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Alterations of neurofluid transport in patients with obstructive sleep apnea and insomnia disorder

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ABSTRACT

Sleep appears to modulate brain-wide neurofluid transport, encompassing the movement and exchange of cerebrospinal and interstitial fluids via perivascular pathways. However, neurofluid transport in common sleep disorders, such as insomnia disorder and obstructive sleep apnea, requires further assessment. In this study, we recruited 159 participants: patients with moderate to severe obstructive sleep apnea (n = 36) or chronic insomnia disorder (n = 62), and healthy controls (n = 61). Participants underwent structural magnetic resonance imaging, polysomnography, the Pittsburgh Sleep Quality Index, and the STOP-Bang questionnaires. Here, neurofluid transport is indirectly assessed using two noninvasive MRI indices (i.e., the perivascular space volume fraction and diffusion tensor imaging along perivascular spaces). Patients with obstructive sleep apnea exhibited a significantly larger perivascular space volume fraction compared with patients with insomnia disorder (p = 0.042) and healthy controls (p = 0.032), whereas no group differences were observed for the diffusion-based index. Partial correlation analyses, adjusted for age, sex, and body mass index, revealed that in obstructive sleep apnea, a larger perivascular space volume fraction was associated with less sleep disturbance ($r = -0.35$, p = 0.04), and diffusion measures increased with snoring severity (r = 0.38, p = 0.03). In insomnia disorder, a larger perivascular space volume fraction was associated with a higher nocturnal wake index (r = 0.38, p = 0.006) and an elevated risk of blood pressure (r = 0.50, $p < 0.001$), while inversely relating to subjective sleep quality ($r = -0.35$, p = 0.01). Our results highlight different patterns of neurofluid transport alterations across obstructive sleep apnea and insomnia disorder.

1. Introduction

Healthy sleep is essential for optimal cognitive functioning and emotional regulation [1,2]. Accordingly, sleep disturbances have been linked to an increased risk for psychiatric disorders such as depression and anxiety 3–5, as well as neurological conditions such as Alzheimer's disease (AD) [6,7]. The most common sleep disorders include insomnia disorder (ID), characterized by the inability to initiate or maintain sleep, affecting approximately 12 % of the population across different countries [8]. Obstructive sleep apnea (OSA) is defined by recurrent episodes of upper-airway collapse during sleep, producing partial (hypopnea) or complete (apnea) airflow obstruction, and is estimated to affect more than one billion people worldwide [9]. Recent evidence indicates a global increase in the prevalence of both disorders, as reflected by rising healthcare expenditures, highlighting their growing significance for public health systems [10].

Emerging evidence suggests a strong link between sleep and the brain's neurofluid transport [11,12], a perivascular pathway responsible

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for the movement and exchange of cerebrospinal fluid (CSF) and interstitial fluids (ISF), as well as removing metabolic waste from the brain interstitium [7,13], which is regulated by astrocytic aquaporin-4 (AQP4) water channels. This brain pathway is often called glymphatic system. It involves the influx of CSF into the brain along periarterial spaces, subsequent movement through the brain parenchyma via AQP4-mediated pathways, and eventual clearance of interstitial fluid via perivenous pathways into the dural sinuses [14,15]. Several studies suggest that neurofluid transport increases during sleep, particularly during non-rapid eye movement (NREM) stages, when expanded extracellular spaces facilitate fluid flow and infra-slow norepinephrine rhythmic oscillations drive CSF into the interstitium [7,12,16].

Assessments of brain's neurofluid transport in humans largely depend on invasive measures of solute transport, namely by way of contrast-enhanced imaging and tracer studies [11]. However, emerging research in clinical AD has led to the synthesis of multiple MRI indices targeted at capturing this pathway non-invasively [7,17]. Preliminary evidence supports a robust association between MRI indices of neurofluid transport and AQP4 deficits [18,19]. Given the strong relationship between neurofluid transport and slow-wave (NREM) sleep, it would be imperative to assess these indices in sleep disorders to determine whether they exhibit similar alterations to those observed in other pathologies. The present study focused on the two most widely reported indices of neurofluid transport: the perivascular space volume fraction (PVSVF) and the diffusion tensor imaging along the perivascular space (DTI-ALPS) index [7,17,20]. Theoretical models integrating these indices have linked them to various components of this pathway, including perivascular influx, AQP4-mediated transport and ISF movement, and efflux [17]. These indices are known to be sensitive to several other factors, including neuroinflammation and white matter morphology, which may confound their interpretation, especially in neurodegenerative diseases [7,21]. Nevertheless, examining PVSVF and DTI-ALPS in ID and OSA may offer new insights into their pathophysiology.

