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USING NEURITE ORIENTATION DISPERSION AND DENSITY IMAGING AND TRACTS CONSTRAINED BY UNDERLYING ANATOMY TO DIFFERENTIATE BETWEEN SUBJECTS ALONG THE ALZHEIMER'S DISEASE CONTINUUM

By

ZANNAN ZHANG

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Approved by

First Reader

Ronald Killiany, Ph.D.
Associate Professor of Anatomy & Neurobiology

Second Reader

Asim Mian, M.D.
Assistant Professor of Radiology
Boston Medical Center

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ABSTRACT

Objective: To assess the involvement of the white matter of the brain in the pathology of Alzheimer's disease. Using Neurite Orientation Density and Dispersion Imaging (NODDI) and the probabilistic white matter parcellation tool Tracula as a means for understanding whether alterations in the white matter underlie changes in perceived cognitive abilities across the spectrum from health aging to Alzheimer's disease.

Method: Data were obtained from 28 participants in the Health Outreach Program for the Elderly (HOPE) at the Boston University Alzheimer's Disease Center (BU ADC) Clinical Core Registry. MRI scans included an MPRAGE T1 scan, multi-b shell diffusion scan and a High Angular Resolution Diffusion Imaging scan (HARDI). Scans were processed with Freesurfer v6.0 and the NODDI Python2.7 toolkit. The resulting data included the orientation dispersion index (ODI) and Fractional Anisotropy (FA) values for cortical and subcortical regions in the DKT atlas space as well as specific Tracts Constrained by Underlying Anatomy (TRACULA) measurements for 18 specific established white matter tracts. Statistical models using measures of pathway integrity (FA and ODI data) were used to assess relationships with Informant Cognitive Change

Index (ICCI), self-described Cognitive Change Index (CCI), and Clinical Dementia Rating (CDR) values.

Results: Measures of white matter integrity within several tracts predicted ICCI and CDR well in statistical models. FA and ODI values of the bilateral superior longitudinal fasciculi, inferior longitudinal fasciculi, and the cingulum bundle tracts were all related to ICCI and CDR. None of the known tracts' FA or ODI values were related to CCI.

Conclusions: Measures of white matter pathway integrity were predictive of ICCI and CDR scores but not CCI. These finding support the notion that self-report of cognitive abilities may be compromised by alterations in insight and reinforce the need for informed study partners and clinical ratings to evaluate potential MCI and AD.

Keywords: MCI, ICCI, CCI, CDR, NODDI, Tracula

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LIST OF ABBREVIATIONS

AD ..... Alzheimer's Disease

AMICO ..... Accelerated Microstructure Imaging via Convex Optimization

BU ADC ..... Boston University Alzheimer's Disease Center

CCI ..... Cognitive Change Index

CDR ..... Clinical Dementia Rating

DKT ..... Desikan-Killiany-Tourville

FA ..... Fractional Anisotropy

HARDI ..... High Angular Resolution Diffusion Imaging

HOPE ..... Health Outreach Program for the Elderly

ICCI ..... Informant Cognitive Change Index

IcVF ..... Intracellular Volume Fraction

MD ..... Mean Diffusivity

MPRAGE ..... Magnetization Prepared Rapid Acquisition Gradient Echo

MRI ..... Magnetic Resonance Imaging

NDI ..... Neurite Density Index

NODDI ..... Neurite Orientation Dispersion and Density Index

ODI ..... Orientation Dispersion

ROI ..... Region of Interest

TRACULA ..... Tracts Constrained by Underlying Anatomy

INTRODUCTION

The ability to noninvasively compare normal and abnormal changes in the brain is perhaps one of the most compelling roles that magnetic resonance imaging (MRI) is capable of providing for *in vivo* human studies of cognitive change over time. Given the limitations of working with human subjects, namely that the inability to acquire pathological samples as one can do in animal studies of aging, human assessment relies on the increasing ability to provide finer details through non-invasive imaging techniques. One imaging technique that is growing in importance is diffusion MRI. Multiple iterations of diffusion imaging have demonstrated reliable 3-D maps of fiber direction can be generated. These maps can provide a measure of what tissue microstructures of the brain look like and how the regions of the brain are connected. These methods provide a basis for understanding of how human brains changes during aging and can be used in conjunction with the multitude of well-established neuropsychological assessments to see how these changes relate to cognition.

Mild Cognitive Impairment and the Alzheimer's Disease Continuum

Alzheimer's disease has an insidious onset that is difficult to differentiate from the normal aging process at its earliest stages. Mild Cognitive Impairment (MCI) represents a stage along the cognitive continuum in between normal aging and a full dementia state (AD) (Mufson et al., 2012). MCI can be difficult to define in a clinical setting (Petersen, 2004) without appropriate testing. The hallmark neuropathological features of MCI and AD are amyloid plaques and neurofibrillary tangles. There are no

clinically available measures of these features leaving us to diagnose MCI and AD based on its cognitive phenotype (Aisen et al., 2017; Petersen, 2004; Zhou, Zhang, Zhao, Qian, & Dong, 2016).

White matter microstructure is an important issue to consider in assessing overall brain function. Cognitive changes have been associated with changes in the white matter leading to the notion that assessments of the white matter aid in the identification of MCI and probable AD (Nagy, Alexander, Thomas, Weiskopf, & Sereno, 2013; Timmers et al., 2016). Changes in white matter microstructure have been demonstrated to be associated with neuronal death resulting from the amyloid plaques and neurofibrillary tangles which are the standard neuropathological features of Alzheimer's disease (Mufson et al., 2012; Varentsova, Zhang, & Arfanakis, 2014). One of the primary goals of this study is to determine if measures of white matter pathway microstructure are related to subjective measures of cognition across the Alzheimer's disease spectrum.

