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Research paper

Alterations of functional connectivity and intrinsic activity within the cingulate cortex of suicidal ideators

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ABSTRACT

The 'default mode network' (DMN), a collection of brain regions including the posterior cingulate cortex (PCC), shows reliable inter-regional functional connectivity at rest. It has been implicated in rumination and other negative affective states, but its role in suicidal ideation is not well understood. We employed seed based functional connectivity methods to analyze resting state fMRI data in 34 suicidal ideators and 40 healthy control participants. Whole-brain connectivity with dorsal PCC or ventral PCC was broadly intact between the two groups, but while the control participants showed greater coupling between the dorsal anterior cingulate cortex (dACC) and dorsal PCC, compared to the dACC and ventral PCC, this difference was reversed in the ideators. Furthermore, ongoing low frequency BOLD signal in these three regions (dorsal, ventral PCC, dACC) was reduced in the ideators. The structural integrity of the cingulum bundle, as measured using diffusion tensor imaging (DTI), also explained variation in the functional connectivity measures but did not abolish the group differences. Together, these findings provide evidence of abnormalities in the DMN underlying the tendency towards suicidal ideation.

1. Introduction

The posterior cingulate cortex (PCC) – a prominent hub within the default mode network (DMN) - shows robust activation and connectivity during the resting state, and relatively greater activation when individuals are not engaging in stimulus-led cognitive tasks (Greicius et al., 2003; Pfefferbaum et al., 2011). The region is thought to play a role in self-referential processing and forms of reflective, internally directed thought (Johnson et al., 2009), and is of particular relevance for understanding the type of neurocognitive processes which may underlie negative affective states – including rumination, brooding and suicidal ideation - that accompany mood disorders. In addition, its functional interaction with distal regions such as medial regions of the prefrontal cortex (PFC), and regions of the temporal and parietal lobes may play a crucial part in this role.

Although the resting state is psychologically unconstrained (Morcom and Fletcher, 2007), alterations in functional connectivity between brain regions that accompany depressive illness may be observed, due to the relationship between mind wandering and negative mood (Smallwood et al., 2009). However, whilst evidence from case controlled studies of depression using resting state fMRI has been plentiful, a reliable signature of altered DMN connectivity has been somewhat elusive (but see Hamilton et al., 2015; Kaiser et al., 2015). Two factors are likely to have impeded identifying such a signature, regardless whether or not it indeed exists.

First, the marked heterogeneity of mood disorders (e.g. Sullivan et al., 1998) is particularly important in this context. This heterogeneity may be manifest in terms of both state (i.e. current mood state) and trait (i.e. the predisposition toward a particular mood state). The unconstrained nature of the resting state may both afford an opportunity to examine rumination, brooding and other negatively-valenced cognition, but also limits the capacity to manipulate them experimentally. In particular, Berman and colleagues (Berman et al., 2011; see also Hamilton et al., 2011) observed heightened connectivity within the DMN during rest periods in MDD patients compared to controls, particularly those who showed higher levels of rumination. Such associations were not observed during task performance.

Individual differences in rumination and brooding are related to suicidal ideation (Miranda and Nolen-Hoeksema, 2007), and components of impaired problem solving and cognitive inflexibility (e.g. McGirr et al., 2012; Miranda et al., 2013; Whitmer and Banich, 2007; Whitmer and Gotlib, 2012) are relevant to each. There are key

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areas of divergence, however, involving the role of impulsivity and entrapment in influencing the onset of suicidal ideation and attempt (Dhingra et al., 2016). Moreover, the morbid aspects of ongoing thought, including the consideration of method and intent in the case of those at risk of suicide, may represent a further aspect of divergence from rumination and brooding. However, to our knowledge, there has been relatively little investigation of resting state neuroimaging in suicidal attempters or ideators (Cao et al., 2015; Fan et al., 2013; Zhang et al., 2016; see Desmyter et al., 2011; Serafini et al., 2016 for reviews). In the present study, we examined connectivity within the DMN within a group of young adults displaying high levels of suicidal ideation and compared them with a cohort of healthy controls.

A second factor that might hinder the identification of an altered DMN signature of negative affective state is the variety of analytical strategies that have been employed to examine functional connectivity. In particular, underspecified seed regions may reduce the reliability of seed-based resting state studies (Cole et al., 2010). Although the PCC is often treated as a single functional entity, recent data-driven modeling approaches have revealed evidence that the region consists of several, distinct regions with particular functions (Bzdok et al., 2015). Leech and colleagues (Leech et al., 2011) identified dorsal and ventral subregions of the PCC, which showed differential interactions with cognitive control networks (CCN e.g. the dorsal anterior cingulate cortex (dACC) and dorsolateral PFC) and the DMN itself. The ventral region was more closely coupled to the DMN but less to the CCN during a simple (0-back) task. However, this pattern changed during the more difficult 2-back task, with coupling with the DMN falling and coupling increasing with the CCN. By contrast, the dorsal PCC region showed the opposite pattern – relatively reduced coupling with the DMN and relatively enhanced coupling with the CCN during the simple task, but increasing and decreasing connectivity respectively during the more difficult condition. The authors argued that the interaction of the two regions is required for the orchestration of large scale networks during tasks of varying complexity. Here, we examined the connectivity of dorsal and ventral PCC seeds separately, and also examined their difference maps, hypothesizing that the ideators would show an altered pattern of connectivity within the DMN.

