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Olfactory identification deficit predicts white matter tract impairment in Alzheimer's disease

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Abstract

Olfactory identification deficit (OID) has been associated with both aging and Alzheimer's disease (AD). In the context of an amnesic disorders, OID predicts conversion to AD. Neuroanatomical correlates could increase specificity and sensitivity and elucidate the mechanistic differences between OID in AD and aging. Cross-sectional analysis of white matter microstructural changes was performed using diffusion tensor imaging (DTI) and tract-based-spatial-statistics in amnesic mild cognitive impairment (aMCI), AD and normal controls (NC) in 66 subjects (26 AD, 15 aMCI, 25 NC). DTI 3-Tesla MRI scans were analyzed and subject level means for fractional

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Conflicts of Interest

MR Woodward has no conflicts to disclose.

N Bergsland has no conflicts to disclose.

J Hagemeier has no conflicts to disclose.

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anisotropy (FA), mean diffusivity (MD), radial and axial diffusivity (λ_1D and $\lambda_{2,3}D$) were calculated. Linear regression models were applied using DTI markers as predictor and OID as outcome. OID was associated with increased λ_1D in aMCI and increased MD, λ_1D and $\lambda_{2,3}D$ in AD. Voxel-wise analyses revealed widespread differences in all markers in AD. There were significant differences in λ_1D in aMCI, particularly in the olfactory tract. OID is correlated with microstructural white matter changes as early as in aMCI. This study may help elucidate the biological basis for olfactory impairment in Alzheimer's disease. Neuroanatomical correlates could help distinguish OID associated with AD and that associated with aging.

Keywords

Olfactory; MRI; diffusion tensor imaging; Alzheimer's disease; Amnesic mild cognitive impairment; White Matter

1. Introduction

Alzheimer's disease (AD) is the most common etiology for dementia and leads to progressive cognitive decline. Due to its high prevalence, accessible and feasible screening and prognostic tools are needed.

Impairment in identification of olfactory stimuli is a common clinical phenomenon in AD, and other neurodegenerative diseases such as Parkinson's disease, as well as in aging. (Berendse & Ponsen, 2006) Up to 85% of patients with early-stage AD exhibit olfactory dysfunction. (Peters et al., 2003) Furthermore, there are congruent pathological changes associated with olfactory identification deficit (OID), including neuronal loss and deposition of amyloid plaques and neurofibrillary tangles in the olfactory bulb and anterior olfactory nucleus. (Ohm & Braak, 1987) Prospective studies have shown that OID infers a risk for development of cognitive decline (Graves et al., 1999; Schubert et al., 2008), and predicts conversion from aMCI to AD. (Devanand et al., 2015; Devanand et al., 2000; Peters et al., 2003)

Diffusion tensor imaging (DTI) exploits the random microscopic movement of water molecules to measure microstructural tissue characteristics *in vivo*, and is sensitive to changes in white matter tract integrity. DTI calculation produces measures of fractional anisotropy (FA), mean diffusivity (MD), and radial and axial diffusivity ($\lambda_{2,3}D$ and λ_1D , respectively). While white matter structural changes have not been studied in the context of the olfactory phenotype in aMCI or AD, the association between olfactory tract changes with AD-specific regional cerebral hypometabolism by FDG PET in aMCI was demonstrated. (Cross et al., 2013) When all subjects, both NCs and aMCI, were considered in the analysis, white matter integrity correlated with the metabolic activity of olfactory processing structures. (Cross et al., 2013) In the aMCI group specific correlation with medial temporal lobe metabolic activity was found, suggesting mesial temporal involvement in AD related olfactory deficit. (Cross et al., 2013) Interestingly, longitudinal observation of regional white matter ultrastructure demonstrated exclusive changes in the hippocampal cingulum in AD as compared to normal aging. (Mayo et al., 2017) These data suggest that the mechanism of OID in aging and in AD and AD-associated aMCI may be different. This

cross-sectional study was designed to assess microstructural changes using DTI in subjects with aMCI, AD and NCs and to compare and contrast them in the context of the olfactory phenotype. We hypothesize that white matter impairment is present within the olfactory tract of participants with amnesic disease (aMCI and AD) and that these white matter impairments are correlated with worse performance on the UPSIT.