High Angular Resolution Diffusion Imaging (HARDI)

Diffusion tensor imaging (DTI) has been the standard model for assessing white matter microstructure though it suffers from numerous limitations due to its assumption of a normal Gaussian distribution of diffusion in which there is only a single fiber direction for each voxel. Newer diffusion techniques have sought to combat by increasing the detail measured in each voxel (Varentsova et al., 2014). One such example is high angular resolution diffusion imaging (HARDI) which is capable of distinguishing fibers in numerous directions combined though this is often limited, as in our study to 64 directions, because of acquisition time limitations. Increasing the directions measured

within each voxel provides a more complete picture of the white matter microstructure (Kuhn et al., 2016). The finer details provided when using HARDI include the ability to discern multiple fiber directions in a single voxel and allows microstructure information that is more consistent with what is known about human brain anatomy from pathological studies (Kuhn et al., 2016). HARDI data has become a standard in probabilistic tractography studies such as we are using in this study due to its ability to distinguish between crossing and kissing fibers (Kuhn et al., 2016).

HARDI data is typically acquired using a single b value, again mainly due to time constraints, and tracts are generated using probabilistic mapping of the underlying anatomy (TRACULA) (Yendiki et al., 2011) integrated into the Freesurfer 6 analysis tools. This tool determines both termination ends of a number of white matter tracts (Yendicki 2011). The Tracula method has been used to differentiate healthy control subjects from those with schizophrenia. It addresses the problem of identifying specific white matter pathways by searching for all possible connections using a global probabilistic approach which allows the algorithm to reliably reconstruct pathways without manual intervention (Yendiki et al., 2011). This automatic probabilistic process is an improvement over previous iterations of tractography which were limited by expert manual intervention.

Multi-b Shell Imaging

Traditional diffusion tensor imaging (DTI) relies on a single shell model. Newer diffusion techniques employ multi-b shell models to evaluate at each voxel the preferred direction of movement and the state of the water - free water versus bound or semi-bound

water (Zhang 2011; Stuyfs 2015). Being able to separate these water in this way enables us to distinguish between axons, glial cells, and the intracellular space of each cell type. Whereas other diffusion methods have an inability to confidently distinguish microstructural changes in fiber direction by only being capable of balancing fractional anisotropy (FA) with mean diffusivity (MD) without accounting for the orientation dispersion of individual axons, relying on the unrealistic assumption that all the axons are sitting perfectly parallel, NODDI is able to include measures that account for the diverse orientation of each individual axon by distinguishing between its intra-cellular and extra-cellular spaces within each voxel (Mah, Geeraert, & Lebel, 2017; Schneider et al., 2017; Timmers et al., 2016; Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012). The NODDI method provides increased sensitivity of fiber density because it accounts for the specific measurements of Neurite Density (ND) and Orientation Dispersion Index (ODI) which are based on the complexity of the fiber structure, a measure that is not incorporated into FA (Mah et al., 2017; Schneider et al., 2017). Neurites consist of both dendrites and axons of neurons; they are directionally complex while axons sit primarily in the white matter and dendrites spread throughout the gray matter (Zhang et al., 2012). They key to the orientation dispersion is that axons in the white matter are smaller than the diffusion voxels and are not limited to one direction within a single voxel, so ODI helps solve the issue of limiting directionality by accounting for additional direction complexity.

Alzheimer's disease patients in the early stages of the disease already exhibit significant microstructural changes in both white matter and gray matter regions of the

brain. Multi-b shell imaging has the potential to provide insight into how changes in white matter or gray matter microstructure might contribute to cognitive impairment early in the AD disease continuum (Parker et al., 2018; Yuan et al., 2016). The NODDI model used in our study has been previously optimized and used in a study to map the cortical surface gray matter in a manner that is complementary to its myloarchitecture by allowing discernment of free water in comparison to bound or semi-bound water (Fukutomi et al., 2018). Improving our understanding of white matter integrity changes in AD using whole brain voxel based analysis is one of benefits of the multi-b shell acquisition use in NODDI (Chung, Seunarine, & Clark, 2016). This has been previously used successfully to study white matter changes during AD across a spectrum of individuals between MCI, AD, and controls (Struyfs et al., 2015). The resulting differences were mainly found in the splenium of the corpus callosum (Struyfs et al., 2015).

Cognitive Assessments

Our study aims to explore the relationship between the independent outcome measures of ODI derived from NODDI and FA from HARDI to disease measured by the clinical dementia rating (CDR), a standard clinical scale of the AD continuum (Morris, 1993). The CDR system is a conclusion reached by consensus of clinicians interpreting a comprehensive scoring table. Additionally, HOPE subjects were evaluated with list learning, trail making, and mini mental state exam (MMSE) neuropsychological tests which focus on separate cognitive domains. An additional goal is to if determine white matter pathway integrity is related to a self-reported and informant-reported cognitive

change indices (CCI and ICCI), both of which assess subject specific cognitive changes with potentially variable accuracy (Rattanabannakit et al., 2016).The ICCI and CCI consist of twenty parallel questions of cognitive ability that is asked of both the participant and an informant to describe the participant's change in cognitive ability of over the past five years (Rattanabannakit et al., 2016). Our study combines AD related morphometry measures with pathway measures of FA and ODI as related to CDR, CCI, and ICCI to support a model that is capable of associating the pathway measures with clinical ratings.

