A preliminary investigation into cortical structural alterations in adolescents with nonsuicidal self-injury

Kinjal K. Patel a,b,* , Margaret A. Sheridan a , Adrienne S. Bonar a , Matteo Giletta c , d , Paul D. Hastings e , Matthew K. Nock f , Karen D. Rudolph g , George M. Slavich h , Mitchell J. Prinstein a , Adam Bryant Miller i

a Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
b Department of Psychology, Old Dominion University, Norfolk, VA, USA
c Department of Developmental, Personality, and Social Psychology, Ghent University, Ghent, Belgium
d Department of Developmental Psychology, Tilburg University, Tilburg, Netherlands
e Department of Psychology, University of California Davis, Davis, CA, USA
f Department of Psychology, Harvard University, Cambridge, MA, USA
g Department of Psychology, University of Illinois at Urbana-Champaign, Champaign, IL, USA
h Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA
i RTI International, Research Triangle Park, NC, USA

ARTICLE INFO

Keywords:
Nonsuicidal self-injury
Adolescence
Magnetic resonance imaging
Brain structure

ABSTRACT

The structural neural correlates underlying youth nonsuicidal self-injury (NSSI) warrant further exploration. Few studies have explored the association between NSSI and brain structure in adolescence, and no studies have investigated differences in the relation between age and brain structure in youth with NSSI. This preliminary investigation examined associations between NSSI history, age, and cortical structure using magnetic resonance imaging in adolescent girls (N = 100, M age = 13.4 years) at increased risk for psychopathology. We conducted whole-brain analyses to investigate the associations between age and cortical structure, NSSI history and cortical structure, and NSSI history as a moderator of the association between age and cortical structure. Results suggested that age was associated with less cortical thickness and surface area in the left and right prefrontal, temporal, and parietal cortex. NSSI history was associated with less left insula and left inferior parietal cortex cortical surface area. Among adolescents with NSSI history, older age predicted greater left inferior parietal cortex surface area and was not associated with left precentral cortex surface area. Among adolescents without NSSI history, older age predicted smaller surface areas as expected with the typical trajectory of neurodevelopment. Overall, our results suggest differences in cortical surface area development in adolescents with NSSI history.

1. Introduction

Adolescence is a developmental period characterized by substantial neurobiological changes (Casey et al., 2008; Giedd et al., 1999; Somerville et al., 2010; Spear, 2000) and is associated with increases in engagement in risky behaviors (Dahl, 2004; Steinberg, 2008), including nonsuicidal self-injury (NSSI). NSSI is defined as direct and deliberate self-harm without intent to die (Nock, 2009). NSSI typically begins in early adolescence around ages 12–14 years old (Ammerman et al., 2018; Whitlock et al., et al., 2011; Zetterqvist et al., 2013), and rates of NSSI are higher in girls as compared to boys (Swannell et al., 2014). Prevalence of NSSI peaks during adolescence, with high rates in both community (18%; Muehlenkamp et al., 2012) and clinical (50%; Asarnow et al., 2011; Nock, 2010) samples. NSSI is associated with significant distress and injury (Glenn and Klonsky, 2013; Klonsky et al., 2014) and is a prospective predictor of suicide attempts (e.g., Asarnow et al., 2011; Guan et al., 2012; Klonsky et al., 2012). Research has examined psychological correlates of NSSI, but few studies have investigated the neural underpinnings of NSSI, which may uncover novel mechanisms contributing to NSSI.
1.1. Theories of NSSI

Prevailing theoretical models of NSSI focus on the reinforcing properties of NSSI. For example, the Four Function Model (FFM) specifically posits NSSI as a behavior that regulates internal/intrapersonal (automatic function) or interpersonal (social function) experiences (Nock and Prinstein, 2004). Within this model, automatic and social functions are reinforced by either generating desired cognitive-affective or social states (positive reinforcement) or by decreasing aversive cognitive-affective or social states (negative reinforcement). Research supports this model (Nock, 2009; Nock and Mendes, 2008; Nock and Prinstein, 2005), and implicates automatic negative reinforcement as the most prevalent function of NSSI (Bentley et al., 2014; Liu, 2017). Similarly, other theories highlighting the reinforcing properties of NSSI suggest that this behavior provides an affect-regulation function (Hooley and Franklin, 2018; Klonsky, 2007), or avoidance or escape from unwanted emotional experiences (Chapman et al., 2006). In sum, these theories suggest that NSSI may aid in reduction of negative affect and often serves a regulatory function among adolescents.

