Resting-State Functional Connectivity of the Precuneus Associated with Suicidality in Adolescents with Major Depressive Disorder

A Thesis

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Abstract

Background: Major depressive disorder (MDD) often begins in adolescence and is associated with increased risk for suicidal thoughts and behaviors, or suicidality. fMRI research investigating suicidality in adolescent populations is limited. Based on the interpersonal theory of suicide, which posits that suicide is the result of perceived burdensomeness and thwarted belongingness, the precuneus is an area of interest in this population due to its role in self-referential processing. Further, examining a potential moderation effect of non-suicidal self-injury (NSSI) may also be of interest, as NSSI may lay the groundwork for the third component of this theory, an acquired capability for suicide. **Method**: Fifty-eight adolescents with a primary diagnosis of MDD completed a self-report measure, which included a suicidality index, and a resting-state fMRI scan. Whole-brain connectivity analyses were conducted using the left and right precuneus as a seed and was correlated with scores on the suicidality index. We also examined whether the presence of greater than 4 lifetime episodes of NSSI moderated any findings. **Results**: While controlling for depression severity, suicidality was positively associated with RSFC between the left precuneus and left pre- and post-central gyri and middle and superior frontal gyri. There was no significant effect of NSSI history on this relationship. **Conclusion**: Increasing levels of suicidality may be associated with hyperconnectivity between the precuneus, an area important in self-referential processing, and areas implicated in empathy, social processing, and reorienting attention. These findings provide a neurobiological complement to the interpersonal theory of suicide and represent possible neurobiological targets for intervention and prevention of suicidal thoughts and behavior.

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Major depressive disorder (MDD) is a troubling issue among the adolescent population as approximately 25% suffer from a depressive disorder by the time they reach adulthood (Kessler, Avenevoli, & Ries Merikangas, 2001). MDD is of interest to suicide-related research as suicidal thoughts or behaviors (suicidality) is one of the symptoms of the disorder (American Psychiatric Association, 2013). In addition, a diagnosis of MDD indicates significantly increased risk for suicide ideation, behavior and deaths (Kessler et al., 2001). Suicide is a leading cause of death among adolescents between the ages of 15-24 and 17.7% of U.S. high school students report having seriously considered suicide in the past year, 8.6% had attempted suicide, and 2.8% made an attempt that required medical attention (CDC, 2015). It is estimated that 98% of those who die by suicide suffer from at least one mental disorder. Because the majority of those who die by suicide suffer from a mood disorder (Bertolote, Fleischmann, De Leo, & Wasserman, 2004), it is important to begin exploring the relationship between suicidal thoughts and behaviors (or suicidality) and brain functioning among adolescents with depression.

Theories of Suicide

Perhaps the first formalized theory of suicide is that originally published by Durkheim in 1897. This theory provides a sociological approach to understanding suicide. Specifically, that increased suicide is due to a failure of society to adequately regulate the individual. According to Durkheim, suicide has a curvilinear relationship with two constructs, resulting in four different types of suicide: (1) social integration, wherein too much results in “altruistic” suicide and too little results in “egoistic” suicide;

and (2) moral regulation, wherein too much results in "fatalistic" suicide and too little results in "anomic" suicide (Durkheim, 1951).

A contemporary theory of suicide is Joiner's interpersonal theory. Although there are parallels between Durkheim's and Joiner's theories, Joiner takes an approach that focuses more on the individual rather than society. The first two of the three components of this theory, perceived burdensomeness and thwarted belongingness, serve as the negative interpersonal states proposed by Joiner (2005). Perceived burdensomeness refers to the belief that one is a burden to in some form—whether it is to family, peers, or to society. This idea has been validated in the literature among adults with borderline personality disorder who have made suicide attempts. Specifically, Brown et al. found that the most frequently endorsed reason for suicide was to "make others better off" (Brown, Comtois, & Linehan, 2002). Thwarted belongingness refers to the belief that one does not have a valuable purpose to his or her group or society and feels alienated. In other words, this component can manifest itself through the feelings of worthlessness and helplessness, which are both symptoms of MDD and are documented risk factors for suicide (Oexle et al., 2016). Both of Joiner's interpersonal states can be viewed as having similarities with Durkheim's "social integration", in which lack of social integration may result in feelings of thwarted belongingness, and too much social integration may result in perceived burdensomeness.

The third component of Joiner's theory is the acquired capability for suicide. This takes the form of maladaptive thoughts and behaviors that lower an individual's natural capacity for self-preservation and may include mentally rehearsing suicide, substance abuse, or non-suicidal self-injury (NSSI). There is evidence that NSSI is associated with

a substantially increased risk for later suicide (Horwitz, Czyz, & King, 2014; Tang et al., 2011; Victor & Klonsky, 2014). Notably, of adolescents who engage in NSSI, 70% report having made a suicide attempt during their lifetime (Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006).

Research examining biological aspects of human behavior has been rapidly expanding in recent years. Despite several studies documenting neurobiological differences among those with suicidality, which are reviewed briefly below, a clear biologically based theory of suicide has yet to emerge. A more general theory that has been applied is that suicide, similar other aspects of psychopathology, may ascribe to a diathesis-stress model (Heeringen, 2012). Specifically, there is an inherent biological risk for suicide (diathesis) that manifests when the individual is exposed to a significant event in his or her environment (stressor). Because this theory is quite broad, it may be beneficial to organize the existing research using the framework of the interpersonal theory. This may assist in narrowing our focus to specific brain regions that may play a role in suicidality.

Neurobiology of Suicide in Adults and Interpersonal Theory

Joiner's first two components of his interpersonal theory involve the perception of being a burden and/or worthless. Because these perceptions can be conceptualized as being highly related to having a tendency toward experiencing negative affect, it is possible that these beliefs may arise from dysregulation within key brain regions that are involved in affective experience, its regulation, and self-referential processing. As reviewed below, post-mortem work as well as studies in adults provides rationale for investigating these particular brain regions.

Post-Mortem Research

Post-mortem research has supported potential anomalies, particularly in the anterior cingulate cortex (ACC), a region involved in cognitive and affective processing (Bush, Luu, & Posner, 2000). The ACC showed decreased myelin basic protein immunoreactivity in MDD and schizophrenia patients who died by suicide (Honer et al., 1999) and astrocytic hypertrophy in MDD patients who died by suicide (Torres-Platas et al., 2011), which are both indices of aberrant white matter structure and suggest potential deficits in neural communication. Additional research has found greater microglia, which indicates subtle white matter damage, in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), ACC, and medial-dorsal thalamus among those who died by suicide compared to those who died of other causes (Schnieder et al., 2014; Steiner et al., 2008).

Structural MRI Research

In addition to post-mortem work, in-vivo studies have documented anomalies in frontal-limbic structures, which are implicated in affective experience and its regulation. Specifically, volume abnormalities have been found among suicidal patients and patients at high risk for suicide in the ACC, amygdala, orbitofrontal cortex (OFC), VLPFC, DLPFC, insula, temporal cortex, hippocampus, and caudate (Ding et al., 2015; Monkul et al., 2007; Soloff et al., 2012; Spoletini et al., 2011; Wagner et al., 2012).