METHODS

Participants

Participants for this study were selected from of the Health Outreach Program for the Elderly (HOPE) study at Boston University's Alzheimer's Disease Center's (ADC) Clinical Core Registry which includes individuals 65 years or older without memory concerns or 50 years and older with memory concerns who must have caregiver or study partner participating (Siwek, 1999). To date, the HOPE study has scanned over 300 individuals. For a period of time a multi-b shell diffusion MRI scan was added to the MRI protocol for this study. All participants with a multi-b shell image were initially selected for this study. This initial group of 31 participants was narrowed down to 29 by excluding individuals who had a differential diagnosis outside of general memory complaints as a possible condition. All of the participants were between the ages of 56-89 and ranged from those self-described as controls without memory concerns to those with likely AD as defined by a consensus diagnosis.

All of the HOPE participants were assessed clinically and with cognitive measures annually and diagnosed by consensus conferences where a group of clinicians (Neuropsychologist, Neurologist, Nurse Practitioner and/or Psychiatrist) carefully assessed the medical history and other related evaluations before coming to a consensus diagnosis. The nurse practitioner clinically evaluated each participant annually and assigned a global Clinical Dementia Rating (CDR) score between 0.0 and 3.0 according to standard scale criteria (Morris, 1993) (Petersen et al., 2014). All subjects were scanned

between 10/12/16 and 5/23/17 with all four MRI sequences completed in a single imaging session.

Table 1. Demographic Data of Participants.

Diagnosis on Continuum	Control	Control with complaint	Cognitive Impairment-Non MCI	MCI-Single	MCI-Multi	AD
CCI						
Mean ± Standard Deviation	14 ± 0.82	20.85 ± 7.02	18 ± 5.66	20 ± 2.83	28	23.33 ± 5.69
ICCI						
Mean ± Standard Deviation	12.25 ± 0.5	19.31 ± 8.53	12.25 ± 0.71	41 ± 2.83	39 ± 2.83	45.8 ± 7.89
CDR						
Mean ± Standard Deviation	0	0.04 ± 0.14	0.25 ± 0.35	.5	.5	1

Imaging

All of the participants in this study were scanned on the same 3.0T Philips Achieva whole body imager located in the Center for Biomedical Imaging on the Boston University Medical School campus. All scans were acquired using a 32-channel headcoil. Two additional diffusion imaging scans were included with the initial MPRAGE required for the study. A high angular resolution diffusion image (HARDI) and a multi-b shell image.

The MRI protocol consisted of 1) a 3D magnetization-prepared rapid acquisition of gradient echo (MPRAGE) MRI sequence with a sense factor of 1.5, TR = 6.7 ms, TE = 3.1 ms, flip angle = 9°, reconstructed voxel size = 1.05 x 1.05 x 1.2 mm, and acquisition

voxel size = 1.11 x 1.11 x 1.2 mm, FOV = 270 mm x 252.2951 mm x 204 mm, 170 sagittal slices. 2) a HARDI sequence with a sense factor of 1, TR = 6.7 ms, TE = 3.1 ms, flip angle = 90°, reconstructed voxel size = 1.75 x 1.75 x 2.0 mm, acquisition voxel size = 2.0 x 2.0 x 2.0 mm, FOV = 224 mm x 224 mm x 120 mm, 60 sagittal slices, Shell one: single b = 3000. 3) a multi-b shell sequence with a sense factor of 1, TR = 6.7 ms, TE = 3.1 ms, flip angle = 90°, reconstructed and acquisition voxel size = 2.5 x 2.5 x 2.5 mm, FOV = 240 mm x 240 mm x 125 mm, 50 sagittal slices, Shell one: b=1000, Shell Two: high b=2000.

The MPRAGE scans were processed using Freesurfer v.6.0. During the initial steps of processing, each scan was skull striped (brainmask) and the white matter, gray matter and pial surfaces were generated. Each scan was visually inspected and conservatively edited to ensure that the various boundaries and volumes conformed to known brain anatomy. This established the anatomical basis for the final segmentation of the cortical and subcortical regions.

Each subject's diffusion DCM images (multi-b shell & HARDI) were converted into NIFTI files using the DCM2Nii converter (dcm2nii, RRID:SCR_014099). The conversion process extracted the b value and directions tables and placed them into separate bvec and bval files which were used in the analyses. The converted MRI files were processed to generate the diffusion data as a single collective value for all the scans for each subject. Prior information derived from the initial Freesurfer editing process allowed for outputs of cortical and subcortical regions extracted using a known human brain atlas for anatomical regions of interest (ROI) analysis. These established gray

matter and white matter regions were compiled in a single chart across all subjects for established thickness and volumes (aparc+asegstats command in Freesurfer) for each ROI. These values were used to compare brain regions to the cognitive assessments collected from each subject.

High Angular Resolution Diffusion Imaging (HARDI)

Individual fiber tracts were extracted from the HARDI scans (in combination with the MPRAGE scans) and these reconstructed white-matter pathways provided the basis for the unique analysis method. Each subject's scans were eddy current corrected using FSL to account for head movement during scanning (Andersson & Sotiropoulos, 2016). Automatic reconstruction of major white matter pathways from HARDI images used global probabilistic tractography with anatomical priors derived from an anatomical atlas and combined with Freesurfer's initial cortical parcellation and subcortical segmentation. These initial parcellations and segmentations constrained the tractography solutions and provided the clearest possible probabilistic tracts for each subject. These 18 known tracts were then assessed independently across averages of their fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) values in relation to the known atlas (Yendicki 2011). Though these white matter values were constrained by the anatomical priors of each tract, this restriction gave values that are exclusively associated with white matter tracts which connect between cortical regions.