Preliminary investigations have reported reduced DTI-ALPS in OSA [22,23] and ID [24,25]. Additionally, a few studies have reported PVS enlargement in OSA [26,27]. However, no study to date has performed cross-disorder comparisons. This distinction is clinically relevant, as OSA and ID differ substantially in their aetiology and nocturnal symptom profiles, particularly with respect to the pronounced sleep fragmentation, hypoxia, and reductions in NREM sleep commonly observed in OSA [28]. Both animal and human studies have demonstrated that fragmented sleep and diminished NREM sleep impair neurofluid transport [29,30], suggesting that disorder-specific symptomatology may differentially contribute to this clearance pathway. On the other hand, various sleep disorders share similar daytime symptoms and comorbidities, suggesting that they have common neurobiological substrates. For example, a large-scale transdiagnostic meta-analysis identified the convergent abnormalities in the subgenual anterior cingulate cortex, amygdala, and hippocampus across several sleep disorders [31]. Thus, a direct comparison of these indices between individuals with OSA and ID is needed to identify similar or distinct neurofluid transport patterns.

This study aims to compare the PVSVF and DTI-ALPS values among patients with OSA, individuals with ID, and healthy controls (HC). We hypothesize that individuals with OSA will show increased PVSVF and reduced DTI-ALPS compared to those with ID, attributable to a higher prevalence of NREM sleep impairment, increased hypoxia and sleep fragmentation, and accelerated brain aging and beta-amyloid accumulation associated with OSA [32,33]. To elucidate how these differences in the aforementioned indices relate to clinical features of OSA and ID, we further incorporate polysomnography (PSG) and two sleep questionnaires to examine associations between objective physiological sleep parameters, subjective sleep quality, PVSVF, and DTI-ALPS indices.

2. Methods

2.1. Participants and sleep assessment

We initially recruited 167 participants for the study. Patients with chronic ID and moderate to severe OSA were recruited from the Sleep Disorders Research Center, Kermanshah University of Medical Sciences in Iran. All patients were interviewed by a sleep specialist (H.K.) and met diagnostic criteria according to the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) [34], and a psychiatric interview, as well as overnight PSG. We also collected self-reported sleep questionnaires, right before brain MRI acquisition from all participants, including the Pittsburgh Sleep Quality Index (PSQI), which represents sleep quality over the last month, and the STOP-Bang questionnaire, which is usually used to screen for symptoms of OSA. Healthy controls were recruited through local advertisement and were defined as those with no neurological, psychiatric, or sleep disorders at present or past and a total PSQI score of less than 5.

Exclusion criteria for all participants included the Apnea-Hypopnea Index (AHI) < 15 for OSA patients (to include only moderate to severe OSA), patients with comorbid insomnia and OSA (COMISA), any chronic medical disease, psychiatric or neurological comorbidities, current use of medication affecting sleep, pregnancy in women, and any contraindications for MRI. Two patients with comorbid periodic leg movement, two patients with hydrocephaly, one patient with brain mass, and three subjects with excessive head movement in the scanner (which caused distortion in the images) were excluded from the study. Finally, analyses were performed on 159 participants, including 62 ID patients, 36 OSA patients, and 61 healthy controls. The included data of some patients with ID overlaps with our previous publications [35–37]. The study was approved by the Ethics Committee of the National Institute for Medical Research Development (IR.NIMAD.REC.1399.086) and Kermanshah University of Medical Sciences (IR.KUMS.REC.1399.259), and written informed consent was obtained from all participants.

2.2. MRI data acquisition

All participants underwent brain imaging using a Siemens Magnetom Avanto 1.5 T MRI whole-body scanner with an 8-channel head coil in Farabi Hospital at Kermanshah University of Medical Sciences. For T1-weighted (T1W) imaging, a 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence was used with the following parameters: TR = 1950 ms, TE = 3.1 ms, flip angle = 15°, field of view (FOV) = 256 × 256 mm^2, matrix size = 256 × 256 mm^2, voxel size = 1 × 1 × 1 mm^3, and 176 sagittal slices. Diffusion-weighted imaging (DWI) data were acquired using a single-shot spin-echo EPI sequence with the following parameters: TR = 10,500 ms, TE = 106 ms, FOV = 256 × 256 mm^2, matrix size = 128 × 128 mm^2, flip angle = 90°, voxel size = 2 × 2 × 2 mm^3, b-values = 0 and 1000 s/mm^2, and 30 diffusion gradient directions. A total of 68 slices were used to cover the entire brain.