In addition to volume anomalies, studies have used diffusion tensor imaging (DTI) to measure differences in white matter microstructure. Among those with bipolar disorder, those who also had previous suicide attempts had compromised white mater in the OFC compared to those with no attempts (Mahon, Burdick, Wu, Ardekani, &

Szeszko, 2012). Further, those with MDD and suicide attempts showed decreased fractional anisotropy (FA; a measure of white matter integrity) in left anterior limb of the interior capsule (a fiber bundle that runs between the thalamus and frontal lobe as well as between other regions), within the right dorsomedial PFC, left medial frontal cortex, OFC, posterior parietal lobe, basal ganglia, and thalamus compared to non-attempters and healthy controls (Jia et al., 2010, 2014; Olvet et al., 2014; Taylor et al., 2015). Decreased FA was also found in the right frontal lobe relative to controls and right lentiform nucleus compared to non-attempters (Jia et al., 2010). These findings, similar to post-mortem results, suggest a possible deficit in neuronal communication among brain regions involved in affective experience and regulation that is particularly pronounced among individuals with high suicidality.

Functional MRI Research

Task fMRI research in adults is relatively well established, particularly when compared to work in adolescents. Similar to post-mortem and structural findings, adult task fMRI studies have also found evidence of functional abnormalities implicating structures involved in affective experience and affect regulation. In regard to affective experience, Olié and colleagues examined fMRI during social threat by examining brain activation in response to an emotional face-viewing task. This is of particular interest as the construct of social threat can be conceptualized as being closely linked to thwarted belongingness. When compared with participants with depression and no suicide attempts, those with depression and past suicide attempts showed greater activation in the OFC and VLPFC in response to angry versus neutral faces; and decreased activity in ACC in response to sad versus neutral faces (Olié et al., 2015). A study also examined

brain activation while participants listened to autobiographical scripts describing the moments before and during a past suicide attempt. This study found that listening to the suicide script, compared to a non-suicide script, resulted in decreased activity in the PFC and that the description of the act itself, when compared to the mental pain preceding the act, elicited increased activity in the medial PFC, ACC, and hippocampus (Reisch et al., 2010). These studies suggest anomalous functioning of regions involved in affective experience and processing.

Studies examining neural functioning during tasks measuring cognitive control may be relevant to regulation of affect. During tasks involving cognitive control, Minzenberg et al. found greater activation among those with suicidal thoughts and behaviors (suicidality) and recent-onset schizophrenia or mood disorders with psychotic symptoms compared to psychiatric controls in the supplementary motor area, premotor cortex, DLPFC, VLPFC, OFC, rostral insula, and dorsal striatum (Minzenberg et al., 2015a, 2015b). Additionally, in a study of decision-making using the Iowa Gambling Task (IGT), those with depression and past suicide attempts had greater activation than those with depression and no suicide attempts in the OFC, dorsal prefrontal cortex, and ACC in response to wins versus losses; and decreased activity in dorsal prefrontal cortex in response to risky versus safe choices (Olié et al., 2015). In contrast to these findings, another study by Minzenberg et al. found decreased activation of several regions within the PFC among those with suicidal histories and recent-onset schizophrenia during a cognitive control task (Minzenberg et al., 2014). However, these discrepancies may be due to differing regions within the PFC as Minzenberg et al. (2014) found decreased activation in the superior and medial frontal gyri, dorsal ACC, and precentral gyrus.

Taken together, these studies suggest aberrations in the functioning of brain structures responsible for cognitive control, which may then impact successful regulation of negative affect.

Additional knowledge about brain functioning is revealed through examination of the functioning of neural networks. This can be achieved via functional connectivity (FC), which examines the correlation of blood oxygen level dependent (BOLD) signal between different regions of the brain. Positive connectivity (or correlation) is considered to reflect brain regions that are in sync with on another and serve similar goals while negative connectivity reflects brain regions that serve opposing goals (Fox et al., 2005). This can be done in the absence of a particular task. The use of resting-state fMRI provides a reliable way to measure task-independent neural functioning. This provides greater generalizability of findings to typical daily activity. Only two studies have examined neural functioning related to suicidality at rest in adults. These studies used amplitude of low frequency fluctuation (ALFF) and regional homogeneity (ReHo), which are both measures of regional FC. The study using ALFF found that suicide attempts in adults with MDD was associated with greater ALFF in superior temporal gyrus (Fan, Wu, Yao, & Dong, 2013). The study using ReHo found that, compared to healthy controls, those with suicide attempts and no diagnosed psychiatric disorder had lower ReHo in left fusiform, inferior frontal, parahippocampal, and middle frontal gyri, and hippocampus, and right angular gyrus and cerebellum. Additionally, those with suicide attempts had higher ReHo in right middle frontal gyrus and inferior parietal lobule and left precuneus (Cao et al., 2015). Taken together, these results suggest deficits in affect regulation, decision-making, and impulsivity.

Neurobiology of Suicide in Adolescents and Interpersonal Theory

Because many psychiatric disorders including MDD begin in adolescence, which is also a time period marked by significant neural development (Giedd et al., 1999; Shaw et al., 2008), investigating suicidality within this population is of high importance. By doing so, we may not only better understand psychopathology in its early stages, but we can also use this information to apply more effective intervention and prevention strategies to promote healthy neurodevelopmental trajectories.

Two studies have examined brain activity related to suicidality in adolescents while completing fMRI tasks requiring cognitive control, which may be applicable to understanding affect regulation. Specifically, during a GoNoGo task involving response inhibition, adolescents with MDD and suicide attempts had decreased activity in the ACC compared to those without suicide attempts (Pan et al., 2011). This is in contrast with findings among middle-aged adults in which there were no differences in brain activation between MDD participants with and without suicidal behavior during a GoNoGo task (Richard-Devantoy, Ding, Lepage, Turecki, & Jollant, 2016). In another study, Pan and colleagues' use of the Iowa Gambling Task revealed that adolescents with MDD and suicide attempts showed decreased activity in the right thalamus compared to MDD with no suicide attempts during high-risk decisions and increased activity in the left caudate compared to healthy controls during low-risk decisions (Pan, Segreti, et al., 2013).

Perhaps more applicable to the interpersonal theory due to the examination of negative affect, one study examined brain activation and functional connectivity in adolescents with suicidality during an emotion-processing task. While viewing angry faces, those with MDD and suicide attempts had greater activation than those with MDD

and no attempts in regions implicated in emotion and regulatory control (Pan, Hassel, et al., 2013). Those with MDD and suicide attempts showed lower activity compared to healthy controls in left somatosensory cortex while viewing happy faces as well as in regions implicated in emotion and regulatory control while viewing neutral faces (Pan, Hassel, et al., 2013).

