body, forceps minor, cingulum (cingulate gyrus), and right superior longitudinal fasciculus	.61 ± .02	.58 ± .02	1.53 [1.53-1.54]
Bilateral anterior thalamic radiation, inferior and superior longitudinal fasciculus, uncinate fasciculus, and corticospinal tract	.51 ± .02	.48 ± .02	1.53 [1.53-1.54]

Table 8. Correlations Between Amygdala RSFC and Emotional and Behavioral Regulation

Control Variables			BIS Attentional	BIS Motor	BIS Nonplanning	BIS Total	DERS Nonacceptance	DERS Goals	DERS Impulse	DERS Awareness	DERS Strategies	DERS Clarity	DERS Total
Age	Right Amygdala-Bilateral dACC and SMA RSFC	Correlation	.116	.102	.224	.172	-.036	.243	.487	.168	.048	.244	.321
		Significance	.599	.642	.303	.433	.876	.288	.025*	.468	.836	.261	.156
		df	21	21	21	21	19	19	19	19	19	21	19
	Right Amygdala-Left Angular Gyrus and Occipital Cortex RSFC	Correlation	.344	.125	.377	.319	-.202	.111	-.254	-.332	-.025	-.103	-.237
		Significance	.108	.570	.076	.138	.381	.631	.267	.141	.915	.640	.301
		df	21	21	21	21	19	19	19	19	19	21	19
	Left Amygdala-Bilateral dACC and SMA RSFC	Correlation	.149	.022	.393	.195	-.041	-.021	.217	.184	-.133	.399	.161
		Significance	.497	.920	.064	.372	.859	.927	.345	.425	.565	.059	.487
		df	21	21	21	21	19	19	19	19	19	21	19
	Left Amygdala-Left Angular Gyrus and Lateral Occipital Cortex RSFC	Correlation	-.097	-.035	-.081	-.081	-.362	-.175	-.421	-.204	-.289	-.129	-.471
		Significance	.661	.874	.713	.712	.107	.449	.058	.376	.204	.558	.031*
		df	21	21	21	21	19	19	19	19	19	21	19
	Left Amygdala-Left Middle and Superior Temporal Gyrus RSFC	Correlation	-.041	.130	.138	.100	-.256	.079	-.288	.018	-.067	.130	-.119
		Significance	.853	.555	.531	.648	.262	.733	.206	.937	.773	.553	.607
		df	21	21	21	21	19	19	19	19	19	21	19
	Left Amygdala-Right Frontal Pole RSFC	Correlation	.048	.278	.007	.171	.190	.477	.468	-.190	.478	.019	.362
		Significance	.827	.199	.976	.435	.410	.029*	.033*	.410	.028*	.933	.107
		df	21	21	21	21	19	19	19	19	19	21	19
	Left Amygdala-Right Inferior and Middle Temporal Gyrus and Temporal Pole RSFC	Correlation	.135	.250	.147	.234	-.095	.099	.152	.163	.064	.242	.151
		Significance	.539	.250	.503	.282	.683	.668	.510	.479	.782	.267	.513
		df	21	21	21	21	19	19	19	19	19	21	19

	Left Amygdala-Right Lateral Occipital Cortex and Angular Gyrus RSFC	Correlation	.237	.470	-.202	.278	.023	.150	.141	-.014	.168	.060	.134
		Significance	.276	.024*	.356	.199	.920	.517	.543	.953	.467	.785	.563
		df	21	21	21	21	19	19	19	19	19	21	19

Correlations were considered significant if $p < .0006$ due to correcting for multiple comparisons (no significant correlations found)
*$p < .05$

Table 9. Correlations Between Amygdala TFC and Emotional and Behavioral Regulation

Control Variables			BIS Attentional	BIS Motor	BIS Nonplanning	BIS Total	DERS Nonacceptance	DERS Goals	DERS Impulse	DERS Awareness	DERS Strategies	DERS Clarity	DERS Total
Age	Left Amygdala-Left Lateral Occipital and Superior Parietal Cortex TFC	Correlation	-.227	-.121	-.033	-.154	.398	-.260	-.018	.226	.030	.046	.152
		Significance	.322	.601	.886	.506	.091	.283	.943	.352	.903	.842	.535
		df	19	19	19	19	17	17	17	17	17	19	17
	Left Amygdala-Right Lateral Occipital and Superior Parietal Cortex TFC	Correlation	-.244	-.026	-.159	-.154	.364	.120	.082	-.034	.325	-.048	.246
		Significance	.287	.910	.492	.506	.126	.625	.739	.890	.175	.835	.311
		df	19	19	19	19	17	17	17	17	17	19	17
	Left Amygdala-Bilateral Frontal Pole, Medial Frontal Cortex, and Paracingulate TFC	Correlation	.040	-.171	-.100	-.112	-.238	-.280	-.136	-.064	-.354	-.124	-.317
		Significance	.862	.458	.665	.628	.326	.246	.580	.795	.137	.593	.186
		df	19	19	19	19	17	17	17	17	17	19	17
	Right Amygdala-Right Lateral Occipital and Superior Parietal Cortex TFC	Correlation	-.379	-.128	.034	-.186	.078	-.019	-.108	-.173	.320	-.291	-.056
		Significance	.090	.581	.882	.420	.750	.939	.659	.479	.182	.200	.819
		df	19	19	19	19	17	17	17	17	17	19	17
	Right Amygdala-Right Lingual Gyrus, Occipital Pole, and Fusiform Gyrus TFC	Correlation	.136	-.018	-.151	-.016	-.062	-.074	-.008	.140	-.041	.351	.081
		Significance	.557	.939	.515	.945	.800	.763	.973	.568	.868	.119	.741
		df	19	19	19	19	17	17	17	17	17	19	17

Correlations were considered significant if $p < .0006$ due to correcting for multiple comparisons (no significant correlations found)

Table 10. Correlations Between dACC PPI and Interpersonal Sensitivity

Control Variables			SCL-90 Interpersonal Sensitivity	PAI Borderline Negative Relationships	RSQ-A Total Score
Age	Right dACC-Left Temporal Occipital Fusiform and Cerebellum PPI	Correlation	-.240	.173	-.291
		Significance	.309	.466	.359
		df	18	18	10
	Right dACC-Right Occipital Pole and Lateral Occipital Cortex PPI	Correlation	.003	-.161	.070
		Significance	.989	.497	.828
		df	18	18	10

Correlations were considered significant if $p < .008$ due to correcting for multiple comparisons (no significant correlations found)

Table 11. Correlations Between Amygdala-dACC RSFC and Interpersonal Sensitivity

Control Variables			SCL-90 Interpersonal Sensitivity	PAI Borderline Negative Relationships	RSQ-A Total Score
Age	Right Amygdala-Bilateral dACC and SMA RSFC	Correlation	.146	.166	.529
		Significance	.518	.460	.077
		df	20	20	10
	Left Amygdala-Bilateral dACC and SMA RSFC	Correlation	.012	.074	.431
		Significance	.956	.743	.161
		df	20	20	10

