CHARACTERIZING WHITE MATTER CONNECTIVITY IN MAJOR DEPRESSIVE DISORDER: AUTOMATED FIBER QUANTIFICATION AND MAXIMUM DENSITY PATHS

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ABSTRACT

Diffusion-weighted imaging allows for *in vivo* assessment of white matter structure, which can be used to assess aberrations associated with disease. Several new methods permit the automated assessment of important white matter characteristics. In the current study we used Automated Fiber Quantification (AFQ) to assess differences between depressed and nondepressed individuals in 18 major white matter tracts. We then used the Maximum Density Path (MDP) method to further characterize group differences identified with AFQ. The results of the AFQ analyses indicated that fractional anisotropy (FA; an index of white matter integrity) along bilateral corticospinal tracts (CST) was higher in depressed than in nondepressed individuals. MDP analyses revealed that white matter anomalies were restricted to four subregions that included the corona radiata and the internal and external capsules. These results provide further evidence that MDD is associated with abnormalities in cortical-to-subcortical connectivity.

Index Terms— Major Depressive Disorder (MDD), automated fiber quantification (AFQ), maximum density paths (MDP), diffusion-weighted imaging, tractography

1. INTRODUCTION

Diffusion-weighted imaging (DWI) allows for the *in vivo* assessment of water diffusion in humans. Because the diffusion of water is influenced by local tissue composition, inferences regarding the composition of brain structure can be made based on measuring this diffusion. A common method of DWI inference uses fibers from tractography algorithms to infer structural white matter connectivity of the brain, which has been used to assess disease states.

A growing literature suggests that white matter structure differs in individuals with Major Depressive Disorder (MDD) compared to healthy controls. Meta-analysis of DWI studies of MDD has revealed that the most consistent findings are related to reduced fractional anisotropy (FA; a measure of white matter integrity) between cortical and subcortical brain regions [1].

Modern diagnosis and treatment of MDD rely on observations of clinical symptoms and patient self-reports. Improvements in diagnosis and treatment may be possible by using neural measures as predictive quantitative indexes. To reach this goal, it is critical that equivalent brain structures be identified in depressed and nondepressed individuals, and that biological properties of these structures differ as a function of the depressive state.

Because tractography algorithms produce large amounts of fibers, clustering analyses are commonly used. Many of these methods rely on constraints provided by white matter atlases that provide probabilistic information regarding tract location.

Automated Fiber Quantification (AFQ) is a method that systematically identifies and quantifies 18 important white matter tracts in the human brain [2]. First, whole-brain tractography is computed. Then, fibers intersecting waypoint ROIs are identified. Next, fiber tracts are refined by removing outlier fibers. The central portion of the tract is established and diffusion properties are calculated at points along this core. AFQ thus allows for the comparison of white matter properties of important fiber tracts across individuals in a systematic and automated manner.

The maximum density path (MDP) approach permits the construction of more compact and localized white matter paths. This method resolves structural characteristics from 67 paths of 50 important white matter regions [3,4]. Information from tractography is utilized by choosing a subset of fiber tracts that correspond to a white matter atlas. A density image graph of these bundles is created (with nodes as voxel locations and edges as a density measure), and seed point pairs are placed at disparate positions along these bundles (as inferred from the white matter atlas). Using a graph search method, the MDP is identified between the two given seed points. This path follows the points of highest density, resulting in a compact representation of tract scale, location, and geometry. Using geodesic curve registration, paths from different individuals can be registered spatially, and variations in localized paths that differ as a function of disorder can be identified.

In the current study, we used these methods in

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combination to assess differences in fiber tracts between individuals diagnosed with MDD and healthy controls. First, we identified differences in fiber groups using AFQ; then, we used MDPs to further characterize subregions associated with the fiber groups identified using AFQ. We hypothesized that regions that connect cortical to subcortical regions would exhibit abnormal FA in depressed compared with nondepressed individuals.

2. METHODS

2.1 Participants

DWI and high-resolution anatomical (T1-weighted) magnetic resonance imaging was obtained in 14 MDD and 18 age-matched healthy control (CTL) participants. All participants were female. The protocol was approved by the Stanford University IRB. Informed consent was collected.

