Research paper

Network basis of suicidal ideation in depressed adolescents

Sarah J. Ordaz\textsuperscript{a,*, b}, Meghan S. Goyerb, Tiffany C. Ho\textsuperscript{b}, Manpreet K. Singh\textsuperscript{a}, Ian H. Gotlib\textsuperscript{b}

\textsuperscript{a} Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Rd., MC 5722, CA, USA
\textsuperscript{b} Department of Psychology, Stanford University, Stanford, CA, USA

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ABSTRACT

Background: Suicidal ideation rates rise precipitously in adolescence, contributing to risk for attempts. Although researchers are beginning to explore the brain basis of attempts in depressed adolescents, none have focused on the basis of ideation, which has implications for prevention. This study examined the association between intrinsic neural network coherence and the severity of suicidal ideation in depressed adolescents.

Methods: Forty adolescents diagnosed with Major Depressive Disorder were administered the Columbia-Suicide Severity Rating Scale and underwent resting-state fMRI. We quantified within-network coherence in the executive control (ECN), default mode (DMN), and salience (SN) networks, and in a non-relevant network consisting of noise signal. We associated coherence in each of these networks with the greatest lifetime severity of suicidal ideation experienced, covarying for motion, age of depression onset, and severity of current depressive and anxious symptoms.

Results: Lower coherence in the left ECN, anterior DMN, and SN were independently associated with greater lifetime severity of suicidal ideation. When including all three significant networks and covariates in a single model, only the left ECN significantly predicted suicidal ideation.

Limitation: Studies with a larger sample size are needed to verify our findings.

Conclusions: Our finding of hypoconnectivity in multiple networks extends emerging evidence for hypoconnectivity in adolescent suicidality and is consistent with theoretical conceptualizations of suicidal ideation as a complex set of cognitions associated with cognitive control, self-referential thinking, and processing salient information. While multiple networks could be targets for effective early interventions, those targeting ECN functionality (cognitive control) may be particularly beneficial.

1. Introduction

Over 800,000 individuals die by suicide annually worldwide (WHO, 2014). In the U.S., suicide is the 10th leading cause of death among all age groups, and the 2nd leading cause of death among adolescents (CDC, 2016), resulting in approximately 5000 adolescent deaths each year (CDC, 2014). These statistics, however, represent only the tip of the iceberg; although exact estimates vary, current epidemiological data indicate that a staggering 4.1–8.6% of U.S. adolescents (1.7–3.6 million individuals) have attempted suicide (CDC, 2015; Nock et al., 2013). In order to prevent suicide attempts and completions, it is imperative that we understand their most relevant precursor – suicidal ideation. Suicidal ideation is defined as thinking about, considering, or planning suicide; it spans a continuum from wishing one were dead to having a specific plan to end one's life; indeed, suicidal ideation is exhibited by almost all attempters (Klonsky et al., 2016; Lewinsohn et al., 1996). While suicidal ideation does not always lead to an attempt, greater severity of suicidal ideation is associated with a higher likelihood of future suicide attempt (Lewinsohn et al., 1996).

The peak onset of suicidal ideation occurs during adolescence. The prevalence of suicidal ideation rises from less than 1% at age ten to 17% by age 18 (Nock et al., 2013). By adolescence, individuals have developed the cognitive capacity to consider and evaluate their own death, but they also exhibit immaturities in cognitive control, self-referential processing, and emotional reactivity; this imbalance has been posited to be associated with adolescent suicidal ideation (Miller et al., 2007). Three large-scale brain networks in particular support these cognitive and emotional processes, encompass a large number of regions throughout the brain, have been widely studied across a wide range of disorders, and have been proposed to be central to aberrant psychological functioning, consistent with the Triple Network Model of psychopathology (Menon, 2011). The executive control network (ECN), which includes the lateral prefrontal cortex, posterior parietal cortex, and the basal ganglia, is involved in exerting goal-directed responses,
including regulating emotions (Menon, 2011). The default mode network (DMN), which includes the medial prefrontal cortex, posterior cingulate, and hippocampus, is involved in self-referential processing. Finally, the salience network (SN), which includes the dorsal anterior cingulate cortex (dACC) and the insula, is implicated in detecting and monitoring threatening stimuli and coordinating responses and in initiating network switching between the externally-oriented ECN and the internally-focused DMN (Uddin, 2015). Importantly, the neural networks that support these processes continue to mature in adolescence (Marek et al., 2015; Sole-Padulles et al., 2016), and are aberrant in adolescents with major depressive disorder (MDD) (Kerestes et al., 2014).

