

Reduced dorsal striatal gray matter volume predicts implicit suicidal ideation in adolescents

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Abstract

Suicidal ideation (SI), a potent risk factor for suicide attempts, increases in adolescence. While alterations in dopaminergic functioning have been implicated in suicidal acts—particularly in adults—we do not know whether morphological alterations in dopamine-rich regions of the brain, such as the striatum, are vulnerability factors for the emergence of SI in adolescents. At baseline, a community sample of 152 adolescents (89 female; mean age: 11.41 ± 1.01 years) completed a magnetic resonance imaging (MRI) scan that was used to estimate gray matter volumes (GMVs) of three striatal structures: caudate, nucleus accumbens and putamen. At a 24 month follow-up session, participants completed a self-report measure of SI frequency [Suicidal Ideation Questionnaire (SIQ)] and the death version of the Implicit Association Test (IAT). Robust linear regression models were conducted to predict SIQ and IAT scores from striatal GMV. Bilateral putamen and left caudate GMV significantly predicted IAT scores (all P s < 0.03). No other associations were significant (all P s > 0.05). Our finding of reduced dorsal striatal GMV predicting implicit SI may indicate that downstream dopaminergic dysfunction is implicated in the development of overt suicidal behaviors. Self-reported SI was not associated with striatal GMV, suggesting that biological correlates of suicide risk may correlate specifically with objective measurements of SI in adolescents.

Key words: putamen; caudate; implicit association test; suicidal ideation; adolescents

Introduction

Suicide is the second leading cause of death among adolescents in the USA (Centers for Disease Control and Prevention); in fact, recent estimates indicate that suicidal behaviors [i.e. suicidal ideation (SI) and attempts inclusive] in this group are rising (Bridge *et al.*, 2015a). Because two-thirds of suicide victims die in their first attempt, it is critical that we identify risk factors prior to any attempt in order to improve the effectiveness of pre-

vention programs (Gibb *et al.*, 2005; Hawton and van Heeringen, 2009). Thus, identifying risk factors for SI is a particularly important task for clinicians and researchers, given that the prevalence of SI increases from <1% in childhood to almost 17% in adolescence, with a precipitous rise beginning around age 12 (Nock *et al.*, 2013). Despite the increasing prevalence of SI in adolescents and evidence that SI may be an important precursor

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to suicide attempts in adolescents (Reinherz et al., 2006; Svetlicic and De Leo, 2012; Nock et al., 2013), few investigators have examined risk factors underlying vulnerability to SI in adolescents prior to the first suicide attempt (Klonsky and May, 2013; Klonsky et al., 2016).

There are several challenges in measuring SI, especially in adolescents. In particular, researchers have relied in large part on explicit (i.e. self-report) measures, which can be problematic for a number of reasons. First, conscious suicidal thoughts are often transient and, consequently, are not likely to be captured when participants are assessed at a single time point in a laboratory setting (Glenn and Nock, 2014; Kleiman et al., 2017). Second, individuals may purposely conceal suicidal thoughts in order to avoid unwanted intervention, such as parental notification or involuntary hospitalization (Busch et al., 2003; Glenn and Nock, 2014). Third, individuals—and, in particular, adolescents—may not have the self-awareness to report accurately on the cognitive processes underlying their behavior (Nock et al., 2010; Weil et al., 2013). To address these limitations, researchers examining risk for suicidal behaviors have begun to use cognitive tasks involving implicit measurements that do not rely on self-report (Cha et al., 2010; Barnes et al., 2016; Harrison et al., 2018). One such task is a version of the Implicit Association Test (IAT) that measures response latencies to speeded judgments of pairs of death-related and self-related words (Nock et al., 2010; Glenn et al., 2017). Several studies have shown that individuals with a history of suicide attempts exhibit pronounced implicit self-identification with death/suicide (Nock et al., 2010; Barnes et al., 2016). In samples of adolescents and young adults recruited from both clinics and the community, scores on the IAT have been found to be associated with suicide risk (i.e. subsequent suicide attempts) above and beyond known risk indicators, including history of prior suicide attempts, which is among the strongest risk factor for attempt (Nock et al., 2010; Harrison et al., 2014). Thus, IAT scores may index vulnerability to engage in subsequent suicidal behaviors. To date, no studies have examined neurobiological predictors of IAT performance; doing so may yield important insights about neural mechanisms that contribute to the emergence of SI. Indeed, more generally, researchers have not yet examined neurobiological risk markers of SI emergence; such studies are needed in order to generate neuroscience-based models of adolescent suicidality, to identify potential new targets for treatment and to guide the development of effective prevention strategies (Cox Lippard et al., 2014).

