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Title Page

Title: Neural reactivity to social punishment predicts future engagement in nonsuicidal self-injury among peer-rejected adolescents

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Abstract

Background: Rates of nonsuicidal self-injury (NSSI) increase dramatically in adolescence. Affective reactivity and adverse social experiences have been linked to NSSI, but it is less known whether these factors may separately or interactively predict NSSI, especially longitudinally. This study combined fMRI and a sociometric measure to test whether a combination of neural (e.g., amygdala) reactivity to social punishment and peer-nominated peer acceptance/rejection predicts NSSI longitudinally in adolescence. Amygdala reactivity was examined as a potential neural marker of affective reactivity to social punishment, which may heighten NSSI risk in contexts of social adversity. **Methods**: 125 adolescents (63 female) completed a social incentive delay task during neuroimaging and school-based peer nominations to measure peer acceptance/rejection. NSSI engagement was assessed at baseline and one-year follow-up. **Results**: Greater amygdala reactivity to social punishment predicted greater NSSI engagement one year later among adolescents with high peer rejection. This effect for the amygdala was specific to social punishment (vs. reward) and held when controlling for biological sex and pubertal development. Exploratory analyses found ventral striatum reactivity to social reward and punishment similarly interacted with peer rejection to predict NSSI, but that amygdala connectivity with salience network regions did not. **Conclusions**: Amygdala reactivity to social punishment, in combination with high peer rejection, may increase NSSI risk in adolescence, possibly via heightened affective reactivity to adverse social experiences. Objective measures of neurobiological and social risk factors may improve prediction of NSSI, while

therapeutic approaches that target affective reactivity and increase prosocial skills may protect against NSSI in adolescence.

Manuscript

Nonsuicidal self-injury (NSSI), or purposeful damage to body tissue without intent to die (1), is prevalent among adolescents, with rates ranging from 17-67% across community and clinical samples (2-3). NSSI typically begins in early to middle adolescence (i.e., ages 12-14 years) and prevalence increases dramatically by late adolescence (4), yet few studies have tested prospective NSSI risk factors during this developmental period. Longitudinal approaches are needed that consider interactions of individual-level risk factors with environmental experiences that may be particularly salient in adolescence.

Clinically, there is robust evidence that NSSI is associated with affective reactivity (5-8) and distressing social experiences (9-10). Emotionally distressing social experiences may precede NSSI across short timescales (10-12) and serve socially-relevant functions under distress (e.g., communicate distress, avoid social situations; 6,13). Individuals frequently endorse both affective and social motivations for engaging in NSSI episodes (14), further suggesting that both social (e.g., adverse social experiences) and affective (e.g., affective reactivity) factors may interact within individuals to predict NSSI. Yet not all adolescents who experience adverse social situations engage in NSSI, and the mechanisms which may make some adolescents susceptible to NSSI in adverse social contexts warrant further investigation.

In particular, it is not well understood how affective reactivity and social experiences may separately or interactively predict NSSI in adolescence, a period when neurodevelopmental changes orient adolescents toward peers and increase sensitivity to social rewards and punishments (15-17). This study tests the hypothesis that neural markers of affective responsivity, when anticipating aversive social stimuli (i.e., social punishment), interact with adolescents' actual social context to predict longitudinal increases in NSSI. Specifically, we test

whether amygdala reactivity to social punishment interacts with adolescents' peer-nominated peer acceptance/rejection to predict NSSI one year later.

Amygdala Reactivity and Adolescent NSSI

Neurobiological vulnerabilities are associated with NSSI in youth, including those which may signal heightened reactivity to adverse experiences in the social environment (18-19). For example, adolescents with NSSI histories exhibit differential peripheral nervous system (e.g., HPA axis, cortisol) responses to acute social stress (20-23). These physiological responses may underlie affective responses to social stress (22,24) and be heightened in adolescence due to pubertal changes in neurobiological stress responsiveness and emotional reactivity (25). While understudied, neural responses to social punishment may similarly suggest underlying processes, such as affective reactivity to social incentives, that may link adverse social experiences and NSSI in adolescence. In tasks involving aversive social feedback (e.g., negative evaluative peer feedback, 26; peer rejection, 27,28; angry faces, 20,29), adolescents with NSSI histories have shown heightened neural activation (i.e., during anticipation and receipt) in multiple regions, including those known to represent affective salience and responsivity to the social environment, such as the amygdala (20,29). However, neuroimaging studies of NSSI in youth are few and cross-sectional. It is unknown whether particular neural, including amygdala, responses to social punishment are prospective risk factors for future NSSI in youth, possibly by amplifying affective reactivity.

Given the amygdala's role in detecting cues in the social environment and modulating affective responses to these cues (30-31), amygdala reactivity to social punishment may be a promising neural marker of NSSI risk. The amygdala is central to representing affective salience and is part of a network of regions implicated in responsivity to salient social stimuli and

generation of affective states (32-34). Importantly, the amygdala has been shown to respond to both social punishment and reward (35-37) and may be particularly engaged during anticipation of these outcomes (38). Social punishment anticipation has been shown to elicit negative affective responses (39-40), and amygdala reactivity during anticipation of social punishment (e.g., peer rejection feedback, angry faces) is thought to underlie heightened emotional reactivity in other psychopathology (e.g., social anxiety) (41-42). These neural responses may be particularly heightened in adolescence and linked to behavioral increases in emotional reactivity in this period (43-46). Social punishment anticipation is also a key motivational driver of behaviors like avoidance, which may be pertinent given some individuals report engaging in NSSI to avoid distressing social situations (6,12).

Amygdala reactivity during social punishment anticipation may therefore reflect heightened affective reactivity to adverse social experiences and predict behaviors such as NSSI, which is frequently linked to affective reactivity in contexts of social distress (5,10,47). Among adolescents, NSSI urges often occur in social contexts (e.g., with peers or friends) (48), and affective distress related to adverse social experiences may predict NSSI across short timescales (10-11). Indeed, adverse social experiences (e.g., peer rejection) are robust correlates of adolescent NSSI (49-50).

Experiences in the Peer Environment

While amygdala reactivity to adverse social experiences may be heightened for many adolescents in this developmental period (51-52), NSSI risk is likely increased in combination with environmental stressors, particularly in the social environment (9,53). Neural reactivity to aversive peer feedback (e.g., peer exclusion) correlates with real-world social vulnerabilities (e.g., less peer connectedness; 54) and may predict elevated risk for psychopathology (e.g.,

internalizing symptoms) only among adolescents with histories of social adversity (e.g., peer victimization; 55). It is thus critical that research consider adolescents' actual social context when testing neural-based risk for NSSI.

Adverse experiences in the peer environment may be particularly relevant. Peer-related stressors (e.g., peer rejection) are among the most frequently cited precipitants of self-injurious behaviors in adolescence (56), a period marked by increases in the frequency and emotional intensity of peer interactions (57) and neurobiological changes that may underlie heightened sensitivity to peer experiences (58). Negative peer experiences are both correlates and risk factors for adolescent NSSI (49-59) and may be stronger predictors of future NSSI than stress in other interpersonal domains (e.g., family) (60). Indeed, multiple aspects of adolescents' peer relationships (e.g., negative beliefs about peers) may contribute to risk (60-61). However, prior work has largely relied on self-report measures of adverse social experiences, which may capture a narrow range of peer experiences and present confounds when assessing adverse peer-related experiences in adolescents with psychopathology (62).

