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Resting-State Network Analysis of Suicide Attempt History

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Abstract

Introduction: Utilization of neuroimaging to understand suicide risk may help link contributions of functional connectivity as a potential dispositional risk factor, inform suicide risk from a biopsychosocial perspective, and provide additional potential targets for intervention. Prior research has identified structural and functional brain differences related to individuals at risk for self-directed violence thoughts and behaviors. Few neuroimaging studies, however, have been informed by an ideation-to-action theoretical framework to examine differences between risk for attempted suicide from risk for suicide-related thoughts. This study aimed to examine resting-state functional network differences between participants with a history of suicide attempt and those with a history of self-directed violence thoughts without an attempt.

Method: Using data from the UK Biobank, this study compared participants with a lifetime history of attempted suicide (*n* = 566) to those with a lifetime history of self-directed violence thoughts without attempts (*n* = 3,447) on within- and between- network resting-state functional connectivity among subnetworks of the lateral frontoparietal (L-FPN), medial frontoparietal (M-FPN), and mid-cingulo-insular (M-CIN) networks.

Results: There were no significant between-group differences for between-network, within-network, or whole-brain functional connectivity after adjusting for age, sex, ethnicity, and body mass index (BMI), and statistical corrections for multiple comparisons.

Discussion: Findings suggest that resting-state network measures, alone, may not differentiate those with a lifetime history of suicide attempt(s) and those with lifetime history of self-directed violence thoughts without attempts. Further study should examine interactions between functional connectivity and psychosocial factors, specific regions of interest, and task-based functional connectivity.

Keywords: Suicide, self-directed violence, fMRI, resting-state, UK Biobank

Resting-State Network Analysis of Suicide Attempt History

Introduction

Worldwide, suicide is a leading cause of death among adults (WHO, 2014). In 2018, suicide deaths accounted for roughly 2% of all deaths across the United States (U.S.), making it the 10th leading cause of death among adults (Drapeau & McIntosh, 2020). In the U.S., for suicide attempts, an average of one suicide attempt occurs every 26 seconds (Drapeau & McIntosh, 2020). For each suicide attempt, it is estimated that many more adults have thought of suicide (Piscopo, Lipari, Cooney, & Glasheen, 2016). Despite increased research on risk factors and prevention efforts, global and national suicide rates have remained largely stagnant in recent years (Alicandro et al., 2019). Within the context of the transition from suicidal thoughts to behavior(s), accurate identification of both proximal and distal risk factors remains elusive, and largely incorporates only self-reported psychosocial factors, (Franklin et al., 2017). There exists a need for novel, interdisciplinary methods to further understand suicide risk, develop useful biomarkers, and improve treatment targets (Huang, Kelly, Bastidas, Nee, & Franklin, 2020).

Biological correlates of suicide remain an underexplored area in suicide prevention (Desmyter, Van Heeringen, & Audenaert, 2011; Huang et al., 2020; Jollant, Lawrence, Olié, Guillaume, & Courtet, 2011; Serafini, Pardini, Pompili, Girardi, & Amore, 2016; van Heeringen & Mann, 2014). Yet, growing evidence suggests that suicide behavior has a biological component. Based on twin studies, the genetic heritability of suicide ideation and attempts ranges between 38-55% (Brent & Melhem, 2008; Fu et al., 2002; Statham et al., 1998; Turecki & Brent, 2016). Aside from initial estimates of genetic risk, it remains unclear which biological processes are involved in suicide risk.

Suicide as a Distinct Clinical Syndrome

Major depressive disorder (MDD) is a substantial risk factor for suicide (Franklin et al., 2017; Nock et al., 2012; Nock et al., 2018). Significant genetic overlap exists between depression and suicide ideation (Linker, Gillespie, Maes, Eaves, & Silberg, 2012; Mullins et al., 2019; Ruderfer et al., 2019; Strawbridge et al., 2019), non-suicidal self-injury (NSSI) (Maciejewski et al., 2017), suicide attempt (Levey et al., 2019), and death by suicide (Docherty et al., 2019) suggesting a potential shared biological etiology. From a public health perspective, higher prevalance rates of depression lend themselves to study more readily than rare occurrences like suicide behaviors. Thus, decades of neuroimaging research into MDD may serve as a framework for understanding biological correlates of suicide-related thoughts and behaviors.

While most suicides occur in the context of psychiatric illness, the majority of psychiatric patients never attempt suicide. This disparity has led many in the field to argue for suicide behavior as a distinct diagnostic criteria (Sisti, Mann, & Oquendo, 2020). In the U.S., studies are confounded by the fact that suicide-related thoughts are diagnostically a symptom of several psychiatric disorders, including MDD and Borderline Personality Disorder. More importantly, treatments solely for underlying psychiatric disorders have not shown promise in reducing suicide-related thoughts and behavior, which has led to the development of treatments specifically targeted to suicide risk (Tarrier, Taylor, & Gooding, 2008). Sisti and colleagues (2020) draw the parallel of sleep disorders and MDD, in that there has been an evolution where hypersomnia and insomnia are seen, not only as symptoms of depression, but also as distinct disorders requiring focused research and treatment. In fact, the International Classification of Diseases categorizes suicide behavior as distinct from mental, behavioral, or neurodevelopmental disorders.

While there is considerable genetic overlap between MDD and suicide behaviors, there is evidence of distinct biological pathways. A population-based twin study (Dutta et al., 2017) found a significant heritable component to suicide ideation which is independent of depression. Those with a history of suicide attempts have polygenic profiles distinct from that of psychiatric diagnosis (Sokolowski, Wasserman, & Wasserman, 2016). Thus, while research on biological correlates of MDD may inform suicide etiology, the two conditions likely are distinct with some overlapping contributors. It is therefore worthwhile to study suicide as a distinct phenomenon from MDD.

A suicide attempt history shares a robust empirical relationship with suicide ideation and non-suicidal self-injury (NSSI), even after controlling for psychiatric diagnoses and factors like impulsivity (E.D. Klonsky, May, & Glenn, 2013). NSSI has outperformed factors like depressive symptoms, hopelessness, and impulsivity as a predictor of suicide attempt (Andover & Gibb, 2010). Suicidal and non-suicidal thoughts and behaviors are best understood collectively as self-directed violence thoughts and behaviors (SDVTB), following classification language recommended by the Centers for Disease Control.

Suicide Ideation-to-Action Framework

Theories regarding suicide within the ideation-to-action framework view SDVTB constructs as discrete and conceptualize distinct factors leading to the development of suicide ideation and its progression to potentially lethal attempts (E.D. Klonsky, Qiu, & Saffer, 2017). The Interpersonal-Psychological Theory (IPT) of Suicide (Joiner, 2007) was among the first psychosocial theories of suicide to posit factors associated with suicide ideation were distinct from factors associated with suicide attempt. Specifically, the IPT hypothesizes that feelings of perceived burdensomeness and thwarted belongingness are likely lead contributors to serious suicide ideation. Under this theory, acquired capability for suicide is required to overcome fears of death and pain and is developed distinctly through exposure to painful and provocative events, e.g., combat exposure and NSSI (Van Orden et al., 2010). An meta-analysis has found modest support for this theory in cross-sectional samples (Chu et al., 2017).

Building on other theories within the ideation-to-action framework, the Three-step Theory (3ST) (E.D. Klonsky & May, 2015) suggests that the combination of pain and hopelessness lead to suicide ideation, which is intensified in the context of lack of connectedness. In addition to acquired capability, the 3ST specifies that dispositional contributors (neurobiological differences, genetic vulnerabilities, and biochemical factors which have been understudied) and practical contributors (knowledge of and access to lethal means) also contribute towards risk for suicide behavior. Under this theory, biological factors may be particularly insightful when differentiating those at risk for suicide attempts vs. completed suicide. A major limitation of this theory is dispositional factors, like biological contributors, have been largely understudied (E.D. Klonsky, Saffer, & Bryan, 2018).

