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A Multilevel Examination of Cognitive Control in Adolescents With Nonsuicidal Self-injury

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ABSTRACT

BACKGROUND: Nonsuicidal self-injury (NSSI), a transdiagnostic behavior, often emerges during adolescence. This study used the Research Domain Criteria approach to examine cognitive control (CC) with a focus on response inhibition and urgency relative to NSSI severity in adolescents.

METHODS: One hundred thirty-eight adolescents, assigned female sex at birth, with a continuum of NSSI severity completed negative and positive urgency measurements (self-report), an emotional Go/NoGo task within negative and positive contexts (behavioral), and structural and functional imaging during resting state and task (brain metrics). Cortical thickness, subcortical volume, resting-state functional connectivity, and task activation focused on an a priori–defined CC network. Eighty-four participants had all these main measures. Correlations and stepwise model selection followed by multiple regression were used to examine the association between NSSI severity and multiunit CC measurements.

RESULTS: Higher NSSI severity correlated with higher negative urgency and lower accuracy during positive no-inhibition (Go). Brain NSSI severity correlates varied across modalities and valence. For right medial prefrontal cortex and right caudate, higher NSSI severity correlated with greater negative but lower positive inhibition (NoGo) activation. The opposite pattern was observed for the right dorsolateral prefrontal cortex. Higher NSSI severity correlated with lower left dorsal anterior cingulate cortex (ACC) negative inhibition activation and thicker left dorsal ACC, yet it was correlated with higher right rostral ACC positive inhibition activation and thinner right rostral ACC, as well as lower CC network resting-state functional connectivity.

CONCLUSIONS: Findings revealed multifaceted signatures of NSSI severity across CC units of analysis, confirming the relevance of this domain in adolescent NSSI and illustrating how multimodal approaches can shed light on psychopathology.

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Nonsuicidal self-injury (NSSI) is the intentional destruction of one's own body tissue without suicidal intent in a manner that is not culturally sanctioned (1). NSSI, which is categorized as impulsive, as opposed to stereotypic or psychosis related, is characteristically associated with tension release or emotion regulation (2). Rates in adolescents are higher (17.2%) than rates in young adults (13.4%) or adults (5.5%) (3), with onset age at 12 years or even earlier (4). NSSI occurs more frequently in females than males (5,6). To guide treatment development, advances are needed in understanding the complex mechanisms behind NSSI.

Recent work has highlighted the potential promise of a multiple-units-of-analysis approach to studying functioning domains [psychological/biological systems outlined in the Research Domain Criteria (RDoC) initiative (7,8)] and for advancing current understanding of the mechanisms underlying adolescent NSSI (9–12). One fundamental RDoC construct that has been implicated in NSSI is cognitive control (CC), which has been defined as follows: "A system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context. Additionally, control processes are engaged in the case of novel contexts, where appropriate responses need to be selected from among competing alternatives" (13). While the broader construct of CC encompasses many different facets, impulsivity is especially relevant to NSSI. Decades ago, "deliberate self-harm syndrome" was considered an impulse control disorder based on the conceptualization that self-injurers have difficulty resisting the impulse/urge to injure themselves (14). Numerous studies using self-report measures have shown a relationship between NSSI and impulsivity (15–21) and lower effortful control (22). However, prior multiunit studies of CC have found weak relationships between self-report and behavioral measures of impulsivity, perhaps because they tap distinct aspects of the construct (23–25).

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When impulsivity is broken down into factors, negative urgency (the tendency to engage in impulsive behavior under conditions of negative affect) (26) has been associated with NSSI over and above other factors such as sensation seeking, low perseverance, or lack of premeditation (27–30) and has been shown to predict NSSI urges longitudinally (31). The RDoC subconstruct of CC that is most relevant to impulsivity is "response selection; inhibition/suppression." Response inhibition (RI) is related to negative urgency more so than other impulsivity traits (32), especially during threatening conditions (33). Accordingly, we focused on the relationship between NSSI severity and RI and urgency (in both negative and positive contexts) within the CC framework. Because urgency is highly related to both NSSI and RI but does not itself fall directly within the RI construct, we broadly refer to CC as the domain encompassing both of these constructs of interest.

Prior studies using case-control designs to examine impulsivity within emotional contexts in NSSI have revealed mixed findings regarding CC performance (34–37). In accordance with RDoC, dimensional versus categorical approaches may be more useful. Furthermore, incorporation of additional units of analysis such as neuroimaging may shed light on the complexity of these mechanisms in relation to NSSI. A small but growing body of neuroimaging studies have indicated NSSI's association with possible neural deficits underlying both emotion processing and impulse regulation [see (38–40)]. One prior study showed that compared with healthy control participants, individuals with NSSI showed higher cingulate cortex activation and lower dorsolateral prefrontal cortex (DLPFC) activation during a CC task (41). However, no prior studies have comprehensively examined CC using a multiple-units approach in adolescents with NSSI.

The current study used an RDoC approach to examine CC using multiple units of analysis in adolescents with a continuum of NSSI severity. These units included self-report, behavior, and structural and functional neuroimaging characterizing the CC network (CCN) (Table 1). We preliminarily examined how these CC variables were related to each other and then tested how different units of CC measures were related to NSSI severity. We hypothesized that NSSI severity would be correlated with greater dysfunction in CC across all units of analysis and that considering all units together would shed new light on the nuances of this complex behavior.

