Radiology

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Association of MRI Indexes of the Perivascular Space Network and Cognitive Impairment in Patients with Obstructive Sleep Apnea

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Conflicts of interest are listed at the end of this article.

See also the editorial by Port in this issue.

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Background: The role of perivascular space (PVS) dysfunction in obstructive sleep apnea (OSA) requires further study.

Purpose: To compare MRI indexes of PVS across patients with differing severities of OSA and relate them with disease characteristics and treatment.

Materials and Methods: This single-center prospective study included healthy controls (HCs) and patients with complaints of snoring who underwent MRI and cognitive evaluation between June 2021 and December 2022. Participants with complaints of snoring were classified into four groups (snoring, mild OSA, moderate OSA, and severe OSA). PVS networks were assessed at MRI using PVS volume fraction, extracellular free water (FW), and diffusion tensor imaging analysis along the PVS (DTI-ALPS). One-way analysis of variance and Pearson correlation were used for analysis. Alterations in PVS indexes and cognitive performance after treatment were assessed in 15 participants with moderate OSA.

Results: A total of 105 participants (mean age, 33.4 years ± 8.9 [SD]; 80 males) and 50 HCs (mean age, 37.0 years ± 8.6; 33 males) were included. Higher mean PVS volume fraction was observed in participants with severe OSA (n = 23) than in patients with mild OSA (n = 36) (0.11 vs 0.10; P = .03). Participants with severe OSA exhibited higher mean FW index (0.11) than both HCs (0.10; P < .001) and patients with mild OSA (0.10; P = .003). All patient groups had lower DTI-ALPS than HCs (range, 1.5–1.9 vs 2.1; all P < .001). DTI-ALPS correlated with cognitive performance on the Stroop Color and Word Test (r range, −0.23 to −0.24; P value range, .003–.005). After treatment, PVS indexes changed (P value range, <.001 to .01) and cognitive performance improved (P value range, <.001 to .03).

Conclusion: Differences in PVS indexes were observed among participants with differing severities of OSA and HCs. Indexes correlated with measures of cognitive function, and changes in indexes and improvement in cognitive performance were observed after treatment in participants with moderate OSA.

Supplemental material is available for this article.

Obstructive sleep apnea (OSA) is a highly prevalent but underdiagnosed sleep-related breathing disorder characterized by recurrent arousal from sleep and intermittent hypoxia (1). OSA has been widely verified as a risk factor for neurodegenerative diseases including Alzheimer disease (2), Parkinson disease (3), and multiple sclerosis (4). However, the underlying neuropathologic mechanism of OSA remains unknown.

The glymphatic system is a recently discovered macroscopic waste clearance system in the central nervous system consisting of networks of perivascular spaces (PVSs) (5). These PVS networks are involved in three essential physiologic activities—cerebrospinal fluid influx (6), cerebrospinal fluid–interstitial fluid exchange (7), and waste clearance (8)—that can be detected indirectly on MRI scans (Fig 1). The glymphatic system is more active during sleep (9) and can be damaged by sleep-related disorders (10). As a sleep-related hypoventilation disorder, OSA could lead to glymphatic system impairment, resulting in decreased clearance of metabolic waste and interstitial solutes, such as amyloid proteins, from the brain parenchyma (9,11).

Previous studies showed that patients with OSA had higher relative area ratios of PVS in both the frontal cortex and the basal ganglia, and this difference was more pronounced in patients with severe OSA than in patients with mild-to-moderate OSA (12). Several studies have also demonstrated that patients with OSA have lower diffusion tensor imaging analysis along the PVS (DTI-ALPS) index values than healthy controls (HCs) (13,14). Moreover, Lee et al (13) found that the DTI-ALPS index was negatively correlated with apnea-hypopnea index (AHI) in sleep stage N. These studies examined only one

Abbreviations

η_p^2 = partial η^2, AHI = apnea-hypopnea index, ANOVA = analysis of variance, BMI = body mass index, DTI-ALPS = diffusion tensor imaging analysis along the PVS, ESS = Epworth Sleepiness Scale, FW = free water, FW-WM = FW in WM, HC = healthy control, OSA = obstructive sleep apnea, PVS = perivascular space, PVSVF = PVS volume fraction, PVSVF-WM = PVSVF in WM, WM = white matter

Summary

Patients with differing severities of obstructive sleep apnea (OSA) exhibited differences in MRI indexes of the perivascular space network, and those with moderate OSA treated with uvulopalatopharyngoplasty showed improvements in these indexes and in cognitive performance.

Key Results

- In this prospective study of 84 participants with differing obstructive sleep apnea (OSA) severity, 21 individuals who snored, and 50 healthy controls, MRI indexes of the perivascular space (PVS) network differed in some comparisons between groups (pairwise *P* value range, <.001 to .03).
- In 15 participants with moderate OSA, changes in MRI indexes of PVS (*P* value range, <.001 to .01) and improvements in cognitive performance (*P* value range, <.001 to .03) were observed after uvulopalatopharyngoplasty.

metric of the PVS network (12–14), and thus more research is needed to further understand the role of PVS network dysfunction in OSA. Additionally, while improvement in cognitive performance after treatment in patients with OSA has been extensively validated (12,15), how treatment impacts the PVS network remains unknown (12).

The aims of this study were to compare MRI indexes of the PVS network (hereafter called PVS indexes) across patients with differing severities of OSA, assess the relationship between these indexes and disease characteristics, and examine whether changes occur after treatment. Based on previous studies, it was hypothesized that *(a)* PVS indexes would show more disruption in patients with more severe OSA; *(b)* there would be a relationship between sleep, PVS indexes, and cognitive dysfunction; and *(c)* impairment of the PVS network and cognition would be reversible with treatment.

Materials and Methods

This prospective study was approved by the local research ethics committee. All patients provided written informed consent before undergoing MRI and cognitive evaluation.

Study Participants

Between June 2021 and December 2022, patients with complaints of snoring were consecutively recruited through the Otorhinolaryngology Department of Nanshan Hospital, Medical School of Shenzhen University, China. Patients were included if they were 18–60 years old, were right-handed, reported a snoring complaint, and completed the MRI examination and minimum 7-hour polysomnography monitoring. Patients were excluded if they had past cranial injury or vascular events, history of alcohol or substance abuse, hypertension, diabetes, major physical illness, HIV, MRI contraindications, or incomplete questionnaires. HCs were recruited through advertisements. Additional exclusion criteria for HCs were self-reported snoring during sleep and Epworth Sleepiness Scale (ESS) score of 6 or more.

Participants with complaints of snoring underwent cognitive testing, MRI, otolaryngologic examination, and polysomnography; HCs underwent cognitive testing, MRI, and otolaryngologic examination. Details of polysomnography are provided in Appendix S1. Approximately 1 hour before the MRI examination, all participants underwent a series of cognitive tests, including number connection tests A and B (16), the serial dotting test (17), the digit symbol test (18), the line tracing test (19), and the Stroop Color and Word Test (20). Additional details on the cognitive tests are provided in Appendix S2.