To date, only one study has examined FC in adolescents with suicidality. In the previously mentioned study, Pan and colleagues also found that adolescents with MDD and suicide attempts, compared to those with no attempts, had reduced functional connectivity between the anterior cingulate cortex (ACC) and bilateral insula while completing an fMRI task that included viewing angry faces (Pan, Hassel, et al., 2013). However, no known study has examined resting-state neural circuitry in adolescents with suicidality, nor examined FC between different brain regions via resting-state functional connectivity (RSFC) in either adolescents or adults with suicidality.

Present Study

As reviewed above, much of the existing literature on suicide in both adults and adolescents has focused on affective experience and its regulation. However, no known study has investigated adolescent suicidality and functioning of brain regions implicated in self-referential processing. Abnormalities of the two components of affective experience and affect regulation can be considered to be essential neurobiological components that lay the groundwork for suicidality. Nonetheless, neural circuitry associated with self-referential processing that may be highly applicable to the interpersonal theory, and thus serve as a third essential component. This is because the occurrence of thwarted belongingness and perceived burdensomeness depend upon the

propensity for an individual to *perceive* those states. In other words, a person at high risk for suicide may have a tendency to feel like a burden or an outsider, regardless of how others actually feel about that person.

Figure 1 provides a visual representation of a working model that integrates both a potential neurobiological theory of suicide as well as the interpersonal theory of suicide. On the left, the diagram depicts deficits in three neurobiological components: (1) affective experience; (2) affective regulation; and (3) self-referential processing. When there are deficits in all three of these areas, the groundwork for the interpersonal theory of suicide is then present. As reviewed above, research on suicidality has documented widespread deficits in affective experience and regulation. However, research investigating the link between suicidality and regions implicated in self-referential processing is limited to the study highlighted below.

One region of particular interest in relation to suicide and negative self-referential processing is the precuneus. The precuneus is a key region of the default mode network (DMN), which is a network of regions that are more active during non-task (or rest) conditions in the scanner (Raichle et al., 2001). DMN abnormalities in psychopathology have been documented extensively in the literature, including in the context of MDD (Peng et al., 2015; Sheline et al., 2009). One study of adults males with depression examined the precuneus in the context of a motor task and found increased task functional connectivity between the precuneus and medial frontal gyrus and putamen among those with suicidal ideation (Marchand et al., 2012). However, no study has examined the functional connectivity of the precuneus in adolescents with suicidality.

The aim of the present study is to (1) address the gap in the literature by examining the association between suicidality in adolescents with MDD and neural functioning of circuits implicated in self-referential processing using rsfMRI; and (2) incorporate Joiner's third component regarding acquired capability of suicide by conducting exploratory follow-up analyses to examine whether a history of NSSI moderates the relationship between suicidality and RSFC.

Given the paucity of literature in this area, the hypotheses of this study are exploratory in nature. However, for our first aim, we anticipate that suicidality will be positively associated with RSFC between the precuneus and regions implicated in negative affect and the salience network. Specifically, this would include the amygdala, insula, and dorsal anterior cingulate. The rationale for this is that it would suggest that, during the absence of goal-oriented activity, those with greater suicidality may have inappropriately increased input from regions involved in negative affect and/or interoceptive awareness to regions involved in self-reflection. Such inappropriate inputs may contribute to the propensity for these individuals to perceive themselves negatively, such as being worthless or a burden, as well as attribute greater importance or salience to these perceptions. For our second aim, which is exploratory, it is anticipated that history of NSSI, a potential indicator for acquired capability for suicide, will moderate this relationship. Specifically, those with a history of NSSI will be driving the relationship between precuneus RSFC and suicidality.

Method

Participants

Adolescents between the ages of 12 and 19 with major depressive disorder were recruited and deemed eligible to participate in the study. Participants were eligible if they had a primary diagnosis of MDD. Exclusion criteria included an IQ below 80 as determined by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), the presence of a neurological or chronic medical condition, or meeting DSM-IV-TR criteria for pervasive developmental disorder, bipolar disorder, or schizophrenia. In addition, participants could not have any MRI contraindications such as claustrophobia, braces, or metal implants.

Measures

Psychiatric Assessments

Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version

All participants completed the Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997), to determine the presence of an Axis I disorder as defined by the DSM-IV-TR. The KSADS-PL consists of a through developmental history and an initial screening interview for each DSM-IV-TR Axis I disorder. For each disorder within the screen that reached a rating above threshold for either current or past symptoms, a supplementary interview for that disorder was also conducted to assess for potential diagnosis. A licensed doctoral-level clinician, or a trained graduate student under the supervision of a licensed psychologist administered these interviews. Interview training included listening and rating four audiotaped KSADS-PL interviews, observing a licensed clinician perform

a minimum of two in-person interviews, and administering a minimum of two in-person interviews with a licensed clinician in the room.

Inter-rater reliability within our lab has been calculated to be 100% for MDD diagnosis, 84.63% for MDD symptom ratings, and 96% for the screen items. Diagnoses were based on consensus between parent and child reports. In addition to a consensus on diagnosis, a consensus was also made on an item within the KSADS-PL that assesses for history of NSSI. This interview included a question as to whether there was a history of NSSI. We focused on those who had a history of greater than 4 episodes of NSSI for our moderation analyses, as we were more interested in those who engaged in more repetitive NSSI instead of those who may have only engaged in NSSI one time and discontinued thereafter.

Inventory of Depression and Anxiety Symptoms

All participants completed the Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al., 2007). This measure results in a variety of indices, including Suicidality and General Depression, which are of interest to this study. The IDAS has a high internal consistency across all indices with $\alpha > .80$ among psychiatric patients and $\alpha > .70$ among high school students. Further, this measure also has high concurrent validity with other well-established measures such as the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996).

Most relevant to this study, the Suicidality Index has been found to represent the suicidality criterion for DSM-IV diagnosis of depression with a correlation between .97 and .99 across samples of psychiatric patients, community adults, and college students as well as with the corresponding interview item on the Interview for Mood and Anxiety

Symptom Composites (IMAS; Kotov, Gamez, & Watson, 2005) with a correlation of .62. Additionally, the Suicidality Index has internal consistency of $\alpha > .85$ among psychiatric patients and $\alpha > .90$ among high school students and test-test reliability of .77. Additional psychometric information can be found in Watson et al., 2007.

MRI Data Acquisition

Data were acquired using a Siemens 3T TIM Trio scanner at the Center for Magnetic Resonance Research at the University of Minnesota. A five-minute structural scan was acquired using a T1-weighted high-resolution magnetization prepared gradient echo (MPRAGE) sequence: TR = 2530ms; TE = 3.65ms; TI = 1100ms; flip angle = 7 degrees; 1mm slices, FOV = 256, voxel size 1x1x1mm; GRAPPA = 2. For the rsfMRI acquisition, which began approximately 30-40 minutes from the beginning of the protocol, participants completed a field map and a six-minute scan during which they were instructed to keep their eyes closed and to not fall asleep. The resting state scan was comprised of 180 contiguous echo planar imaging (EPI) whole brain volumes with TR = 2000ms; FOV = 256; voxel size 3.43x3.43x4mm; 34 slices; 64x64 matrix.

