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Widespread white matter but focal gray matter alterations in depressed individuals with thoughts of death ☆

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ABSTRACT

Background: Past work demonstrates that depressed individuals with suicidal thoughts or behaviors exhibit specific neuroanatomical alterations. This may represent a distinct phenotype characterized by specific findings on neuroimaging, but it is unclear if these findings extend to individuals with milder thoughts of death. We examined this question in outpatients with recurrent Major Depressive Disorder not receiving antidepressant treatment.
Methods: We examined 165 subjects: 53 depressed without thoughts of death, 21 depressed with thoughts of death, and 91 healthy comparison subjects. Participants completed 3 T cranial MRI, including anatomical and diffusion tensor imaging acquisitions. Automated methods measured regional gray matter volumes in addition to cortical thickness. White matter analyses examined diffusion measures within specific fiber tracts and included voxelwise comparisons.
Results: After adjustment for multiple comparisons, the depressed group with thoughts of death did not exhibit differences in regional gray matter volume, but did exhibit reduced cortical thickness in frontoparietal regions and the insula. This depressed group with thoughts of death also exhibited widespread white matter differences in fractional anisotropy and radial diffusivity. These differences were observed primarily in posterior parietal white matter regions and central white matter tracts adjacent to the basal ganglia and thalamus.
Conclusions: Mild thoughts of death are associated with structural alterations in regions of the salience network, default mode network, and thalamocortical circuits. Further work is needed to understand the pathological basis of these findings.

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1. Introduction

Suicide is one of the most devastating outcomes of Major Depressive Disorder (MDD). Although suicidal thoughts are seen in many neuropsychiatric conditions, individuals with depressive disorders are at particular risk, with reported prevalence of lifetime suicide risk between 2% and 7% (Bostwick and Pankratz, 2000; Bradvik et al., 2008). Importantly, suicidal thoughts are not unique to MDD and many patients with MDD never exhibit suicidal thoughts or behaviors. This suggests that, regardless of diagnosis, there may be distinct underlying neural differences that are associated with increased risk of suicidal thoughts and behavior.

Even in the absence of clear suicidal ideation, milder symptoms are common in MDD, including feelings of being better off dead or passively wishing for death. Such clinical presentations are common, as thoughts that life is not worth living occur in 15% of younger individuals seeking mental health treatment, with an additional 16% reporting thoughts of death or suicidal ideation (Scott et al., 2012). Comparable or higher rates are seen in older populations (Rurup et al., 2011; Scocco and De Leo, 2002). Despite the frequency of these milder symptoms, it is unclear if the neural differences observed in more severe suicidal ideation are also observed in individuals with milder symptoms.

Most work examining neural contributors to suicidality in MDD focused on severely affected individuals at high risk or with a history of suicide attempts. These studies identified widespread differences across frontal, temporal and parietal lobes (Hwang et al., 2010; Wagner et al., 2012). Suicidality is associated with smaller volumes of the anterior cingulate cortex (Wagner et al., 2011; Wagner et al.,

Abbreviations: DepNS, Depressed, no suicidality or thoughts of death; DepSI, Depressed, with suicidality or thoughts of death; FA, Fractional Anisotropy; FDR, False Discovery Rate; OFC, Orbitofrontal Cortex; RD, Radial Diffusivity; TBSS, Tract-Based Spatial Statistics.

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2012; Willeumier et al., 2011), insula (Soloff et al., 2012; Willeumier et al., 2011), orbitofrontal cortex (OFC) (Monkul et al., 2007; Soloff et al., 2012), and dorsolateral prefrontal cortex (Wagner et al., 2012). Reductions in perfusion and metabolism are also observed in many of these regions (Willeumier et al., 2011). Suicidality is further associated with subcortical differences, including smaller volumes of the caudate and basal ganglia (Vang et al., 2010; Wagner et al., 2011) but larger volumes of the amygdala (Monkul et al., 2007) and thalamus (Lopez-Larson et al., 2013). Suicidality in MDD is also associated with white matter alterations, with microstructural abnormalities reported in frontal white matter (Olvet et al., 2014) and the fronto-thalamic circuit, including the anterior limb of the internal capsule, right lentiform nucleus and OFC (Jia et al., 2013). Reduced corpus callosum volumes are also associated with suicide attempts in mood disorders (Cyprien et al., 2011; Matsuo et al., 2010; Nery-Fernandes et al., 2012). Jointly, this work suggests that structural alterations in a range of networks are involved in suicidal thoughts and behavior. Many of these regions are implicated more broadly in depression, yet may be involved differently or to a greater extent than observed in non-suicidal depression.

Clear suicidal ideation and suicidal behaviors are the severe end of this symptom spectrum, but milder symptoms including thoughts of death and passive wishes for death are common. It is unclear if the neuroanatomical findings observed in high-risk suicidal individuals are also present in individuals with milder thoughts and lower risk. In this study, we hypothesized that even milder thoughts of death would be associated with gray matter volumetric differences and white matter microstructural differences. We utilized this past literature to identify gray and white matter regions that we a priori expected to exhibit differences in depressed subjects reporting thoughts of death while also conducting whole-brain analyses. We then tested for group differences using both regional volumetric measures and voxel-based approaches.