Researchers have now begun to examine how brain function may be aberrant in adolescents with any type of suicidal behaviors; to date, however, none have focused on the brain basis of suicidal ideation in adolescents with MDD. One group of three studies, all conducted with the same sample of depressed adolescents, have compared task-evoked functional activation in depressed attempters and depressed non-attempters (Pan et al., 2013a, 2011, 2013b). While engaged in various emotional processing tasks, attempters exhibited higher levels of activation in an ECN node (Pan et al., 2013b) and lower levels of activation in a DMN node (Pan et al., 2013a). With regard to the SN, attempters exhibited higher levels of activation in the dACC during an emotional processing task but lower levels of dACC activation during an executive function task (Pan et al., 2011). In part, the discrepancy in findings concerning dACC function may reflect not only the task-specificity of the findings, but also that the results were obtained through region-of-interest analyses, making it difficult to interpret the findings without understanding how these regions are functionally connected. One of these studies did examine functional connectivity, which is important because it reflects the functional integrity of a broader communication system (Satterthwaite and Baker, 2015). The authors reported reduced functional connectivity between two nodes of the SN (dACC and insula) in attempters, but findings were specific to angry-face stimuli (Pan et al., 2013b), limiting their generalizability. Similarly, a recent study examining varying levels of suicidal ideation among bipolar adolescents with a history of an attempt found decreased connectivity in the anterior DMN during neutral face viewing (Johnston et al., 2017).

While these task-specific connectivity findings are important in beginning to elucidate the brain basis of suicidal behavior in adolescents, these studies utilized disparate emotion processing tasks and obtained discrepant findings, signaling the need for understanding intrinsic (i.e., task-independent) neural networks associated with suicidal behaviors. Understanding the intrinsic neural network basis of suicidal ideation in adolescents can help delineate the pathophysiological underpinnings of emerging suicidality, identify youth at risk for subsequent attempts, and isolate a sensitive target for assessing the efficacy of interventions.

The present study was designed to examine intrinsic network coherence in depressed adolescents who were experiencing varying levels of suicidal ideation, and to test the strength of the associations between suicidal ideation and network coherence of the ECN, DMN, and SN. We defined network coherence as the strength of functional connectivity within a network. This enabled us to assess task-independent, stable, patterns of intrinsic functional signals that are known to reflect structural connections (Greicius et al., 2009). We focused on suicidal ideation in the context of MDD because depression is the strongest psychiatric predictor of suicidal ideation in adolescence (Nock et al., 2008). Based on theories of suicide that implicate processes of cognitive control over behavior, self-referential processing, and emotional reactivity that are supported by the ECN, DMN, and SN, and on the task-based fMRI studies reviewed above, we hypothesized that severity of suicidal ideation would be related to strength of coherence within ECN, DMN, and SN, but not within a non-relevant (i.e., noise) network. In generating hypotheses concerning the directionality of findings regarding strength of network coherence, we were guided by results of the adolescent functional connectivity studies reviewed above that reported decreased connectivity within DMN among adolescent bipolar attempters with varying degrees of ideation (Johnston et al., 2017) and decreased connectivity within SN in adolescent suicide attempters as compared to non-attempters (Pan et al., 2013b). Given the lack of literature, we also explored the directionality of the association between ECN coherence and severity of ideation.

