White Matter Degeneration Pathways Associated With Tau Deposition in Alzheimer Disease

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Abstract (339/350)

Background and Objective: The dynamics of white matter (WM) changes are understudied in Alzheimer’s disease (AD). Our goal was to study the association between flortaucipir PET and WM health using NODDI and evaluate its association with cognitive performance. Specifically, we focused on NODDI’s Neurite Density Index (NDI), which aids in capturing axonal degeneration in WM and has greater specificity than single-shell diffusion MRI methods.

Method: We estimated regional flortaucipir PET SUVRs from three regions corresponding to Braak stage I, III/IV, and V/VI to capture the spatial distribution pattern of the 3R/4R tau in AD. Then, we evaluated the associations between these measurements and NDIs in 29 candidate WM tracts using Pearson correlation and multiple regression models. Results: Based on 223 participants who were amyloid positive (mean age of 78 y/o and 57.0% male, 119 cognitively unimpaired, 56 MCI, 48 dementia), the results showed that WM tracts NDI decreased with increasing regional Braak tau SUVRs. Of all the significant WM tracts, the uncinate fasciculus (r = -0.274 for Braak I, -0.311 for Braak III/IV, and -0.292 for Braak V/VI, p < 0.05) and cingulum adjoining hippocampus (r = -0.274, -0.288, -0.233, p < 0.05), both tracts anatomically connected to areas of early tau deposition, were consistently found to be within the top five distinguishing WM tracts associated with flortaucipir SUVRs. The increase in tau deposition measurable outside the medial temporal lobes in Braak III-VI was associated with a decrease in NDI in the middle and inferior temporal WM tracts. For cognitive performance, WM NDI had similar coefficients of determination (r²=31%) as regional Braak flortaucipir SUVRs (29%), and together WM NDI and regional Braak flortaucipir SUVRs explained 46% of the variance in cognitive performance. Discussion: We found spatially dependent WM degeneration associated with regional flortaucipir SUVRs in Braak stages, suggesting a spatial pattern in WM damage. NDI, a specific marker of axonal density, provides complementary information about disease staging and progression in addition to tau deposition. Measurements of WM changes are important for the mechanistic understanding of multifactorial pathways through which AD causes cognitive dysfunction.

Introduction
Cerebral white matter (WM) plays a central role in the brain's cognitive function by acting as the connectivity infrastructure of the cerebral cortex. However, WM changes in Alzheimer’s disease (AD) are not as well understood as gray matter (GM), because GM is the site of primary AD pathological changes, specifically, deposition of hyperphosphorylated tau and amyloid-beta peptide. On the other hand, evidence from structural and functional connectivity studies indicates...
that WM integrity is key to efficient cognitive functioning and suggests that understanding WM integrity changes as a function of aging and age-related pathologies such as AD can provide insights into the disease process.

Advances in diffusion MRI (dMRI), particularly those incorporating multi-shell diffusion MRI techniques, such as Neurite Orientation Dispersion and Density Imaging (NODDI), enable us to capture sub-voxel tissue-specific microstructural properties. Traditionally, diffusion tensor imaging (DTI) has been the most widely available and used dMRI model to study brain microstructure in vivo. Although DTI can be fit using single-shell diffusion MRI, it cannot handle the multiple diffusion environments that typically exist in any given voxel, creating problems for specificity and interpretability. Newer multi-shell MRI acquisitions support more appropriate modeling (such as NODDI). NODDI models the voxel contents as neurites (thin pipes, nominally axons), the spaces between them, and freely diffusing water (CSF and/or interstitial fluid). It provides three separate measures: (a) neurite density index (NDI, a proxy for axonal density), (b) orientation dispersion index (ODI), and (c) isotropic volume fraction (ISOVF, the fraction of water in the voxel that is freely diffusing). All are dimensionless values from 0 to 1, and ODI is 0 for completely parallel neurites and 1 for isotropically distributed neurites. Both DTI and advanced dMRI studies coupled with pathology studies have helped us better understand WM changes due to increased tau burden. Postmortem study evidence suggests that there is a complex interplay between the degeneration of fiber pathways and cortical tau pathology and the earlier changes to the WM microstructure in AD. Previous studies also provided in vivo evidence of the spread of tau pathology through structurally connected brain regions obtained by dMRI in cognitively normal individuals, typical AD, and pathologically staged AD. Moreover, a recent study showed a negative association between WM connectivity and tau PET measurements in the early Braak regions and suggested the synergistic effect of tau and dysconnectivity on neurocognitive performance.