In this context, measures of brain structure—which have relatively high test-retest reliability and for which researchers have developed widely accepted pre-processing protocols—can be used to begin to elucidate neurobiological vulnerability to SI in adolescents. For example in a recent multi-site study, Gifuni and colleagues compared subcortical gray matter volumes (GMVs) of 73 suicide attempters with a history of both mood disorders and suicidal acts, 89 psychiatric controls with a history of mood disorders but no history of suicidal acts and 91 healthy controls with no history of disorder or suicidal behaviors. Although there were no differences among the three groups in subcortical GMV, the lethality of the last suicidal act was significantly associated with reduced bilateral nucleus accumbens (NAcc) GMV within the group of suicide attempters (Gifuni et al., 2016). In a meta-analysis comparing adolescents and adults with a history of suicidal behavior and a psychiatric disorder to psychiatric controls across six structural imaging studies, van Heeringen and colleagues found that individuals with a history of suicidal behavior exhibited reduced caudate GMV (van Heeringen et al.,

2014). Because the NAcc and caudate contain a relatively high density of dopamine receptors, these findings are consistent with postmortem studies that have reported dopaminergic alterations in the striatum (Oquendo et al., 2014). Specifically, studies have shown reduced dopamine-related metabolites in the NAcc, caudate and putamen but not in the amygdala or hippocampus (Bowden et al., 1997a) as well as reduced dopamine in response to a dopaminergic agonist in depressed patients who later died by suicide (Pitchot et al., 2001). Nevertheless, there have been very few neuroimaging studies of suicide risk in the context of SI (Cox Lippard et al., 2014).

It is also important to note that of the few neuroimaging studies on SI, most have been small case-control investigations. Further, little research has been conducted examining neurobiological correlates of SI in adolescents; indeed, there are no studies of neurobiological predictors of IAT performance (Cox Lippard et al., 2014). When attempting to identify neurobiological markers associated with suicidality, even a large meta-analysis testing whether subcortical GMV was associated with history of suicidal attempts in patients with Major Depressive Disorder (MDD), one of the strongest psychiatric risk factors for suicide, was limited by the clinical heterogeneity of patients—including medication exposure and severity and duration of illness (Renteria et al., 2017). Therefore, a more promising approach may be to examine SI prospectively in a sample with as few complex clinical confounds as possible.

In the present study we examined prospectively whether striatal GMV predicts the early emergence of SI in a community sample of 152 young adolescents who span the age range during which epidemiological studies have indicated dramatic increases in rates of SI (Nock et al., 2013). Importantly, the majority of these adolescents have not yet exhibited clinical symptoms and none have engaged in suicide attempts; therefore, we can identify neurobiological risk factors for SI that are not confounded by clinical conditions and that are measurable before any onset of any suicide attempts. In addition, we took a multi-method approach to measuring risk for SI by assessing not only explicit self-report symptoms of SI but also implicit cognitive vulnerability using the IAT. Given the limited literature in this area, we hypothesized broadly that reduced GMV regions centrally involved in dopaminergic function—namely the caudate, NAcc and putamen—would be associated with higher scores on both the explicit and implicit measures of SI.

Methods

Participants

Participants were children between the ages of 9 and 13 recruited from the San Francisco Bay Area community for a longitudinal study of neurodevelopment through adolescence (grant number: R37MH101495). For the present study, participants were included in final analyses if they provided usable structural magnetic resonance imaging (MRI) scans at the baseline session (see 'Segmentation of caudate, NAcc and putamen' below and in the Supplementary data for more details) and if they completed at least one of the measures of SI at follow-up. Thus, we included data from 152 adolescents (89 female; mean age: 11.44 ± 1.01 years at baseline) who successfully completed the MRI scan; at follow-up, 150 participants completed the Suicidal Ideation Questionnaire (SIQ; see below) and 118 participants successfully completed the IAT. At baseline, inclusion criteria in

addition to age were that the children be proficient in English. Exclusion criteria were any contraindications for MRI (e.g. metal implants, braces, claustrophobia), a history of major neurological or medical illness and severe learning disabilities that would make it difficult for participants to comprehend and complete the study procedures. Females who reported having started menses were excluded, and boys were matched to girls on pubertal stage using self-report Tanner staging (Morris and Udry, 1980). Participants were compensated for their participation. The study was approved by the Stanford University Institutional Review Board; participants and their parent/legal guardian gave assent and informed consent, respectively.