Correlations were considered significant if $p < .008$ due to correcting for multiple comparisons (no significant correlations found)

Table 12. Correlations Between Uncinate GFA and Emotional and Behavioral Regulation

Control Variables			BIS Attentional	BIS Motor	BIS Nonplanning	BIS Total	DERS Nonacceptance	DERS Goals	DERS Impulse	DERS Awareness	DERS Strategies	DERS Clarity	DERS Total
Age	Bilateral uncinate fasciculus, inferior and superior longitudinal fasciculus, corticospinal tract, and anterior thalamic radiation	Correlation	-.501	-.398	-.265	-.483	-.065	-.025	-.203	-.155	.286	-.163	-.088
		Significance	.011*	.049*	.201	.014*	.769	.908	.353	.481	.186	.436	.691
		df	23	23	23	23	21	21	21	21	21	23	21

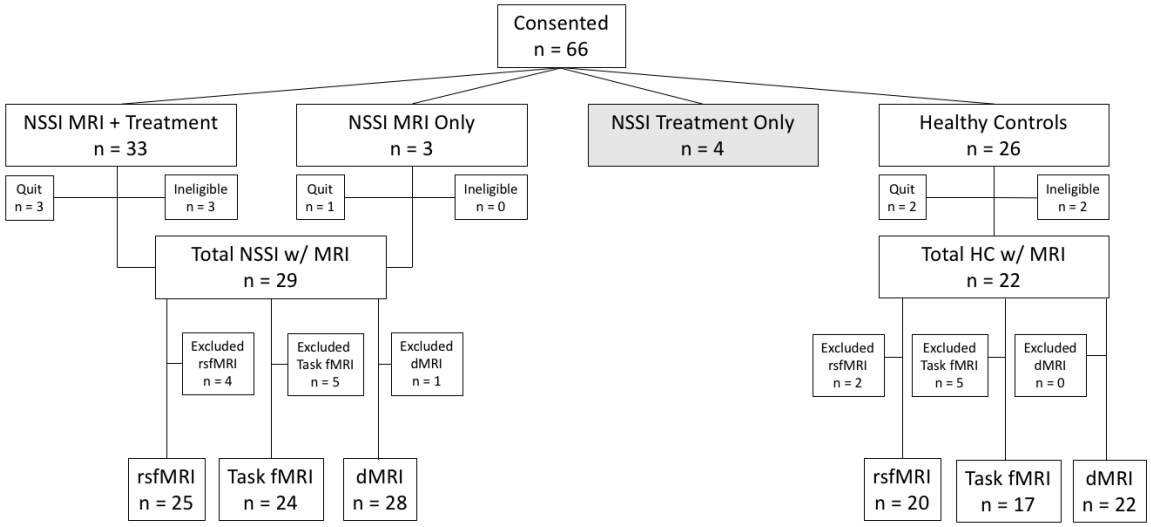
Correlations were considered significant if $p < .005$ due to correcting for multiple comparisons (no significant correlations found)
*$p < .05$

Table 13. Correlations Between Cingulum GFA and Interpersonal Sensitivity

Control Variables			SCL-90 Interpersonal Sensitivity	PAI Borderline Negative Relationships	RSQ-A Total Score
Age	Right Cingulum, Superior Longitudinal Fasciculus, and Forceps Major GFA	Correlation	-.089	-.322	.042
		Significance	.681	.125	.891
		df	22	22	11
	Bilateral Cingulum, Callosal Body, and Forceps Minor GFA	Correlation	.026	-.268	.116
		Significance	.903	.205	.705
		df	22	22	11

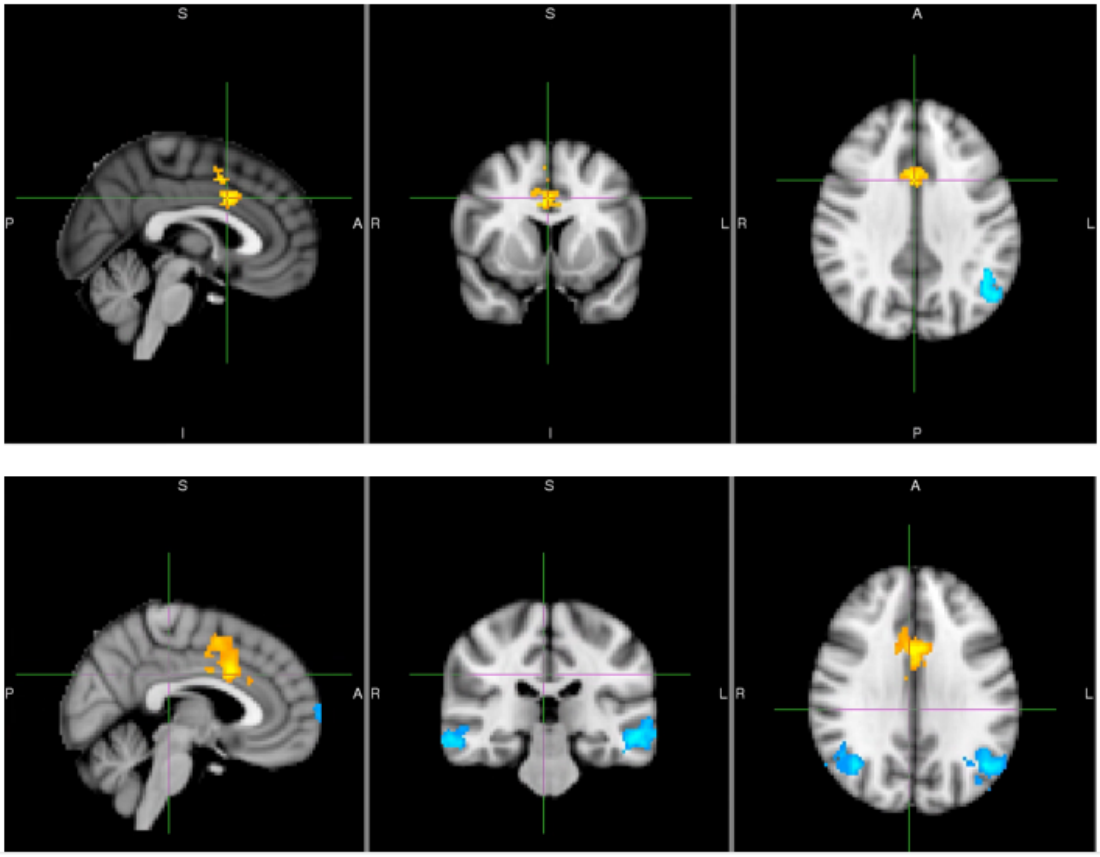
Correlations were considered significant if $p < .008$ due to correcting for multiple comparisons (no significant correlations found)

