Title

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

Journal

Social Cognitive and Affective Neuroscience, 13(11)

Authors

Ho, Tiffany

Cichocki, Anna

Gifuni, Anthony

et al.

Publication Date

2018-11-08

DOI

10.1093/scan/nsy089

Peer reviewed

OXFORD

Social Cognitive and Affective Neuroscience, 2018, 1215–1224

doi: 10.1093/scan/nsy089
Advance Access Publication Date: 25 September 2018
Original article

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

Tiffany C. Ho,[1,2] Anna C. Cichocki,[1] Anthony J. Gifuni,[3] M. Catalina Camacho,[4] Sarah J. Ordaz,[2] Manpreet K. Singh,[4] and Ian H. Gotlib[1]

[1]Department of Psychology, Stanford University, Stanford, CA 94305, USA, [2]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA 94304, USA, [3]McGill University and Douglas Mental Health University Institute, Montreal, Quebec, Canada and [4]University of Pittsburgh, Center for Neuroscience, Pittsburgh, PA 15260, USA

Correspondence should be addressed to Tiffany C. Ho, Room 169, Jordan Hall, 450 Serra Mall Building #420, Stanford, CA 94305, USA.
E-mail: tiffnie@stanford.edu.

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 *Ps* < 0.03). No other associations were significant (all *Ps* > 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 prevention 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

Received: 20 June 2018; **Revised:** 11 September 2018; **Accepted:** 23 September 2018

to suicide attempts in adolescents (Reinherz *et al.*, 2006; Sveticic 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 an 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 describe in more detail below, at follow-up, participants also completed suicide-related measures: the IAT and the SIQ.

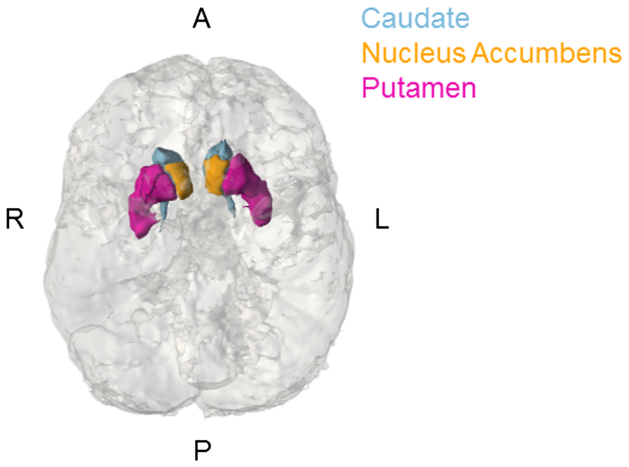

Fig. 1. Gray matter segmentations of the striatum. All GMV and total ICV estimates were extracted in individual brain space. Structures visualized here are from a representative subject, displayed from an inferior perspective. A = anterior; P = posterior; R = right; L = left.

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 *Ps* < 0.0001) but not with higher IAT d-scores (both *Ps* > 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 *Ps* > 0.1) Neither age at baseline nor at follow-up was associated with SIQ scores (all *Ps* > 0.3) or IAT scores (all *Ps* > 0.06). Finally, males and females did not differ in SIQ, IAT or CDI scores at baseline or follow-up (all *Ps* > 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 *Ps* > 0.1). None of the striatal GMV variables was significantly associated with SIQ scores (all *Ps* > 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 *Ps* > 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 *Ps* > 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]
Race/ethnicity			
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%
Family income			
<$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%
Parental level of education			
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-