1.2. Neural structural correlates and NSSI

Neural structure in the prefrontal cortex and parietal cortex may be associated with NSSI given their substantial role in emotion regulation (Etkin et al., 2015; Goldin et al., 2008; Ochsner et al., 2004), self-regulation (Heatherton and Wagner, 2011; Langner et al., 2018; Palacios-Barrios and Hanson, 2019), and cognitive control (Luna et al., 2015; Vijayakumar et al., 2014). Initial research reveals structural neurobiological alterations in adolescents with a history of NSSI. A recent study found that self-injuring adolescent girls (ages 13–19) show regional reductions in gray matter volume in the insular and right inferior frontal cortex when compared to age-matched peers (N = 40; Beauchaine et al., 2019). Another study comparing adolescent girls with NSSI history (ages 14–18, N = 50) to an age- and gender-matched healthy control group found that NSSI history was associated with lower regional gray matter volume in the insular cortex and anterior cingulate cortex (ACC; Ando et al., 2018). Of note, only Beauchaine et al. (2019) reported covarying for age in their statistical models, and neither study explored whether NSSI altered age-related changes in the brain. Examining the role of age is paramount to further understanding of how the developmental patterns of cortical structure may differ based on NSSI history.

1.3. Typical changes in cortical structure during adolescent development

Prior research has quantified brain maturation during childhood and adolescence by measuring cortical thickness and surface area either across time or for participants of different ages (Mills and Tannes, 2014). Cortical surface area and thickness are distinct structural components with unique cellular and genetic origins (Geschwind and Rakic, 2013; Kremen et al., 2013; Panizzon et al., 2009), that represent independent measures of cortical structure. Longitudinal magnetic resonance imaging (MRI) studies show that cortical thickness decreases approximately linearly across childhood and adolescence for most of the cortex (Giedd et al., 1999; LeWinn et al., 2017; Mills et al., 2014a; Tannes et al., 2017; Wierenga et al., 2014). In contrast, cortical surface area increases during childhood but then decreases across adolescence (LeWinn et al., 2017; Raznahan et al., 2011; Tannes et al., 2017; Wierenga et al., 2014), following a non-linear trajectory. Thus, typical neurodevelopment during adolescence is characterized by cortical thinning and decreases in cortical surface area. Additional evidence suggests that expansion of cortical thickness is complete by age 2, while the expansion of cortical surface area continues into childhood and early adolescence (Gilmore et al., 2018; Lyall et al., 2015), demonstrating that these measures of cortical structure are independent of one another, follow different trajectories, and develop at different rates.

Refinement of neural structure during adolescence, characterized by decreases in cortical surface area and thickness, may reflect improvement in behaviors including emotion regulation and cognitive control (Vijayakumar et al., 2014). However, excessive reductions in cortical structure during this sensitive developmental period may be detrimental. Although research has not directly examined whether NSSI is associated with age related changes in neural structure, related psychological conditions alter the association between age and cortical development. For example, in longitudinal analyses, depressive symptoms are associated with accelerated cortical thinning of the frontal lobe in adolescents (Bos et al., 2018; Luby et al., 2016). Given existing work suggesting that neurodevelopmental trajectories vary with behavior and symptoms, it is possible that similar associations may emerge with NSSI.

1.4. The current study

Developmental cognitive neuroscience research demonstrates that widespread decreases in cortical thickness and cortical surface area occur during adolescence. These changes may be particularly relevant to understanding adolescents’ engagement in health risk behaviors, including NSSI. Few studies have explored the association between NSSI and brain structure in adolescence, and no studies have investigated whether there are differences in the relation between age and brain structure in NSSI populations.