Figure 1. CONSORT Diagram of Participants



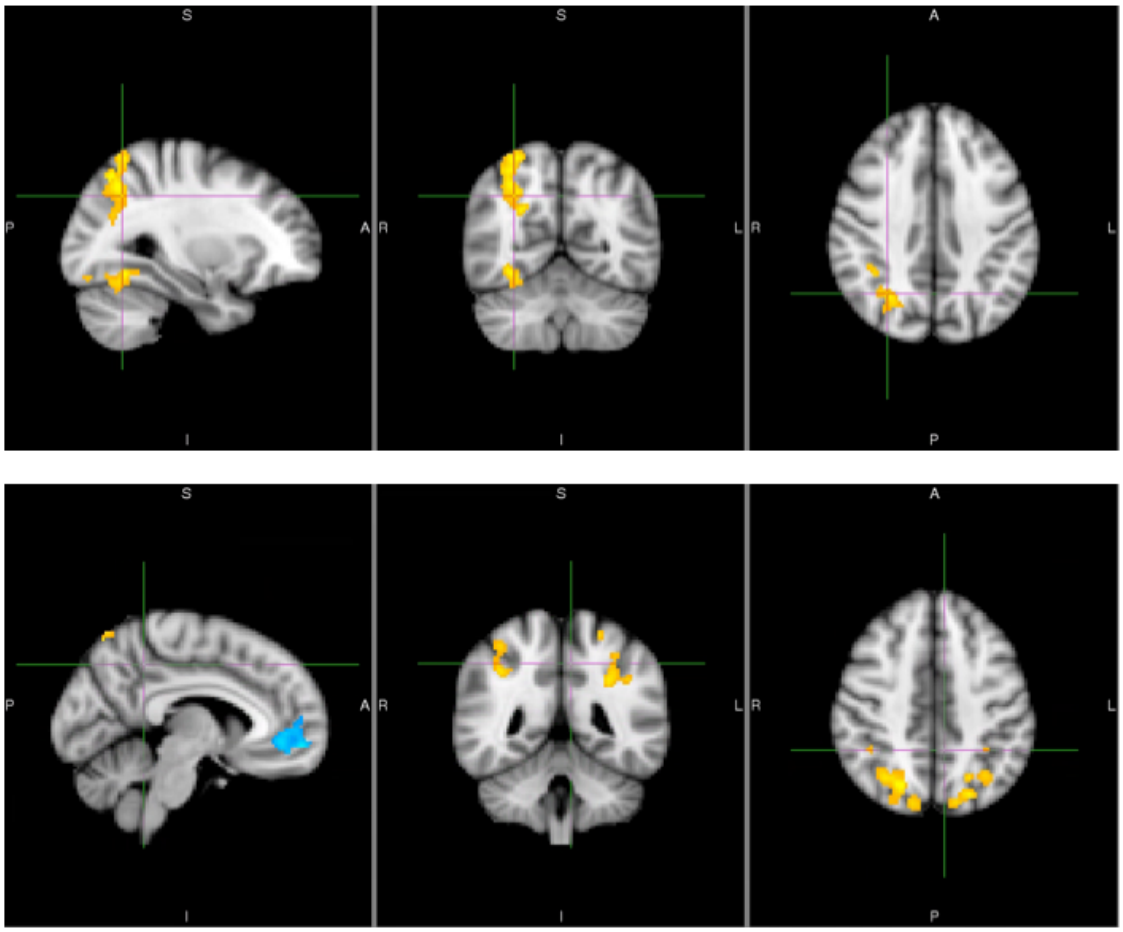
This figure illustrates the breakdown of participants between the consent phase to the final numbers for each group for each MRI modality. Further information for the NSSI Treatment Only group was not included as it is beyond the scope of the study.

Figure 2. Right and Left Amygdala RSFC



Top: Warm colors indicate regions in which adolescents with NSSI had greater right amygdala RSFC than HC: bilateral dorsal cingulate and supplementary motor area. Cool colors indicate regions where adolescents with NSSI had lower amygdala RSFC than controls: left angular gyrus and lateral occipital cortex. *Bottom:* Warm colors indicate brain regions where adolescents with NSSI had greater left amygdala RSFC than HC: bilateral cingulate and supplementary motor area. Cool colors indicate regions where adolescents with NSSI had lower amygdala RSFC than controls: (1) right lateral occipital cortex and angular gyrus; (2) right frontal pole; (3) right inferior temporal gyrus, middle temporal gyrus, and temporal pole; (4) left middle temporal gyrus and superior temporal gyrus; and (5) left angular gyrus and lateral occipital cortex.

Figure 3. Right and Left Amygdala TFC



Top: Warm colors indicate brain regions where adolescents with NSSI had greater right amygdala TFC than controls: (1) right lingual gyrus, occipital pole, and occipital and temporal fusiform; and (2) right lateral occipital cortex and superior parietal lobule. *Bottom:* Warm colors indicate brain regions where adolescents with NSSI had greater left amygdala TFC than controls: bilateral lateral occipital cortex and superior parietal lobule. Cool colors indicate brain regions where adolescents with NSSI had lower amygdala TFC than controls: bilateral frontal pole, medial frontal cortex, and paracingulate.