2.2 DWI and MRI Data Acquisition

DWI and T1-weighted imaging data were acquired with a 3T Discovery MR750 (GE Medical Systems, Milwaukee, WI, USA), at the Stanford Center for Neurobiological Imaging. A diffusion-weighted, dual-spin-echo, single-shot, echo-planar imaging sequence that included 64 2-mm thick slices in 96 unique directions (with b = 2000 s/mm^2; voxel resolution 2x2x2 mm^3) was collected. DWI scan duration was 15 min 1 s. For anatomical localization, high-resolution T1-weighted scans were acquired (sagittal spoiled gradient sequence [SPGR], 0.9x0.9x0.9 mm^3 resolution).

2.3 Automated Fiber Quantification (AFQ)

2.3.1 Diffusion Weighted Imaging Processing

The freely available mrDiffusion software was used for all AFQ-related analyses (i.e., preprocessing, tractography, and fiber tract identification: www.white.stanford.edu). Effects from subject motion were attenuated using 6-parameter rigid-body realignment. A mean non-diffusion weighted image was created by averaging all motion-corrected b = 0 image volumes. DWI images were registered to the mean b = 0 image. The mean b = 0 image was aligned to the high-resolution anatomical image. DWI data were then resampled to 2 mm isotropic voxels. Resampling was completed by combining the motion correction and the anatomical registration transforms into an omnibus transform and subsequently resampling the data using trilinear interpolation [5]. The rotation components of the omnibus transform were applied to the gradient directions to retain initial orientation. A robust fitting method was used to estimate tensors [6].

2.3.2 Fiber Tract Identification

A summary of the AFQ method follows (for further detail see [2]). Whole brain tractography was estimated by seeding white matter voxels with FA greater than 0.3. For a given fiber group, fibers that intersect waypoint regions of interest (ROIs) were identified. Each identified fiber was then scored based on its correspondence with a standard fiber tract probability map. Low-scoring fibers were discarded. Fibers were then represented as a 3D Gaussian distribution and fibers that deviated substantially from the mean tract were culled. The given fiber group was then restricted to the central section of fibers that spanned the waypoint ROIs. Next, 100 equidistant points along each fiber were identified, and the position of a fiber group core was determined by the mean location of each node. FA was then assessed at each core node by calculating a weighted average FA measurement across fibers. Weights were calculated based on the Mahalanobis distance of each fiber node from the fiber core. The mean FA of each fiber core was then computed.

2.4 Maximum Density Paths (MDP)

2.4.1 MDP: Imaging Preprocessing and Tractography

FSL's eddy correction was used for DWI preprocessing. An optimized global probabilistic method was used for tractography estimation [7,8]. For each subject, 35,000 fibers were estimated. The Automatic Registration Toolkit (ART; [9,10]) was used for nonlinearly transforming T1-weighted data to subject-specific DWI space.

2.4.2 MDP: Fiber Clustering

The primary steps of the MDP procedure are presented below (for further detail see [3,4]). Fifty white matter ROIs were obtained from the Johns Hopkins University diffusion tensor imaging white matter atlas. These white matter tract ROIs were transformed to DWI space using ART. Previously estimated fibers were selected based on their intersection with these white matter tract ROIs, thus defining fiber clusters. An intersection score was then defined for each intersecting fiber by computing the number of ROI voxels through which the given fiber passes. Fibers with high intersection scores were considered to be part of a white matter fiber tract. Low-scoring fibers were considered spurious and discarded. On a voxel-wise basis, the number of intersecting fibers was calculated. This resulted in a fiber density representation for each ROI. Fiber density representations were smoothed with a Gaussian kernel.

2.4.3 MDP: Cluster Representation

Compact representations of the identified fiber bundle were then computed. First, each fiber density representation was treated as a graph (i.e., a set of nodes [here, voxels] connected by undirected edges). Edge values were weighted inversely by the sum of voxel densities (i.e., the fiber densities of the two connected voxels). From this graph definition, the path of voxels with the highest number of fibers connecting two seed points was identified using Dijkstra's algorithm [11], a graph search method that finds shortest paths between nodes. The two seed points were used as start and end nodes in the graph search and were identified previously in the ROI atlas. In order to better condition the paths for registration, they were smoothed with a Gaussian kernel. This resulted in the compact representations of tracts, that is, MDPs.