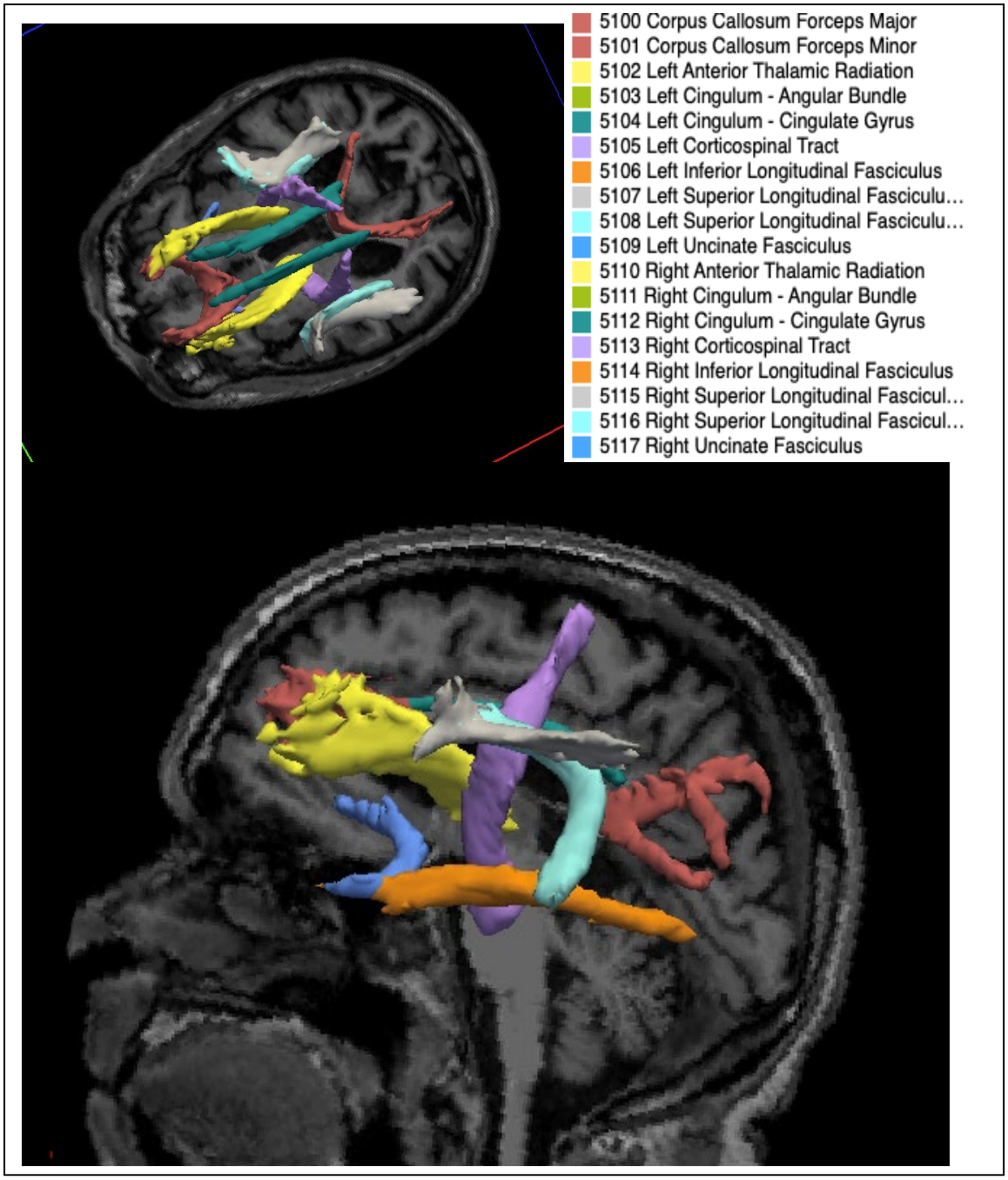

Figure 1. TRACULA – All eighteen available tracts and their color designations according to standard TRACULA procedure. Tracts have been displayed on top of a T1 image for anatomical clarity.

Multi-b Shell

We used the neurite orientation dispersion and density imaging (NODDI) Python2.7 toolbox with AMICO optimization to obtain both an orientation dispersion index (ODI) from both the gray and white matter of the brain (Daducci et al., 2015; Zhang et al., 2012). The created NODDI maps were aligning with the known atlas generated from the TRACULA processing described above. Each ODI value in the map was assessed using the same standard segmentations and parcellations.

ODI and TRACULA Overlay

To assess each white matter tract, the HARDI and multi-b shell image processing methods were combined so that ODI and FA were assessing the same tracts using the same anatomical definitions. This required using established TRACULA statistics extraction by renaming the basic NODDI file outputs for each tract and rerunning the same extraction process with ODI as a replacement for FA. This provided a mechanism for direct comparison between ODI and FA in the same anatomical space.