2. Methods

2.1 Study Participants

This was an MRI substudy of a larger, previously reported study. (Woodward et al., 2017) 73 subjects underwent 3 Tesla MRI at the MRI Center at the University at Buffalo. During processing, seven subjects were excluded (4 AD, 1 aMCI, 2 NC) due to excessive motion or other scan-related artifacts, resulting in the inclusion of 66 subjects (26 AD, 15 aMCI, 25 control) in the final analyses.

The diagnosis of Amnesic Mild Cognitive Impairment (aMCI) was based on the Petersen criteria. (Petersen et al., 1999) Probable AD was diagnosed based on NINCDS-ADRDA criteria. (Blacker et al., 1994) Final diagnoses were assigned after consensus review. Subjects whom fulfilled McKeith criteria for possible or probable Lewy-body dementia were excluded. (McKeith et al., 2005) The methodology of the Texas Alzheimer Research and Care Consortium project has been described. (O'Bryant et al., 2008) Exclusion criteria included a Hachinski score >4 and clinical or imaging evidence of a stroke, upper respiratory infection or active allergies. The control group consisted of non-demented subjects; inclusion criteria were the following: age over 65 years, normal performance on activities of daily living, and CDR global score 0 (by surrogate historian). All subjects underwent neuropsychological testing which included MMSE, Clinical Dementia Rating, Digit Span, Trail-Making Test Part A and B, Wechsler Memory Scale (WMS3 or -R), Logic Memory I story A and WMS3 or R Logical Memory II story A, Boston Naming Test, FAS Verbal Fluency, North American Adult Reading Test, WMS-Visual Reproduction I and II, Geriatric Depression Scale, Lawton-Brody Activities of Daily Living, Physicians Self Maintenance Scale and Instrumental Activities of Daily Living. (Benton, 1994; Folstein, Folstein, & McHugh, 1975; Kaplan, 1983; Lawton & Brody, 1969; Morris, 1993; Reitan, 1955; Spreen, 1998; Wechsler, 1997; Yesavage et al., 1982) NC subjects were excluded if any NPT measure had a Z-score <-1.5. The University of Buffalo IRB approved the study and informed consent was obtained from each research participant.

2.2 University of Pennsylvania Smell Identification Test

Odor identification was measured by the University of Pennsylvania Smell Identification Test (UPSIT) at the time of enrollment, within three months of neuropsychological testing. (Doty et al, 1984) The UPSIT is a 40 item scratch and sniff smell identification test with forced selection multiple choice format (Sensonics, Inc., Haddon Heights, NJ).

2.3 Magnetic Resonance Imaging

All subjects were scanned with diffusion-weighted imaging (DWI) on a 3T GE Signa MR imaging system (GE Healthcare, Milwaukee, Wisconsin), with a maximum slew rate of 150

T/m/s and maximum gradient amplitude in each orthogonal plane of 40 mT/m (zoom mode). All scans were acquired using an 8-channel head and neck coil, and were prescribed parallel to the subcallosal line in an axial-oblique orientation. DWI sequences parameters were: TR 7000 ms, TE 92 ms, $b=900 \text{ s/mm}^2$, 25 diffusion directions, 1 $b=0 \text{ s/mm}^2$, voxel size $2.0 \text{ mm} \times 2.0 \text{ mm} \times 4.5 \text{ mm}$, 2 repetitions.