The overarching hypothesis of our work was that there would be significant WM damage local to the regional tau deposition that would be a contributor to poor cognition, and NDI from dMRI can help capture this WM damage. To test this hypothesis, our primary aim was to identify and quantify the extent of WM damage by NDI throughout the brain as a function of the florataucipir PET signal in the regions featured in Braak stages. The secondary aim was to evaluate the clinical relevance of the WM changes to cognitive performance. For this work, we identified individuals along the AD continuum from the population-based sample of Mayo Clinic Study of Aging (MCSA) and clinically referred participants from Mayo Alzheimer's Disease Research Center (ADRC).
Materials and methods

Selection of Participants
This current study included participants from two datasets, i.e., MCSA and ADRC. The inclusion criteria included: usable Aβ-PET, Flortaucipir-PET, multi-shell dMRI (NODDI), and complete cognitive assessments. Due to widespread evidence that tau deposition is significant and spreads out of the medial temporal lobe due to the presence of amyloidosis, we limited this study to Aβ+ participants to generate a more characteristic spatial distribution pattern of tau deposition seen in the late-onset AD. We further limited dementia participants in ADRC to be 65+ years of age.

MCSA participants: MCSA is a prospective population-based study cohort that was designed to investigate the incidence and prevalence of mild cognitive impairment and dementia among the residents of Olmsted County, Minnesota. The Olmsted County population was enumerated using the Rochester Epidemiology Project medical records-linkage system in 2004. Participants underwent detailed clinical evaluation, including neuropsychological evaluation with consistent standards, and participated in imaging scans. All included MCSA participants had Aβ deposition based on a PiB-PET cutoff.

ADRC participants: From Mayo ADRC, we included clinically diagnosed AD dementia patients older than 65-year-old to help focus on late-onset AD (who are more likely to have typical patterns of tau deposition identified by Braak stages).

Standard protocol approvals, registrations, and patient consent
The study was reviewed and approved by the Mayo Clinic and Olmsted Medical Center institutional review boards. All participants were provided with written information, and written consent was collected from all participants/caregivers. The basic collected demographic information includes age, biological gender, and years of education.

Data availability
The data used in this study will be made available upon reasonable request following MCSA and ADRC study procedures.

Imaging

MRI acquisition and processing:
All MRI was acquired on two identical 3T Siemens Prisma scanners with 64-channel receiver coils and multi-band capability. All participants underwent the same imaging acquisition protocol. The dMRI processing included denoising, eddy current distortion and head motion correction, Gibbs ringing correction, and Rician debiasing. NODDI estimation (NDI, ODI, and ISOVF) was done using Accelerated Microstructure Imaging via Convex Optimization (AMICO). The JHU “Eve” WM atlas was warped (FA to FA) to participant native space to generate the regional NODDI measures. In this study, we only focused on NDI as the measurement for WM integrity because we were interested in axonal density changes of a function of tau. Mean NDI measures were computed for 29 WM tracts (eTable 1) and then computed the voxel-number weighted average of left and right hemispheres for each region of interest (ROI). Figure 1 illustrates the NDI distribution in our cohort, separated into three cognitive groups: cognitive unimpaired (CU), mild cognitive impairment (MCI), and dementia.
Amyloid and tau PET imaging:
Amyloid and tau deposition were measured in vivo through PiB PET and flortaucipir PET, respectively. The imaging acquisition and processing procedures were described previously. From PiB PET scans, we extracted the global amyloid standard uptake value ratio (SUVR) by averaging the median uptake values in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions and then normalizing by the median PiB PET uptake in the cerebellar crus grey matter. We used a previously established amyloid positivity cutoff of SUVR≥1.48.