2. Methods

2.1. Participants

We recruited 40 depressed adolescents (30 female) ages 14–17 years who were native English speakers through the Pediatric Mood Disorders Program at Stanford School of Medicine, community mental health clinics, media advertisements, and flyers posted throughout the San Francisco Bay Area. Inclusion criteria included having a current episode of Major Depressive Disorder (MDD) according to DSM-IV criteria, assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-PL) (Kaufman et al., 1997) and the Child Depression Rating Scale (Jain et al., 2007). Exclusion criteria included: 1) meeting DSM-IV criteria for Bipolar Disorder, a psychotic disorder, or substance dependence; 2) contraindications for scanning; and 3) a lifetime history of neurological (including severe head injuries), cardiovascular, or any other major medical problems. Participants and parents provided written informed assent/consent and were compensated. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

No participants had to be excluded as a result of poor quality of scan data or motion. The ethnic composition of this sample was 15% Hispanic/Latino/a and 85% non-Hispanic/Latino/a. Racial composition of this sample was: 62% Caucasian, 20% Asian-American, 5% Black/African-American, 13% multiracial/other. Demographic information, psychiatric comorbidities, psychotropic medication usage, socioeconomic status, and mean age and pubertal status are presented in Tables 1, 2. Eighteen participants who were taking psychotropic medications at the time of the study continued their treatment regimen during study participation.

2.2. Measures

At the first laboratory session, adolescents were administered the K-
SADS-PL separately to confirm diagnosis of MDD, presence of an ongoing episode, and to assess age of first onset of MDD and current and lifetime Axis I disorders. All interviews were conducted by research staff who had established excellent symptom and diagnostic reliability (k > .9). Final diagnostic decisions were made by a licensed psychologist (SJO) and board-certified child and adolescent psychiatrist (MKS).

Participants were administered the Columbia-Suicide Severity Rating Scale (C-SSRS) Lifetime version through clinical interview to assess the most severe suicidal ideation in the adolescent’s lifetime (Posner et al., 2011). Participants were asked if they have ever experienced a wish to be dead (score of 1); non-specific thoughts of wanting to end one’s life (2); active suicidal ideation with some intent but without intent to act (3); active suicidal ideation with any method and plan (4); or active suicidal ideation with a specific plan and intent (score of 5). Participants were assigned the value corresponding to the score of their highest endorsement. Participants were also asked to rate current severity of suicidal ideation, with “current” defined as within the last two weeks. The C-SSRS also queries number of lifetime attempts (actual, aborted, and interrupted), and current and lifetime self-injurious behaviors. The C-SSRS has demonstrated high sensitivity and specificity (Posner et al., 2011). In addition, all adolescents completed the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) to assess severity of depressive symptomatology. The PHQ-9 is a reliable measure with demonstrated criterion and construct validity in depressed adolescents (Richardson et al., 2010). Adolescents also completed the Multidimensional Anxiety Scale for Children (MASC) to assess anxious symptomatology; this measure has demonstrated reliability and validity (March et al., 1997). Finally, adolescents completed a self-reported Tanner staging to assess pubertal status (Marshall and Tanner, 1968).

2.2.1 Neuroimaging data acquisition

Please see Supplement 1 for details.

2.3. Data preprocessing

We selected a preprocessing stream based on evidence comparing approaches to minimize confounds without introducing noise and to ensure appropriate ordering of preprocessing steps (Hallquist et al., 2013; Jo et al., 2013; Power et al., 2014; Satterthwaite et al., 2013; Van Dijk et al., 2012; Yan et al., 2013). Given controversies regarding how best to deal with confounds, we selected an approach demonstrated to be effective in similar data sets of youth (Jo et al., 2013; Satterthwaite et al., 2013). We present details regarding our approach to addressing confounds and preprocessing in Supplement 2.

