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Adolescent suicide attempts and ideation are linked to brain function during peer interactions

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ABSTRACT

Understanding the neural correlates of social interaction among depressed adolescents with suicidal tendencies might help personalize treatment. We tested whether brain function during social interaction is disrupted for depressed adolescents with (1) high suicide ideation and (2) recent attempts. Depressed adolescents with high suicide ideation, including attempters (n = 45;HS) or low suicide ideation (n = 42;LS), and healthy adolescents (n = 39;HC), completed a version of the Cyberball peer interaction task during an fMRI scan. Groups were compared on brain activity during peer exclusion and inclusion versus a non-social condition. During peer exclusion and inclusion, HS youth showed significantly lower activity in precentral and postcentral gyrus, superior temporal gyrus, medial frontal gyrus, insula, and putamen compared to LS youth; and significantly reduced activity in caudate and anterior cingulate cortex compared to HC youth. In a second analysis, suicide attempters (n = 26;SA) were compared to other groups. SA adolescents showed significantly higher activity in ACC and superior and middle frontal gyrus than all other groups. Brain activity was significantly correlated with negative emotionality, social functioning, and cognitive control. Conclusions: Adolescent suicide ideation and attempts were linked to altered neural function during positive and negative peer interactions. We discuss the implications of these findings for suicide prevention efforts.

1. Introduction

Suicide is the second leading cause of death among adolescents (World Health Organization, 2014), and suicide rates have increased worldwide in the last half century (Nock et al., 2008). These alarming statistics underscore the urgent need to identify and address risk factors for suicide, particularly during adolescence. Depression (Brent et al., 1993) and social alienation (King and Merchant, 2008) are major risk factors for suicide ideation and attempts among adolescents. However, few individual factors are sensitive and specific predictors of suicide ideation (thoughts of suicide) or transition to attempts (Franklin et al., 2017). Research that examines understudied neurodevelopmental mechanisms of both suicide ideation and attempts might help improve suicide prediction and treatment.

Peer relationships become salient during adolescence (Nelson et al., 2005), helping to promote healthy social growth as youth learn to successfully navigate new social challenges. However, the importance of peer interaction also renders adolescents vulnerable to distress, depression, and suicide ideation when they experience social rejection, peer aggression, and/or lack social support. Given the role of social alienation in suicide ideation and attempts, and the heightened risk for suicide among depressed adolescents, it is important to determine how the neural basis of social processing in depressed adolescents is associated with suicide attempts and ideation (Monkul et al., 2007).

Depression has been associated with altered function in neural networks that include the pre-frontal cortex and striatum (Forbes and Dahl, 2012; Minzenberg et al., 2015), but the activity of those regions among depressed adolescents during social interaction has rarely been studied. While the neural correlates of social exclusion have been evaluated among healthy participants (For a review see, Cacioppo et al., 2013; Rotge et al., 2015), past research has rarely included clinically depressed adolescents or addressed suicide behavior. Additionally, it is unknown how brain activity is linked to differences in psychological dimensions such as cognitive control, negative affect, and social function, which may contribute to suicide in the context of social challenges and personality differences (Braquehais et al., 2010; Bridge et al., 2015;

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Ghahramanlou-Holloway et al., 2012; Klonsky and May 2010; Trakhtenbrot et al., 2016).

1.1. The neurophysiology of social exclusion

The neural correlates of social exclusion are often evaluated using a computer-simulated ball-tossing game called "Cyberball Task" in which participants are included and then excluded by virtual peers (Williams et al., 2000). Meta-analyses show that, during exclusion versus inclusion, the Cyberball task reliably produces feelings of ostracism (Bridge et al., 2015) and increased activation in regions involved in pain and distress, including the subgenual anterior cingulate (sgACC) (Rotge et al., 2015) and anterior insula (Eisenberger et al., 2003), as well as in areas supporting social cognition, such as the inferior orbitofrontal cortex (Cacioppo et al., 2013) and medial and ventrolateral areas of the prefrontal cortex (mPFC, and vlPFC) (Sebastian et al., 2010). Notably, unlike actual interactions, youth undergoing prior versions of the Cyberball task passively observe virtual peers instead of actively participating.

A small but growing number of studies have examined associations between neural responses during the Cyberball task and depression, self-injury, or suicidality. Of particular interest to understanding the pathophysiology of depression, higher sgACC activity during social exclusion versus inclusion has been associated with larger increases in depressive symptoms over 1-year follow-up in healthy adolescents in *a priori* region-of-interest (ROI) analyses (Masten et al., 2011). In another study, depressed adolescents with non-suicidal self-injury (NSSI) demonstrated increased activation of the medial and ventrolateral prefrontal cortex relative to depressed adolescents without NSSI and to healthy controls during social exclusion versus inclusion (Groschwitz et al., 2016). Rejection during the Cyberball task has also been linked with suicide attempt history in adult women: depressed women with or without previous suicide attempts reported higher social distress following the Cyberball task, and suicide attempters showed decreased activity in the insula and supramarginal gyrus during exclusion relative to inclusion (Olie et al., 2017).

Additional studies have used a Chatroom Interaction Task (Silk et al., 2014) to evaluate neural responses during peer interaction in relation to depression. Participants in the Chatroom Interact Task receive rigged acceptance and rejection feedback from virtual online peers after a perceived exchange of biographies and photographs. In one study using this task, depressed youth showed greater prefrontal, anterior cingulate cortex (ACC), and insula response during peer rejection versus acceptance compared to healthy adolescents using an *a priori* ROI approach (Silk et al., 2014). Additionally, in a study that compared neural response to social acceptance versus a motor control condition in the Chatroom Interaction Task, adolescent offspring of depressed parents relative to offspring of non-depressed parents had blunted response in the ventral striatum, ACC, and inferior frontal cortex; and increased response in the precuneus and cuneus, superior and medial temporal gyri, middle frontal gyrus, and precentral gyrus (Olino et al., 2015). These studies provide evidence that depression is associated with disruptions in neural response during social rejection and acceptance.