More rigorous measures are needed to provide ecologically valid indices of adverse peer experiences—including peer rejection, given its association with NSSI (57). A different, underutilized approach in this literature involves the use of sociometric measures, which rely on peers' views of an adolescent and capture cumulative, peer-related experiences across peer informants. Specifically, sociometric measures using peer nominations of how well one is liked among peers offer a global, ecologically valid marker of peer status (63-64). For decades, developmental psychologists have used peer-nominated peer rejection scores to capture adolescents who experience higher levels of peer victimization, social exclusion, ostracism, poor friendship quality, and numerous other adverse peer experiences (65). A sociometric measure of

peer rejection may moderate the influence of neural reactivity on NSSI risk—whereby adolescents who exhibit neural (i.e., amygdala) sensitivity to social punishment, and who also experience greater peer rejection, may be at elevated risk.

Current Study

This longitudinal study aims to understand the real-world social contexts in which neural reactivity to the social environment may increase future NSSI risk in adolescence by combining fMRI with a sociometric index of peer acceptance/rejection. First, we tested whether greater amygdala reactivity during social punishment anticipation predicted increases in NSSI engagement one year later. Specifically, adolescents completed a social incentive delay (SID) task in which they anticipated and sought to avoid social punishment (i.e., scowling peer face) and anticipated and sought to gain social reward (i.e., smiling peer face). Past work suggests that neural activity during anticipation of social reward and punishment in the SID may reflect individual differences in adolescents' sensitivity to the social environment (16,66). Second, and primarily, we tested the interaction of amygdala reactivity to anticipation of social punishment with school-based peer acceptance/rejection to examine whether longitudinal associations between amygdala reactivity and NSSI were strongest among adolescents experiencing greater levels of real-world peer rejection.

Supplemental analyses tested amygdala connectivity with three "salience network" regions (i.e., VS; insula; subgenual anterior cingulate cortex, sgACC) to further examine patterns of amygdala responsivity to social punishment that may heighten, or attenuate, NSSI risk (see Supplement). Exploratory analyses tested activation in these salience network regions during social reward and punishment anticipation, and amygdala reactivity during social reward anticipation, to examine region (i.e., amygdala) and feedback condition (i.e., social punishment)

specificity. By jointly considering individual-level neural responses and environment-level stressors in a longitudinal design, this study tests vulnerability-stress models of NSSI risk using objective measures. The large, demographically diverse sample stands in contrast to prior neuroimaging studies of adolescent self-injurious thoughts and behaviors, which have largely relied on smaller samples examined cross-sectionally (18).

Methods and Materials

Participants

Participants were recruited from a larger longitudinal study in a diverse, rural community in the southeast United States. Eligibility required that participants be at least 11 years, 10 months old. Exclusion criteria included diagnosis of a learning disability, history of seizures or head trauma, or dental work involving metal. Adolescent participants and parent/guardian(s) provided written assent/consent, according to the university's IRB. Of the original 143 participants who completed the fMRI scan, two were excluded from analyses due to not completing the scan, two for excessive motion (>2mm across more than 10% of volumes), one for technical errors, one for an MRI artifact, and 12 for missing NSSI data at follow-up, leading to a total sample of 125 adolescents (M_{age}=12.82, *SD*=0.53; 50.4% female). The sample was diverse with regards to race/ethnicity (31.2% White; 23.2% Black; 32.8% Hispanic/Latinx; 8.8% mixed; 4.0% other) and socioeconomic background[1] (Area Deprivation Index: *M*=67.30, *SD*=17.66).

Adolescent participants completed self-report measures of NSSI at baseline and one-year follow-up, and a sociometric nomination procedure at baseline, in school. Adolescent participants and primary caregiver(s) attended an fMRI scan session in the same academic year

(days between school assessment and scan: *M*=165, *SD*=78). Adolescents were trained in the SID task and acclimated to a mock scanner before the scan.

Measures

Social incentive delay (SID) task. Participants completed the SID task (67) during fMRI to measure neural responses when anticipating (i.e., attempting to gain and avoid) social rewards and punishments (Figure 1). Primary analyses focused on social punishment anticipation. See Supplement for further task description.

Nonsuicidal self-injury. NSSI was assessed with a questionnaire adapted from prior research (68-70). Items assessed past-year engagement (i.e., number of times) in five NSSI behaviors (i.e., cutting or carving skin, inserting objects under nails or skin, burning skin, scraping or picking skin to the point of drawing blood, hitting self on purpose) using a 5-point scale commonly used to assess health risk behaviors in community samples (1=*Never*, 2=*1-2 times*; 3=*4-5 times*; 4=*6-9 times*; 5=*10 or more times*). NSSI engagement was calculated as the mean of past-year NSSI engagement across the five behaviors (i.e., higher scores indicating more engagement), yielding acceptable internal consistency (Cronbach's α=.70-.74).

Peer acceptance/rejection. Peer acceptance/rejection was measured using a standard sociometric peer nomination procedure in school classrooms. Adolescents were provided an alphabetized roster of all grademates, counterbalanced A-Z or Z-A, and asked to identify an unlimited number of peers they "liked most" and "liked least." As in past research (63), a standardized difference score between standardized (i.e., within grade) "liked-most" and "liked-least" nominations was calculated to yield a social preference score (i.e., peer acceptance/rejection), with higher scores indicating greater peer acceptance and lower scores indicating *greater peer rejection* (63). Sociometric procedures have been shown to be reliable

and valid, and are considered among the most ecologically valid, robust approaches for assessing peer rejection (63,71).

Demographic measures. Participants self-reported their biological sex and race/ethnicity. Socioeconomic status and pubertal development were assessed using the ADI Index (ADI; University of Wisconsin, 2018) and Pubertal Development Scale (PDS; 72), respectively (see Supplement).

fMRI Data Acquisition and Analysis

Imaging data were collected using a 3 Tesla Siemens Prisma MRI scanner. MRI data acquisition and preprocessing are described in the Supplement. Individual level, fixed-effects analyses were estimated using the general linear model convolved with a canonical hemodynamic response function in SPM8. Six motion parameters were modeled as regressors of no interest. Using the parameter estimates from the GLM, linear contrast images comparing each of the conditions of interest were calculated for each individual. The primary contrast of interest was social punishment anticipation (i.e., angry face) versus neutral anticipation (i.e., blurred face) to examine neural activation during social punishment anticipation (i.e., controlling for neutral), given evidence linking sensitivity to anticipated social punishment in socioaffective salience regions and psychopathology in adolescents (15,36,66). Individual level subject contrasts were submitted to random effects, group-level analyses in GLMFlex (73). To examine amygdala reactivity, we utilized bilateral amygdala as our region of interest (ROI), defined using the Harvard-Oxford Atlas (Harvard Center for Morphometric Analysis). Parameter estimates of amygdala activation were extracted from the condition of interest (i.e., social punishment anticipation vs. neutral). Connectivity analyses are reported in the Supplement.