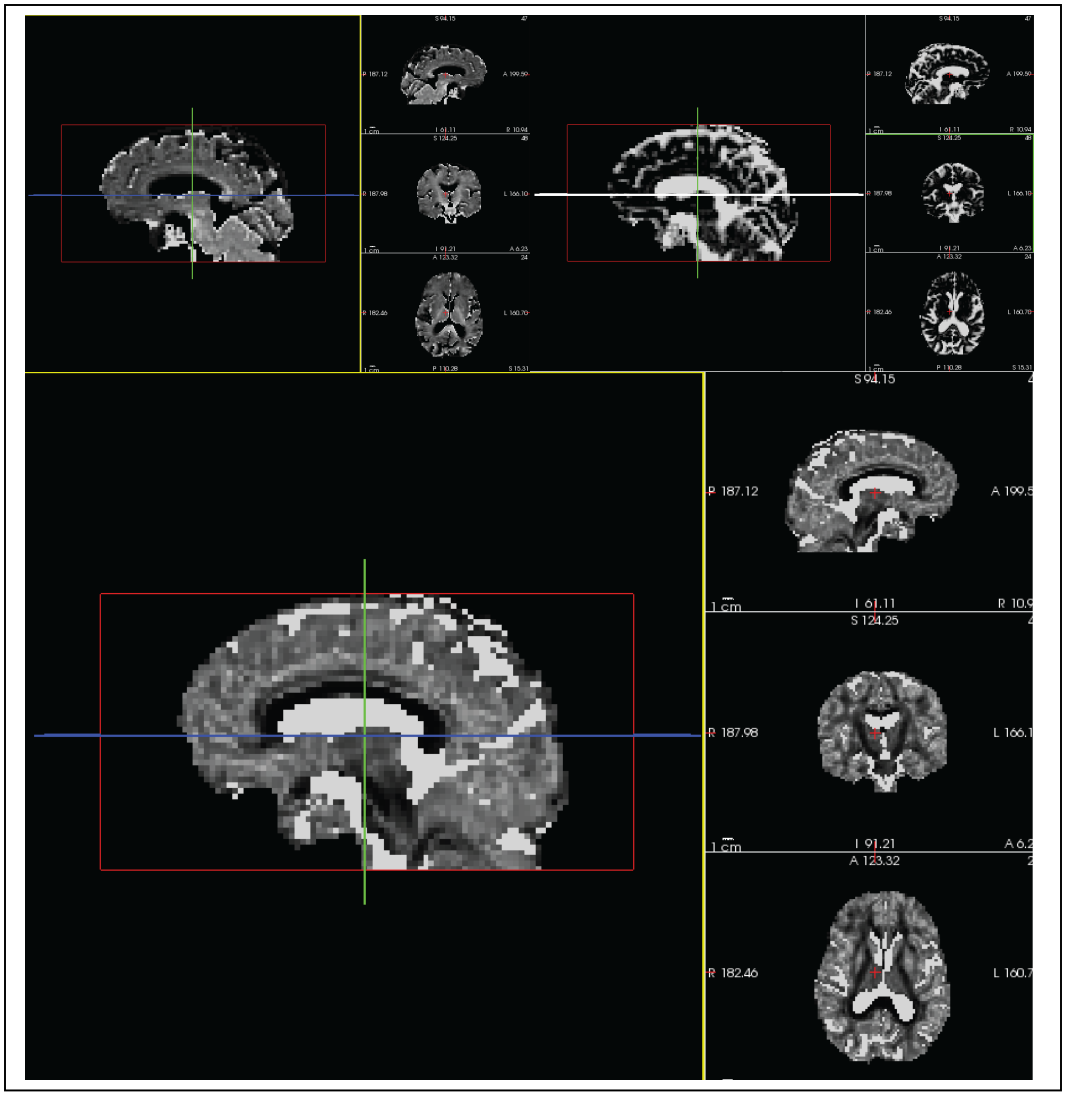

Figure 2. NODDI measures – IcVF intra-cellular volume fraction - top left, ISOVF isotropic volume fraction- top right, ODI orientation dispersion - bottom

Statistical Analysis

Cortical and Subcortical

Independent samples t tests were used to compare unedited and edited images to assess the changes between each round of editing. This preliminary assessment was used

to establish the effectiveness of our initial editing. These tests showed significant differences (p's < 0.05) between the initial and edited volumes.

The next step in our statistical analysis was to assess the relationships between the cortical and subcortical regions from Freesurfer for the diffusion data independent of the NODDI and TRACULA outputs. These cortical and subcortical volumes and thickness measures were used to establish whether the relationship between these volumes would align with the literature's already established identifiers of MCI and AD.

These analyses used multiple linear regression in a stepwise model with the false discovery rate correction available in JMP Pro 14.0. A series of stepwise models were used for data reduction. The three stepwise measures generated from Freesurfer v6.0 included estimated total intracranial volume (eTIV), 68 cortical volumes, 12 subcortical volumes, the right and left hippocampal volumes, the right and left entorhinal cortex volumes, and the right and left amygdala volumes. The specific brain regions were chosen due to their well-established role in AD from the known literature on disease progression.

The inclusion of eTIV forced into the analysis was to control for potential differences between due to overall brain volume (i.e. as found between men and women). To control for multi-collinearity, correlations were calculated between all freesurfer output regions using an arbitrary threshold of 0.7.

A secondary background analysis also looked for a relationship between CDR, ICCI and CCI using an ordinal logistic regression. For the final analyses, multiple

regression was used to determine if the parcellations or segmentations could predict either CCI or ICCI.

FA and ODI Measures

FA and ODI segmentation values extracted from both scan types were included in multiple regression analysis. The specific cortical and subcortical regions included for this analysis were as follows: left and right hippocampus, left and right entorhinal cortex, and left and right amygdala. The ODI values for each segment were compared to the FA values of that same segment. These regions were entered into a stepwise nominal logistic regression model consisting of both the right and left volumes of each region.