Figure 4. dACC PPI during Emotion Blocks

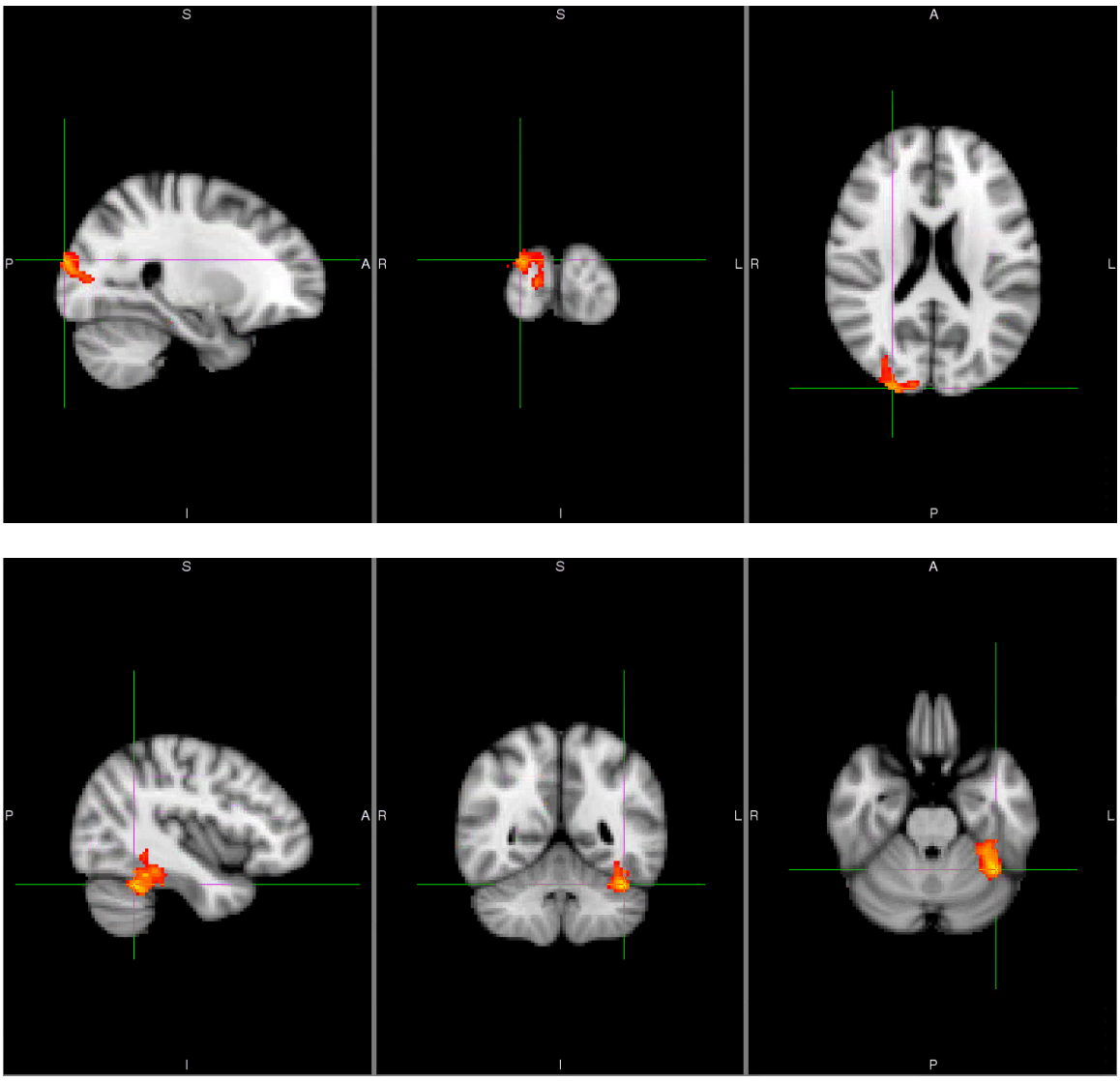
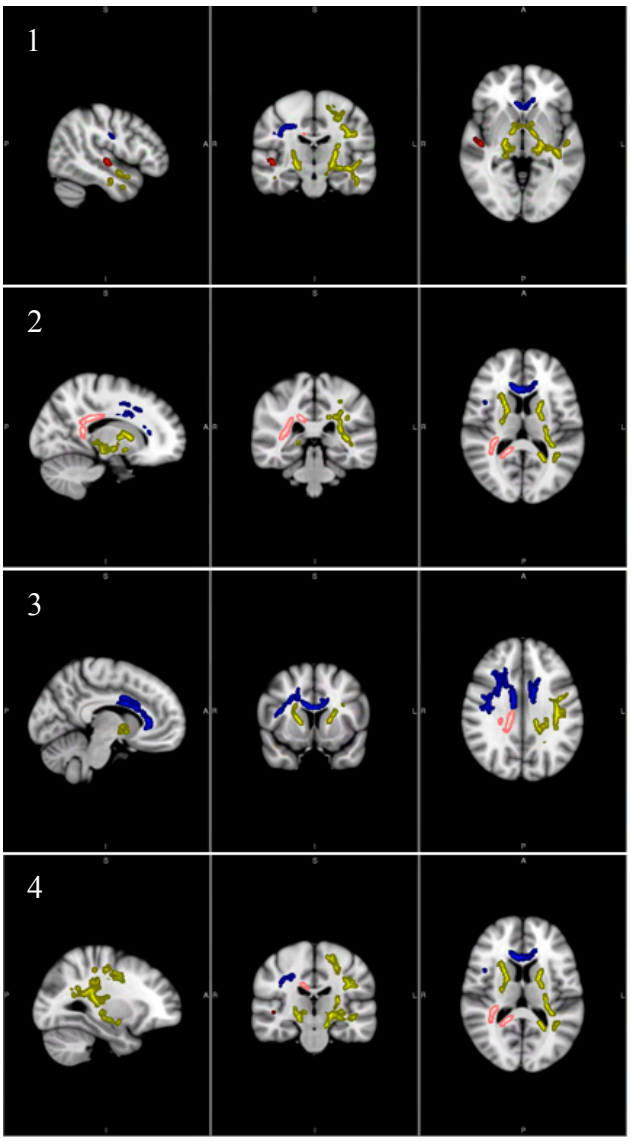


Figure shows brain regions in which those NSSI had positive right dACC connectivity during the emotion blocks while HC had high negative connectivity. *Top:* Right occipital pole and lateral occipital cortex. *Bottom:* Left temporal occipital fusiform gyrus, temporal fusiform gyrus, and cerebellum.

Figure 5. Significant GFA Clusters (HC > NSSI)



Images above each focus on one cluster in which there was a significant difference in GFA. Each cluster is also represented with a different color: (1) *Red*: right inferior longitudinal fasciculus; (2) *Pink*: right callosal body, forceps major, superior longitudinal fasciculus, and cingulum (hippocampus); (3) *Blue*: bilateral callosal body, forceps minor, cingulum (cingulate gyrus), and right superior longitudinal fasciculus; and (4) *Yellow*: bilateral anterior thalamic radiation, inferior and superior longitudinal fasciculus, uncinate fasciculus, and corticospinal tract.

Appendix A

Rejection Sensitivity Questionnaire-Adolescent Additional Information

For the exploratory scales of total, anxiety, and expectation for parent, friend, and stranger/acquaintance, internal consistency fell in the good to excellent range (α range of .82-.91). Further information regarding the internal consistency of the RSQ-A can be found in the table below.

RSQ-A Internal Consistency (n = 36)

Scales	**# of Items**	**Cronbach's α**	**α Interpretation**
Total Score	24	.95	Excellent
Total Anxiety	12	.91	Excellent
Total Expectation	12	.91	Excellent
Parent Scales			
Parent Total Score	8	.89	Good
Parent Anxiety	4	.86	Good
Parent Expectation	4	.85	Good
Friend Scales			
Friend Total Score	8	.87	Good
Friend Anxiety	4	.85	Good
Friend Expectation	4	.85	Good
Stranger/Acquaintance Scales			
Stranger/Acquaintance Total Score	8	.91	Excellent
Stranger/Acquaintance Anxiety	4	.82	Good
Stranger/Acquaintance Expectation	4	.82	Good

Rejection Sensitivity Questionnaire-Adolescent

Each of the items below describes things people sometimes ask of others. Please imagine that you are in each situation. You will be asked to answer the following questions:

1) How concerned or anxious would you be about how the other person would respond?
2) How do you think the other person would be likely to respond?