In this preliminary study, we first examined associations between age and cortical thickness and surface area in a sample of adolescent girls. Consistent with prior research, we hypothesized that increased age would be associated with reductions in cortical thickness and surface area. Next, we investigated group differences in cortical thickness and surface area in adolescents with versus without NSSI history. We hypothesized that lifetime history of NSSI would be associated with less cortical thickness and surface area in the prefrontal cortex and parietal cortex. Finally, we examined the association between age and neural structure in adolescents with NSSI history versus without NSSI history. We hypothesized that NSSI history would moderate the association between age and cortical surface area and cortical thickness. Because cortical thickness and surface area tend to decline in the age range of our sample (LeWinn et al., 2017; Mills et al., 2014a; Tannes et al., 2017; Wierenga et al., 2014), we expected that the relation between age and decreased cortical structure would be stronger among adolescents with a history of NSSI compared to those without a history of NSSI. We also expected these differences would remain significant while controlling for well-known correlates of NSSI, including depressive symptoms (Schreiner et al., 2017) and medication use (Quevedo et al., 2016).

2. Method

2.1. Participants

Participants (N = 138) were drawn from a larger parent study of 229 girls examining risk for depression and self-injurious thoughts and behaviors. For the parent study, participants were recruited from a variety of sources, including Internet ads, flyers, university listserv e-mails, and medical chart reviews. A mixture of typically developing youth and youth with increased risk for self-injurious thoughts and behaviors (e.g., depression history, childhood adversity, prior suicidal thoughts), who were between the ages of 9 and 14, and assigned female sex at birth as reported by caregivers during screening were enrolled and followed for 12 months in the parent study. Exclusion criteria for the parent study included endorsement of intellectual disability, autism, pervasive developmental disorders, active and/or history of psychotic disorder, chronic physical illness that would impact blood draws or inflammatory markers (of interest to the larger parent study), and lack of ability to speak/read English. Study eligibility was determined using a brief screening procedure. Caregivers responded to a series of yes/no single-item questions for each of the exclusion criteria listed above. For the
present study, the same exclusion and inclusion criteria described above applied to those with and without NSSI histories. MRI scan exclusion criteria included history of head trauma, left-handedness, metal braces, pregnancy, and any other MRI contraindications (e.g., metal in body).

Of the 229 parent study participants, 138 (60%; ages 9–17 years, \( M = 12.55, SD = 2.00 \)) girls completed the MRI scan visit. There were no significant differences in age, \( t(227) = -1.80, p = .07 \), depressive symptoms, \( t(224) = -0.61, p = .54 \), and NSSI, \( p^2(1) = 3.23, p = .07 \), between participants who enrolled in the subsequent MRI visit and those who did not. Participants’ assent and caregiver consent was obtained prior to study participation. All procedures were approved by the local university institutional review board.

For the present study, initial analyses included MRI data from 135 (ages 9–17 years, \( M = 12.57, SD = 2.80 \)) participants: two participants were excluded due to unusable data (excessive head motion) and one participant was excluded due to a structural brain abnormality. Initial models were run with all 135 participants, however results appeared to be strongly driven by age (see Supplement). To reduce the strong influence of age, we implemented an age-matching procedure similar to approaches by others (Asarnow et al., 2014; Chen et al., 2010; Gotlib et al., 2010), resulting in a sample of 100 participants (ages 9–17 years, \( M = 13.40, SD = 1.61 \)): 50 participants with NSSI and 50 age-matched participants with no NSSI. The age-matching procedure reduced but did not eliminate the confound of age. Thus, in whole brain analyses, we controlled for the effects of age. Additionally, we examined age as a moderator of the association between NSSI and cortical structure. Hereafter, statistics reported will be from these 100 participants unless otherwise noted. These 100 participants self-identified as Black or African-American (\( n = 30, 30\% \)), Asian (\( n = 3, 3\% \)), White (\( n = 49, 49\% \)), American Indian or Alaska Native (\( n = 2, 2\% \)), Hispanic/Latinx (\( n = 5, 5\% \)), and mixed race (\( n = 11, 11\% \)). Table 1 presents demographic and other study variables by group.