2.4. Operationalizing network coherence

We defined network coherence as the strength of the association between time courses of all voxels within an identified network. Following preprocessing, we obtained a metric of resting-state functional connectivity for each individual within each intrinsic network of interest using a combination of group probabilistic independent components analysis (ICA) and dual regression analyses. Group ICA is a multivariate signal-processing method (Beckmann et al., 2005; Kiviniemi et al., 2003) that we selected over seed-based correlation because (1) it accounts for multiple voxel-voxel relations in order to obtain an interacting network of voxels; (2) it permits data-driven exploration of the spatial-temporal properties of functional neuroimaging data; and (3) group ICA followed by a dual regression approach has been shown to have higher short- and long-term test-retest reliability than does seed-based analysis (Smith et al., 2014; Zuo et al., 2010).

We conducted group ICA using FSL 5.0.6 MELODIC software version 3.14, specifying 25 components. Specifically, a set of ICA components derived from the whole sample was generated and used to elicit individual maps of a comparable network for statistical analysis. Group components that were identified from group ICA were visually inspected and the networks of interest (ECN, DMN, and SN) and the non-relevant network (noise) were identified on the basis of neuroanatomical components by trained raters (SJO). Consistent with published studies (Kelly et al., 2010; Zuo et al., 2010), we identified a noise component as a network in which activation was not biologically plausible because it corresponded to sources of artifact, including head motion, cerebrospinal fluid, and the superior sagittal sinus. These networks are displayed in Fig. 1 and include lateralized ECNs (ECNR; ECNL), one network comprising the anterior subdivision of the DMN (DMNA), another comprising the ventral subdivision (DMNV), a SN, and a noise network. The ECNR and ECNL each included the right- or left-lateralized superior, medial, and inferior frontal gyri of the lateral prefrontal cortex, the posterior parietal cortex, the caudate nucleus, and the contralateral cerebellum. The DMNA was dominated by the ventromedial prefrontal cortex and mid-cingulate gyrus, and also included areas of the superior frontal gyrus and the posterior cingulate gyrus. The DMNV was dominated by the hippocampus, posterior cingulate gyrus, and precuneus, and also included components of the posterior parietal cortex, frontal eye fields, and ventromedial prefrontal cortex. The SN included the dorsal anterior cingulate cortex, anterior insula, lateral prefrontal cortical areas, and the cerebellum.

The set of spatial maps from the group-average analysis was used to generate individual-specific versions of the spatial maps and associated timeseries using dual regression (Beckmann et al., 2009; Filippini et al., 2009). First, for each individual, the group-average set of spatial maps was regressed into the individual’s 4D space-time dataset, resulting in a set of individual-specific timeseries, one per group-level spatial map. Second, those timeseries were regressed into the same 4D dataset, resulting in a set of individual-specific spatial maps, one per group-level spatial map. Each spatial map contained regression weights that index
each voxel’s functional connectivity with all other voxels within the identified network, while controlling for the influence of other networks, some of which may reflect artifacts such as physiological noise. We used Z-scores that normalize by the residual within-subject noise. We then applied the group mask for a given component to the individual-level spatial map for the corresponding component and averaged values within this mask to produce a metric of network coherence for each individual. Thus, this network coherence metric is an average normalized correlation between the timecourse of each voxel within the group-identified network and all other voxels within that network. This approach has previously been published (Ordaz et al., 2017; Van Duijvenvoorde et al., 2015) and is comparable to other published metrics of network homogeneity (Cui et al., 2017; Guo et al., 2014; Uddin et al., 2008).

2.5. Statistical analyses

A priori statistical analyses were conducted using SPSS software version 23 (IBM Corporation). We used t-tests, ANOVAs, and correlational analyses to test any potential confounding relations between
demographic and psychiatric characteristics and our outcome: maximum lifetime severity of suicidal ideation. We then probed the relation between network coherence and these metrics of suicidal ideation using ordinary least squares (OLS) multiple regression; we controlled for any demographic or psychiatric variable that was associated with suicidal ideation. For theoretical reasons, we also controlled for relative motion to ensure this would not confound resting-state functional connectivity estimates, and we controlled for severity of depressive and anxious symptoms, so that we could estimate the neural basis of suicidal ideation independent of severity of psychopathology. Lastly, when multiple networks were significant, we entered them all into a single regression to understand the unique associations of each network after accounting for the others. To examine the specificity of lifetime suicidal ideation, we also conducted OLS multiple regression using suicidal ideation as a dependent variable and logistic regression using lifetime history of attempts as a dependent variable. The same covariates were used to ensure comparability of models.

