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Hippocampal subfield-specific connectivity findings in major depressive disorder using 7 Tesla diffusion MRI

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Abstract

Objective—Diffusion magnetic resonance imaging (dMRI) enables non-invasive characterization of white matter (WM) structures *in vivo*. Literature suggests that certain WM tracts are affected in major depressive disorder (MDD). Hippocampal-specific dMRI measures have not been explored in MDD. We use 7 Tesla dMRI to investigate changes in hippocampal subfield connectivity of MDD patients.

Methods—Eighteen MDD patients and eighteen matched healthy volunteers underwent 7 Tesla MRI. The hippocampal formations were segmented by subfields and tractography was performed to determine streamline count (SC), fractional anisotropy (FA), and mean diffusivity (MD) in patients and controls. Significant subfield connectivity measures were also correlated with age at depression onset.

Results—Compared with controls, MDD patients exhibited reduced SC in the molecular layer of the left dentate gyrus ($p < 0.001$). SC count in the left dentate gyrus was shown to positively correlate with age at disease onset ($p < 0.05$). Increased MD was observed in fibers emanating from both the left ($p = 0.0001$) and right ($p < 0.001$) fimbriae in MDD patients.

Conclusions—Increased MD of tracts in the fimbriae suggests compromised neuronal membranes in the major hippocampal output gate. Reduced SC of the dentate gyri also infers a disruption of normal cellular processes such as neurogenesis. These findings may have significant

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Conflict of interest

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implications for identifying biomarkers of MDD and elucidating the neurobiological underpinnings of depression.

Keywords

Depression; diffusion-weighted imaging; hippocampal subfields; tractography; biomarkers

1. Introduction

Major depressive disorder (MDD) is a highly disabling and costly psychiatric disease, affecting approximately 6.6% of the US population (Kessler et al., 2003, Greenberg et al., 2003). Correct diagnosis of MDD remains challenging, and current diagnostic tools are limited in both sensitivity and specificity (Paris, 2014). Despite significant efforts to develop new pharmacological therapies, fewer than 40% of MDD patients achieve remission after initial treatment (McGrath et al., 2014). While clinical features of MDD such as anhedonia and melancholia are relatively easy to classify and may be indicative of prognosis, they are not reliable predictors of the efficacy of specific drug treatments within individual patients (Leuchter et al., 2009).

Neuroimaging is increasingly being applied to further the understanding of the neurobiology of psychiatric illness, and may help to overcome current limitations in diagnosis and monitoring of patients with psychiatric disease. Much of this research has been focused on MDD, and various imaging findings, such as altered cerebral metabolism and white matter atrophy, have been associated with a depressed phenotype and even related to treatment outcome (Leuchter et al., 2009). However, further biomarker research is necessary to augment our understanding of MDD pathophysiology, provide more tailored methods of diagnosing MDD subtypes, and better monitor treatment response in depressed patients. Novel imaging techniques acquired at ultra-high field with high spatial resolution offer promise for detecting subtle changes in the brain that underlie MDD symptomatology, especially in areas that are implicated in mood regulation.

The hippocampus is well-studied in the context of depression due to its role in cognition and emotion (Thomas et al., 2007, Sapolsky et al., 2000, Bremner et al., 2000, McKinnon et al., 2009, MacQueen et al., 2003, Pham et al., 2003). The hippocampus is also a highly stress-sensitive structure (Thomas et al., 2007) that is adversely affected by elevated levels of glucocorticoids in MDD patients (Sapolsky et al., 2000). Therefore, there is reason to believe that subtle structural changes may occur in the hippocampus in MDD patients. While reduced hippocampal volume has been reported in a number of studies (Bremner et al., 2000, McKinnon et al., 2009, MacQueen et al., 2003), recent research has focused on measuring changes that occur in the anatomically and functionally distinct hippocampal subfields (Huang et al., 2013, Teicher et al., 2012, Ballmaier et al., 2008). The unique molecular profiles of these subfields confer regional vulnerability to neurotoxic damage (Sapolsky et al., 2000). The dentate gyrus and Cornu Ammonis (CA) 3 are among the most implicated subfields in MDD (Sapolsky et al., 2000), however, evidence suggests that other subfields may also be affected by exposure to prolonged stress (Teicher et al., 2012). A number of studies have exploited volumetric analysis on the hippocampal subfields to

confirm that volumes of dentate gyrus and CA3 are reduced in MDD patients (Huang et al., 2013, Teicher et al., 2012, Ballmaier et al., 2008). While these studies add to our understanding of the morphometric changes that occur in MDD, they do not provide information about the structural connectivity of the hippocampal subfields, and to our knowledge no such studies have been performed.