### 2.2. Procedures

The parent study included a baseline study visit and three follow-up time points (4, 8, and 12-months, 75.7–85.7% retention). At baseline, adolescents and parents completed clinical interviews and self-report questionnaires described below. On a diagnostic structured clinical interview at baseline, 70.3% of participants from the whole MRI study sample met criteria for at least one disorder and 34.8% of participants met criteria for an internalizing disorder diagnosis. The MRI scan visit involved a high resolution T1 weighted scan and other functional MRI scans that are not the focus of the present manuscript. On average, the MRI scan visit was completed 5.5 months after the baseline study visit (\( M = 168.35 \) days, \( SD = 230.67 \) days).

### 2.3. Image acquisition and processing

Scanning was performed on a 3.0-T Siemens Prisma Scanner, using a 32-channel head coil.1 We followed standard pediatric scanning acquisition parameters. T1-weighted multiecho MPRAGE volumes (anatomical scans) were acquired (repetition time = 2530 msec, echo time = 1.670–7.25 msec, flip angle = 7°, field of view = 192 × 192 mm, 176 slices, in-plane voxel size = 1 mm). T1-weighted images were analyzed with the FreeSurfer image analysis suite (version 6.0) which performs automated cortical reconstruction and segmentation of the brain to estimate cortical thickness and surface area (Fischl et al., 2002, 2004). The automated segmentation and reconstruction results were inspected for all participants. Where necessary, manual adjustments were made to optimize accurate placement of gray/white and gray/cerebrospinal fluid borders (overseen by KP). Each brain was rerun through recon-all following edits, inspected, and edited again if indicated. After reconstruction, the cortex was parcellated based on the structure of gyr and sulci using the Desikan-Killiany atlas (Desikan et al., 2006). FreeSurfer has demonstrated good test-retest reliability across scanner manufacturers and field strengths (Han et al., 2006) and has been used in prior samples of children (e.g. Luby et al., 2016; Mahone et al., 2011).

### 2.4. Measures

#### 2.4.1. Self-injurious thoughts and behaviors

Trained research assistants administered the Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock et al., 2007), a structured clinical interview assessing history of self-injurious thoughts and behaviors, at baseline and follow-ups. The present analyses focused on NSSI presence (1) or absence (0) with the question “Have you ever purposefully hurt yourself without wanting to die?”. History of NSSI prior to baseline was assessed at the baseline visit. At each follow-up assessment, participants reported any NSSI occurring since the last assessment time point. Participants were considered to have a lifetime history of NSSI if they reported engaging in NSSI either prior to baseline or within any follow-up assessment time point. The SITBI demonstrates strong interrater and test-retest reliability (Nock et al., 2007).

#### 2.4.2. Depressive symptoms

Depressive symptoms at baseline were measured using the Mood and Feelings Questionnaire (MFQ; Costello and Angold, 1988), a 33-item self-report inventory that measures depressive moods and behaviors over the past two weeks. Missing items on the MFQ were mean imputed, if 80% or more of items had valid responses. We excluded four items referring to suicidal ideation to eliminate confounds between suicidal and non-suicidal self-injurious thoughts and the remaining 29 items were summed with higher scores indicating higher levels of depressive symptoms. The MFQ is a reliable and valid measure of depressive symptoms among children and adolescents (Wood et al., 1995; Burleson Daviss et al., 2006) and demonstrated high internal consistency in the parent study sample (Cronbach’s α = 0.93).

#### 2.4.3. Medication usage

At the MRI scan visit, information about medication usage was obtained from the accompanying guardian. Fifty-five youth (55%) in the study sample endorsed medication usage (e.g., psychiatric, allergy) which is included as a covariate in the final model. Specifically, 44% of the study sample endorsed psychiatric medication usage and 24% of the sample endorsed allergy medication usage.

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1 Two participants used a 20-channel head coil due to head size (see supplement).
2.5. Data analysis plan

Descriptive statistics were computed in SPSS Version 27. We examined group differences on main study variables using independent-samples t-tests and chi-square differences tests using an alpha threshold value of 0.05. In the subsample used in these analyses, 24 participants (24%) missed one or more follow-up assessments. If participants did not complete a follow-up assessment, we conservatively estimated no NSSI engagement occurred in the months prior to that particular follow-up assessment.