3. Results

3.1. Participant characteristics

Demographic and clinical characteristics of the sample are presented in Tables 1, 2. In addition, a detailed list of medications and comorbid diagnoses is presented in the Supplement (Tables S1 and S2). As shown in Table 1, lifetime severity of suicidal ideation was not associated significantly with sex, race/ethnicity, highest parental education, total household income, age, or pubertal status. Levels of relative motion (mean relative displacement; described in Supplement 2) during fMRI acquisition, total household income, age, or pubertal status. Levels of relative motion were not significantly associated with suicidal ideation (See Table 1); motion was associated with network coherence in ECNR, (r(38) = -.361, p = .022) and noise network (r(38) = .948, p = .001), but not in other networks (|r|(|38| < .229, ps > .155). Therefore, in addition to having used multiple approaches during preprocessing to account for motion (i.e., excluded participants with motion beyond a threshold, regressed multiple motion parameters and physiological artifacts as part of the nuisance regression; see Supplement 2 for details), we also controlled for motion in our analyses (Satterthwaite et al., 2012).

Table 2 highlights that, not surprisingly, participants who had previously attempted suicide reported higher severity of most severe suicidal ideation. This was not the case for those with a history of nonsuicidal self-injury (NSSI). Further, severity of suicidal ideation was associated significantly with age of depression onset, but not with lifetime exposure to psychotropic medication, psychotherapy participation, the presence of psychiatric comorbidities, or depressive symptom severity (PHQ-9) or anxious symptom severity (MASC). Although PHQ-9 or MASC scores were not significantly associated with suicidal ideation severity, we wanted to ensure that depressive and anxiety symptom severity were not confounding variables. Therefore, in subsequent regression analyses, we controlled for PHQ-9 and MASC scores, in addition to motion and age of depression onset.

3.2. Network associations with lifetime suicidal ideation

For each of the five networks of interest and the non-relevant network, we conducted regression analyses relating network coherence to lifetime severity of suicidal ideation and positively associated with each other (r(38) = .510, p = .001). Participants with history of attempts also reported higher levels of lifetime ideation (r(36.7) = .560, p = .000) and trend-level higher current ideation (t(38) = -1.90, p = .065). Each of the five networks of interest and the non-relevant network were assessed in separate regressions, using the same centered covariates included in the initial lifetime regression to ensure comparability. Unstandardized coefficients for network coherence, p-values, and effect sizes are shown in the second and third set of columns in Table 3 for current severity of suicidal ideation and presence of a prior attempt, respectively. For current suicidal ideation, only ECNL coherence was associated with the outcome variable, and this was at a trend level with a medium effect size (ΔR^2 = .079). Similarly, ECNL was the only network for which coherence was associated with attempts, and this was also at a trend level with a medium effect size (ΔR^2 = .081).