Statistical Analysis

NSSI variables were log transformed to reduce positive skew. Little's MCAR test examined randomness of missing data (i.e., 1.6% missing baseline NSSI) and was not significant, $\chi^2(8)=4.16$, $p=.84$, indicating MCAR. Missing data were handled using listwise deletion. There was no evidence of multicollinearity (VIF values=1.05-1.28; Tolerance values=.78-.95). Linear regressions examined associations between amygdala reactivity and NSSI engagement at one-year follow-up, controlling for baseline NSSI engagement. In moderation analyses, predictor and moderator variables were mean centered prior to calculating interaction terms. Simple slopes were tested at low (-1 SD; i.e., high peer rejection), average (mean), and high (+1 SD; i.e., high peer acceptance) levels of peer acceptance/rejection. The Johnson-Neyman technique was used to determine significance regions (74). Connectivity analyses are described in the Supplement. Sensitivity analyses also examined the positive (i.e., 'liked-most') and negative (i.e., 'liked-least') dimensions of social preference as separate moderators (see Supplement).

Biological sex and pubertal development were correlated with at least one predictor and/or outcome variable(s) and examined as covariates in sensitivity analyses. Exploratory analyses examined other salience network ROIs (i.e., VS, insula, sgACC) and positive feedback (i.e., social reward anticipation) to test whether results were specific to the amygdala and to social punishment. Benjamini-Hochberg procedure (75) was used at FDR of .05 to control for multiple comparisons.

Results

Nonsuicidal self-injury was endorsed by 37.6% at baseline and 25.6% at one-year follow-up; 4.8% were new onset cases at follow-up (20.8% maintenance; 16.8% cessation). Amygdala reactivity was not correlated with peer acceptance/rejection at baseline. Amygdala

reactivity and peer acceptance/rejection were significantly, inversely correlated with baseline NSSI. Biological sex and pubertal development, but not socioeconomic status, were correlated with baseline and/or one-year NSSI (Table 1). ANOVAs showed no differences in amygdala reactivity, peer acceptance/rejection, or NSSI (i.e., baseline, one-year) based on race/ethnicity (*F*s=0.64-1.86, *p*s=.12-.64).

Prospectively, amygdala reactivity did not predict one-year NSSI engagement, controlling for baseline NSSI engagement (*B*=.008, *p*=.789, CI=-.053-.069). As hypothesized, a significant interaction of amygdala reactivity with peer acceptance/rejection was found for prediction of one-year NSSI (*B*=-0.110, *p*=.017, CI=-.199- -.020) (Table 2). At high levels of peer rejection, greater amygdala reactivity was associated with greater NSSI engagement at one-year follow-up (*B*=0.142, SE=0.062, *p*=.026) (Figure 2). Amygdala reactivity was not associated with one-year NSSI at average peer acceptance/rejection (*B*=0.042, SE=0.033, *p*=.210) or high levels of peer acceptance (*B*=-0.058, SE=0.041, *p*=.159). The simple slope of amygdala reactivity on NSSI was significant and positive at greater than 0.47 SDs below, and significant and negative at greater than 1.63 SDs above, the mean on peer acceptance/rejection (Figure 3). In sensitivity analyses, this was shown to be specific to the positive dimension of social preference, with post hoc probing showing an identical pattern of findings (see Supplement). In sensitivity analyses controlling for biological sex and pubertal development (see Supplement), amygdala reactivity remained predictive of one-year NSSI (Table S1), such that greater amygdala reactivity was associated with greater one-year NSSI at high levels of peer rejection (*B*=0.129, SE=0.063, *p*=.043).

In exploratory analyses, the interaction of VS reactivity with peer acceptance/rejection was associated with one-year NSSI for both social punishment and reward anticipation, such that

greater VS reactivity during both conditions was associated with greater one-year NSSI at high levels of peer rejection (*B*s=0.094-0.122, SEs=0.044-0.046, *p*s=.008-0.033). Counter to findings for social punishment, the interaction of amygdala reactivity to social *reward* with peer acceptance/rejection was not associated with one-year NSSI (*B*=-.072, *p*=.130, CI=-.166-.022) (see Supplement).

Discussion

Research has begun to examine neural correlates of NSSI in adolescence and has not yet tested these as prospective risk factors. Further, prior work has not considered functional neural markers alongside the actual social contexts in which adolescents' NSSI behaviors may onset or persist. This study provides a novel contribution by showing that amygdala reactivity during anticipation of social punishment interacts with a robust index of peer acceptance/rejection to predict future NSSI. This builds on prior work showing that neural activation to aversive peer-related stimuli (i.e., peer exclusion) may be linked to future psychopathology specifically among adolescents experiencing real-life, adverse peer experiences (55), and extends this to NSSI examined longitudinally. Findings enhance clinical understanding of adolescent self-injurious behaviors by considering interactions of neurobiological and social risk factors assessed objectively (77-78).

As expected, results revealed that greater amygdala reactivity during anticipation of social punishment predicted greater NSSI engagement one year later among adolescents with lower peer-nominated social preference,[2] above and beyond baseline NSSI engagement. Adolescents who are both more sensitive to the prospect of social punishment and who may experience greater actual social adversity in their peer network may be at risk for NSSI given associations between affective distress, peer victimization, and self-injurious behaviors (10-

12,49-50). The amygdala is implicated in responsivity to salient social stimuli and generation of affective states and, as hypothesized, may underlie affective reactivity to social punishment (36-37,42). Affective reactivity is a robust risk factor for NSSI (7,79), which may be engaged in to regulate aversive emotions (6,80) via relatively immediate changes in affective and physiological arousal (81-84). Indeed, affect regulation following NSSI has been posited as a mechanism underlying reinforcement of these behaviors (6). Adolescents with greater amygdala reactivity to social punishment may therefore experience heightened affective responses during anticipated social punishment, which may increase NSSI risk for youth who are also less well-liked by peers and who may experience greater peer rejection. Rejection experiences themselves may confer further vulnerability given associations between chronic social adversity and neurobiological stress responses (e.g., heightened amygdala reactivity, 85,86; maladaptive HPA axis responses, 87,88) that may underlie affective reactivity to social stress (25,89). Adolescents experiencing greater peer rejection may be at risk for heightened affective reactivity across multiple neurobiological systems (22,90) that increase NSSI risk in stressful peer contexts.

While not initially hypothesized, amygdala reactivity may also be linked to NSSI among adolescents with lower social preference (i.e., lower 'liked-most' scores specifically, as shown in sensitivity analyses) via other affect-related mechanisms, such as biased self-referential processing or self-criticism. Activation in limbic regions, including the amygdala, is heightened during exposure to personally-relevant negative content (91), suggesting these regions may subserve generation of negative affective states in response to negative self-relevant information. Heightened amygdala activation has been shown in nonclinical and self-injuring adolescent samples during processing of negative self-referential feedback from others, such as criticism (92-93). Self-criticism or self-punishment may motivate engagement in NSSI for certain

individuals (94-96), and adolescents experiencing peer rejection may also be more likely to make critical self-referential attributions regarding peer experiences (97). Amygdala reactivity may possibly be linked to NSSI via involvement in self-related emotional responses or negative self-processing biases during social punishment anticipation. Indeed, social punishment—even in the form of scowling reactions from peers, as in the SID task—may be a highly salient form of negative, self-relevant feedback in adolescence, when neurodevelopmental changes permit increased appraisals and comparisons with peers and contribute to identity development (51).