To study tau deposition and its correlation to WM integrity changes, we extracted flortaucipir SUVRs at a regional level. Flortaucipir PET images were first registered on our in-house ADIR122 GM atlas (available at nitrc.org/projects/mcalt/), and regional flortaucipir SUVRs were calculated on selected regions that have been recognized as the typical regions for Braak staging. Braak staging model describes the spatial distribution pattern of tau protein with increasing disease severity: transentorhinal cortex (Stage I) and hippocampus (Stage II), inferior and medial temporal cortex along with posterior cingulum cortex (Stage III and IV), and finally, the isocortex of the frontal and parietal lobes (Stage V and VI) which are shown as part of Figure 2A and eTable 2. Specifically in this study, regions that were featured in the same Braak stage were grouped together as Braak regions. They only serve as a region map to estimate regional SUVRs, instead of staging criteria. Additionally, we did not include the region featured in Braak stage II because of contamination of the choroid plexus signal with the hippocampal tau signal.

Figure 3 illustrates flortaucipir SUVRs distribution at three Braak regions.

Cognitive Evaluation
All participants underwent a concise cognitive evaluation at the time of image acquisition and were administered the Short Test of Mental Status, which was transformed into Mini-Mental State Examination (MMSE). Short Test of Mental Status is a quick questionnaire clinical cognitive evaluation that is similar to the commonly used MMSE, and its performance has been clinically validated.

Statistical analyses
The association between WM integrity and Braak stage was estimated using two methods, i.e., Pearson correlation coefficient analysis, and multiple linear regression analysis. We performed Pearson correlation to separately compute associations between each of the 29 WM NDI measures and flortaucipir PET SUVRs measured at three Braak staging regions, as well as with MMSE. These Pearson correlation coefficients were adjusted for age, sex, years of education, and global PiB PET SUVR. A significant issue with solely relying on Pearson correlation coefficients analysis was that correlation analysis separately investigates the association between each WM NDI with the output variable (Braak flortaucipir SUVR) and WM measures in the brain are highly collinear.

We also fit a multiple linear regression model with 29 WM NDIs as the input variables and flortaucipir PET SUVRs from three Braak stage regions, or MMSE, as the output. With the multiple linear regression model, we were able to investigate the significance of each WM tract in the progression of tau deposition or cognitive impairment by comparing the weights extracted from the trained multiple linear regression model. To identify the important WM tracts to AD
staging after accounting for collinearity, we utilized the least absolute shrinkage and selection operator (LASSO) to the multiple linear regression model. We adjusted the LASSO penalty coefficients to limit to ten input variables with non-zero linear weights. We used the coefficient of determination, $r^2$, as a measure of goodness-of-fit. The coefficient of determination is the proportion of variation in the output variable explained by the input variable. Values range from 0 to 1, with higher values corresponding to a better fit to the data.

Results
Extracted Study Cohort
Based on our inclusion criteria, we assembled a total study cohort of 223 participants (180 participants were included from MCSA and 43 participants from the ADRC database), with an average age of 77.55 years (std 8.39) years, and 57.0% (127/223) were male. Among these 223 participants, 119 were cognitively unimpaired, 56 participants were diagnosed with MCI, and 48 were dementia (two with AD dementia and three with Lewy body dementia). Both MCSA and ADRC study participants undergo similar imaging protocols, clinical diagnosis criteria, and quality control procedures. A detailed cohort characteristic description can be found in Table 1, where continuous variables were represented as mean and standard deviation and count for the categorical variables.

White matter NDI negatively correlated with flortaucipir SUVRs in Braak staging regions
Based on the partial Pearson correlation analyses, only a subset of 29 WM tracts showed significant correlations ($p < 0.05$) with flortaucipir SUVR. NDI in ten WM tracts was significantly and negatively correlated with tau deposition in Braak I region. 17 WM tracts were negatively correlated with flortaucipir SUVRs in Braak III/IV and Braak V/VI regions. We focused only on these WM tracts with significant correlation coefficients for the rest of this paper. The negative correlation between WM NDI and tau deposition describes an anticipated trend -- higher tau deposition leads to a lower fraction of axons in the white matter bundle.