Table 1. Multilevel Measures of Cognitive Control

Units of Analysis	Measure
Brain	
Structure	Bilateral dACC, rACC, mPFC, DLPFC cortical thickness
	Bilateral caudate and putamen volume
Function	Bilateral dACC, rACC, mPFC, DLPFC, caudate, and putamen activity during NoGo conditions within negative and positive contexts (negative > scrambled and positive > scrambled contrasts) during the emotional Go/NoGo task
Connectivity	Mean cognitive control within-network resting-state functional connectivity
Behavior	Accuracy in Go (no-inhibition) and NoGo (inhibition) conditions within positive and negative contexts RT in correct Go conditions d-prime within positive and negative contexts as z(hit) − z(FA)
Self-report	Negative and positive urgency scores from the UPPS-P

dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FA, false alarm; mPFC, medial PFC; rACC, rostral ACC; RT, reaction time; UPPS-P, Urgency (negative), Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale.

METHODS AND MATERIALS

Overview

This work is part of a longitudinal study, BRIDGES (Brain Imaging Development of Girls' Emotion and Self), the overarching goals of which are to examine CC, sustained threat (9), and self-knowledge constructs longitudinally in an NSSI-enriched sample (see the BRIDGES Project in the Supplement). Recruitment procedures and sample details have been provided elsewhere (9). The current work is based on data collected primarily at the first assessment. The study was approved by the institutional review board at the University of Minnesota.

Participants

Inclusion criteria were assigned female sex at birth, 12 to 16 years of age with or without a history of NSSI, and postmenarchal. Exclusion criteria were magnetic resonance imaging (MRI) contraindications; having a clinical condition that would potentially confound brain findings such as a neurological disorder, major medical illness, or current substance abuse disorder; and (although NSSI can occur in the context of these disorders) having a primary psychotic disorder, bipolar disorder, or autism that might confound findings due to significant associated neurodevelopmental abnormalities. Participants provided informed assent; parents/guardians gave consent. Families were compensated for each visit.

Clinical Assessments

Diagnostic interviews were conducted separately with adolescents and parents using the Kiddie Schedule of Affective Disorders and Schizophrenia-Present and Lifetime Version (42,43), and the Self-Injurious Thoughts and Behaviors Interview (44) was administered to the adolescents. NSSI severity, our primary outcome variable, was defined as the lifetime number of NSSI episodes based on the Self-Injurious Thoughts and Behaviors Interview. To address skewness, this variable was log-transformed to allow for the data to be used appropriately in regression models.

Parents reported their gross income and whether adolescents were currently taking psychotropic medications. IQ was estimated based on the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence test (45), and depression severity was assessed using the Beck Depression Inventory–Revised (46); these were used as covariates in follow-up analyses.

Self-report Assessment of CC in Emotion Contexts: Negative and Positive Urgency

Adolescents completed the Urgency (negative), Premeditation (lack of), Perseverance (lack of), Sensation Seeking, and

Positive Urgency Impulsive Behavior Scale (47), a 59-item inventory measuring dimensions of impulsivity. According to the rationale provided previously, we focused on negative and positive urgency, i.e., the tendency to engage in impulsive behavior in negative or positive affective contexts.

MRI Data Acquisition

Neuroimaging was conducted at the Center for Magnetic Resonance Research at the University of Minnesota using a Siemens 3T Prisma scanner and a 32-channel receive-only head coil, using the Human Connectome Project multiband sequences. See the Neuroimaging Details in the Supplement for detailed information on the acquisition.

Emotional Go/NoGo Task

We measured RI in emotion contexts using a modified Go/NoGo task, which measures the ability to inhibit a dominant response in the context of affective pictures as task-irrelevant distractors (48). Letters were presented sequentially in a small box at the center of the screen superimposed on negative, positive, neutral, or scrambled images in the background; images were selected from the International Affective Picture System (49), which had an equal number of neutral, positive, and negative valence ratings. Participants were instructed to ignore the images and respond as quickly as possible with a button press to the presentation of each letter (Go), except the letter X (NoGo). The task was presented using E-Prime (Psychological Software Tools Inc.) in the MRI scanner. See the Go/NoGo Task Details in the Supplement for more details on the task.

Behavioral performance was measured by accuracy on Go (no-inhibition) and NoGo (inhibition) trials across emotional backgrounds and reaction time on accurate Go trials for each background. In addition, an overall measure of behavioral performance was indexed by d-prime for negative and positive backgrounds, the standardized difference between the hit rate (accuracy on Go trials) and false alarm rate (commission errors on NoGo trials) distributions. Larger values of d-prime indicate better performance, i.e., higher hit rate and low false alarm rate (see Go/NoGo Task Details in the Supplement).

Hereafter, we use the term negative inhibition to refer to cognitive inhibition in the context of negative backgrounds and positive inhibition to refer to cognitive inhibition in the context of positive backgrounds; inhibition refers to NoGo trials, and no-inhibition refers to Go trials.

Neuroimaging Data Preprocessing

Human Connectome Project pipelines were used to process neuroimaging data (50). See the Neuroimaging Details in the Supplement for a detailed description of the processing steps, quality checks, and handling of head motion.