4. Discussion

This is the first study to examine the associations between suicidal ideation and coherence of multiple intrinsic functional neural networks in adolescents diagnosed with MDD. Our focus on the network basis of suicidal ideation rather than attempts is important given that ideation is a risk factor for the emergence of attempts; indeed, clinical and psychological variables have been shown to predict attempts only to the extent that they predict ideation, and, further, suicide attempts are influenced by situational factors such as means and timing that are less guided by one’s biology (Klonsky et al., 2016). Ideation appears earlier in development than do suicide attempts and can be assessed on a continuum; therefore, elucidating its brain basis in adolescence contributes to our understanding of a critical predictive biomarker. Further, our focus on networks is important, not only because individual brain regions do not function in isolation, but also because maturation of network connectivity is a central feature of brain development during adolescence (Marek et al., 2015; Sole-Padulles et al., 2016). We hypothesized that higher levels of suicidal ideation, measured by the most severe ideation in the adolescent’s lifetime, would be associated with lower coherence in DMN and SN; further, we explored the directionality of the association between ECN coherence and levels of suicidal ideation, given related literatures suggesting both positive and
negative relations. We found that lower levels of ECNL, DMNA, and SN coherence were all associated with greater lifetime severity of suicidal ideation in this sample of depressed adolescents. Importantly, this finding held after controlling for a number of confounding factors, including motion, age of depression onset, severity of depressive symptoms, and severity of anxious symptoms. Follow-up exploratory analyses revealed that these findings were not driven by certain subcomponents of these networks, but rather the entire network. Further, when including all networks in a single regression, ECNL emerged as the strongest correlate of lifetime severity of suicidal ideation.

Our results fit with findings of decreased connectivity in DMNA and SN in studies of adolescent attempters (Johnston et al., 2017; Pan et al., 2013b) and adult ideators (Chase et al., 2017; Du et al., 2017) and stand in contrast to a study showing increased connectivity in the DMN among depressed adolescent ideators (Zhang et al., 2016). However, because these studies have generally focused on attempts, examined circumscribed seeds, and only examined one network at a time, our findings extend these results by highlighting that aberrations across multiple networks, and specifically decreased connectivity within networks, is also characteristic of high levels of suicidal ideation, which is distinct from attempts but can precede them. Our finding implicating multiple networks is important because it supports formulations that suicidal ideation is a complex construct reflecting a diversity of cognitive processes supported by the ECNL, DMNA, and SN (Lewinsohn et al., 1996). First, the ECNL engages in cognitive control to support goal-directed behavior, which is consistent with the conceptualization that suicidal ideation reflects difficulty regulating emotions to support adaptive goals (Gould et al., 2003). Our finding of decreased ECNL coherence is consistent with evidence for decreased structural connectivity in depressed adults with suicidal ideation compared to healthy controls (Myung et al., 2016).

The DMN participates a self-regulatory process involving one's understanding of one's place in the world, and the DMNA in particular is dominated by the rostral anterior caudate and ventromedial PFC, areas also implicated in integrating emotional and cognitive inputs and using regulatory processes to keep them in balance, processes that are awry when one contemplates death as a response to one's circumstances (Menon, 2011). Our finding is consistent with evidence of decreased DMN coherence in young adults with suicidal ideation compared to healthy controls (Chase et al., 2017). Lastly, the SN detects and monitors salient (i.e., behaviorally-relevant and potentially threatening) internal and external stimuli and then coordinates responses to such stimuli (Uddin, 2015). Although individuals with suicidal behaviors are posited to be disproportionately guided by threatening, salient stimuli (Klonsky et al., 2016), our findings suggest that individuals under-response to such stimuli. This is consistent with other studies showing that adolescent suicide attempters show blunted physiological responses to social stressors (Melhem et al., 2016; O'Connor et al., 2017). Interestingly, stimulating the nodes of the SN leads individuals to perceive the expectation of imminent challenge and to be motivated to overcome such challenges (Parvizi et al., 2013). It is possible that the hypo-connectivity we see here reflects the lack of will/feeling of mastery to overcome imminent challenges.

We also examined the association between these networks and other metrics of suicidality – namely severity of current suicidal ideation and a history of an attempt – in order to understand the specificity of the relation. Consistent with our framework that lifetime history of suicidal ideation is a more sensitive metric than is a history of attempts, we found only a trend-level association and for the same ECNL network that emerged as the strongest association for lifetime suicidal ideation.

The same was true for current history of suicidal ideation. Seeing as the results are so similar across regressions, it is not surprising that all three of these suicide metrics are strongly associated with each other. Although these metrics all seem to be tapping a similar overall construct, lifetime severity is statistically more sensitive than are attempt because it is continuous rather than binary and, theoretically, is not
Further clouded by means availability. Moreover, lifetime severity of ideation may be more strongly associated with network coherence than is current ideation because network coherence reflects a trait-like history of co-activation rather than a state (Greicius et al., 2009).