Notably, studies employing the Cyberball task have not included a non-social comparison condition to examine effects of *both inclusive and rejecting* social interactions on brain function. Depressed adolescents, particularly those with suicide ideation or a history of suicide attempts, may also show abnormal brain activity during positive social interaction (Schaefer et al., 2006). In support of this hypothesis, adolescent depression and depression risk is associated with abnormal neural responses to both negative and positive social events (Forbes and Dahl, 2012; Olino et al., 2015), and a history of suicide attempts among adolescents with bipolar disorder is associated with reduced amygdala-prefrontal connectivity while viewing positive (happy) and neutral faces (Johnston et al., 2017). Depressed or suicidal adolescents may show differential neural processing of global social interaction (both exclusion and inclusion) compared to healthy individuals, but neural responses during both exclusion and inclusion have not been examined in depressed adolescents or adolescents with high suicide ideation or attempts.

1.2. Links between suicidality and individual differences

In addition to clinical factors, individual characteristics that affect relationships, such as social withdrawal and lack of closeness to others, may bias the ways in which social interactions are processed, and even lead to further experiences of exclusion. Furthermore, traits such as impulsivity, and/or lack of cognitive control, and high negative affect have been linked to adolescent suicide attempts (Bridge et al., 2015; Braquehais et al., 2010). Therefore, brain activity that differs between suicidal and non-suicidal depressed youth might also be associated with traits including impulsivity, high negative affect and indications of impaired social function.

1.3. The present study

We examined links between intense suicide ideation and/or suicide attempts and neural activity during peer interactions using a variation of the Cyberball task that included requesting the ball during both inclusion and exclusion conditions. This study is the first to examine whether suicide thoughts or behavior in adolescents are associated with neural response during social interaction. In contrast to previous uses of this task, our study compared neural response during social inclusion and exclusion to a non-social practice comparison condition and used a whole brain level rather than ROI analyses. Based on previous research linking depressive symptoms to prefrontal cortex (PFC), ACC, and insula responses during social exclusion (Masten et al., 2011; Silk et al., 2014), we predicted disruption in neural function during social exclusion relative to a non-social practice task. We also compared neural response during social inclusion to a non-social practice task to evaluate whether depressed adolescents with suicidal thoughts and behavior exhibit hypersensitivity during any social challenge. Specifically, we predicted that PFC, including ACC, as well as limbic activity during social exclusion versus a non-social control condition would be: (1) highest in depressed adolescents who had recently attempted suicide (SA) compared to depressed and healthy peers; (2) greater in depressed adolescents with high suicide ideation (HS) relative to depressed adolescents with low suicide ideation (LS) and healthy controls (HC); and (3) greater in LS adolescents compared to HC adolescents. Finally, we expected that individual differences in social functioning, negative emotionality, and cognitive control (Stewart et al., 2017) would be correlated with activity in the PFC, ACC and limbic areas during social interaction.

2. Methods

2.1. Participants and symptom measures

Depressed and healthy adolescents were recruited from two metropolitan sites (site 1 $n = 87$; site 2 $n = 39$). Institutional Review Boards at both sites approved procedures. Depressed adolescents were either in a crisis inpatient unit (due to recent attempts or serious threats), were outpatients being evaluated or treated for major depressive disorders, or responded to flyers and radio ads. Parents gave informed consent for their children to participate in the study, and adolescents provided assent.

Inclusion criteria included a primary diagnosis of a depressive disorder for depressed adolescents, or the absence of current and past psychiatric diagnoses or suicidal ideation for healthy controls (HC). Psychiatric diagnoses were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS, Kaufman et al., 1997), and depression symptom severity was indexed using the Child Depression Rating Scale (CDRS, Poznanski et al., 1979). Reliability for depression diagnosis was high (kappa = 0.834).

Suicide ideation was indexed by standardizing and averaging suicide items from the K-SADS and CDRS. A median split of the averaged z-score composite was used to classify depressed youth as either high or low in suicide ideation (respectively, HS and LS). The latter group included participants without suicide ideation or fleeting passive thoughts. Suicide attempts (lifetime or recent) were documented via the K-SADS. Participants who attempted suicide within the past 3 months, regardless of suicide ideation, were classified as suicide attempters (SA) for analyses with four groups (SA, HS, LS, HC). SA (with only 6 exceptions) also reported high suicide ideation and were in the HS group for the 3-groups analyses. No HS youth had a history of attempts in the four-group analyses. However, SA and HS had similarly high suicide ideation in the 4-group analyses and differed only in whether they had ever acted or not on such thoughts. Similar groupings with this sample has yielded differences between HC, LS, HS and SA during a self-recognition task (Alarcón et al., 2019. in press; Quevedo et al., 2016). Depression severity was indexed by CDRS score minus the suicide ideation item to avoid construct overlap between suicide thoughts and depression severity in analyses. Additional measures included the Pubertal Development Scale (PDS, Petersen et al., 1985), Behavior Assessment System for Children (BASC-2, Reynolds and Kamphaus, 1998), and the Multidimensional Personality Questionnaire (MPQ, Tellegen, 2008). IQ was assessed using the Wechsler Abbreviated Scale of Intelligence to (Wechsler, 1999).