1. You ask your parents for extra money to cover living expenses or to buy something you really need.

How concerned or anxious would you be over whether or not your parents would help you out?	very unconcerned 1	2	3	4	5	very concerned 6
I would expect that my parents would not mind helping me out.	very unlikely 1	2	3	4	5	very likely 6

2. You approach a close friend to talk after doing or saying something that really upset him/her.

How concerned or anxious would you be over whether or not your friend would want to talk with you?	very unconcerned 1	2	3	4	5	very concerned 6
I would expect that he/she would want to talk with me to try to work things out.	very unlikely 1	2	3	4	5	very likely 6

3. You ask someone you don't know well to coffee or lunch.

How concerned or anxious would you be over whether or not the person would want to go?	very unconcerned 1	2	3	4	5	very concerned 6
I would expect that the person would want to go with me.	very unlikely 1	2	3	4	5	very likely 6

4. You ask your friend to go on a vacation with you and/or your family.

How concerned or anxious would you be over whether or not your friend would want to go with you?	very unconcerned 1	2	3	4	5	very concerned 6
I would expect that he/she would want to go with me.	very unlikely 1	2	3	4	5	very likely 6

5. While walking out of a store, you trip and everything in one of your bags falls to the ground. You see a couple of people you know walking by you.

How concerned or anxious would you be over whether or not these people will help you?	very unconcerned 1	2	3	4	5	very concerned 6
I would expect that they would help me	very unlikely 1	2	3	4	5	very likely 6

6. You talk to your parents about a personal problem you have been having.

How concerned or anxious would you be over whether or not your parents will listen?	very unconcerned 1	2	3	4	5	very concerned 6
I would expect that my parents would want to listen to me.	very unlikely 1	2	3	4	5	very likely 6

7. You ask a friend if you can borrow something of his/hers.

How concerned or anxious would you be over whether or not your friend would want to loan it to you? very unconcerned 1 2 3 4 5 6 very concerned

I would expect that he/she would willingly loan me it. very unlikely 1 2 3 4 5 6 very likely

8. You ask your parents to come to an event that is important to you.

How concerned or anxious would you be over whether or not your parents would want to come? very unconcerned 1 2 3 4 5 6 very concerned

I would expect that my parents would want to come. very unlikely 1 2 3 4 5 6 very likely

9. You ask a friend to do you a big favor.

How concerned or anxious would you be over whether or not your friend would do this favor? very unconcerned 1 2 3 4 5 6 very concerned

I would expect that he/she would willingly do this favor for me. very unlikely 1 2 3 4 5 6 very likely

10. You go to a party and notice someone on the other side of the room and then you ask him/her to dance.

How concerned or anxious would you be over whether or not the person would want to dance with you? very unconcerned 1 2 3 4 5 6 very concerned

I would expect that he/she would want to dance with me. very unlikely 1 2 3 4 5 6 very likely

11. You ask your parents for help with something important.

How concerned or anxious would you be over whether or not your parents will help you? very unconcerned 1 2 3 4 5 6 very concerned

I would expect that my parents would want to help me. very unlikely 1 2 3 4 5 6 very likely

12. You walk by a group of people you know and they are whispering.

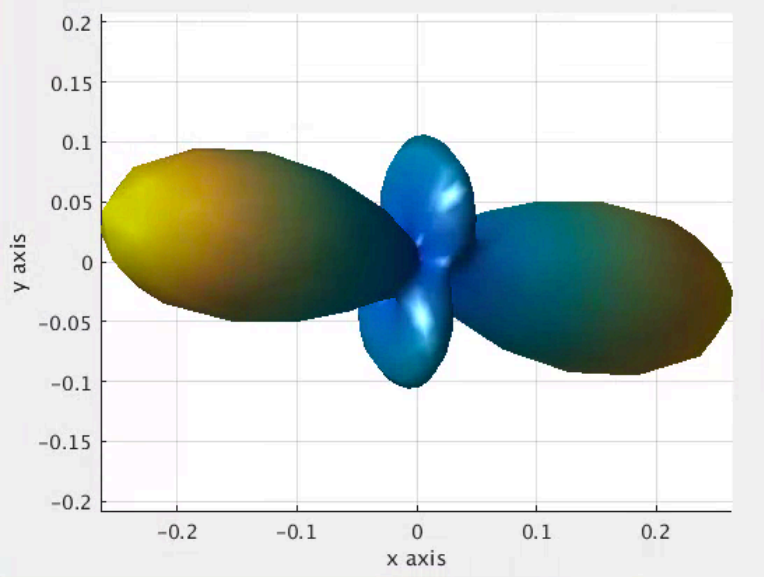
How concerned or anxious would you be over whether or not they are talking about you? very unconcerned 1 2 3 4 5 6 very concerned

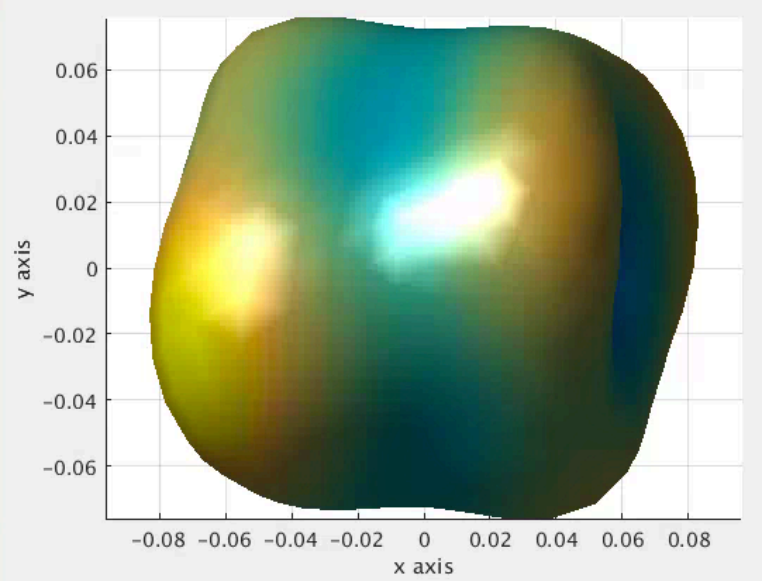
I would expect that they are talking about me. very unlikely 1 2 3 4 5 6 very likely

Appendix B

Example ODF Outputs

The orientation distribution function (ODF) was calculated for each voxel for each participant using custom MATLAB tools. ODFs were then used to create generalized fractional anisotropy (GFA) maps. The image on the top depicts a result for a voxel that shows high GFA (value closer to 1). The image on the bottom depicts a result for a voxel that shows low GFA (value closer to 0).