Qualities of different peer contexts may also contribute to NSSI risk. NSSI, like other risk behaviors, may be socialized within peer groups (98-99), and future research might explore whether, for adolescents with lower social preference, amygdala reactivity to social punishment (e.g., via affective reactivity) or affiliation with self-injuring peers is most relevant to elevated NSSI risk in these peer contexts. Conversely, prosocial experiences or qualities of positive peer contexts may buffer against NSSI risk, as greater amygdala reactivity was associated with less frequent NSSI one year later at very high levels of social preference. Sensitivity analyses showing effects to be specific to the positive dimension of social preference may contextualize this protective effect by demonstrating that adolescents with amygdala sensitivity who are, indeed, very well-liked (i.e., high 'liked-most' scores)—versus minimally liked or moderately disliked (high 'liked-least' scores)—may be at less risk for NSSI. This is consistent with findings that high peer acceptance may protect against externalizing symptoms and other risk behaviors (e.g., substance use) in youth (100), possibly via increased opportunity to receive prosocial feedback, or other self-esteem or emotional benefits of positive peer relations (101).

The importance of adolescents' peer contexts is further emphasized by results showing that amygdala reactivity was not predictive of future NSSI in main effects analyses. This was

surprising in light of cross-sectional evidence for altered amygdala reactivity (i.e., activation and connectivity) among adolescents with NSSI histories (102-105), including to social feedback (e.g., angry faces; 20,29). Prior cross-sectional findings may be driven by contemporaneous associations between socioaffective processing and NSSI that do not emerge longitudinally. Counter to expectation, we also found a cross-sectional, inverse correlation between amygdala reactivity and baseline NSSI. This nevertheless mirrors studies showing decreased amygdala activation during anticipation or simulation of pain, which may indicate a mechanism to attenuate pain-related stress responses in aversive contexts (104,106). Hypoactive or attenuated amygdala responses may be also be a consequence of NSSI itself (i.e., habituation to NSSI and aversive or pain-related stimuli; 22,107).

Our primary finding for the amygdala was specific to social punishment, and not reward, anticipation. For adolescents with lower social preference (i.e., greater peer rejection), amygdala sensitivity to threat of social punishment (vs. possibility of social reward) may be relevant to NSSI risk, consistent with evidence linking NSSI to affective reactivity in contexts of social distress (5,10,47). Exploratory analyses also revealed significant effects for the VS during anticipation of both social reward and punishment. The VS, like the amygdala, is implicated in anticipation of rewards and punishments, especially in adolescents (32,38,45,108). In particular, VS activation may indicate the behavioral salience of stimuli—the likelihood that an individual needs to engage in an important behavioral response in reaction to a stimulus (109). For adolescents who are less accepted by their peers, neural sensitivity in these key social-affective salience regions may increase NSSI risk via heightened affective reactivity and behavioral potentiation to the social environment (110). Reactivity in these regions has also been posited to explain differences in social motivational sensitivity (32,38-39), which may implicate other

NSSI-relevant mechanisms. Neural sensitivity when avoiding aversive stimuli (e.g., social punishment anticipation) and approaching appetitive incentives (e.g., social reward anticipation) may underlie motivational processes that map onto empirically-supported, socially-relevant motivations for NSSI, such as interpersonal avoidance or support-seeking (6,13).

The present study revealed that a combination of neural reactivity and lower social preference may increase risk for future NSSI in adolescence. Amygdala reactivity to social punishment may be a neural marker of affective reactivity to adverse social experiences and temporally precede NSSI engagement among youth experiencing less acceptance and greater rejection among peers in real life. Results should be interpreted in light of several limitations. Neural processes that may represent NSSI risk factors are complex and implicate multiple neural networks. This investigation primarily tested regional amygdala activity, and three additional salience network regions in exploratory analyses. Studies adopting a network neuroscience approach might further examine social, cognitive, and affective processes (e.g., self-referential processing, emotion regulation) (93,111) implicated in NSSI in adverse peer contexts. Interpretation of results would be further aided by data on the peer contexts in which NSSI may be most likely to occur (e.g., peer influence effects). A study strength was use of a sociometric measure to isolate the unique effects of adverse peer experiences measured objectively, which avoided confounding social stress exposure with other stress-related processes (e.g., cognitive appraisals of stress) that may contribute to risk (112). Interventions to increase prosocial peer relationships may be helpful in reducing NSSI risk among adolescents who may be more likely to exhibit affective reactivity to social experiences.

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Footnotes

1. Area Deprivation Index (ADI; University of Wisconsin, 2018) scores in this sample indicated that participants came primarily from relatively deprived areas.

2. In sensitivity analyses, this interaction effect was shown to be specific to the 'liked-most' dimension of social preference (i.e., a significant association at low levels of 'liked-most' scores). Low scores on the 'liked-most' dimension of social preference are considered indices of low peer acceptance/high peer rejection [113].

Figure/Table Titles and Legends

Table 1. Descriptive statistics and bivariate correlations among study variables.
Note: Descriptive statistics and correlations for NSSI use the log transformed variables. Pearson's correlations are presented for all variables except biological sex. Point-biserial correlations are presented for correlations between biological sex and other variables. VS=ventral striatum; sgACC=subgenual anterior cingulate cortex; NSSI=nonsuicidal self-injury; SES=socioeconomic status; ADI=Area Deprivation Index (University of Wisconsin, 2018). ***p* < .05 ****p* < .01
[a] Females had greater NSSI engagement at one-year follow-up and more advanced pubertal development compared to males.

Table 2. Adolescents' peer acceptance moderates the association between amygdala reactivity and frequency of NSSI at one-year follow-up.
Note: NSSI=nonsuicidal self-injury.

Figure 1. Social Incentive Delay task.
Note: Trials consist of a circle, diamond, or triangle cue; a jittered crosshair delay; a white square target prompting participants to press a button; and feedback (e.g., angry face). Cues and corresponding feedback are depicted in the lower panel of the figure.

Figure 2. The interaction effect of amygdala reactivity and peer acceptance/rejection on NSSI engagement at one-year follow-up.
Note: Simple slopes were plotted at low (-1 SD; high peer rejection), average (mean), and high (+1 SD; high peer acceptance) levels of peer acceptance/rejection. The simple slope of amygdala reactivity on one-year NSSI engagement was significant at high peer rejection. For interpretability, amygdala reactivity (x-axis) and one-year NSSI engagement (y-axis) were z-transformed, such that negative scores represent below average amygdala reactivity and NSSI engagement, respectively; whereas positive scores represent above average amygdala reactivity and NSSI engagement, respectively. NSSI=nonsuicidal self-injury.

Figure 3. Conditional values of peer acceptance/rejection by values of the simple slope of one-year NSSI engagement regressed onto amygdala reactivity.
Note: The dotted vertical lines indicate regions of significance, where simple slopes outside this region are significant. Confidence bands in grey show continuously plotted confidence intervals for simple slopes corresponding to all conditional values of peer acceptance/rejection (i.e., moderator).

