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RESEARCH ARTICLE

Altered fornix integrity is associated with sleep apnea-related hypoxemia in mild cognitive impairment

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Abstract

INTRODUCTION: The limbic system is critical for memory function and degenerates early in the Alzheimer's disease continuum. Whether obstructive sleep apnea (OSA) is associated with alterations in the limbic white matter tracts remains understudied.

METHODS: Polysomnography, neurocognitive assessment, and brain magnetic resonance imaging (MRI) were performed in 126 individuals aged 55–86 years, including 70 cognitively unimpaired participants and 56 participants with mild cognitive impairment (MCI). OSA measures of interest were the apnea-hypopnea index and composite variables of sleep fragmentation and hypoxemia. Microstructural properties of the cingulum, fornix, and uncinate fasciculus were estimated using free water-corrected diffusion tensor imaging.

RESULTS: Higher levels of OSA-related hypoxemia were associated with higher left fornix diffusivities only in participants with MCI. Microstructure of the other white

matter tracts was not associated with OSA measures. Higher left fornix diffusivities correlated with poorer episodic verbal memory.

DISCUSSION: OSA may contribute to fornix damage and memory dysfunction in MCI.

KEYWORDS
Alzheimer's disease, dementia, fornix, free water-diffusion tensor imaging, hypoxia, limbic system, memory, mild cognitive impairment, sleep apnea, sleep, white matter

Highlights

- Sleep apnea-related hypoxemia was associated with altered fornix integrity in MCI.
- Altered fornix integrity correlated with poorer memory function.
- Sleep apnea may contribute to fornix damage and memory dysfunction in MCI.

1 | BACKGROUND

Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders in older age.[1] The estimated prevalence of its moderate to severe form (defined by an Apnea-Hypopnea Index [AHI] ≥15/h) is about 30% among individuals older than 60 years.[1] OSA is characterized by repetitive narrowing of the upper airways during sleep, leading to sleep fragmentation and hypoxemia.[1] Epidemiological studies suggest that OSA may be independently associated with the risk of developing Alzheimer's disease (AD).[2–6] In addition, there is evidence for a correlation between OSA severity and AD biomarkers measured in the cerebrospinal fluid[7,8] and by nuclear imaging.[9–12]

However, OSA is not yet recognized as one of the modifiable risk factors for dementia,[13] and the mechanisms by which OSA may increase the risk of AD remain largely unknown. One potential mechanism could be the detrimental effect of OSA-related hypoxemia, which could promote tissue alterations in AD-related brain regions. OSA-related hypoxemia has been associated with gray matter changes in the medial temporal lobe, including volume loss[14–16] and edema.[17] Yet, no study has extended these findings to assess the link between OSA and microstructural integrity of limbic white matter tracts that represent the main afferent and efferent pathways of the medial temporal lobe.

The limbic tracts are of clinical importance because of their pivotal role in memory function[18] and because they are among the first white matter tracts to degenerate in the AD continuum.[19] Microstructural changes in the limbic tracts,[20–22] particularly in the fornix,[21,22] have already been detected among individuals with mild cognitive impairment (MCI). Moreover, altered microstructure of limbic tracts has been correlated with poorer memory function[22,23] and progression to AD.[21,24–26]

Diffusion magnetic resonance imaging (MRI) allows the microstructure of white matter to be studied in vivo by measuring water diffusion.[27] However, conventional diffusion tensor imaging (DTI) measures have limitations, such as partial volume effects, which may be particularly important in the AD continuum where atrophy leads to *ex vacuo* increases of cerebrospinal fluid and free water (FW) in brain tissue.[28,29] To overcome this problem, the FW index obtained from FW-DTI indicates the fraction of signal explained by freely diffusing water in the extracellular space and is considered to be related to inflammation, atrophy, and extracellular edema.[28] Importantly, FW correction to conventional DTI measures of fractional anisotropy and diffusivity improves tissue specificity and appears to capture subtle alterations across the AD continuum not always detectable with the conventional DTI approach.[30]

The relationship between OSA and white matter microstructure is complex and only partially understood. OSA has been associated with higher diffusivity and lower fractional anisotropy, suggesting chronic white matter damage.[31–33] However, OSA has also been associated with lower diffusivity with or without concomitant variations in fractional anisotropy, a pattern that suggests acute white matter alterations potentially due to intracellular edema and/or reactive gliosis.[34–36] Gaps remain in the literature. Few studies investigating the association between OSA and white matter microstructure have included older adults at risk for dementia,[34,37,38] and none has explored the moderating role of MCI on this association. Although some studies have used a tract-specific approach,[32,33,39] none has focused on the limbic white matter tracts. Finally, studies have not yet analyzed FW-DTI measures in OSA.

This study aimed at characterizing the relationship between OSA and FW-DTI measures of the main limbic white matter tracts – namely the fornix, cingulum, and uncinate fasciculus – in a sample of cognitively unimpaired (CU) participants and participants with MCI aged 55 years and older. We also examined the moderating role of cognitive status (CU vs. MCI) on this relationship. Based on previous neuroimaging studies on OSA[14–17] and the AD continnum,[20–22] we hypothesized that higher levels of OSA-related hypoxemia would be associated with altered integrity of the limbic tracts, especially in individuals with MCI.

2 | METHODS

2.1 | Participants

We included participants aged 55–86 years old, who were recruited between 2012 and 2020 for studies on OSA and MCI conducted in Montreal and Sherbrooke (Canada), as previously described.[17,40] All potential participants were first contacted by phone to assess their eligibility for the study. Exclusion criteria were the inability to communicate in French or English, less than 7 years of education, treatment for OSA, sleep disorders other than untreated OSA (e.g., central sleep apnea, chronic insomnia disorder, or rapid eye movement sleep behavior disorder), neurological diseases (e.g., epilepsy or Parkinson's disease), psychiatric diseases (e.g., major depressive disorder or anxiety disorder), cerebrovascular or pulmonary diseases (e.g., history of stroke or chronic obstructive pulmonary disease), body mass index (BMI) >40 kg/m^2, uncontrolled diabetes or hypertension, drug or alcohol abuse, contraindication for MRI, and use of psychotropic medication. Eligible participants proceeded to an in-laboratory visit, which included a polysomnography (PSG), a neurocognitive assessment, and questionnaires. Finally, participants were invited to return for a brain MRI session. A total of 134 participants completed the entire protocol. We excluded participants with insufficient pulse oximeter quality during PSG ($n = 3$), features compatible with rapid eye movement sleep behavior disorder during PSG ($n = 2$), structural lesions on MRI ($n = 1$), failure in MRI acquisition/processing ($n = 1$), and recent diagnosis of pulmonary disease ($n = 1$). The final sample consisted of 126 participants. The average time between PSG and MRI was 2.7 ± 2.4 months.