Specifically, the uncinate fasciculus (UNC, $r = -0.274$ for Braak I, -0.311 for Braak III/IV, and -0.292 for Braak V/VI), cingulum adjoining hippocampus (CGH, $r = -0.274$, -0.288, -0.233), and inferior fronto-occipital fasciculus (IFO, $r = -0.221$, -0.258, -0.242) ranked consistently in the top five WM tracts based on their associations with flortaucipir SUVRs in all three Braak regions. Hippocampus emerged in the top five WM tracts only for Braak I regions but not in later Braak regions. On the contrary, middle temporal WM (MTWM) and inferior temporal WM (ITWM) showed strong correlations with Braak III/IV and Braak V/VI regions, but not with Braak I regions. A detailed correlation coefficient rank of each WM NDI to flortaucipir SUVRs in three Braak regions can be found in Figure 2, B–C, where each WM tract is represented as a triangle symbol, with its correlation coefficients to all three Braak stage SUVRs illustrated by the height of each corner. To account for the effect of vascular disease on WM health, we also conducted a sensitivity analysis using systemic vascular risk conditions as an additional covariate. In this analysis, the associations between tau deposition and WM NDI were similar. The order of correlation significance of the WM tracts of interest remains the same as well, suggesting that vascular disease does not significantly alter our study findings.
Another line of evidence that supports the association between WM NDI and tau burden can be deduced based on the variance explained from the multiple linear regression models with 29 WM NDI as the input variables and Braak flortaucipir SUVRs as outcomes. These 29 WM NDIs accounted for 30.15% variance of the flortaucipir SUVR in Braak I region, 27.80% to flortaucipir SUVRs in Braak III/IV regions, and 19.92% to Braak V/VI regions, respectively. Moreover, when the input parameters were reduced from 29 to 10 most contributing and independent NDIs selected by LASSO, the regression model still explained 15.02% variance of Braak I flortaucipir SUVR, 17.67% to Braak III/IV flortaucipir SUVR, and 13.70% to Braak V/VI flortaucipir SUVR.

**White matter tracts impacted by tau contribute to lower cognitive performance**

Since tau deposition was shown to be closely correlated with cognitive impairment and we found associations between WM integrity and tau deposition, we extended our investigation to evaluate the association between WM NDI and cognitive performance. Out of 29 WM tracts, only 12 ROIs showed significant correlations (p < 0.001) with MMSE score (Table 2). There were positive correlations between WM NDI and MMSE performance as expected – a greater fraction of tissue in the axons, i.e., less axonal damage, contributed to better cognitive performance.

The ROIs that showed the highest correlation to MMSE were the middle temporal WM (MTWM, r = 0.362), inferior occipital WM (IOWM, r = 0.328), cingulum adjoining hippocampus (CGH, r = 0.323), superior fronto-occipital fasciculus (SFO, r = 0.322), and cingulum (CGC, r = 0.315). Figure 4 shows all significant correlation coefficients between WM NDI and MMSE.

**Information provided by WM NDI comparable to flortaucipir PET for the describing cognitive performance**

The effectiveness of NDI in capturing variability in cognitive performance being similar to flortaucipir PET has several implications. Therefore, we investigated the association of NDI and tau SUVR to MMSE through multiple regression models.

Regression with 29 WM NDI measures to MMSE achieved a coefficient of determination ($r^2$) of 31%, while flortaucipir SUVRs extracted from three Braak regions provided a coefficient of determination of 29%. When both Braak flortaucipir SUVRs and WM NDIs (i.e., 29 NDI and 3 Braak flortaucipir SUVR as the input variable) were combined to regress to MMSE through linear regression models, the combined model reached a coefficient of determination of 46%. This observation indicated that NDI could provide information on cognition and this information was equivalent to the information provided by tau PET when SUVR is measured in the Braak regions. Also, the information captured by NDI and tau deposition in describing cognitive performance was complementary and non-overlapping because there was an increase in the coefficient of determination when both sets of measurements were combined.
Discussion
We investigated the associations between tau burden and WM damage as measured by NDI on cognitive performance. The main conclusions were (i) there was significant spatially dependent WM degeneration associated with regional tau deposition extracted from regions featured in Braak staging model. (ii) NDI from these WM tracts may aid in the description of Braak stages as well as clinical disease stages through the association of cognitive performance. (iii) Worsening WM NDI derived from dMRI provides complementary and non-overlapping information to flortaucipir PET scans and highlights multiple pathways through which AD pathology contributes to cognitive dysfunction. (iv) WM diffusion changes using dMRI could be a useful alternative imaging approach for assessing AD-related damage and staging of the disease.

White matter integrity dynamics with tau deposition
There is widespread evidence that tau aggregation is strongly correlated with cognitive impairment\(^{31-33}\). Flortaucipir PET has been shown to map well to the gold standard of pathology\(^{34}\), capture disease progression\(^{35, 36}\), and are predictive of clinical disease progression\(^{28, 37-39}\). Tau deposition measured by Flortaucipir PET in the Braak I regions has also been shown to be associated with a lower cognition\(^ {40}\).