4.1. Clinical implications

This study highlights the integral role played by multiple networks implicated in high levels of suicidal ideation in adolescents with depression. Such findings underscore the potential utility of interventions for suicidal ideation that have multiple targets – specifically, in improving cognitive control and emotion regulation processes, in reframing how one thinks about oneself and one's place in the world, and finally, in redirecting attention away from salient inputs and preventing them from guiding subsequent goals and thought processes. Such interventions may include cognitive-behavioral and mindfulness-based interventions that include building cognitive control/emotion regulation capacities, reframing self-schemas, and building awareness of attentional processes to redirect attention away from salient inputs. Indeed, the dominant empirically-supported clinical interventions for adolescents presenting with suicidal ideation, Dialectical Behavior Therapy (DBT) (Mehlum et al., 2014; Miller et al., 2007) and Attachment-Based Family Therapy (Diamond et al., 2010), are broad treatments that target all of these multiple components. While its breadth is in part why it is thought to be successful, this also makes it a resource-heavy treatment for providers and families. Our finding that ultimately ECNL network coherence may be the strongest predictor of ideation suggests that the cognitive control/emotion regulation capacities supported by ECNL should be retained above all else as core components of streamlined versions of these therapies. Interestingly, recent mindfulness-based interventions in adults have shown the capacity to alter connectivity within ECN (Tären et al., 2017), and mindfulness skills are among those taught in DBT.

4.2. Limitations and future directions

One limitation of this study was our focus on suicidal ideation in the context of depression. Although depression is the psychiatric illness that most strongly predicts suicidal ideation, suicidal behaviors are trans-diagnostic constructs that are evident in the context of other disorders, including bipolar disorder and post-traumatic stress disorder (Nock et al., 2009). In addition, suicidal ideation in the context of a single disorder such as depression may be a heterogeneous phenomenon supported by multiple distinct neurobiological underpinnings. In this sample, most participants had a comorbid disorder; however, severity or duration of suicidal ideation did not differ as a function of the presence of these comorbidities. Larger studies are necessary to examine distinct subtypes of suicidal ideation within and between various psychiatric diagnoses in order to examine associated connectivity phenotypes. As a related point, our sample included both males and females (although mostly females). Given well-documented sex differences in rates of suicidal ideation and attempt (WHO, 2014) and in brain morphology and function during adolescence (Satterthwaite et al., 2015), it is possible that there are sex differences in the neural basis of suicidal ideation. Future studies are needed to examine these questions regarding heterogeneity and potential sex differences in the brain basis of suicidal ideation. Future studies are also needed to expand on the ICA-based approach to examine how seed-to-seed connectivity varies as a function of suicidal ideation. Such research has begun to highlight how amygdala connectivity may be altered in depressed adult suicide attempters (Kang et al., 2017), and rostral anterior cingulate cortex connectivity may be altered in depressed adult ideators (Chase et al., 2017; Du et al., 2017). Future research would benefit to examine regions well-established in affective psychopathologies (i.e., the amygdala) and those that connect multiple neural networks (e.g., areas of the ACC).

The emphasis of this study on the network basis of suicidal ideation rather than of attempts is novel and crucial for understanding precursors of the potentially irreversible act of a suicide attempt; a next step will be to examine the network functioning in at-risk youth prior to the emergence of any degree of suicidal ideation and to examine the transition from ideation to attempts (i.e., Deshpande et al., 2016; Klonsky et al., 2016). The first could highlight the earliest stages of the pathological developmental process and could inform intervention efforts. The second could further identify the individuals at highest risk for death. Thus, longitudinal research is needed to follow youth at highest risk for developing suicidal ideation in order to track changes in network function as suicidal thoughts emerge, escalate in severity and duration, and eventually lead to attempt.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2017.09.021.

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