2.2 | Sleep assessment

Participants were evaluated with an all-night in-laboratory polysomnography (PSG) including a 17- or 19-channel electroencephalogram (EEG) montage, two electrooculograms, an electrocardiogram, and three surface electromyography (one submental and two for right and left anterior tibialis muscles). An oronasal canula, an oronasal thermistor, and a thoraco-abdominal strain gauge were used in addition to a transcutaneous finger pulse oximeter to measure respiratory variables and oxygen saturation. The scoring of sleep stages and respiratory events was done according to the 2012 American Academy of Sleep Medicine criteria by experienced sleep technologists.[41] Apnea was defined as a reduction of airflow of ≥90% for at least 10 seconds, and hypopnea was defined as a reduction of airflow of ≥30% for at least 10 seconds associated with an oxygen desaturation ≥3% and/or an arousal.[41] The following PSG variables were analyzed: total sleep time, proportion of sleep stages, sleep efficiency, awakening index (number of transitions to wake per hour of sleep), arousal index (number of arousals per hour of sleep), AHI, oxygen desaturation index (ODI) ≥3% and ≥4% (ODI-3 and ODI-4, respectively), mean oxygen saturation during sleep (mean SpO_2), and percentage of sleep time with oxygen saturation (TST) <90% and <92% (TST90 and TST92, respectively). None of the participants met criteria for central sleep apnea.[42] All participants with an AHI ≥15/h met criteria for OSA (i.e., they presented predominantly obstructive respiratory events).[42] OSA status was dichotomized into non-OSA (AHI <15/h; $n = 76$) or OSA (AHI ≥15/h; $n = 50$). PSG variables demonstrating differences by OSA status (Table 1) were included in a principal component analysis (PCA). We used the criterion of eigenvalues = 2 and a varimax rotation, to extract a composite variable of sleep fragmentation (PCA_sleep fragmentation) and a composite variable of hypoxemia (PCA_hypoxemia) related to OSA (Table 2).[15,17,43] The AHI was analyzed as an independent variable because (i) it is the current defining variable for OSA severity, and (ii) when included in the PCA, it demonstrated >0.5 loading for both PCA components. Therefore, the OSA measures of interest of the study were: AHI, PCA_sleep fragmentation, and PCA_hypoxemia.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed and cited the appropriate articles. Obstructive sleep apnea (OSA) is increasingly recognized as a potential risk factor for Alzheimer's disease (AD). However, the mechanisms underlying this association remain poorly understood. Little is known about the relationship between OSA and the microstructure of the limbic white matter tracts, which are known to degenerate early in the AD continuum.
2. **Interpretation**: In this cross-sectional study, OSA-related hypoxemia was associated with altered fornix integrity in individuals with mild cognitive impairment (MCI), but not in cognitively unimpaired individuals. Altered fornix integrity correlated with poorer episodic verbal memory. These findings suggest that OSA may contribute to fornix damage and memory dysfunction in MCI.
3. **Future directions**: Future longitudinal studies should examine whether OSA accelerates fornix deterioration and memory decline in the AD continuum.

2.3 | Neurocognitive assessment

A comprehensive battery of neurocognitive tests assessed attention and processing speed, executive functions, episodic verbal memory, language, and visuospatial skills. We used the following criteria for the diagnosis of MCI: (1) an objective cognitive impairment defined as a z-score ⩽1.5 standard deviations below normative data on at least two measures of the same cognitive domain, or a Montreal Cognitive Assessment (MoCA)[44] score <26 points and a z-score ⩽1.5 standard deviations on at least one measure in two different cognitive domains; (2) preserved independence in activities of daily living assessed by the Activities of Daily Living Inventory[45] or during an interview; (3) psychiatric condition or medication use cannot better explain the

TABLE 1 Sample characteristics.

Parameter	Non-OSA groups		OSA groups		Test	Post hoc
	Non-OSA/CU (A)	Non-OSA/MCI (B)	OSA/CU (C)	OSA/MCI (D)		
No. of participants	39	37	31	19		
Demographic characteristics						
Age, years	67.7 ± 7.4	68.0 ± 9.0	68.3 ± 6.9	69.0 ± 8.0	F = 0.1	
Women, *n* (%)	18 (46.2)	14 (37.8)	8 (25.8)	9 (47.4)	$\chi^2 = 3.7$	
Education, years	15.6 ± 3.2	14.1 ± 3.8	16.0 ± 3.2	13.6 ± 3.7	F = 3.1*	A, C > D; B < C
Clinical characteristics						
BMI, kg/m^2	25.6 ± 3.7	26.0 ± 3.6	28.4 ± 3.6	27.1 ± 3.3	F = 4.1*	A, B < C
ESS, points	7.2 ± 4.9	6.5 ± 4.8	8.9 ± 5.6	8.5 ± 4.5	F = 1.6	
Vascular Burden Index ≥2, *n* (%)	8 (20.5)	8 (21.6)	6 (19.4)	4 (21.1)	$\chi^2 = 0.0$	
Anxiety symptoms, *n* (%)	6 (15.4)	5 (13.5)	4 (12.9)	4 (21.4)	$\chi^2 = 0.7$	
Depressive symptoms, *n* (%)	1 (2.6)	4 (10.8)	5 (16.1)	1 (5.3)	$\chi^2 = 4.5$	
Sleep characteristics						
Total sleep time, min	372.4 ± 59.9	355.9 ± 66.9	370.9 ± 49.7	360.7 ± 40.5	F = 0.7	
Stage N1, %	15.7 ± 7.2	16.4 ± 8.7	28.9 ± 15.8	23.1 ± 11.1	F = 10.8*	A, B < C, D
Stage N2, %	57.9 ± 7.8	58.6 ± 7.9	50.1 ± 12.9	52.3 ± 9.1	F = 6.2*	A, B > C, D
Stage N3, %	9.3 ± 10.6	8.1 ± 7.9	6.0 ± 6.0	8.2 ± 4.7	F = 0.9	
REM sleep, %	17.0 ± 5.5	16.8 ± 4.9	15.0 ± 4.9	16.3 ± 5.2	F = 1.0	
Sleep efficiency, %	80.0 ± 11.4	77.9 ± 11.5	80.5 ± 9.6	81.4 ± 8.8	F = 0.6	
Awakening index, events/h	5.7 ± 2.7	5.8 ± 3.0	8.6 ± 5.6	7.4 ± 3.7	F = 4.3*	A, B < C
Arousal index, events/h	10.5 [8.1, 13.2]	10.7 [7.6, 14.3]	19.0 [15.7, 30.1]	18.4 [10.7, 22.3]	H = 32.6*	A, B < C, D
AHI, events/h	6.0 [3.5, 8.5]	6.1 [2.3, 11.0]	31.8 [20.5, 45.8]	28.2 [19.9, 33.5]	H = 90.1*	A, B < C, D
ODI-3, events/h	2.4 [0.5, 5.2]	1.8 [0.5, 3.9]	18.0 [10.4, 24.9]	12.8 [4.1, 17.0]	H = 60.6*	A, B < C, D
ODI-4, events/h	0.6 [0.0, 1.8]	0.2 [0.0, 1.5]	8.0 [3.5, 13.2]	5.6 [1.6, 7.7]	H = 53.4*	A, B < C, D
Mean SpO_2, %	94.8 ± 1.2	95.2 ± 1.1	94.0 ± 1.1	93.4 ± 1.5	F = 7.7*	A, B > C, D
TST90, %	0.1 [0.0, 0.5]	0.1 [0.0, 0.4]	1.9 [0.5, 4.4]	1.2 [0.3, 2.7]	H = 40.9*	A, B < C, D
TST92, %	0.6 [0.0, 2.4]	0.4 [0.0, 2.5]	9.1 [3.1, 19.3]	7.7 [1.5, 13.6]	H = 41.5*	A, B < C, D