Biological Correlates of Suicide

Genetic Correlates of Suicide. Multiple genome-wide association studies have identified polygenic risk scores linked to history of suicide attempt and death (Docherty et al., 2019; Ruderfer et al., 2019; Strawbridge et al., 2019). Recent genome-wide association studies have found potential loci related to suicide attempts in individuals with major depressive disorder, bipolar disorder, and mood disorders (Docherty et al., 2019; Mullins et al., 2019). Using the UK Biobank dataset, including data from nearly 40,000 individuals with a history of self-directed violence thoughts, deliberate self-harm, or suicide attempt, researchers found genetic differences in genes related to brain circuitry formation and maintenance, brain abnormalities, and psychopathology between those with a history of suicidality and healthy controls (Strawbridge et al., 2019).

From an epigenetic perspective, preliminary studies have found differential DNA methylation patterns which characterize those with a history of suicide behaviors (Kouter, Zupanc, & Videtič Paska, 2019) versus those who have died by suicide (Roy & Dwivedi, 2017), in the genetic loci associated with brain-derived neurotrophic factor and the hypothalamic-pituitary-adrenal axis (Cheung, Woo, Maes, & Zai, 2020). These studies have shed light on important gene-environment interactions, highlighting how early-life adversity and psychiatric disorders are related to epigenetic modifications related to later death by suicide (Labonté et al., 2012). Investigating biological processes associated with suicide provides a “bottom-up” complementary approach to traditional “top-down” theory studies that could inform suicide risk from a biopsychosocial perspective and provide potential targets for intervention.

Structural Brain Correlates of Suicide. From a theoretical perspective, the stress-diathesis model of suicide posits an interactional relationship between psychosocial stressors and biological susceptibility to SDVTB (van Heeringen, 2012). In line with this theory, research targeting the neurobiological correlates of suicide begins to explain why, given similar psychosocial histories and stress exposures, some people experience suicide-related thoughts and behaviors while others do not (van Heeringen, Bijttebier, Desmyter, Vervaet, & Baeken, 2014). Neuroimaging techniques can provide insight into the underlying biology of suicide-related thoughts and behaviors and potential therapeutic targets (Courtet, Gottesman, Jollant, & Gould, 2011). Specifically, magnetic resonance imaging (MRI) is a noninvasive imaging technology to produce three-dimensional images of matter by exciting and then detecting changes in the rotational axis of proteins found in water found within body tissues. Structural imaging is commonly used to identify differences in both brain gray and white matter.

A growing literature suggests that structural differences exist in the brains of those with a history of SDVTB and those without. Several studies have found reduced gray matter volumes among those with a history of suicide attempts, but there is little convergence on specific locations of these differences due to sampling and procedural differences between studies (Huang et al., 2020). A recent meta-analysis of 20 papers including samples differentiated by suicide attempt, suicide ideation and plan, NSSI, and suicide death found that more than ten experiments reported reduced gray matter volumes, but in aggregate there were no statistically significant differences using the coordinate-based meta-analytic neuroimaging analyses Activation Likelihood Estimation (ALE) or the more lenient Multi-level Kernel Density Analysis (MKDA) approach (Huang et al., 2020). Study authors noted the large degree of sampling heterogeneity between studies, small sample sizes, and imaging standards reduced the ability to quantitatively compile findings across studies (Huang et al., 2020). Unfortunately, studies were diverent in many says including: samples varied in SDVTB (definition and types), in control groups (including comparisons between attempt history, ideation, and NSSI with suicidal control groups, psychiatric controls, and healthy controls), in sample size (ranged from 18 to 272), and in imaging modality. Thus, results from the meta-analysis indicated structural brain differences likely exist between those with a history of STB and those without, but further studies are needed to parse out and better specify these differences (Huang et al., 2020). Extant literature is limited, in that most published studies compare those with a history of STB to healthy controls rather than directly comparing those with a history of attempts to a history of suicide-related thoughts. Such studies may misinterpret factors associated with general psychopathology as exclusive to suicidality and give little insight into the transition from ideation to attempt (Huang et al., 2020; Schmaal et al., 2019).

Fewer studies have examined the association between brain white matter connections and SDVTB. Taylor and colleagues (2015) found widespread white matter differences in fractional anisotrophy and radial diffusivity, measures reflecting structural integrity of white matter and neuronal connections, comparing individuals with a recent history of SDVT and MDD to those with MDD alone. In particular, alterations were found in the ventral cingulum which connects posterior and temporal default mode network regions. In a study comparing those with a history of suicide attempt to a combined sample of healthy controls and those with SDVT without attempt, Olvet and colleagues

(2014) found reduced fractional anisotrophy in the dorsomedial prefrontal cortex which is also prominently involved in the default mode network. Taken in sum, results from initial studies on white matter differences associated with SDVTB suggests further study into larger networks like the default mode network is warranted (Schmaal et al., 2019).

Functional Imaging Correlates of Suicide. Functional imaging is complementary to other imaging techniques, providing information about alterations in circuit-level interactions between multiple brain regions. It allows for exploration of large-scale networks and interactions and provide a systems-level understanding of brain function (Bressler & Menon, 2010). Functional magnetic resonance imaging (fMRI) is a noninvasive procedure which distinguishes changes in localizedbrain activity, as measured by blood-oxygenated dependent level (BOLD) blood flow which is considered a proxy for neuronal activation. Use of BOLD fMRI techniques means enhanced spatial resolution, but unfortunately results in lower temporal resolution than other functional imaging modalities.

Differences between individuals with a history of SDVTB and those without have been shown during both task-activation and resting-state imaging modalities, though there has been large discrepancies between results across studies (Huang et al., 2020). Resting-state is utilized to discriminate between regional associations that occur in a resting versus a task-negative state. In their meta-analysis, Huang and colleagues (2020) used their more lenient MKDA (10-15 mm kernel) analysis combining both task and resting-state modalities to find hyperactivation in subcortical regions like the left posterior cingulate cortex, right amygdala, and left hippocampus among those with SDVTB. The right hypothalamus was the only area which showed statistically different changes in hypoactivation. Notably, researchers concluded areas of SDVTB-related hyperactivation were significantly associated with internally-oriented processes like mentalizing, emotion, and memory, while hypoactivation was associated with pain (Huang et al., 2020). This suggests that individuals with SDVTB may attend more readily to internal processes than control samples. The meta-analysis did not find any consistent differences when analyses were reduced to studies that used psychiatric or suicide-related controls (Huang et al., 2020).

Task-based imaging modalities evaluate the regional changes associated with a specified task. Specifically among studies that utilized cognitive or affective tasks, the meta-analysis found hyperactivation in the right posterior cingulate cortex and superior frontal gyrus during affective tasks among participants with a history of SDVTB as compared to psychiatric and healthy controls (Huang et al., 2020). Brain activation patterns at rest, or during a resting state, display a high degree of spatio-temporal organization that is robust across individuals and elucidate neurofunctional abnormalities in psychiatric disorders (Fornito & Bullmore, 2010; Woodward & Cascio, 2015). Resting-state functional magnetic resonance imaging (rsfMRI) is highly reliable and requires minimal active collaboration from the participant (e.g., laying in the scanner as still as possible and remaining awake). Thus, it provides information about brain functioning without being biased by task performance during scanning (Liemburg et al., 2012; Serafini et al., 2016). Studies have found differences between those with a history of suicide-related thoughts and behaviors and those without, though specific findings vary widely by control group, sample size, and imaging methods in both cortical and subcortical brain regions (Schmaal et al., 2019).