To test study hypotheses, we conducted general linear models (GLM) using the whole-brain vertex-wise analysis tool in FreeSurfer to examine associations between NSSI, age, cortical surface area, and thickness. The data were smoothed using a 10 mm full-width half-maximum Gaussian kernel prior to statistical analysis. The Different-Offset, Different-Slope (DODS) model option in FreeSurfer was used for the GLM analyses (Fischl and Dale, 2000). To reduce type 1 error, results from each GLM were cluster-threshold corrected at p < 0.05 and then an additional cluster-level correction based on two-tailed Monte Carlo simulation at p < 0.05 ( Hagler et al., 2006). Results were visualized by overlaying significant clusters on an inflated cortical surface using FreeSurfer.

First, we examined the effect of exact age on cortical thickness or cortical surface area controlling for lifetime history of NSSI. Second, we investigated whether a lifetime history of NSSI (vs. no lifetime history of NSSI) was associated with differences in cortical thickness or cortical surface area controlling for exact age at the MRI scan visit. Finally, we examined interactions between NSSI history and age predicting cortical thickness or cortical surface area. Whole-brain models covaried for depressive symptoms and medication use.2

To probe significant interactions between age and NSSI history, we conducted simple slopes analyses (see Supplement for more details).

3. Results

3.1. Descriptive analyses

Forty girls (40%) reported a history of NSSI at baseline. Additionally, 10 girls reported NSSI at some point in the follow-up (and did not report NSSI at the baseline assessment). In total, 50 girls (50%) reported lifetime NSSI at some point during the study observation period. Table 1 presents results from univariate analyses. Youth in the NSSI group were older (M_age = 13.83 years, SD = 1.66) as compared to those in the non-NSSI group, (M_age = 12.96 years, SD = 1.44; t(98) = 2.78, p < 0.01, d = 0.56); additionally, depressive symptoms were higher in the NSSI group (M = 19.23, SD = 12.72) as compared to non-NSSI group (M = 9.39, SD = 6.96; t(98) = 4.80, p < 0.001, d = 0.96). We also found a significant association between medication usage and NSSI history ( χ²(1) = 6.83, p < 0.01).

3.2. Whole brain models

3.2.1. Cortical thickness

Consistent with hypotheses, whole-brain vertex-wise analyses revealed that age was associated with less cortical thickness in the left and right prefrontal and temporal cortex, controlling for the effect of NSSI history, depressive symptoms, and medication usage (Table 2, Fig. 1). Whole-brain vertex-wise analyses controlling for age, depressive symptoms, and medication usage did not reveal any associations between NSSI group membership and cortical thickness. In addition, whole-brain vertex-wise analyses indicated that there was no significant interaction between age and NSSI history predicting cortical thickness.

3.2.2. Cortical surface area

Results of whole-brain vertex-wise analyses indicate that age was associated with less cortical surface area in the left and right prefrontal and parietal cortex, controlling for the effect of NSSI history, depressive symptoms, and medication usage (Table 3, Fig. 2).

3.2.3. Cortical surface area and NSSI history

Consistent with hypotheses, whole-brain vertex-wise analyses revealed that NSSI history was associated with less cortical surface area in left inferior parietal cortex and the left insula, controlling for the effect of age, depressive symptoms, and medication usage (Table 4, Fig. 3). In addition, there was a significant interaction between age and NSSI history predicting cortical surface area in the left inferior parietal cortex and left precentral cortex (Table 5, Fig. 4). Simple slopes analyses revealed that among adolescents without NSSI history, older age predicted less cortical surface area in the left inferior parietal cortex (b = -0.03, p < 0.001) and left precentral cortex (b = -0.02, p < 0.001) as expected with the trajectory of typical adolescent neurodevelopment. Contrary to hypotheses, among adolescents with NSSI history, older age predicted more surface area in the left inferior parietal cortex (b = 0.01, p = 0.04) and was not associated with surface area in the left precentral cortex (b = 0.004, p = 0.37; Table 6, Figs. 5 and 6).