Diffusion magnetic resonance imaging (dMRI) is a noninvasive technique that can be used to characterize white matter architecture *in vivo* (Rodrigues et al. 2018, Le Bihan et al., 2001). In an unrestricted medium, such as bulk water, the diffusion behavior of water molecules lacks directional bias and is termed “isotropic;” this pattern can be modeled with a Gaussian distribution (Rodrigues et al. 2018, Le Bihan et al., 2001). With increasing structure, diffusion of water may be restricted in one or more directions. This is particularly apparent relative to axonal myelin sheaths of white matter, since water diffuses more rapidly along the longitudinal axis of axons than it does perpendicular to these axons (Le Bihan et al., 2001). This “anisotropic” water movement is used to model the fiber orientation distribution within white matter, and to derive measures of microstructural integrity (Le Bihan et al., 2001). Streamline count (SC) is a metric that quantifies the number of streamlines between brain regions, and reflects the number of axons coupling these regions (Jones et al., 2015). Fractional anisotropy (FA) is a measure of microstructure that reflects the degree to which water movement is directionally constrained, and diminished FA is usually associated with loss of white matter organization or demyelination (Bijanki et al., 2015). Lastly, mean diffusivity (MD) is a non-directional measure of total magnitude of diffusion within a voxel. While pathology, such as acute ischemia, can be associated with reduced MD (Mukherjee et al., 2008), increased MD is more frequently associated with pathology (Bijanki et al., 2015, Mukherjee et al., 2008, Rovaris et al., 2005). Common disease processes that modify biological membranes and increase permeability of confining barriers in white matter include multiple sclerosis (Rovaris et al., 2005), temporal lobe epilepsy (McDonald et al., 2008), and autism spectrum disorders (Nagae et al., 2012). The resolution of dMRI is benefitted by ultra-high field strengths, such as those employed in 7 Tesla (7T) scanners, as they provide increased signal to noise ratio (SNR) and superior spatial resolution (Polders et al., 2011).

The primary objective of this study was to measure hippocampal subfield-specific connectivity using high-resolution dMRI-based tractography and evaluate group differences in SC, FA, and MD between MDD patients and healthy controls. We hypothesized that tracts emanating from a number of hippocampal subfields would be blunted in MDD patients. Identification and characterization of imaging markers of depression could facilitate diagnosis of biological subtypes of depression and help differentiate similar diagnostic categories. Additionally, since some preclinical studies have indicated that successful antidepressant treatment may diminish or even reverse stress-induced changes in the hippocampus (Pham et al., 2003, Malberg et al., 2003), we may identify imaging biomarkers capable of detecting subtle structural changes that might serve as valuable tools for monitoring treatment efficacy.

2. Methods and Materials

2.1. Participants

Eighteen MDD patients (6 females with mean age of 34.2 years, standard deviation (SD) 10.4 years; 12 males, mean 42.2 years, SD 11.4 years) were recruited through the Mood and Anxiety Disorders Program at the Icahn School of Medicine at Mount Sinai. Eligible patients had a primary diagnosis of major depressive disorder, without psychotic features, assessed by the Structured Clinical Interview for DSM-IV Disorders (SCID-IV) (First et al., 1995) or the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV) (First et al., 2015). Participants were excluded if they had a current diagnosis of obsessive-compulsive disorder, alcohol or substance abuse in the previous year, or lifetime history of a psychotic illness, bipolar disorder, or neurological disease. Each patient was age and gender-matched with neurologically and psychiatrically healthy volunteer participants (6 females: mean 36.5 years, SD 12.1 years; 13 males, mean 42.2 years, SD 11.4 years). Healthy controls had no current or lifetime neurological or psychiatric disorder as determined by the SCID-IV or SCID-5-RV. The protocol was approved by the local Institutional Review Board, and after the study was fully explained to participants, written informed consent was obtained by a member of the study team.