In their review of structural and functional neuroimaging studies, Schmaal and colleagues (2019) proposed a tentative model for the development of suicide-related thoughts and behaviors from a neurological perspective. These investigators suggested abnormalities in an extended ventral prefrontal cortex system (including the anterior cingulate cortex [ACC], insula, medial and lateral orbitofrontal cortices, rostral prefrontal cortex [rPFC], mesial temporal regions, ventral striatum, lateral temporal lobe, posterior cingulate cortex [PCC], precuneus, and cerebellum) and the connections between these regions are associated with excessive negative and blunted positive internal states that may lead to suicide ideation. A more lateral and dorsal system (consisting of the dorsomedial prefrontal cortex [dmPFC], dorsolateral prefrontal cortex [dlPFC], and dorsal ACC [dACC] with the inferior frontal gyrus [IFG] and rPFC) may facilitate suicide thoughts moving into behaviors through their role in cognitive control of thought, emotion, and behavior and cognitive flexibility (Schmaal et al., 2019). Thus, this model posits that correlated and anticorrelated functional networks may contribute towards the development of suicide thoughts and behaviors. Unfortunately, for the purposes of this study, their review includes studies with a large degree of heterogeneity in STB and control groups, which limits interpretation using an ideation-to-action framework.

Brain Network Analyses

There are a number of different analytic methods applied to resting-state or task-based fMRI data, including voxel-based, seed-based, and functional network analyses. Neuroscientists have increasingly recognized the brain is organized into intrinsic functional networks, or networks of regions that are commonly correlated or anticorrelated with each other at a given time (Buckner & DiNicola, 2019; Fox, Zhang, Snyder, & Raichle, 2009; Schaefer et al., 2018; Yeo et al., 2011). As recommended by Uddin, Yeo, and Spreng (2019), an anatomical taxonomy should be used to refer to these networks rather than a functional taxonomy to allow for reproducibility and consistency with international studies. Because large-scale functional networks have increasingly been associated with multiple roles, traditional cognitive nomenclature like “attention network” diminishes the role of these networks in other tasks and reduces reproducibility between research groups. Thus, an anatomical taxonomy will be emphasized in this paper (“dorsal frontoparietal network” rather than “attention network”).

One network thought to be highly relevant for this study is the medial frontoparietal network (M-FPN; functionally referred to as the “default mode network”), which consists of multiple smaller networks and includes parts of the mPFC, PCC, and hippocampus. This network is involved in self-referential processing, autobiographical memory retrieval, and future-oriented thinking (Buckner, Andrews-Hanna, & Schacter, 2008; Buckner & DiNicola, 2019). Another potentially relevant network that has been identified is the lateral frontoparietal network (L-FPN; functionally referred to as the “cognitive/executive control network”), which consists of lateral prefrontal regions along the middle frontal gyrus including the rostral and dorsolateral prefrontal cortex and the anterior inferior parietal lobule. This network is involved in goal-directed responses, emotion regulation, and some attentional processes (Cole, Repovš, & Anticevic, 2014; Seeley et al., 2007; Uddin et al., 2019). The mid-cingulo-insular network (M-CIN; functionally referred to as the “salience network”) consists of the dACC, bilateral anterior insula, and anterior midcingulate cortex. This network is involved in the detection of behaviorally relevant environmental stimuli and coordinating responses (Seeley et al., 2007; Uddin et al., 2019). Other identified potentially relevant networks include the occipital (“visual”), pericentral (“somatomotor”), and dorsal frontoparietal (“attention”) networks (Uddin et al., 2019).

Triple network theory. The Triple Network Theory (Menon, 2011) posits three of the aforementioned networks, medial frontoparietal, lateral frontoparietal, and midcingulo-insular networks (which are functionally the default mode, cognitive/executive control, and salience networks), support the majority of cognitive and emotional processes and are central to clinically-concerning psychological dysfunction. Dysfunction in any of the three networks can lead to impaired cognitive and emotional functioning. Specifically, Menon (2011) posits that weak salience detection and mapping of goal-relevant stimuli and internal mental events from and into the midcingulo-insular network gives rise to aberrant engagement of the lateral frontoparietal network. L-FPN dysfunction compromises cognition and goal-relevant adaptive behavior. Aberrant M-FPN organization and weak engagement or disengagement of the M-FPN by salient events is associated with altered self-referential mental activity (like rumination). Weak M-CIN mapping can arise from several input factors including, for example, atypical stimulus mapping, reward/motivational signal dysfunction and impaired access to attentional/working memory resources for cognitively demanding tasks. The Triple Network Theory posits dysfunction in any core network can impact the other two networks, with clinical manifestations that transcend the primary deficit (Menon, 2011). For example, Menon (2011) suggested in individuals with depression, M-FPN is coupled to M-CIN activity.

Two studies to date have directly tested the triple network theory in relation to suicide-related thoughts or behaviors. In the first study, Ordaz and colleagues (2018) examined the relationship between within-network M-FPN, L-FPN, and M-CIN functional connectivity among different brain regions within the same network and lifetime suicide ideation severity in a sample of 40 adolescents diagnosed with MDD. They found that increased within-network functional connectivity in each of the three networks was independently associated with greater lifetime severity of suicide ideation (i.e. longer duration, less controllability, higher frequency). This suggests suicide ideation in individuals with MDD may be related to a complex set of cognitions associated with cognitive control, self-referential thinking, and processing salient information (Ordaz, Goyer, Ho, Singh, & Gotlib, 2018). While this study represents an important contribution to the understanding of suicide ideation, its lack of comparison to those who have attempted suicide limits speculation about neural correlates of suicide behaviors.

In the second study, Malhi and colleagues (2019) compared network connectivity of 25 individuals with a history of suicide attempt and current mood disorder to 54 individuals with mood disorder, but no history of attempted suicide, in each of the three networks and the basal ganglia network. They found that increased posterior M-FPN activity was associated with past-month suicide ideation or behavior, linking recent suicidality to default mode activity and potentially self-referential thinking (Malhi, Das, Outhred, Gessler, et al., 2019). The lack of a control group with a history of suicide-related thoughts limits interpretations; M-FPN connectivity differences could be related to ideation, behavior, or both. While both studies represent important contributions, neither accounted for important potentially confounding variables or had sufficient sample size to directly examine between-network connectivity.

Current Study

Because of sample size constraints, only 7% of studies targeting above questions have compared those with history of attempted suicide to controls with a history of self-directed violence thoughts (SDVT) without self-injurious behavior (Huang et al., 2020). This limits possible conclusions regarding the transition from ideation to attempt. Prior to large-scale neuroimaging databases, neural correlates of suicide could not be studied because of insufficient sample sizes. Current studies have largely been underpowered and lack covariates to study this topic. Thus, studies with large sample sizes are needed to investigate neural network differences in those with a history of attempted using a SDVT and controlling for potentially confounding variables.

The current study aimed to build upon prior research by examining resting-state functional brain network connectivity between those with a lifetime history of suicide attempt and those with a lifetime history of self-directed violence thoughts but no lifetime suicide attempts. Specifically, the present study assessed the relationship between suicide attempt history with network activation in the medial frontoparietal network, lateral frontoparietal network, and midcingulo-insular network using the UK Biobank cohort, adjusting for several potential confounding variables (age, sex, ethnicity, and BMI). This is the largest neuroimaging study of suicide behavior to date.

Aims & Hypotheses

Aim 1. Compare resting-state connectivity within medial frontoparietal (default mode), lateral frontoparietal (executive control), and midcingulo-insular (salience) network regions between individuals with a history of suicide attempt versus those with a history of self-directed violence thoughts (SDVT) without an attempt.

Hypothesis 1. In line with the triple network theory (Menon, 2011), those with a lifetime history of suicide attempt in comparison to those with a history of SDVT without an attempt would likely demonstrate greater connectivity within the medial frontoparietal and midcingulo-insular networks but lower within-network connectivity among lateral frontoparietal regions.