Finally, the ODI values were combined with the FA values from each TRACULA derived tract. Each tract was then used a continuous variable for the stepwise model. An ordinal logistic fit model was created for CDR and each tract. Multiple linear regression models were created for ICCI and CCI. These models were used to determine the predictive value of the ODI or FA values within each tract. The forceps minor of the corpus callosum tract was excluded from the overlay because it over fit the model.

RESULTS

Neither ICCI nor CCI were shown to predict CDR indicating that each of these assessments are independent.

Cortical and Subcortical ROIs

The cortical thickness measures not have a predictive relationship with CCI, ICCI, or CDR. Even accounting for the inclusion of only regions well associated with MCI and AD. The r-squared values from the fit of these models were all below 0.3 with none of the predictors (regions) displaying any significant value. Left hemisphere entorhinal cortex and left hippocampus were not significantly correlated with CCI (R^2 = 0.2916, F ratio = 4.527, $p < 0.1346$) nor was the right hippocampus (R^2 = 0.2916, F ratio = 4.527, $p < 0.1346$). Right hippocampus (R^2 = 0.21099, F ratio = 2.1393, $p < 0.05585$), left hippocampus (R^2 = 0.21099, F ratio = 2.1393, $p < 0.05585$), and left amygdala (R^2 = 0.21099, F ratio = 2.1393, $p < 0.07918$) were also not significantly correlated with CDR. Right amygdala volume was significant with ICCI but did not have a strong fit (R^2 = 0.1692, F ratio = 5.2962, $p < 0.02964$).

Cortical and subcortical volume measures similarly did not have a predictive relationship with CCI or ICCI. Though differing slightly from the parcellations, CDR and ICCI were closer to accounting for the variability in the data set. Analysis of CCI produced no values for the model. The right hippocampus (R^2 = 0.4796, F ratio = 5.2985, $p < 0.1720$), right amygdala ($p < 0.1720$), and left hippocampus ($p < 0.1720$) were all not significant predictors of ICCI. As for CDR, the right hippocampus (R^2 = 0.6587, F ratio =

15.4385, $p < 0.00056$), left amygdala ($p < 0.00881$), and right amygdala ($p < 0.00957$) were all predictors of CDR with a whole model accounting for about 66% of the variability in the model.

ODI and FA Comparisons

ODI and FA values of cortical and subcortical regions produced similarly non-predictive associations with CCI, ICCI, and CDR. All six regions included with ODI and FA models had r-squared values below 0.2.

The FA measures for the left hemisphere entorhinal ($R^2 = 0.1672$, F ratio = 2.2090, $p < 0.1761$) and left amygdala ($p < 0.1761$) were a poor fit for CCI. FA values for the right hippocampus ($R^2 = 0.1284$, F ratio = 1.8417, $p < 0.1251$) and right hemisphere entorhinal ($p < 0.1251$) were also a poor fit for ICCI. FA measures in the left hemisphere entorhinal ($R^2 = 0.0541$, F ratio = 1.2356, $p < 0.23358$) was also a poor fit for CDR.

Similarly, ODI measures was not related to CCI for the left hemisphere entorhinal ($R^2 = 0.2916$, F ratio = 4.5270, $p < 0.1346$) and left hippocampus (, $p < 0.1346$). ODI was a significant predictor of ICCI with the right amygdala ($R^2 = 0.1692$, F ratio = 5.2962, $p < 0.0297$), but the r-squared value was low and indicated an unreliable model.

ODI was also insufficient as a predictor for CDR in the right hippocampus ($R^2 = 0.21099$, F ratio = 2.1393, $p < 0.0559$), left hippocampus ($p < 0.0559$), and left amygdala ($p < 0.0792$).

Mixed ODI and FA Predictive Model

The model combining ODI and FA values from the same anatomical regions proved to be a significant predictor of ICCI and CDR but far less so for CCI.

The model showed that a number of white matter tract values were related to ICCI. The results were often bilateral with the temporal superior longitudinal fasciculus from FA ($R^2 = 0.99997$, F ratio = 4333.994, L: $p < 0.00006$, R: $p < 0.00197$). ODI on the right hemisphere for the temporal superior longitudinal fasciculus was also significant in this model ($p < 0.00074$). The parietal superior longitudinal fasciculus also demonstrated bilateral predictability for ODI values (L: $p < 0.00478$, R: 0.00006). FA for the right hemisphere parietal superior longitudinal fasciculus also proved predictive ($p < 0.00006$). The left anterior thalamic radiation was predictive with its ODI ($p < 0.00006$) and FA ($p < 0.00006$) values. The interior longitudinal fasciculus was also significant both sides of FA (L: $p < 0.00039$, R: $p < 0.00154$). The cingulum bundles both supracallosal and infracallosal were also highly predictive of ICCI. These included the bilateral FA values for the cingulate gyrus supracallosal bundles (L: $p < 0.00016$, R: $p < 0.00006$) as well as the left hemisphere ODI value ($p < 0.00006$). The cingulum angular infracallosal bundles were predictive from ODI for both hemispheres (L: $p < 0.00006$, R: $p < 0.00007$) as well as on the right side for FA ($p < 0.02180$). The right hemisphere uncinate also proved predictive from FA ($p < 0.00006$) and ODI ($p < 0.00029$) values. ODI also considered the right hemisphere cortical spinal tract ($p < 0.01752$) as predictive of ICCI. Age ($p < 0.00139$) and MMSE ($p < 0.00006$) were also chosen by the stepwise model to be significantly predictive of ICCI status.