Table 1. Descriptive statistics and bivariate correlations among study variables

Variable	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
1. Amygdala reactivity	--									
2. Amygdala-VS	-0.15	--								
3. Amygdala-Insula	-0.05	0.38**	--							
4. Amygdala-sgACC	-0.11	0.51**	0.13	--						
5. Peer acceptance/ rejection	0.02	0.06	-0.14	-0.05	--					
6. NSSI engagement (baseline)	-0.22*	-0.01	0.09	0.06	-0.22*	--				
7. NSSI engagement (1-year follow-up)	-0.11	0.05	0.17	0.08	-0.14	0.60**	--			
8. Biological sex[a]	0.05	0.06	0.05	0.08	0.10	0.13	0.20*	--		
9. Pubertal development	-0.12	0.16	-0.01	0.19*	0.04	0.22**	0.20*	0.36**	--	
10. SES (ADI score)	-0.08	-0.08	0.00	-0.03	0.01	-0.03	-0.12	-0.10	-0.01	--
Mean	0.08	0.12	-0.00	0.13	0.15	0.18	0.12	--	2.42	67.30
SD	0.64	0.83	0.77	0.96	0.90	0.31	0.26	--	0.63	17.66

Note: Descriptive statistics and correlations for NSSI use the log transformed variables. Pearson's correlations are presented for all variables except biological sex. Point-biserial correlations are presented for correlations between biological sex and other variables. VS=ventral striatum; sgACC=subgenual anterior cingulate cortex; NSSI=nonsuicidal self-injury; SES=socioeconomic status; ADI=Area Deprivation Index (University of Wisconsin, 2018). ***p* < .05 ****p* < .01

[a] Females had greater NSSI engagement at one-year follow-up and more advanced pubertal development compared to males.

Table 2. Adolescents' peer acceptance moderates the association between amygdala reactivity and NSSI engagement at one-year follow-up

Variable	*ΔR²*	*B (SE)*	*p*	95% CI
Step 1. Covariate	.352			
NSSI engagement (baseline)		0.510 (0.063)	.000	0.385-0.635
Step 2. Main effects	.001			
Amygdala reactivity		0.008 (0.031)	.793	-0.053-0.069
Peer acceptance		-0.004 (0.022)	.846	-0.048-0.039
Step 3. Interaction	.031			
Amygdala reactivity x Peer acceptance		-0.110 (0.045)	.017	-0.199- -0.020
Total R^2	.384			

Note: NSSI = nonsuicidal self-injury.

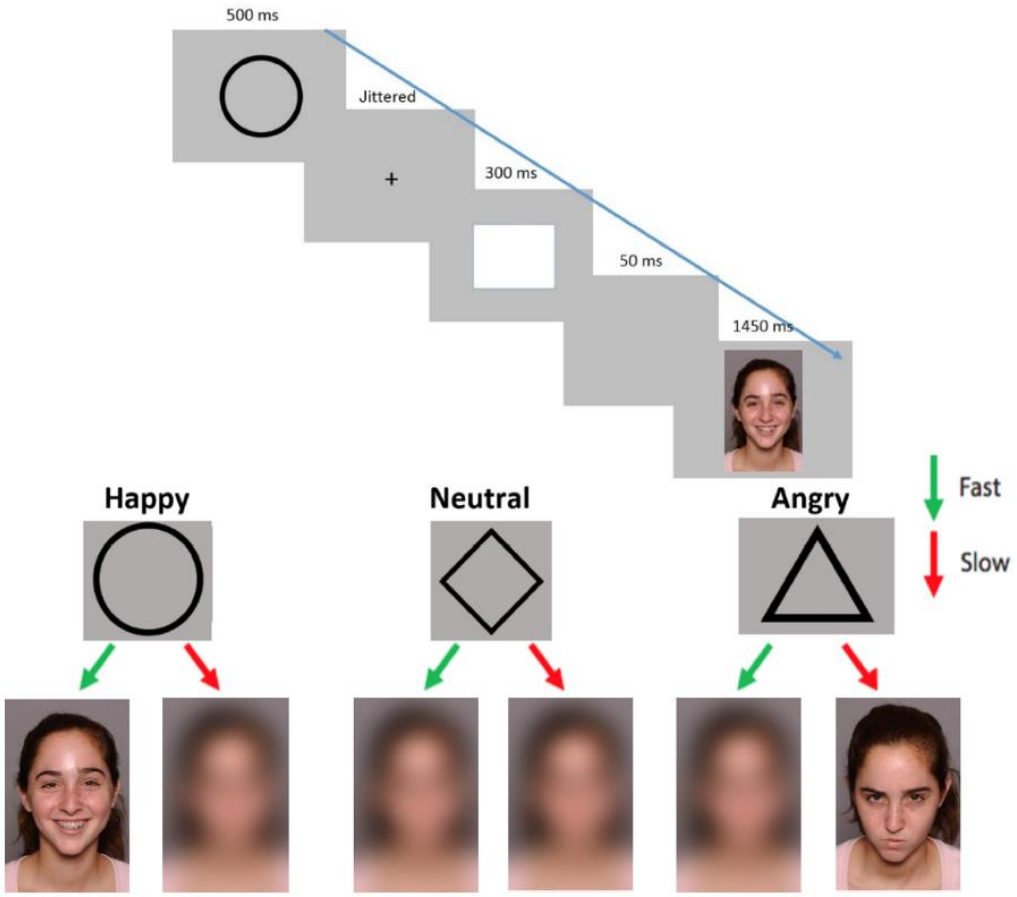
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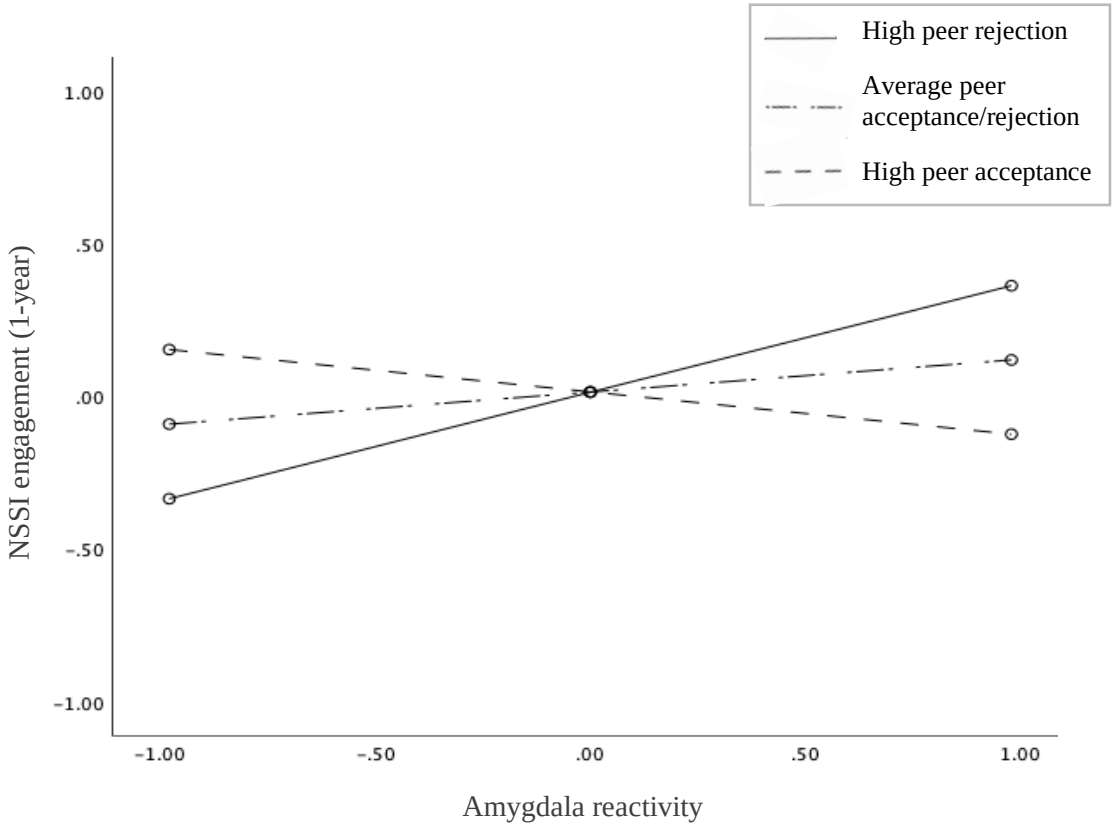
Figure 1.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Average peer acceptance/rejection
High peer acceptance
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1.00
Amygdala reactivity

Figure 2.