Clinical assessments

At the baseline and follow-up sessions, participants and a parent/legal guardian visited the laboratory, provided demographic and health history information and completed the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (Kaufman et al., 2000). The K-SADS-PL was used to determine current and past diagnoses for several Axis I disorders, including depressive and anxiety disorders. To assess self-report severity of depression and to use these values as covariates in our analyses, participants completed the 10-item Children's Depression Inventory (CDI; Kovacs, 1992). Participants completed an MRI session at baseline after their initial interview session (mean interval: 4.19 ± 3.99 weeks) at which T1-weighted anatomical scans were acquired.

Baseline MRI scans

All MRI scans were acquired at the Center for Cognitive and Neurobiological Imaging at Stanford University using a 3 T Discovery MR750 (GE Medical Systems, Milwaukee, WI) equipped with a 32-channel head coil (Nova Medical, Wilmington, MA). All participants underwent a high-resolution T1-weighted anatomical scan acquired using a spoiled gradient (SPGR) sequence (TR/TE/TI = 6.24/2.34/450 ms; flip angle = 12° ; 190 sagittal slices; 0.9 mm isotropic voxels; total scan time: 5:15); these images were used for subcortical GMV segmentation.

Segmentation of caudate, NAcc and putamen

Estimates of total intracranial volume (ICV), which we used as a covariate in our analyses, and GMV of the caudate, NAcc, and putamen, were obtained using the FreeSurfer software suite (version 5.3; available at: <http://surfer.nmr.mgh.harvard.edu/>) for automated segmentation of subcortical GMV (Fischl, 2002). This segmentation approach is widely used, is robust against anatomic variability and has comparable accuracy to manual labeling techniques (Fischl et al., 2002). All segmentations were visually inspected for processing and segmentation errors (see [Supplementary data](#) and [Supplementary Table S1](#) for more details). See [Figure 1](#) for segmentations from a representative participant.

Follow-up assessment

A follow-up assessment was conducted ~24 months after the baseline assessment (mean interval: 22.53 ± 5.66 months), at which participants completed the same interviews and measures that were administered at baseline. In addition, as we

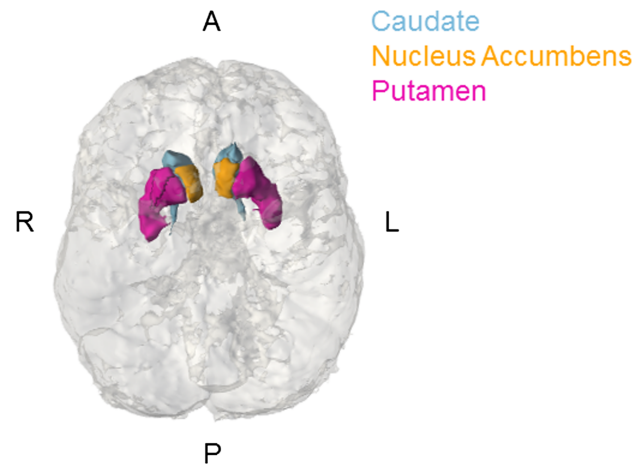


Fig. 1. Gray matter segmentations of the striatum. All GMV and total ICV estimates were extracted in individual brain space. Structures visualized here are from a representative subject, displayed from an inferior perspective. A = anterior; P = posterior; R = right; L = left.

describe in more detail below, at follow-up, participants also completed suicide-related measures: the IAT and the SIQ.

IAT

The IAT is a computer-based categorization task that assesses individuals' automatic associations; IATs have been found to have good reliability (Cunningham et al., 2001), construct validity (Nosek et al., 2005) and predictive validity (Greenwald et al., 2009). We programmed a MATLAB (the Mathworks, Natick, MA) version of the death IAT using Psychtoolbox (<http://psychtoolbox.org/>); stimulus presentation and scoring code available on Github: <http://www.github.com/tiffanycheingho> based on previous work (Nock et al., 2010). The IAT measures response times (RT) when categorizing words associated with each of the following four categories: *death*, *life*, *me* and *not me* (see [Supplementary data](#) for more details). Response latencies to classify words in the *death or me* and *life or me* categories were recorded in milliseconds and analyzed using the standard IAT algorithm (Greenwald et al., 2003) to calculate a net difference (d-score). Here, positive scores indicate that individuals responded faster when *death* and *me* are paired (and, presumably, have a stronger implicit association with the self) compared to when *life* and *me* are paired, and negative scores indicate that individuals responded faster when *life* and *me* are paired compared to when *death* and *me* are paired. Participants with more than 18 test trials deemed guesses (RT < 30 ms) or lapses in attention (RT > 10 s) were excluded from analyses including the IAT. Based on these criteria, 3 of the participants who completed the IAT were excluded, leaving 118 participants included in all analyses involving the IAT.