Recent literature suggests that WM integrity in AD may be more correlated with tau than with Aβ protein\(^ {9, 41}\). However, the dynamics of WM changes as a function of tau deposition may be complicated. Animal models and computational models suggested that tau protein propagates through structural connectivity which could either be by trans-synaptic passage of altered tau protein or by altered synaptic homeostasis without actual physical passage of a damaged tau molecule\(^ {42}\). Healthy WM tracts are the pathways through which tauopathy is propagated through anatomically connected brain regions\(^ {43}\). However higher local tau accumulation may also be detrimental to the health of WM tracts\(^ {44}\). A vivid analogy can be found between cars/highways and tau/WM connectivity – A wide and smooth highway enables faster traffic and may also attract higher traffic load; meanwhile, a high traffic load also increases the road’s deterioration rate and eventually cause the entry pathways to break down. In this work, we focused on studying the relationships between WM tract health as a function of flortaucipir SUVRS in Braak regions with the hypothesis that the spatio-temporal progression of tau in the typical AD continuum, where tau is believed to first appear in the entorhinal cortex located in the medial temporal lobe and eventually observed throughout the entire isocortex, will be reflected in progressive deterioration of WM. Understanding these relationships has important implications not only for evaluating disease progression but also for understanding the mechanisms through which AD pathology contributes to cognitive decline and dementia.

We found that decline in WM integrity measured by NDI was associated with increased tau deposition in AD, particularly in the regions implicated in histopathological staging\(^ {16, 35}\). Our findings extend the previous DTI and NODDI studies that demonstrated the association between WM degeneration and tau pathology\(^ {8, 9, 11, 15}\) and further demonstrated the progressive involvement of different WM structures as disease progresses out of the medial temporal lobe.

The most significant negative association between WM NDI and tau deposition in Braak Staging I and III/IV were found in uncinate fasciculus (UNC) and cingulum adjoining hippocampus.
(CGH). UNC is traditionally considered a part of the limbic cortex, connects the limbic structures in the medial temporal region to the frontal lobes, (i.e., a direct bridge between early and late Braak regions,) and plays an important role in episodic memory. The UNC was found to be the most consistent tract impacted by tau deposition in Braak I-VI, and this finding is supported by UNC’s anatomical proximity to regions of early tau deposition and its key role in the limbic system. Future work will benefit from investigating the causal pathways through which UNC may play a role in early stages of AD. The impact of tau in Braak I and III/IV regions was also observed on CGH WM, which is the most studied tract for tau propagation in AD and connects the medial temporal lobe to the posterior cingulate cortex. Given that posterior cingulate cortex is a major cortical hub with widespread connectivity to the entire brain, CGH WM’s key role in tau accumulation outside the medial temporal lobe has been confirmed by our findings. Hippocampal WM tract had stronger associations with Braak I flortaucipir SUVR as opposed to III-VI as expected due to anatomical proximity.

As the extent of AD pathology moves out from Braak I to Braak III-VI, WM dysconnectivity in the temporal lobes (MTWM and ITWM) showed strong correlations with flortaucipir SUVRs. Inferior temporal cortex has been implicated as a core region for tau pathology. Previous studies have shown synaptic loss and regional cortical thinning in the inferior temporal gyrus in MCI and dementia in AD. Our current work further emphasized the connectivity in inferior, middle, and to some extent, superior temporal regions as important. Consistent with our findings, a previous study demonstrated a negative correlation between tau PET tracer (18F-THK5351) and NDI in the bilateral lateral and medial temporal lobes, suggesting tau and neuroinflammation as the possible cause of reduced NDI in amyloid positive participants. In addition, in line with the Braak staging, Wen et al. assessed the relationship between GM Tau-PET signal and WM microstructure using NODDI and found most significant spatial association patterns originated from medial temporal lobe and then extended into posterior occipital and parietal regions and then to frontal lobes.