2. Methods

2.1. Participants and assessments

Participants were outpatients at Duke University between the ages of 20 and 50 years. Depressed participants had a DSM-IV diagnosis of recurrent MDD, as assessed by the Mini-International Neuropsychiatric Interview (MINI, version 5.0) (Sheehan et al., 1998) and interview with a study psychiatrist (WDT). Following an approach used by others (Sheline et al., 1999), we used the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) to identify the number of past major depressive episodes and the cumulative duration of depression, summing over all episodes. Corroborating information was obtained when possible.

Entry criteria included onset of first depressive episode before age 35 years and a Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) of 15 or greater. Entry criteria also specified no antidepressant use in the last month; however, most subjects reported no antidepressant use for at least three months or longer. Eligible control subjects had neither any lifetime history of psychiatric disorders nor any history of psychotropic medication use.

Exclusion criteria included other lifetime DSM-IV Axis I disorders including substance abuse or dependence, although anxiety symptoms occurring exclusively during depressive episodes were allowable. Subjects were excluded for Axis II disorders determined by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First et al., 1997). Additional exclusion criteria included: history of psychosis, use of illicit substances in the last month, ECT in the last 6 months, a family history of bipolar disorder, any unstable medical condition, any history of neurological illness or head injury, or MRI contraindications. Participants who reported acute intent or plans for suicide were excluded and referred for emergent treatment.

The Duke University Medical Center Institutional Review Board approved this study. All participants provided informed consent. As data analyses were conducted at Vanderbilt University, the Vanderbilt University Institutional Review Board also approved these procedures.

Depressed participants were dichotomized based on the presence or absence of current thoughts of death or suicide as determined on the clinician-administered MINI. The MINI suicidality assessment includes 9 questions assigned differentially weighted scores. The majority of questions focus on the last 30 days with an additional question assessing any lifetime history of suicide attempts. Presence of thoughts of death was determined as a score of 1 or greater, with a score of 1 indicating thoughts of being better off dead or wishing for death. The score increases with thoughts of self-injury, suicidal intent, plan, or past attempts. A score of 0 indicates no thoughts of being better off dead.

2.2. MRI acquisition

Cranial MRI was performed using the eight-channel parallel imaging head coil on a whole-body MRI system (Trio, Siemens Medical Systems, Malvern, PA). Parallel imaging was employed with an acceleration factor of 2. Duplicate T1-weighted image sets were acquired during the scan session using a sagittal MPRAGE sequence with TR/TE = 2300/3.46 ms, a 240 Hz/pixel bandwidth, a 256 × 256 matrix, a 240 mm diameter field-of-view, 160 slices with a 1.2 mm slice thickness, yielding an image with voxel sizes of 0.9 × 0.9 × 1.2 mm. Similarly, two identical 20-direction diffusion-weighted acquisitions were acquired during the session using a single shot 2D diffusion tensor echo planar pulse sequence in the axial plane. Parameters included TR/TE = 10,200/93 ms, a 1396 Hz/pixel bandwidth, a 256 mm diameter field of view, 75 slices with a 2 mm slice thickness yielding an image with voxel sizes of 2 × 2 × 2 mm, 2 signal averages, with 20 diffusion directions, each with a b-value of 1000 s/mm^2 plus an acquisition of b = 0 s/mm^2.

2.3. Volumetric MRI analyses

For both volumetric and DTI analyses, we conducted both evidence-guided regional measures and atheoretical voxelwise group comparisons. All volumetric measures were calculated using FreeSurfer (version 5.1) software running in a high-performance Linux cluster environment. The FreeSurfer methods used to derive cortical and subcortical brain volumes have been previously described (Dale et al., 1999; Fischl et al., 2002, 2004). Cortical parcellation used the Desikan–Killiany Atlas (Desikan et al., 2006); in each hemisphere, this method identified 33 cortical and 7 subcortical gray matter regions (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus). Intracranial volume was assessed using the method implemented in FreeSurfer. We visually inspected the data by overlaying the surfaces and subcortical segmentations over the T1 data. Individual slices in each orientation were assessed for errors. No manual corrections were needed.

In secondary analyses, we tested for differences in cortical thickness using Freesurfer's QDEC module. This was an exploratory approach to test for differences not captured using our atlas-based comparisons. In this method, cortical thickness is computed as the shortest distance between any point on the pial surface and the gray/white boundary and vice-versa; these two values are averaged (Fischl and Dale, 2000). Maps were smoothed using the standard Gaussian kernel of 10 mm. We used a General Linear Model (GLM) to test for differences in cortical thickness between diagnostic groups, including age as a nuisance variable. Correction for multiple comparisons was carried out using the Monte Carlo simulation method with a $p < 0.05$. Data were tested against an empirical null distribution of maximum cluster size by running 10,000 synthesized Gaussian noise simulations with an initial threshold of $p < 0.05$. Right and left hemispheres were tested separately.