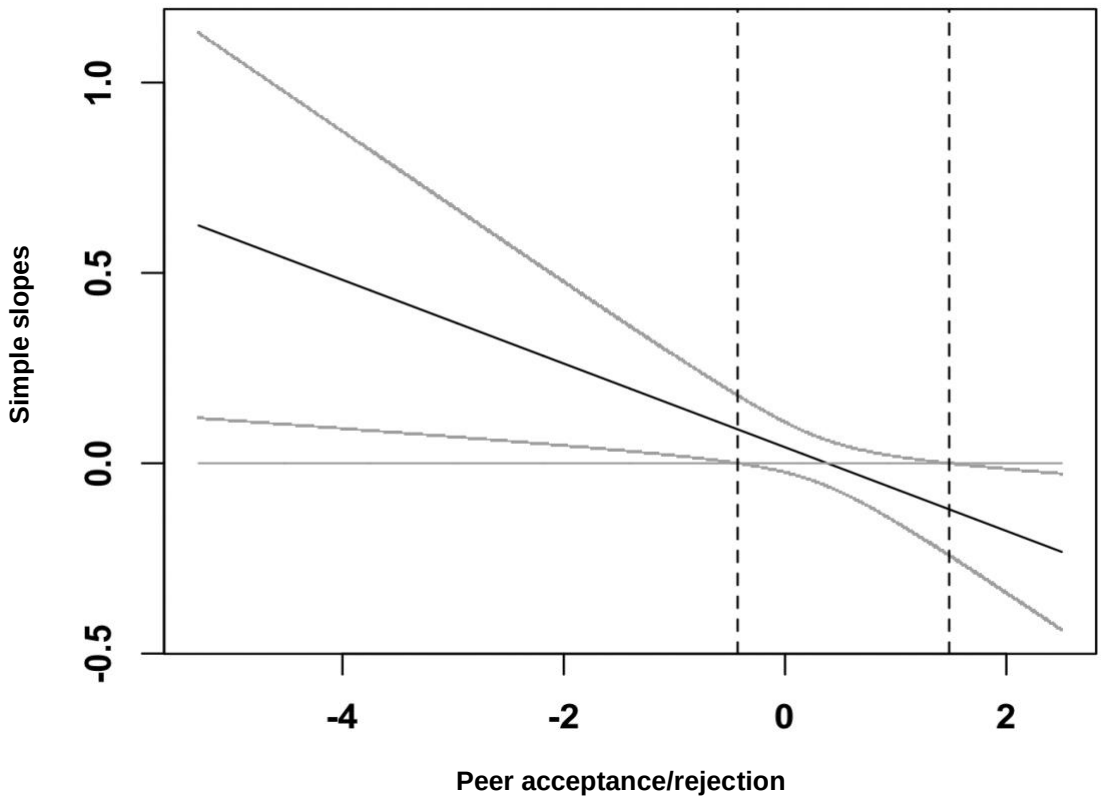

Figure 3.

SUPPLEMENTARY INFORMATION

Neural Reactivity to Social Punishment Predicts Future Engagement in Nonsuicidal Self-Injury Among Peer-Rejected Adolescents

Pollak *et al.*

Supplemental Methods and Materials

Measures

Demographic measures. To determine socioeconomic status, participants' residential addresses were used to derive an objective score on the Area Deprivation Index (ADI; University of Wisconsin, 2018) based on U.S. census data. ADI scores in this sample indicated that participants came primarily from relatively deprived areas. Pubertal Development was assessed using the Pubertal Development Scale (PDS; 72), a 5-item self-report measure assessing gender-specific physical development (e.g., body hair, growth spurts, breast development). Items are rated on a 4-point scale (1=*No development*, 4=*Development seems complete*), except the menarche item (i.e., dichotomous: 1=*No*, 4=*Yes*). A mean score was computed, with higher scores indicating more advanced pubertal development. The PDS yields scores with adequate to good reliability (115), including in this sample (Cronbach's α=.67).

Social incentive delay (SID) task. Trials began with a cue signaling whether social feedback was a potential social reward, punishment, or neither (500 ms). Cues were a different shape for each condition and presented in a random order. Prior to the scan, participants learned which cue was associated with which social feedback type and completed 12 practice trials. Cues were followed by a jittered crosshair (*M*=2.0 sec, range: 0.48-3.90 sec) and then a target (a white square; 300 ms), at which point participants were instructed to press a button as quickly as possible. Display of social feedback (1450 ms) was dependent on trial type (i.e., cue) and participant's reaction time. Following social feedback, a jittered crosshair (*M*=2.3 sec, *range*: 0.5-4.2 sec) was presented before the next trial. Participants completed two task rounds (116 trials total; 48 reward, 48 punishment, 20 neutral). In the social punishment condition, a hit earned a blurred face (i.e., neutral) and a miss earned an angry face (i.e., social punishment). In the neutral condition, both hits and misses were followed by a blurred face (i.e., neutral). In the social reward condition, a hit earned a happy face (i.e., social reward) and a miss earned a blurred face (i.e., neutral).

To prevent ceiling or floor performance and ensure participants performed at approximately 50% accuracy (i.e., to ensure relatively equal positive and negative social feedback), the time required for a successful hit was adaptive, starting at .30 seconds for the first trial and adding or subtracting .02 seconds after a miss or hit, respectively, with an upper bound of .50 seconds and a lower bound of .16 seconds. To make the task motivationally salient, age-matched adolescent faces posing emotional facial expressions were used as social rewards and punishments. Faces were photographs of racially diverse adolescents (24 faces, 12 female) from the National Institute of Mental Health Child Emotional Faces Picture Set (NIMH-ChEFS) (116). The average overall hit rate was 48.7% (*SD* = 5.9), social reward hit rate was 49.1% (*SD* = 8.7), social punishment hit rate was 46.5% (*SD* = 7.7), and neutral hit rate was 47.0% (*SD* = 12.7). Three participants only had one round of usable fMRI data from the task (e.g., due to early exit from scanner or technical issues) but were included in analyses because they met a priori requirements for the number of trials needed per condition (e.g., 8 hits, or above 15% hit rate). The SID task was modeled as event-related with eight conditions (i.e., three anticipation conditions: social reward, social punishment, neutral), two outcome conditions for social reward and social punishment (i.e., hit and miss), and one outcome condition for neutral. Anticipation conditions were modeled at the onset of the cue and duration of zero.