Appendix C

Whole-Brain Activation during Emotion Face-Matching Task

The following supplementary materials serve to provide additional information regarding the preprocessing and analyses of whole-brain activation during the emotion face-matching task.

Method

Task fMRI Analyses: Brain Activation

We used FEAT to conduct brain activation analyses. For each participant, we conducted linear regression analyses in FEAT to examine brain activation individually. Brain activation analyses included the following contrasts: Emotion vs. Fixation and Emotion vs. Shape. We were primarily interested in the results of the Emotion vs. Shape contrast. Nuisance regressors were also included: WM, CSF, volumes of excess motion, and the six motion parameters. This resulted in whole-brain RSFC maps for each amygdala ROI. Data from the resulting beta contrast maps of these analyses were then used for group comparisons.

Results

Group Differences in Brain Activation During Task

The NSSI group had greater Emotion vs. Shape contrasts than controls in several clusters: (1) right angular gyrus; (2) left middle temporal gyrus and planum polare; (3) left cerebellum; and (4) left superior frontal gyrus and bilateral frontal pole, ACC, and paracingulate. These clusters are depicted in Figure S1. In contrast, the NSSI group had lower activation than controls in (1) right lateral occipital cortex and (2) right putamen.

These clusters are depicted in Figure S2. Further details about the clusters can be found in Table S1.

During Emotion trials, the NSSI group had greater activation relative to fixation than HC in bilateral frontal pole, paracingulate, ACC, and superior and middle frontal gyri (Figure S3). In contrast, the NSSI group had lower activation than controls in several clusters: (1) left putamen; (2) right putamen, pallidum, caudate, and thalamus; and (3) right lateral occipital cortex, occipital pole, occipital fusiform gyrus, and inferior temporal gyrus (Figure S4). Further information can be found in Table S2.

Within-group analyses indicated that both groups had activation in the amygdala (Figure S5). However, there were no between-group differences in amygdala activation.

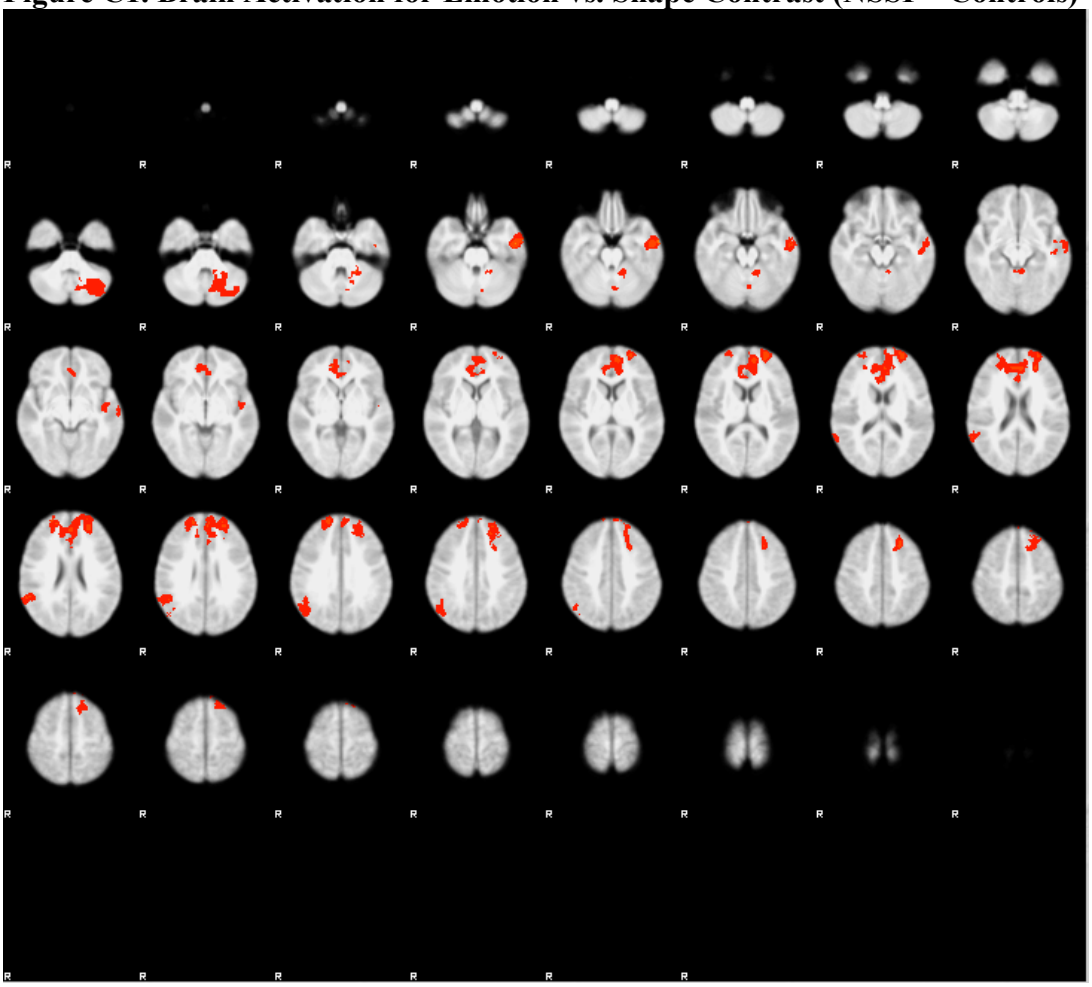
Table C1. Location, size and peak z-values of the significant clusters in the overall brain activation group analyses (Emotion vs. Shape)

Brain Regions	Contrast	Control Mean z-stat	NSSI Mean z-stat	# of Voxels	MNI Coordinates of Peak Voxel (x, y, z)	Peak z-value
Right angular gyrus	NSSI>HC	-3.47 ± 1.49	-.89 ± 1.38	586	50, -68, 30	3.72
Left middle temporal gyrus and planum polare		-3.22 ± 1.04	-1.28 ± 1.36	692	-62, -4, -24	4.86
Left cerebellum		-.65 ± .84	1.07 ± .85	951	-20, -46, -32	4.06
Bilateral frontal pole, ACC, paracingulate, and *left* superior frontal gyrus		-3.25 ± .89	-1.23 ± 1.39	4175	-24, 58, 12	4.56
Right lateral occipital cortex	HC>NSSI	7.58 ± 1.20	4.82 ± 2.11	468	26, -86, -18	3.59
Right putamen		1.07 ± -.97	-.54 ± 1.17	613	32, -20, -6	3.85