Defining the CCN for Neuroimaging Metrics

We used an a priori–defined CCN applied to all neuroimaging modalities to consistently examine the same network across different types of brain assessments. We selected cortical regions known to be crucial for both cognitive and emotion regulation, which are functionally inseparable (51): cognitive (dorsal) and emotional (rostral) subregions of the anterior cingulate cortex (ACC), which is a key region for RI, especially when there is emotion interaction (52); ACC subregions that demonstrate distinct inhibitory roles for cognition and emotion (53); medial prefrontal cortex (mPFC), being a key region not only for inhibitory control but also for attention and emotion (54,55); and the DLPFC, being one of the well-established CCN regions (56) and more importantly being involved in regulating emotion and behavior (41). We also included the caudate and putamen, which are critical for behavioral control and automated responses (57–60). Because this study focused primarily on the RI subconstruct of the CC domain, we limited our CCN selection around the middle and lateral frontal cortices and key basal ganglia regions, but, for example, not the dorsal parietal cortex, which is sometimes included in CCNs (56), because it is not specifically implicated in RI (61). See Figure 1 for the cortical parcellations from the Glasser Atlas (62) that were selected for the current study's CCN (see Glasser Parcellations Selected for this Study in the Supplement). Caudate and putamen parcellations were obtained from the Harvard-Oxford Subcortical Atlas (63).

Structural. For the cortical regions, cortical thickness values from Glasser regions in the CCN were extracted from the Human Connectome Project–derived vertexwise thickness maps by calculating the weighted average of thickness according to surface area of regions of interest (ROIs) as follows:

$$\frac{(ROI1_{thickness} * ROI1_{surfarea}) + (ROI2_{thickness} * ROI2_{surfarea}) + (ROI3_{thickness} * ROI3_{surfarea})}{ROI1_{surfarea} + ROI2_{surfarea} + ROI3_{surfarea}} \quad (1)$$

For the subcortical regions, volumes were calculated using FreeSurfer's "asegstats2table" function and then adjusted to participants' intracranial brain volumes.

Task Functional MRI. FSL FEAT (64) was used to conduct a whole-brain regression analysis measuring neural activation during the Go/NoGo task. Our contrasts of interest were negative > scrambled and positive > scrambled. The scrambled condition was used as a comparison because it does not elicit an emotional response, thereby allowing us to capture brain activations during cognitive inhibition specifically within an emotional context. Average *z* scores within the left and right CCN ROIs for these contrasts were extracted for further analyses.

Resting-State Functional Connectivity. The CIFTI-space gray-ordinatewise time series were used to create average time series for each of the Glasser (cortical) and Harvard-Oxford (subcortical) parcellations. CCN ROI time series were extracted, cross-correlated, and Fisher's z-transformed to yield *z* scores representing resting-state functional connectivity (RSFC) in each connection. These were averaged across all CCN ROIs (Figure 1) to yield a single measure of CCN RSFC per person.

Statistical Analyses

As a preliminary step, we conducted correlation analyses with listwise exclusion to examine relationships among all the study variables. To address our main aim (understanding how

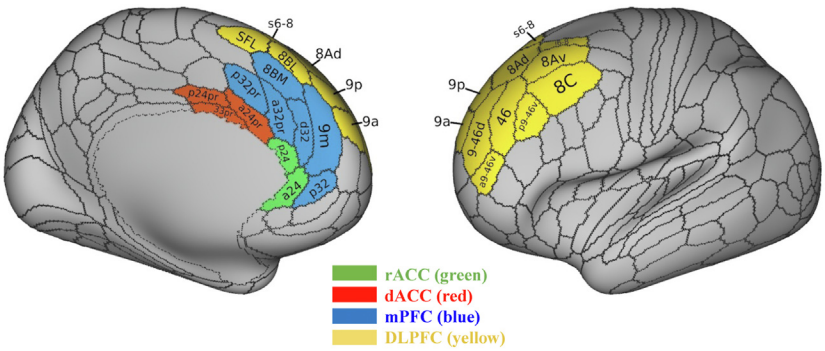

Figure 1. Locations of Glasser regions of interest selected for the cognitive control network in the current study. All regions of interest were selected from both left and right hemispheres. For example, the rostral anterior cingulate cortex (rACC) includes 2 Glasser parcels (p24 and a24) as both left and right; thus, the rACC includes 4 Glasser parcels. Likewise, the dorsal ACC (dACC) includes 6 (left and right 33pr, a24pr, p24pr), the medial prefrontal cortex (mPFC) includes 12 (left and right p32pr, a32pr, d32, p32, 8BM, 9m), and the dorsolateral prefrontal cortex (DLPFC) includes 26 parcels (left and right 8C, 8Av, i6-8, s6-8, SFL, 8BL, 9p, 9a, 8Ad, p9-46v, a9-46v, 46, 9–46d). See Glasser Parcellations Selected for This Study in the Supplement for explanations of abbreviations.

multilevel CC measures predict lifetime NSSI severity), we first applied a stepwise variable selection procedure that iterates through a large number of intermediate models to identify the model that optimizes Akaike information criterion. This optimized model consisted of the combination of variables that together best explained the variance of NSSI severity while penalizing overly complex models. We then tested how the variables in this best explanatory model predicted NSSI severity using multiple linear regression. To ensure that our results were robust to outliers, we used the same variables in robust regression models (65) and found very similar results (see Results).

Follow-up analyses tested whether any significant effects from correlation and regression analyses could be explained by age, income, IQ, depressive symptoms, and medication status. We also ran a regression model including only these covariates and compared that to our optimal model using an analysis of variance test to make sure that this model explained NSSI severity significantly better than the covariate-only model.

Different rates of missingness across variables posed a challenge for application of imputation methods. Therefore, we used all possible data available for each analysis; however, because of the various missing data patterns across variables, sample sizes in each regression model changed depending on the combination of variables.

All statistical analyses were conducted in R (R Core Team, 2015; https://www.R-project.org/). Figures were produced using the packages ggplot2 (66) and ggcorrplot (67).