2.3. PVS segmentation and quantification

The pre-trained SHIVAI U-net was used to segment PVS in high-resolution T1-weighted MRI scans [38]. Weights were obtained from https://github.com/pboutinaud/SHiVAi. FreeSurfer parcellations were used to identify PVS clusters in the centrum semiovale, basal ganglia, and hippocampus. The total PVS volume was then calculated by summing the volumes of all identified clusters. To account for individual variations in brain size, the PVS volume fraction (PVSVF) was obtained by dividing the total PVS volume by the total intracranial volume (ICV) [39].

2.3.1. DTI-ALPS index calculation

The DTI-ALPS index was derived from the ratio of mean diffusion values in the x-axis in the projection fibers (Dxproj) and associative

fibers (Dxassoc) to the mean diffusion values in the y-axis in the projection fibers (Dyproj) and the z-axis in the associative fibers (Dzassoc) [20]. In the projection fiber region, dominant fibers are oriented along the z-axis, with x and y axes perpendicular to these fibers. In the associative fiber region, dominant fibers are oriented along the y-axis, with x and z axes perpendicular to these fibers. The observed differences in water molecule behavior, between diffusion along the x-axis in both regions (Dxproj and Dxassoc) and perpendicular diffusion (Dyproj and Dzassoc), reflect diffusion occurring within an efflux pathway, which is shaped by the surrounding vascular space.

The DTI-ALPS index was calculated automatically using an open-source pipeline (https://github.com/gbarisano/alps), which integrates FSL 6.0.5 (https://fsl.fmrib.ox.ac.uk/fsl/) and MRtrix3 (https://www.mrtrix.org/) to process data from left, right, and average across the entire brain. The Fractional Anisotropy (FA) maps and diffusivity maps along the x-, y-, and z-axes were generated from DWI images using the FSL command line tool “dtifit." The FA map for each subject was then co-registered to the JHU-ICBMFA template, and the resulting transformation matrix was applied to all diffusivity maps using the FSL command line tool “flirt." Based on the JHU-ICBM-DTI-81 white matter Labeled Atlas, the projection and association fibers at the level of the lateral ventricle body were identified as the superior corona radiata and the superior longitudinal fasciculus. ROIs were automatically defined as 5 mm diameter spheres in the regions of bilateral projection and association fibers, which were then applied to the diffusivity maps of all subjects. The diffusivity values for Dxx, Dyy, and Dzz in the bilateral superior corona radiata and the superior longitudinal fasciculus regions were automatically extracted for calculating the ALPS index [40]. We performed a visual inspection of the DTI images and the color-coded FA maps for all participants. Additionally, we reviewed the quality-control images generated by the automated pipeline to confirm the accurate placement of the regions of interest (ROIs). Participants with poor image quality or incorrect ROI placement were excluded from the study. After quality control, a total of 36 OSA patients, 62 individuals with insomnia, and 61 healthy controls were included in the final analysis.

2.4. Statistical analyses

Demographic and clinical data were assessed between each pair of groups (HC vs ID, HC vs OSA, and ID vs OSA) by independent samples t-tests, and Chi-square test for categorical characteristics using SPSS, v27.0 (SPSS Inc., Chicago, Illinois). The primary analysis for comparing PVSVF and DTI-ALPS indices among the three groups was performed using analysis of covariance (ANCOVA) and post-hoc *t*-test, adjusted for multiple comparisons using the Bonferroni correction. This analysis was conducted within the framework of the general linear model (GLM), with age, sex, and Body Mass Index (BMI) included as covariates. Regarding the inclusion of BMI as a covariate, it was added because BMI has been shown to influence neuroimaging metrics, including brain structure and cerebrovascular function, as well as PVS volume [39]. Given the potential effects of BMI on neurofluid transport and brain morphology, we included it to control for its confounding effect and better isolate the relationships between other variables and PVS volume.