Aim 2. Compare resting-state connectivity between medial frontoparietal (default mode), lateral frontoparietal (executive control), and midcingulo-insular (salience) network regions between individuals with a history of suicide attempt versus those with a history of SDVT without an attempt.

Hypothesis 2. In line with the triple network theory (Menon, 2011) and prior fMRI research in SDVTB, those with a lifetime history of suicide attempt in comparison to those with a lifetime history of SDVT without an attempt would likely demonstrate lower between-network connectivity among the medial frontoparietal, lateral frontoparietal, and midcingulo-insular network regions.

Exploratory Aim 3. Compare whole-brain resting-state activation between individuals with a history of suicide attempt versus those with a history of SDVT without an attempt.

Exploratory Hypothesis 3. Given the absence of well-powered studies exploring whole-brain resting-state in relation to SDVTB, we do not have specific hypotheses about which additional networks will be implicated in exploratory analyses.

Method

Participants

The UK Biobank is a population-based biomedical study of roughly 500,000 participants from Great Britain (England, Scotland, and Wales) between the ages of 40 and 69 (Miller et al., 2016). Procedurally, participants first attended an initial visit and answered demographic and medical questions. Several weeks later, participants were invited to complete an online mental health follow-up questionnaire packet. Those who answered “yes” to the question “Have you deliberately harmed yourself, whether or not you meant to end your life?” (UK Biobank field 20480) were prompted to answer further detailed questions regarding “harm behaviours.” Among those questions were “Have you harmed yourself with the intention to end your life?” (suicide attempt history; UK Biobank field 20483) and “Have you contemplated harming yourself (for example, by cutting, biting, hitting yourself, or taking an overdose)?” (suicide-related thought history; UK Biobank field 20485). For the purposes of this study, this latter endorsement has been defined as “self-directed violence thoughts” (SDVT) in line with the CDC self-directed violence classification system.

A subsample of participants underwent magnetic resonance imaging (MRI) neuroimaging procedures, including structural and functional imaging (Miller et al., 2016). Participants were excluded from MRI imaging if they reported any of the following neurological conditions/incidents: dementia, Parkinson’s disease, brain cancer, brain hemorrhage, brain abscess, aneurysm, cerebral palsy, encephalitis, head injury, nervous system infection, head or neurological injury, trauma, stroke, or other chronic neurodegenerative problem (Miller et al., 2016).

The current study included the subsample of 4,013 participants with a self-reported lifetime history of suicide attempt or self-directed violence thoughts and had valid functional neuroimaging data. A participant flowchart leading to the final study sample is depicted in Figure 1. Of those included in the final sample, 566 (14.1%) reported lifetime history of suicide attempt and 3,447 (85.9%) reported lifetime history of self-directed violence thoughts without attempt.

MRI Acquisition and Processing

MRI data were acquired in a Siemens Skya 3T scanner using a standard Siemens 32-channel head coil (Miller et al., 2016). Briefly, 3D T1-weighted MPRAGE were acquired at 1 x 1 x 1 mm (208 x 256 x 256 field of view [FOV] matrix) and 2 x 2 x 2 (104 x 104 x 72 FOV matrix), respectively. Preprocessing was done using FSL tools by the UK Biobank team (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Initial preprocessing included "defacing" for participant anonymity via linear transformation to mask out facial structures. Preprocessing of T1 data included skull stripping, bias field correction, warping to MNI space using FNIRT (Andersson, Jenkinson, & Smith, 2007), and tissue-type segmentation using FAST (Zhang, Brady, & Smith, 2001) to differentiate cerebrospinal fluid, gray, and white matter volumes and generate 139 image-derived phenotypes (IDPs). For further information, detailed UK Biobank data acquisition and preprocessing protocol (https://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf) and associated documentation (http://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf) are freely available online.

For resting-state functional MRI (rsfMRI) procedures, participants were instructed to “keep their eyes fixated on a crosshair, relax, and think of nothing in particular.” Resting-state fMRI data were acquired using a resolution of 2.4 x 2.4 x 2.4 (88 x 88 x 64 FOV matrix) with TR = 0.735 s, TE = 39 ms, and GE-EPI with x8 multislice acceleration, no iPAT, flip angle 52° over 6 minutes (490 timepoints) (Miller et al., 2016). Data preprocessing, group-independent components analysis (ICA) parcellation, and connectivity estimation were carried out by UK Biobank with FSL packages. These include motion correction with MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), grand-mean intensity normalization with a single multiplicative factor, high pass temporal filtering with a Gaussian-weighted least squares straight line fitting (sigma as 50.0 s), EPI unwarping using field map scanned before collection, gradient distortion correction (GDC) unwarping, and removal of structural artefacts using an ICA-based X-noiseifier (Ritchie et al., 2018). Gross preprocessing failures were visually inspected by UK Biobank and removed (Miller et al., 2016). Group-ICA parcellated preprocessed EPI images were fed into the MELODIC tool of FSL to generate 100 ICA components (55 were used for analysis after 45 were removed due to noise after visual-quality control) (found here https://www.fmrib.ox.ac.uk/datasets/ukbiobank/index.html) (Ritchie et al., 2018; Shen et al., 2018). A lower resolution 21x21 matrix of ICA components was used for analysis of the three major networks, as they represent larger functional networks in each single component (https://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf).

Analyses

Time series data from the 21 components were used for connectivity analysis, using each component as a node. A 21 x 21 partial matrix of fully-normalized partial temporal correlations were derived for each participant, as they represent direct connections better than full temporal correlations and control for the strength of other connections (Ritchie et al., 2018; Shen et al., 2018). For each component, a larger number indicates stronger temporal connectivity while positive or negative values represent valence.

Prior to analysis, the strength of each connection was multiplied by the sign of its group mean per recommendation of Smith and colleagues (2015). This allowed for investigation of the degree to which temporal connectivity differed by history of suicide attempt without combining positive and negative effects and losing information about the absolute magnitude (Ritchie et al., 2018). The association between history of attempted suicide and the strength of connections was tested using the *glm* function in R, controlling for age, sex, ethnicity, and body mass index (BMI). Demographic factors such as age, sex, and ethnicity were included as covariates as they are associated with differences in both suicide attempts (E David Klonsky, May, & Saffer, 2016) and resting-state functional connectivity (Alfaro-Almagro et al., 2020; Ritchie et al., 2018; Smith & Nichols, 2018). Due to low cell counts, ethnicity was coded as a binary variable with Non-Hispanic White and Non-White categories. BMI was calculated as weight (kg)/height^2 (m). BMI was included as a covariate as higher BMI is associated with both lower risk for completed suicide (Klinitzke, Steinig, Blüher, Kersting, & Wagner, 2013) and altered functional connectivity strength within the M-FPN (Kullmann et al., 2012) for both men and women.

For Aim 1, 14 general linear regressions were performed comparing those with a history of suicide attempt to those with SDVT without an attempt for within-network nodes representing the three networks of interest. For Aim 2, 31 general linear regressions were performed comparing those with a history of suicide attempt to those with SDVT without an attempt for between-network nodes representing the three networks of interest. For Aim 3, 165 general linear regressions were performed comparing those with a history of suicide attempt to those with SDVT without an attempt for the remainder of the 21 nodes (165 comparisons). False discovery rate (FDR) correction was applied over each set of tests using the *p.adjust* function in R, setting $q < 0.05$ as the significance level (Shen et al., 2018). Subsequent additional sensitivity analyses were conducted using comparisons from Aims 1 and 2 without covariates.