Participants were classified into the following four groups: snoring (AHI ≤ 5), mild OSA (5 < AHI ≤ 15), moderate OSA (15 < AHI ≤ 30), and severe OSA (AHI > 30). In addition, oxygen desaturation index (defined as the number of episodes of oxygen desaturation of ≥3% per hour of sleep), lowest oxygen saturation (percentage), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), and ESS score were also collected for all participants.

Fifteen participants with moderate OSA also underwent MRI, portable sleep monitoring, and cognitive assessment 3–6 months after uvulopalatopharyngoplasty.

MRI Acquisition

A 3.0-T MRI scanner (SIGNA Architect; GE HealthCare) with a 48-channel head coil was used to obtain three-dimensional T1-weighted and diffusion-weighted images. The same instrument and protocol were used for follow-up imaging of participants with moderate OSA. Additional details are provided in Appendix S3.

Image Analysis

Radiologists were blinded to age, sex, group, cognitive test performance, and clinical data when they analyzed images. Image processing, PVS segmentation, and DTI-ALPS index calculation were performed by one author (S. Lin, with 4 years of experience in neuroimaging), and DTI-ALPS index calculation was independently repeated by a second author (Y.L., with 1 year of experience in neuroimaging). The free water (FW) index calculation was conducted by a third author (L.Q., with 13 years of experience in MRI scan processing).

Image processing.—Three-dimensional T1-weighted imaging data were processed using FreeSurfer 5.3.0 *(http://surfer.nmr.mgh.harvard.edu/)* to obtain intensity nonuniformity–corrected T1-weighted images and white matter (WM) masks (21). The longitudinal stream was used for participants who underwent follow-up imaging (22). The segmentation results were inspected and corrected manually. Diffusion-weighted imaging data were processed in volumetric space using FMRIB Software Library version 6.0 *(https://fsl.fmrib.ox.ac.uk/fsl/docs/#/)* (23).

PVS volume fraction in WM.—PVS regions within the WM, characterized by thin linear structures with a signal similar

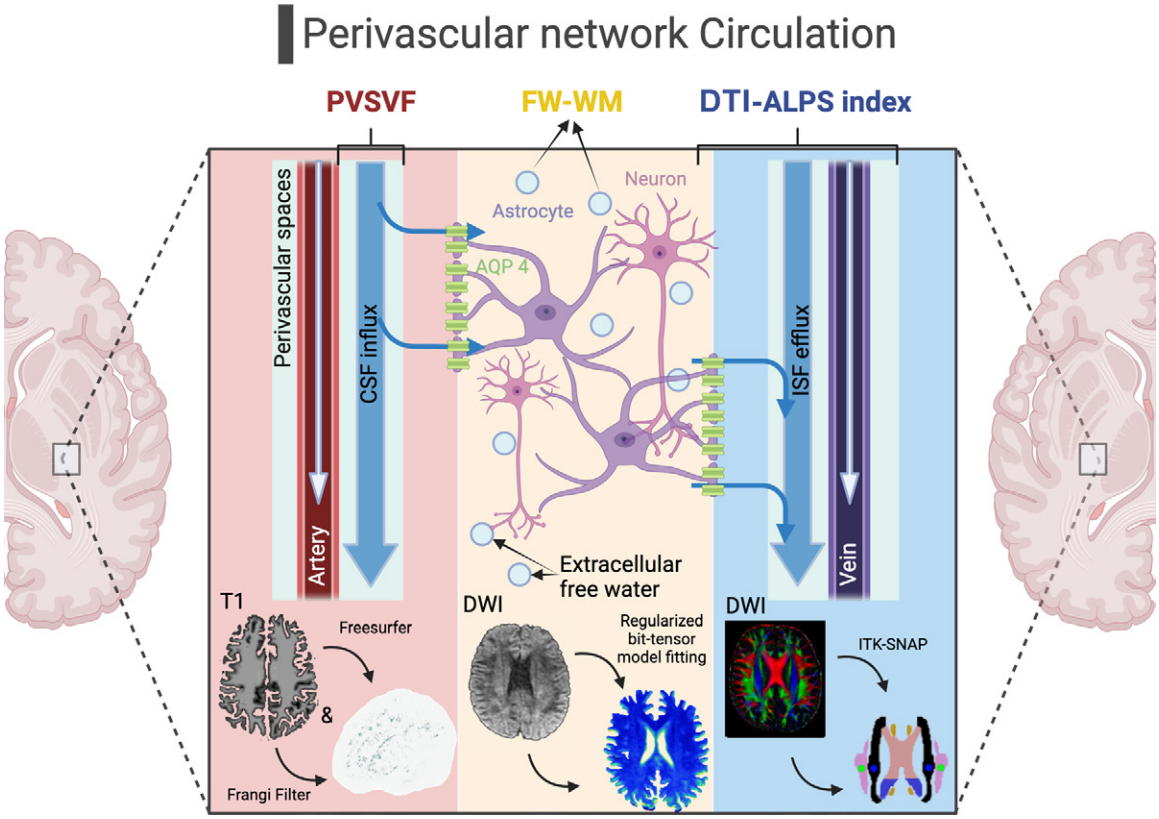

Figure 1: Diagram of three essential physiologic activities in perivascular space (PVS) network circulation and basic concepts of proposed MRI measurements. Cerebrospinal fluid (CSF) influx into the periarterial space of the glymphatic system can be represented by PVS volume fraction (PVSVF), calculated using the FreeSurfer pipeline and Frangi filter algorithm. Exchange between periarterial cerebrospinal fluid and parenchymal interstitial fluid (ISF), facilitated by the aquaporin 4 (AQP 4) protein, can be represented by free water in white matter (FW-WM), derived from diffusion-weighted imaging (DWI). Clearance, referring to the perivenous efflux of brain interstitial waste products, can be represented by the diffusion tensor imaging analysis along the PVS (DTI-ALPS) index, determined using diffusion tensor imaging and ITK-SNAP software.

to cerebrospinal fluid, were initially segmented on processed T1-weighted images using the Frangi filter algorithm (24). The segmentation method was in accordance with previous studies (25), and additional details are provided in Appendix S4. Ultimately, individual PVS volume fraction (PVSVF) in WM (PVSVF-WM) was estimated as the ratio of PVS volume in WM to intracranial volume, thus eliminating potential effects of interindividual variability in brain size (Fig 2A).

FW in WM.—Volume fraction maps were generated from processed diffusion-weighted images (25) using a regularized bitensor model and the open-source software package Dipy *(https://dipy.org/)* (26). Mean FW in WM (FW-WM) excluding the PVS regions was then calculated for each participant (Fig 2B).