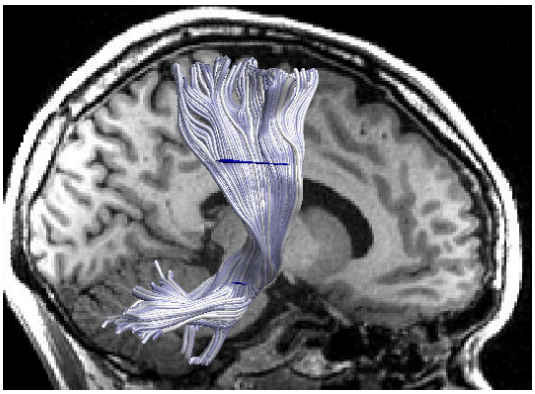

FIGURE 1
AFQ CORTICOSPINAL TRACT
200 fibers rendered from right corticospinal tract (CST) identified using AFQ. Blue lines indicate waypoint regions of interest used to identify the CST. Mean FA values were compared between groups along the fiber group's core (not visualized).

2.4.4 MDP: Registration

After computing MDPs for all seed point pairs (67 total) in the 50 white matter tract ROIs for each subject, the paths were registered in order to assess group differences. This was accomplished using geodesic curve registration, which estimated the mean MDPs across all subjects and used it as target to compute point-wise correspondences. The method that was used to match 3D curves using geometric features is described in [12,13]. This resulted in a transform that was used to align corresponding points along each MDP.

2.5 Analyses Plan

First, using two-sample *t*-tests, mean FA values were compared for the 18 fibers identified using AFQ. Next, MDPs associated with fiber groups identified with AFQ were aggregated. Finally, FA values from corresponding points along each identified MDP were compared between groups using two-sample *t*-tests.

2.6 Multiple Comparisons Correction

A False Discovery Rate (FDR; $q = 0.05$; [14]) procedure was used to correct for multiple comparisons for tests of mean FA from tracts identified with AFQ. In addition, FDR was used to correct for multiple comparisons within points along each MDP.

3. RESULTS

3.1 AFQ

AFQ identified 18 fiber groups. Of these, two exhibited differences between MDD and CTL participants: the left and right CST tracts (Table 1; Fig. 1).

3.2 MDP Identification

Given observed differences in the fiber bundled labeled by AFQ as CST, 7 of the available 50 MDP regions of interest were selected for further analysis. These 7 regions included 24 unique MDPs that either overlap, or are associated with CST projections. These MDPs are summarized in Table 2.

TABLE 1
GROUP DIFFERENCES IN AFQ FA

AFQ Fiber Group	CTL FA		MDD FA		p-value*
	M	*SD*	*M*	*SD*	
L Corticospinal Tract	0.620	0.020	0.644	0.020	< 0.002
R Corticospinal Tract	0.614	0.021	0.639	0.015	< 0.0001

Group differences in fractional anisotropy (FA) along AFQ identified fiber tracts. *A false discovery rate (FDR) method was used to correct for multiple comparisons for each statistical test. CTL = control participants; MDD = Major Depressive Disorder participants. *M* = mean; *SD* = standard deviation; L = left; R = Right.

TABLE 2
WHITE MATTER ROIS FOR MDPS

MDP White Matter Region	Number of seed pairs (per hemisphere)
Corticospinal tract	1
Anterior Limb of the Internal Capsule	2
Posterior Limb of the Internal Capsule	2
Anterior Corona Radiata	2
Superior Corona Radiata	2
Posterior Corona Radiata	2
External Capsule	1

White matter regions of interest (ROIs) included in the present analyses. All ROIs were bilateral. Number of seed pairs indicates the number of unique MDPs computed in the given region of interest.