Results

Participant Characteristics

A total of 4,013 participants were included in analysis of neuroimaging correlates. Participants were on average 52.75 years old (SD = 7.13, range = 40-70 years old) at the time of their initial study visit. Women represented 65.7% of the sample ($n = 2637$) and 97.8% of the sample were non-Hispanic White. Those with a history of suicide attempt were more likely to be female, χ^2 (1, 4013) = 5.97, $p = 0.0146$, compared with those with a history of SDVT without an attempt. Groups did not differ significantly based on age or ethnicity. Demographic characteristics for the overall sample and by group are presented in Table 1.

Within-network Connectivity

To compare within-network resting-state functional connectivity between participants with a lifetime history of suicide attempt to those with a history of SDVT without an attempt, 14 general linear models were conducted, adjusting for age, sex, ethnicity, and BMI. Ten models compared groups on M-FPN within-network connectivity, one compared groups on L-FPN within-network connectivity, and three compared groups on M-CIN within-network connectivity. As shown in Table 2, no models revealed statistically significant differences between groups after adjusting for multiple corrections (FDR $q > 0.05$). Subsequent sensitivity analyses conducted without covariates similarly did not reveal statistically significant differences between groups after adjusting for multiple corrections (FDR $q > 0.05$).

M-FPN Within-network Connectivity. Prior to FDR correction for multiple comparisons, two of the ten models showed altered connectivity within the M-FPN. Participants with a history of suicide attempt had lower connectivity between node 1 and node 7 in comparison to those with a history of SDVT without attempt, $t(1, 4013) = -2.04$, $p = 0.0419$, FDR $q = 0.2217$. These nodes included connectivity between areas of the ventromedial prefrontal cortex (node 1) with areas of the retrosplenial and medial temporal cortices (node 7). Participants with a history of suicide attempt had greater connectivity between node 14 and node 20 in comparison to those with a history of SDVT without attempt, $t(1, 4013) = 2.11$, $p = 0.0354$, FDR $q = 0.2217$. These nodes include connectivity between areas of the anterior cingulate and orbitofrontal cortices (node 14) with areas of the posterior precuneus and posterior cingulate cortex (node 20). Figure 2 depicts significant between-network group differences prior to FDR correction.

L-FPN Within-network Connectivity. One model examined group differences on connectivity between nodes associated with the L-FPN. As shown in Table 2, this model did not reveal statistically significant differences between groups.

M-CIN Within-network Connectivity. Prior to FDR correction for multiple comparisons, one of the three models showed differences in connectivity within the M-CIN. Participants with a history of suicide attempt had lower connectivity between node 13 and node 18 in comparison to those with a history of SDVT without attempt, $t(1, 4013) = -1.98$, $p = 0.0475$, FDR $q = 0.2217$. As depicted in Figure 2c, these nodes include connectivity between areas of the left cingulo-opercular cortex (node 13) with areas of the putamen, striatum, and basal ganglia (node 18).

Between-network Connectivity

To compare within-network resting-state functional connectivity between participants with a lifetime history of suicide attempt to those with a history of SDVT without attempt, 31 general linear models were conducted, adjusting for age, sex, ethnicity, and BMI. Ten models compared groups on M-FPN to L-FPN between-network connectivity, 15 compared groups on M-FPN to M-CIN between-network connectivity, and six compared groups on L-FPN to M-CIN between-network connectivity. As shown in Table 3, no models revealed statistically significant differences between groups after adjusting for multiple corrections (FDR $q > 0.05$). Subsequent sensitivity analyses conducted without covariates similarly did not reveal statistically significant differences between groups after adjusting for multiple corrections (FDR $q > 0.05$)

L-FPN with M-FPN. Prior to FDR corrections for multiple comparisons, one of ten models showed altered connectivity between nodes associated with the L-FPN with nodes associated with the M-FPN. Participants with a history of suicide attempt had increased connectivity between node 16 (L-FPN) and node 7 (M-FPN) in comparison to those with a history of SDVT without attempt, *t*(1, 4013) = 2.97, FDR *q* = 0.046. These nodes include connectivity between areas of the anterior and dorsolateral prefrontal cortex (node 16) with areas of the retrosplenial and medial temporal cortices (node 7).

M-FPN with M-CIN. Prior to FDR corrections for multiple comparisons, one of fifteen models showed altered connectivity between nodes associated with the M-FPN with nodes associated with the M-CIN. Participants with a history of suicide attempt had greater connectivity between node 13 and node 14 in comparison to those with a history of SDVT without attempt, *t*(1, 4013) = 2.05, *p* = 0.0401, FDR *q* = 0.3447. These nodes include connectivity between areas of the left cingulo-opercular cortex (node 13) with areas of the anterior cingulate and orbitofrontal cortices (node 14).

L-FPN with M-CIN. Prior to FDR corrections for multiple comparisons, one of six models examined group differences on connectivity between nodes associated with the L-FPN with nodes associated with the M-CIN. Participants with a history of suicide attempt had greater connectivity between node 16 (L-FPN) and node 18 (M-CIN) in comparison to those with a history of SDVT without attempt, *t*(1, 4013) = 3.09, *p* = 0.0020, FDR *q* = 0.0620. These nodes include connectivity between areas of the anterior and dorsolateral prefrontal cortex (node 16) with areas of the putamen, striatum, basal ganglia, and thalamus (node 18). Figure 3 depicts significant between-network group differences prior to FDR correction.

Whole-brain Connectivity

In exploratory analyses of whole-brain group differences, 165 general linear regressions were performed comparing those with a history of suicide attempt to those with SDVT without attempt for the remainder of the 21 nodes. No models revealed statistically significant differences between groups after adjusting for multiple corrections (FDR $q > 0.05$).

Discussion

In the largest neuroimaging study of suicide behavior to date, we found no significant differences between individuals with self-reported lifetime history of suicide attempt(s) when compared to those with self-reported history of SDVT without an attempt after correcting for multiple comparisons. Specifically, we found no significant group differences in within- or between-network connectivity among nodes of the M-FPN, L-FPN, or M-CIN. Further, there were no significant group differences on exploratory whole-brain connectivity analyses.

Despite its sample size powered to detect small effects, this study did not find significant within-network, between-network, or whole-brain connectivity differences between participants with a lifetime history of attempted suicide when compared to those with a history of SDVT without attempt after correcting for multiple comparisons. These results contrast with several smaller studies that previously found resting-state differences between those with a history of suicide attempt and psychiatric controls (Cao et al., 2015; Kang et al., 2017; Malhi, Das, Outhred, Gessler, et al., 2019). These findings are consistent with growing trends in brain science research showing reduced effects upon replication in larger samples (Button et al., 2013). Functional neuroimaging studies have, in particular, been underpowered (David et al., 2013; Szucs & Ioannidis, 2020), with an inverse relationship between sample size and number of significant findings. The average sample size of neuroimaging studies of SDVTB is around 48 (Huang et al., 2020), which indicates that many previously found differences may be spurious and related to Type I error than to true differences.

From the perspective of ideation-to-action frameworks like the 3ST, null findings in the present study suggest that dispositional factors measured by neuroimaging markers likely do not have a simple or direct relationship with the transition from suicide-related thoughts to behaviors. Rather, the ideation-to-action theoretical framework would necessitate an examination of the interaction among biopsychosocial factors – more specifically, dispositional (biological, genetic), acquired (learning), practical aspects activating a progression from suicide ideation to suicide actions. Thus, future research should investigate the complex interplay among factors from the perspective of the 3ST to fully understand differences between these groups.