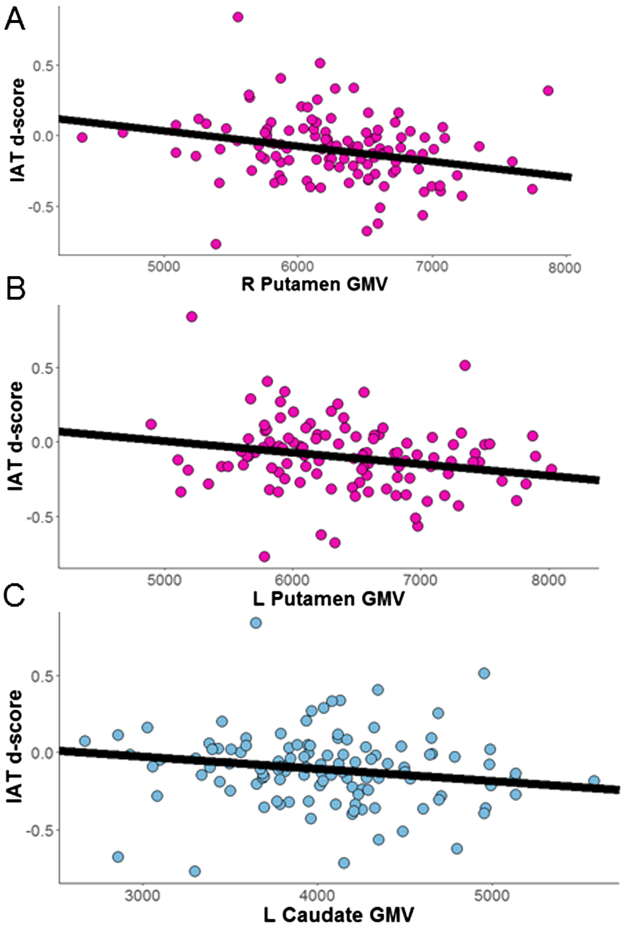

Fig. 2. Reduced GMV of the dorsal striatum predict IAT d-scores. Higher IAT d-scores at follow-up were significantly associated with reductions in GMV of the **(A)** right putamen, **(B)** left putamen and **(C)** left caudate. For visualization, all data points are raw values and all intercept and slopes 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 (Martinot *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.

Funding

This work was supported by the American Foundation for Suicide Prevention (PDF-1-064-13 to T.C.H.), the National Institute of Mental Health (R37MH101495 to I.H.G., K01MH10 6805 to S.J.O.), the Klingenstein Third Generation Foundation (Fellowship Award in Child and Adolescent Depression to T.C.H.), Stanford University Precision Health and Integrated Diagnostics (PHIND to I.H.G. and T.C.H.), National Institute of Mental Health (to M.K.S.), the National Institute of Aging (to M.K.S.), the Brain Behavior Foundation (to M.K.S.), the Stanford Child Health Research Institute (to M.K.S.), Neuronetics, and Johnson & Johnson (to M.K.S.).

Acknowledgements

We wish to thank Jaclyn Schwartz for feedback and Holly Pham, Meghan Goyer, Lucinda Sisk, Monica Ellwood-Lowe, Sophie Schouboe and Alexandra Price for assistance with data collection. Finally, we wish to thank the participants and their families for contributing to our study. I.H.G. serves on the scientific board of MindStrong Health and M.K.S. serves on the advisory board of Sunovion. M.K.S. serves on the Advisory Board of Sunovion.

References

Alex, K.D., Pehek, E.A. (2007). Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacology & Therapeutics*, **113**(2), 296–320.

Angold, A., Costello, E.J. (2006). Puberty and depression. *Child and Adolescent Psychiatric Clinics of North America*, **15**(4), 919–37 ix.

Arulpragasam, A.R., Cooper, J.A., Nuutinen, M.R., Treadway, M.T. (2018). Corticoinsular circuits encode subjective value expectation and violation for effortful goal-directed behavior. *Proceedings of the National Academy of Sciences of the United States of America*, **115**(22), E5233–42.

Auerbach, R.P., Millner, A.J., Stewart, J.G., Esposito, E.C. (2015). Identifying differences between depressed adolescent suicide ideators and attempters. *Journal of Affective Disorders*, **186**, 127–33.