DTI-ALPS index.—The DTI-ALPS index was calculated from diffusion-weighted imaging data using the DTIFIT tool of the FMRIB Software Library (23) and ITK-SNAP (27), following previous studies (27,28). More details are provided in Figure 2C and Appendix S4. The intraclass correlation coefficient was used to estimate interobserver agreement.

Statistical Analysis

For demographic data, continuous variables and categorical variables were compared between groups using one-way analysis of variance (ANOVA) and χ^2 tests, respectively. The Kolmogorov-Smirnov test was used to assess the distribution of the data. One-way ANOVA was used to assess group differences in clinical data, PVS indexes, and cognitive performance, and Tukey post hoc analyses were performed to determine the group contributing to the difference. Age and sex were set as covariates in the comparison of PVS indexes (more details provided in Appendix S5). Pearson correlation analysis was performed to assess the relationships among sleep, PVS indexes, and cognitive performance. The paired-samples *t* test was used to assess changes in variables in participants with moderate OSA before and after uvulopalatopharyngoplasty. The least significant difference method was used for multiple comparison corrections. Partial η^2 (η_p^2) and Cohen *d* are reported as measures of effect size for ANOVA and paired-samples *t* tests, respectively. The threshold for statistical significance was $P < .05$. Statistical analyses were conducted by two authors (S. Li and X.L.) in SPSS (version 25.0; IBM).

Sample size calculation was based on G*Power 3.1 (five groups; effect size, 0.4; significance level, 0.05; power, 0.95) (29).

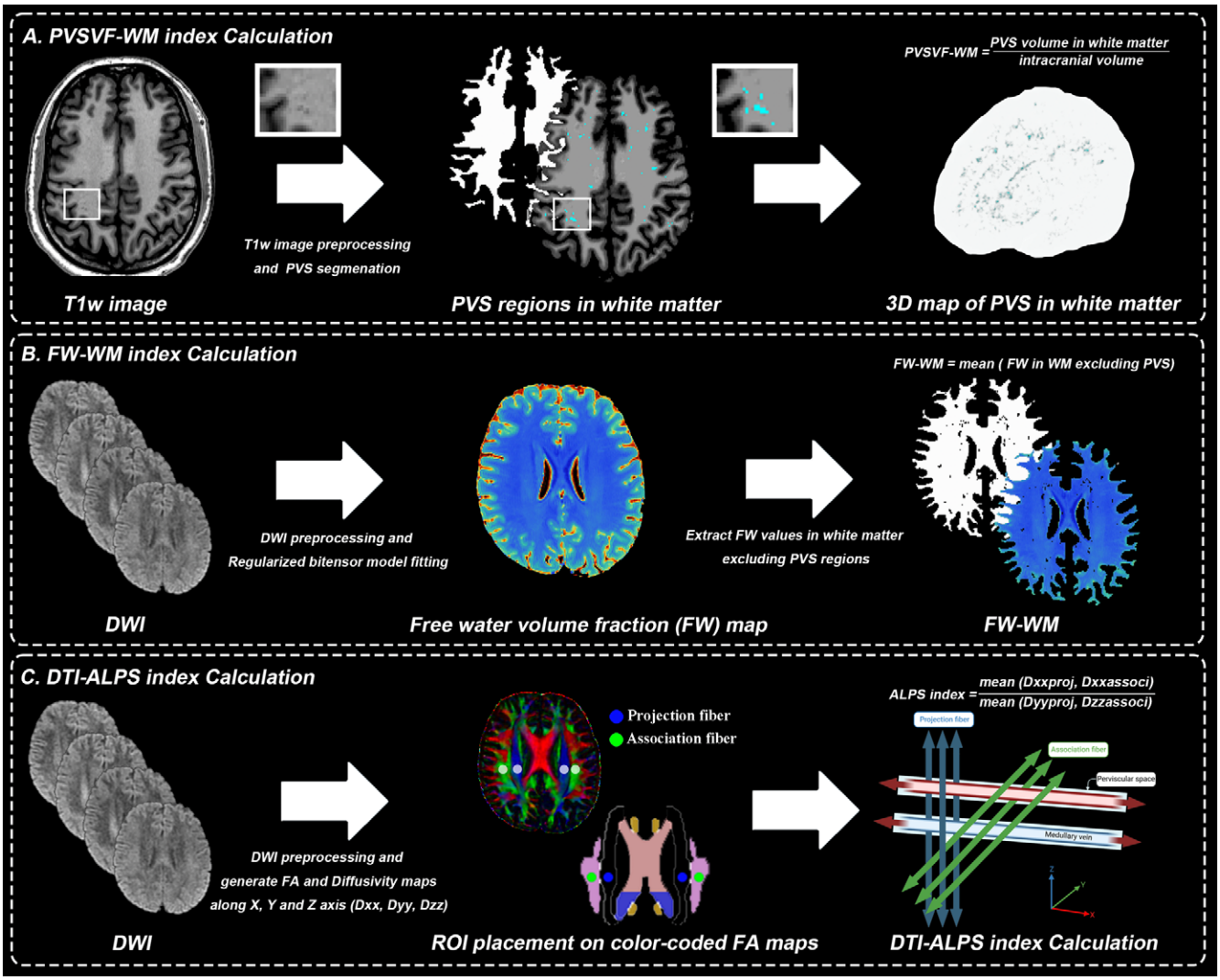

Figure 2: Diagram of MRI indexes of the perivascular space (PVS) network. **(A)** PVS segmentation was performed on preprocessed T1-weighted (T1w) images by applying the Frangi filter before the PVS regions were extracted from the white matter (WM). PVS volume fraction in WM (PVSVF-WM) was calculated as PVS volume in WM divided by intracranial volume. 3D = three-dimensional. **(B)** Free water (FW) volume fraction maps were generated using diffusion-weighted imaging (DWI) and regularized bitensor model fitting. The FW in WM (FW-WM) index was calculated as the mean FW volume fraction within the WM excluding the PVS regions. **(C)** Fractional anisotropy (FA) and individual diffusivity maps were generated from diffusion-weighted images using the ordinary least squares method in the DTIFIT tool of the FMRIB Software Library. In the sections of the lateral ventricle body, regions of interest (ROIs) 4 mm in diameter were placed on bilateral projection fibers and association fibers. The diffusivities of these regions of interest along the directions of the x-axis (right-left; Dxx), y-axis (anterior-posterior; Dyy), and z-axis (inferior-superior; Dzz) were extracted and averaged on both sides of the brain. Finally, the diffusion tensor imaging analysis along the PVS (DTI-ALPS) index was calculated as mean($Dxx_{association}$, $Dxx_{projection}$)/mean($Dzz_{association}$, $Dyy_{projection}$).