RESULTS

Participants

Demographic and clinical information for this sample is provided in Table 2. Figure 2 summarizes the activities completed by all participants in this study, capturing missing data and dropout, which are further detailed in BRIDGES Project in the Supplement.

Correlation of All Study Variables (n = 75)

We observed a consistent pattern of many strong correlations within each level of analysis. Accuracy and reaction time for Go trials during positive inhibition and age correlated positively with activation during negative inhibition in mostly left medial prefrontal regions, whereas positive urgency scores correlated negatively with positive and negative inhibition performance (NoGo accuracy and d-prime) and with right mPFC, right dorsal ACC (dACC), and right and left putamen activations during negative inhibition and left dACC during positive inhibition. CCN RSFC correlated negatively with negative inhibition performance (d-prime), negative no-inhibition performance (Go accuracy), age, medication status, and more importantly with NSSI severity (Figure 3A). The ACC stood out among other CCN regions: left dACC activation during positive inhibition correlated negatively with positive no-inhibition performance and both positive and negative urgency scores; left rostral ACC (rACC) activation during negative inhibition correlated positively with all positive performance measures. However, most of these findings did not remain significant when adjusted for age, income, Beck Depression Inventory, Wechsler Abbreviated Scale of Intelligence, and medication status, except correlations with left dACC activation during positive inhibition. Moreover, negative no-inhibition performance became significantly negatively correlated with activation during negative and positive inhibition in almost all CCN regions, and left DLPFC cortical thickness (CT) became positively correlated with activation during position inhibition in the medial frontal cortex (Figure 3B).

Relationships Between Multilevel CC Variables and NSSI Severity (n = 84)

Stepwise model testing revealed that the variables in the model that best explained NSSI severity (Akaike information criterion = −72.56) were 1) self-report measures: negative urgency; 2) behavioral measures: positive and negative Go accuracy; 3) activation during negative inhibition: right DLPFC, right mPFC, right caudate, right putamen, left DLPFC, left dACC, left putamen; 4) activation during positive inhibition: right DLPFC, right mPFC, right rACC, right dACC, right caudate, right putamen; 5) structural: right DLPFC, right mPFC, right rACC, and left dACC CT; and 6) connectivity: CCN RSFC.

When applied using only these variables, the linear regression model significantly predicted NSSI severity (adjusted R^2 = 0.47, $F_{21,62}$ = 4.53, $p < .001$): higher NSSI severity was predicted by higher negative urgency; higher right mPFC and right caudate activations during negative inhibition and higher right DLPFC and right rACC activations during positive inhibition; and higher left dACC CT. Furthermore, higher NSSI severity

Table 2. Demographic and Clinical Characteristics of BRIDGES Participants

	Mean (SD) or *n* (%)
Demographic Characteristics	
Age, Years, *n* = 134	14.52 (1.25)
Race, *n* = 139	
Asian	6 (4.48%)
American Indian/Alaska Native	3 (2.24%)
Black/African American	6 (4.48%)
More than one race	14 (10.45%)
Other race	1 (0.75%)
White	109 (81.34%)
Ethnicity, Hispanic/Latino, *n* = 134	14 (10.45%)
Gross Income per Year, *n* = 134	
$0–$24,999	9 (6.77%)
$25,000–$39,999	15 (11.28%)
$40,000–$59,999	10 (7.52%)
$60,000–$89,999	20 (15.04%)
$90,000–$179,999	54 (40.60%)
Over $180,000	26 (19.55%)
Clinical Characteristics	
Lifetime Total NSSI Episodes, *n* = 138	127 (0.82)
Psychotropic Medication, *n* = 138	63 (45.65%)
SSRIs	46 (33.33%)
Antipsychotics	4 (2.90%)
Anxiolytics	8 (5.80%)
Other	5 (3.62%)
BDI-II Score, *n* = 132	15.84 (14.02)
BSSI Score, *n* = 135	5.91 (8.16)
WASI Score, *n* = 128	108.53 (11.48)
UPPS-P Score, *n* = 110	
Positive urgency	1.87 (0.74)
Negative urgency	2.40 (0.74)
Other Clinical Diagnostics[a]	
Major depressive disorder	91 (65.94%)
General anxiety disorder	49 (35.51%)
Attention-deficit/hyperactivity disorder	41 (29.71%)
Phobia	33 (23.91%)
Posttraumatic stress disorder	30 (21.74%)
Social anxiety	23 (16.67%)
Panic disorder	17 (12.32%)
Separation anxiety	16 (11.59%)
Obsessive-compulsive disorder	11 (7.98%)
Persistent depressive disorder	10 (7.25%)
Oppositional defiant disorder	6 (4.35%)
Substance use disorder	3 (2.17%)

For categorical variables, data are reported with *n* (%), whereas for continuous variables, data are reported as mean (SD).

BDI-II, Beck Depression Inventory II; BRIDGES, Brain Imaging Development of Girls' Emotion and Self; BSSI, Beck Scale for Suicidal Ideation; NSSI, nonsuicidal self-injury; SSRI, selective serotonin reuptake inhibitor; UPPS-P, Urgency (negative), Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale; WASI, Wechsler Abbreviated Scale of Intelligence.

[a]No bipolar I or II, conduct disorder, or schizophrenia diagnoses in this dataset. All diagnoses listed include past, current, and recurrent diagnoses, which can be comorbid with each other.

was predicted by lower positive Go condition accuracy; lower right DLPFC and right putamen activations during negative inhibition; lower right mPFC and right caudate activations during positive inhibition; lower right rACC CT; and lower CCN RSFC. Figure 4 shows the associations between NSSI severity and these key variables via regression plots.