Procedure

The University of Minnesota Institutional Review Board approved this study. Adolescents with MDD were recruited from inpatient and outpatient clinics at the University of Minnesota as well as from advertisements in the community. Parents or legal guardians of interested participants completed an initial phone screening to assess inclusion and exclusion criteria. Those who appeared eligible to participate were invited to the University of Minnesota to complete consent/assent followed by an initial assessment. During this visit, participants and their parents/legal guardians (when

applicable) received additional study information and completed informed consent/assent. If under 18, the adolescent and the legal guardian completed separate interviews, after which a consensus was obtained regarding diagnosis. Either a clinician or a graduate student under practicum supervision conducted all interviews. Participants that were deemed eligible were invited for a subsequent visit to complete MRI scanning. This included a 6-minute rsfMRI scan, during which they were instructed to lie awake with their eyes closed. Participants received monetary compensation for their time after each visit.

Statistical Analyses

Demographics and Clinical Data

Demographic and clinical data information was analyzed with SPSS Version 21 to calculate descriptive statistics including means, standard deviations, and frequencies of variables. To increase the level of specificity of our findings to suicidality, level of depressive symptoms, as measured by the General Depression Index on the IDAS, was entered as a covariate. However, due to the overlap of items between the Suicidality Index and General Depression Index, we subtracted the scores of the overlapping items from the total on the General Depression Index for each individual. There was a significant correlation between the Suicidality Index and the General Depression Index ($r = .644$, $p < .001$) and also the General Depression Index minus overlapping Suicidality Index items ($r = .541$, $p < .001$).

Resting-State fMRI Preprocessing

FreeSurfer Version 5.3 (surfer.nmr.mgh.harvard.edu) was used to create anatomically based ROIs, cerebral spinal fluid (CSF) and white matter (WM) from the T1

data. We chose to use FreeSurfer ROIs as opposed to spherical ROIs due to the ability of FreeSurfer to tailor these regions based on each individual's anatomy. This is opposed to spherical ROIs, which are created using the same coordinates for each person and do not account for individual differences in anatomy. FreeSurfer output was visually inspected for parcellation errors. When errors occurred, they were manually corrected on a slice-by-slice basis before proceeding to the next steps in the processing pipeline. For the fMRI data, denoising was completed using RETROICOR (Glover, Li, & Ress, 2000) to remove physiological noise (heart rate and respiration), which were monitored during resting-state data acquisition. The FMRIB software library (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and custom-developed tools in MATLAB were used to conduct image processing. The field map was used to correct for magnetic field inhomogeneity-induced geometric distortion. CSF and WM created previously using FreeSurfer were aligned to each individual's fMRI data using FLIRT and mean BOLD time series within these regions were extracted using *fslmeants*. We performed a regression of eight nuisance variables: WM, CSF, and six motion parameters on each other voxel's time series.

Based on the procedures by Power and colleagues (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), we conducted data scrubbing. During this step, volumes were excluded if they had a DVARS value above 8 and/or a framewise-dependent value above 0.5. The volume prior and the two volumes following were also removed. Participants with greater than 1/3 of volumes removed (60/180) were excluded from analyses. This resulted in 58 for our final group analyses.

Functional Connectivity Analysis

After extracting the timeseries of our regions of interest (ROIs), which included left and right precuneus, we performed first-level individual connectivity analyses using FEAT for each ROI. We entered each ROI in a general linear model as the primary regressor with no temporal derivative, temporal filtering, or convolution. Pre-stats, stats, and post-stats were generated using 5mm spatial smoothing and FILM prewhitening. At this step, each individual scan was registered to MNI standard space (Mazziotta, Toga, Evans, Fox, & Lancaster, 1995). For the higher-level analyses, which included the whole group, we used demeaned Suicidality Index scores from the IDAS as primary regressors to examine whole-brain connectivity for each ROI. Corrected scores on the General Depression Index (described above) were demeaned and entered as a covariate. We used Gaussian Random Field theory to correct for multiple testing across voxels using a cluster z-threshold of 2.3 and a corrected $p < .025$ to correct for the two separate RSFC analyses (right and left precuneus). Significant clusters were used as masks to extract average z-scores from each participant's unthresholded connectivity maps. These values were then used for subsequent analyses in SPSS.

Moderation Effect of NSSI History on Suicidality-Precuneus RSFC

SPSS Version 21 was used to examine whether a history of greater than 4 episodes of NSSI moderated the relationship between suicidality and precuneus RSFC. This was done by conducting a linear regression using two different models. The first model included mean-centered individual Suicidality Index scores and whether or not the participant engaged in greater than 4 episodes of NSSI as the independent variables. The second model included the interaction term calculated by multiplying the two

independent variables from the first model. For both models, the extracted z-scores from significant precuneus RSFC clusters were used as the dependent variable.

Results

Demographic and Clinical Characteristics

A total of 58 participants diagnosed with MDD were included in the present study due to complete and usable IDAS and rsfMRI data (Figure 2). Four participants were recruited from either the inpatient or outpatient clinics and did not complete the KSADS-PL as a primary diagnosis of MDD was confirmed during their visit. Thus, these individuals are missing data typically assessed with the KSADS-PL, such as comorbidity and NSSI history. Participants were predominantly female (77.6%), European American (70.7%), and right handed (90.9%). Approximately one-quarter of participants were taking antidepressants at the time of the MRI scan (25.9%). The majority of participants had a comorbid disorder (65%). Over one-third of the sample endorsed greater than 4 episodes of NSSI (39.7%). Additional information regarding participant characteristics can be found in Table 1. Graphical representations of IDAS variables of General Depression Index, General Depression Index (corrected), and Suicidality can be found in Figures 3-5.

When examining group differences between those who did versus those who did not have a history of greater than 4 lifetime episodes of NSSI, there were no significant differences in corrected general depression severity (M *NSSI* = 52.17, M *no NSSI* = 51.61, $t(52) = .880$) or level of suicidality (M *NSSI* = 13.26, M *no NSSI* = 10.52, $t(52) = .090$).

Resting-State fMRI Results

RSFC between the left precuneus and left pre- and post-central gyri, superior parietal lobule, and middle and superior frontal gyri was positively associated with suicidality while controlling for depression severity ($r = .542, p < .001$). This cluster was comprised of 1043 voxels and the maximum z-statistic of this cluster was 3.69. The peak cluster was located at MNI coordinates -38, -12, 56, which was in the vicinity of the left precentral gyrus. There were an additional five local maxima with z-statistics ranging from 2.99 to 3.24 in the vicinities of the left pre and postcentral gyri, superior parietal lobule, and middle frontal gyrus. Additional cluster information can be found in Table 2 and Figures 6 and 7.

Additionally, because 65% of participants had a comorbid disorder and 25.9% were taking antidepressants at the time of the MRI scan, post-hoc analyses were performed on the RSFC results to determine whether this finding held while controlling for these variables. This finding did continue to hold while controlling for current comorbidity and medication status ($r = .599, p < .001$).