2.2. Cyberball task

The Cyberball task was completed 1–2 weeks after the psychological evaluation. Participants were told that they would play a virtual ball-tossing game with two other participants (Williams et al., 2000). The task started with a non-social "practice" condition (tossing the ball to the right or left of the empty screen via button presses, 28 throws, 39 s). This condition was included to control for neural activity in visual and motor areas that are not thought to actively respond to social challenges.

The social interaction portion of the task consisted of three blocks, in fixed order: participants were included (received the ball 50% of the time) for 20 throws (inclusion block; 33 s); excluded (never received the ball) for 20 throws (exclusion block; 33 s); and finally, included again for 13 throws (short inclusion; 15 s) to diminish distress. A fixation cross was displayed for 15 s after the practice condition and at the end of the task. Participants were told they could request the ball at any point via button press and that other players could do the same. This manipulation sought to increase ecological validity of the game, as real-life social interactions are rarely passive: individuals get to retort or react to instances of rejection or actively respond while included in a game. Participants were debriefed about the deception following the Cyberball task completion and completed the "Need Threat" questionnaire (Zadro et al., 2004).

2.3. Neuroimaging acquisition

Neuroimaging data were collected using 3.0 Tesla Siemens Trio MRI scanners in both sites. Data were preprocessed and analyzed with Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm). Data were realigned to the first volume in the time series to correct for head motion. Realigned images were co-registered with the subject's anatomical image, segmented, normalized to standard Montreal Neurological Institute (MNI) template, and spatially smoothed with a Gaussian kernel of 7 mm full-width at half-maximum (FWHW). Trials were modeled with the Canonical Hemodynamic Response Function. Details regarding preprocessing, motion and scanner site effects can be found in Supplement 1.

2.4. Analyses

Effects of condition were estimated for each participant using 1st level analyses that yielded activity maps for inclusion > practice and exclusion > practice. Analyses included all tosses or trials in each trial block. Two sets of 2nd whole brain level (WBL) analyses were conducted to examine the effects of Group, Condition, and their interaction. In the first set of 2nd level analyses, the effects of Group (HS, LS, HC), Condition (inclusion-practice, exclusion-practice), and their interaction were assessed with a full factorial design which permits for inclusion of covariates (see Supplementary Table 3 for the effects of task conditions). The second set of analyses examined suicide attempters (SA) separately using a full factorial design with four groups (SA, HS, LS, and HC), Condition, and their interaction. In addition to the above analyses, we regressed whole brain activity on the continuous measure of suicidal ideation among the entire sample, which yielded no significant clusters (see Supplement Section V1. Additional Analyses). Variables that differed between the groups or that could affect imaging results (scanning site, depression severity, IQ, pubertal status, gender, family income) were included as covariates in all tests. Additionally, to control for the potential effect of cannabis use on brain function (Gonzalez, 2007), which was higher in the HS versus all other groups, we covaried for cannabis use. Significant clusters from omnibus whole-brain analyses were then saved as masks and used in pair-wise group comparison analyses to clarify the direction and brain localization of the omnibus results (See Supplemental Table 6). Regions were identified using xjview in SPM12 and confirmed with the Talairach deamon software. Of note, analyses run without those key covariates yielded activity in areas with large white matter clusters, which are controversial (Fraser et al., 2012; Yarkoni et al., 2009) and not of interest in the present study.

To correct for multiple comparisons, we calculated whole-brain, voxel-wise and cluster extent thresholds via Monte Carlo simulations using 3dClustSim in AFNI (v.18.2.06) and a smoothing kernel of 17.89 18.68 8.34 estimated via the AFNI 3dFWHMx function. This resulted in the following cluster-extent threshold corresponding to $p < 0.01$, FWE-corrected: $k > 211.8$ voxels for the 3 groups and $k > 337$ for the 4 groups. Only clusters larger than these thresholds are reported. Eigenvalues were extracted for mean BOLD response across each cluster with significant group differences for use in correlation analyses and graphs in SPSS (v. 22).

Individual differences. Extractions for clusters that differentiated groups were correlated with individual psychological dimensions using bivariate Pearson correlation analyses within each group in SPSS (see Table 2). We hypothesized that low cognitive control (mean Z-scores of cognitive control from the MPQ minus Z-scores of attention problems from the BASC), poor social function (mean Z-scores of social withdrawal from the CDRS subtracted from Z-scores of social closeness from the MPQ), and negative emotionality (Z-standardized raw MPQ score) would be characteristics shared by adolescents with high suicide ideation or suicide attempts.

Additional analyses. In addition to group comparisons, suicide ideation was examined as a continuous variable within depressed participants. Suicide ideation (z-scores from suicide items on the K-SADS and CDRS averaged) was regressed on brain function during both inclusion > practice and exclusion > practice among depressed subjects. Additionally, to provide comparison to previous Cyberball studies and supplement our planned comparisons of Inclusion > Practice and Exclusion > Practice, we tested the effect of Group on Exclusion > Inclusion and found no significant areas of activity between our groupings. We also examined the role of gender, bullying (sampled via the K-SADS) and medications (reported by parents) as between-subject factors to predict social brain function. Need threat was also compared between groups (see Supplemental material).

Table 1
Group differences in BOLD response during social vs non-social situations in the cyberball task. Note the first cluster is divided into two peaks due to its large size.