In the subsequent analysis, partial correlation was used to examine the relationships between polysomnographic parameters, the scores for each component of the PSQI and STOP-Bang questionnaires, and the neurofluid transport indices. The analyzed polysomnographic parameter scores included total sleep time, sleep efficiency, AHI, respiratory disturbance index (RDI), average SpO_2, minimal SpO_2, SpO_2 Time <90 %, snore index, wake index, and average heart rate. We additionally analyzed the PSQI total score and its seven components (C1: Subjective Sleep Quality, C2: Sleep Latency, C3: Sleep Duration, C4: Habitual Sleep Efficiency, C5: Sleep Disturbances, C6: Use of Sleeping Medication, C7: Daytime Dysfunction), as well as the STOP-Bang total score and its eight components (STOP1: Snoring, STOP2: Tiredness, STOP3: Observed Apnea, STOP4: High Blood Pressure, STOP5: BMI, STOP6: Age, STOP7: Neck Circumference, STOP8: Gender). Notably, these correlation analyses were conducted exclusively on patient groups. The covariates of the partial correlation analyses in this study were age, gender, and BMI. Statistical significance was set at $p < 0.05$ for all tests.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are presented in Table 1. No significant differences were observed in age, wake index, or average heart rate between individuals with ID and OSA. ID patients and healthy controls had no significant differences in age or BMI, but the OSA group had a significantly higher age than the control group. Therefore, we considered age, gender, and BMI as covariates. Compared to ID patients, individuals with OSA exhibited significantly higher total sleep time, sleep efficiency, AHI, RDI, SpO_2 Time <90 %, snore index, average heart rate, and STOP-Bang scores ($p < 0.05$). Conversely, ID patients demonstrated significantly higher PSQI scores, wake index, and both average and minimal SpO_2 levels compared to those with OSA ($p < 0.05$).

3.2. PVSVF enlargement in patients with OSA

To address the non-normal distribution of PVSVF data (as seen in Fig. 1A), we employed a Generalized Linear Model (GLM) with a Gamma distribution and log link. After adjusting for age, sex, and BMI in this model and applying Bonferroni correction, we observed significantly higher PVSVF in OSA patients compared to healthy controls ($p = 0.032$) and ID patients ($p = 0.042$).

In contrast, the DTI-ALPS index data were normally distributed, and assumptions were met for an Analysis of Covariance (ANCOVA). The ANCOVA, adjusting for the same covariates, revealed no significant differences in the mean DTI-ALPS index between the three groups (Fig. 1B).

3.3. Association of DTI-ALPS index and PVSVF with clinical scores

Partial correlation analysis was performed after correction for age, gender, and BMI. In patients with OSA, no significant correlations were observed between the PVSVF and DTI-ALPS with PSG variables (Fig. 2A). The PVSVF demonstrated a negative correlation with the component 5 (sleep disturbances) score of the PSQI questionnaire ($r = -0.35$, $p = 0.04$) (Fig. 2B). Additionally, DTI-ALPS exhibited a positive correlation with the component 1 (snoring) score of the STOP-Bang questionnaire in OSA ($r = 0.38$, $p = 0.03$) (Fig. 2C).

In patients with ID, PVSVF was positively correlated with both the wake index in PSG ($r = 0.38$, $p = 0.006$) and component 4 (high blood pressure) score of the STOP-Bang questionnaire ($r = 0.5$, $p = 0.001$) (Fig. 2D and F). We also observed a negative correlation between PVSVF and the component 1 (subjective sleep quality) score of the PSQI questionnaire ($r = -0.35$, $p = 0.01$) (Fig. 2E). There was no significant correlation between DTI-ALPS and sleep measurements in the ID group.

4. Discussion

4.1. Main findings

Our findings demonstrated that OSA patients showed higher PVSVF values compared to ID and HC groups, whereas no group differences emerged for the DTI-ALPS index. Subsequently, we examined how these indices related to clinical characteristics within each disorder. Regarding PVSVF scores, the OSA group showed that higher PVSVF was associated with lower self-reported sleep disturbances on the PSQI, while no associations with PSG parameters were observed. In contrast, within the ID group, higher PVSVF values were related to increased

Table 1
Demographics and clinical data.

Variables	ID (n = 62)	OSA (n = 36)	Controls (n = 61)	*P* Value ID vs OSA vs HC	*Post-hoc P* Value HC vs ID	HC vs OSA	ID vs OSA
Age (years)	44.7 ± 11	48.4 ± 10	41.1 ± 11.7	0.008*	0.084	0.003*	0.098
Sex (M:F)	20:42	26:10	31:30	<0.001*	0.037*	0.034*	<0.001*
BMI (kg/m2)	26.2 ± 4	28.7 ± 3	25.5 ± 3.9	<0.001*	0.34	<0.001*	0.003*
Total Sleep time	5.07 ± 1.76	5.9 ± 1.3	_	_	_	_	0.011*
Sleep Efficiency	66.48 ± 21.8	76.6 ± 18.5	_	_	_	_	0.024*
AHI	3.23 ± 3.06	29.01 ± 15.4	_	_	_	_	<0.001*
RDI	5.47 ± 6.2	30.7 ± 16.67	_	_	_	_	<0.001*
Average SpO_2	93.8 ± 1.6	91.1 ± 2.4	_	_	_	_	<0.001*
Minimal SpO_2	88.7 ± 3.6	79.8 ± 6.8	_	_	_	_	<0.001*
SpO_2 Time <90 %	0.06 ± 0.27	1.33 ± 1.72	_	_	_	_	<0.001*
Snore Index	53 ± 76.3	268.6 ± 226.5	_	_	_	_	<0.001*
Wake Index	7.1 ± 7.7	5.2 ± 2.9	_	_	_	_	0.16
Average HR	67.6 ± 8.9	68.5 ± 6.9	_	_	_	_	0.59
PSQI Total Score	15.6 ± 2.8	8.1 ± 4.5	2.4 ± 1.08	<0.001*	<0.001*	<0.001*	<0.001*
STOP-BANG Total Score	1.96 ± 1.07	4.08 ± 1.4	_	_	_	_	<0.001*

