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Short communication

History of suicide attempt and right superior temporal gyrus volume in youth with treatment-resistant major depressive disorder

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ABSTRACT

Background: Growing evidence suggests an endophenotype for suicidality, including brain morphometric features, could provide an improved platform for suicide risk assessment. Reduced right superior temporal gyrus (rSTG) volumes have been implicated in suicidality across psychiatric disorders. Treatment-resistant depression (TRD) has unique neurobiology and adolescents with TRD are at increased suicide risk. Here, we investigated whether reduced rSTG volume was present in adolescents with TRD and history of suicide attempt.

Methods: 45 adolescents - 14 with history of suicide attempt and TRD, 14 without a suicide attempt history and TRD, and 17 healthy controls - underwent magnetic resonance imaging and reconstructed rSTG volumes were compared. Depressive and anxious symptoms were assessed with Hamilton depression and anxiety rating scales, and differences between attempters and non-attempters were explored.

Results: Adolescents with TRD and history of suicide attempt showed reduced rSTG volume compared to healthy controls. Exploratory analyses revealed greater diurnal variation in depressive symptoms in the suicide attempt group compared to non-attempters.

Limitations: Sample size and temporal separation between suicide attempt date and data collection limits interpretation of findings.

Conclusions: Reduced rSTG volume may serve as a marker of suicide attempt in adolescence and specific symptom features may have a role in suicide risk assessment. Presently, risk assessment is limited by patient self-report and clinical judgement. A biological model of suicidality will be key to improve risk assessment and could lead to novel treatment approaches. Our findings extend previous results and contribute to our neurobiological understanding of suicidality.

Introduction

Suicide is the second leading cause of death in 15–29 year olds worldwide (WHO, 2016), and major depressive disorder (MDD) is a main risk factor for suicide. Presently, suicide risk assessment is limited, relying on patient self-reports and subjective judgement by clinical professionals. By comparison, neural structural differences may provide more objective markers of suicidality and are often more accessible than measures of brain function. An objective, biological model of suicidality would identify those at risk (Sudol and Mann, 2017) and provide targets for future neurobiologically-informed interventions. Previous studies report distinct neurobiological profiles in those with a history of suicide attempt and suggest that structural differences not otherwise associated with MDD may be associated with suicide risk. This proposes a unique endophenotype for suicidal behavior (Wagner et al., 2012). The superior temporal gyrus plays a role in

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emotional processing and has been repeatedly implicated in suicidality in numerous psychiatric conditions (Sudol and Mann, 2017). Pan et al. (2015) reported reduced right superior temporal gyrus volume (rSTG) in youth with MDD and suicide attempt history (Pan et al., 2015). However, MDD is a heterogeneous disorder that demonstrates unique biotypes (Drysdale et al., 2017). Treatment-resistant depression (TRD), a subtype of depression, represents 30–60% of MDD cases (Fava, 2003) and is associated with unique neural correlates (Yamamura et al., 2016), but the relationship between TRD and suicidal behaviors has not yet been investigated morphometrically. In the current study, we investigate differences in rSTG volume in TRD adolescents with and without a history of suicide attempt. We hypothesize that, consistent with the findings of Pan et al. (2015), reduced rSTG volumes will be observed in the suicide attempt group.

Methods

Two groups of adolescents (12–21 years of age) were recruited through advertisements and the primary care network of Calgary: (1) a primary diagnosis of MDD and failure to respond to at least one trial (≥ 8 weeks) of adequate dose selective serotonin reuptake inhibitor (SSRI) medication (TRD group), and (2) healthy controls (HC). Exclusion criteria included left-handedness (due to concurrent recruitment for repetitive transcranial magnetic stimulation study), epilepsy, other neurological or psychiatric diagnoses, and pregnancy. The final sample was comprised of 28 TRD adolescents – 14 suicide attempt (SA) and 14 no suicide attempt (NSA) – and 17 healthy controls. All participants and parents/guardians provided written consent in accordance with the University of Calgary's Conjoint Health Research Ethics Board (CHREB). See Table 1 for a summary of demographics.

The Present and Lifetime version of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (Kaufman et al., 1997) was used to assess present/lifetime psychiatric symptoms, as well as medication and suicide attempt history. In the SA group, these were clear attempts, not gestures. For questions regarding suicidal acts (seriousness and medical lethality) a response of 3 was required. The Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959) provided an indication of anxiety symptom severity. Hamilton Depression Rating Scale 17 and 21-item versions (HAM17 and HAM21 respectively) (Hamilton, 1967), assessed depressive symptoms.