Notes: Data are presented as mean ± standard deviation, median [interquartile range] or number of participants (%). Data were analyzed using one-way analyses of variance (F), Kruskal–Wallis tests (H), or chi-squared tests (χ^2).
Abbreviations: AHI, Apnea-Hypopnea Index; BMI, body mass index; CU, cognitively unimpaired; ESS, Epworth Sleepiness Scale; MCI, mild cognitive impairment; ODI-3, oxygen desaturation index ≥3%; ODI-4, oxygen desaturation index ≥4%; OSA, obstructive sleep apnea; REM, rapid eye movement; SpO_2, oxygen saturation; TST90, percentage of sleep time with oxygen saturation <90%; TST92, percentage of sleep time with oxygen saturation <92%.
*$p < 0.05$.

presence of cognitive impairment; and (4) absence of dementia. Cognitive status was dichotomized into CU ($n = 70$) or MCI ($n = 56$). Most participants with MCI were considered to have amnestic MCI ($n = 46$), as they presented a z-score ⩽1.5 standard deviations on at least two measures in the memory domain, or a MoCA[44] score < 26 points and a z-score ⩽1.5 standard deviations on at least one measure in two different cognitive domains including the memory domain. The remaining participants with MCI were considered to have non-amnestic MCI ($n = 10$). The Rey Auditory Verbal Learning Test (RAVLT)[46] was used to assess episodic verbal memory. The following RAVLT scores were analyzed[46]: sum of the trials 1–5, immediate recall, and delayed recall. Further details on neurocognitive assessment are presented in Table S1.

2.4 | MRI acquisition and processing

Participants underwent neuroimaging acquisition at the Neuroimaging Functional Unit of the Montreal Geriatric University Institute, with either a Siemens Magnetom Trio Tim 3T ($n = 85$) or an upgraded Siemens Magnetom Prisma 3T ($n = 25$), or at the Sherbrooke University Institute of Geriatrics with a Philips Ingenia 3T ($n = 16$). For the Siemens Magnetom Trio Tim 3T, the acquisition parameters used were those of the Massachusetts General Hospital (Boston, Massachusetts, USA). Image acquisition in the upgraded Siemens Magnetom Prisma 3T and Philips Ingenia 3T were performed according to the Canadian Dementia Imaging Protocol (https://www.cdip-pcid.ca).

TABLE 2 Principal component analysis.

Parameter	Components	
	PCA_sleep fragmentation	PCA_hypoxemia
Stage N1	0.93*	0.18
Stage N2 (inverted)	0.77*	0.15
Awakening index	0.81*	0.10
Arousal index[a]	0.77*	0.29
ODI-3[a]	0.22	0.86*
ODI-4[a]	0.18	0.88*
Mean SpO_2 (inverted)	0.10	0.79*
TST90[a]	0.22	0.87*
TST92[a]	0.20	0.93*
Variance explained	32.1%	43.5%

Note: *Loading > 0.5.
Abbreviations: ODI-3, oxygen desaturation index ≥3%; ODI-4, oxygen desaturation index ≥4%; PCA, principal component analysis; SpO_2, oxygen saturation; TST90, percentage of sleep time with oxygen saturation <90%; TST92, percentage of sleep time with oxygen saturation <92%.
[a]Log-transformed variable.

Diffusion-weighted images were processed using TractoFlow Atlas–Based Segmentation[47] and FreeWater pipeline (https://github.com/scilus/freewater_flow). FW modeling was performed using the accelerated microstructure imaging via convex optimization to calculate FW-DTI measures in each voxel.[48] The limbic white matter tracts of interest were the cingulum, fornix, and uncinate fasciculus, which were extracted in each hemisphere. The cingulum and uncinate fasciculus were extracted using RecoBundlesX (https://github.com/scilus/rbx_flow).[49–52] The fornix was reconstructed using the Bundle Specific Tractography approach (https://github.com/scilus/bst_flow)[53,54] due to its high curvature, narrow shape, and location adjacent to ventricular space. The FW-DTI measures of interest were computed for each tract using TractometryFlow (https://github.com/scilus/tractometry_flow):[49,51,55] FW index (unit = absolute value ranging from 0 to 1), tissue fractional anisotropy (FA_T; unit = absolute value ranging from 0 to 1), tissue mean diffusivity (MD_T; unit = 10^{-3} mm^2/s), tissue axial diffusivity (AxD_T; unit = 10^{-3} mm^2/s), and tissue radial diffusivity (RD_T; unit = 10^{-3} mm^2/s). We also analyzed data from five rostro-caudal sections of the tracts, which were extracted using a tractometry pipeline.[56] Voxels located at the head of the tracts (rostral position) were connected to Section 1 and those located at the tail (caudal position) were connected to Section 5.[56] Further details on MRI acquisition and processing are available in the Supplementary material.