TABLE 3
GROUP DIFFERENCES IN MDP FA

White Matter Region*	Total Points	Points with Group Differences	% of Points
L External Capsule	48	6**	12.5
R Superior Corona Radiata	17	1	5.9
R Posterior Limb Internal Capsule	17	14	82.4
L Posterior Limb Internal Capsule	16	6	37.5

Group differences in fractional anisotropy (FA) along maximum density paths associated with the corticospinal tract (CST). *For each of these analyses only one of two MDPs exhibited point-wise group differences. **3 of the 6 L external capsule points that exhibited group differences were associated with greater FA in the CTLs group. In all other regions each point exhibited higher FA in the MDDs group. L = left; R = right.

3.3 MDP Results

Point-by-point FA values were assessed across 24 MDPs identified to be related to AFQ's CST. Of these, four exhibited point-wise differences between groups that survived correction for multiple comparisons using FDR (Table 3, Fig. 2). The right posterior limb of the internal capsule exhibited the largest percentage of points differing between groups (76.5%). All difference points were characterized by greater FA in the depressed group, except 3 of 6 points in the left external capsule.

6. DISCUSSION

AFQ and MDP analyses represent complementary and highly sensitive methods for the identification of white matter microstructure. Using AFQ, we found that the structural integrity of bilateral CSTs is greater in currently

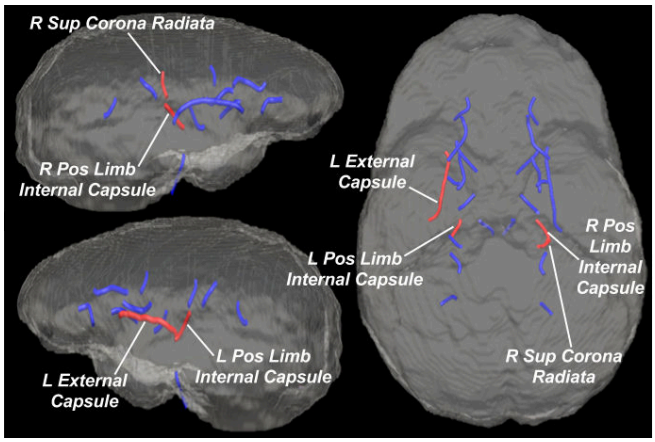

FIGURE 2
GROUP DIFFERENCES IN MDP FA
Group differences in fractional anisotropy (FA) along maximum density paths associated with the corticospinal tract (CST). MDPs with significant point differences between groups are colored red, all others are colored blue. R = right; L = left; Pos = posterior; Sup = superior.

depressed individuals relative to nondepressed controls. This finding enabled us to use the MDP procedure to further examine these differences, where we found FA at points along the left external capsule, right superior corona radiata, and bilateral posterior limbs of the internal capsule to differ between groups.

Previous research has shown that MDD is associated with reduced connectivity between subcortical and cortical regions [1]. In the current study we found that AFQ identified CST tracts and MDP points in MDD participants exhibited greater FA than in nondepressed individuals. One exception to this is that half of the points of the left external capsule in which there were group differences were associated with greater FA in CTL participants. This raises the possibility that variation in FA in depression is dependent on white matter location. Indeed, although previous research has most consistently found reductions in FA associated with depression, there is also evidence of increases in FA associated with depression (e.g., [15]).

MDD is often characterized by psychomotor agitation or retardation; the neurophysiological bases of these difficulties, however, are currently unclear. Although anomalies in striatal and motor region functioning has been documented in MDD (e.g., [16]), it is not clear whether psychomotor difficulties are due to 'downstream' structural abnormalities such as anomalies in the CST, given the role of CST in trafficking motor signals. The current findings provide initial evidence that the CSTs may be involved in these motor-related deficits.

Given the wide variety of function associated with the CST and related connectivity (e.g., corona radiate, internal capsule), it will be important in future research to examine the relation of differences in FA observed in these regions to depressive symptomatology.

The present findings are important in demonstrating anomalies in white mater connectivity associated with the CST in MDD. In addition, the current study demonstrates that integration of AFQ and MDP approaches may be particularly useful in clinical settings, given their automated nature (thus eliminating the need for manual scoring and reducing bias that may result from such scoring), and robust representation of white matter in compact formats.

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