Participants underwent magnetic resonance imaging (MRI) at the Alberta Children's Hospital on a GE Healthcare Discovery MR750w 3.0T scanner. Structural image parameters were as follows: axial acquisition, TR = 8.268 ms, TE = 3.152 ms, TI = 600, flip angle = 10°, slice thickness = 0.8 mm, 226 slices, 300 × 300 matrix. A 0.8cubic millimeter resolution is within the necessary Nyquist frequency limit to accurately map brain cortex topography.

MRI datasets underwent reconstruction via FreeSurfer software (Version 5.3), described in detail online (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation) (Dale et al., 1999; Fischl and Dale, 2000). Regions of interest (ROI) – namely the rSTG – and total brain volumes were extracted and analyzed with SPSS Version 22.0. One-way analysis of covariance (ANCOVA) examined the main effect of each group ROI volume with age, gender, and total brain volume as covariates. To further assess differences between groups, post hoc pairwise comparison p-values underwent Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) false discovery rate of 0.1.

Exploratory analyses included differences in: rSTG volume between TRD and HC investigated via a Welch's *t*-test; clinical assessment scores between the groups (collected on the date of MRI acquisition), and selected assessment item scores between SA and NSA investigated via independent *t*-tests; frontal and temporal regional cortical thickness between HC, SA, and NSA via an analysis of variance (ANOVA), Bonferroni adjustment for multiple comparisons, $p < 0.05/44 = 0.0011$.

Results

Groups did not significantly differ in age or biological sex. One-way ANCOVA indicated a significant difference in rSTG volume between SA, NSA and HCs ($F(2,39) = 3.274$, $p = 0.048$, $\eta = 0.144$; Fig. 1). Post-hoc pairwise comparison revealed that the SA group had significantly smaller rSTG volumes compared with HCs ($p = 0.018$), which remained significant following the Benjamini-Hochberg procedure. There was no significant difference demonstrated between TRD and HC rSTG volumes ($p = 0.143$).

The two TRD groups did not differ in HAMA or HAM17 scores; however, they did differ in HAM21 scores (independent *t*-test, $t(26) = 2.176$, $p = 0.039$). Exploration of the 5 HAMD items distinguishing the HAM21 from the HAM17 found that SAs had greater diurnal variation score (item 18A; independent *t*-test, $t(26) = 2.162$, $p = 0.04$), but no further differences were noted. Finally, there was no difference in frontal and temporal regional cortical thickness between HC, NSA, and SA (following Bonferroni correction $p < 0.0011$; Table 2).

Discussion

As hypothesized, rSTG volume was reduced in adolescents with TRD and suicide attempt history. Pan et al. (2015) reported the same results in an adolescent MDD sample and suggested that, given the role of the rSTG in social emotion processing, reduced grey matter volume may be a marker of social-emotional evaluation abnormalities in SAs. rSTG volume reduction and suicidality has been reported in a number of psychiatric disorders (Sudol and Mann, 2017). Despite comorbid diagnoses (i.e., social anxiety disorder, ADHD) and the potential for related structural confounds in this TRD population, our findings bolster the association of rSTG volume and suicidality. This work adds to the evidence of a distinct endophenotype for suicidal behaviour and adds to the proposal made by Pan et al. (2015), that reduced rSTG volume may be a marker of suicide attempt history in adolescence.

Exploratory analysis found that SAs had a higher diurnal variation

Table 1
Basic study demographics. Variables of interest in adolescent treatment-resistant depression with and without history of suicide attempt and healthy controls. Right superior temporal gyrus and total brain volume calculated with FreeSurfer (version 5.3).

Total		Treatment-resistant depression		
		Suicide attempters	Non-attempters	Controls
Sex (female)	**45 (24)**	14 (7)	14 (6)	17 (11)
Age (mean ± standard deviation)		17.48 ± 1.741	18.17 ± 1.837	18.00 ± 2.666
Right superior temporal gyrus volume		11,923.357 ± 932.62	12,258.643 ± 1495.20	12,907.824 ± 2005.99
Total brain volume		1,179,943.00 ± 113,421.77	1,193,294.07 ± 106,559.31	1,171,067.24 ± 105,650.46
Diurnal variation (HAMD item 18A)				
	No variation	3	7	17
	Worse in A.M.	1	3	0
	Worse in P.M.	10	4	0