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Applying a free-water correction to diffusion imaging data uncovers stress-related neural pathology in depression

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ABSTRACT

Diffusion tensor imaging (DTI) holds promise for developing our understanding of white-matter pathology in major depressive disorder (MDD). Variable findings in DTI-based investigations of MDD, however, have thwarted development of this literature. Effects of extra-cellular free-water on the sensitivity of DTI metrics could account for some of this inconsistency. Here we investigated whether applying a free-water correction algorithm to DTI data could improve the sensitivity to detect clinical effects using DTI metrics. Only after applying this correction, we found: a) significantly decreased fractional anisotropy and axial diffusivity (AD) in the left inferior fronto-occipital fasciculus (IFOF) in MDD; and b) increased self-reported stress that significantly correlated with decreased IFOF AD in depression. We estimated and confirmed the robustness of differences observed between free-water corrected and uncorrected approaches using bootstrapping. We conclude that applying a free-water correction to DTI data increases the sensitivity of DTI-based metrics to detect clinical effects in MDD.

1. Introduction

Major depressive disorder (MDD) is a severe and debilitating psychiatric illness, which leads all diseases, psychiatric and otherwise, in terms of lost years of productive life (Organization, 2004). Moreover, conventional pharmacological treatments for depression have shown only modest effectiveness in treating MDD (Trivedi et al., 2006). These modest treatment effects have mandated continued investigation into the biological bases of depression. With the popularization of endocrine assays and structural neuroimaging techniques, depression has been investigated increasingly as a neurodegenerative disorder where stressors leading up to and following the onset of MDD figure prominently in the course of the illness (Sapolsky, 1996, 2000). The formulation of MDD as a neurodegenerative illness has largely born out empirically, with reliable volumetric decreases of limbic and perilimbic regions observed in depression (Campbell et al., 2004; Goodkind et al., 2015; Hamilton et al., 2008; Videbech and Ravnkilde, 2004). Moreover, data from post-mortem investigations indicate that loss of glial cells is the primary cellular constituent of neurodegeneration in depression (Bowley et al., 2002; Hamidi et al., 2004).

The investigation of neural degeneration in MDD has intensified with the advent of diffusion imaging techniques—such as diffusion tensor imaging (DTI)—for estimating regional white matter microstructure. In understanding depression, the appeal of measuring white-matter structure with techniques such as DTI is twofold. First, DTI could aid in testing hypotheses of MDD as a "disconnection syndrome" in which, for example, activity in limbic regions intensifies due to impaired connectivity with cortical regions implicated in emotional control (Mayberg, 1997; Mayberg et al., 1999). Second, and relatedly, DTI can be used to identify white matter regions that have incurred damage or atrophy potentially due to direct or downstream effects of neurotoxic stress (Lee et al., 2002).

As DTI data in investigations of MDD continue to accrue, there are indications that improvements to this method might be required given that findings have varied considerably across studies. Perhaps the clearest indication of this variability in results is that meta-analyses of DTI findings in MDD have, themselves, yielded disparate findings. For example, two meta-analyses synthesizing reports of regional abnormalities in MDD in fractional anisotropy (FA)—a DTI-based index proposed to reflect axonal organization (Pierpaoli et al., 1996)—yielded findings that were spatially non-overlapping and/or conflicting. One meta-analysis reported FA decreases in the inferior fronto-occipital fasciculus,

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inferior longitudinal fasciculus, and posterior thalamic radiation (Liao et al., 2013), while another meta-analysis reported FA decreases in the superior longitudinal fasciculus and FA *increases* in the inferior fronto-occipital fasciculus (Murphy and Frodl, 2011).

The inconsistent findings in DTI investigations of MDD could stem from variability in extra-experimental factors such as gender composition and medication status which, for example, have been shown to account for variability in diffusion imaging studies of schizophrenia (O'Donnell and Pasternak, 2015). It is important to consider, however, that DTI metrics are influenced by contributions of different tissue compartments, including cerebrospinal fluid and extracellular water (Pierpaoli et al., 1996). Thus, if we aim to investigate neural structural pathology in MDD, the partial volume effects of extracellular water that are not part of the tissue could negatively impact the sensitivity and specificity of our DTI metrics. Recently, Pasternak and colleagues developed an algorithm for identifying and separating the effects of extracellular free water on DTI metrics—a process shown to improve DTI-based tract reconstruction (Pasternak et al., 2009) and tissue specificity (Metzler-Baddeley et al., 2012). By using this approach, the effects of extra-cellular free-water on DTI metrics can be removed, leaving them both more sensitive to detecting cellular pathological alterations than standard, uncorrected metrics, and less susceptible to detecting spurious effects aliasing free-water differences. Indeed, this technique has been used to unmask between-group differences in DTI metrics in dementia onset (Maier-Hein et al., 2015), mild cognitive impairment (Berlot et al., 2014), and acute concussion (Pasternak et al., 2014), as well as to identify spurious between-group DTI effects associated with mild cognitive impairment (Berlot et al., 2014), normal aging (Metzler-Baddeley et al., 2012), acute concussion (Pasternak et al., 2014), and schizophrenia (Pasternak et al., 2012b; Pasternak et al., 2015). Finally, free-water correction has been recently applied to one DTI study of MDD, which found a negative correlation between hedonic tone and FA within the medial forebrain bundle (Bracht et al., 2015) in remitted depressed as well as healthy individuals.