Whole-brain analysis	Condition	Cluster size (K)	*p*(K)	Hemisphere	MNI			*F*
					x	y	z	
*Suicide ideation and peer interactions**								
Insula and putamen, inferior parietal lobule (IPL) BA 3, 4, 6, 13, 22, 31, 40, 43	Omnibus test	1245	0.00	Right	24	−34	40	15.55
					52	−26	24	15.12
Caudate, lentiform nucleus and pallidum, anterior cingulate cortex		302	0.00	Left and right	−08	−04	−04	13.34
Precentral and postcentral gyrus, BA 1, 2, 3, 4, 6		337	0.00	Left	−40	−28	60	12.82
*Suicide attempts and peer interactions: SA > HS = LS = HC**								
Anterior cingulate cortex, superior and middle frontal gyrus, BA 9, 10, 32	Omnibus test	568	0.00	Left and right	08	42	20	13.12

* See supplement for the follow-up pairwise comparison tests that yielded the direction of results.

3. Results

Participant characteristics are reported in Tables S1 and S2. As expected, the groups differed on depression severity, which was controlled for in analyses.

3.1. Suicide ideation and peer interactions

Analyses examining effects of Group (HS, LS, HC), Condition, and their interaction resulted in significant effects of group in a cluster comprised by the precentral and postcentral gyrus; a cluster encompassing the inferior parietal lobule (IPL), insula, and putamen; and a cluster encompassing the head of the caudate, lentiform nucleus and pallidum as well as parts of the ACC; see Table 1, Fig. 1, and Supplemental Table 6.

Follow-up pairwise comparison tests indicated that, compared to LS, HS had *lower* activity in the left precentral and postcentral gyrus; and in the inferior parietal lobule (IPL), insula, and putamen. Compared to HC, HS had lower insula and putamen activity, and lower activity in the head of the caudate, the lentiform nucleus and pallidum, and ACC. However, HS showed *higher* IPL activity relative to HS. The IPL was the only region in which HS showed higher activity relative to another group. There were no significant differences between LS and HC in pairwise comparisons.

3.2. Suicide attempts and peer interactions

Analyses that examined the effects of Group (SA, HS, LS, HC), Condition, and their interaction resulted in a main effect of Group in portions of the ACC and superior and middle frontal gyrus. Follow-up tests indicated that SA youth showed higher activity compared to HS and LS in the ACC and Superior and Middle Frontal Gyrus; Fig. 2, Table 1, Supplemental section V, Supplemental Table 6. There were no Group by Condition interactions.

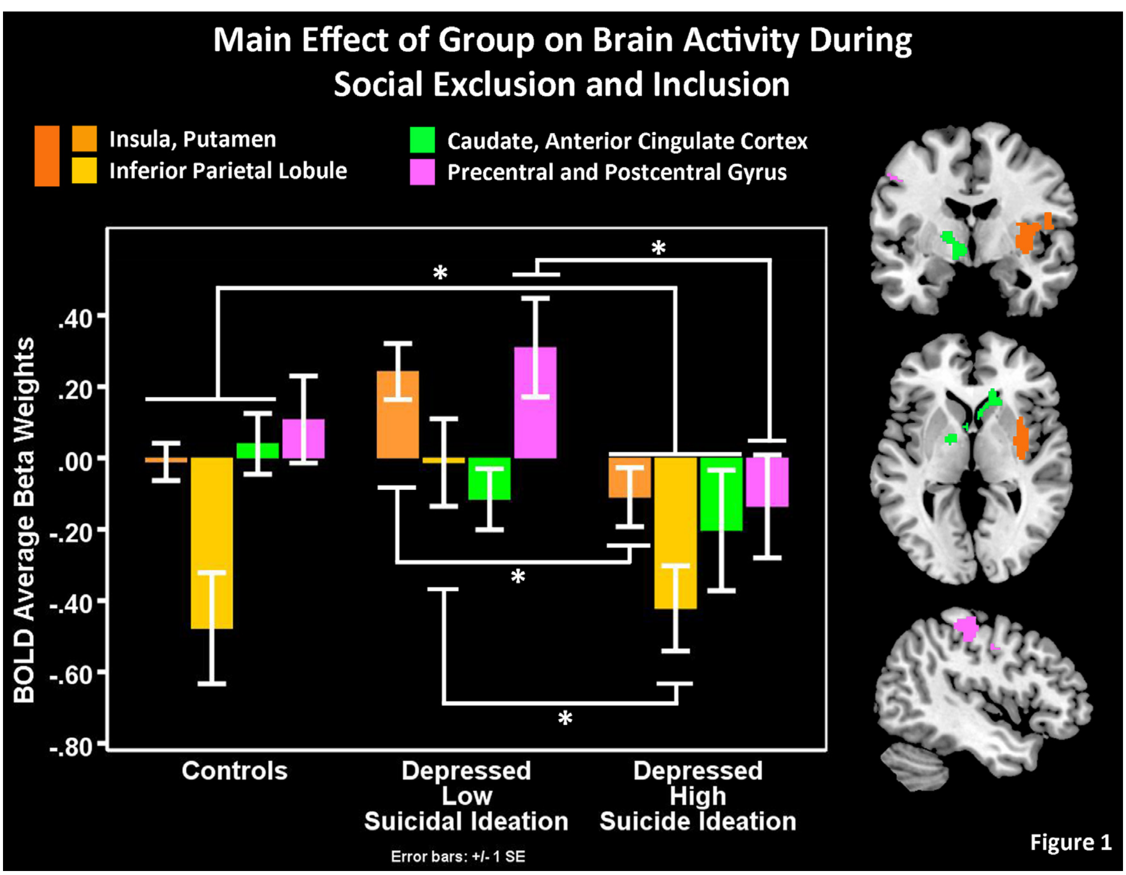

Fig. 1. HS adolescents showed lower blood oxygen level dependent (BOLD) neural activity in the precentral and postcentral gyrus, and in the superior temporal gyrus, medial frontal gyrus, insula, and putamen, compared to LS youth; and reduced BOLD response in caudate and anterior cingulate cortex compared to HC youth. Note: Error bars show +/− 1 SE. * indicates significant difference.