Results

Study Participants

A total of 58 HCs were initially recruited, of whom three were excluded due to the potential occurrence of respiratory pauses during sleep and five were excluded for having an ESS score of 6 or more. Among the 115 patients with complaints of snoring initially recruited, two were excluded due to incomplete MRI examinations and eight were excluded for not completing the minimum 7-hour polysomnography monitoring. Ultimately, 50 HCs (mean age, 37.0 years ± 8.6 [SD]; 33 males, 17 females) and 105 participants with complaints of snoring were included in the study (Fig 3).

Among the 105 participants with complaints of snoring, 21 were classified in the snoring group (mean age, 29.4 years ± 7.2; 12 males), 36 in the mild OSA group (mean age, 33.5 years ± 10.9; 25 males), 25 in the moderate OSA group (mean age, 36.3 years ± 9.0; 21 males), and 23 in the severe OSA group (mean age, 33.3 years ± 5.6; 22 males) (Table). Age and sex differed across groups (age, $P = .01$; sex, $P = .02$). For pairwise comparisons, see the Table.

Mean oxygen desaturation index (ANOVA, $\eta_p^2 = 0.67$; $P < .001$) and mean lowest oxygen saturation (ANOVA, $\eta_p^2 = 0.65$; $P < .001$) differed among patient groups and decreased with increasing OSA severity. Additionally, mean BMI (ANOVA, $\eta_p^2 = 0.40$; $P < .001$) and mean ESS score (ANOVA, $\eta_p^2 = 0.83$;

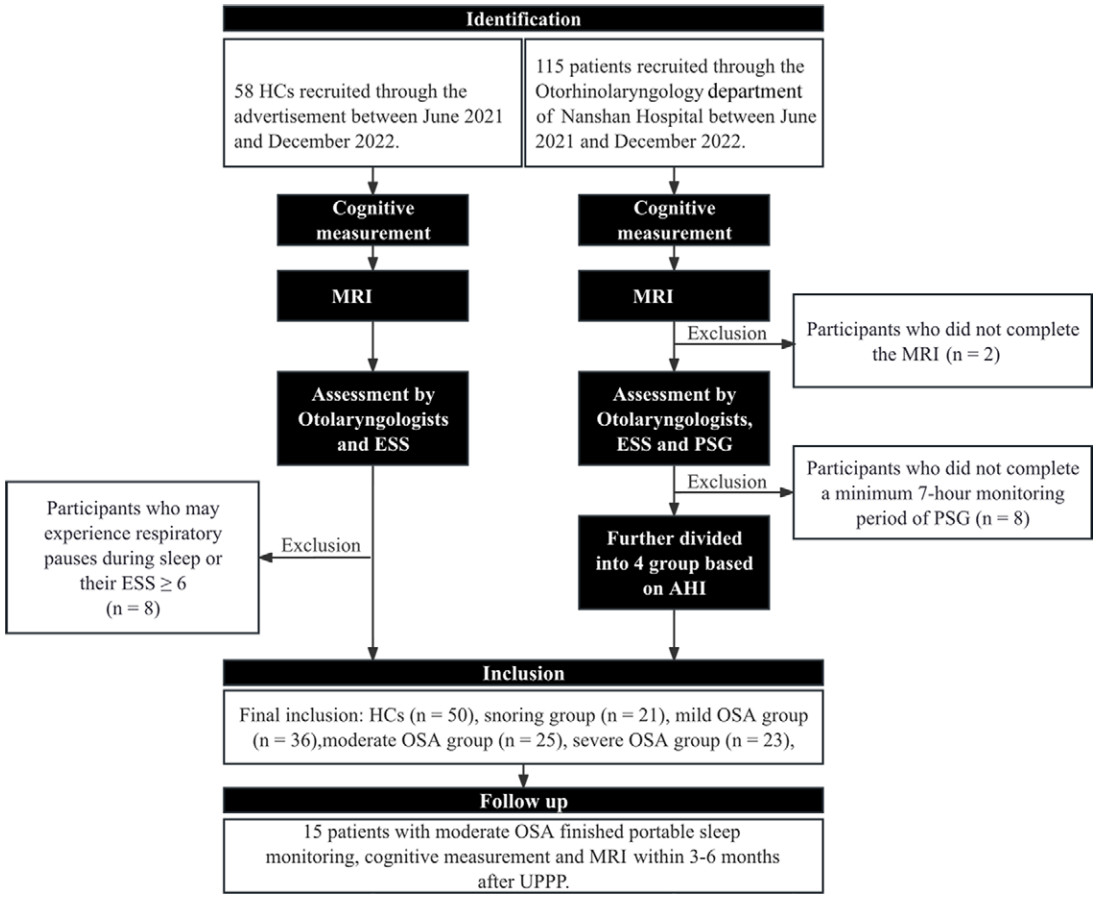

Figure 3: Flow diagram shows the participant selection process for healthy controls (HCs) (left) and patients with complaints of snoring (right). Two patients with obstructive sleep apnea (OSA) were excluded due to incomplete MRI examinations, and eight patients with OSA were excluded for not completing the minimum 7-hour polysomnography monitoring. Cognitive measurements included number connection tests A and B, the serial dotting test, the digit symbol test, the line tracing test, and the Stroop Color and Word Test. After MRI, participants underwent assessment by an otolaryngologist, Epworth Sleepiness Scale (ESS) assessment, and polysomnography (PSG) as shown. The follow-up process for participants with moderate OSA who underwent uvulopalatopharyngoplasty (UPPP) is also indicated. AHI = apnea-hypopnea index.

$P < .001$) differed among the HC and patient groups, with BMI and ESS values increasing with disease severity.

Cognitive Performance

Participants with OSA exhibited significantly poorer cognitive performance than HCs in some comparisons (pairwise η_p^2 range, 0.06–0.08; P value range, .01–.03). Specifically, for time spent on number connection test A, participants in both the moderate (46.8 seconds ± 19.8) and severe (48.8 seconds ± 19.2) OSA groups spent more time than HCs (mean time, 38.5 seconds ± 14.0) and participants in the mild OSA group (38.4 seconds ± 13.4) (pairwise P value range, .009–.03). Additionally, participants in the severe OSA group spent more time on number connection test A than participants in the snoring group (39.3 seconds ± 11.7; pairwise $P = .04$). More cognitive performance comparisons among the HC and patient groups are provided in the Table and Figure 4A.

PVS Indexes

After adjusting for age and sex, PVS indexes differed among the HC and patient groups (PVSVF-WM: $\eta_p^2 = 0.04$, $P = .04$; FW-WM: $\eta_p^2 = 0.14$, $P < .001$; DTI-ALPS: $\eta_p^2 = 0.29$, $P < .001$). Compared with the mild OSA group, the severe OSA group exhibited higher mean PVSVF-WM (0.11 ± 0.011 vs 0.10 ± 0.011; $P = .03$) and higher mean FW-WM (0.11 ± 0.007 vs 0.10 ± 0.010; $P = .003$) (Fig 4B). Additionally, participants in the severe OSA group exhibited higher mean FW-WM than HCs (0.11 ± 0.007 vs 0.10 ± 0.006; $P < .001$) and lower mean DTI-ALPS than the snoring group (1.5 ± 0.4 vs 1.9 ± 0.3; $P < .001$). Both the mild OSA group (1.7 ± 0.3) and the moderate OSA group (1.7 ± 0.4) exhibited lower mean DTI-ALPS than the HCs (2.1 ± 0.4; both $P < .001$). The comparison of other diffusivity values among the HC and patient groups is presented in Figure S1 and Table S1. Results of these analyses repeated with BMI as an additional covariate are provided in Appendix S6 and Figure S2.