Table C2. Location, size and peak z-values of the significant clusters in the overall brain activation group analyses (Emotion vs. Fixation)

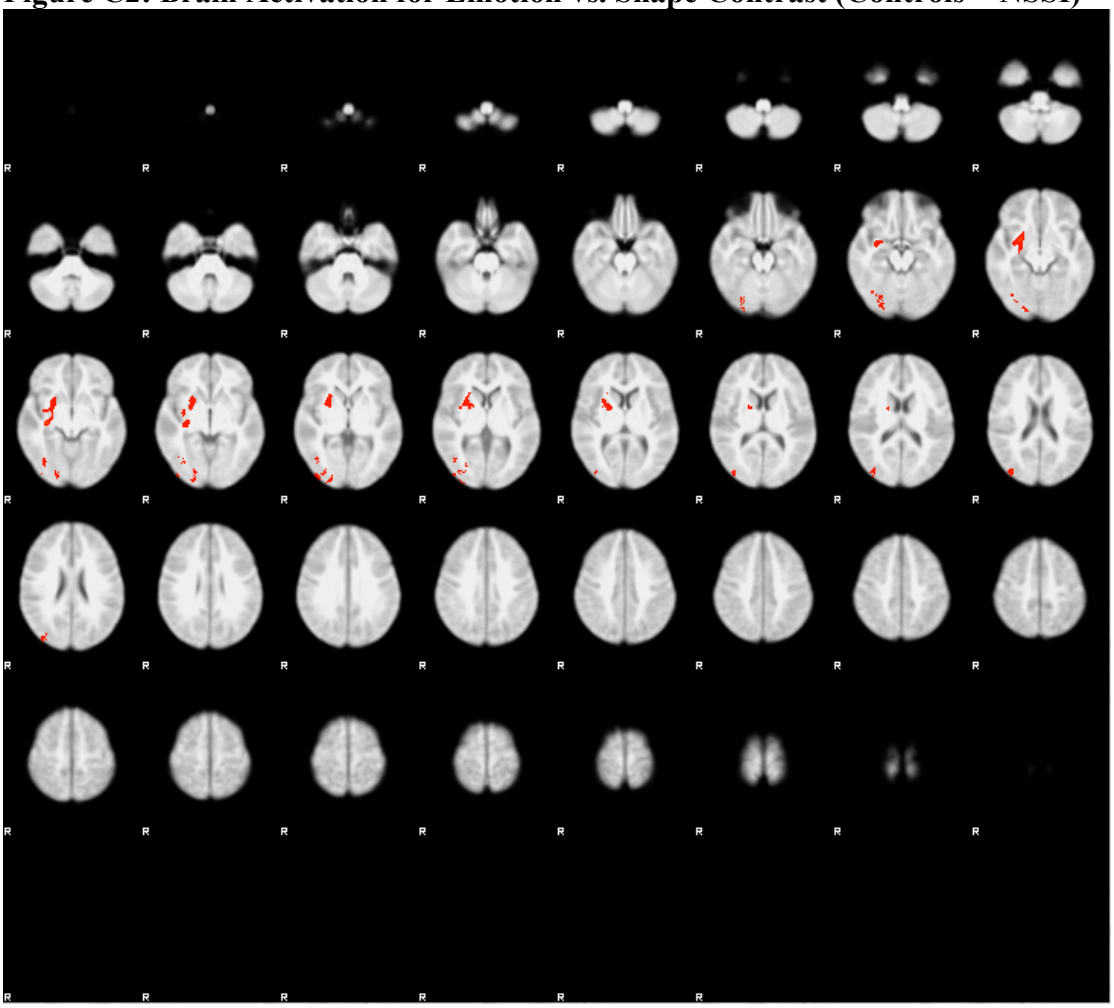
Brain Regions	Contrast	Control Mean z-stat	NSSI Mean z-stat	# of Voxels	MNI Coordinates of Peak Voxel (x, y, z)	Peak z-value
Bilateral frontal pole, paracingulate, ACC, and superior and middle frontal gyri	NSSI>HC	-2.74 ± 1.22	-1.03 ± 1.14	3142	-24, 58, 10	4.98
Left putamen	HC>NSSI	.69 ± .81	-.85 ± .98	613	-24, 2, -10	4.44
Right putamen, pallidum, caudate, and thalamus		.72 ± .71	-.66 ± .97	1078	24, 10, -10	4.48
Right lateral occipital cortex, occipital pole, occipital fusiform gyrus, and inferior temporal gyrus		6.18 ± 1.34	3.67 ± 1.72	1598	34, -84, 2-	4.08

Figure C1. Brain Activation for Emotion vs. Shape Contrast (NSSI > Controls)



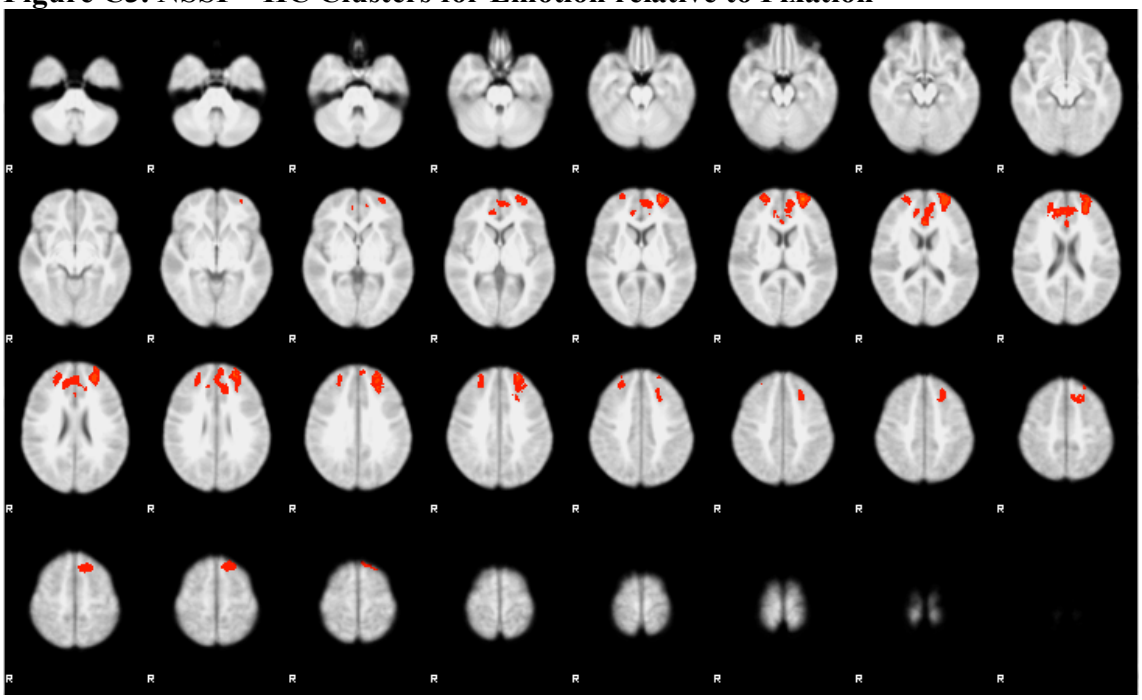
The NSSI group had greater brain activation in the Emotion vs. Shape contrasts than HC in several clusters: (1) right angular gyrus; (2) left middle temporal gyrus and planum polare; (3) left cerebellum; and (4) left superior frontal gyrus and bilateral frontal pole, ACC, and paracingulate.