With regards to within-network connectivity, this study did not find significant differences between participants with a lifetime history of attempted suicide when compared to those with history of SDVT without attempt after correcting for multiple comparisons. Previously, Malhi and colleagues (2019) found within-network connectivity differences in the M-FPN when comparing those with attempted suicide to healthy controls, but did not find differences when those with attempted suicide were compared to mood disorder patients (Malhi, Das, Outhred, Bryant, et al., 2019). Lending additional support to this growing consensus, a recent study comparing 35 depressed adolescents with lifetime history of attempted suicide to 18 adolescents with mood disorder without a suicide attempt history did not find within-network differences when looking at regions within the M-FPN and M-CIN (Cao et al., 2020). This suggests that within-network differences may be too subtle to detect when using psychiatric or SDVT controls. Future studies should investigate differences between SDVT and suicide behavior subgroups on specific regions of interest within these larger networks.

With regards to between-network connectivity, this study did not find significant differences between participants with a lifetime history of attempted suicide when compared to those with history of SDVT without attempts after correcting for multiple comparisons. This is consistent with Mahli and colleagues (2019) who did not find between-network connectivity when comparing those with attempted suicide to healthy controls or mood disorder patients. Perhaps using these groups, differences between networks may be better detected during tasks designed to activate target brain networks. In their meta-analysis, Huang and colleagues (2020) suggested that, compared to all controls (healthy and psychiatric), those with SDVTB collectively showed hyperactivation of the right posterior cingulate cortex and superior frontal gyrus during pooled affective tasks, suggesting potential alterations between the M-FPN and L-FPN during affective processes. Larger studies are needed to more fully investigate potential between-network differences during cognitive, affective, and social tasks.

Finally, this study did not find other significant whole-brain connectivity differences between participants with a lifetime history of attempted suicide when compared to those with history of SDVT without attempt. As noted above, null findings may reflect the need for more nuanced investigation and interpretation of the interplay between dispositional, practical, and acquired factors to differentiate those with a history of attempt from SDVT alone (E.D. Klonsky & May, 2015). It has been noted widely within suicidology literature that differentiating factors uniquely associated with suicide attempt has been a challenge for the field (Franklin et al., 2017).

In light of FDR corrections, significant results found prior to corrections for multiple comparisons should be interpreted with caution. In terms of between-network functional connectivity, lifetime history of attempted suicide was associated with increased connectivity between nodes of the L-FPN with nodes of the M-FPN and M-CIN when compared to lifetime history of SDVT without attempt. These results point to a potential role of L-FPN activation at rest, particularly among areas of the anterior and dorsolateral prefrontal cortex, in differentiating those with lifetime history of suicide attempt from those with a lifetime history of SDVT without attempt. Ordaz and colleagues (2018) found that lower coactivation of L-FPN regions was associated with greater lifetime severity of suicide ideation in a sample of 40 adolescents with MDD Further, our findings of differences among a specific subnetwork of the L-FPN are contrary to their findings of the network in its entirety. These differences may reflect our sample size, measurement differences, choice to focus on those with a history of attempt, and study population.

The L-FPN subnetwork highlighted in this study includes sections of the anterior and dorsolateral prefrontal cortex. The anterior prefrontal cortex has been implicated in monitoring and meta-cognitive processes (Baird, Smallwood, Gorgolewski, & Margulies, 2013), and has not been widely associated with SDVTB. The dlPFC is involved in the conscious active control of planned behavior and cognition (Fleming & Dolan, 2012; Menon, 2011). Results of this study are inconsistent with findings of elevated activation while performing cognitive tasks with lower resting activation in SDVTB samples

(Schmaal et al., 2019). Increased activation of the dlPFC differentiated participants with a history of suicide attempt from those with a history of ideation without attempts during a continuous performance task (Minzenberg et al., 2015), while decreased resting regional cerebral glucose metabolism in the dlPFC was found among individuals with suicide plans in a study using positron emission tomography (van Heeringen, Wu, Vervaet, Vanderhasselt, & Baeken, 2017). In light of current study findings, dlPFC activation may reflect a differentiation between ideation history and SDVT for further investigation.

This study found possible differences in L-FPN connectivity with other key brain networks among individuals with a lifetime history of suicide attempt. Results are consistent with meta-analytic findings that increased between-network connectivity between frontoparietal and M-FPN systems characterize MDD when compared to healthy controls (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). It has been hypothesized that, in depression, imbalanced connectivity between control systems and networks involved with both internal (M-FPN) and external (M-CIN) attention may reflect attention biases (Kaiser et al., 2015). In respect to suicide, increased interconnectivity between cognitive control subnetworks and networks associated with both internal and external stimuli may reflect similar attention biases when compared to those with SDVT without attempt. Further task-based studies should examine the role of attention bias in this population.

Covariate use in neuroimaging studies is highly diverse, with some studies reporting use of zero covariates and others using as many as 14 covariates in analyses (Hyatt et al., 2020). Smith and Nichols (2018) highlight how large datasets, in particular, are especially susceptible to artifactual associations due to confounding effects in neuroimaging research. Alfaro-Almagro and colleagues (2020) caution consideration of covariates, particularly in relation to IDP imaging data in the UK Biobank. Both research groups suggest motion correction and noise removal to reduce imaging-related artifacts in analysis, both of which were conducted prior to these analyses. Further, near duplication of findings after sensitivity analyses in this study conducted without covariates increases confidence that lack of robust findings were not due to covariate selection.

There are several noteworthy limitations to this study. Without a comprehensive lifetime suicide history and risk assessment (e.g., using instruments such as the Columbia Suicide Severity Rating Scale), it is difficult to discern the temporal relationship between suicide attempt history and functional connectivity differences. Participants were 53 years old, on average, thus SDVTB could have occurred decades prior. Researchers have suggested that functional markers may be better than structural anatomical markers at clinically differentiating those who are acutely suicidal in the future, as suicide thoughts are typically time-limited (Balcioglu & Kose, 2018; Rudd, 2000). Future studies should make efforts to incorporate time since SDVTB to account for potential differences in time.

Relatedly, without a comprehensive lifetime suicide history and risk assessment, there are several confounding variables. Using a SDVT control group, we were unable to parse those with lifetime thoughts of suicide from those with lifetime thoughts of NSSI. While a SDVT control group is a strength compared to previous studies, there may be important distinctions between those who have thought of NSSI from those who have thought of suicide to consider (Ren et al., 2019). Further, we were unable to differentiate those a history of a single suicide attempt from those with multiple attempts. Those with a history of multiple attempts are thought to have distinct features, including impulsivity and borderline personality disorder traits and associated symptoms, that may reflect differences in functional neuroimaging markers (Boisseau et al., 2013). Though our study used a stringent control group, there may be variability within functional connectivity within SDVTB groups. Future studies should more rigorously define groups and explore differences between those with a history of NSSI, suicide ideation, suicide attempt, and multiple attempts.

Strengths of this study include its sample size, use of a SDVT control group, and corrections for multiple comparisons to avoid spurious findings. In terms of outcome measures, this study utilized empirically-supported anatomical markers for network nodes, IDP markers for network connectivity which have been validated in previous studies (Ritchie et al., 2018; Shen et al., 2018), and comparison of groups based on both theory- (Aim 1 and 2) and data-driven (Aim 3) outcomes. This study on within- and between-network connectivity in those with a history of suicide attempt adds to the growing literature of biological correlates of SDVTB.

Conclusions

In the largest neuroimaging study to date regarding suicide attempt behavior, this study found that history of attempted suicide, when compared to those with a history of SDVT without attempt, was not associated with within- or between-network connectivity differences in the M-FPN, L-FPN, M-CIN or other subnetworks after controlling for multiple comparisons. Findings highlight the need for well-powered neuroimaging analyses. Dispositional risk factors, like those measured by functional neuroimaging, may be less straightforward and rather may interact with practical and acquired risk factors in differentiating those at risk for SDVT from suicide attempt. Overall, this provides support for further study into the complex relationship between brain function and suicidality.

Table 1. Demographic characteristics for the overall sample and by group.