Data were processed using FMRIB's Software Library (FSL). (Jenkinson et al, 2012) First, raw DTI images were corrected for motion and eddy current distortion. Then, to eliminate all nonbrain tissue, we extracted and deskulled the original $b=0$ images (with no diffusion-weighting) using the Brain Extraction Tool (BET). Brain masks were manually edited to ensure inclusion of the ventral surface of the forebrain (containing the olfactory tract). Next, FA, MD, radial diffusivity ($\lambda_{2,3}D$), and axial diffusivity (λ_1D) maps were estimated via a diffusion tensor model calculated using FSL's FDT tool. Finally, voxelwise inter-group statistical analysis of the DTI data was performed by using TBSS. Briefly, TBSS performs voxel-wise comparison while simultaneously adjusting for individual tract location variability by projecting individual scans onto an FA-derived 3D skeleton. (Smith et al., 2006)

In addition, because we *a priori* hypothesized changes in the olfactory tract, we manually created an olfactory tract mask in the projected DTI skeleton space. Using the TBSS projections, we then calculated and evaluated averaged metrics along this tract between patients and diagnostic groups.

2.4 Statistical Analysis

Demographical characteristics, including age, MMSE and years of education were analyzed using one way ANOVA with a Fisher LSD post hoc to examine between group differences. Difference in age of onset between aMCI and AD patients were assessed using a Student's t -test. A Chi-square test was used to examine participant sex while a Fisher exact test was used for ApoE4 allele frequency.

Subject-level means for FA, MD, $\lambda_{2,3}D$ and λ_1D in the whole WM skeleton and within the bilateral olfactory tract were entered into a one way ANCOVA to compare diagnostic groups, including age, ApoE4 alleles and sex as covariates. Additionally, a Pearson correlation coefficient test was run to examine correlation between UPSIT performance and both whole brain and OT DTI findings.

The relationships between these same measures (for both whole WM skeleton and bilateral olfactory tract) and performance on the UPSIT, were also assessed using a general linear model with age and sex as covariates. Voxel-wise non-parametric permutation tests (using FSL's randomise tool) were used on TBSS-derived maps to produce spatially-specific statistical maps of group differences in DTI measures, as well as to produce maps of the relationships between UPSIT performance and DTI markers. To adjust for multiple spatial comparisons, family-wise correction including threshold-free cluster enhancement was employed, and results were considered significant at a corrected p value of 0.05. (Smith & Nichols, 2009)

3. Results

Demographic characteristics are presented in Table 1. APOE frequencies in each disease category were similar to previous reports and consistent with the diagnostic group expectations. Age and sex were not equally distributed between control and disease groups, the mean age for the NC group was significantly younger than that of the aMCI and AD groups. Thus both age and sex were included in the statistical models as covariates in whole brain and olfactory tract ROI means, as well as TBSS.

Whole WM skeleton subject-level means, presented in Table 2, were significantly different between controls and AD patients for FA, MD, $\lambda_{2,3}D$ and λ_1D . There were significant differences in MD, $\lambda_{2,3}D$ and λ_1D between controls and aMCI; however, no differences were found between aMCI and AD. When examining differences in subject-level means within the olfactory tract ROI there were significantly decreased values in the AD group vs. NCs for MD, $\lambda_{2,3}D$ and λ_1D ($p=0.019$, $p=0.017$ and $p=0.021$, respectively) (Table 3).

Correlations between UPSIT performance and DTI markers are presented in Table 4. For NC, there were no statistically significant associations between whole WM skeleton FA, MD, $\lambda_{2,3}D$ or λ_1D and UPSIT performance. There was, however, a trend toward significance in λ_1D ($p=0.060$). Within the olfactory tract ROI, there were also no significant relationships between DTI markers and UPSIT performance in NC. For the aMCI group, there was a significant negative association between performance on UPSIT and λ_1D within whole WM skeleton ($p=0.035$) as well as a non-significant trend within the olfactory tract ROI ($p=0.061$). Among participants with AD, there were significant negative associations between performance on UPSIT and whole WM skeleton MD, $\lambda_{2,3}D$ and λ_1D ($p<0.001$ for each). There were no significant associations within the olfactory tract ROI.