Moderation Effect of NSSI History on Suicidality-Precuneus RSFC

There was no significant moderation effect of a history of engaging in greater than 4 episodes of NSSI ($\Delta R^2 = .004$, p = .486).

Discussion

This is the first study to examine the RSFC of suicidality among adolescents with MDD. The purpose of this study was to highlight the role of self-referential processing in suicidality by investigating the functional connectivity of the precuneus. Contrary to predictions, suicidality was not significantly associated with RSFC between the precuneus and regions typically associated with negative affect and threat. However,

higher levels suicidality was significantly associated with greater RSFC between the left precuneus and left pre- and post-central gyri and middle and superior frontal gyri. The pre-and post-central gyri include the primary motor and somatosensory cortex respectively. The somatosensory area is often implicated in studies of empathy and social perception (Gallese, Eagle, & Migone, 2007; Lawrence et al., 2006). Further, it has been associated with early stages of emotion induction (Rudrauf et al., 2009) and the experience of social rejection (Kross, Berman, Mischel, Smith, & Wager, 2011). Thus, the association between suicidality and precuneus RSFC with this region suggests greater emotional sensitivity and perception during self-referential processing.

Abnormal functioning and connectivity within the middle frontal gyrus has been documented studies of adults and adolescents with MDD (Guo et al., 2012; Jiao et al., 2011; Wu et al., 2011; Zhang et al., 2016). Additionally, increased precuneus-middle frontal gyrus connectivity is consistent with previous task fMRI research investigating suicidality in adult males with MDD (Marchand et al., 2012). The middle frontal gyrus is considered to be where both ventral and dorsal attention networks converge and plays a role in reorienting attention (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015). Further, reduced cortical thickness of the middle and superior frontal gyri has been associated with impulsivity in adolescence (Schilling et al., 2013) and has been linked to motor impulsivity in particular (Holmes, Hollinshead, Roffman, Smoller, & Buckner, 2016). These findings suggest that those with greater suicidality may allocate greater attentional resources and cognitive control in relation to self-referential processing.

Potential treatment implications of these findings may be that those with greater levels of suicidality may benefit from either mentalization-based psychotherapy or

cognitive behavioral strategies that focus on cognitive distortions surrounding interpersonal interactions. These strategies may focus on normalizing the hyperconnectivity between the precuneus and primary motor and somatosensory cortices in particular. Future intervention research investigating this relationship will be imperative in the advancement of personalized interventions for psychopathology.

Strengths and Limitations

This is the first study to date to examine the RSFC associated with suicidality in a sample of adolescents with MDD. Further, the sample size is relatively large compared to previous work incorporating suicidality and neuroimaging. This study also utilized highly conservative preprocessing strategies, such as "scrubbing" to remove whole brain volumes that exceed a certain threshold of motion (Power et al., 2012). This strengthens findings as it provides high-quality data that are less likely to be compromised due to motion artifacts.

Aside from its strengths, this study's cross-sectional design greatly reduces the ability to make inferences regarding whether anomalous RSFC is the cause or result of suicidal thoughts and behavior. In addition, although the present study failed to find an effect of NSSI on our findings, this may be due to the substantial overlap of NSSI with measures of suicidality. Specifically, the IDAS includes questions regarding self-harm without differentiation between suicidal and non-suicidal intent. This highlights the importance of using measures that successfully differentiate between these behaviors. Fortunately, interest in studying NSSI has surged in recent years and thus, more attention has been given in differentiating suicidal from NSSI behavior.

Future Directions

It is noteworthy that the current literature on the neurobiology of suicide examines different aspects of suicidality. Specifically, these studies vary in examining the neurobiology associated with completed suicide, suicide attempts, and suicidal ideation. Continued work will be important in disentangling whether there are varying neurobiological phenomena that differentiate these levels of suicidality, or whether these neurobiological phenomena overlap across these levels of suicidality and thus exist on continuum (i.e. suicidal ideation is associated with less, while suicide attempts and completions are associated with more, neurobiological dysregulation).

Future research would benefit from looking at suicidality across diagnostic categories to better understand the thoughts and behaviors themselves without the confines of one particular disorder. Additionally, the use of psychiatric control groups would be highly useful as a way to disentangle the potential confounds of disorder presentation. Research must also consider a longitudinal perspective that identifies adolescents who are at-risk for suicidality and follows them throughout adolescent development. In doing so, we may be able to identify predictive biomarkers that may aid in the advance of more successful prevention strategies.

Conclusions

Suicidal thoughts and behavior is an important construct to examine thoroughly as it has consistently been one of the leading causes of death among our nation's young people (CDC, 2015). This study takes an important step to understand the brain mechanisms associated with suicidality at rest in adolescents with MDD. Specifically, we found hyperconnectivity of the precuneus with regions associated with the sensation of emotion, social processing, and attention. These findings provide support that

neurobiological deficits in the areas of affective experience, affective regulation, and self-referential processing, may lay the groundwork for the interpersonal theory of suicide. Additional research is needed to more closely tie these neurobiological areas to that of the interpersonal theory of suicide. Finally, research is also needed to investigate how neural circuitry relates to specific symptoms and/or behaviors rather than to a broad disorder. Specifically, suicidal thoughts and behaviors occur among more adolescents than just those with MDD. Thus, to better understand this serious issue, researchers must begin to examine suicidality regardless of diagnosis. In doing so, we will be able to use this information to inform more effective prevention and intervention strategies that target neurobiological deficits.

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Table 1. Participant Characteristics