The values which predicted CDR included several tracts as well. Bilateral ODI values for the cingulum angular infracallosal bundle (R^2 = 0.998594, F ratio = 315.6197, L: $p < 0.00011$, R: $p < 0.01322$) were highly significant as was the FA value for the right hemisphere ($p < 0.000001$). FA for the right hemisphere cingulate gyrus supracallosal bundle was also highly significant ($p < 0.000001$). The left hemisphere temporal superior longitudinal fasciculus was significant with FA ($p < 0.000001$) while the left hemisphere FA ($p < 0.00001$) and right hemisphere ODI were significant for the parietal superior longitudinal fasciculus *(*$p < 0.00314$). Left and right hemisphere anterior thalamic radiation FA (L: $p < 0.000001$, R: $p < 0.000001$) was also significant. Bilateral FA values (L: $p < 0.000001$, R: $p < 0.000001$) for the interior longitudinal fasciculus were also significant. Bilateral ODI values for the corticospinal tract was also significant (L: $p <$ 0.00055, R: while FA ($p < 0.00001$) was predictive with the left hemisphere. The forceps major was significant for both ODI ($p < 0.00005$) and (FA $p < 0.04245$). ODI also included the right hemisphere uncinate ($p < 0.00020$). This model also chose MMSE ($p <$ 0.00001) as a strong predictor of CDR as well.

Though the CCI model chose to use the right hemisphere cingulate gyrus FA and MMSE scores as potential values (R^2 = 0.236682, F ratio = 3.2557, $p < 0.1989$), both were not significant in predicted CCI scores. CCI proved to be a poor model for the overlay.

DISCUSSION

This study sought to better understand if there is a relationship between subjective measures of cognitive ability and white matter microstructural integrity as evaluated with both high resolution FA values and detailed ODI values. Using statistical models we found that a number of measures of white matter tract integrity were related to both the ICCI and CDR scores. In contrast, these same statistical models failed to show meaningful relationships between the measures of white matter integrity and the participants' own evaluation of their cognitive ability through CCI.

Association White Matter Connections

White matter tracts connect specific cortical areas and support various cognitive functions. The medial temporal lobe (MTL) where the hippocampus, entorhinal cortex, and parahippocampal cortex are well associated with memory deficits, so it is not surprising that white matter tracts which connect to the MTL were often the most significant predictors in our models of ICCI and CDR (Mufson et al., 2012; Petersen et al., 2014; Zhou et al., 2016). White matter alterations in studies of MCI populations has been investigated using meta-analyses, and the most commonly sighted pathway with white matter abnormalities is the fornix which facilitates bilateral connections between the hippocampi on both sides of the brain (Yu, Lam, & Lee, 2017). Also this analysis showed the uncinate fasciculus and parahippocampal cortices are regions of significant alterations (Yu et al., 2017). This is consistent with the findings of our study in that hemisphere connections such as the corpus callosum were significantly related to CDR

and multiple white matter tracts that connect the temporal lobe to the rest of the brain such as the superior longitudinal fasciculi, cingulum bundles, and the uncinate were often significant predictors (both FA and ODI values) of ICCI and CDR. The longitudinal fasciculi and cingulum bundle also connect the MTL to frontal cortices and cingulate gyrus respectively. Finally, since the uncinate fasciculus connects the MTL to the orbitalfrontal cortex, it is not surprising that it has been implicated in MCI (Yu et al., 2017).

Independent Cognitive Assessment

The ability of the ICCI and CDR measure to assess one's ability relies on a the evaluator's knowledge of the participant in order to accurately assess individualize change. Informant rated assessments of participants such as ICCI have been previously cited as consistent with clinical assessment (Rattanabannakit et al., 2016). All of the study partners/informants in the HOPE study were spouses, children, or close friends who interacted with the participants multiple times per week and have known the participants for at least five years before beginning the study.

Participants in this study were over the age of 55 with or without memory complaints. These complaints could be voiced by either the participant themselves (CCI) or their study partner (ICCI). There are a multitude of studies in the literature focusing on the public health perspective of cognitive impairment as a continuum. Though considerable attention in this literature has been focused on memory complaints little attention has been paid to whether the complaint originates from the individual or a study partner. Our finding highlight a lack of relationship between CCI in comparison to ICCI.

This is important as evidence suggests that subjective cognitive complaints are a precursor to future cognitive deficits (Kryscio et al., 2014; Reisberg et al., 2008; Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Self-reporters of cognitive complaints have a higher risk of MCI and higher levels of AD-like brain pathology that is unassociated with cognitive impairment (Kryscio et al., 2014).

Previous NODDI studies have focused on alterations in gray matter structures between AD and healthy controls (Parker et al., 2018). Probable AD has been liked to atrophy in the entorhinal, interior temporal, middle temporal, fusiform, and precuneus cortices (Petersen, 2004; Petersen et al., 2014; Silbert, Howieson, Dodge, & Kaye, 2009). Gray matter assessment included NDI measurements corrected for cortical thickness. The findings of these studies are consistent with that of our study in that many of the cortical regions that were found to be important are served by the white matter pathways found to have predictive alterations in white matter structure in our study.