2.2. Imaging acquisition

All imaging was acquired on a 7 T whole body scanner (Magnetom, Siemens Healthcare, Erlangen, Germany). A SC72CD gradient coil was used (max slew rate = 200T/m/s, $G_{\max} = 70$ mT/m), with a single channel transmit and 32-channel receive head coil (Nova Medical, Wilmington, MA, USA). The MRI protocol included a T_1 -weighted MP2RAGE sequence: TR = 6000ms, TE = 3.62ms, field of view (FOV) = 240mm $\times$ 320mm, resolution = 0.7mm isotropic. A coronal-oblique T_2 -weighted turbo spin echo (T_2 TSE) sequence was also acquired: TR = 6900ms, TE = 69ms, FOV = 202mm $\times$ 202mm, resolution = 0.4mm $\times$ 0.4mm $\times$ 2mm. Lastly, a high-angular-resolved diffusion-weighted imaging (HARDI) dMRI sequence was acquired: $b = 1200$ s/mm², TR = 7200ms, TE = 67.6ms, FOV = 240mm $\times$ 240mm, resolution = 1.05mm isotropic. The dMRI images were skull-stripped and corrected for eddy currents using FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl), and corrected for gradient non-linearities.

2.3. Hippocampal segmentation

Freesurfer (<http://surfer.nmr.mgh.harvard.edu>) version 6.0 was used to perform an automated cortical reconstruction and volumetric segmentation of the T_1 -weighted images. The hippocampi were then segmented using Freesurfer by leveraging the high in-plane resolution of the T_2 -TSE images. Freesurfer segmented the hippocampus into the following subfields: parasubiculum, hippocampal fissure, presubiculum, subiculum, CA1, CA2/3, CA4, granule cell layer of dentate gyrus (GC-DG), hippocampal-amygdala transition area (HATA), fimbria, and molecular layer of the dentate gyrus. The results of the segmentation are shown in Figure 1.

The hippocampal fissure and the HATA were excluded from analysis due to unreliable fitting and data collection in these regions. Additionally, because of the significant

challenges with accurately delineating the CA4 *in vivo* (Yushkevich et al., 2015), the authors chose to exclude this region from the analysis as well. The authors also decided to combine the subiculum, presubiculum and parasubiculum into one region (subicular complex) and the molecular and granule cell layers of the dentate gyrus into one region (dentate gyrus) due to similar concerns about the software's accuracy in segmenting such small structures (Yushkevich et al., 2015).

2.4. Tractography

The T₁-weighted images were segmented into 5 tissue types: gray matter, white matter, ventricles, non-ventricular cerebrospinal fluid and lesion(s) using Freesurfer. A gray-white matter boundary was created from this segmentation, and points along this interface were used to seed anatomically constrained tractography. Constrained spherical deconvolution was used to calculate the fiber orientation distributions, and tensor metrics were obtained throughout the whole brain using MRtrix3 (Brain Research Institute, Melbourne, VIC, Australia). Probabilistic tractography was performed in MRtrix3. To demarcate fibers emanating from individual subfields, the hippocampal subfield segmentation image was inserted into Freesurfer's default parcellation image (Desikan-Killiany atlas), replacing the left and right hippocampi. Whole-brain connectomes were generated using the 'tck2connectome' command in MRtrix3. The underlying FA and MD images were sampled to generate connectomes containing diffusion indices for fibers emanating from each subfield. Figure 2 shows the workflow used to perform hippocampal subfield-specific tractography.