Data are presented as mean ± SD, ID: ID, OSA: obstructive sleep apnea, BMI: body mass index, AHI: apnea-hypopnea index, RDI: respiratory disturbance index, AverageSpO_2: average oxygen saturation, MinimalSpO_2: minimal oxygen saturation, SpO_2 Time: oxygen saturation time, AverageHR: average heart rate, PSQI: Pittsburgh Sleep Quality Index.

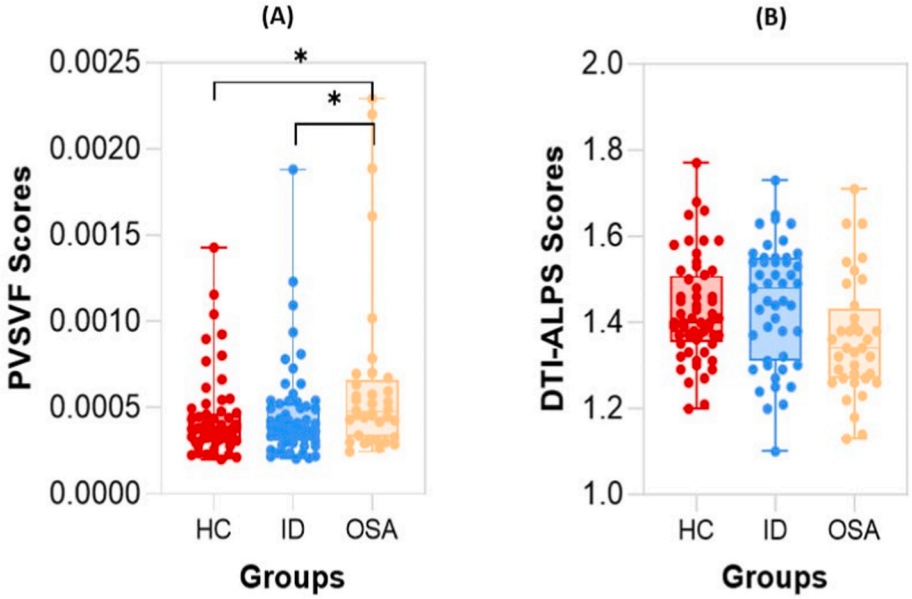

Fig. 1. Between-group differences in perivascular space (PVS) volume fraction and diffusion tensor image analysis along the perivascular space (DTI-ALPS) index among the patients with insomnia disorder (ID), obstructive sleep apnea (OSA), and healthy control (HC) (covariates include age, gender, and BMI). *p < 0.05, Asterisks indicate Bonferroni-corrected significance levels from the adjusted model (covariates: age, sex, BMI).

nocturnal wakefulness, indicative of greater sleep fragmentation, as well as to the hypertension component of the STOP-Bang questionnaire, pointing toward an elevated cardiovascular risk profile. Moreover, higher PVSVF in the ID group was linked to poorer subjective sleep quality on the PSQI. Considering the DTI-ALPS index, significant associations emerged only in the OSA group, where higher values were correlated with greater snoring severity on the STOP-Bang questionnaire. Of note, these indices only reflect proxy markers of neurofluid transport and should not be taken as direct evidence of increased or decreased glymphatic influx or efflux.