Clinical Viability

Our results also highlight that NODDI measures can be used as a complementary assessment to FA. The inclusion of ODI adds value to standard diffusion models and allows for greater specificity for the underpinnings of microstructural substrates to white matter change (Timmers et al., 2016). ODI accounts for more of the directionality associated with the fiber bundles which provides a more concrete assessment of white matter integrity. A recent study of whole brain g-ratio volumes uses NODDI and multi-echo gradient echo myelin water imaging to measure the ratio of the volume of axons in relation to fibers in each voxel of an image. This study pointed to the corticospinal tract

and optic radiation as a fiber bundles which showed different myelin and axonal volume fraction which could potentially be used to decipher fiber tracking further (Jung et al., 2018). More research needs to be done with NODDI to create a full picture of what ODI can actually assess in terms of brain region integrity analysis, but the future of the method is promising.

Limitations

The sample size of this study was a limitation due to the short period of time in which all scan types required for the study analysis were available. Certainly the inclusion of more participants would influence the predictors in the various statistical models. This study only included *in vivo* measures of MCI and probable AD from a single session. Some longitudinal studies of MCI and AD follow participants for the duration of their disease (Kryscio et al., 2014). Perhaps the inclusion of longitudinal data over time would allow post mortem amyloid plaque and neurofibrillary tangle assessments of the brain tissue. This could also be used to further validate the white matter measurements included in this study.

Imaging parameters described for this study were optimized for the center's scanner and thereby may not represent what is the optimal sequence that can be used by other scanner types at other locations. Other additional additions to the NODDI model can be included in future studies to account for anisotropic orientation dispersion of fanning and bending neurites which was not included in our assessment. The Bingham-NODDI model can be sufficiently assessed using two shell HARDI acquisition to enhance white matter microstructure measurements (Tariq, Schneider, Alexander,

Gandini Wheeler-Kingshott, & Zhang, 2016). An ongoing discussion on biomarkers must also contribute to future studies on white matter microstructure as this study adds more to the conversation of brain anatomy based changes which may indicate change before cognitive assessments are administered.

CONCLUSION

White matter pathway integrity as measured by ODI and FA were associated with ICCI and CDR not self-assessed CCI in statistical models. These findings support the notion that a self-report of cognitive abilities is potentially compromised by alterations in patient insight. There remains a need for informed study partners as a critical portion of better understanding cognitive impairment and cognitive change over time. The inclusion of study partners can capture additional insight into the participants already assessed by clinical ratings.

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CURRICULUM VITAE

Zannan Zhang

1992

zannan@bu.edu

484-557-3719

Academic Training:

5/2019 M.S.	Boston University School of Medicine, Boston, MA, Anatomy & Neurobiology – *In Progress*
4/2014 B.S.	University of Pittsburgh, Pittsburgh, PA; Summa cum laude, Anthropology, Communication & Rhetoric

Employment:

11/2017-Present	Part-time Instructor, CorePower Inc., Boston, MA
6/2018-7/2018	Minor course Instructor (Emerging Pathogens), Oxbridge Academic Programs, Boston, MA
9/2014-8/2017	Full-time Museum Educator, Wagner Free Institute of Science, Philadelphia, PA
1/2014-7/2014	Part-time Docent, Carnegie Museum of Natural History, Pittsburgh, PA

Research Experience:

3/2018-present	Student Research Assistant, Center for Biomedical Imaging - Cognitive Neurobiology Laboratory, Boston University School of Medicine, Boston, MA

1/2018-3/2018	Student Research Assistant, Brain Plasticity and Neuroimaging Laboratory, Boston University School of Medicine, Boston, MA
1/2014-4/2014	Autopsy Intern, University of Pittsburgh Medical School Humanity Gifts Registry, Pittsburgh, PA
1/2013-4/2013	Anatomy Laboratory Intern, University of Pittsburgh Medical School Gross Anatomy Lab, Pittsburgh, PA
9/2011-4/2012	Assistant Research Volunteer, Carnegie Museum of Natural History, Pittsburgh, PA

Field Experience:

6/2013-7/2013	Student Excavator, Astypalaia Bioanthropological Field School, Astypalaia, Greece

Departmental and Community Committees:

5/2018-8/2018	Coordinator, MRI Shortcourse, Anatomy & Neurobiology, Boston University School of Medicine, Boston, MA
10/2017-5/2018	Giussepina Raviola Memorial Symposium Planning Committee, Anatomy & Neurobiology, Boston University School of Medicine, Boston, MA
10/2014-7/2017	Member, Partner Steering Committee, Philadelphia Science Festival, Philadelphia, PA

Certificates:

6/2017	Adult & Pediatric First Aid/CPR/AED, American Red Cross

2/2018	Good Clinical Practices Training, Collaborative Institutional Training Initiative
2/2018	Human Subjects Protection Training, Collaborative Institutional Training Initiative
2/2018	MRI Initial Safety Training Certification - Green

Volunteer Experience:

10/2017-Present	Volunteer Yoga Instructor, Integrative Medicine, Boston University School of Medicine
4/7/2018	Volunteer, Set in the City for high school girls, Boston University Photonics Center
3/27/2018	Volunteer, Brain Lab Station Volunteer for Pentucket High School Students, BUSM
3/24/2018	Volunteer, Neuroscience Graduate Student Organization Outreach, Museum of Science, Boston, MA

Honors:

5/2013	John H. Tsui Memorial Grant; University of Pittsburgh Nationality Rooms Scholarships
5/2013	Jane C. Waldbaum Archaeological Field School Scholarship
5/2013	Dietrich School of Arts and Sciences Summer Undergraduate Research Award