In order to systematically assess the usefulness of applying a free-water correction to studies of white-matter integrity in depression, we asked in the present study whether applying a free-water elimination process to DTI data would improve the sensitivity of voxel-wise comparisons of depressed and healthy samples with respect to DTI metrics. These metrics included FA, axial diffusivity (AD), and radial diffusivity (RD). In coherently aligned white matter fibers, AD has been found to be sensitive to identifying axonal degeneration (Wheeler-Kingshott and Cercignani, 2009) and RD has been shown to reliably estimate myelin integrity (Song et al., 2002). We hypothesized that, relative to conventional DTI indices that are not corrected for free water, applying a free-water correction to DTI data would result in improved detection of depression-related abnormalities in DTI metrics, as well as in more statistically reliable correlations between DTI metrics and measures of stress, the latter a process associated with neural degeneration in depression (Sapolsky, 1996).

2. Methods and materials

2.1. Participants

Seventeen females with MDD (38.9 ± 11.4 year; range = 20–55 years) and 18 healthy control (HC) female (33.2 ± 12.0 year; range = 20–55 years) participants were included in this study. Participants were recruited from local psychiatric outpatient clinics as well as through website postings. All participants: (1) were between the ages of 18 and 60; (2) had no reported history of brain injury or lifetime history of primary psychotic ideation or mania; (3) had no reported substance abuse within the past six months; and (4) had no physical limitations that prohibited them from undergoing a magnetic resonance imaging (MRI) examination. No depressed or HC participants were taking psychotropic medication at the time of the study. All depressed participants met criteria for a DSM-IV diagnosis of MDD on the basis of the Structured Clinical Interview for DSM (SCID; First et al., 1995). None of the control participants met criteria for any current or past DSM Axis I disorder. This study was approved by the Western Institutional Review Board, and all participants signed informed consent prior to study participation.

All participants completed the Beck Depression Inventory-II (BDI-II), and three measures of stress: the Perceived Stress Scale (PSS), the Penn State Worry Questionnaire (PSWQ), and the Panic Disorder Severity Scale (PDSS). The BDI-II is a 21-item self-report instrument that measures depression severity (Beck et al., 1979). The PSS is a 10-item scale developed for measuring the degree to which situations in an individual's life are appraised as stressful (Hewitt et al., 1992). The PSWQ is a 16-item questionnaire for measuring worry at the trait level (Salarifar and Pouretemad, 2012). Finally, the PDSS is a seven-item instrument for measuring severe stressors including acute anxiety and phobia and their consequences with respect to daily functioning (Houck et al., 2002).

2.2. Acquisition of MRI data

Our MRI data were acquired using a 3 Tesla scanner (GE Discovery MR750) with a brain-dedicated receive-only 32-element coil array optimized for parallel imaging (Nova Medical, Inc.). DTI was performed using 30 diffusion-encoding directions (b-value = 1000 s/mm^2, TR/TE = 8800/78.1 ms, with acquisition matrix = 96 × 96, reconstruction matrix = 256 × 256, field of view (FOV) = 25.6 × 25.6 cm, slice thickness = 2 mm, inter-slice spacing 0.2 mm, 69 axial slices, acceleration factor R = 2 in the phase encoding direction) and with one b0 image. T1-weighted anatomical images were acquired using a parallel magnetization-prepared rapid gradient-echo sequence with sensitivity encoding (FOV = 240 mm, 190 slices, slice thickness = 0.9 mm, image matrix = 256 × 256, TR/TE = 5/2.012 ms, acceleration factor R = 2 in the phase encoding direction, flip angle = 8 degrees).

2.3. Preprocessing and analysis

DTI raw data were processed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Diffusion Toolbox (FDT; Behrens et al., 2003) included in the FMRIB Software Library (FSL, version 5.0.4; Smith et al., 2004). First, for each participant, a brain mask was defined by applying the Brain Extraction Toolbox (Smith, 2002) to the unweighted image (b-value = 0). Following translation and rotation estimation across acquisitions in three dimensions, the raw DTI images were corrected for motion and eddy currents and relative-motion parameters were estimated from the transformation matrices for each subject (Ling et al., 2012). All individual subject scans with translational or rotational motion estimates greater than three standard deviations (SDs) from the mean were excluded from further analysis. Gradient orientations were compensated prior to calculating b-matrices in order to account for the rotational component of registration. DTI free-water corrected and uncorrected maps were then calculated by using an in-house MATLAB script. The free-water maps were computed by fitting the following model at each voxel (Pasternak et al., 2009):

$$A_g(D,f) = f\exp\left[-bg^T Dg\right] + (1-f)\exp\left[-bd_{water}\right]$$

where A_g is the modeled attenuated signal (normalized by b0) for the applied diffusion gradient g, and b is the b-value (1000 s/mm^2). The first term reflects the tissue compartment; D is the diffusion tensor of this compartment, f is the fractional volume of the compartment, and g^T is the transpose of the vector g. The second term reflects an isotropic free-water compartment with a fractional volume of $(1-f)$; d_{water} is the diffusion coefficient, set to the diffusivity of water at body temperature (3×10^{-3} mm^2/s).