After controlling for age, income, Beck Depression Inventory, Wechsler Abbreviated Scale of Intelligence, and medication status ($n = 75$, adjusted $R^2 = 0.57$, $F_{26,48} = 4.77$, $p < .001$), the model still significantly predicted NSSI severity; the significant associations with greater NSSI severity generally held, with some new relationships between NSSI severity and CC measures emerging as marginally significant or losing significance. Table 3 shows the results for the model predicting NSSI severity with the best explanatory variables both with and without covariates.

Furthermore, we found that our best explanatory model, which accounted for 47% of the variance, predicted NSSI severity significantly better than a model consisting of only covariates ($p < .05$), which accounted for only 40% of the variance. This best explanatory model explained NSSI severity even better when controlling for the covariates by accounting for 57% of the variance (Table 3).

DISCUSSION

This study used an RDoC approach to examine CC in adolescents with a continuum of NSSI severity. Key strengths of this work include an integrative multiple-units-of-analysis approach, utilization of a transdiagnostic recruitment strategy, a relatively large (compared with prior CC/NSSI studies) sample of adolescents exhibiting a range of NSSI severity, and the consideration of impulsive behavior in both negative and positive emotion contexts. One key observation was that the CCN in adolescents with NSSI showed divergent activation patterns depending on the valence of the inhibitory context. In addition, we observed a lateralization effect in both structural and functional brain measures wherein significant associations between NSSI severity and CCN activations during positive inhibition emerged in the right hemisphere, which is the side of the brain most commonly implicated in emotion (68,69). Moreover, we demonstrated that a specific combination of CC measures from different units of analysis together explained NSSI severity significantly better than a combination of some key demographic and clinical measures. This combination of CC measures explained NSSI severity even better when the combination was controlled for those demographic and clinical measures. Overall, the findings revealed multifaceted neural and behavioral signatures of NSSI severity across units of analysis, confirming the relevance of this domain in adolescent NSSI and illustrating how multimodal approaches can shed light on the complexity of how RDoC domains operate in the context of psychopathology.

Consistent with prior work (19,30,70), self-reported and behavioral impulsivity were significantly correlated in this study. More specifically, somewhat distinct from Allen *et al.* (32), who found different association patterns between positive and negative conditions, negative urgency here was negatively correlated with performance during both positive and negative inhibitory conditions (NoGo) but not with performance in Go

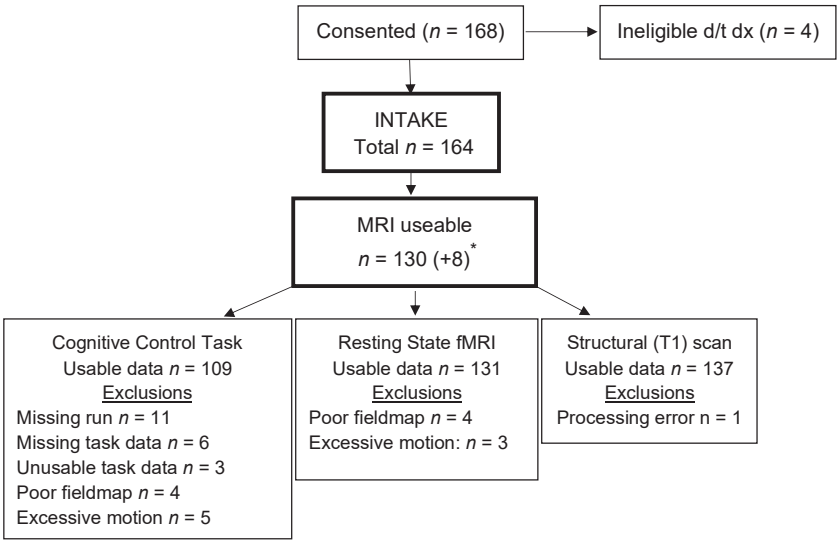

Figure 2. BRIDGES CONSORT diagram for cognitive control. *130 magnetic resonance imaging (MRI) scans were conducted at the year 1 time point. Eight individuals who did not have their scans conducted during the first year completed an MRI session at their second-year visit, bringing the total number of scans to 138. d/t, due to; dx, diagnosis; fMRI, functional MRI.

conditions. The more the adolescents viewed themselves as more impulsive in the negative context, the worse they performed in positive inhibition. Furthermore, after controlling for covariates, negative Go accuracy correlated inversely with activation during negative and positive inhibition in almost all CCN regions. Moreover, when considered with variables from other units of analysis, higher NSSI severity was significantly associated with worse positive Go accuracy. Notably, for the same task in healthy adolescents, negative context impaired inhibitory performance (48). Taken together, the frequent occurrence of negative emotional states (71,72) and sustained threat (9) in adolescents with NSSI may set the stage for impaired accuracy in the context of positive versus negative emotion due to less practice with positive emotional states. This could suggest an adaptive process at the neural level that does not rise to the level of awareness; in their daily lives, adolescents with severe NSSI still perceive themselves as more impulsive in the context of negative emotion.