2.6. Statistical analysis

The SC of each subfield was calculated by adding all of the streamlines between the subfield and the rest of the brain regions. The average FA and MD of all of the fibers emanating from each subfield were also calculated. Statistical analyses were carried out in R Version 3.3.3 (<https://www.r-project.org/>). Differences between groups were investigated using independent two-tailed Mann-Whitney U t-tests. Because 6 regions of the hippocampus were analyzed for three separate analyses, a Bonferroni-corrected significance threshold of 0.002 was set. All p-values that fell below this threshold were considered significant. Multiple linear regression was used to assess the correlations between the significant group differences and age at disease onset in depressed patients.

3. Results

3.1 Streamline Counts of the Hippocampal Subfields

Subfield-specific probabilistic tractography was acquired in the 18 MDD patients and 18 matched controls (Figure 3). MDD patients exhibited a significantly reduced SC of left dentate gyrus (Mean: 5574.4 streamlines, SD: 1690.0 streamlines) compared with the controls (Mean: 8784.9 streamlines, SD: 1287.7 streamlines), $p < 0.001$ (Table 1). The volume of dentate gyrus was compared in MDD patients and controls and showed no significant difference, $p > 0.05$. Multiple linear regression revealed a significant positive correlation between SC in the left dentate gyrus and age at disease onset ($r = 0.51$, $p = 0.035$) (Figure 4). There were no other subfields that showed abnormal SC.

3.2 Mean Diffusivity of the Hippocampal Subfields

The MD of the hippocampal subfield fibers in MDD patients and controls are shown in Table 2.

The average MD of the fibers emanating from the left fimbria in MDD patients (M: 7.66×10^{-4} mm²/s, SD: 4.9×10^{-5} mm²/s) was significantly increased compared with controls (M: 7.14×10^{-4} mm²/s, SD: 5.3×10^{-5} mm²/s), $p < 0.001$. The fibers from the right fimbria also displayed significantly increased MD in MDD patients (Mean: 7.87×10^{-4} mm²/s, SD: 5.5×10^{-5} mm²/s) compared with controls (Mean: 7.25×10^{-4} mm²/s, SD: 4.8×10^{-5} mm²/s), $p < 0.001$. Neither the left ($r = -0.18$, $p = 0.50$) nor the right fimbria ($r = -0.05$, $p = 0.86$) were significantly correlated with age at disease onset (Figure 4). The FA of the hippocampal subfield fibers were not significantly different in MDD patients compared with controls.

4. Discussion

This study employed high-resolution dMRI at 7T to acquire tractography of the individual hippocampal subfields in MDD patients. We measured SC, FA, and MD to evaluate potential abnormalities in number of streamlines from each subfield (SC) as well as the microstructural integrities of those fibers (FA and MD).

One of the main findings in this study was reduced SC of the left dentate gyrus in patients with MDD. We also found a significant positive correlation with the SC of the left dentate gyrus and age at disease onset, suggesting that patients diagnosed with MDD earlier in their lives show greater reduction in SC in this region. Yushkevich et al. reviewed numerous methodologies for hippocampal segmentation, including Freesurfer, and found that segmentation of the dentate gyrus shows very good agreement between softwares (Yushkevich et al., 2015). The ability to accurately delineate the boundaries of the dentate gyrus is likely because the stratum radiatum and lacunosomoleculare layer separating CA from dentate gyrus is very hypointense on T2-weighted imaging and provides an objective boundary to identify automatically (Yushkevich et al., 2015). Precise segmentation, combined with the fact that we combined the two constituent layers of the dentate gyrus into one larger structure, allowed us to perform accurate subfield-specific tractography in this hippocampal sub-region.

The dentate gyrus is well studied in the context of anxiety and depression, in part because it is one of only two areas in the adult brain that exhibits neurogenesis (Samuels et al., 2011). The neurogenesis hypothesis of depression postulates that reduced production of new neurons in the dentate gyrus is a neurobiological substrate underlying depression (Samuels et al., 2011). The mechanism behind this hypothesis is believed to involve elevated concentrations of glucocorticoids in MDD that impair neurogenesis (Samuels et al., 2011). A number of neuroimaging studies have found reduced dentate gyrus volume in MDD patients (Treadway et al., 2015, Frodl et al., 2002). However, the findings presented in this study are the first to report reduced connectivity of the dentate gyrus *in vivo*. While this finding aligns with the neurogenesis hypothesis and many prior studies (Thomas et al., 2007, Sapolsky et al., 2000, Pham et al., 2002, Malberg et al., 2003, Samuels et al., 2011), there are conflicting reports of the effects of stress of the hippocampus (Conrad et al., 2008), and

more work is required to validate this finding. Additionally, connectivity changes of the dentate gyrus may useful markers for monitoring antidepressant efficacy, and is an area of future investigation in our group.