fMRI data acquisition and analysis

The SID task was presented on a computer screen and projected through a mirror. A high-resolution structural T2*-weighted echo-planar imaging (EPI) volume (TR=2000ms; TE=25ms; matrix=92 x 92; FOV=230mm; 37 slices; slice thickness=3mm; voxel size 2.5 x 2.5 x 3 mm3) was acquired coplanar with a T2*-weighted structural matched-bandwidth (MBW), high-resolution, anatomical scan (TR=5700ms; TE=65ms; matrix=192 x 192; FOV=230mm; 38 slices; slice thickness=3mm). In addition, a T1* magnetization-prepared rapid-acquisition gradient echo (MPRAGE; TR=2400ms; TE=2.22ms; matrix=256 x 256; FOV=256mm; sagittal plane; 208 slices; slice thickness=0.8mm) was acquired. The orientation for the EPI and MBW scans was oblique axial to maximize brain coverage and reduce noise.

fMRI preprocessing was conducted using FSL (MRIB's Software Library, version 6.0; www.fmrib.ox.ac.uk/fsl) and included the following steps: Skull stripping using BET (117); motion correction with MCFLIRT (118); spatial smoothing with Gaussian kernel of full width at half maximum (FWHM) 6 mm; high-pass temporal filtering with a filter width of 128 s (Gaussian-weighted least-squares straight line fitting, with sigma=64.0s); grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and individual level ICA denoising for motion and physiological noise using MELODIC (version 3.15) (119) combined with an automated signal classifier (Neyman-Pearson threshold = .3) (120). For the spatial normalization, the EPI data were registered to the T1 image with a linear transformation, followed by a white-matter boundary-based transformation (BBR) (121) using FLIRT; linear and non-linear transformations to standard Montreal Neurological Institute (MNI) 2-mm brain were performed using Advanced Neuroimaging Tools (ANTs) (122) and then spatial normalization of the EPI image to the MNI.

For analyses examining amygdala connectivity with three regions (i.e., VS, insula, sgACC), we conducted psychophysiological interaction (PPI) analyses using a generalized form of the context-dependent PPI from the automated generalized PPI (gPPI) toolbox in SPM (119). The amygdala was used as the seed region. Time series were extracted from the amygdala and served as the physiological variable. Trials were convolved with the canonical HRF to create the psychological regressor. The physiological and psychological variables were multiplied to create the PPI term. Each participant's individual gPPI model included a deconvolved BOLD signal alongside the psychological and interaction term for each event type. To assess amygdala coupling with VS, insula, and sgACC, we extracted parameter estimates from the conditions of interests using VS, insula, and sgACC region of interest, respectively, for each participant. The VS and insula were obtained from the Harvard-Oxford Atlas. The sgACC was structurally defined using prior work that identifies a sgACC cluster, and shows links between amygdala-sgACC coupling and NSSI among adolescents (123). To ensure that our sgACC ROI is more medial and does not overlap with the corpus callosum, we further defined the mask to be more medial (MNI: 0, 30, -2; 12mm sphere; 925 voxels). All masks were bilateral (Figure 1S).

Supplemental Results

Sensitivity analyses examining positive and negative 'social preference' dimensions

While social preference has traditionally been computed as a subtraction-based difference score, in light of potential limitations of this approach, a sensitivity analysis was conducted with the positive dimension (i.e., 'liked-most') and negative dimension (i.e., 'liked-least') of social

preference as separate moderators. Mirroring results using the 'social preference' score, a significant interaction of amygdala reactivity to social punishment with the positive dimension ('liked-most' scores) was found for prediction of one-year NSSI (*B*=-0.091, *p*=.009, CI=-.159- -.023). At low levels of peer acceptance (-1 SD below the mean on 'liked-most'), greater amygdala reactivity was associated with greater NSSI engagement at one-year follow-up (*B*=0.120, SE=0.051, *p*=.022). Amygdala reactivity was not associated with one-year NSSI at average (*B*=0.028, SE=0.031, *p*=.362) or high (*B*=-0.063, SE=0.040, *p*=.122) levels of peer acceptance (mean and +1 SD above the mean on 'liked-most' scores, respectively). The simple slope of amygdala reactivity on NSSI was significant and positive at greater than 0.56 SDs below, and significant and negative at greater than 1.42 SDs above, the mean on the positive dimension of social preference ('liked-most' scores), suggesting a protective effect at higher levels of 'liked-most' scores. The interaction of amygdala reactivity to social punishment with the positive dimension of social preference ('liked-most' scores) remained significant when controlling for biological sex and pubertal development (*B*=-0.083, *p*=.020, CI=-.152- -.013; see below for discussion of demographic covariates). The interaction of amygdala reactivity to social punishment with the negative dimension of social preference ('liked-least' scores) was not significant (*B*=0.018, *p*=.705, CI=-.075-.110).

Sensitivity analyses examining demographic covariates

Because biological sex was correlated with one-year NSSI and pubertal development was correlated with baseline and one-year NSSI, both were included as covariates in supplemental sensitivity analyses. Race/ethnicity and socioeconomic status (i.e., ADI scores) were not related to predictor (i.e., amygdala reactivity, peer acceptance/rejection, baseline NSSI) or outcome (i.e., one-year NSSI) variables and therefore not included as covariates to preserve model parsimony.

The interaction of amygdala reactivity with peer acceptance/rejection remained predictive of one-year NSSI when including biological sex and pubertal development as covariates (Table S1). Amygdala reactivity to social punishment was associated with one-year NSSI at high peer rejection (-1 SD; *B*=0.129, SE=0.063, *p*=.043), but not at average peer acceptance/rejection (mean; *B*=0.036, SE=0.034, *p*=.281) or high peer acceptance (+1 SD; *B*=-0.056, SE=0.041, *p*=.172).

Sensitivity analyses examining additional ROIs and social feedback type (i.e., social reward)

The interaction of VS reactivity to social punishment with peer acceptance/rejection was associated with one-year NSSI engagement (*B*=-0.097, *p*=.009, CI=-0.169- -0.025). Mirroring results for the amygdala in primary study analyses, greater VS reactivity to social punishment predicted greater NSSI engagement at high peer rejection (-1 SD; *B*=0.122, SE=0.046, *p*=.008), but not at average peer acceptance/rejection (mean) or high peer acceptance (+1 SD; *B*s=-0.053-0.035, SEs=0.030-0.043, *p*s=.217-.245). Interaction effects for amygdala and for VS reactivity to social punishment remained significant after Benjamini-Hochberg correction. Interactions of insula and sgACC reactivity to social punishment with peer acceptance/rejection were not associated with one-year NSSI (*B*s=-0.051- -0.080, *p*s=.169-.254). When controlling for biological sex and pubertal development, the interaction of VS reactivity to social punishment with peer acceptance/rejection remained significant (*B*=-0.088, *p*=.020, CI=-0.162- -0.014), such that VS reactivity remained predictive of one-year NSSI engagement at high peer rejection (-1 SD; *B*=0.110, SE=0.047, *p*=.021), but not at average peer acceptance/rejection (mean) or high peer acceptance (+1 SD; *B*s=-0.050-0.030, SEs=0.030-0.044, *p*s=.257-.320).