Interobserver Agreement for DTI-ALPS Index

Good agreement was observed between two radiologists for DTI-ALPS index (intraclass correlation coefficient, 0.78 [95% CI: 0.71, 0.84]) (Table S2).

Demographic, Clinical, and Cognitive Characteristics of Participants

Variable	HCs (n = 50)	Participants with Snoring (n = 21)	Participants with Mild OSA (n = 36)	Participants with Moderate OSA (n = 25)	Participants with Severe OSA (n = 23)	P Value*
Age (y)	37.0 ± 8.6	29.4 ± 7.2†	33.5 ± 10.9	36.3 ± 9.0‡	33.3 ± 5.6	.01
Age range (y)	24–53	21–50	19–58	20–56	26–44	…
Sex§						
Male	33 (66)	12 (57)	25 (69)	21 (84)‡	22 (95)†‡‖	.02
Female	17 (34)	9 (43)	11 (31)	4 (16)	1 (5)	
AHI	NA	2.3 ± 1.2	9.3 ± 2.7‡	20.2 ± 4.4‡‖	57.4 ± 18.7‡‖#	<.001
ODI	NA	0.9 ± 0.7	6.4 ± 4.5‡	16.3 ± 9.7‡‖	50.1 ± 26.1‡‖#	<.001
Lowest O_2 saturation (%)	NA	91.0 ± 3.4	84.9 ± 4.5‡	79.8 ± 6.6‡‖	62.9 ± 12.9‡‖#	<.001
BMI	21.3 ± 1.7	22.4 ± 2.93	24.8 ± 3.18†‡	25.39 ± 3.23†‡‖	28.47 ± 4.6†‡‖#	<.001
ESS	2.2 ± 1.1	2.4 ± 1.6	4.8 ± 1.8†‡	9.9 ± 2.0†‡‖	14.7 ± 3.7†‡‖#	<.001
NCT-A (sec)	38.5 ± 14.0	39.3 ± 11.7	38.4 ± 13.4	46.8 ± 19.8†‖	48.8 ± 19.2†‡‖	.02
NCT-B (sec)	37.7 ± 12.8	38.5 ± 12.9	38.3 ± 11.1	44.5 ± 15.4†	46.9 ± 17.2†‡‖	.03
DST (no. of matches)	54.3 ± 13.5	54.9 ± 9.8	52.1 ± 10.8	50.8 ± 11.6	46.9 ± 12.5	.12
LTT (sec)	42.7 ± 12.6	44.1 ± 14.9	43.2 ± 12.7	43.2 ± 17.0	42.0 ± 8.1	.99
SDT (sec)	40.8 ± 10.6	40.5 ± 4.9	41.0 ± 10.1	41.3 ± 11.5	41.5 ± 12.0	>.99
Stroop Color and Word Test						
Total off time (sec)	67.9 ± 22.1	64.3 ± 9.5	73.2 ± 21.5	73.4 ± 16.2	78.6 ± 24.8	.12
Total on time (sec)	79.1 ± 25.2	77.60 ± 15.9	87.8 ± 22.1	90.8 ± 23.0†‡	97.2 ± 28.0†‡	.01
Total on time minus off time (sec)	11.1 ± 9.7	13.3 ± 11.8	14.6 ± 7.8	17.40 ± 10.9†	18.6 ± 8.5†	.02
Total on time plus off time (sec)	147.0 ± 46.4	141.9 ± 23.4	161.0 ± 42.9	163.9 ± 38.6‡	175.8 ± 52.2†‡	.02

Note.—Continuous variables are presented as means ± SDs, and groups were compared using one-way analysis of variance. The least significant difference method was used for multiple comparison corrections. AHI = apnea-hypopnea index, BMI = body mass index (calculated as weight in kilograms divided by height in meters squared), DST = digit symbol test, ESS = Epworth Sleepiness Scale, HC = healthy control, LTT = line tracing test, NA = not applicable, NCT-A = number connection test A, NCT-B = number connection test B, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, SDT = serial dotting test.

* P values are for comparison across the five groups, except for AHI, ODI, and lowest O_2 saturation, which are across only the four patient groups because HCs did not undergo polysomnography.

† P < .05 versus the HC group.

‡ P < .05 versus the snoring group.

§ The categorical variable sex is presented as number of participants, with percentages in parentheses. Groups were compared using the χ^2 test.

‖ P < .05 versus the mild OSA group.

# P < .05 versus the moderate OSA group.

Correlations among Polysomnographic Characteristics, PVS Indexes, and Cognitive Performance

Among all participants, PVSVF-WM and FW-WM were positively correlated with AHI (r = 0.22 [95% CI: 0.03, 0.40] and 0.31 [95% CI: 0.12, 0.48]; P = .02 and .001, respectively), oxygen desaturation index (r = 0.26 [95% CI: 0.07, 0.44] and 0.35 [95% CI: 0.16, 0.51]; P = .006 and <.001), and ESS score (r = 0.18 [95% CI: 0.02, 0.34] and 0.33 [95% CI: 0.18, 0.47]; P = .02 and <.001) (Fig 5). Additionally, DTI-ALPS index was negatively correlated with time spent on the Stroop Color and Word Test (on time: r = −0.23 [95% CI: −0.35, −0.06], P = .004; off time: −0.23 [95% CI: −0.36, −0.06], P = .005; on time plus off time: −0.24 [95% CI: −0.36, −0.06], P = .003), AHI (r = −0.50 [95% CI: −0.63, −0.34]; P < .001), oxygen desaturation index (r = −0.48 [95% CI: −0.62, −0.31]; P < .001), and ESS score (r = −0.48 [95% CI: −0.60, −0.35]; P < .001).

Sleep, Cognitive Performance, and PVS Indexes after Uvulopalatopharyngoplasty

Of the 25 participants with moderate OSA, 15 (60%) underwent uvulopalatopharyngoplasty and were reexamined at a median of 4.9 months (IQR, 1.8 months) after the procedure. After treatment, these participants showed decreased PVSVF-WM and FW-WM values and increased DTI-ALPS index values (Fig 6). In addition, they spent less time processing conflicting information (on time minus off time on the Stroop Color and Word Test), less time on number connection tests A and B, and less time on the line tracing test. They also completed a greater number of tasks on the digit symbol test.