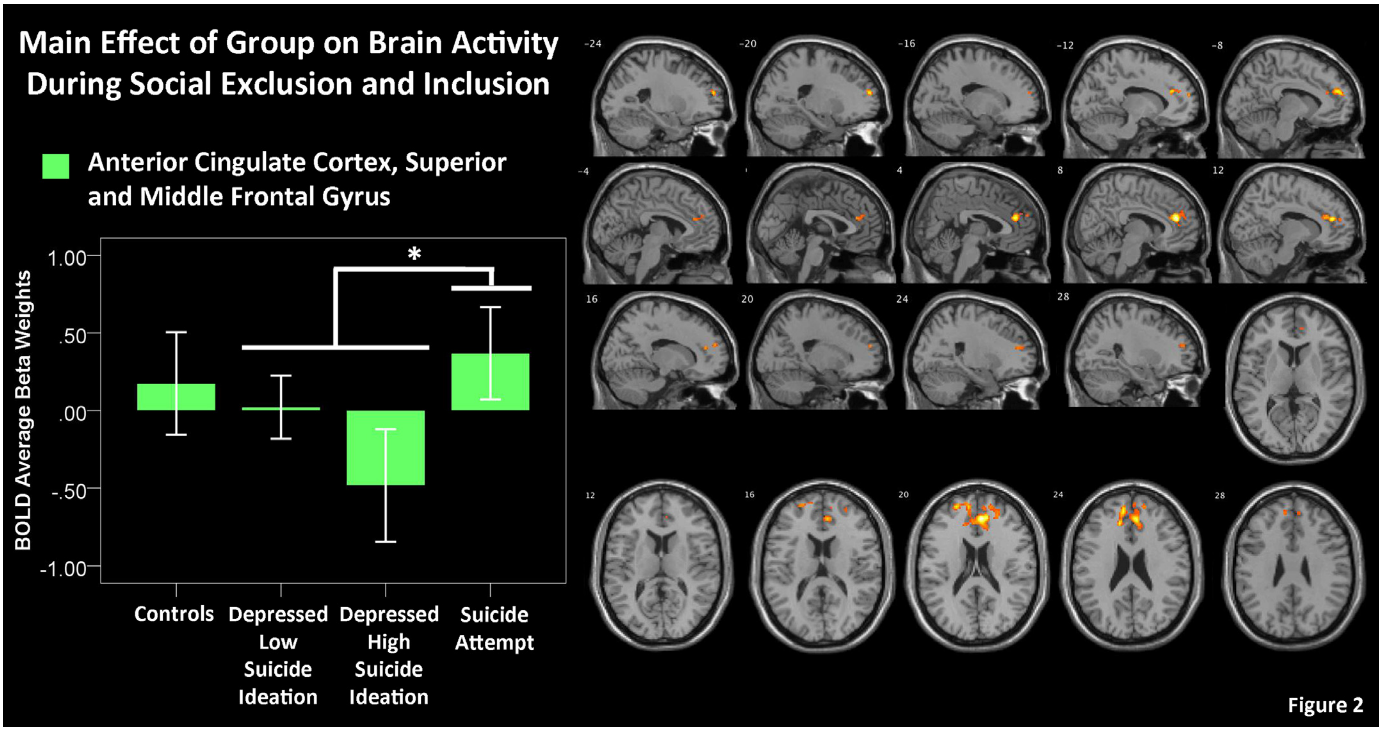

Fig. 2. Effect of recent suicide attempts on brain activity during social interactions. SA adolescents show higher anterior cingulate cortex and superior and middle frontal gyrus during social interactions compared to all other adolescents who do not differ significantly from each other. Note: Error bars show +/− 1 SE. * indicates significant difference.

3.3. *Individual differences in suicide-related traits*

High ACC, superior and middle frontal activity, which characterized SA relative to HC youth, was correlated with better social function in SA and HS groups (Fig. 3), positively correlated with negative emotionality in controls, and negatively correlated with cognitive control in healthy control youth. Additionally, high activity in the IPL/insula/putamen cluster, that was hypoactive in HS versus LS youth, was correlated with worse social function in LS adolescents. Precentral and postcentral gyrus activity, which was less active in HS than HC youth, was negatively correlated with cognitive control in LS adolescents. Finally, high caudate and ACC activity, which characterized HC relative to HS youth, was correlated with high negative emotionality in controls; see Table 2.

4. Discussion

Consistent with our hypotheses, the results from this study link suicide ideation in adolescents todisrupted neural function in regions of the insula and ACC (among other regions) during social interaction. Activity differences were not limited to social exclusion – they were present during both peer inclusion *and* exclusion versus the non-social practice condition – and the often-used exclusion versus inclusion contrast yielded no significant differences between groups (see Supplements). This study is the first to link adolescent suicide ideation to disrupted brain function during social interaction.