While we did not observe any significant group differences in the FA of fibers emanating from the hippocampal subfields, some regions did exhibit increased MD in MDD patients. MD is a sensitive but non-specific dMRI scalar known to increase as a result of tissue degeneration from neuronal membrane damage (Jones et al., 2015, Bijanki et al., 2015, Rovaris et al., 2005, Lutz et al., 2008). We observed significantly increased MD within the left and right fimbriae. Interestingly, this effect was shown bilaterally in the major output structure of the hippocampus (Lutz et al., 2008). Efferent fibers from the fimbriae project to other parts of the limbic system and the cortex, and damage to these connections may underlie or contribute to emotional disturbances in MDD patients (Lutz et al., 2008). While previous studies have found volumetric reductions in the fimbriae (MacQueen et al., 2003), ours is the first to report microstructural damage to fibers coming out of this sub-region in MDD patients.

A number of previous studies have reported increased MD in certain brain regions in depressed patients, including the brainstem (Raison et al., 34), cingulum, corpus callosum, and the prefrontal cortex (Nenonen et al., 2015). Because MD is non-specific and can be altered by various molecular processes (Mukherjee et al., 2008, Rovaris et al., 2005), it is difficult to pinpoint the exact mechanism responsible for elevated MD in the fimbriae. One possible explanation for our finding of increased MD in this region is inflammation. The relationship between inflammation and depression is still unclear, however, inflammatory processes are increasingly being recognized as important factors in depression pathophysiology (Song et al., 2014). MD is known to increase in the presence of inflammation, as a result of swelling and increased cellular water content, which allows increase water diffusion in biological tissue (Benedetti et al., 2011). Compromised neuronal fibers emanating from this output gate of the hippocampus may be an effect of neuroinflammation and contribute to fronto-limbic network dysfunction in MDD, accounting for some of the emotional and cognitive deficits observed in MDD patients.

The main limitation of this study was the relatively small number of participants. This may have limited detectability of some subfield-specific findings. While 7T MRI provides excellent resolution and contrast, it also carries more contraindications than lower field strengths, making patient recruitment criteria more stringent than criteria for clinical imaging at lower field strengths (Feng et al., 2015, van der Kolk et al., 2013). Future work will expand the number of participants in this study, and focus on the subfields that were implicated in this preliminary investigation.

We also recognize the potential effects from partial voluming, imperfections in motion correction, and inherent spatial blur in this study. In order to minimize these effects, we excluded hippocampal subfields that were very small or could not be accurately delineating on T₂-TSE imaging (Yushkevich et al., 2015). We also amalgamated a number of smaller constituent regions into their larger subfield (subicular complex and dentate gyrus) to mitigate the inherent effects of partial voluming. We believe that the sub-regions evaluated

in this study were i) large enough to be visualized and segmented on high-resolution T₂-TSE imaging, and ii) accurately probed with 1.05 mm isotropic dMRI resolution, and that our findings reflect true biological effects in the hippocampal sub-regions.

The significant public health cost as well as the increasing incidence of MDD has spurred research efforts to understand the neurobiological underpinnings of the disease (Klerman et al., 1989). However, the paucity of neuroimaging biomarkers for MDD and other psychiatric disorders has delayed attempts aimed at finding new pharmacological therapies for depression (Savitz et al., 2013). Many promising experimental drugs have also failed at late stages of development, partly due to this lack of neuropathological targets (Savitz et al., 2013). Additionally, DSM-5 is currently used for clinical diagnosis of MDD and its empirical approach to diagnosis (trial and error) fails to accurately diagnose some patients (Savitz et al., 2013). Lastly, pharmacological therapy monitoring is a clinical challenge, as many MDD patients will take weeks to respond to initial drug treatment (Leuchter et al., 2009). Imaging biomarkers that can monitor progress and predict remission would be more desirable than the standard method of “watchful waiting”, and may allow clinicians to correct ineffective treatment courses more rapidly (Leuchter et al., 2009).