SIQ-junior high

To measure explicit SI, we used the junior high version of the SIQ, a 15-item self-report measure that assesses the frequency of a range of SI (e.g. 'I wished that I had never been born' to 'I thought about killing myself.'; Reynolds, 1987). The SIQ is designed for use with adolescents ages 12 and older and, thus, validated in our sample age range; it has high internal consistency, test-retest

reliability and predictive validity (Reynolds, 1987). Two of the 152 participants in our study did not complete this measure (but did complete the IAT), leaving 150 participants included in all analyses involving the SIQ.

Statistical analyses

Using 'rlm' from the MASS package in R (version 3.3.2), we conducted robust linear regressions with M-estimation Huber weighting, which reduces the influence of outliers by weighing observations according to their residuals, to predict suicide-related outcomes (IAT d-scores, SIQ scores) from baseline measures of GMV (caudate, NAcc, putamen; left and right separately). To evaluate significance, we used the 'pt' function in R to compute the *P*-value associated with the given *t*-statistic and degrees of freedom for each model. Given the non-normal distribution of SIQ scores, we used Spearman rank correlations (ρ) to estimate associations between continuous variables and SIQ scores and Pearson's correlation (*r*) to estimate associations between continuous variables and IAT d-scores to determine which covariates to include in our final statistical models. We decided to include age at both assessments as covariates in our model to account not only for variation in brain anatomy but also to model duration length between baseline and follow-up. Importantly, total ICV was included as a covariate in our analyses because of our focus on subcortical GMV as primary predictors. Whereas age at scan was not significantly associated with total ICV ($B = 21167 \pm 12940$; $t_{150} = 1.636$, $P = 0.104$), there were, unsurprisingly, significant sex differences in total ICV, such that females had significantly smaller total ICV ($t_{150} = -3.223$, $P = 0.0016$). Thus, for consistency, we used the same covariates in all of robust linear regression models: age at baseline, age at follow-up, Tanner stage at baseline, CDI scores at baseline, CDI scores at follow-up and total ICV. As a supplemental analysis, we reran our models including sex as a binary factor.

Results

Demographics and clinical information

Demographic and clinical characteristics of the participants are presented in Table 1. Thirty-one participants met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for a current or lifetime Axis-I disorder at the baseline assessment, and 19 met DSM-IV criteria for a current (or since last visit) Axis-I disorder at the follow-up assessment (7 of these 19 participants were new onsets; the remaining 12 had received a diagnosis at T1). See the [Supplementary data](#) and [Supplementary Table S2](#) for more details.

Variables correlating with implicit and explicit measures of SI

A correlation matrix of our primary variables is presented in Table 2. Briefly, higher CDI scores at baseline and at follow-up were significantly associated with higher SIQ scores (both P s < 0.0001) but not with higher IAT d-scores (both P s > 0.7). While Tanner stage at baseline was not associated with SIQ scores ($\rho_{148} = -0.159$, $P = 0.052$), a more advanced Tanner stage at baseline was significantly associated with lower IAT d-scores ($r_{117} = -0.179$, $P = 0.024$). Tanner stage at follow-up was not significantly associated with either SIQ or IAT

d-scores (all P s > 0.1). Neither age at baseline nor at follow-up was associated with SIQ scores (all P s > 0.3) or IAT scores (all P s > 0.06). Finally, males and females did not differ in SIQ, IAT or CDI scores at baseline or follow-up (all P s > 0.1).

Caudate, NAcc, putamen volumes and implicit and explicit measures of SI

Reduced bilateral putamen GMV significantly predicted higher IAT d-scores (left: $B = -7.782 \times 10^{-5} \pm 2.980 \times 10^{-5}$, $t_{100} = 2.597$, $P = 0.011$; right: $B = -1.086 \times 10^{-4} \pm 3.218 \times 10^{-5}$, $t_{105} = -3.374$, $P = 0.001$). Reduced left caudate GMV also significantly predicted higher IAT d-scores ($B = -7.906 \times 10^{-5} \pm 3.794 \times 10^{-5}$, $t_{104} = 2.597$, $P = 0.039$). No other striatal GMVs were significantly associated with IAT d-scores (all P s > 0.1). None of the striatal GMV variables was significantly associated with SIQ scores (all P s > 0.1). Please see Figure 2 for more details. Please see the Supplementary data for results when including sex (coded as a binary factor) as a covariate.