**Healthier white matter reflects better cognitive performance**
Our study provides strong evidence that subtle WM microstructural changes due to increasing tau deposition cannot be discounted and significantly contributes to cognitive impairment. The increased explained variance by both tau and WM feature indicates that the underlying mechanism for cognitive impairment in AD is multi-factorial. Most of the AD research so far has been focused on the degree of tau deposition and the resulting gray matter damage from tau. However, it is noteworthy that cognitive impairment is due to the cumulative consequence of multiple factors, such as Aβ, tau, loss of neurons and synapses, axonal degradation, etc. Therefore, identifying multiple mechanisms and measuring these to map the causal evolution of disease processes is critical.

**NODDI’s clinical usefulness for disease stage and progression assessment**
Diffusion MRI is accessible, non-invasive, and is often acquired as part of routine MRI, often a part of participant screening for clinical trials and research studies. Modern MRI scanners are increasingly equipped with multi-band capability, enabling them to capture advanced dMRI images needed for the generation of NDI from NODDI without hardware modifications. Based on the results shown in this work, NDI provides information about AD disease progression and stage and may be an invaluable clinical tool in early-stage AD.
Strengths and Limitations

The present study has some strengths and limitations. A major strength is the availability of advanced diffusion MRI, flortaucipir-PET, and cognitive scores in two well-characterized samples covering the AD continuum. Though there was limited availability of longitudinal data to investigate the temporal dynamics between NDI and tau progression, we utilized Braak staging as a template model for describing the tau deposition progression in typical AD. Another weakness is that we considered Braak staging to be a rather coarse description model for tau deposition in typical AD. The deviation from this typical progression of tau (seen in >60% of individuals) is widely recognized. Given the measurements of regional tau we considered, there are remaining variances in cognition that can be explained by WM. It is possible that better tau assessment methods (imaging acquisition-processing/inclusion of more regions) could further explain the stronger association contributed by WM. Still, the simplistic approach we took allowed us to deduce the WM involvement more clearly. For the statistical analyses, we also considered the weakness could be found in the number of statistical tests included in this study. A large number of statistical tests will likely lead to a high risk of Type I error. However, given the exploratory nature of this study and the interest in individual regions and tracts as opposed to a universal hypothesis, we did not choose to reduce that probability while increasing the probability of a Type II error through a smaller significance cut-off or multiple comparisons adjustment. Validation of the results through future studies will be required to confirm these findings. Additionally, the samples in this study were convenience samples and we did not provide power calculation. Given the number of different tests and because each set of circumstances would require a new calculation, power calculations were not feasible at the current phase.

Future work will focus on the temporal dynamics utilizing multimodal biomarkers that capture distinctive properties in various phases of the disease.

http://links.lww.com/WNL/C742
http://links.lww.com/WNL/C743

References

Table 1. Characteristics of the study cohort. Characteristics of the study cohort. Demographics, cognition, vascular markers, and AD markers from two studies were shown: Mayo Alzheimer’s Disease Research Center (ADRC) and Mayo Clinic Study of Aging (MCSA).

<table>
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<tr>
<th>Characteristics</th>
<th>MCSA (n=180)</th>
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<tbody>
<tr>
<td></td>
<td>Cognitive Unimpaired (n=119)</td>
<td>Cognitive Impaired (n=61)</td>
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<td>Demographics and Cognition</td>
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<td>MMSE</td>
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<td>AD Markers</td>
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<td>2.39 (0.59)</td>
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<tr>
<td>Tau SUVR</td>
<td>1.24 (0.13)</td>
<td>1.37 (0.23)</td>
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### Table 2: Correlation coefficients between each WM NDI ROIs and tau deposition in Braak Stages and MMSE. The full list of the ROIs and their Braak assignment can be found in eTable 1.