2.5 | Questionnaires

The Epworth Sleepiness Scale estimated daytime sleepiness.[57] Presence of cardiovascular risk factors (hypertension, hypotension, dyslipidemia, and diabetes) and diseases (history of coronary artery disease, cardiac arrhythmia, carotid stenosis, and transient cerebral ischemia) was recorded to calculate the Vascular Burden Index (one point for each condition).[58] The Vascular Burden Index was dichotomized into <2 (no significant vascular burden) or ≥2 points (significant vascular burden).[58] We considered scores ≥14 points on the Beck Depression Inventory-II[59] or ≥5 points on the Geriatric Depression Scale[60] to reflect significant depressive symptoms. For the definition of significant anxiety symptoms, we used a cutoff of ≥8 points on the Beck Anxiety Inventory[61] or the Geriatric Anxiety Scale.[62]

2.6 | Statistical analyses

Descriptive statistics examined sample characteristics by OSA and cognitive status (i.e., non-OSA/CU vs. non-OSA/MCI vs. OSA/CU vs. OSA/MCI). Comparisons between groups were performed using one-way analyses of variance, Kruskal–Wallis tests, and chi-squared tests. Differences in FW-DTI measures of each limbic tract were tested by OSA status (i.e., participants without OSA vs. participants with OSA) and by cognitive status (i.e., CU participants vs. participants with MCI) using one-way analyses of covariance (ANCOVA), controlling for age, sex, and tract volume (divided by total intracranial volume).

In the primary analyses of the study, hierarchical linear regressions were used to test the hypothesis that cognitive status interacts with OSA measures (i.e., AHI, PCA_sleep fragmentation, or PCA_hypoxemia) to predict FW-DTI measures of limbic tracts (outcome variables). Control variables were age, sex, BMI, Epworth Sleepiness Scale, Vascular Burden Index, and tract volume (divided by total intracranial volume), which were entered into the analyses in Step 1. Cognitive status and OSA measures were entered in Step 2, while the interaction between cognitive status and OSA measures was entered in Step 3. Associations between OSA measures and FW-DTI measures were assessed in the whole sample (if there was no significant interaction with cognitive status) or separately in the CU and MCI groups (if there was a significant interaction with cognitive status). Of note, adding time between PSG and MRI as a covariate did not change the results (data not shown), so this covariate was not included in the regression models to avoid overfitting.

We performed secondary analyses focusing only on the limbic tracts that showed significant results in the primary analyses. First, in cases where PCA_sleep fragmentation or PCA_hypoxemia components showed significant associations with FW-DTI measures, we repeated the analyses using their individual PSG variables to understand which specific variables primarily drove the results. Second, associations between OSA measures and FW-DTI measures were tested along rostro-caudal sections of limbic tracts to understand whether they were present throughout the tract or only in specific sections. Third, we assessed associations of FW-DTI measures with RAVLT scores (outcome variables) using hierarchical linear regressions. Control variables were age, sex, education, Epworth Sleepiness Scale, depressive symptoms, anxiety symptoms, and tract volume (divided by total intracranial volume). Similar to the primary analyses, control variables were entered in Step 1, whereas cognitive status and

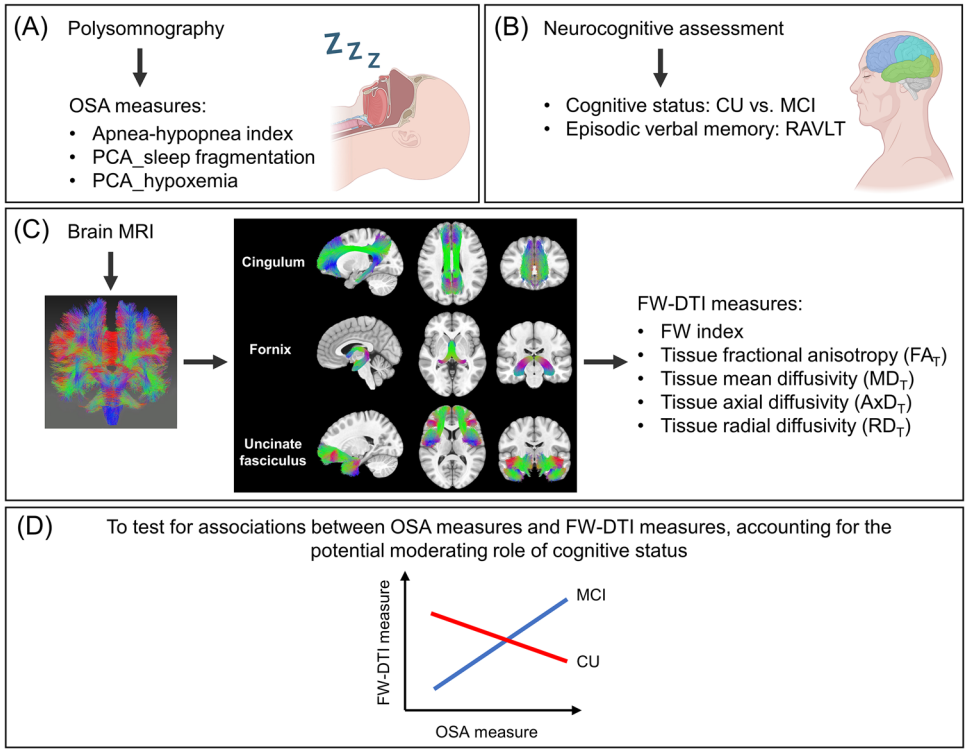

FIGURE 1 Overview of the methods. (A) Polysomnographic variables related to obstructive sleep apnea (OSA) were included in a principal component analysis (PCA) to extract the composite variables PCA_sleep fragmentation and PCA_hypoxemia, while the apnea-hypopnea index was analyzed as a single variable. (B) The neurocognitive assessment allowed us to dichotomize the sample into cognitively unimpaired (CU) or mild cognitive impairment (MCI), and episodic verbal memory was tested with the Rey Auditory Verbal Learning Test (RAVLT). (C) We performed whole brain tractography, extracted the limbic white matter tracts of interest in each hemisphere, and calculated averaged free water (FW)-corrected diffusion tensor imaging (DTI) measures for each tract. (D) The primary analyses tested for associations between OSA measures and FW-DTI measures in the whole sample (if there was no significant interaction with cognitive status) or in the CU group and the MCI group separately (if there was a significant interaction with cognitive status). The images in (A) and (B) were adapted from BioRender.com.

FW-DTI measures were entered in Step 2. The interaction between cognitive status and FW-DTI measures was entered in Step 3. Associations between FW-DTI and RAVLT scores were examined in the whole sample (if there was no significant interaction with cognitive status; in this case, because RAVLT scores were causally related to MCI [i.e., they were used to determine the diagnosis of MCI], cognitive status was not included as a covariate to avoid overfitting) or within the CU and MCI groups (if there was a significant interaction with cognitive status).