Supplemental analyses examining effects of clinical diagnoses

As a supplemental analysis, we examined the effects of clinical diagnoses on our findings. When we compared the 38 participants who met criteria for a DSM diagnosis at either baseline or at follow-up with all other participants using Welch's *t*-tests, we found no significant differences in SIQ scores ($t_{44.97} = 1.602$, $P = 0.116$), in IAT d-scores ($t_{63.25} = 1.450$, $P = 0.152$) or in any of the striatal GMV measurements (all P s > 0.6). Similarly, including clinical diagnosis as a dummy-coded binary variable in our robust linear regression models did not change any of our results.

Supplemental analyses demonstrating specificity of effects in dorsal striatum

Prior works have demonstrated that the dopaminergic alterations associated with suicide completion were in the NAcc, caudate and putamen but not in the amygdala and hippocampus (Bowden et al., 1997a, b). As a supplemental analysis to demonstrate the specificity of our findings to the striatum, we used the robust linear regression models previously described above to examine whether amygdala and hippocampal GMV significantly predicted IAT d-scores and SIQ scores. All associations were non-significant (all P s > 0.1).

Discussion

In this study, we recruited 152 adolescents from the community and assessed GMV of three key dopaminergic structures potentially implicated in suicidality: caudate, NAcc and putamen. We tested whether GMV of these striatal regions predicted measures of SI assessed ~2 years later. Importantly, we used a multi-method approach to assess SI; in addition to an explicit measure assessed using self-report, we also assessed SI objectively using the IAT, a computerized test that has been shown to predict subsequent suicide attempts in adolescents above and beyond traditional risk factors for attempt (Nock et al., 2010; Barnes et al., 2016). We found that reduced bilateral putamen GMV

Table 1. Sample demographic and clinical characteristics for participants. All values are reported as mean (s.d.). Numbers in brackets [] indicate the number of participants who did not respond

	All (n = 152)	SIQ only (n = 150)	IAT only (n = 118)
SIQ score	5.99 (9.88)	5.99 (9.88)	6.31 (10.74)
IAT d-score	-0.097 (0.24)	-0.096 (0.24)	-0.097 (0.24)
CDI (baseline)	2.22 (2.55) [2]	2.17 (2.46) [2]	2.22 (2.54) [2]
CDI (follow-up)	2.49 (2.76) [1]	2.50 (2.77) [1]	2.45 (2.63)
Sex (M/F)	63/89	62/88	53/65
Age (baseline)	11.41 (1.01)	11.41 (1.00)	11.39 (1.06)
Age (follow-up)	13.42 (1.18)	13.29 (1.12)	13.63 (1.29)
Tanner (baseline)	2.07 (0.77)	2.08 (0.77)	2.04 (0.73)
Tanner (follow-up)	3.41 (0.93)	3.42 (0.94)	3.56 (0.94)
Medication (baseline)	5% [2]	4% [2]	4% [2]
Medication (follow-up)	5% [4]	5% [4]	5%
Handedness (% R dominant)	93% [2]	92% [2]	93% [2]
<u>Race/ethnicity</u>			
White/Caucasian	51%	51%	48%
African American	8%	8%	6%
Hispanic	7%	7%	7%
Asian	12%	12%	14%
Biracial	17%	17%	20%
Other	5%	5%	5%
<u>Family income</u>			
<\$5000	1%	1%	1%
\$5001-10 000	2%	2%	3%
\$10 001-15 000	1%	1%	1%
\$15 001-25 000	3%	4%	2%
\$25 001-35 000	2%	2%	3%
\$35 001-50 000	4%	4%	4%
\$50 001-75 000	10%	10%	10%
\$75 001-100 000	13%	13%	14%
\$100 001-150 000	26%	26%	25%
\$150 001+	33%	32%	34%
No response	5%	5%	3%
<u>Parental level of education</u>			
No GED/no high school diploma	1%	1%	1%
GED/high school diploma	1%	1%	2%
Some college	15%	15%	14%
2 year college degree	11%	11%	11%
4 year college degree	40%	40%	42%
Master's degree	26%	26%	28%
Professional degree	3%	3%	2%
Doctorate degree	2%	2%	0%
No response	1%	1%	2%

Table 2. Correlations between variables of interest and SIQ scores and IAT d-scores

	SIQ score	IAT d-score
SIQ score	-	-
IAT d-score	0.019	-
Age (baseline)	0.059	-0.131
Age (follow-up)	0.074	-0.163
Tanner (baseline)	0.159	-0.214*
Tanner (follow-up)	0.013	-0.081
CDI (baseline)	0.387**	-0.090
CDI (follow-up)	0.665**	-0.029

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

and reduced left caudate GMV significantly predicted stronger subsequent implicit self-associations with death on the IAT in adolescents. Interestingly, no subcortical GMV measures

examined in this study significantly predicted explicit self-report measures of SI. Together, these findings suggest a unique role of the dorsal striatum in representing SI risk and highlight the importance of using implicit methods to detect possible suicide-related cognitions and behaviors in adolescents.