With respect to brain activation correlates of NSSI severity, we also observed patterns that diverged according to context valence (Figure 4E). For example, higher NSSI severity was associated with greater activation of the right mPFC during negative inhibition, but lower activation during positive inhibition. In contrast, the opposite pattern was seen for the right DLPFC; higher NSSI severity was associated with greater activation during positive inhibition but lower activation during negative inhibition. A similarly complex pattern was observed for the subcortical CCN regions; while the right caudate results mirrored those of right mPFC, the nearby region of the right putamen was inversely associated with NSSI severity during negative inhibition. These findings highlight the complex interactions of emotion, cognition, and psychopathology in the brain; when tasked with inhibiting impulses, valence affects how adolescents recruit their neural resources, and this varies by severity of NSSI.

We found a negative relationship between NSSI severity and CCN RSFC. Although it focuses on a different network, this result is consistent with prior work showing lower amygdala-frontal RSFC (9,10) and lower network coherence in default mode and salience networks (73) in youth with NSSI. However, a global association between NSSI and functional connectivity is likely not the case. For example, Ho *et al.* (74) found that adolescents with NSSI had greater connectivity between the default mode network and the central executive network (similar to the CCN in this study). Hence, these findings are likely to vary depending on the circuit being probed.

With respect to structure, the region with the strongest associations with NSSI severity was the ACC, with a lateralization effect within different subregions; higher NSSI severity was associated with thicker left dACC, but thinner right rACC. Furthermore, after controlling for covariates, higher NSSI severity became marginally associated with thicker right DLPFC. While there are still relatively few structural MRI studies that have considered correlates of NSSI, these findings contrast with the direction of findings from prior studies reporting that suicidal risk is associated with thinner cortices in various frontal areas (75–78). Interestingly, a gene transcription/neuroimaging study showed recently that NSSI-associated cortical thickness differences in youth with NSSI were linked to cellular component morphogenesis of astrocytes and excitatory neurons (79). Taken together, the current findings further highlight the value of multimodal approaches to help understand how multiple systems may be operating in concert with each other in the context of complex behaviors such as NSSI.

Limitations

First, despite the relatively substantial size of this clinically enriched sample, the inclusion of multiple types of data per person introduced the risk of missing data across levels, thereby reducing power for analyses requiring all data types. Second, although a standard regression approach was appropriate for these data, considering the limits of other penalized regression approaches (e.g., Ridge or