Figure C2: Brain Activation for Emotion vs. Shape Contrast (Controls > NSSI)



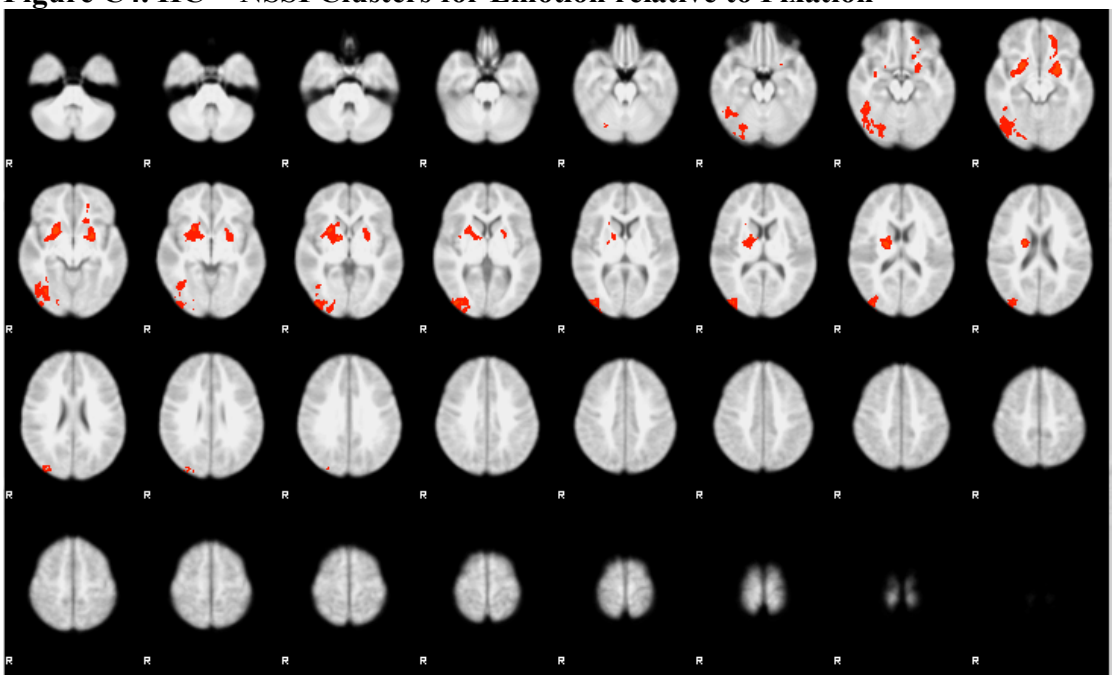
The NSSI group had lower activation than controls in (1) right lateral occipital cortex and (2) right putamen.

Figure C3. NSSI > HC Clusters for Emotion relative to Fixation



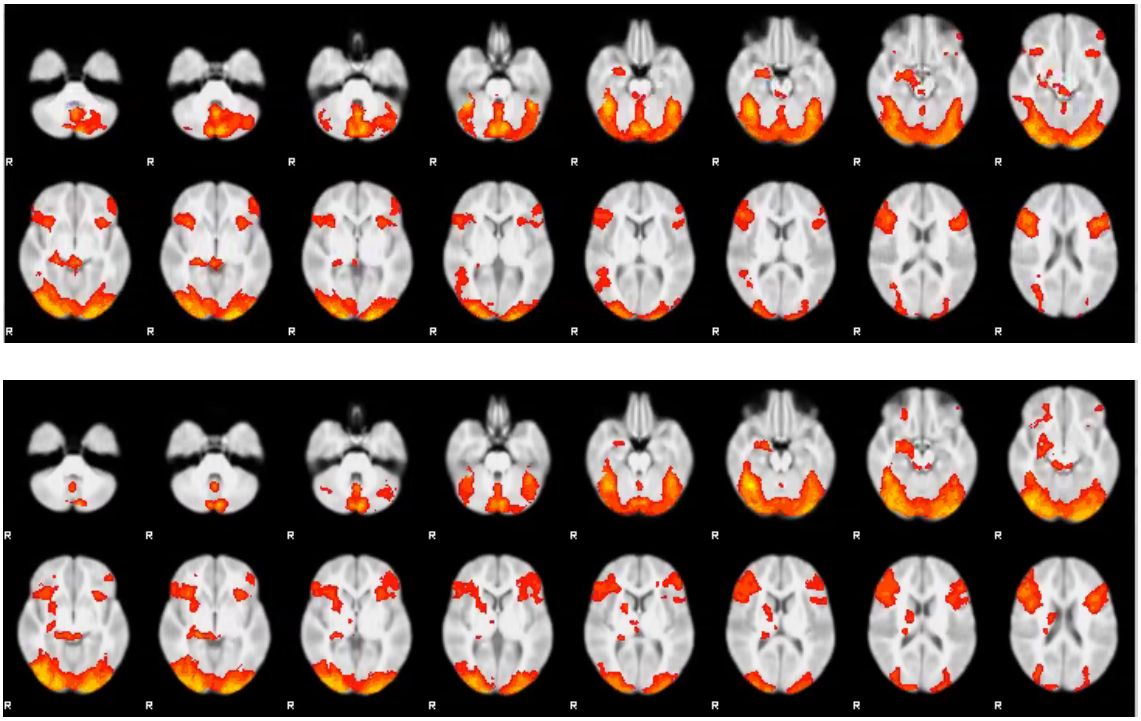
During Emotion trials, the NSSI group had greater activation relative to fixation than HC in bilateral frontal pole, paracingulate, ACC, and superior and middle frontal gyri

Figure C4. HC > NSSI Clusters for Emotion relative to Fixation



NSSI group had lower activation than controls in several clusters: (1) left putamen; (2) right putamen, pallidum, caudate, and thalamus; and (3) right lateral occipital cortex, occipital pole, occipital fusiform gyrus, and inferior temporal gyrus

Figure C5. Mean Within-Group Brain Activation for Emotion versus Shape Contrast



Top images show mean activation maps for the NSSI group. Bottom images show mean activation maps for the HC group.