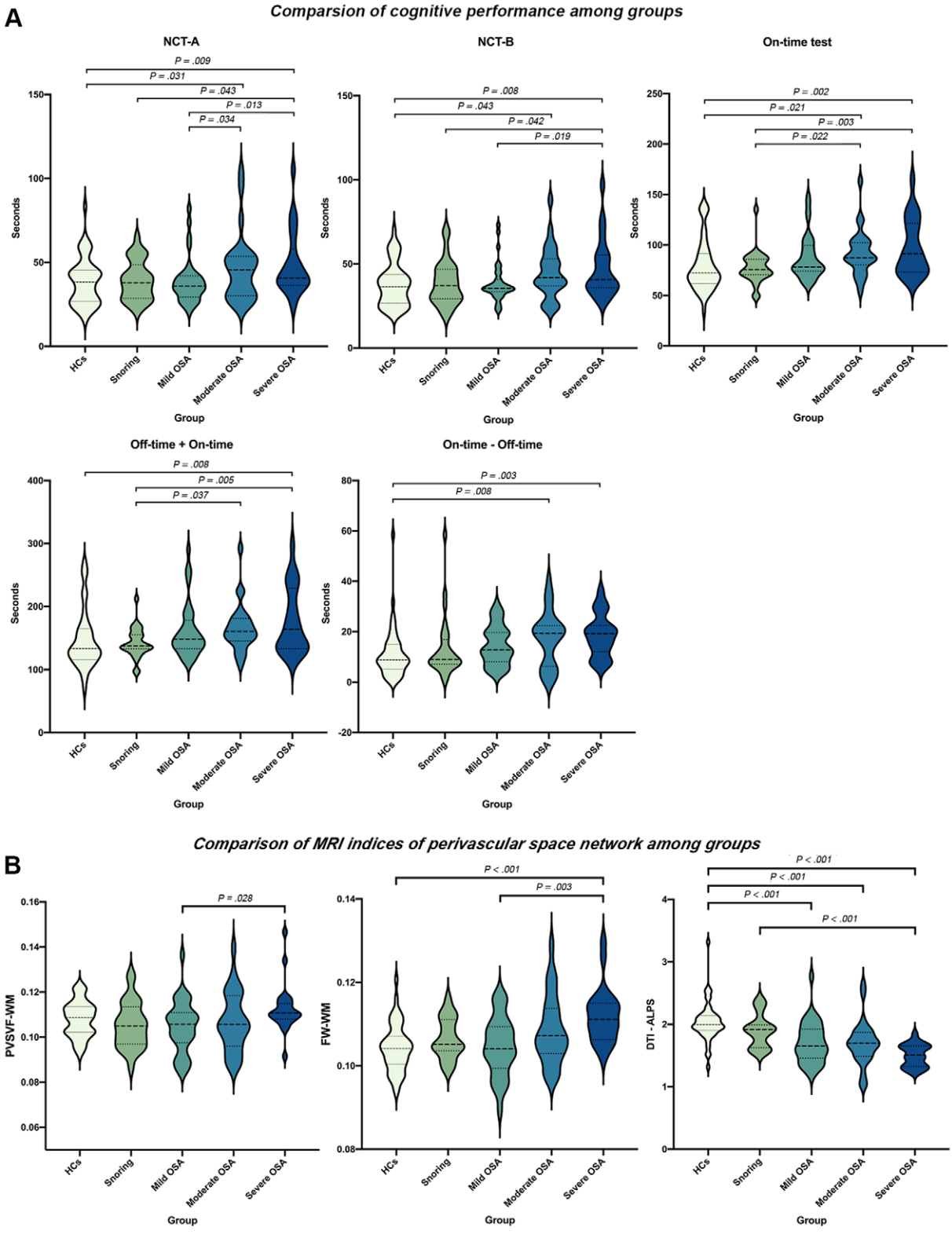

Figure 4: **(A)** Violin plots show pairwise comparisons of cognitive performance measures, including number connection test A (NCT-A), number connection test B (NCT-B), and measures from the Stroop Color and Word Test: on time, on time plus off time (ie, total time on test), and on time minus off time (ie, the time spent processing conflicting information). Differences were observed between healthy controls (HCs, *n* = 50) and participants with severe obstructive sleep apnea (OSA) for all measures (*P* value range, .002–.009) and between participants with mild OSA (*n* = 36) and severe OSA (*n* = 23) for number connection tests A and B (*P* = .01 and .02, respectively). **(B)** Violin plots show pairwise comparisons of MRI indexes of the perivascular space (PVS) network, including PVS volume fraction in white matter (PVSVF-WM), free water in white matter (FW-WM), and diffusion tensor image analysis along the PVS (DTI-ALPS). Differences were observed between HCs (*n* = 50) and participants with severe OSA (*n* = 23) for FW-WM and the DTI-ALPS index (*P* < .001 for both) and between participants with mild versus severe OSA for PVSVF-WM and FW-WM (*P* = .03 and .003, respectively). The width of each curve corresponds to the frequency of data points in that region. The dashed line represents the median, and the dotted lines represent the lower and upper quartiles. Groups were compared using the Tukey post hoc test.