4.1. *Neural response to social interaction in adolescents with high suicide ideation or suicide attempt*

HS youth in the present study showed mostly *blunted* response during all social interaction versus a non-social condition, including in regions involved in interoceptive processing (insula) (Critchley et al., 2004; Pollatos et al., 2005); reward anticipation and motivation, (putamen) (Subramaniam et al., 2015; Baez-Mendoza and Schultz, 2013), conflict and prediction error (ACC and regions of the caudate) (Garrison et al., 2013), somatosensory perception and representation of emotional response (postcentral gyrus) (Kragel and LaBar, 2016; Adolphs, 2003), and motor activity (precentral gyrus) (Nebel et al., 2014). Blunted response in these regions could reflect reduced self-awareness, future-orientation, and cognitive and behavioral effort for social incentives in HS youth. In contrast, SA youth showed *higher* activity in the ACC and frontal gyrus than all other youth during social interaction. Given that HS adolescents showed *hypo*activation in non-overlapping regions (Supplemental Fig. 1) and had similar suicide ideation levels as SA, different neurobiological substrates might be associated with thinking about versus acting on suicide thoughts. It has been hypothesized that suicide ideation and attempts are qualitatively different phenomena with distinct risk factors (Klonsky et al., 2016). While high suicide ideation might be associated with blunted neural activity during all social interactions; youth who act on suicide thoughts might show heightened emotional distress or/and heightened emotion regulation needs during social situations. Our finding is consistent with previous reports that depressed adolescents with a history of suicide attempts showed higher ACC and dorsolateral prefrontal cortex activation while viewing slightly threatening faces (50% angry) compared to depressed adolescents without such history (Pan et al., 2013). The Cyberball task might represent a similar ambiguously threatening social scenario, during which at-risk adolescents show inefficient emotion regulation and attention during social engagement. Abnormal or high recruitment of ACC and frontal cortex might represent a potential biological marker for suicide attempts.

History of suicide attempt may also be associated with different social processing-related neural disruptions than depression. In the only other study to examine associations between suicidality and neural response during the Cyberball task, *decreased* insula and supramarginal gyrus activity to social exclusion versus inclusion was observed in adult women with depression and a history of suicide attempt compared to depressed women without a history of suicide attempt and healthy controls (Olie et al., 2017). In contrast, suicide attempters in this study showed *higher* activity than all other groups in the ACC and middle

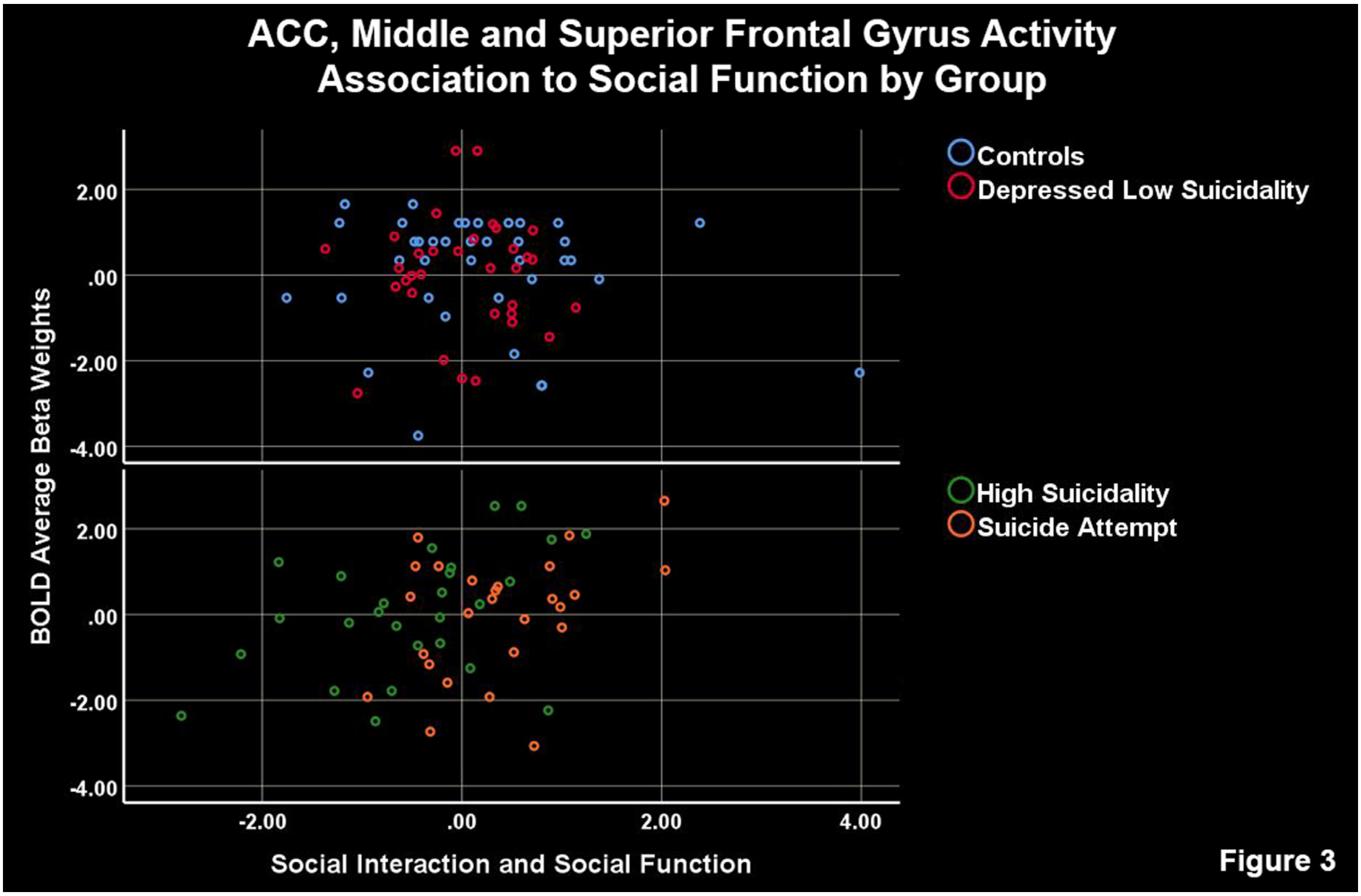

Fig. 3. Bivariate correlation between reported social interaction/social function (X axis) and ACC/Middle and superior frontal gyrus activity during Cyberball (Y axis) by group.