The interaction of VS, but not amygdala, reactivity to social *reward* with peer acceptance/rejection was also associated with one-year NSSI engagement (*B*=-0.097, *p*=.014, CI=-0.173- -0.020), such that such that the greater VS reactivity predicted greater NSSI engagement at high peer rejection (-1 SD; *B*=0.094, SE=0.044, *p*=.033), but not at average peer acceptance/rejection (mean) or high peer acceptance (+1 SD; *B*s=-0.081-0.007, SEs=0.028-0.046, *p*s=.08-.81). This remained significant controlling for biological sex and pubertal development (*B*=-0.090, *p*=.024, CI=-0.169- -0.012), such that the association between VS reactivity to social reward and one-year NSSI engagement was marginally significant at high peer rejection (-1 SD; *B*=0.084, SE=0.044, *p*=.057), and was statistically significant at >1.10 SDs below the mean on peer acceptance/rejection (i.e., using the Johnson-Neyman technique). For social reward, interactions of other ROIs (i.e., amygdala, insula, sgACC) with peer acceptance were not associated with NSSI (*B*s=-0.072- -0.059, *p*s=.130-.336, CIs=-0.185-0.064).

No ROI was associated with one-year NSSI engagement in main effect analyses for either social reward (*B*s=-0.047-0.020, *p*s=.241-.697, CIs=-0.125-0.076) or punishment (*B*s=-0.011-0.044, *p*s=.166-.782, CIs=-.030-.106).

Amygdala connectivity: Introduction, analyses, results, and discussion

Connectivity with salience network regions

Amygdala connectivity with other regions may further reveal patterns of amygdala responsivity to social punishment that may heighten, or attenuate, NSSI risk. In particular, interactions of the amygdala with the ventral striatum (VS), insula, and subgenual anterior cingulate cortex (sgACC)—three regions in the salience network that collectively indicate increased salience of stimuli—may indicate patterns of amygdala hyperarousal or downregulation that may subserve more or less adaptive responses, including affective responses, to social punishment. Amygdala connectivity with the VS may be a developmental precursor to amygdala-PFC connectivity and underlie greater affective responsivity before development of more mature regulation (i.e., via connectivity with the prefrontal cortex) (124), while amygdala connectivity with the insula and sgACC may indicate hypervigilance to social punishment or threat, and perhaps heightened emotional processing following negative social feedback (125-127). Amygdala connectivity with these regions, including in response to negative social feedback, has been associated with social adversity, behavioral vulnerabilities (e.g., disinhibition), and internalizing symptoms in adolescents (127-129). Aberrant amygdala connectivity with multiple regions has been shown cross-sectionally in adolescents with NSSI (130-134), but it is unknown whether amygdala connectivity with these salience network regions may be markers of risk (or resilience) for future NSSI, possibly by modulating affective reactivity following social punishment. Therefore, additional linear regression analyses examined whether amygdala connectivity with each of these three regions predicted increases in NSSI one year later, as well as interactions of amygdala connectivity variables with peer acceptance for prediction of future NSSI. Amygdala connectivity variables (i.e., amygdala-VS, amygdala-insula, amygdala-sgACC) were examined in separate models as predictors of one-year NSSI engagement. All models controlled for NSSI engagement at baseline.

Connectivity results

Amygdala connectivity variables (i.e., amygdala-VS, amygdala-insula, amygdala-sgACC) were not correlated with peer acceptance or NSSI engagement at baseline (Table 1). None of the three amygdala connectivity variables predicted one-year NSSI engagement in models controlling for baseline NSSI engagement (*B*s=.011-.040, *p*s=.11-.60, CIs= -.029-.089). Peer acceptance did not moderate associations of any amygdala connectivity variables with NSSI engagement at one-year follow-up (*B*s= -.023- -.001, *p*s=.28-.97, CIs= -.071-.060).

Connectivity discussion

Counter to hypothesis, interactions of amygdala connectivity with peer acceptance were unrelated to future NSSI risk. It may be that the salience network (e.g., VS, insula, sgACC) does not uniformly covary with NSSI, and differential amygdala-based connectivity patterns may predict different pathways of NSSI risk. Research has shown distinct subgroups of those who engage in NSSI (e.g., emotional reactivity, behavioral impulsivity) (135-136), and distinct amygdala connectivity pathways may contribute to NSSI risk (i.e., via distinct mechanisms) for different adolescents. Individual differences in connectivity patterns may have contributed to lack of significant connectivity findings in this sample. Indeed, the amygdala is one of the most connected brain regions (137), and future research might explore whether amygdala connectivity with other regions (e.g., those explicitly involved in self-regulation, such as the dorsolateral prefrontal cortex) predicts NSSI. Future research might also take a more data-driven seed to voxel approach to examine whether amygdala connectivity with any other voxels spanning the brain is associated with NSSI.

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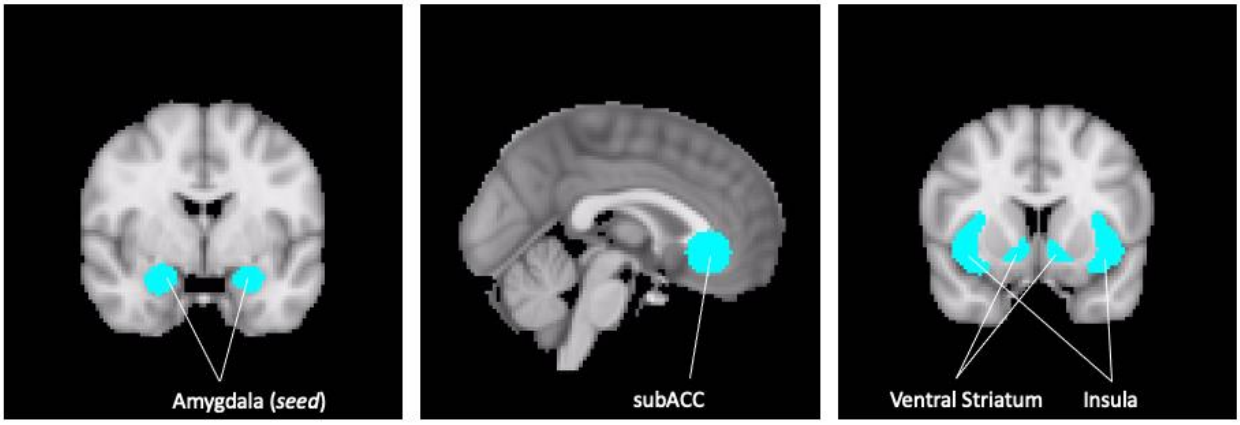

Figure S1. Regions of interest used for gPPI analyses.

Note: All masks are bilaterally defined.

Table S1. Sensitivity regression analyses predicting one-year NSSI engagement with additional covariates

Variable	*ΔR²*	*B (SE)*	*p*	95% CI
Step 1. Covariates	.370			
NSSI engagement (baseline)		0.489 (0.064)	.000	0.362-0.616
Biological sex		0.061 (0.041)	.138	-0.020-0.142
Pubertal development		0.017 (0.033)	.619	-0.049-0.082
Step 2. Main effects	.001			
Amygdala reactivity		0.005 (0.031)	.874	-0.056-0.066
Peer acceptance		-0.009 (0.022)	.681	-0.053-0.035
Step 3. Interaction	.026			
Amygdala reactivity x Peer acceptance		-0.102 (0.045)	.026	-0.192- -0.012
Total R^2	.397			

Note: NSSI = nonsuicidal self-injury.