4. Discussion

The overarching aim of this study was to examine whether NSSI history in adolescents was associated with differences in cortical surface area and thickness, and to explore how NSSI history may be associated with age-related changes in the brain. We replicated previous results in representative samples (LeWinn et al., 2017; Ramzahan et al., 2011; Tanne et al., 2017; Wierenga et al., 2014), showing that increased age was associated with decreased cortical surface area and thickness broadly in prefrontal and parietal cortex. Furthermore, consistent with previous work showing reductions in cortical volume in adolescents with NSSI history (Ando et al., 2018; Beauchaine et al., 2019), we found less surface area in the left insula and left inferior parietal cortex in adolescents with NSSI history compared to adolescents with no NSSI history.

The insular cortex is involved in the integration of emotional and cognitive information during decision making (Menon and Uddin, 2010). Decreased activation of the insula is associated with risky decision-making during adolescence (Eshel et al., 2007) and it is theorized that the ongoing development of this neural structure may bias adolescents towards affectively driven actions and decisions (Smith et al., 2014). Engagement in health-risk behaviors, such as NSSI, could be influenced by insular dysfunction during adolescence. Moreover, the left insular cortex is involved in socio-emotional processing including emotion recognition, empathy, and social cognition (Fan et al., 2011; Uddin et al., 2017), and the insula is substantially implicated in emotion regulation (Goldin et al., 2008; Grecucci et al., 2013). Specifically,

### Table 2

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Cluster size</th>
<th>Z-value of cluster</th>
<th>Peak MNI coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mm²)</td>
<td>x y z</td>
<td></td>
</tr>
<tr>
<td>Left superior frontal</td>
<td>23,568.27</td>
<td>-4.92</td>
<td>-12.2 -9.0 46.7</td>
</tr>
<tr>
<td>Left lingual</td>
<td>1929.01</td>
<td>-3.37</td>
<td>-13.1 -80.2 -6.4</td>
</tr>
<tr>
<td>Left inferior temporal</td>
<td>1791.81</td>
<td>-2.46</td>
<td>-41.7 -55.5 -8.2</td>
</tr>
<tr>
<td>Right isthmuscingulate</td>
<td>12,664.89</td>
<td>-7.08</td>
<td>-4.6 -46.4 28.4</td>
</tr>
<tr>
<td>Right posterior cingulate</td>
<td>6090.83</td>
<td>-4.71</td>
<td>5.3 -8.5 39.6</td>
</tr>
<tr>
<td>Right caudal middle frontal</td>
<td>2720.65</td>
<td>-4.91</td>
<td>33.2 13.9 26.7</td>
</tr>
<tr>
<td>Right supramarginal</td>
<td>1667.08</td>
<td>-3.50</td>
<td>44.6 -33.8 26.3</td>
</tr>
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</table>

mm² = millimeters squared. MNI = Montreal Neurological Institute. Significant clusters are shown at the p < 0.05 level.
Goldin et al. (2008) found greater insula activation was associated with expressive suppression, which can be defined as attempts to hide, or reduce, emotional expression (Gross and Levenson, 1993). Expressive suppression is an inefficient form of emotion regulation, and prior research has shown that expressive suppression may play a role in the onset and maintenance of NSSI in adolescents (Hasking et al., 2010; Andrews et al., 2013). It may be that attempts to suppress or hide away emotions (expressive suppression) represent a form of avoidance, or escape from, unwanted emotional experiences. Indeed, avoidance or escape from aversive emotional experiences has been posited as a reinforcing function of NSSI (Chapman et al., 2006; Haywood et al., 2023). Our results suggest atypical development of neural regions involved in emotional processing and regulation in adolescents with a history of NSSI.

The main effect of NSSI history predicting cortical surface area in the left inferior parietal cortex was qualified by a significant interaction with age. Contrary to hypotheses, age was associated with more cortical surface area in the left inferior parietal cortex and was not associated with surface area in the left precentral cortex among adolescents with NSSI history. Among adolescents without NSSI history, a more typical pattern was observed whereby age was associated with reduced cortical surface area in the left inferior parietal cortex and left precentral cortex. Although preliminary, these results suggest NSSI history is associated with a deviation from typical neurodevelopment during adolescence that has not been observed previously.