	Overall (*n* = 4,013)		Group 1: SA (*n* = 566)		Group 2: SDVT (*n* = 3,447)			
	Frequency	Percent	Frequency	Percent	Frequency	Percent	χ^2	*p*
Age, Mean (SD), *t* statistic	52.75 (range = 40-70)	(7.13)	52.90	(6.97)	52.90	(7.16)	-0.02	0.9807
Gender								
Female	2637	65.7%	398	70.3%	2239	65.0%	**5.97**	**0.0146**
Male	1376	34.3%	168	29.7%	1208	35.0%		
Race/Ethnicity†								
Non-Hispanic White	3925	97.8%	556	98.2%	3369	97.7%	0.49	0.4833
Non-White	79	2.0%	9	1.6%	70	2.0%		
Prefer not to answer	7	0.2%	0	0%	7	0.2%		
Do not know	1	0%	1	0.2%	0	0%		
BMI, Mean (SD), *t* statistic	26.62	(4.62)	27.03	(4.98)	26.55	(4.56)	**-2.18**	**0.0293**

Note. Data reported as n (%), unless otherwise specified. Group 1 (SA) = Lifetime History of Suicide Attempt(s); Group 2 (SDV) = Lifetime History of Self-Directed Violence Thoughts (SDVT) Alone.

†One participant in Group 2 was missing data on race/ethnicity and was coded as “prefer not to answer” for subsequent analyses. Due to expected counts <5, race/ethnicity chi-square analysis was conducted using only Non-Hispanic White and Non-White categories without “Prefer not to answer” or “Do not know.”

Table 2. Comparisons of two selected groups on within-network resting-state connectivity among the medial frontoparietal, lateral frontoparietal, and midcingulo-insular networks.

Network	Network 1 (Node)	Network 2 (Node)	*t*-value	SE	β	*p*-value	FDR-adjusted *q*-value
Medial Frontoparietal	M-FPN (1)	M-FPN (7)	-2.04	0.04	-0.03	0.0419*	0.2217
	M-FPN (1)	M-FPN (9)	1.00	0.04	0.02	0.3180	0.7420
	M-FPN (1)	M-FPN (14)	-0.61	0.04	-0.01	0.5404	0.8406
	M-FPN (1)	M-FPN (20)	1.70	0.04	0.03	0.0894	0.3132
	M-FPN (7)	M-FPN (9)	-0.808	0.04	-0.01	0.4189	0.8378
	M-FPN (7)	M-FPN (14)	0.33	0.03	0.01	0.7430	0.9378
	M-FPN (7)	M-FPN (20)	0.02	0.04	<0.01	0.9816	0.9828
	M-FPN (9)	M-FPN (14)	0.16	0.03	<0.01	0.8697	0.9828
	M-FPN (9)	M-FPN (20)	-0.70	0.04	-0.01	0.4825	0.8406
	M-FPN (14)	M-FPN (20)	2.11	0.03	0.03	0.0354*	0.2217
Lateral Frontoparietal	L-FPN (5)	L-FPN (16)	0.02	0.04	<0.01	0.9828	0.9828
Midcingulo-Insular	M-CIN (13)	M-CIN (18)	-1.37	0.02	-0.02	0.1702	0.4766
	M-CIN (13)	M-CIN (21)	-1.98	0.04	-0.03	0.0475*	0.2217
	M-CIN (18)	M-CIN (21)	0.04	<0.01	<0.01	0.9724	0.9828

Note. Group 1 (SA) = Lifetime History of Suicide Attempt(s); Group 2 (SDVT) = Lifetime History of Self Directed Violence Thoughts (SDVT) Alone; BMI = body mass index; SE = standard error; FDR = false discovery rate; M-FPN = medial frontoparietal network; L-FPN = lateral frontoparietal network; M-CIN = midcingulo-insular network. All models adjusted for age, sex, ethnicity, and BMI

Table 3. Comparisons of two selected groups on between-network resting-state connectivity among the medial frontoparietal, lateral frontoparietal, and midcingulo-insular networks.

Networks	Network 1 (Node)	Network 2 (Node)	*t*-value	SE	β	*p*-value	FDR-adjusted *q*-value
Lateral frontoparietal with medial frontoparietal	M-FPN (1)	L-FPN (5)	-1.29	0.04	-0.02	0.1968	0.7365
	M-FPN (1)	L-FPN (16)	-1.45	0.05	-0.02	0.1463	0.6479
	L-FPN (5)	M-FPN (7)	-0.51	0.04	-0.01	0.6090	0.8581
	L-FPN (5)	M-FPN (9)	-1.06	0.04	-0.02	0.2883	0.7365
	L-FPN (5)	M-FPN (14)	-0.25	0.03	>-0.01	0.8056	0.9249
	L-FPN (5)	M-FPN (20)	1.92	0.04	0.03	0.0550	0.3447
	M-FPN (7)	L-FPN (16)	2.53	0.04	0.04	0.0113*	0.1759
	M-FPN (9)	L-FPN (16)	-0.84	0.04	-0.01	0.3990	0.7731
	M-FPN (14)	L-FPN (16)	0.523	0.04	0.01	0.6013	0.8581
	L-FPN (16)	M-FPN (20)	-0.43	0.04	-0.01	0.6694	0.9023
Medial frontoparietal with midcingulo-insular	M-FPN (1)	M-CIN (13)	-0.90	0.03	0.01	0.3703	0.7731
	M-FPN (1)	M-CIN (18)	-0.33	0.03	-0.01	0.7433	0.9217
	M-FPN (1)	M-CIN (21)	-1.08	0.04	-0.02	0.2816	0.7365
	M-FPN (7)	M-CIN (13)	-0.70	0.03	-0.01	0.4845	0.7904
	M-FPN (7)	M-CIN (18)	-1.15	0.02	-0.02	0.2509	0.7365
	M-FPN (7)	M-CIN (21)	-1.95	0.04	-0.03	0.0556	0.3447
	M-FPN (9)	M-CIN (13)	0.59	0.04	0.01	0.5586	0.8581
	M-FPN (9)	M-CIN (18)	0.12	0.03	<0.01	0.9087	0.9633
	M-FPN (9)	M-CIN (21)	0.73	0.04	0.01	0.4630	0.7904
	M-CIN (13)	M-FPN (14)	2.05	0.03	0.03	0.0401*	0.3447
	(6)	M-FPN (14)	-0.27	0.03	>-0.01	0.7850	0.9249
	M-FPN (14)	M-CIN (18)	0.33	0.08	0.01	0.7400	0.9217
	M-FPN (14)	M-CIN (21)	-1.52	0.03	-0.02	0.1276	0.6479
	M-CIN (18)	M-FPN (20)	0.07	0.02	<0.01	0.9435	0.9633
	M-FPN (20)	M-CIN (21)	0.05	0.04	<0.01	0.9633	0.9633
Lateral frontoparietal with midcingulo-insular	L-FPN (5)	M-CIN (13)	-0.71	0.04	-0.01	0.4773	0.7904
	L-FPN (5)	M-CIN (18)	-0.87	0.03	-0.01	0.3834	0.7731
	L-FPN (5)	M-CIN (21)	-1.02	0.04	-0.02	0.3089	0.7365
	M-CIN (13)	L-FPN (16)	0.20	0.03	<0.01	0.8389	0.9298
	L-FPN (16)	M-CIN (18)	3.09	0.03	0.05	0.0020**	0.0620
	L-FPN (16)	M-CIN (21)	1.18	0.04	0.02	0.2378	0.7349

Note. Group 1 (SA) = Lifetime History of Suicide Attempt(s); Group 2 (SDVT) = Lifetime History of Self Directed Violence Thoughts (SDVT)Alone; BMI = body mass index; SE = standard error; FDR = false discovery rate; M-FPN = medial frontoparietal network; L-FPN = lateral frontoparietal network; M-CIN = midcingulo-insular network. All models adjusted for age, sex, ethnicity, and BMI.