4.2. Research in context

Our findings align with the literature regarding the enlargement of PVSVF in patients with OSA [26,27], supporting the notion of attenuated neurofluid flow along perivascular pathways. In contrast, we observed no comparable findings in ID. Previous work has demonstrated that slow, high-amplitude waves during NREM sleep give rise to oscillatory vasomotor patterns that are thought to facilitate fluid movement within the PVS [41]. Sleep architecture alterations, as seen in OSA [42], may disrupt this exchange and could thereby contribute to the increased PVS volume observed in our study. Additionally, evidence suggests that extracellular spaces are more contracted in OSA, a mechanism that may further attenuate neurofluid transport [43]. Prior work has highlighted attenuated DTI-ALPS values in ID [24,25] as well as in OSA compared to HC [22,23]. While our data revealed a similar trend in OSA, this effect did not reach statistical significance, which may be due to our limited sample size, cohort-specific factors, MRI scanner (1.5 T), or other methodological variabilities. Indeed, the DTI-ALPS index is influenced by various physiological factors and sensitive to ROI placement, thereby limiting cross-study comparability [21].

Existing studies have demonstrated associations between poor sleep symptom characteristics and neurofluid transport. For instance, increased sleep fragmentation has been proposed as a risk factor for the dysregulation of neurofluid transport [30]. In contrast, in OSA, we observed a negative association between PVSVF and the PSQI sleep