Before being used in the PCA and hierarchical linear regressions, a natural log transformation (ln[variable + 1]) was performed for the PSG variables with a right-skewed distribution and occasional values equal to 0 (arousal index, AHI, ODI-3, ODI-4, TST90, and TST92). We tested the assumptions of ANCOVA and hierarchical linear regressions (no violations were observed). Results of hierarchical linear regressions were expressed as standardized beta coefficients (β) and 95% confidence interval (CI). For the descriptive statistics, ANCOVAs, and secondary analyses, we considered tests with p-values <0.05 as significant. For the primary analyses, we lowered the significance threshold to tests with p-values <0.01. A description of how missing data were handled is provided in the Supplementary material. Analyses were performed using IBM SPSS Statistics version 26.0 (Armonk, NY, USA). An overview of the methods is presented in Figure 1.

3 | RESULTS

3.1 | Characteristics of the sample

The sample consisted of 126 participants aged 68.2 ± 7.8 years (range: 55–86 years) of whom 49 (38.9%) were women. Sample characteristics by OSA and cognitive status are summarized in Table 1. Compared to the non-OSA/CU and OSA/CU groups, the non-OSA/MCI and OSA/MCI groups had fewer years of education. The OSA/CU group had a higher BMI compared to the non-OSA groups. Compared to the non-OSA groups, the OSA groups had higher sleep fragmentation (higher stage N1, awakening index, and arousal index as well as lower stage N2) and higher hypoxemia (higher ODI-3, ODI-4, TST90, and TST92 as well as lower mean SpO_2).

3.2 | Microstructure of the limbic white matter tracts by OSA status and by cognitive status

There were no differences in FW-DTI measures between participants without OSA and those with OSA (Table S2). Compared with CU participants, those with MCI had lower FA_T and higher diffusivities (MD_T,

AxD_T, and RD_T) in the left and right fornix, while no differences were observed for the FW index. The CU and MCI groups showed no microstructural differences in the cingulum and uncinate fasciculus (Table S3).

3.3 | Principal component analysis

The sleep fragmentation and hypoxemia variables that showed differences between the non-OSA groups and the OSA groups were included in the PCA. This analysis resulted in two components, PCA_sleep fragmentation and PCA_hypoxemia, which explained 75.6% of the total variance. The loadings of the variables on each component are shown in Table 2.

3.4 | OSA measures, microstructure of the limbic white matter tracts, and moderating role of cognitive status

There were three significant interactions indicating that cognitive status moderated the associations between PCA_hypoxemia and left fornix diffusivities (MD_T: $\beta = 0.45$, $p = 0.007$; AxD_T: $\beta = 0.46$, $p = 0.008$; RD_T: $\beta = 0.42$, $p = 0.009$). These moderating effects explained from 4.1% to 4.8% of the variance (Table 3). A decomposition of significant interactions showed that in participants with MCI, higher levels of PCA_hypoxemia were associated with higher left fornix diffusivities (MD_T: $\beta = 0.43$, $p = 0.005$; AxD_T: $\beta = 0.41$, $p = 0.004$; RD_T: $\beta = 0.41$, $p = 0.008$). These positive associations between PCA_hypoxemia and left fornix diffusivities were not observed among CU individuals (Figure 2A–E). Figure 2F illustrates the changes in the diffusion ellipsoid shape of the tissue and extracellular/FW compartments that, according to our results, are associated with higher levels of PCA_hypoxemia in participants with MCI. No significant findings were found for the other OSA measures or the other white matter tracts (Tables S4 and S5).

3.5 | Secondary analyses

Secondary analyses focused on FW-DTI measures of the left fornix. First, we sought to assess which specific PSG variable of hypoxemia contributed to the significant results in the MCI group. All variables of hypoxemia were associated with higher left fornix diffusivities in individuals with MCI, except ODI-3, which showed trends toward significant associations. TST90 and TST92 showed the strongest associations, followed by ODI-4, and then by mean SpO_2 (Table S6). Of note, the results were similar when examining only participants with amnestic MCI (i.e., after exclusion of 10 participants with non-amnestic MCI; Table S7).

Second, we examined associations between PCA_hypoxemia and FW-DTI measures along the five rostro-caudal sections of the left fornix in participants with MCI. Associations between PCA_hypoxemia, MD_T, and RD_T were relatively homogeneous along the entire tract, as they were observed in all sections except Section 4, which showed trends toward significant associations. Associations between PCA_hypoxemia and AxD_T were limited to Section 2, but we observed trends toward significant associations in the other sections (Figure 3).

Third, we tested associations between left fornix microstructure and RAVLT scores. Hierarchical linear regressions revealed a significant moderating effect of cognitive status on the association between left fornix FA_T and RAVLT immediate recall (Table S8). However, decomposition of this interaction showed no significant association between left fornix FA_T and RAVLT immediate recall in the CU group or the MCI group. Other potential associations were assessed in the whole sample. Lower FA_T and higher diffusivities in the left fornix were significantly associated with poorer RAVLT scores (Table 4).

4 | DISCUSSION

This study examined associations between OSA features and microstructure of the limbic white matter tracts in CU individuals and individuals with MCI aged 55 and over. Higher levels of OSA-related hypoxemia were associated with higher FW-corrected diffusivities (MD_T, AxD_T, and RD_T) in the left fornix only among individuals with MCI. Notably, higher left fornix diffusivities correlated with poorer episodic verbal memory. Although causality cannot be inferred from cross-sectional analyses, these results suggest that OSA, through hypoxemic mechanisms, may contribute to fornix damage and memory dysfunction in MCI. The opposite scenario, that is, that fornix alterations would increase OSA-related hypoxemia seems unlikely because, to our knowledge, the fornix is not involved in the pathophysiology of OSA and/or the mechanisms leading to hypoxemia.

The fornix represents a central element of limbic circuits and is one of the most important structures related to memory function.[63] Consistent with our findings, the degree of fornix damage has been correlated with memory impairment in normal aging[23,25] and MCI.[21,22] Histopathological studies have reported degeneration of the fornix in mouse models of AD[64] and human patients with AD.[65] Congruent with the histopathological findings, DTI studies have reported fornix microstructural abnormalities in MCI and AD.[20–22,26,66] In a study by Zhuang et al., individuals with "early" amnestic MCI, defined by a conversion from normal cognition to amnestic MCI within the past 2 years, showed white matter alterations that were confined to the fornix, even in the absence of hippocampal atrophy.[67] These findings suggest that fornix microstructural alterations may be a sensitive marker for incipient amnestic MCI.[67] The fact that the fornix appears to be one of the earliest white matter tracts to degenerate in MCI may explain the significant associations with OSA observed in the present study and the lack of associations related to the cingulum and the uncinate fasciculus.