Auerbach, R.P., Pisoni, A., Bondy, E., *et al.* (2017). Neuroanatomical prediction of Anhedonia in adolescents. *Neuropsychopharmacology*, **42**(10), 2087–95.

Auerbach, R.P., Stewart, J.G., Johnson, S.L. (2016). Impulsivity and suicidality in adolescent inpatients. *Journal of Abnormal Child Psychology*, **45**(1), 91–103.

Balcioglu, Y.H., Kose, S. (2017). Neural substrates of suicide and suicidal behaviour: from a neuroimaging perspective. *Psychiatry and Clinical Psychopharmacology*, **28**(3), 1–15.

Barnes, S.M., Bahraini, N.H., Forster, J.E., *et al.* (2016). Moving beyond self-report: implicit associations about death/life prospectively predict suicidal behavior among veterans. *Suicide & Life-threatening Behavior*, **47**(1), 67–77.

Bowden, C., Cheetham, S.C., Lowther, S., Katona, C.L., Crompton, M.R., Horton, R.W. (1997a). Reduced dopamine turnover in the basal ganglia of depressed suicides. *Brain Research*, **769**(1), 135–40.

Bowden, C., Theodorou, A.E., Cheetham, S.C., *et al.* (1997b). Dopamine D1 and D2 receptor binding sites in brain samples from depressed suicides and controls. *Brain Research*, **752**(1–2), 227–33.

Braams, B.R., van Duijvenvoorde, A.C., Peper, J.S., Crone, E.A. (2015). Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. *The Journal of Neuroscience*, **35**(18), 7226–38.

Brent, D.A., Melhem, N.M., Oquendo, M., *et al.* (2014). Familial pathways to early-onset suicide attempt: a 5.6-year prospective study. *JAMA Psychiatry*, **72**(2), 160–8.

Brent, D.A., Oquendo, M., Birmaher, B., *et al.* (2004). Familial transmission of mood disorders: convergence and divergence with transmission of suicidal behavior. *Journal of the American Academy of Child and Adolescent Psychiatry*, **43**(10), 1259–66.

Bridge, J.A., Asti, L., Horowitz, L.M., *et al.* (2015a). Suicide trends among elementary school-aged children in the United States from 1993 to 2012. *JAMA Pediatrics*, **169**(7), 673–7.

Bridge, J.A., Reynolds, B., McBee-Strayer, S.M., *et al.* (2015b). Impulsive aggression, delay discounting, and adolescent suicide attempts: effects of current psychotropic medication use and family history of suicidal behavior. *Journal of Child and Adolescent Psychopharmacology*, **25**(2), 114–23.

Busch, K.A., Fawcett, J., Jacobs, D.G. (2003). Clinical correlates of inpatient suicide. *The Journal of Clinical Psychiatry*, **64**(1), 14–9.

Cha, C.B., Augenstein, T.M., Frost, K.H., Gallagher, K., D'Angelo, E.J., Nock, M.K. (2015). Using implicit and explicit measures to predict nonsuicidal self-injury among adolescent inpatients. *Journal of the American Academy of Child and Adolescent Psychiatry*, **55**(1), 62–8.

Cha, C.B., Najmi, S., Park, J.M., Finn, C.T., Nock, M.K. (2010). Attentional bias toward suicide-related stimuli predicts suicidal behavior. *Journal of Abnormal Psychology*, **119**(3), 616–22.

Cohen, J.R., Asarnow, R.F., Sabb, F.W., *et al.* (2010). A unique adolescent response to reward prediction errors. *Nature Neuroscience*, **13**(6), 669–71.

Cox Lippard, E.T., Johnston, J.A., Blumberg, H.P. (2014). Neurobiological risk factors for suicide: insights from brain imaging. *American Journal of Preventive Medicine.*, **47**(3 Suppl 2), S152–62.

Cunningham, W.A., Preacher, K.J., Banaji, M.R. (2001). Implicit attitude measures: consistency, stability, and convergent validity. *Psychological Science*, **12**(2), 163–70.

