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Research paper

Network basis of suicidal ideation in depressed adolescents

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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,

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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-

Table 1
Demographic characteristics of the sample and association with suicidal ideation.

	% or Mean	Severity of lifetime suicidal ideation
Sex		t(38) = .110, p = .913
F	75%	
M	25%	
Race/Ethnicity		t(38) = .880, p = .384
Non-Hispanic Caucasian	53%	
Minority	48%	
Highest parental education		F(2) = 1.009, p = .374
< 4-year college degree	30%	
4-year college degree	35%	
Advanced degree	35%	
Total household income		t(38) = .383, p = .704
< 150 K	50%	
> = 150 K	50%	
Age	16.15 (1.12)	r(38) = −.042, p = .799
Pubertal status (Tanner Average)	4.53 (.55)	r(38) = −.140, p = .388
Relative motion during scanning (mm)	.04 (.02)	r(38) = .040, p = .804

***p < .001, **p < .010, *p < .050, +p < .100.