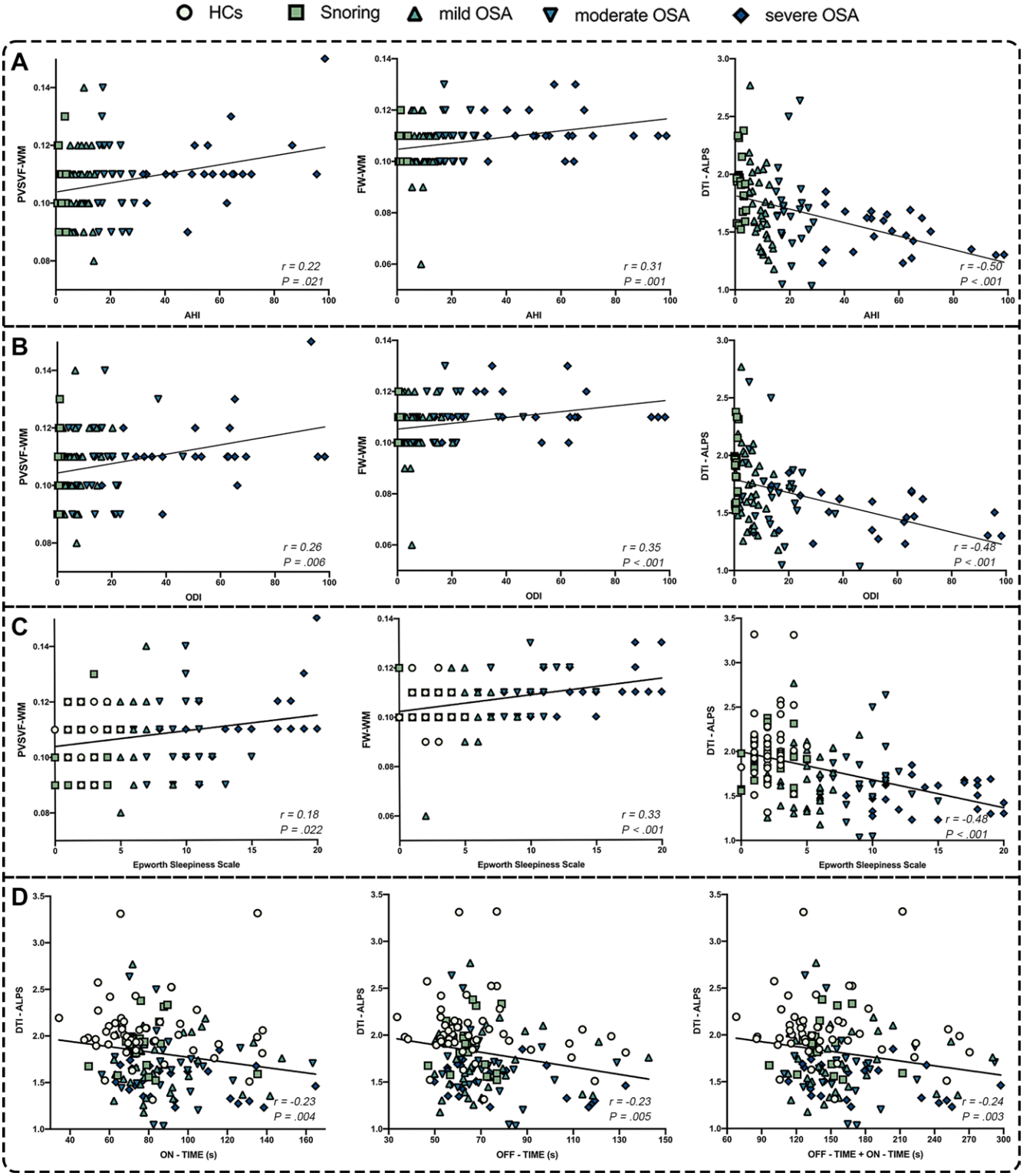

Figure 5: Pearson correlation assessing the relationship between MRI indexes of the perivascular space (PVS) network and clinical characteristics or cognitive performance in all groups. **(A–C)** Scatter plots show correlation between MRI indexes of the perivascular network and **(A)** apnea-hypopnea index (AHI) (*r* range, −0.50 to 0.31; *P* value range, <.001 to .02), **(B)** total oxygen desaturation index (ODI) (*r* range, −0.48 to 0.35; *P* value range, <.001 to .006), and **(C)** Epworth Sleepiness Scale (*r* range, −0.48 to 0.33; *P* value range, <.001 to .02). **(D)** The diffusion tensor imaging analysis along the PVS space (DTI-ALPS) index was negatively correlated with time spent on the Stroop Color and Word Test (less time spent indicates better performance), including on time, off time, and on time plus off time (*r* range, −0.24 to −0.23; *P* value range, .003–.005). FW-WM = free water in white matter, HC = healthy control, OSA = obstructive sleep apnea, PVSVF-WM = PVS volume fraction in white matter.

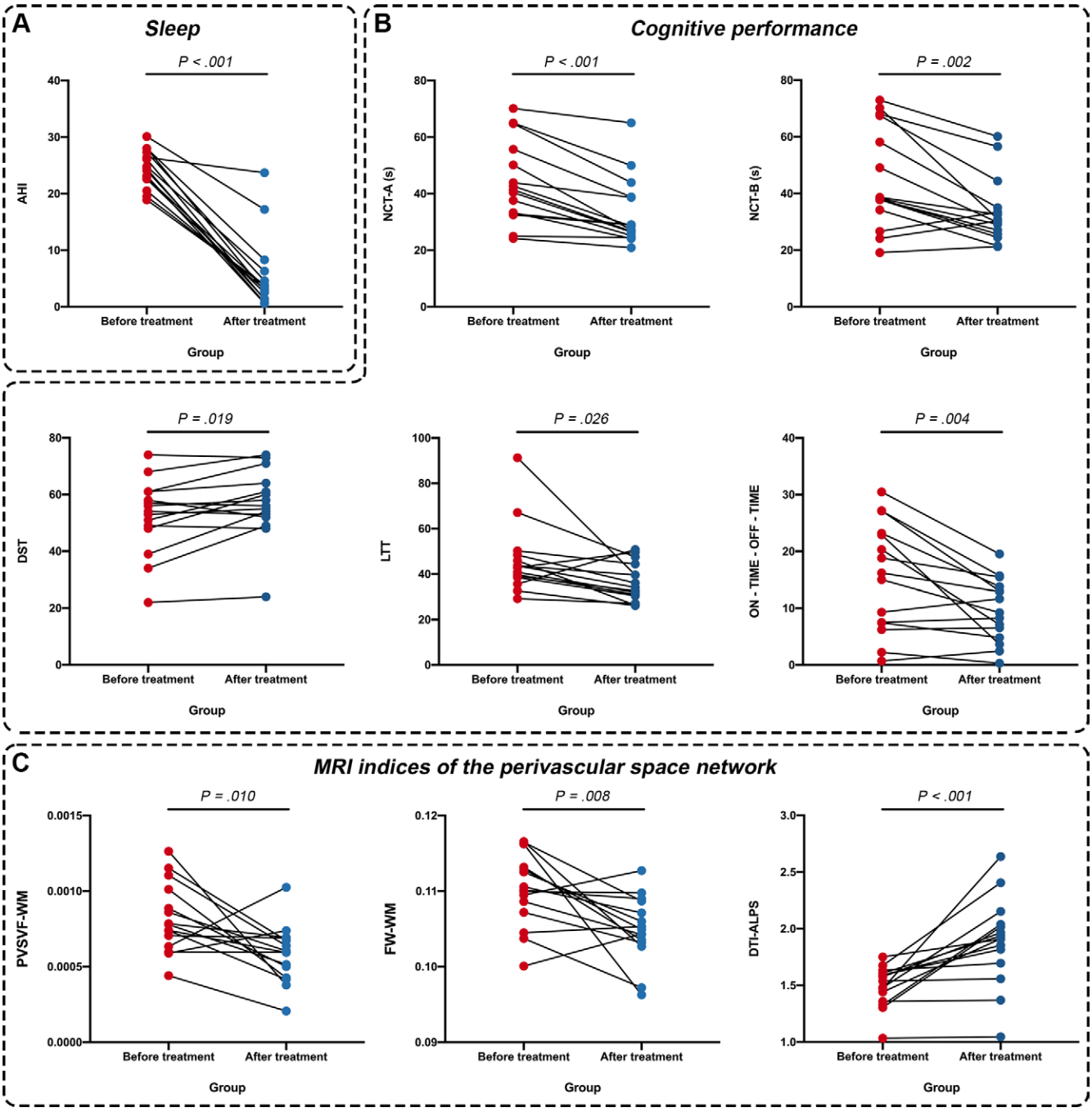

Figure 6: Comparison of metrics in 15 participants with moderate obstructive sleep apnea before and after uvulopalatopharyngoplasty treatment shows improvement in **(A)** apnea-hypopnea index (AHI) (*P* < .001), **(B)** cognitive performance (*P* value range, <.001 to .03), and **(C)** MRI indexes of perivascular space (*P* value range, .001–.01). Metrics before and after treatment were compared using the paired-samples *t* test. DTI-ALPS = diffusion tensor imaging analysis along the perivascular space, DST = digit symbol test, FW-WM = free water in white matter, LTT = line tracing test, NCT-A = number connection test A, NCT-B = number connection test B, PVSVF-WM = perivascular space volume fraction in white matter.