More recent statistical considerations of resting state functional connectivity have highlighted ambiguities with the commonly employed Pearson's R statistic (Cole et al., 2016) and, by consequence, related methods of statistical association. In particular, this measure of connectivity is a function of the covariance between regions – which is assumed to reflect the capacity for information transfer between regions - but also their variance. It is therefore possible that two groups may show similar covariance between regions, but differ with respect to irrelevant variance: a sole reliance on correlation would be misleading in this context. A related possibility is that the intrinsic activity of a given region might be altered within particular frequency components of the signal, which may provide some indirect influence on raw variance estimates. More importantly, it may reflect alterations in ongoing neural processing in that region that may have ramifications for functional connectivity (Baria et al., 2013). We therefore also examined intrinsic low-frequency activity – given that this dominates rsfMRI BOLD signal - of the key DMN nodes, in order to provide further characterization of DMN activity.

Finally, following van den Heuvel and colleagues (van den Heuvel et al., 2008), we examined the extent to which alterations in structural connectivity, as measured using diffusion tensor imaging (DTI), were responsible for any functional changes observed, particularly focusing on the cingulum bundle.

2. Methods

2.1. Participants

79 total adult participants were assessed, five participants (2SI, 3HC) were excluded due to excessive movement (total movement > 3 mm), leaving a final sample of 74. In addition, three of the control participants did not have DTI data. Participants were age 18–35 and consisted of 40 healthy controls (HC) with no personal or family history of psychiatric disorder or suicide attempt; and 34 patients with current suicidal ideation (SI) which was determined at recruitment during the screening process, and was confirmed at the study visit with the Suicidal Ideation Questionnaire (SIQ: cut off score > 20) and the Columbia Suicide Severity Rating Scale (C-SSRS: cut off score 4 or 5 for the first two questions). About half of the SI population had a history of previous suicide attempt (n=18). All healthy controls needed to have scored below clinical cutoffs on all self-report measures in addition to having no current or past suicidal ideation and behavior.

Participants were screened by the psychiatrist with respect to safety to participate in an fMRI study, ability to commit to a safety plan and not engage in self-harm while participating in the study. Participants were also screened by the psychiatrist with respect to present or past psychotropic medication, mental health treatment, and suicidal behavior, with the latter using the Columbia Suicide History Form. Current psychiatric symptomatology and suicidal ideation/behavior were assessed by the interview-rated suicidal ideation and behavior, using the C-SSRS, self-reported depression and anxiety using the PHQ-9 and State-Trait Anxiety Scale, suicidal ideation using the SIQ, and both narrow and broad band psychopathology using the Adult Self-Report. Patient diagnoses and medication status were obtained via medical records, and symptom inventories describe current symptoms (see Table 1).

The sample was recruited from the UPMC Clinical and Translational Science Institute Registry, UPMC outpatient clinical services, advertisements, and existing studies within our lab. Exclusion criteria included neurological disorders, head injury, Verbal Subtest of the Wechsler Intelligence Test (Wechsler, 1999) score < 80, use of sedative medication, drug or alcohol disorder or positive urine drug screen, pregnancy, MRI ineligibility, and psychosis. Any SI with suicide attempt causing neurological damage or long term physiologic effects was excluded.

Ethical approval for the study was obtained from both the University of Pittsburgh and the Carnegie Mellon University Institutional Review Boards, and informed consent was obtained for all participants.

2.2. MRI acquisition sequences

Neuroimaging data were collected using a 3.0 T Siemens Magnetom Verio MRI scanner in the Scientific Imaging and Brain Research Center at Carnegie Mellon University with a 32-channel Siemens receive coil. BOLD Resting State images were acquired with a 5 min Siemens gradient echo planar imaging (ep2d-bold) sequence with eyes open (300 successive brain volumes) covering 20 axial slices (5.0 mm thick; repetition time: 1000 ms; echo time: 25 ms; FOV: 200 mm; flip angle: 60°; matrix=64×64; GRAPPA acceleration (iPAT) factor: 2). Field map images were also acquired (repetition time: 572 ms; echo time: 5.00 ms; echo time2: 7.46 ms; FOV: 230 mm; flip angle: 70°; matrix: 96×96).

Structural three dimensional axial magnetization prepared rapid acquisition gradient echo (MPRAGE) images were acquired (repetition time: 1700 ms; echo time: 2.48 ms; inversion time: 900 ms; flip angle: 9°; FOV: 256 mm; matrix: 256×256). Diffusion-weighted structural images were acquired using the multi-band sequences (version R011 for Syngo VB17A) with the monopolar cmrr_mbep2d_diff sequence provided by the University of Minnesota Center for Magnetic Resonance Research (https://www.cmrr.umn.edu/multiband/) in 54 slices (matrix: 96×96, FOV: 230 mm; 2.4-mm isotropic voxels; TR=2264 ms; TE=74.8 ms; multi-band acceleration factor: 3; number of diffusion encoded directions: 30; diffusion b-value: 1000s/mm^2, number of non-diffusion encoded images: 4; bandwidth: 1860 Hz/