Higher levels of OSA-related hypoxemia were associated with higher fornix diffusivities, but not with FA_T or FW index. It is interesting to note that an increase in diffusivities may be more sensitive than a decrease in fractional anisotropy to characterize microstructural differences in limbic tracts between AD patients and elderly controls.[68]

TABLE 3 Hierarchical regression analyses with cognitive status and PCA_hypoxemia predicting left fornix microstructure.

	Left fornix														
	FW index			FA_T			MD_T			AxD_T			RD_T		
Predictors	β	R^2	ΔR^2	β	R^2	ΔR^2	β	R^2	ΔR^2	β	R^2	ΔR^2	β	R^2	ΔR^2
Step 1		14.6%	14.6%**		19.7%	19.7%**		9.6%	9.6%*		6.0%	6.0%		12.7%	12.7%*
Age	−0.09			−0.29**			0.26*			0.19			0.28**		
Sex	−0.67**			−0.50*			−0.01			−0.29			0.14		
BMI	−0.02			0.03			−0.10			−0.09			−0.09		
ESS	−0.03			0.03			−0.05			−0.06			−0.04		
Vascular Burden Index	0.23			0.01			0.20			0.18			0.20		
Left fornix volume	0.05			−0.13			0.01			0.02			0.01		
Step 2		15.4%	0.9%		24.1%	4.4%*		15.6%	6.0%*		9.9%	3.9%		19.3%	6.6%**
MCI	0.16			−0.42*			0.43*			0.32			0.46**		
PCA_hypoxemia	0.07			−0.07			0.16			0.15			0.16		
Step 3		17.3%	1.9%		25.2%	1.1%		20.3%	4.7%**		14.7%	4.8%**		23.3%	4.1%**
MCI×PCA_hypoxemia	0.29			−0.22			0.45**			0.46**			0.42**		

Notes: Data are presented as standardized beta coefficients (β), R^2, and R^2 changes (ΔR^2). Data were analyzed by hierarchical linear regression models using FW-DTI measures as outcome variables. Step 1: age (continuous), sex (men vs. women), body mass index (continuous), Epworth Sleepiness Scale (continuous), Vascular Burden Index (<2 vs. ≥2 points), and left fornix volume (divided by total intracranial volume; continuous). Step 2: Step 1 + cognitive status (CU vs. MCI) and PCA_hypoxemia (continuous). Step 3: Step 2 + interaction term MCI×OSA_hypoxemia.

Abbreviations: AxD_T, tissue axial diffusivity; BMI, body mass index; CU, cognitively unimpaired; FA_T, tissue fractional anisotropy; FW, free water; MCI, mild cognitive impairment; MD_T, tissue mean diffusivity; PCA, principal component analysis; RD_T, tissue radial diffusivity.