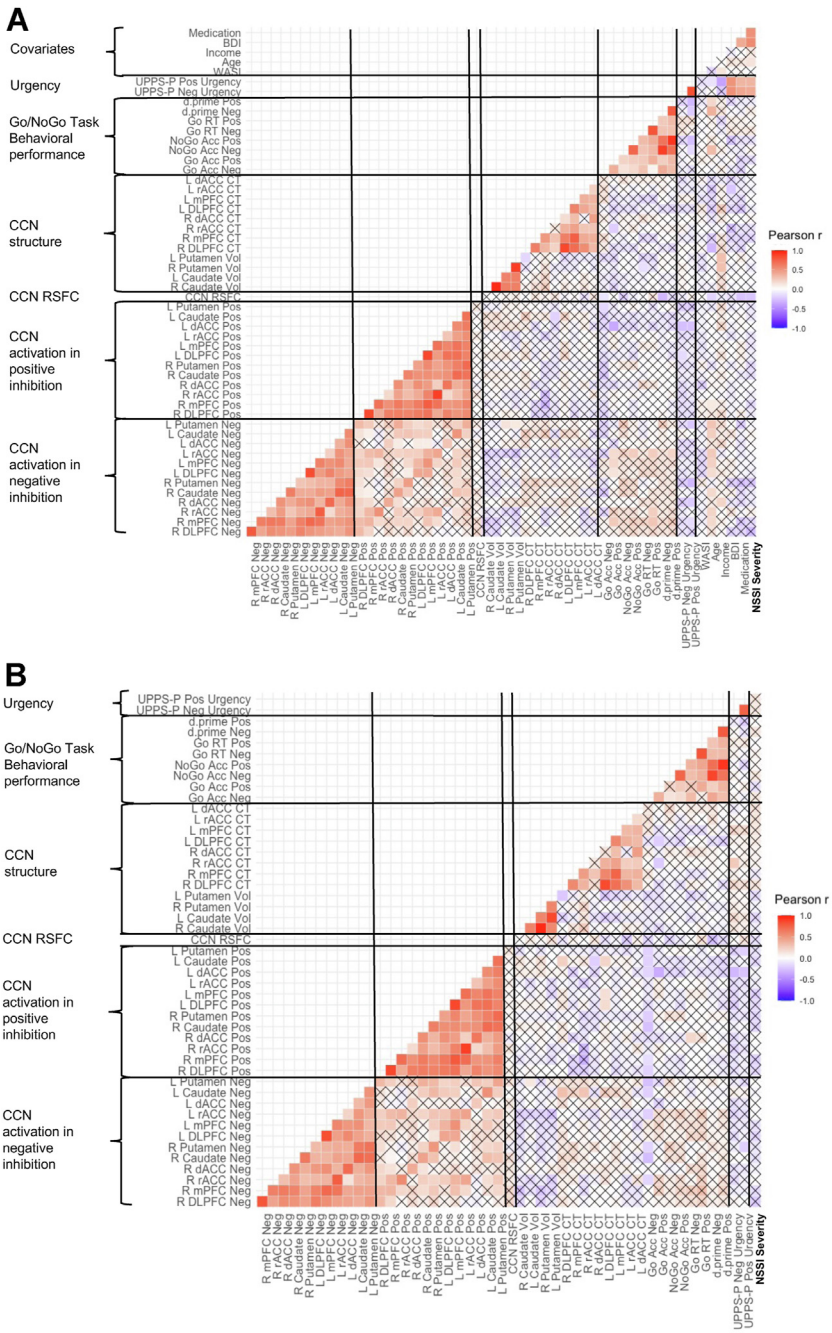

Figure 3. Correlations. **(A)** Correlations between all variables. **(B)** Correlations between all cognitive control (CC) variables after controlling for the covariates. Acc, accuracy; ACC, anterior cingulate cortex; BDI, Beck Depression Inventory; CCN, CC network; CT, cortical thickness; dACC, dorsal ACC; DLPFC, dorsolateral prefrontal cortex; L, left; mPFC, medial prefrontal cortex; Neg, negative; NSSI, nonsuicidal self-injury; Pos, positive; R, right; rACC, rostral ACC; RSFC, resting-state functional connectivity; RT, reaction time; UPPS-P, Urgency (negative), Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale; Vol, volume; WASI, Wechsler Abbreviated Scale of Intelligence.

bootstrapping), our data's correlation structure, and the lack of a validation sample, this approach should not be considered as true predictive modeling. Third, generalizability is limited by the exclusion of adolescents who were assigned male sex at birth and relatively low rates of racial and ethnic minorities in our sample. Fourth, the key outcome measure of NSSI severity (self-reported lifetime episodes) may have flaws such as recall bias and the fact that some adolescents tend to underreport while others overreport. Fifth, to optimize power by limiting the number of CC variables, we used an average within-network connectivity metric, which precludes interpretations regarding specific connections within the CCN. Furthermore, while the current research focused primarily on how CC (across multiple units of analysis) relates to NSSI and limited the analyses of connectivity to examining within the CCN (without testing other networks), other work has found that connectivity between the CCN and the default mode network was greater in adolescents with versus without NSSI (73), underscoring the potential value