Figure 1. Flowchart of case selection.

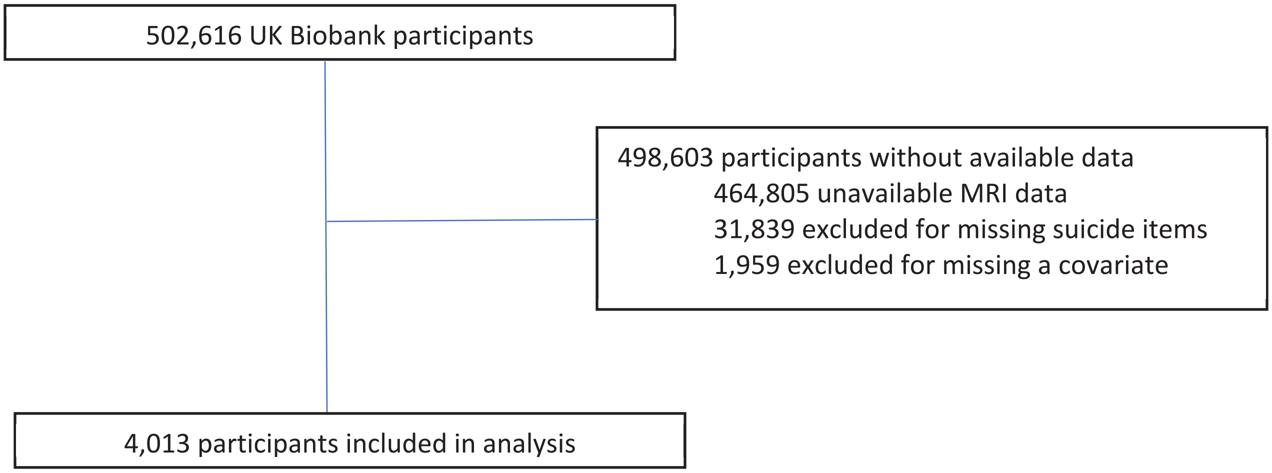


Figure 2. Lifetime suicide attempt(s) was associated with altered within-network connectivity in M-FPN when compared with lifetime SDV ideation alone prior to FDR correction for multiple comparisons. Those with a history of suicide attempt had lower connectivity between M-FPN nodes 1 and 7 (blue line) and greater connectivity between M-FPN nodes 14 and 20 (red line). Lifetime suicide attempt(s) was also associated with lower connectivity between M-CIN nodes 13 and 21 (blue line) prior to FDR correction for multiple comparisons. Models were adjusted for age, sex, ethnicity, and BMI.

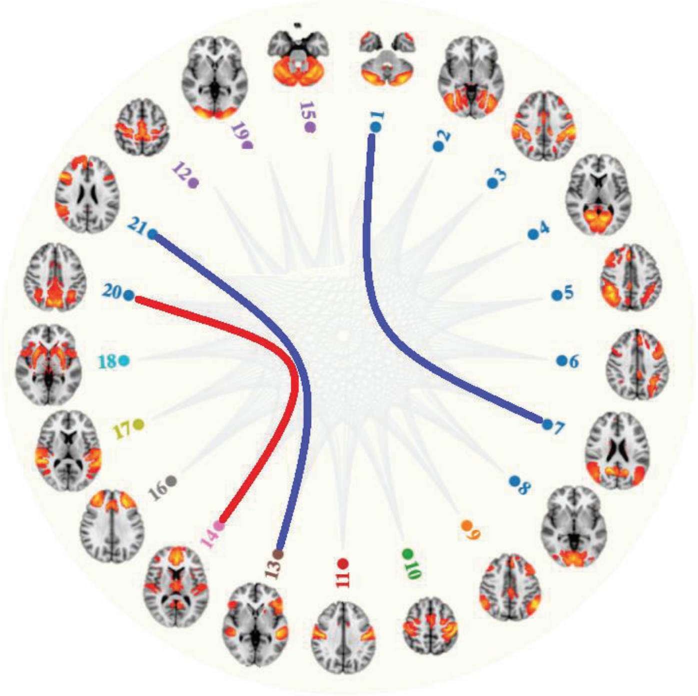
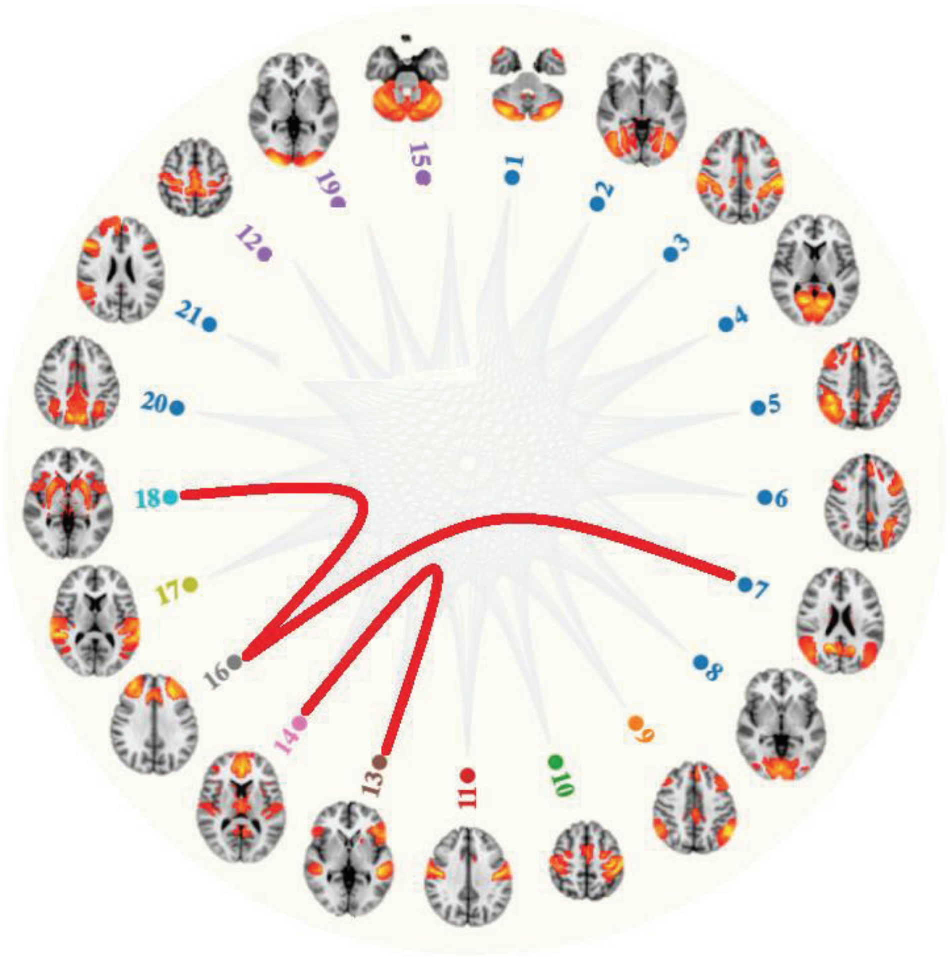


Figure 3. Lifetime suicide attempt(s) was associated with stronger connectivity (red lines) between the lateral frontoparietal network (node 16) and medial frontoparietal network (node 7) and midcingulo-insular network (node 18) when compared with lifetime SDV thoughts alone prior to FDR correction for multiple comparisons. Lifetime suicide attempt(s) was also associated with greater connectivity between the medial frontoparietal network (node 14) and the midcingulo-insular network (node 13). Models were adjusted for age, sex, ethnicity, and BMI.



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