TBSS voxel-wise analysis between diagnostic groups showed significantly increased MD, $\lambda_{2,3}D$ and λ_1D as well as decreased FA in AD vs. NC in a diffuse pattern throughout the brain. Additionally, there was diffusely increased MD and $\lambda_{2,3}D$ in the aMCI group vs NC. Voxel-wise analyses of associations between performance on UPSIT and DTI markers demonstrated no areas of significant association in NCs. In the aMCI group, there were areas of significant association (corrected $p<0.05$) between λ_1D and UPSIT performance (Figure 1). The effect was primarily localized to the right olfactory tract, best demonstrated in Panel A of Figure 1. In contrast, there were diffuse white matter tracts in which there was a significant association between DTI markers and UPSIT performance in the AD group. Associations were found for FA, MD, $\lambda_{2,3}D$ and λ_1D . In AD, alterations were detected in the mesial temporal structures (right more than left) and in the posterior subcortex as shown in Panel B of Figure 1.

4. Discussion

Significant differences in whole brain white matter tract microstructure were identified between NCs, aMCI and AD (Table 2). These findings were expected and are consistent with the existing literature on DTI in amnesic disorders. (Clerx et al., 2012) Interestingly, it has been suggested that λ_1D and MD are most sensitive to early changes seen in AD.

(Acosta-Cabronero et al., 2012) In our cohort, there were significant differences in λ_1D , MD and $\lambda_{2,3}D$ between NCs and aMCI while FA was only significant between controls and AD. There were no significant differences between aMCI and AD in any of the DTI markers, likely due to sample size. Furthermore, our findings suggest diffuse neuronal loss in AD with Wallerian degeneration as the likely mechanism, similar to reports by Clerx and Acosta-Cabronero.

OID was associated with WM tract impairment as evidenced by significant correlations between whole brain subject level means for DTI markers and UPSIT performance, particularly in aMCI and AD. In aMCI, whole WM skeleton λ_1D correlated with UPSIT ($p=0.035$) suggesting early axonal involvement. Increases in λ_1D are thought to reflect axonal loss along a tract. While this interpretation may be confounded in tracts with multiple crossing fibers, it is noteworthy that the OT has a relative paucity of crossing fibers. (Wheeler-Kingshott & Cercignani, 2009) Future analyses might utilize diffusion spectrum imaging to better address this problem. In AD, OID was associated with λ_1D , MD and $\lambda_{2,3}D$. The OID association pattern is similar to the disease association pattern of parameters: in aMCI λ_1D correlates with disease and with UPSIT, and in AD λ_1D , MD and $\lambda_{2,3}D$ shows disease and OID association. This suggests that the axonal loss progresses over the disease course. Olfactory tract means showed a trend in λ_1D in aMCI ($p=0.061$) when the olfactory phenotype was not considered.

In the context of the olfactory phenotype, OID association with white matter tract impairment showed a regional difference in aMCI compared to the aged NCs. Olfactory tract microstructural changes were associated with OT in aMCI and there was no similar association in NCs. This finding suggests that there could be mechanistic differences between OID associated with an amnestic disorder in contrast to aging. The CNS involvement in aMCI suggests a central mechanism, likely involving a Wallerian degeneration of olfactory tract neurons, while the lack of it in normal aging may be more indicative of a peripheral mechanism for OID. The OID olfactory tract association in AD did not reach statistical significance, likely due to decreased robustness of the statistics due to restricted UPSIT distribution.

In the neurodegenerative group (AD and aMCI), although this was a cross sectional study, we can infer that the OT is affected early in the aMCI stage, followed by aMCI expansion of disease-related change into the mesial temporal and posterior structures in the AD stage. This is consistent with previous reports, where microstructural changes were studied in the context of brain regional hypometabolism by FDG-PET, and in which metabolic and WM tract changes were shown to expand to the temporal lobe and posteriorly in an AD pattern (Cross et al., 2013) A longitudinal study using the ADNI data reported change over time in the hippocampal cingulum in patient with AD (Mayo et al., 2017) Early OT involvement was reported in Parkinson disease associated OID as well. (Rolheiser et al., 2011) Rolheiser, et al report decreased FA within an olfactory ROI similar to the region studied in our analysis. While the exact mechanism for OID in AD and Parkinson's disease are not yet known, it is particularly interesting that early changes occur within the olfactory tract.