superior frontal gyrus. Differences in the location and direction of neural disruption between studies may be related to neurodevelopmental differences between study samples (adult women versus adolescents) and/or differences in the fMRI contrast conditions (exclusion versus inclusion, relative to inclusion and exclusion versus non-social practice). However, both studies suggest that depression, suicidal thoughts, and suicidal behaviors are associated with different neural signatures, and these present study suggests that there may be disruptions in interpreting and processing social cues regardless of level of social reciprocity. This notion is supported by empirical findings of impaired recognition of complex social emotions in depressed adults who had attempted suicide or who endorsed intense hopelessness and

Table 2
Correlations between social brain activity (inclusion + exclusion > nonsocial practice condition) and individual differences.

	Social function	Negative emotionality	Cognitive control
Healthy controls			
Precentral/postcentral gyrus	0.070	−0.125	0.104
Inferior parietal lobule, insula, putamen	0.064	−0.278	−0.074
Caudate, anterior cingulate cortex	−0.219	0.410*	−0.124
ACC, middle and superior frontal gyrus	−0.179	0.553*	−0.358*
Low suicide ideation			
Precentral/postcentral gyrus	−0.304	0.045	−0.415*
Inferior parietal lobule (IPL), insula, putamen	−0.440*	−0.172	−0.141
Caudate, anterior cingulate cortex	−0.246	−0.117	−0.022
ACC, middle and superior frontal gyrus	0.029	0.245	−0.282
High suicide ideation			
Precentral/postcentral gyrus	−0.120	0.246	−0.016
Inferior parietal lobule, insula, putamen	−0.254	0.033	0.154
Caudate, anterior cingulate cortex	0.068	−0.030	0.014
ACC, middle and superior frontal gyrus	0.436*	−0.001	−0.229
Suicide attempters			
ACC, middle and superior frontal gyrus	0.393*	−0.057	0.013

ACC/sup frontal area that is more active in suicide attempters.
(1) Positively correlated with social function in SA subjects, (2) Positively correlated with negative emotionality and negatively correlated with attention/cog control in controls.
* $p < 0.05$.

suicide behavior (Szanto et al., 2012).

Regions with group differences here undergo significant changes in function and connectivity across adolescence. ACC, medial frontal, and superior temporal regions are part of the "social brain network," whose activity during social tasks tends to increase across adolescence (Burnett et al., 2011). HS youth showed blunted neural activity during social interaction in these regions, while SA adolescents showed hyperactivity. This finding might reflect differing neural development among depressed adolescents who think about suicide versus those who act on such thoughts. In addition, caudate and putamen, whose activity was blunted in HS youth, are regions involved in reward processing that tend to show increased activity across adolescence in healthy development (Casey et al., 2008). This may reflect globally blunted reward processing in HS adolescents similar to depressed adolescents generally (Forbes and Dahl, 2012), or a more domain specific failure to find social interactions rewarding to the same extent as their peers.

Our findings suggest that perturbed social processing might characterize adolescents at risk for suicide attempts. Though social alienation has been linked to suicidal thoughts and behaviors (Horton et al., 2015; Joiner et al., 2009), and suicidal thoughts and behaviors often begin during adolescence (Gould et al., 2003), the current study is the first to link adolescent suicide ideation and attempts to disruptions in brain response during social interactions. Disruptions in social brain function that differentiated HS, LS, and SA groups remained after adjusting for severity of depression and substance use. Thus, neural activity perturbations during social interaction among adolescents with intense suicide ideation or/and with attempts is not fully accounted for by severity of depression symptoms or comorbid behaviors more common in severely depressed adolescents. The causal relationships between social brain dysfunction and suicide, however, cannot be determined from this study. One possibility is that neural dysfunction might lead to poor interpretation of social cues, impairing interpersonal relationships and subsequently leading to suicidal ideation and behavior. Alternatively, chronic rejection may influence brain function during social challenges in adolescence, and group differences observed here may reflect that process.

4.2. Neural response to social interaction in adolescents with depression versus healthy controls

Previous work linked depression in adolescence to hyperactivity in the prefrontal cortex, ACC, and insula during social exclusion relative to inclusion (Silk et al., 2014; Masten et al., 2011). Furthermore, research with the same task and sample as the present study found that depressed adolescents (LS and HS) had insula hyperresponsivity during peer exclusion relative to inclusion, while healthy adolescents showed insula *hyperresponsivity* during peer inclusion relative to exclusion (Jankowski et al., 2018). In the present study, LS and HS youth had increased response during social interaction versus a non-social condition in neural regions involved in attentional control and social processing (inferior parietal lobule, IPL) (Adamczyk et al., 2018; Hopfinger et al., 2000; Igelstrom and Graziano, 2017). These data suggest that depressed youth may devote more cognitive resources to both positive and negative social interaction than healthy adolescents. Differences in the specific locations of disruption between this study and previous research with the Cyberball task may reflect differences in the comparison conditions for measurement of BOLD response, with previous studies evaluating social inclusion relative to exclusion and this study comparing social interaction to non-social practice.