Dalley, J.W., Roiser, J.P. (2015). Dopamine, serotonin and impulsivity. *Neuroscience*, **215**, 42–58.

Der-Avakian, A., Markou, A. (2016). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences*, **35**(1), 68–77.

Dombrovski, A.Y., Siegle, G.J., Szanto, K., Clark, L., Reynolds, C.F., Aizenstein, H. (2011). The temptation of suicide: striatal gray matter, discounting of delayed rewards, and suicide attempts in late-life depression. *Psychological Medicine*, **42**(6), 1203–15.

Ducasse, D., Loas, G., Dassa, D., *et al.* (2017). Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis. *Depression and Anxiety*, **35**(5), 382–92.

Ellis, B.J. (2004). Timing of pubertal maturation in girls: an integrated life history approach. *Psychological Bulletin*, **130**(6), 920–58.

Ernst, M., Pine, D.S., Hardin, M. (2006). Triadic model of the neurobiology of motivated behavior in adolescence. *Psychological Medicine*, **36**(3), 299–312.

Fischl, B. (2002). FreeSurfer. *NeuroImage*, **62**(2), 774–81.

Fischl, B., Salat, D.H., Busa, E., *et al.* (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, **33**(3), 341–55.

Gibb, S.J., Beautrais, A.L., Fergusson, D.M. (2005). Mortality and further suicidal behaviour after an index suicide attempt:

a 10-year study. *The Australian and New Zealand Journal of Psychiatry*, **39**(1–2), 95–100.
Gifuni, A.J., Ding, Y., Olie, E., *et al.* (2016). Subcortical nuclei volumes in suicidal behavior: nucleus accumbens may modulate the lethality of acts. *Brain Imaging and Behavior*, **10**(1), 96–104.
Glenn, C.R., Kleiman, E.M., Coppersmith, D.D.L., *et al.* (2017). Implicit identification with death predicts change in suicide ideation during psychiatric treatment in adolescents. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, **58**(12), 1319–29.
Glenn, C.R., Nock, M.K. (2014). Improving the short-term prediction of suicidal behavior. *American Journal of Preventive Medicine*, **47**(3 Suppl 2), S176–80.
Greenwald, A.G., Nosek, B.A., Banaji, M.R. (2003). Understanding and using the implicit association test: I. an improved scoring algorithm. *Journal of Personality and Social Psychology*, **85**(2), 197–216.
Greenwald, A.G., Poehlman, T.A., Uhlmann, E.L., Banaji, M.R. (2009). Understanding and using the implicit association test: III. meta-analysis of predictive validity. *Journal of Personality and Social Psychology*, **97**(1), 17–41.
Haber, S.N., Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*, **35**(1), 4–26.
Harrison, D.P., Stritzke, W.G., Fay, N., Ellison, T.M., Hudaib, A.R. (2014). Probing the implicit suicidal mind: does the death/-suicide implicit association test reveal a desire to die, or a diminished desire to live? *Psychological Assessment*, **26**(3), 831–40.
Harrison, D.P., Stritzke, W.G.K., Fay, N., Hudaib, A.R. (2018). Suicide risk assessment: trust an implicit probe or listen to the patient? *Psychological Assessment*. doi: 10.1037/pas0000577.
Hashemi, P., Dankoski, E.C., Lama, R., Wood, K.M., Takmakov, P., Wightman, R.M. (2012). Brain dopamine and serotonin differ in regulation and its consequences. *Proceedings of the National Academy of Sciences of the United States of America*, **109**(29), 11510–5.
Hawton, K., van Heeringen, K. (2009). Suicide. *Lancet*, **373**(9672), 1372–81.
Just, M.A., Pan, L., Cherkassky, V.L., *et al.* (2018). Machine learning of neural representations of suicide and emotion concepts identifies suicidal youth. *Nature Human Behaviour*, **1**, 911–9.
Kaufman, J., Birmaher, B., Brent, D.A., Ryan, N.D., Rao, U. (2000). K-Sads-Pl. *Journal of the American Academy of Child and Adolescent Psychiatry*, **39**(10), 1208.
Kleiman, E.M., Turner, B.J., Fedor, S., Beale, E.E., Huffman, J.C., Nock, M.K. (2017). Examination of real-time fluctuations in suicidal ideation and its risk factors: results from two ecological momentary assessment studies. *Journal of Abnormal Psychology*, **126**(6), 726–38.
Klonsky, E.D., May, A.M. (2013). Differentiating suicide attempters from suicide ideators: a critical frontier for suicidology research. *Suicide & Life-threatening Behavior*, **44**(1), 1–5.
Klonsky, E.D., May, A.M., Saffer, B.Y. (2016). Suicide, suicide attempts, and suicidal ideation. *Annual Review of Clinical Psychology*, **12**, 307–30.
Knowlton, B.J., Patterson, T.K. (2016). Habit formation and the striatum. *Current Topics in Behavioral Neurosciences*, **37**, 275–95.
Kovacs, M. (1992). *Children's Depression Inventory: Manual*, Multi-Health Systems Inc., North Tonawanda, NY.
Luking, K.R., Pagliaccio, D., Luby, J.L., Barch, D.M. (2016). Reward processing and risk for depression across development. *Trends in Cognitive Sciences*, **20**(6), 456–68.
Martinot, M., Bragulat, V., Artiges, E., *et al.* (2001). Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. *The American Journal of Psychiatry*, **158**(2), 314–6.
Meyer, J.H. (2012). *Neuroimaging High Risk States for Suicide*, CRC Press/Taylor & Francis, Boca Raton, FL
Miller, A.B., McLaughlin, K.A., Busso, D.S., Brueck, S., Peverill, M., Sheridan, M.A. (2018). Neural correlates of emotion regulation and adolescent suicidal ideation. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, **3**(2), 125–32.
Morris, N.M., Udry, J.R. (1980). Validation of a self-administered instrument to assess stage of adolescent development. *Journal of Youth and Adolescence*, **9**(3), 271–80.
Nock, M.K., Banaji, M.R. (2007). Prediction of suicide ideation and attempts among adolescents using a brief performance-based test. *Journal of Consulting and Clinical Psychology*, **75**(5), 707–15.
Nock, M.K., Green, J.G., Hwang, I., *et al.* (2013). Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*, **70**(3), 300–10.
Nock, M.K., Park, J.M., Finn, C.T., Deliberto, T.L., Dour, H.J., Banaji, M.R. (2010). Measuring the suicidal mind: implicit cognition predicts suicidal behavior. *Psychological Science.*, **21**(4), 511–7.
Nosek, B.A., Greenwald, A.G., Banaji, M.R. (2005). Understanding and using the implicit association test: II. method variables and construct validity. *Personality and Social Psychology Bulletin*, **31**(2), 166–80.
O'Doherty, J.P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Current Opinion in Neurobiology*, **14**(6), 769–76.
Oquendo, M.A., Galfalvy, H., Sullivan, G.M., *et al.* (2016). Positron emission tomographic imaging of the serotonergic system and prediction of risk and lethality of future suicidal behavior. *JAMA Psychiatry*, **73**(10), 1048–55.
Oquendo, M.A., Sullivan, G.M., Sudol, K., *et al.* (2014). Toward a biosignature for suicide. *The American Journal of Psychiatry*, **171**(12), 1259–77.
Ordaz, S.J., Goyer, M.S., Ho, T.C., Singh, M.K., Gotlib, I.H. (2018). Network basis of suicidal ideation in depressed adolescents. *Journal of Affective Disorders*, **226**, 92–9.
Pitchot, W., Hansenne, M., Ansseau, M. (2001). Role of dopamine in non-depressed patients with a history of suicide attempts. *European Psychiatry*, **16**(7), 424–7.
Quevedo, K., Ng, R., Scott, H., *et al.* (2016). Ventral striatum functional connectivity during rewards and losses and symptomatology in depressed patients. *Biological Psychology*, **123**, 62–73.
Reinherz, H.Z., Tanner, J.L., Berger, S.R., Beardslee, W.R., Fitzmaurice, G.M. (2006). Adolescent suicidal ideation as predictive of psychopathology, suicidal behavior, and compromised functioning at age 30. *The American Journal of Psychiatry*, **163**(7), 1226–32.
Renteria, M.E., Schmaal, L., Hibar, D.P., *et al.* (2017). Subcortical brain structure and suicidal behaviour in major depressive disorder: a meta-analysis from the ENIGMA-MDD working group. *Translational Psychiatry*, **7**(5), e1116.
Reynolds, W.M. (1987). *Suicidal Ideation Questionnaire (SIQ)*, Odessa, FL: Psychological Assessment Resources.
Schreiner, M.W., Klimes-Dougan, B., Cullen, K.R. (2018). Neural correlates of suicidality in adolescents with major depression: resting-state functional connectivity of the precuneus and posterior cingulate cortex. *Suicide & Life-threatening Behavior*. doi: 10.1111/sltb.12471.