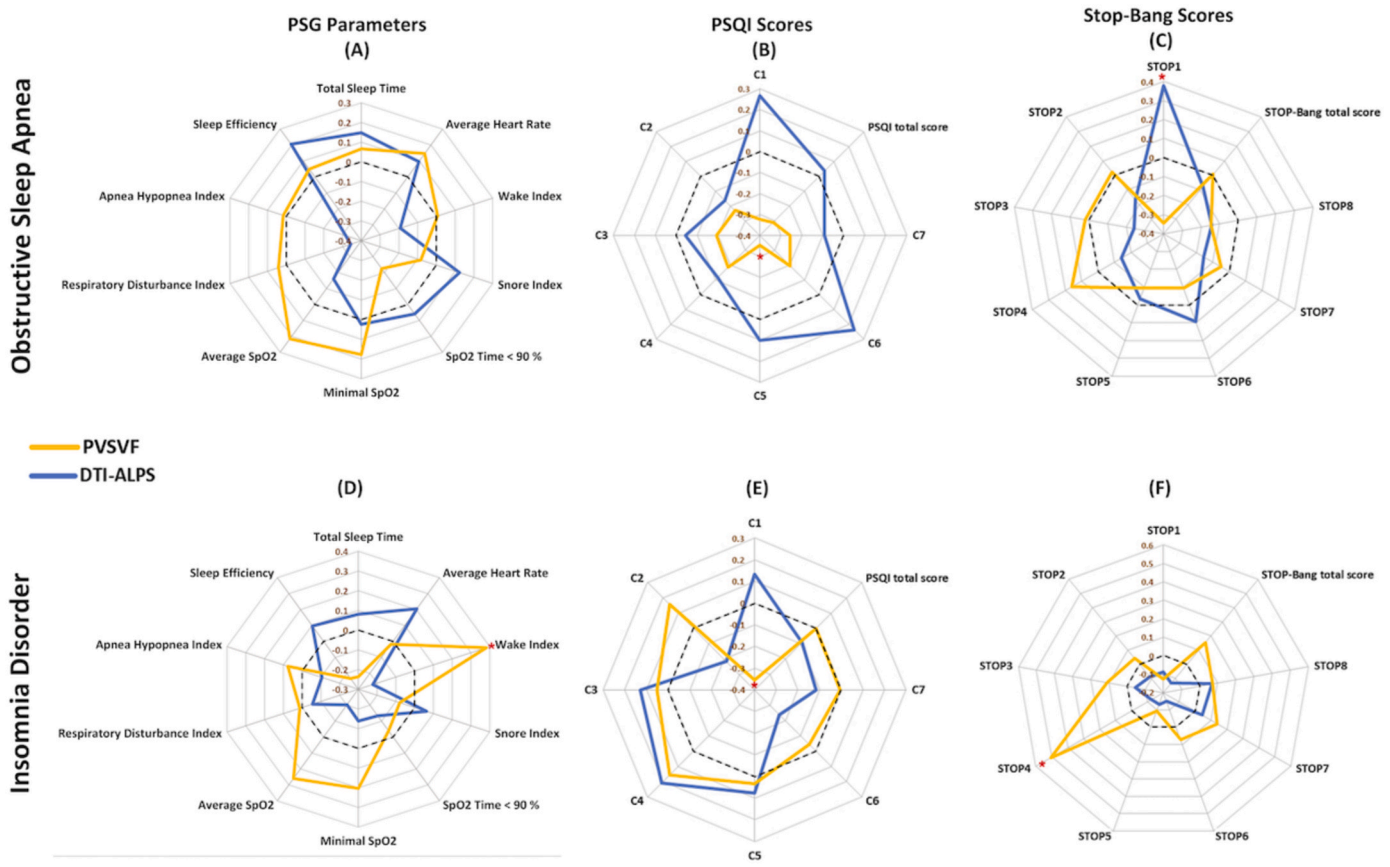

Fig. 2. Partial correlation analyses (after correction for age, gender, and BMI) between the DTI-ALPS index and perivascular space volume fraction (PVSVF) with polysomnographic parameters and components of sleep questionnaires in individuals with ID (ID) and obstructive sleep apnea (OSA). *Statistical significance was set at $p < 0.05$ (uncorrected for multiple comparisons).
PSQI: Pittsburgh Sleep Quality Index, C1 to C7: PSQI questionnaire component 1 score to component 7 score (C1: Subjective Sleep Quality, C2: Sleep Latency, C3: Sleep Duration, C4: Habitual Sleep Efficiency, C5: Sleep Disturbances, C6: Use of Sleeping Medication, C7: Daytime Dysfunction), STOP1 to STOP8: STOP-Bang questionnaire component 1 score to component 8 score (STOP1: Snoring, STOP2: Tiredness, STOP3: Observed Apnea, STOP4: High Blood Pressure, STOP5: BMI, STOP6: Age, STOP7: Neck Circumference and STOP8: Gender).

disturbance component. Similar discrepancies have also been reported in previous studies, with higher sleep efficiency being positively associated with greater PVS volume [44], and both higher sleep efficiency and better sleep quality likewise showing positive associations with PVS volume in another cohort [45]. A systematic review of 51 studies investigating sleep characteristics and neurofluid transport revealed substantial heterogeneity in reported results as well as considerable variation across assessment methods [46]. Accordingly, a recall bias cannot be excluded in our study, as sleep quality was derived from subjective self-reports.

We observed that increased snoring was associated with increased DTI-ALPS values, a finding which is inconsistent with a recently published phenome-wide association study [47]. This study examined around 40,000 participants from the UK Biobank and demonstrated that greater snoring severity was associated with lower DTI-ALPS indices. This notion is further supported by findings from a rodent model where continuous positive airway pressure (CPAP) administration led to an increase in CSF flow, as demonstrated by dynamic contrast-enhanced MRI [48]. These results could indicate that OSA-associated snoring may contribute to a dysregulation of neurofluid transport, which could be stabilized through the application of CPAP. Our contradictory findings may, however, be attributable to the characteristics of our study cohort. Despite high AHI values, many subjects with OSA reported low levels of snoring. This self-reported score might therefore not adequately capture the severity of apnea as captured by objective measures, thereby limiting its validity as a marker of disease burden and reducing its explanatory power regarding the association between snoring and DTI-ALPS indices.

In individuals with ID, PVSVF was positively associated with the PSG-derived wake index, indicating that greater sleep fragmentation corresponds to an increased perivascular space burden. This pattern aligns with evidence from animal models, where prolonged sleep fragmentation over 30 days significantly reduced CSF influx into the brain [49]. Experimental work in mice further indicates that sleep fragmentation is associated with reduced expression of AQP4 [30], a key mediator of fluid exchange between perivascular spaces and the interstititum [50]. In line with this notion, complete deletion of the AQP4 gene has been shown to substantially impair solute transport into the brain parenchyma [51]. As such, the observed PVSVF increase may be an indicator of reduced AQP4 polarization in sleep disorders, though direct measurements are required to confirm this. In addition to its effect on AQP4 localization and morphology, sleep fragmentation exerts neuronal effects by inducing hyperactivation of the locus coeruleus, a structure that is characteristically downregulated during sleep [43]. This process is mediated by the release of norepinephrine within the locus coeruleus, which disrupts its normal inhibitory function during sleep. The resulting hyperactivity interferes with the generation of rhythmic oscillations that support cerebral fluid exchange. Interestingly, Zolpidem, which patients with insomnia disorder widely use, suppressed such norepinephrine oscillations and neurofluid flow [16].

PVSVF also correlated positively with the blood pressure component of the STOP-Bang questionnaire in ID, indicating a potential association

of PVS enlargement with elevated blood pressure and increased cardiovascular risk. This observation is supported by prior human studies showing detrimental effects of vascular risk factors, including elevated diastolic blood pressure and smoking, on neurofluid transport as indexed by reduced DTI-ALPS values [52]. Complementary animal data corroborate this interpretation, demonstrating that hypertension induces pathological CSF reflux into the ventricles, indicative of abnormal CSF dynamics, an effect exacerbated under chronic exposure [53].