Our findings implicate striatal systems, and in particular the dorsal striatum, as important for vulnerability to SI in adolescents. The putamen and caudate comprise the dorsal striatum, which has been demonstrated in both human and non-human primate research to be critical for reward-based reinforcement learning (O'Doherty, 2004; Haber and Knutson, 2010; Tricomi and Lempert, 2014; Knowlton and Patterson, 2016). Specifically, neurons in these structures code for signals related to reward probability (Haber and Knutson, 2010; Tricomi and Lempert, 2014); whereas the putamen may be involved more strongly in stimulus-action encoding and effortful signaling, the cau-

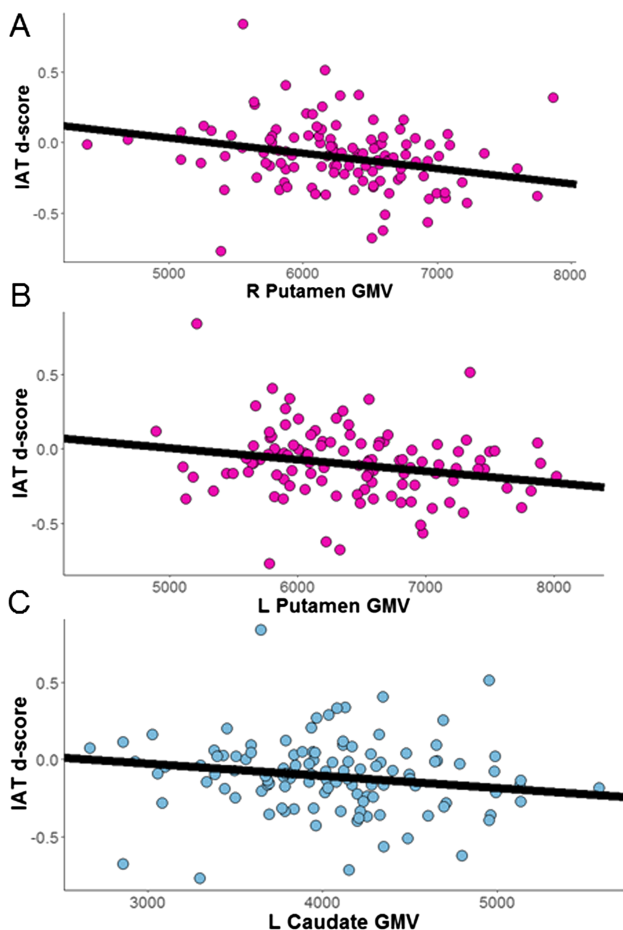


Fig. 2. Reduced GMV of the dorsal striatum predict IAT d-scores. Higher IAT d-scores at follow-up were significantly associated with reductions in GMV of the (A) right putamen, (B) left putamen and (C) left caudate. For visualization, all data points are raw values and all intercept and slopes are estimated from robust linear regression models that include age at baseline, age at follow-up, Tanner stage at baseline, CDI scores at baseline, CDI scores at follow-up and total ICV as covariates.

date may represent expectation violation and reward prediction errors (Haber and Knutson, 2010; Tricomi and Lempert, 2014; Arulpragasam et al., 2018). In contrast, the ventral striatum, composed primarily of the NAcc, appears to be sensitive to reward magnitude and salience (Haber and Knutson, 2010). Not surprisingly, alterations in both the dorsal and the ventral striatum have been associated with depression and suicidality (Quevedo et al., 2016). In contrast to research suggesting that alterations in the ventral striatum are indicative of risk for developing depression (Luking et al., 2016), some researchers have posited that alterations in the dorsal striatum are implicated in suicidality (Balcioglu and Kose, 2017); this is consistent with our findings that reduced GMV of the dorsal striatum predicts implicit SI above and beyond the effect of depressive symptoms. Given the complex role of the putamen and caudate in both reward processing and motor response generation, one possibility is that aberrations in the dorsal striatum increase suicide-related risk through altered reward processing and diminished hedonic capacity (i.e. anhedonia), which may be initially manifested as a cognitive vulnerability to developing SI and, eventually, explicit thoughts of SI. These aberrations in the dorsal striatum may also

increase risk for suicide through impulsive acts that underlie or lead to eventual suicide attempts (Zhang et al., 2014).