*$p < 0.05$,

**$p < 0.01$.

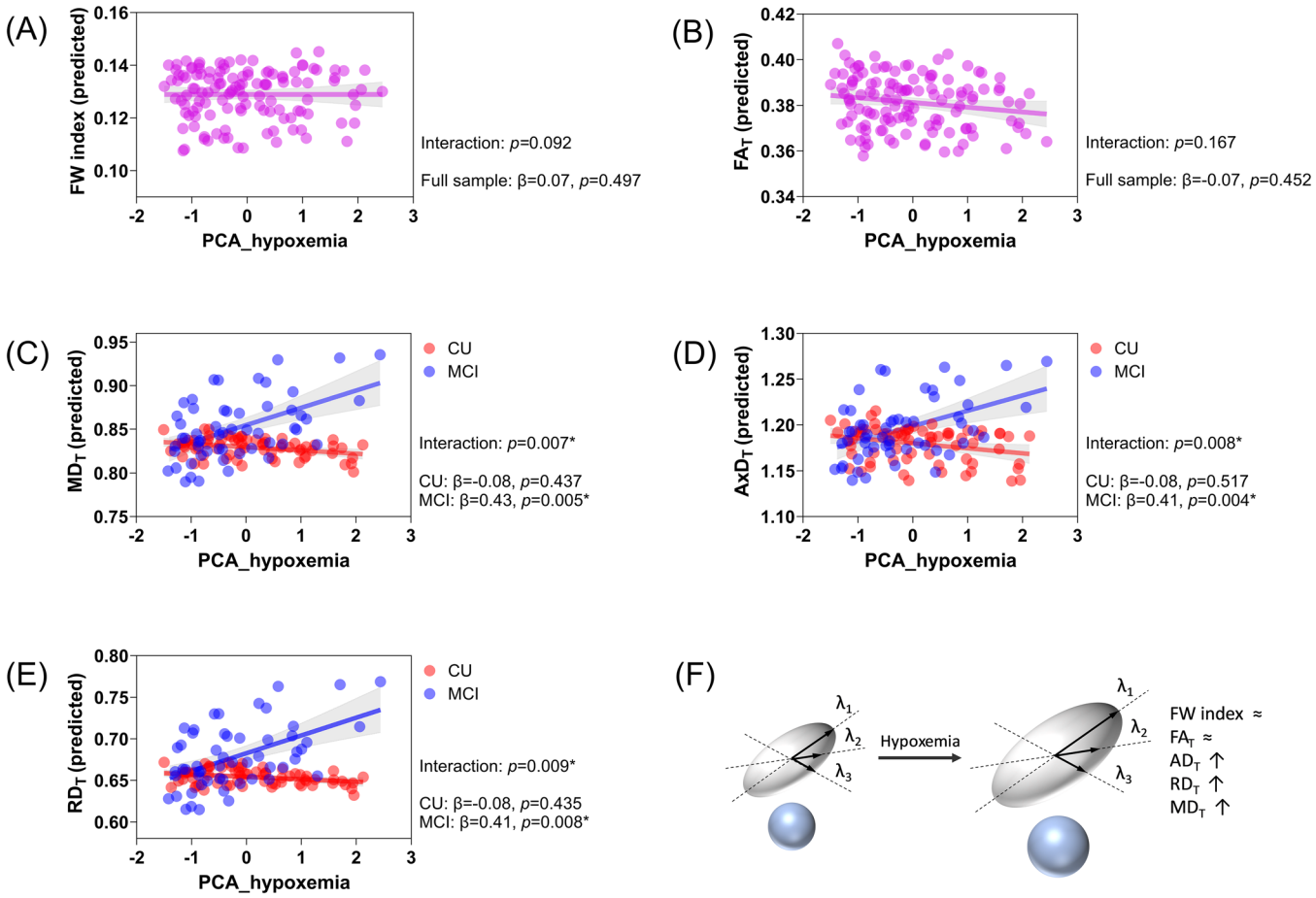

FIGURE 2 Associations between OSA-related hypoxemia and left fornix microstructure. (A–E) Scatter plots showing the associations between PCA_hypoxemia and FW-DTI measures of the left fornix. The y-axis shows the predicted values from the regression analyses adjusted for age (continuous), sex (men vs. women), body mass index (continuous), Epworth Sleepiness Scale (continuous), Vascular Burden Index (<2 vs. ≥2 points), left fornix volume (divided by total intracranial volume; continuous), and cognitive status (CU vs. MCI). The solid line is the regression line and the gray area represents the 95% confidence interval. (F) Changes in the diffusion ellipsoid shape of the tissue compartment (gray ellipsoid) and the extracellular/FW compartment (blue sphere) associated with higher levels of hypoxemia in participants with MCI. Our results indicate that hypoxemia is associated with an increase in the three diffusivities (MD_T, AxD_T, and RD_T), a constant FA_T (which is consistent with a proportional increase in $\lambda 1$, $\lambda 2$, and $\lambda 3$), and a constant FW index (which is consistent with a proportional increase in the tissue compartment and the FW/extracellular comportment). Note that the changes in the shape of the diffusion ellipsoid are shown here for illustrative and conceptual purposes (i.e., these changes are conceptually consistent with our results, but the magnitudes of the changes are not scaled or calculated based on our data). *$p < 0.01$. AxD_T, tissue axial diffusivity; CU, cognitively unimpaired; DTI, diffusion tensor imaging; FW, free water; MCI, mild cognitive impairment; MD_T, tissue mean diffusivity; OSA, obstructive sleep apnea; PCA, principal component analysis; RD_T, tissue radial diffusivity; λ, eigenvalue.

Importantly, a relatively proportional increase in the three diffusivities is known to result in a constant fractional anisotropy,[68] which may explain why we did not observe an association of hypoxemia with FA_T. Furthermore, an increase in the extracellular/FW compartment that is relatively proportional to that observed in the tissue compartment will result in a constant FW index and may explain the lack of association between OSA-related hypoxemia and FW index in our study. The fornix microstructural alterations observed here in association with hypoxemia appear to reflect complex tissue changes that may involve both axonal swelling and extracellular edema. These microstructural changes may precede the more severe stages of neurodegeneration, which would show axonal atrophy, resulting in decreased FA_T, decreased AxD_T, and increased FW index.

In a previous study by our group on the same sample, OSA-related hypoxemia was not associated with hippocampal atrophy, but with higher hippocampal volume in individuals with MCI, probably due to extracellular edema, as this association disappeared after volume correction for FW contamination.[17] Therefore, in the present study, the link between OSA-related hypoxemia and microstructural alterations in the fornix appears to be detectable "early," even before significant associations with hippocampal atrophy. In addition, the microstructural alterations associated with OSA-related hypoxemia appeared to be relatively homogeneous along the fornix, opening up the possibility of a direct detrimental effect of hypoxemia on the fornix rather than secondary alterations dependent on hippocampal degeneration. However, this remains a hypothesis that has not been tested in the present study.

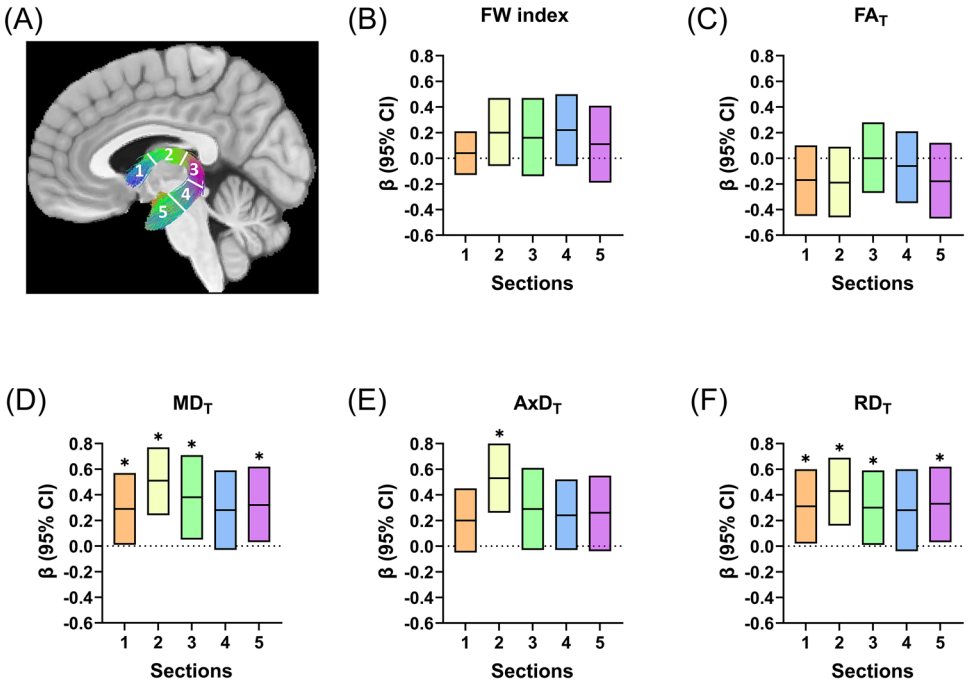

FIGURE 3 Associations between OSA-related hypoxemia and left fornix microstructure along its rostro-caudal sections in participants with MCI. (A) Sagittal view of the left fornix showing the five rostro-caudal sections. (B–F) Associations between PCA_hypoxemia and FW-DTI measures of the left fornix along the rostro-caudal sections in participants with MCI, adjusted for age (continuous), sex (men vs. women), body mass index (continuous), Epworth Sleepiness Scale (continuous), Vascular Burden Index (<2 vs. ≥2 points), and left fornix volume (divided by total intracranial volume; continuous). The central line represents the standardized beta coefficient (β), while the upper and lower lines represent the 95% confidence interval (CI). $^*p < 0.05$. AxD$_T$, tissue axial diffusivity; DTI, diffusion tensor imaging; FA$_T$, tissue fractional anisotropy; FW, free water; MCI, mild cognitive impairment; MD$_T$, tissue mean diffusivity; OSA, obstructive sleep apnea; PCA, principal component analysis; RD$_T$, tissue radial diffusivity.