<table>
<thead>
<tr>
<th>WM ROIs</th>
<th>Braak I ($p&lt;0.05$)</th>
<th>Braak III/IV ($p&lt;0.05$)</th>
<th>Braak V/VI ($p&lt;0.05$)</th>
<th>MMSE ($p&lt;0.001$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncinate Fasciculus (UNC)</td>
<td>-0.27</td>
<td>-0.31</td>
<td>-0.29</td>
<td>0.31</td>
</tr>
<tr>
<td>Cingulum adjoining Hippocampus (CGH)</td>
<td>-0.27</td>
<td>-0.29</td>
<td>-0.23</td>
<td>0.32</td>
</tr>
<tr>
<td>Hippocampus (Hippo)</td>
<td>-0.23</td>
<td>-0.23</td>
<td>-0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior Fronto-Occipital Fasciculus (IFO)</td>
<td>-0.22</td>
<td>-0.26</td>
<td>-0.24</td>
<td>0.29</td>
</tr>
<tr>
<td>Inferior Temporal WM (ITWM)</td>
<td>-0.20</td>
<td>-0.28</td>
<td>-0.25</td>
<td>0.29</td>
</tr>
<tr>
<td>Middle Temporal WM (MTWM)</td>
<td>-0.19</td>
<td>-0.28</td>
<td>-0.25</td>
<td>0.36</td>
</tr>
<tr>
<td>Superior Temporal WM (STWM)</td>
<td>-0.17</td>
<td>-0.23</td>
<td>-0.23</td>
<td>0.31</td>
</tr>
<tr>
<td>Cingulum (CGC)</td>
<td>-0.15</td>
<td>-0.19</td>
<td>-0.17</td>
<td>0.32</td>
</tr>
<tr>
<td>Inferior Occipital WM (IOWM)</td>
<td>-0.14</td>
<td>-0.24</td>
<td>-0.22</td>
<td>0.33</td>
</tr>
<tr>
<td>Lateral Fronto-Orbital WM (LFOWM)</td>
<td>-0.14</td>
<td>-0.14</td>
<td>-0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Angular WM (AWM)</td>
<td>NS</td>
<td>-0.14</td>
<td>-0.15</td>
<td>NS</td>
</tr>
<tr>
<td>External Capsule (EC)</td>
<td>NS</td>
<td>-0.16</td>
<td>-0.18</td>
<td>0.26</td>
</tr>
<tr>
<td>Fornix (FX)</td>
<td>NS</td>
<td>-0.15</td>
<td>-0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Rectus WM (RWM)</td>
<td>NS</td>
<td>-0.14</td>
<td>-0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Splenium of Corpus Callosum (SCC)</td>
<td>NS</td>
<td>-0.17</td>
<td>-0.16</td>
<td>0.30</td>
</tr>
<tr>
<td>Superior Fronto-Occipital Fasciculus (SFO)</td>
<td>NS</td>
<td>-0.14</td>
<td>-0.17</td>
<td>0.32</td>
</tr>
<tr>
<td>Supramarginal WM (SMWM)</td>
<td>NS</td>
<td>-0.15</td>
<td>-0.16</td>
<td>0.27</td>
</tr>
</tbody>
</table>

NS=Non-significant
**Figure 1: NDI at each significant ROIs.** These ROIs were the WM tracts that showed a significant correlation with flortaucipir SUVrs. Note that the NDI difference is more distinctive between CU and the other two groups, indicating NDI can be an early detectable change associated with AD-caused cognitive impairment. The full list of the ROIs and their abbreviation definition can be found in eTable 1.
Figure 2: Braak Stage regions and corresponding significant WM tracts. (a) Gray matter regions that have been assigned to each Braak stage. In typical AD, tau protein accumulation has been shown to start from the entorhinal cortex located in the medial temporal lobe and eventually spread to the whole isocortical area; (b) Top-3 WM tracts to each corresponding Braak stage region, ranked by the correlation coefficient; (c) Summary of WM tracts NDI correlation to three Braak regions, ranked by their total correlation coefficients to flortaucipir PET SUVRs from all three Braak regions. (Interpretation Example) Each WM tract was represented by one triangular radar symbol. Tract’s correlation coefficient to Braak I, Braak III/IV, and Braak V/VI flortaucipir SUVR was represented by the height of each corner. The exemplar triangular figure to the right bottom corner demonstrates a WM track with correlation coefficients of -0.1, -0.2, and -0.3 to Braak I, III/IV, and V/VI flortaucipir SUVR respectively. The full list of the ROIs and their abbreviation definition can be found in eTable 1.
Figure 3: Flortaucipir SUVs at three Braak regions. The group-level difference in between the Dementia group and the other two groups are distinctive in Braak III/IV, and V/VI regions. However, the difference between CU and MCI groups is less in Braak III-VI. The specific regions included in each Braak Region can be found in eTable 2.

Figure 4: Correlation Coefficient between WM NDI and MMSE. Gray area represents 95% confidence interval. The threshold for statistical significance was set at \( p\text{-value}=0.001 \). The full list of the ROIs and their abbreviation definition can be found in eTable 1.
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