The left precentral cortex contains the primary and supplementary motor areas that are responsible for execution of voluntary motion (Porro et al., 1996). In addition to involvement in motor function, the left precentral cortex may aid other cognitive abilities such as response inhibition (Bush et al., 1998; Carter et al., 1997). Throughout adolescence, cognitive and executive function typically becomes refined, both behaviorally and neurally (Casey et al., 2005; Constantinidis and Luna, 2019; Vijayakumar et al., 2014). However, it may be the case that the development of these processes is altered in adolescents with NSSI history. In fact, prior research reveals that individuals with a history of NSSI show impaired response inhibition in the context of negative emotional stimuli (Allen and Hooley, 2015, 2019). Our results are consistent with these findings and may suggest that NSSI history is associated with deviations in typical neurodevelopment in regions responsible for motor and cognitive function. Given the cross-sectional nature of our findings, we are unable to determine whether altered neurodevelopment in the precentral cortex preceded or followed the development of NSSI. This represents an important area for future research.

We also observed a significant interaction between NSSI and age predicting more cortical surface area in the left inferior parietal cortex. The left inferior parietal cortex is typically associated with integrating input from sensory, emotion, and motor systems and acts as a convergence zone for conceptual functions including social cognition and language (Binder and Desai, 2011; Saalasti et al., 2019). Additionally, the left inferior parietal cortex is implicated in semantic processing...
(Saalasti et al., 2019), defined as an ability to access knowledge in reasoning and problem solving (Binder et al., 2009). Semantic processing is a component of cognitive reappraisal, which is a commonly employed emotion regulation strategy (Ochsner and Gross, 2005; Ochsner et al., 2012), and emotion regulation difficulties are viewed as a core component of engagement in and maintenance of NSSI behavior (Adrian et al., 2011; Gratz and Roemer, 2008). The present data add to the body of research suggesting that there may be alterations in neural regions subserving emotion regulation, thereby conferring risk for NSSI.

This will need to be confirmed using larger, longitudinal research designs in conjunction with behavioral measures or tasks assessing emotion regulation.

Interestingly, our findings also indicated that cortical thickness did not differ in adolescents with NSSI history compared to adolescents without NSSI history and NSSI did not moderate the association between age and cortical thickness. Prior research has suggested that cortical surface area and thickness are distinct structural components and have unique cellular and genetic origins (Geschwind and Rakic, 2013; Kremen et al., 2013; Panizzon et al., 2009). Furthermore, cortical surface

### Table 4

<table>
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<tr>
<th>Brain area</th>
<th>Cluster size (mm²)</th>
<th>Z-value of cluster</th>
<th>Peak MNI coordinate</th>
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<tbody>
<tr>
<td>Left inferior parietal</td>
<td>5403.22</td>
<td>-2.89</td>
<td>-34.9  -87.8  13.1</td>
</tr>
<tr>
<td>Left insula</td>
<td>4293.23</td>
<td>-2.85</td>
<td>-35.2  5.0    14.0</td>
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NSSI = Nonsuicidal self-injury. mm² = millimeters squared. MNI = Montreal Neurological Institute. Significant clusters are shown at the p < 0.05 level.

### Table 5

<table>
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<tr>
<th>Brain area</th>
<th>Cluster size (mm²)</th>
<th>Z-value of cluster</th>
<th>Peak MNI coordinate</th>
</tr>
</thead>
<tbody>
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<td>Left inferior parietal</td>
<td>5763.63</td>
<td>3.31</td>
<td>-35.4  -87.6  13.3</td>
</tr>
<tr>
<td>Left precentral</td>
<td>3616.71</td>
<td>2.93</td>
<td>-53.0  -2.7    7.8</td>
</tr>
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</table>

NSSI = Nonsuicidal self-injury. mm² = millimeters squared. MNI = Montreal Neurological Institute. Significant clusters are shown at the p < 0.05 level.
area and thickness develop and mature independent of one another (Raznahan et al., 2011; Wierenga et al., 2014). Results from our study suggests that alterations in surface area, rather than cortical thickness, may account for the volumetric differences that have been previously associated with NSSI history in adolescence (Ando et al., 2018; Beaufort et al., 2019). The specificity of these results with regards to cortical measurement warrant replication and further longitudinal research should examine the neuroanatomical mechanisms that may account for this difference.