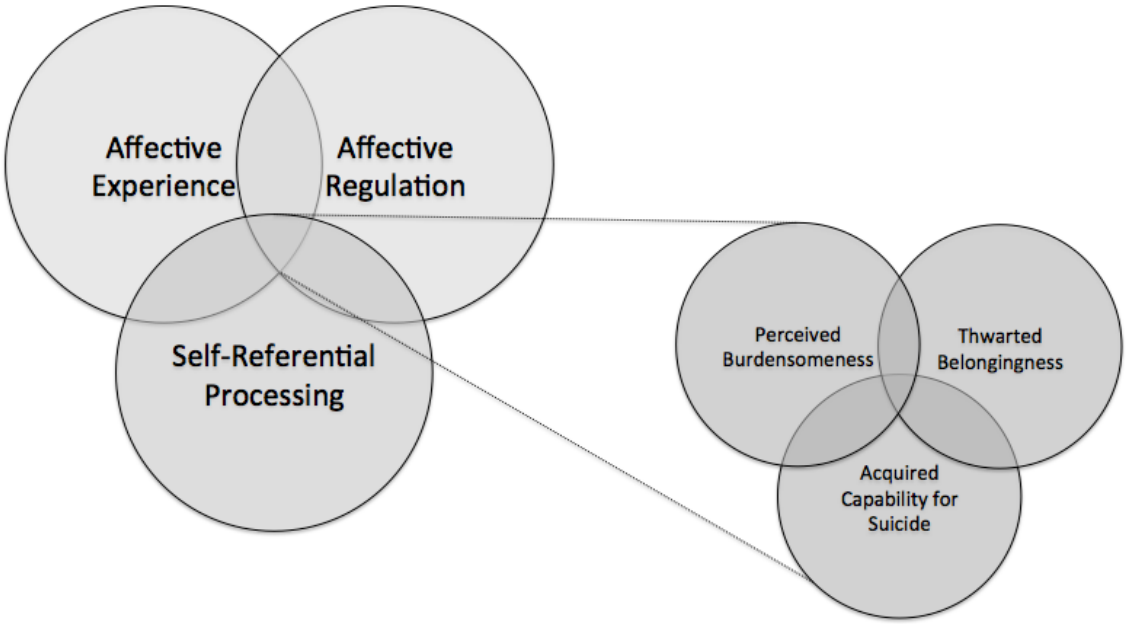
Demographic Characteristics (N = 58)	
Age (mean years ± SD)	15.78 ± 1.86
Gender (male/female)	13/45
Right Handed	50 (n = 55)
Socioeconomic Status (mean ± SD)	48.28 ± 10.44 (n = 40)
Intelligence Quotient (IQ)	107.60 ± 14.98 (n = 56)
***Ethnicity* – n (%)**	
Caucasian	41 (70.7%)
African American	6 (10.3%)
Hispanic	5 (8.6%)
Asian	0 (0%)
Native American	1 (1.7%)
Other	5 (17.2%)
Illness History, Description, Etc	
IDAS Suicidality Index (mean ± SD)	12 ± 6.25
IDAS General Depression Index (mean ± SD)	56.59 ± 14.51
IDAS General Depression Index *corrected* (mean ± SD)	52.40 ± 13.12
Duration of current episode (mean months ± SD)	10.07 ± 12.23
Global Assessment of Functioning (mean ± SD)	54.19 ± 8.18
Age of Onset (mean years ± SD)	12.29 ± 2.19
Current Antidepressant Medication – n (%)	15 (25.9%; n = 53)
Current Comorbid Anxiety – n (%)	35 (60.3%; n = 55)
History of >4 Episodes of NSSI	23 (39.7%; n = 54)
Previous Suicide Attempts – n (%)	11 (19%; n = 55)

Table 2. Cluster Information

Overall Cluster	**Voxels**	**P**	**Z-Max**	**X**	**Y**	**Z**
	1043	<0.0005	3.69	-38	-12	56
Local Maxima			**Z-Stat**	**X**	**Y**	**Z**
Left Precentral Gyrus			3.69	-38	-12	56
Left Superior Parietal Lobule			3.24	-32	-42	60
Left Postcentral Gyrus			3.06	-48	-18	46
Left Postcentral Gyrus			3.00	-34	-26	38
Left Precentral/Middle Frontal Gyri			3.00	-36	-6	56
Left Precentral Gyrus			2.99	-30	-20	66

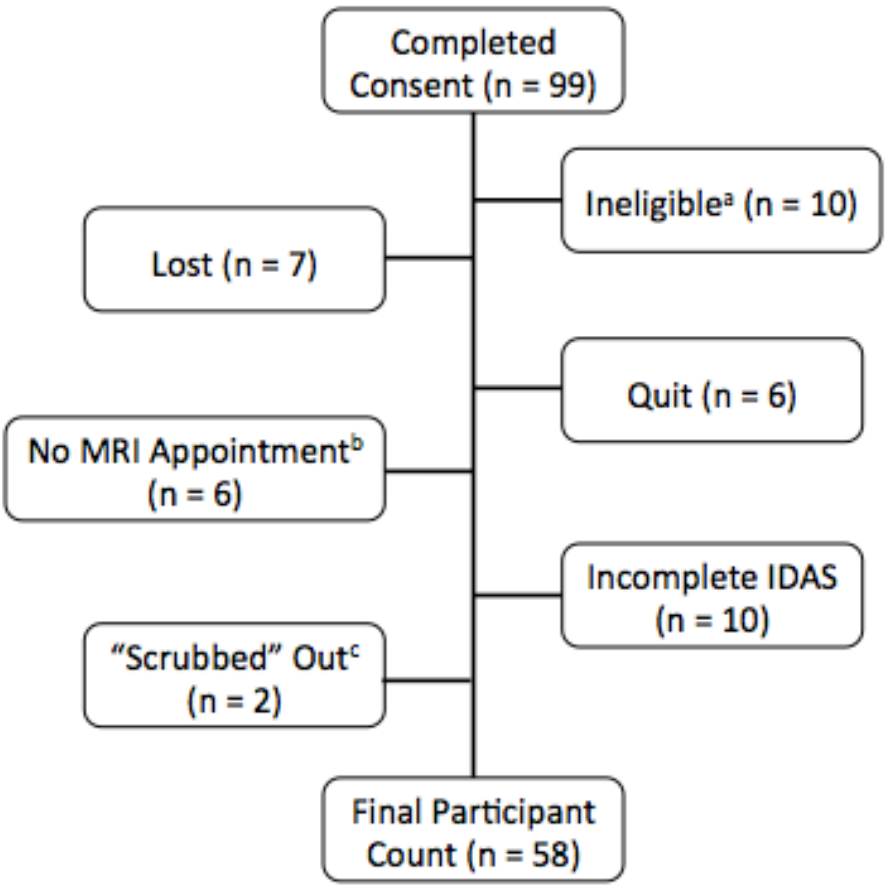
Table depicts information regarding overall cluster and local maxima of the significant precuneus RSFC cluster. X, Y, and Z represent MNI coordinates.

Figure 1. Merger of Possible Neurobiological and Psychological Contributors to Suicide