The right temporal involvement in the TBSS analysis is consistent with the voxel-wise volumetric analysis that was reported previously. (Alves et al., 2015) Both the voxel-wise volumetric and the TBSS-based diffusion analyses revealed early right temporal involvement. The right temporal lobe is implicated in olfactory memory. While olfactory memory was not directly measured, the correlation between UPSIT and olfactory memory was reported to be strong, at $r=0.67$. (Toumbier & Doty, 2007) With respect to amnesic disorder, OID predicts conversion from aMCI to AD with a ROC-based area under the curve (AUC) of 0.62. The imaging data, both volumetric and diffusion-based, suggest that OID measures early right mesialtemporal involvement. As the majority of patients present with verbal memory impairment initially, OID reveals bilateral involvement, and points to bilateral pathology, thus increasing the likelihood of a neurodegenerative process.

There are several limitations of this cross-sectional exploratory study that need to be considered. This study had a relatively modest sample size (the ADNI dataset, 23 AD, 88 aMCI and 44 NC were presented in the analysis). (Nir et al., 2013) This may have prevented us from detecting associations that are biologically relevant. Larger, well-powered studies are needed and our data could be the foundation for power calculations. Additionally, as a retrospective sub-study, the imaging protocol was not designed with the specific intention of examining diffusion characteristics within the olfactory tract. Ventral regions of the brain overlying the sinuses present particular challenges for EPI neuroimaging techniques like diffusion imaging, due to increased susceptibility. As previously noted, the control group was significantly younger than the aMCI and AD groups. Advanced age is associated with progressive neuronal loss as well as changes in both MD and FA. (Bendlin et al., 2010) The demographic differences in the groups may have confounded the analysis; however correction for sex and age differences were accounted for in the statistical model as covariates. Additionally, it is important to note that within group analyses, such as correlation with UPSIT performance and TBSS (Table 4 and Figure 1 respectively) are not affected.

Future studies would benefit from a larger sample size, as well as balancing such covariates as age, sex and vascular burden. Furthermore, a study with a more robust sample size and refined, high-resolution imaging could allow for further analyses utilizing masks of the olfactory tract as well as analyzing DTI markers while controlling for global FA values. It may also be interesting to correlate our findings with neuronal markers of amyloid burden.

The clinical phenomenon of olfactory impairment in amnesic disorders has been well established and an association between olfactory impairment and white matter tract impairment has been previously reported. (Segura et al., 2013) However, this is the first study to establish a direct association between olfactory impairment and white matter tract impairment in aMCI and AD. Our findings, particularly within the aMCI population, serve to further validate the utility of a smell test as a risk stratification tool for amnesic disorders by elucidating a potential neuroanatomical mechanism. It is notable that in the AD group, there was widespread impairment in white matter integrity and a strong, diffuse association between olfactory impairment and white matter damage. The participants in the AD cohort were relatively early in disease progression with a mean MMSE of 22.96. This suggests that white matter tract impairment is an important feature of Alzheimer's pathology. Based on