Furthermore, imaging studies of infants and adolescents demonstrate that cortical thickness expansion and growth is complete by age 2, while surface area expansion continues into childhood and early adolescence (Gilmore et al., 2018; Lyall et al., 2015). It is possible that variability in environmental experiences in childhood and adolescence could impact cortical surface area development, due to the ongoing refinement and plasticity of this brain measure (Mackes et al., 2020). Additionally, alterations in overall cortical surface area and the trajectory of development in cortical surface area associated with NSSI in adolescence may reflect underlying vulnerabilities with which individuals enter adolescence. Variation in cortical surface area and trajectory of development of cortical surface area have been associated with stressful early life experiences (Gehred et al., 2021; Hodel et al., 2015; Machlin et al., 2019; Opel et al., 2019) which have been linked with NSSI (Cassels et al., 2018; Zetterqvist et al., 2014), and could be one potential source of these vulnerabilities. It will be important for future research to further examine these potential transactional relations between cortical structure, NSSI, and early life stress exposure.

Our results are preliminary and should be interpreted within the context of several limitations. First, because the study was conducted in the context of a larger parent study, our results may not generalize to larger samples of adolescents and these results need to be reproduced and elaborated on in samples including boys. Second, the present

<table>
<thead>
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<th>Variable</th>
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<tbody>
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<td>Left inferior parietal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSSI absence</td>
<td>-0.03</td>
<td>.01</td>
<td>.001</td>
</tr>
<tr>
<td>NSSI presence</td>
<td>.01</td>
<td>.01</td>
<td>.04</td>
</tr>
<tr>
<td>Left precentral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSSI absence</td>
<td>-0.02</td>
<td>.01</td>
<td>.00</td>
</tr>
<tr>
<td>NSSI presence</td>
<td>.004</td>
<td>.01</td>
<td>.37</td>
</tr>
</tbody>
</table>

NSSI = Nonsuicidal self-injury. SE = standard error.

Fig. 4. Note. Nonsuicidal self-injury history and age are associated with larger cortical surface areas in the left inferior parietal cortex and left precentral cortex. Results are cluster-corrected with a cluster-forming threshold of \( p < 0.05 \) and a clusterwise significance of \( p < 0.05 \), adjusted for 2 hemispheres.

Fig. 5. Note. Nonsuicidal self-injury (NSSI) history moderates the relation between age and left inferior parietal cortical surface area. Early and late adolescence were defined as -1 SD and +1 SD, respectively (\( M_{\text{age}} = 13.40, SD = 1.61 \)).
analyses are cross-sectional, which limits inferences that can be made about the timing of NSSI relative to the development of structural deviations in the brain. Because our hypotheses are developmental in nature, future research that can parse timing of cortical development and emergence of NSSI would greatly strengthen our understanding of these relations. Third, our measurement of observed lifetime history of NSSI possibly was overly conservative due to censoring the minimal amount of missing data during the observation period. Fourth, although consistent with past approaches, our choice to age-match participants further limits our ability to draw strong conclusions about the developmental trajectory of brain development and NSSI in our sample. A larger age range that is followed longitudinally may allow for better detection of age-related structural alterations spanning adolescence. Finally, it should be noted that the cluster-forming threshold ($p < 0.05$) used in analyses may be susceptible to false-positive rates (Greve and Fischl, 2018) and future research with larger samples should ensure adequate power to conduct analyses with more stringent thresholds.

Despite these limitations, this preliminary study represents an important first step to better understand the relationship between neural development and NSSI in adolescence. Our results suggest differences in the development of cortical surface area in adolescents with NSSI history versus those without NSSI history, specifically in regions that may be involved in higher-order cognition, integration of sensory and affective information, and regulatory behaviors. This study thus lays the foundation for future research into neural risk factors associated with NSSI history in adolescence.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Data and preparation of this manuscript was supported by grants from the National Institutes of Mental Health (K01MH116325, R01MH107479, R01MH107479-51, R01MH115004).

Supplementary materials


References


Fig. 6. Note. Nonsuicidal self-injury (NSSI) history moderates the relation between age and left precentral cortical surface area. Early and late adolescence were defined as -1 SD and +1 SD, respectively ($M_{age} = 13.40, SD = 1.61$).
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