Stewart, J.G., Glenn, C.R., Esposito, E.C., Cha, C.B., Nock, M.K., Auerbach, R.P. (2017). Cognitive control deficits differentiate adolescent suicide ideators from attempters. *The Journal of Clinical Psychiatry*, **78**(6), e614–21.

Sveticic, J., De Leo, D. (2012). The hypothesis of a continuum in suicidality: a discussion on its validity and practical implications. *Mental Illness*, **4**(2). doi: 10.4081/mi.2012.e15.

Tricomi, E., Lempert, K.M. (2014). Value and probability coding in a feedback-based learning task utilizing food rewards. *Journal of Neurophysiology*, **113**(1), 4–13.

Tschernegg, M., Pletzer, B., Schwartenbeck, P., Ludersdorfer, P., Hoffmann, U., Kronbichler, M. (2015). Impulsivity relates to striatal gray matter volumes in humans: evidence from a delay discounting paradigm. *Frontiers in Human Neuroscience*, **9**, 384.

van Heeringen, K., Bijttebier, S., Desmyter, S., Vervaet, M., Baeken, C. (2014). Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinate-based meta-analysis of structural and functional MRI studies. *Frontiers in Human Neuroscience*, **8**, 824.

Vang, F.J., Ryding, E., Traskman-Bendz, L., van Westen, D., Lindstrom, M.B. (2010). Size of basal ganglia in suicide attempters, and its association with temperament and serotonin transporter density. *Psychiatry Research*, **183**(2), 177–9.

Weil, L.G., Fleming, S.M., Dumontheil, I., *et al.* (2013). The development of metacognitive ability in adolescence. *Consciousness and Cognition*, **22**(1), 264–71.

Whittle, S., Simmons, J.G., Byrne, M.L., *et al.* (2015). Associations between early adrenarche, affective brain function and mental health in children. *Social Cognitive and Affective Neuroscience*, **10**(9), 1282–90.

Winer, E.S., Bryant, J., Bartoszek, G., Rojas, E., Nadorff, M.R., Kilgore, J. (2017). Mapping the relationship between anxiety, anhedonia, and depression. *Journal of Affective Disorders*, **221**, 289–96.

Winer, E.S., Nadorff, M.R., Ellis, T.E., Allen, J.G., Herrera, S., Salem, T. (2014). Anhedonia predicts suicidal ideation in a large psychiatric inpatient sample. *Psychiatry Research*, **218**(1–2), 124–8.

Zhang, H., Chen, Z., Jia, Z., Gong, Q. (2014). Dysfunction of neural circuitry in depressive patients with suicidal behaviors: a review of structural and functional neuroimaging studies. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, **53**, 61–6.