the results of this analysis, further studies examining olfactory identification deficits and white matter tract impairment in a larger population and higher resolution imaging focusing on the olfactory pathway and AD related cortical and subcortical areas is warranted. Several questions have not been addressed regarding OID in aging and in neurodegenerative diseases. Although cognitive testing has been studied longitudinally, (Gross et al., 2014; Rebok, Brandt, & Folstein, 1990) olfactory deficit has not been in the context of memory deficit. (Devanand et al., 2015; Devanand et al., 2000; Tabert et al., 2005; Woodward et al., 2017) Both cognitive and olfactory abilities are highly variable between (Rebok et al., 1990) individuals. Due to the high variance a cross-sectional design cannot assess the relationship between OID and memory loss unambiguously. OID may not equally involve all smells, and age and disease specific vulnerability of specific smells have not been studied. Studies in AD mainly used scratch and sniff tests where the odorants are natural compounds, frequently composites of multiple molecules and thus interactions with several OR receptors are observed. (Devanand et al., 2015; Devanand et al., 2000; Ohm & Braak, 1987; Peters et al., 2003; Tabert et al., 2005). Due to the combinatorial model of olfaction, this approach results in instability of the discriminatory value of the specific smells. (Devanand et al., 2015; Devanand et al., 2000; Ohm & Braak, 1987; Peters et al., 2003; Secundo, Snitz, & Sobel, 2014; Tabert et al., 2005) Monomolecular OR activation will likely reduce some of the noise. More in depth olfactory phenotyping with multimodal imaging and longitudinal observation may markedly improve olfactory deficit as a screening or risk stratification tool.

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Highlights

- Odor identification and 3 Tesla MRI diffusion tensor imaging with whole brain and a region of interest including the olfactory tract were obtained for controls, MCI and AD
- Whole brain white matter microstructure was significantly impaired in aMCI and AD compared with controls and in the olfactory tract of AD vs. controls.
- TBSS analysis showed impairment in olfactory identification was associated with increased axial diffusion in MCI, particularly in the olfactory tract
- TBSS analysis showed impairment in olfactory identification was associated with increased axial, radial and mean diffusion, as well as decreased fractional anisotropy in AD in a widespread pattern

Figure 1.

Tract Based Spatial Statistics demonstrates that white matter tract impairment (lower fractional anisotropy (FA), elevated mean diffusivity (MD), axial diffusivity ($\lambda_1 D$) and radial diffusivity ($\lambda_{2,3} D$)) is correlated with poor performance on the UPSIT. Multiple comparisons were corrected using non-parametric permutation tests with threshold-free cluster enhancement. Voxels reaching statistical significance are red ($p < 0.05$). Early changes are seen particularly in the olfactory tract in aMCI and appear to spread posteriorly to the temporal and occipital lobes in AD.

Table 1

Demographic information for participants (25 NC, 15 aMCI, 26 AD).

	NC (<i>n</i> =25)	aMCI (<i>n</i> =15)	AD (<i>n</i> =26)
	Mean (SD)	Mean (SD)	Mean (SD)
Age	67.36 (0.93)^{a,b}	73.53 (2.84)	77.63 (1.88)
Age at Onset	N/A	70.64 (2.84)	72.56 (1.88)
MMSE	28.64 (1.78)^b	26.27 (2.05)^c	22.96 (4.50)
	<i>n</i> female (%)	<i>n</i> female (%)	<i>n</i> female (%)
Sex	19 (76.0) ^a	6 (40.0)	15 (57.7)
ApoE4 Alleles	<i>n</i> (%)	<i>n</i> (%)[†]	<i>n</i> (%)[‡]
0	17 (68.0) ^b	5 (33.3)	4 (15.4)
1	8 (32.0) ^b	6 (40.0)	12 (46.2)
2	0 (0.0) ^b	0 (0.0)	4 (15.4)
	Mean (SD)	Mean (SD)	Mean (SD)
40-item UPSIT	30.88 (7.19)^{a,b}	23.93 (9.15)	21.38 (7.09)

Significant differences in age, Mini Mental Status Examination (MMSE) and University of Pennsylvania Smell Identification Test (UPSIT) were calculated using a one-way ANOVA with a post hoc Fisher LSD test. Significant difference in Age at Onset was calculated using a one-sided Student's t-test. Sex was calculated using a Chi-square test. ApoE4 alleles were calculated using a Fisher exact test.