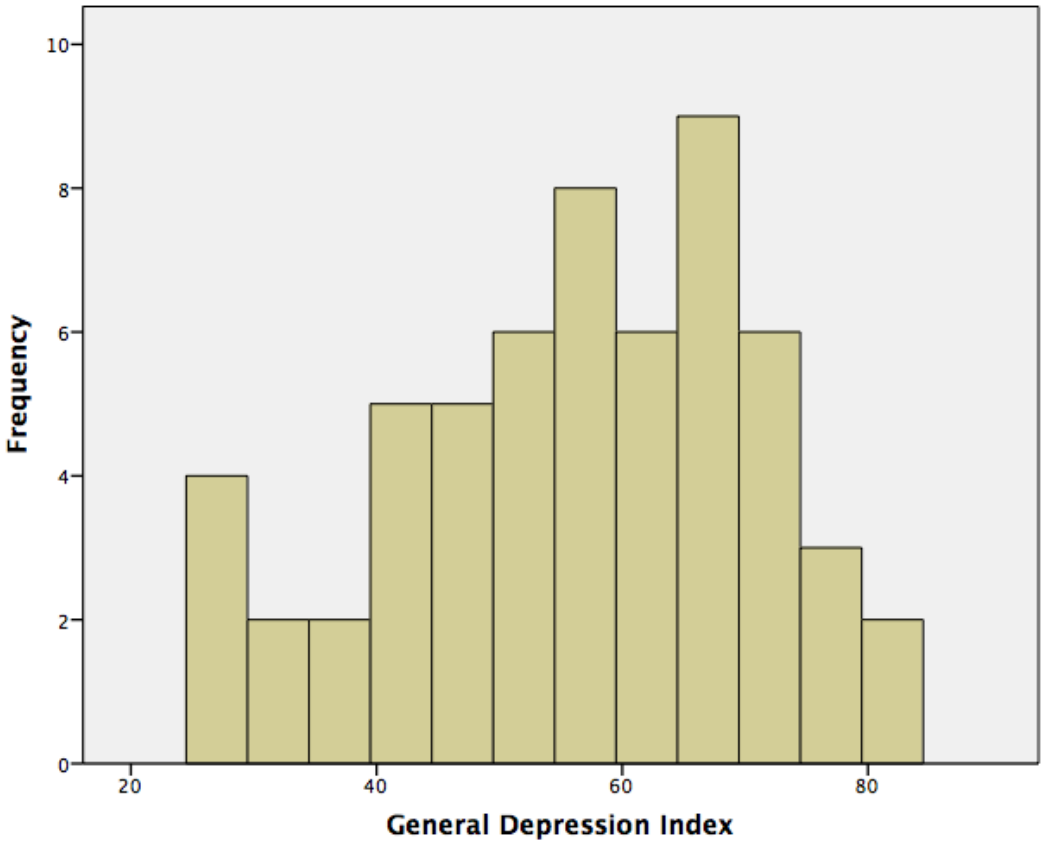
The above figure is a working model that integrates both a potential neurobiological theory of suicide as well as the interpersonal theory of suicide. On the left, the diagram depicts deficits in three neurobiological components: (1) affective experience; (2) affective regulation; and (3) self-referential processing. It is possible that the groundwork for the interpersonal theory of suicide is present when there are deficits in all three neurobiological components

Figure 2. CONSORT Diagram of Participants



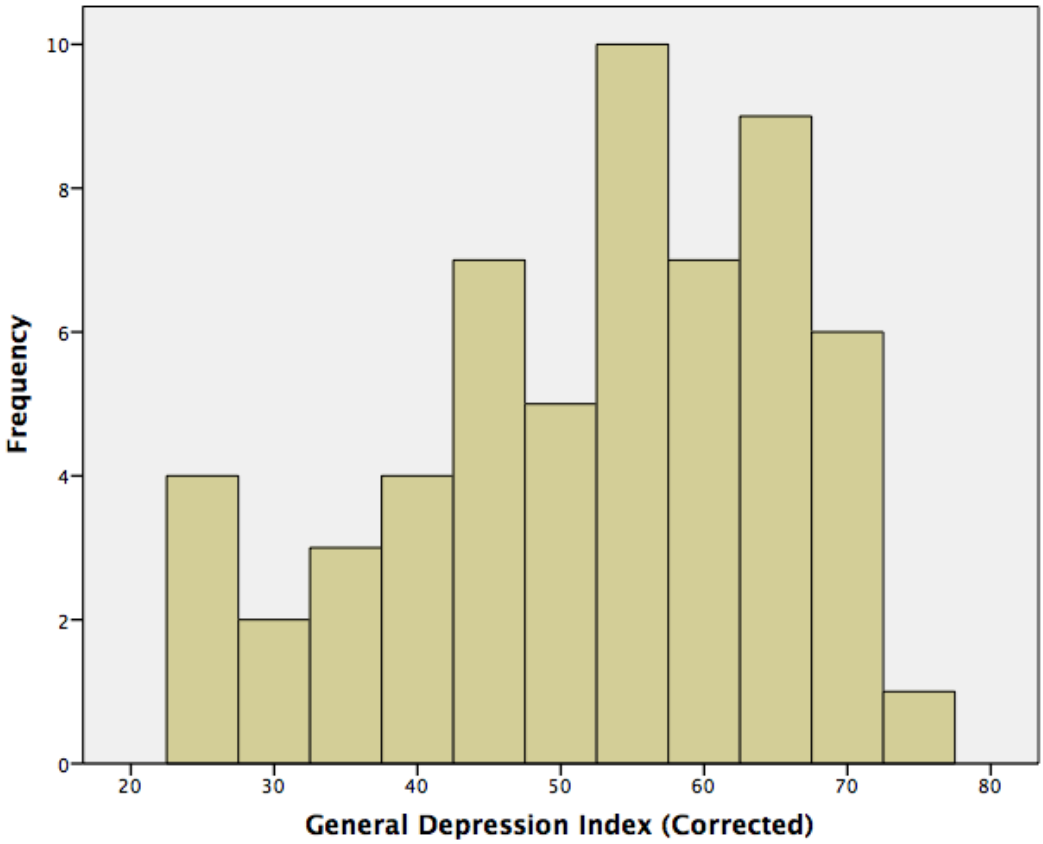
[a] Participants were deemed ineligible due to failure to meet diagnostic criteria for MDD, presence of exclusionary diagnoses (neurological or chronic medical condition, pervasive developmental disorder, bipolar disorder, or schizophrenia), IQ < 80, or current drug use
[b] Some participants completed other parts of the larger research study with the exception of MRI scan. This was primarily due to MRI contraindications (i.e. braces)
[c] During the imaging preprocessing stream, participants were excluded if over 60 of the 180 volumes were removed due to excessive motion

Figure 3. Histogram of General Depression Index



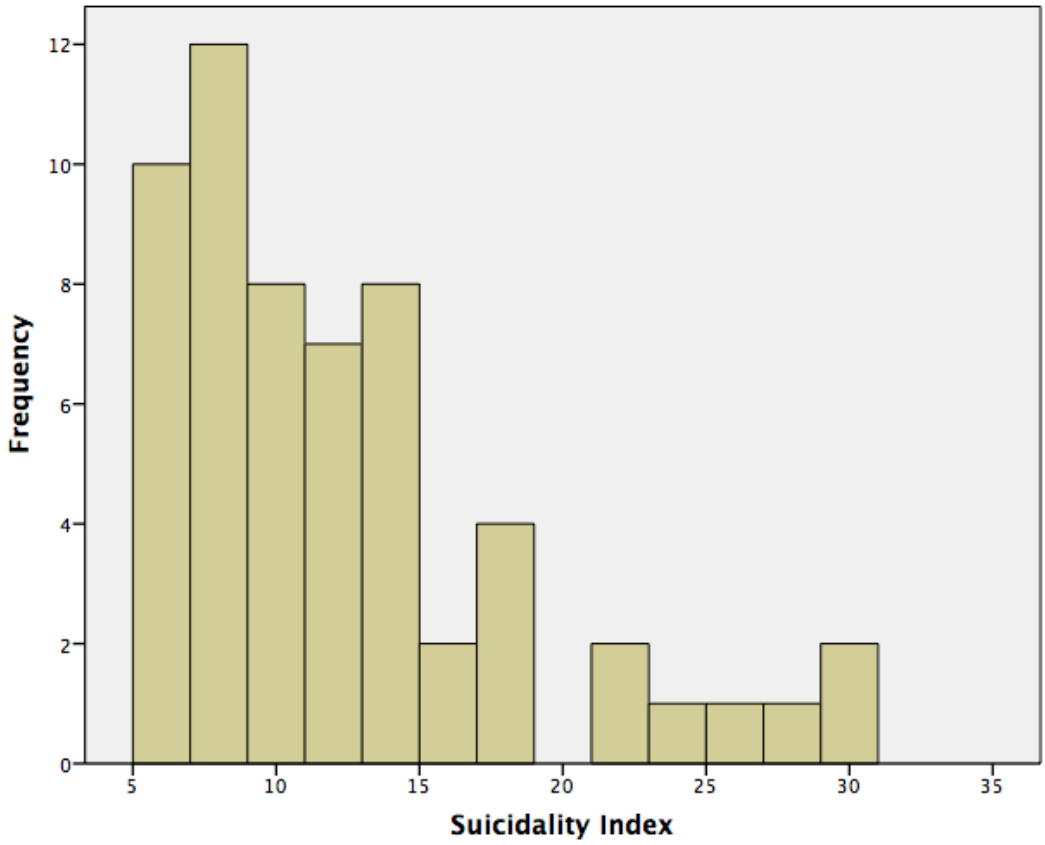
The above histogram shows the distribution of scores on the General Depression Index as measured by the IDAS