Moreover, no evidence of a difference in mean FW-WM or DTI-ALPS was observed between HCs and participants with moderate OSA after treatment (Table S3).

Discussion

The glymphatic system is a glial-dependent waste clearance system formed by the perivascular space (PVS) network, which is more active during sleep and may be damaged by sleep-related diseases. However, the role of PVS network dysfunction in obstructive sleep apnea (OSA) is still unclear. The aim of this study was to compare MRI indexes of the PVS network across individuals with differing severities of OSA, assess the relationship between these indexes and disease characteristics, and examine if changes occur after treatment. The present study demonstrated that PVS indexes differed in some comparisons among participants with differing severities of OSA and healthy controls (pairwise *P* value range, <.001 to .03). Moreover, diffusion tensor imaging analysis along the PVS

index correlated with measures of cognitive performance on the Stroop Color and Word Test (r range, −0.23 to −0.24; P value range, .003–.005). Finally, in the follow-up cohort of 15 participants with moderate OSA who underwent uvulopalatopharyngoplasty, we observed changes in PVS indexes and improvements in cognitive performance after treatment (Cohen d range, 0.45–1.55; P value range, <.001 to .03).

In our study, PVSVF-WM and FW-WM were positively correlated with AHI (r = 0.22 [95% CI: 0.03, 0.40] and 0.31 [95% CI: 0.12, 0.48]; P = .02 and .001, respectively) while DTI-ALPS index was negatively correlated with AHI (r = −0.50 [95% CI: −0.63, −0.34]; P < .001). The latter is consistent with findings reported by Roy et al (14) and Lee et al (13), who observed that patients with OSA had lower DTI-ALPS index values than HCs. Additionally, Lee et al (13) reported a negative correlation between DTI-ALPS index and AHI in patients with OSA. These results suggest recurrent arousal from sleep and intermittent hypoxia as the cause of perivascular clearance impairment.

Using dynamic contrast-enhanced MRI methods, Wang et al (12) revealed lower drainage function (higher peak concentrations and lower washout rates) in patients with OSA versus HCs. Further, they observed that the relative area ratios of PVS in the frontal cortex and the basal ganglia were higher in patients with severe OSA than in patients with mild-to-moderate OSA (12). Similarly, in our study we observed differences between participants with mild and severe OSA for some PVS indexes (PVSVF-WM, P = .03; FW-WM, P = .003). Of note, these differences remained after adjusting for BMI (PVSVF-WM, P = .03; FW-WM, P = .004) and thus cannot be explained by differences in BMI between groups. We also found no evidence of a difference in PVS indexes between participants who snored and HCs (pairwise P value range, .28–.86), which may be due to individuals who snore being able to maintain a normal sleep structure (30,31).

A negative correlation was observed between DTI-ALPS index and cognitive performance on the Stroop Color and Word Test (r = −0.23, −0.23, and −0.24 for on time, off time, and on time plus off time, respectively; P = .004, .005, and .003), suggesting that PVS network dysfunction may underlie cognitive impairment in individuals with OSA. PVS network dysfunction in patients with OSA may result in insufficient metabolic waste and interstitial solute clearance (9,32), which causes neurotoxicity in the brain and leads to cognitive decline (33). Recent animal studies have supported this hypothesis (9,34). In an animal model, Xie et al (9) observed that sleep deprivation was associated with a marked reduction in the clearance of various cerebrospinal fluid metabolites, amyloid β accumulation, and increased interstitial space volume fraction. Thus, PVS network impairment may be a possible pathologic mechanism underpinning cognitive dysfunction in patients with OSA.

We found that participants with moderate OSA who underwent uvulopalatopharyngoplasty showed improved PVS indexes and cognitive performance 3–6 months after treatment (P value range, <.001 to .03). The prompt recovery of cognitive performance in participants with OSA after treatment has been well documented (12,15). Canessa et al (15) reported that memory, attention, and executive function improved promptly in patients with OSA after initiation of continuous positive airway pressure treatment. More recently, Wang et al (12) demonstrated that 1 month after starting continuous positive airway pressure treatment, patients with OSA showed no evidence of a difference from controls for certain PVS parameters at dynamic contrast-enhanced MRI. However, longitudinal changes in cognitive performance were not fully examined in their study (12). The present study adds to the current literature that both the PVS indexes and cognitive performance improved after uvulopalatopharyngoplasty treatment (12,15). Therefore, the PVS indexes could serve as imaging markers for monitoring treatment efficacy (12,25,33).

The present study has several limitations. First, the number of participants in the snoring and OSA groups was small, as was the number of participants who were followed up after treatment. Therefore, this study may have been underpowered for certain analyses, and the findings need to be validated with a larger sample size. Second, while participants in the snoring group underwent overnight polysomnography, HCs did not. Future studies need to include polysomnography examination in the HC group because defining the HC group based on self-reported snoring and ESS score likely fails to exclude 3% of individuals with OSA (35). Third, only participants treated for moderate OSA were followed up; thus, whether PVS indexes and cognitive performance can be improved in patients with severe OSA remains unexplored. Finally, in addition to age, sex, and BMI, future studies need to adjust for other potential factors (eg, genetic variations) that may influence the PVS network.

In conclusion, differences in MRI indexes of the perivascular space (PVS) network were observed in participants with differing severities of obstructive sleep apnea (OSA) and healthy controls; the indexes correlated with measures of cognitive function; and changes in indexes and improvement in cognitive performance were observed after treatment in participants with moderate OSA. Higher PVS fraction volume in white matter (WM) and free water in WM, as well as a lower diffusion tensor imaging analysis along the PVS index, may reflect a higher risk of cognitive dysfunction in patients with OSA and, following further validation, could potentially be used as markers for screening and monitoring cognitive impairment in these patients. Additionally, as PVS indexes and cognitive impairment changed in patients with moderate OSA who underwent uvulopalatopharyngoplasty, PVS indexes may serve as a marker to monitor longitudinal treatment efficacy. Further histologic studies are needed to elucidate the neurobiologic features underlying these PVS index changes in patients with OSA.

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