^a = significant difference between NC and aMCI;

^b = significant difference between NC and AD;

^c = significant difference between aMCI and AD;

[†] = ApoE4 status missing for 4 aMCI subjects;

[‡] = ApoE4 status missing for 6 AD subjects

Table 2

Whole white matter TBSS skeleton means for diffusion markers of white matter tract integrity by diagnostic group were calculated using a one-way ANCOVA with age and sex as covariates.

	FA	MD (10^{-3} mm ² /sec)	λ_1 D (10^{-3} mm ² /sec)	$\lambda_{2,3}$ D (10^{-3} mm ² /sec)
NC	0.406 $\pm$ 0.018	8.59 $\pm$ 0.30	12.38 $\pm$ 0.34	7.00 $\pm$ 0.30
aMCI	0.398 $\pm$ 0.025	9.27 $\pm$ 0.66	13.17 $\pm$ 0.71	7.33 $\pm$ 0.64
AD	0.385 $\pm$ 0.030	9.56 $\pm$ 0.61	13.36 $\pm$ 0.60	7.60 $\pm$ 0.63
	NC vs AD: $p=0.010$	NC vs aMCI: $p=0.002$	NC vs aMCI: $p=0.001$	NC vs aMCI: $p=0.004$
		NC vs AD: $p<0.0001$	NC vs AD: $p<0.0001$	NC vs AD: $p<0.0001$

FA = fractional anisotropy, MD = mean diffusivity, λ_1 D = axial diffusivity and $\lambda_{2,3}$ D = radial diffusivity

Table 3
Olfactory Tract ROI means for FA, MD, λ_1 D and $\lambda_{2,3}$ D by diagnostic group

Olfactory tract ROI means for markers of white matter tract integrity by diagnostic group were calculated using a one-way ANCOVA with age, sex and ApoE4 alleles as covariates.

	FA	MD (10^{-3} mm ² /sec)	λ_1 D (10^{-3} mm ² /sec)	$\lambda_{2,3}$ D (10^{-3} mm ² /sec)
NC	0.282 ± 0.027	1.85 ± 0.24	2.33 ± 0.26	1.61 ± 0.23
aMCI	0.272 ± 0.023	1.97 ± 0.27	2.45 ± 0.30	1.73 ± 0.26
AD	0.268 ± 0.032	2.04 ± 0.25	2.54 ± 0.27	1.79 ± 0.24
		NC vs AD: $p=0.035$	NC vs AD: $p=0.039$	NC vs AD: $p=0.031$

Table 4
Correlates between UPSIT and FA, MD, λ_1 D and $\lambda_{2,3}$ D

Whole white matter TBSS skeleton and olfactory tract means for markers of white matter tract integrity and their association with UPSIT scores were calculated within each diagnostic group using Pearson correlation coefficient test.

Whole white matter skeleton means				
	FA	MD	$\lambda_{2,3}$D	λ_1D
NC	0.001 ($p=0.995$)	-0.191 ($p=0.360$)	-0.152 ($p=0.467$)	-0.206 ($p=0.323$)
aMCI	0.095 ($p=0.736$)	-0.485 ($p=0.067$)	-0.485 ($p=0.032$) *	-0.433 ($p=0.107$)
AD	0.379 ($p=0.056$)	-0.598 ($p=0.001$) **	-0.622 ($p=0.001$) **	-0.571 ($p=0.002$) **
Olfactory tract means				
	FA	MD	$\lambda_{2,3}$D	λ_1D
NC	0.148 ($p=0.481$)	-0.125 ($p=0.553$)	-0.082 ($p=0.698$)	-0.149 ($p=0.478$)
aMCI	0.283 ($p=0.307$)	-0.455 ($p=0.089$)	-0.455 ($p=0.066$)	-0.434 ($p=0.106$)
AD	0.094 ($p=0.649$)	-0.033 ($p=0.872$)	-0.012 ($p=0.954$)	-0.045 ($p=0.825$)

*
 (= p 0.05,

**
 = p 0.005)