Supporting this model is evidence that altered structure and function in the putamen and caudate are associated with symptoms of anhedonia and poorer impulse control in both non-clinical and clinical samples (Martino et al., 2001; Dalley and Roiser, 2015; Der-Avakian and Markou, 2016). For example several researchers have found that anhedonia is in association with SI independently of depression symptoms (Winer et al., 2014, 2017; Auerbach et al., 2015; Ducasse et al., 2017). Recently, Auerbach and colleagues reported that reduced putamen GMV in female adolescents prospectively predicted severity of anhedonia 3 months later (Auerbach et al., 2017). Larger caudate GMV has also been shown to be positively correlated with delay discounting in a sample of psychiatrically healthy adults (Tschernegg et al., 2015). Further, smaller caudate GMV has been reported in suicide attempters (Vang et al., 2010) and alterations in frontostriatal circuitry, which support executive functioning and goal-directed behavior, have also been reported in depressive patients with suicidal behaviors (Zhang et al., 2014). In a study of late-life depression, Dombrovski and colleagues found that patients with a history of suicide attempt had smaller putamen GMV than did non-suicidal patients and healthy controls (Dombrovski et al., 2011). Interestingly, aberrations in serotonin metabolism or serotonin transporter binding in the putamen have also been found in suicide attempters (Meyer, 2012; Oquendo et al., 2014, 2016); given evidence of serotonergic regulation of dopamine neurotransmission and the complex interactions between these two neurotransmitter systems (Alex and Pehek, 2007; Hashemi et al., 2012), it will be important for future researchers to systematically explore these mechanisms and to establish the links between morphological alterations in the dorsal striatum and downstream dopaminergic (and serotonergic) dysfunction. Nevertheless, our results in light of these findings collectively highlight the possibility that morphological reductions in the dorsal striatum represent a neuroanatomical vulnerability to the development of SI, potentially through altered reward pathways and impaired impulse control.

In contrast to other studies of adolescents with psychiatric disorders in which IAT d-scores were strongly correlated with self-report measures of SI (Harrison et al., 2014; Glenn et al., 2017), in the present study these two measures were not significantly associated. Our sample of adolescents, however, is notably younger than the participants who have been studied in prior investigations of the IAT (Nock et al., 2010; Harrison et al., 2014; Barnes et al., 2016; Glenn et al., 2017); therefore, they may not have the emotional maturity or capacity for self-reflection to accurately and explicitly report their thoughts and feelings about death and suicide (Weil et al., 2013). Consistent with this view, we found that an earlier developmental stage at baseline, as assessed by self-report Tanner, was associated with larger IAT d-scores. As youth mature, their ability to reflect on concepts such as suicidality likely shifts toward more explicit communication. Indeed, whereas we found inverse associations between Tanner stage and IAT d-scores, we found positive associations between Tanner stage and SIQ scores. Alternatively, the association we found between Tanner stage and IAT d-scores could be related to the putative involvement of pubertal onset, tempo and timing in the subsequent development of psychiatric disorders (Ellis, 2004; Angold and Costello, 2006; Whittle et al., 2015); future studies are needed to investigate both of these possibilities more systematically. Finally, unlike the majority of previous investigations examining variants of the IAT in adolescents (Nock and Banaji, 2007; Cha et al., 2015; Glenn et al., 2017), our participants

were not recruited on the basis of clinical symptomatology or history of suicidal or non-suicidal self-injurious behaviors. In this regard, our study sample, in which there were minimal clinical symptoms and no history of suicide attempts, is ideally suited for identifying neurobiological risk factors before the onset of suicide attempts or other suicidal behaviors. Thus, our results critically highlight the need for multi-methodological assessments of SI in youth and, in particular, the use of methods that do not rely on self-report.

Limitations and future directions

This is the first study to examine neuroanatomical predictors of the IAT in an adolescent sample. Nevertheless, it is critical to note that no participants attempted suicide, which limited our ability to confidently assess suicide risk; thus, the results of the present study are likely capturing neural vulnerabilities indexing SI risk. Predicting risk factors well before an attempt occurs by focusing on predictors of the emergence of ideation is nonetheless an extremely important endeavor, particularly in youth. We are continuing to follow this sample for 5 more years and will be extremely well positioned to explore predictors of suicide attempt and mechanisms underlying the transition from ideation to attempts. Another limitation in our study design is that we did not have baseline assessments of SIQ or IAT and were thus unable to track changes in these constructs over time; we are continuing to monitor suicide-related outcomes in this sample to determine whether the implicit self-associations assessed at this single time point index risk for SI, or even for suicide attempts, in the future. Given the difficulty of identifying robust risk factors of suicidality, conducting longitudinal multi-methodological assessments of SI will allow researchers to carefully investigate how and why SI develops, how these thoughts are maintained or fluctuate over time, and, ultimately, which mechanisms lead ideators to go on to attempt suicide.