Cognitive status modified the relationship between OSA and fornix microstructure, as significant associations were observed only in individuals with MCI and not in CU participants. The lower fornix integrity in our participants with MCI (which was probably not yet advanced enough in CU participants) may have made the association with hypoxemia visible. It is intriguing why only the left fornix was associated with hypoxemia. We can speculate that this is because most of our participants with MCI meet the criteria for amnestic MCI. Indeed, the diagnosis of amnestic MCI was primarily based on lower performance in episodic verbal memory, mainly dependent on the integrity of the left hippocampus-fornix pathway part of the Papez circuit.[63] Therefore, our participants with amnestic MCI could have had a marked loss of integrity of the left Papez circuit, which might have favored the observation of unilateral significant results. To test this hypothesis, we compared the integrity of the left and right fornix in our participants with MCI. The left fornix showed lower FA$_T$ than the right fornix, consistent with lower microstructural integrity (Table S9).

Few DTI studies have reported voxel-wise microstructural alterations in the fornix of patients with OSA.[34,69,70] However, these studies have not used a tract-specific approach to extract fornix-specific microstructural properties and did not perform correction for FW contamination.[34,69,70] In the present study, only the markers of OSA-related hypoxemia, but not AHI or sleep fragmentation, were associated with fornix alterations. These results are consistent with experimental animal studies, which have shown that intermittent hypoxemia[71] and hypoxia-ischemia[72–75] promote fornix damage. The negative impact of OSA-related hypoxemia on brain health is not surprising. Previous neuroimaging studies have found a correlation between the degree of nocturnal hypoxemia and morphometric changes in the brain, including in the medial temporal lobe.[14–17] Furthermore, hypoxemia, rather than sleep fragmentation, has been shown to predict greater cognitive decline in older adults with OSA in population-based cohort studies.[76–78]

This study has strengths, including the diagnosis of OSA based on the gold standard PSG, the analysis of the moderating role of MCI, and the use of a FW-DTI approach. However, our study also presents limitations. The cross-sectional design did not allow us to make causal inferences about the observed associations. However, in the light of current knowledge of neuroanatomy and OSA pathophysiology, our findings open up the possibility of a detrimental effect of OSA-related hypoxemia on fornix microstructure. The sample was selected by excluding participants with significant psychiatric, neurologic, or respiratory comorbidities, thus the results may not be generalizable to the entire population of patients with OSA and MCI. The use of multiple scanners for neuroimaging acquisition could potentially have an impact on the analyses; however, we followed a protocol designed to limit this problem. Current FW imaging relies on a bitensor model, which allows

TABLE 4 Associations between left fornix microstructure and RAVLT scores.

	RAVLT trials 1 to 5		RAVLT immediate recall		RAVLT delayed recall	
Left fornix	***β* (95% CI)**	***p*-Value**	***β* (95% CI)**	***p*-Value**	***β* (95% CI)**	***p*-Value**
FW index	−0.04 (−0.20, 0.13)	0.674	−0.14 (−0.30, 0.03)	0.101	−0.05 (−0.22, 0.11)	0.530
FA_T	0.23 (0.07, 0.39)	0.004*	–	–	0.21 (0.04, 0.38)	0.015*
CU	–	–	−0.03 (−0.20, 0.14)	0.702	–	–
MCI	–	–	0.17 (−0.06, 0.39)	0.145	–	–
MD_T	−0.20 (−0.35, −0.05)	0.011*	−0.26 (−0.41, −0.11)	<0.001*	−0.18 (−0.34, −0.02)	0.027*
AxD_T	−0.13 (−0.28, 0.02)	0.082	−0.22 (−0.38, −0.07)	0.004*	−0.12 (−0.28, 0.04)	0.135
RD_T	−0.22 (−0.38, −0.07)	0.004*	−0.27 (−0.43, −0.11)	<0.001*	−0.20 (−0.36, −0.04)	0.013*

Notes: Data were analyzed by hierarchical linear regression models using RAVLT scores as outcome variables. Step 1: age (continuous), sex (men vs. women), education (continuous), Epworth Sleepiness Scale (continuous), depressive symptoms (yes vs. no), anxiety symptoms (yes vs. no), and left fornix volume (divided by the total intracranial volume; continuous). Step 2: Step 1 + left fornix FW-DTI measures (FW index, FA_T, MD_T, AxD_T, or RD_T; continuous). Only the standardized beta coefficients (β) and 95% confidence intervals (CI) of the associations between left fornix FW-DTI measures and RAVLT scores (step 2) are presented.

Abbreviations: AxD_T, tissue axial diffusivity; CU, cognitively unimpaired; DTI, diffusion tensor imaging; FA_T, tissue fractional anisotropy; FW, free water; MCI, mild cognitive impairment; MD_T, tissue mean diffusivity; RAVLT, Rey Auditory Verbal Learning Test; RD_T, tissue radial diffusivity.

*$p < 0.05$.

estimation of FW compartment in voxels with a single fiber population but not in those with containing two or more fiber populations. Future advances could allow more robust estimation of the FW fraction by using a multishell diffusion MRI sequence. Finally, our results should be interpreted with the caveat that multiple testing increases the risk of type 1 error. However, the use of more stringent thresholds may have the effect of increasing the likelihood of type 2 error. Thus, by lowering the threshold for statistical significance to *p*-values <0.01 in our primary analyses, we attempted to strike a balance between managing the chances of making type 1 or type 2 errors. We invite researchers to consider that our results need to be confirmed by experimental replication.

In conclusion, this study revealed an association between OSA-related hypoxemia and microstructural alterations in the fornix among individuals with MCI. The results suggest that OSA may play a role in the fornix damage and memory dysfunction observed in MCI. Further cross-sectional studies are needed to confirm this observation. Longitudinal studies should examine whether OSA accelerates fornix deterioration and memory decline across the AD continuum.

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CONFLICT OF INTEREST STATEMENT

Maxime Descoteaux is a co-founder and shareholder of Imeka Solutions Inc. (www.imeka.ca). Nadia Gosselin has received sponsorships and/or honoraria from Jazz Pharmaceuticals, Eisai, and Paladin, but they were not related to the present study. The other authors have no financial or nonfinancial disclosure to declare. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

The research protocols were all approved by institutional ethics committees (#2012-697, #12-13-008, #2010-468, and #MP-32-2018-1537), and participants gave their written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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