Depression, but not suicide ideation, was also linked to blunted caudate, lentiform nucleus, pallidum and ACC activity during social interaction in the present study. The caudate is implicated in reward processing and social cooperation (Bhanji and Delgado, 2014; King-Casas et al., 2005), as well as associative learning, behavioral preparedness, and prediction error (Pasupathy and Miller, 2005). Decreased caudate activity in all depressed youth (HS and LS) during social interaction might reflect disturbed interpersonal valuation and connection, or reduced encoding of prediction error regarding others' behaviors. The ACC, which lies at the interface of cortical and limbic regions, enables conflict detection, emotion regulation, error monitoring and effortful performance (Etkin et al., 2011; Krill and Platek, 2009; Margulies et al., 2007). Previous studies showed *higher* sgACC activation in depressed adolescents relative to controls during rejection versus acceptance using a ROI approach, and this finding was believed to reflect increased emotional distress and/or emotion regulation (Silk et al., 2014). By contrast, low ACC activation (though not sgACC) during *all* social interactions in depressed (HS and LS) youth, shown here, might reflect decreased monitoring and regulation of conflicting and emotionally salient events (see Pizzagalli (2011), for a review of frontocingulate dysfunction in depression). The differences between the findings of Silk et al. (2014) and the present study might reflect differences in depression severity, medications, use of ROI vs. WBL analyses and social tasks. For example, Silk et al. (2014) evaluated social rejection relative to acceptance in the Chatroom Interaction Task with ROI analyses and only 10% of depressed adolescents were medicated, whereas this study evaluated social interaction relative to non-social practice in the Cyberball task, half of our depressed sample were medicated which might indicate higher representation of severely depressed youth in our sample (Supplemental Table 1).

4.3. Individual differences in suicide-related traits

Activation in regions that differed between groups was differentially correlated with social function, negative affect, and cognitive control within the groups. Higher ACC and middle and superior frontal gyrus activity during social interactions was correlated with better social function only in HS and SA youth. This is an intriguing finding, particularly given that high activity in this cluster was correlated with high negative emotionality and low cognitive control in HC. This suggests that in HC, high prefrontal activity during social interactions is linked to distress, regulation of affect, or/and enhanced monitoring. However, among depressed youth with high suicide ideation or/and who attempted suicide, this region's activity might serve a compensatory function (e.g., to control negative affect during any social challenge). It should be noted that depressed adolescents showed lower social function than controls (see Supplemental text VI). Alternatively, social function could be more widely distributed in HS and SA, whereas HC might have a restricted social function distribution but more variability in negative emotionality (Fig. 3). In contrast, high IPL, insula, and putamen activity was linked to lower social function only in the LS group, potentially reflecting these area's compensatory roles during social interaction in depressed youth with low suicide ideation. Future research is necessary to replicate and extend these findings.

HS adolescents had lower activity compared to LS adolescents in the precentral and postcentral gyrus, which support motor and somatosensory functions. However, HS youth did not differ from HC in those regions' activity. High pre/post central gyrus activity was linked to lower cognitive control in the LS group, suggesting a compensatory response. This region has not, to our knowledge, been previously associated with depression or suicidality, so more research is needed to articulate its role in these clinical conditions.

High caudate and ACC activity was linked to negative emotionality only in healthy adolescents in the present study. Perhaps heightened conflict monitoring, and/or higher emotion regulation needs, are associated with more negative emotionality in healthy adolescents with sub-clinical symptoms. This is consistent with findings in healthy youth showing that higher sgACC activity during social exclusion predicted higher depressive symptoms one year later (Masten et al., 2011).

5. Limitations

Our sample was mostly white, which might impact attributions and neural response during the Cyberball task; the extent to which race influences attributions during the task is currently unknown. Second, we assessed suicide attempts and ideation through clinical interviews but did not measure suicidality or depression severity at scanning time. Although this might explain the reported group differences, we covaried for symptom severity at intake, and only 1–2 weeks separated intake and scanning sessions. Third, the Cyberball task design that aimed to increase social salience and ecological validity likely contributed to disrupted neural responses during both social inclusion and exclusion. Unreciprocated ball requests during inclusion might have been perceived as social exclusion or expectancy violation, perhaps contributing to the lack of Group by Conditions interactions. In addition, we may be underpowered to detect stronger and consistent effects for individual differences regarding the psychological constructs of interest and their associations with brain function. Unfortunately, due to a programming error, reaction times and frequency of button presses to request the ball were incorrectly recorded. Consequently, these results need to be replicated with more diverse samples, with longer versions of the present task and/or with previous versions of the task. This study cannot determine if abnormal neural function during social interaction preceded suicidal ideation or attempts, or if suicide ideation or attempts drive abnormal brain function during social interactions. Furthermore, environmental conditions related to developing depression and suicide risk—such as peer exclusion—may influence both brain function and psychopathology. This work is a starting point for longitudinal research to assess how peer environments, suicide risk, and brain function contribute to trajectories of suicide ideation and attempts, and how to prevent suicide morbidity.

Author contributions

Madeline Harms: Writing and revision of the introduction and discussion, editing all sections of the paper, and final draft of the manuscript. Behavioral analysis and coding and reliability of diagnostics.

Melynda D. Casement: Analysis consultation, writing and major revision of discussion section, major revision and editing of introduction, revisions for final draft of the manuscript.

Jia Yuan Teoh: Primary data analyses, figures and tables generation.

Riley Wedan: Revision and writing of introduction and discussion. Supplementary analyses.

Karina Quevedo: Writing of supporting grant, data collection, manuscript writing. Coding and reliability of diagnostics.

Hannah Scott: Data collection and supplementary analysis.

Sarah Ruiz: Coding and reliability of diagnostics

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.05.001.

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