Further, we did not include self-report measures or cognitive tasks assessing anhedonia or impulsivity. It will be critical for future studies both to corroborate our findings and to also directly test our formulation that elevated anhedonia symptoms and poorer impulse control mediate associations between dorsal striatum GMV and explicit thoughts of SI and suicide attempts, respectively. We also did not obtain information on family history of psychiatric illness and suicidal behaviors (suicides or suicidal attempts), which is a strong predictor of adolescent suicidality (Brent et al., 2004, 2014). Interestingly, researchers have found that familial depressive symptoms partially explain elevated risk of familial transmission of suicidality and that family history of suicidal behaviors is related to measures of impulsivity (Bridge et al., 2015b), consistent with the formulation of the role of poorer impulse control in adolescent suicidal behaviors (Auerbach et al., 2015, 2016, 2017b; Stewart et al., 2017). It is critical that future studies recruit samples that are enriched for being at elevated risk for SI based on the basis of several factors (e.g. environmental risk, familial risk, clinical risk) and that they also include family history as a predictor in their analyses.

Lastly, our study focused exclusively on structural MRI patterns and specifically on subcortical GMV, as candidates for elucidating the neural vulnerability for SI risk. While there is some evidence implicating cortical regions in suicidal thoughts and behaviors—including the cingulate cortex, the insula and orbitofrontal cortex (see Oquendo et al., 2014 and Cox Lippard et al., 2014 for reviews)—we focused on the striatum not only

because of its potential role in the etiology of suicidality but also because of its importance in typical adolescent development of motivational and reward-related inhibitory processes as well as in adolescent mental health (Ernst et al., 2006; Cohen et al., 2010; Braams et al., 2015). Nevertheless, other neuroimaging modalities, such as fMRI, may be more sensitive for probing mental states associated with SI and have typically identified several cortical regions.

For instance, in one study resting-state fMRI in 40 adolescents with MDD, Ordaz and colleagues reported that reduced network coherence in central executive, default mode and salience networks was associated with most severe lifetime ideation (Ordaz et al., 2018). Similarly, Schreiner and colleagues recently reported in a sample of 58 adolescents with MDD that higher self-reported suicidal symptoms were associated with resting-state hyperconnectivity between left precuneus and left primary motor cortex, left somatosensory cortices and middle and superior frontal gyri as well as hypoconnectivity between left posterior cingulate cortex and left cerebellum, lateral occipital cortex and temporal occipital fusiform gyrus (Schreiner et al., 2018). In a task-based fMRI study, Miller et al. (2018) reported that, compared to 32 adolescents with no history of SI, 14 adolescents with a history of SI had greater activation in dorsolateral prefrontal cortex during emotional regulation of negatively valenced images and reduced activation in dorsolateral prefrontal cortex, temporoparietal junction and cerebellum during passive viewing of these images. Finally, Just and colleagues recently used machine learning algorithms to differentiate 17 suicidal ideators from non-ideators based on high-dimensional neural patterns assessed during reflection of abstract concepts (e.g. 'death', 'cruelty', 'trouble', 'carefree', 'good' and 'praise') (Just et al., 2018). While these studies have identified potentially important functional markers—particularly in cortical areas—associated with SI in adolescents, there is notable heterogeneity among these results. Future studies integrating multimodal neuroimaging approaches with multi-methodological assessments of SI in larger samples will help clarify which functional and structural markers are associated with SI risk, history of SI or suicide attempt and active SI.

Conclusions

This study is the first to demonstrate that GMVs of the dorsal striatum significantly predict *implicit* self-associations with death in a community sample of adolescents; in contrast, no subcortical volumes examined in this study significantly predicted *explicit* self-report measures of SI. Self-report SI may not be based on altered volumetric brain changes, whereas objective and implicitly assessed behavioral measures of SI may be related to observable changes in brain morphometry. Together, our findings point to a unique role of the dorsal striatum in representing vulnerability to SI and underscore the importance of using implicit methods to detect suicide-related risk in adolescents.

Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest. All authors declare no biomedical conflicts of interest and all funding agencies and companies listed here played no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

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