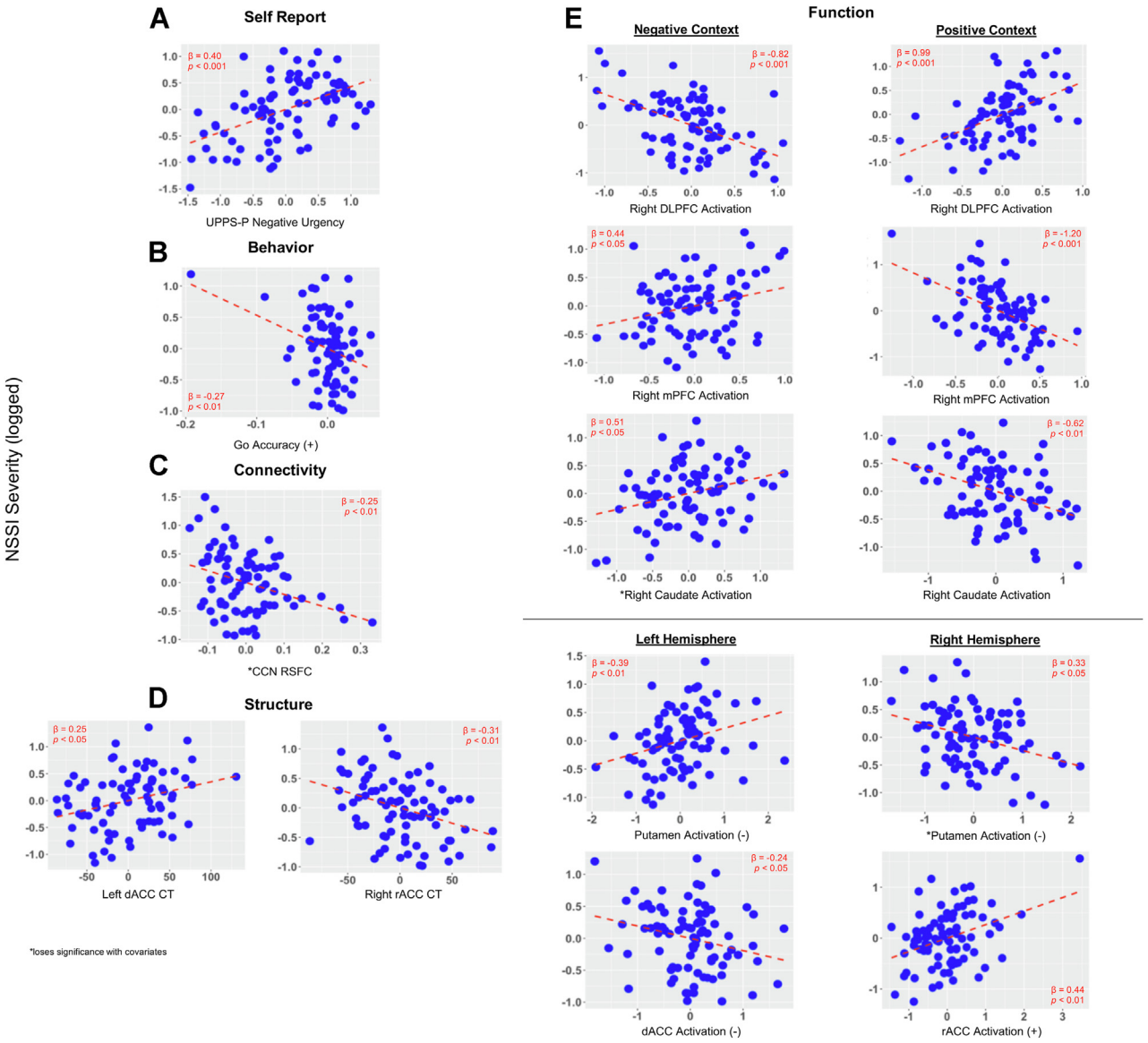

Figure 4. Significant associations between nonsuicidal self-injury (NSSI) severity and the best explanatory variables. Capital letters refer to different units of analysis: **(A)** Self-report; **(B)** behavior; **(C)** connectivity; **(D)** structure; and **(E)** function. For all graphs, x-axes represent log-scaled NSSI lifetime episodes, and y-axes represent cognitive control (CC) measures that form the best explanatory model. To highlight divergent patterns, graphs are grouped according to the brain region's association with NSSI severity in the left and right hemisphere or in the negative and positive context. An asterisk denotes CC measures that lost their significant association with NSSI severity when the best explanatory model controlled for the covariates. CCN, CC network; CT, cortical thickness; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; rACC, rostral ACC; RSFC, resting-state functional connectivity; UPPS-P, Urgency (negative), Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale.

of looking beyond the CCN in future work. Sixth, although they are distinct phenomena, because they commonly co-occur, disentangling NSSI from depression in adolescents may be impossible to do completely (80). Seventh, CC has many facets, not all of which were considered here. For example, working memory performance, task-switching capabilities, and flexibility in goal-directed thoughts and behaviors would also be excellent CC candidates for future studies that would shed more light on NSSI. Finally, cross-sectional analyses limit interpretations with respect to development and teasing out questions related to state versus trait. For example, it may be that some of the variables here are more reflective of NSSI only when measured in close temporal sequence with NSSI events (state), while others may be predictive of current (or past) NSSI regardless of measurement time.

Conclusions

These findings begin to paint a picture of the complex ways in which CCN structure and function maps onto NSSI severity

Table 3. Multiple Regression Analysis Results With Multilevel Cognitive Control Variables That Made It to the "Best Explanatory Model" as Predictors and NSSI Lifetime Episodes (log-transformed) as the Outcome Variable

Model Results				Without Covariates	With Covariates
The Best Explanatory Model				Adjusted R^2 = 0.47, $F_{21,62}$ = 4.53, $p < .001$, n = 84	Adjusted R^2 = 0.57, $F_{26,48}$ = 4.77, $p < .001$, n = 75
Level of Analysis	Measure	Inhibition Context	CCN Region	Parameter Estimate (Standardized), p Value (Only If Marginally Significant)	
Self-report	UPPS-P Urgency	Negative	NA	0.40***	0.30*
Behavior	Go/NoGo task Go accuracy	Positive		−0.27** (***with robust regression)	−0.24* (**with robust regression)
		Negative		0.16	0.17
Brain Measures for CCN Network	Structure: cortical thickness	NA	Right rACC	−0.31**	−0.24*
			Right mPFC	−0.20	−0.19 (*with robust regression)
			Right DLPFC	0.19 (marginally significant with robust regression)	0.22, p = .07 (*with robust regression)
			Left dACC	0.25* (***with robust regression)	0.20, p = .05
	Go/NoGo task activation	Positive	Right dACC	0.15	0.24, p = .05
			Right rACC	0.44**	0.48** (***with robust regression)
			Right mPFC	−1.20***	−1.20***
			Right DLPFC	0.99***	0.77**
			Right caudate	−0.62** (***with robust regression)	−0.46* (**with robust regression)
			Right putamen	0.18	0.13
			Left hemisphere	–	–
		Negative	Right mPFC	0.44**	0.49*
			Right DLPFC	−0.82***	−0.73***
			Right caudate	0.51*	0.22
			Right putamen	−0.39**	−0.25
			Left dACC	−0.24* (marginally significant with robust regression)	−0.21* (marginally significant with robust regression)
			Left DLPFC	0.22	0.07
			Left putamen	0.33* (marginally significant with robust regression)	0.37*
	RSFC	NA	Average within CCN	−0.25**	−0.12
Covariate-Only Model				Adjusted R^2 = 0.40, $F_{5,91}$ = 13.96, $p < .001$, n = 97	
Covariates	Age	NA		0.12	
	Income			0.15, p = .07	
	BDI-II			0.43***	
	Medication status			0.33*** (**with robust regression)	
	WASI			−0.05	

Variables whose significance level changed with the robust regression are indicated with parentheses. *significant at $p < .05$; **significant at $p < .01$; ***significant at $p < .001$.

BDI-II, Beck Depression Inventory II; CCN, cognitive control network; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; NA, not applicable; NSSI, nonsuicidal self-injury; rACC, rostral ACC; RSFC, resting-state functional connectivity; RT, reaction time; UPPS-P, Urgency (negative), Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale; WASI, Wechsler Abbreviated Scale of Intelligence.

and how results from different units of analysis can help us piece together different parts of the story. Future work integrating results from other RDoC domains [e.g., sustained threat (9), self-knowledge] will allow a deeper understanding of how different neurobiological profiles may interact (concurrently and over time) to increase risk in different adolescents. This integrative research may suggest novel approaches for using profiles of biological data to characterize clinically relevant subgroups of adolescents, which could potentially be useful in guiding treatment selection. Furthermore, while the RDoC domains are notably distinct, these investigations may suggest points of overlap (e.g., neural hubs of intersecting networks) that could be potential high-impact treatment targets for future clinical trials. Finally, longitudinal integrative research will be critical to understand dynamics (how clinical and biological trajectories of risk and adaptation evolve and

interact over the course of adolescence) that will inform timing of neurobiologically informed interventions for youth with NSSI.

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