Figure 4. Histogram of General Depression Index (Corrected)



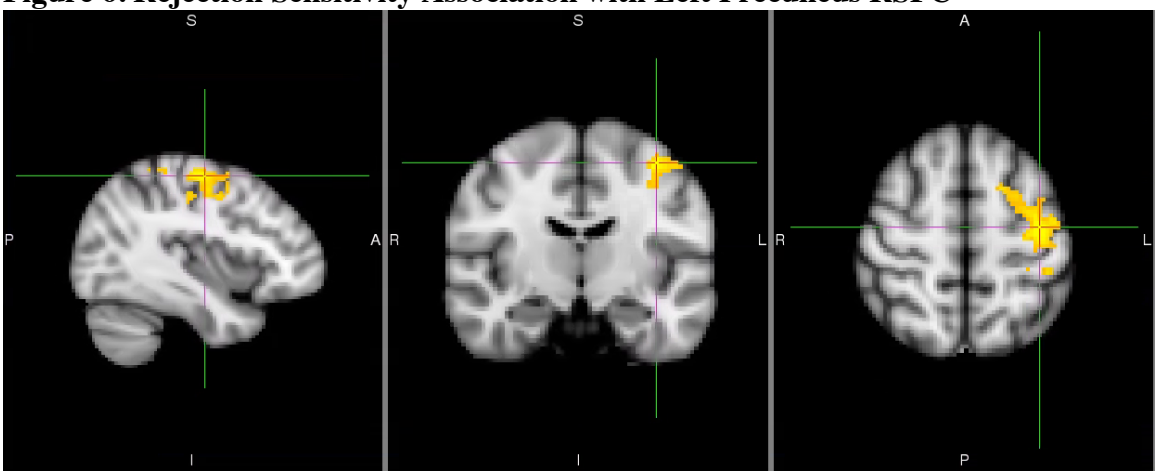
The above histogram shows the distribution of scores for the corrected General Depression Index as measured by the IDAS. This was calculated by subtracting the ratings on items from the General Depression Index that overlapped with items on Suicidality Index

Figure 5. Histogram of Suicidality Index



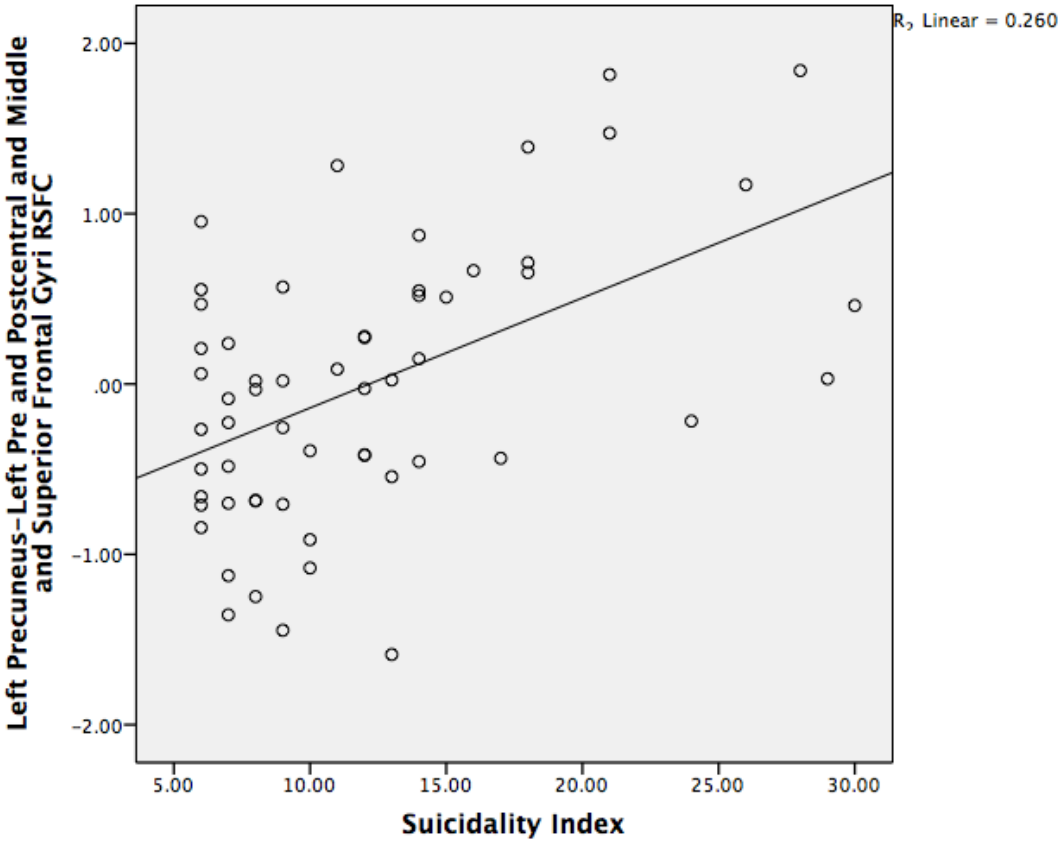
The above histogram shows the distribution of scores for the Suicidality Index as measured by the IDAS

Figure 6. Rejection Sensitivity Association with Left Precuneus RSFC



After controlling for overall depression symptoms, there was a positive association between rejection sensitivity and RSFC between the left precuneus and the above cluster (left pre and postcentral gyri, superior parietal lobule, and middle and superior frontal gyri). This image shows the location of the peak voxel (MNI Coordinates: -38, -12, 56)

Figure 7. Scatterplot of Suicidality Index versus Precuneus RSFC



The above scatterplot visually depicts the correlation between the IDAS Suicidality Index and RSFC between the left precuneus and left pre and postcentral gyri and middle and superior frontal gyri