Ultra-high field MRI may be useful for identifying viable biomarkers for psychiatric disorders, by elevating previously unnoticed pathology above the threshold of detectability in MDD patients. In this study we used 7 T dMRI to perform subfield-specific tractography in the hippocampus and measured SC, FA, and MD of tracts emanating from these subfields. We report for the first time subfield-specific connectivity differences in MDD patients, and found overall reduced connectivity in the hippocampi of MDD patients. We believe that these findings could have significant implications for the diagnosis, treatment, and monitoring of patients with MDD and help to further elucidate the neurobiological underpinnings of psychiatric illness.

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Figure 1.

Coronal slice of a T₂-TSE image with red arrowheads pointing to the hippocampi (A), 3-dimensional rendering of the right hippocampus (quadrantic surface erosion), (B), T₂-TSE coronal slice of the hippocampus (C1) with segmentation overlaid (C2). T₂-TSE axial slice of the hippocampus (D1) with segmentation overlaid (D2). 3-dimensional exemplar of CA2/3 (blue) within the right hippocampus (quadrantic surface erosion) (E).

Figure 2.

A schematic of the work-flow. The dMRI images (A) were used to perform whole-brain probabilistic tractography (B). The T₁-weighted images (C) were used for the whole-brain segmentation (D). Both the T₁-weighted and T₂-TSE images (E) were used to segment the hippocampus (F). Tractography was performed in the hippocampal subfields (G) and structural connectomes (H) were generated.

Figure 3. 3-dimensional rendering of the hippocampi (A), probabilistic tractography of the hippocampi (B), the fimbriae (orange) within the hippocampi (C), fibers to/from only the fimbriae (D), a subtraction image with tractography from the whole hippocampi and the fibers from only the fimbriae in white (E).

Table 1.

Mean (standard deviation) of the SC for the hippocampal subfields. *p*-values below the Bonferroni-corrected significance threshold are shown in bold-face.

	LEFT HEMISPHERE			RIGHT HEMISPHERE		
	MDD	Control	<i>p</i> -value	MDD	Control	<i>p</i> -value
Subicular complex	13590.8	14170.0	0.67	13908.8	17634.4	0.06
CA1	11699.8	11548.6	0.89	8962.1	8698.1	1.0
Dentate Gyrus	5574.4	8784.9	0.0006	7209.8	7836.0	0.44
CA2/3	5680.9	4019.3	0.09	4603.4	3887.8	0.42
Fimbria	2616.9	3235.0	0.31	2559.6	2950.2	0.46
Whole Hippocampus	39162.8	41757.7	0.56	37243.7	41006.6	0.42

Abbreviations: CA, Cornu Ammonis

Table 2.

Mean (*p*-value) of the mean diffusivities ($\text{mm}^2/\text{s} \times 10^{-4}$) of the tracts emanating from the hippocampal subfields. *p*-values below the Bonferroni-corrected significance threshold are shown in bold-face.

	LEFT HEMISPHERE			RIGHT HEMISPHERE		
	MDD	Control	<i>p</i> -value	MDD	Control	<i>p</i> -value
Subicular complex	7.23	7.02	0.17	7.19	7.01	0.37
CA1	7.30	7.18	0.70	7.32	7.21	0.62
Dentate Gyrus	7.35	7.18	0.40	7.38	7.18	0.10
CA2/3	7.52	7.22	0.29	7.24	7.22	0.91
Fimbria	7.66	7.14	0.0006	7.87	7.25	0.0001
Whole Hippocampus	7.40	7.22	0.37	7.42	7.19	0.07

Abbreviations: CA, Cornu Ammonis