4.3. Differential role of OSA and ID on neurofluid transport and their link to dementia

There is a wealth of evidence linking sleep disorders such as OSA and ID as risk factors of Alzheimer's disease and other dementias [32,54,55]. Our findings provide a potential explanation for understanding the differential contribution of OSA and ID to AD vulnerability. The more pronounced alterations in PVSVF and DTI_ALPS in OSA concur with prior evidence demonstrating a robust association between OSA and AD 32,56–59, whereas the relationship between ID and AD remains less consistent [54,60]. This difference may be related to diverging pathophysiology, as OSA is characterized by considerable sleep fragmentation, intermittent hypoxia, oxidative stress, and neuroinflammation [61]. Experimental models have shown that inflammation can expand so-called dead-space domains within the extracellular space through astrocytic swelling [62]. These domains impede diffusion and may not be fully reversible [62]. In a clinical context, chronic hypoxia and inflammation in OSA may progressively compromise extracellular space permeability, thereby impairing the clearance of toxic metabolites such as amyloid-beta (Aβ) [43]. Although ID has likewise been associated with elevated inflammatory markers [63], mendelian randomization studies indicate that inflammation is unlikely to be causally attributable to ID per se, but rather to comorbid conditions linked to systemic inflammation [64]. This distinction may explain why OSA, more than ID, confers an increased risk for attenuation in neurofluid transport via hypoxia-driven inflammatory pathways. The more pronounced cognitive deficits frequently reported in OSA compared with ID may thus reflect inflammation-induced attenuation of neurofluid transport, potentially contributing to cognitive impairment [65].

Unlike ID, OSA is characterized by recurrent apneic episodes, during which upper airway collapse leads to additional mechanical perturbations that may compromise neurofluid transport. These events increase intrathoracic and intracranial pressures and induce hemodynamic disturbances [28], thereby impairing the transport of metabolites from the interstitial fluid into the CSF [66]. Moreover, hypoxia-induced elevations in venous pressure may restrict CSF drainage via the dural lymphatic system [43], further promoting the accumulation of Aβ and tau [33], and potentially contributing to an elevated risk of AD. The symptomatologic differences between OSA and ID imply a heightened risk of attenuation in neurofluid transport in OSA, a notion that is supported by our findings. Such vulnerability may contribute to the stronger and more consistent association observed between OSA and AD. Whether the observed alterations in PVSVF are primarily attributable to a dysregulation of neurofluid transport, hypoxia-related neuroinflammation, intrathoracic pressure alterations, or all of the above, remains a topic for further studies using invasive methods.

4.4. Methodological strengths, limitations, and future directions

Our study has some methodological and conceptual strengths. First, it compared two non-invasive indices of neurofluid transport, which have been discussed as potential markers of glymphatic function, providing new insights into their behavior in disordered sleep. Second, the design enabled a direct comparison of two highly prevalent sleep disorders, theorizing about disorder-specific contributions to alterations in PVSVF and DTI-ALPS and their implications for brain morphology and neurofluid flow. Finally, the inclusion of both objective (PSG) and subjective measures (PSQI and STOP-Bang questionnaires) provided a more comprehensive characterization of various contributing factors. Given that ID is predominantly defined by subjective sleep quality [67], exclusive reliance on objective parameters would insufficiently capture the clinical phenotype. The combined use of subjective and objective sleep data, therefore, offered a more complete evaluation of sleep disorders in relation to glymphatic function.

Despite its strengths, this study has inevitable limitations that merit further discussion. A more valid approach for assessing neurofluid transport in humans is intrathecal administration of gadolinium-based contrast agents, which allows direct evaluation of clearance [68], which was not available for us. In contrast, the present study relied on non-invasive MRI indices, which do not allow for an explicit quantification of neurofluid exchange but rather indirectly estimate neurofluid transport with reduced sensitivity [17]. Our use of PVSVF and DTI-ALPS operationalizes neurofluid transport indirectly. These proxies do not quantify CSF-ISF exchange rates or directionality. In addition, there is a lack of a comprehensive cardiovascular assessment. Although analyses were adjusted for age, sex, and BMI, and the blood pressure component of the STOP-Bang questionnaire was included as a proxy, direct measures such as blood pressure readings, heart rate variability, lipid and glucose levels, and vascular comorbidities were not collected. Future studies should include detailed cardiovascular and metabolic profiling to better understand its impact on glymphatic function in sleep disorders and whether and how glymphatic impairment can explain the pathophysiology of the interplay between sleep disorders and dementia. In addition, the present PVS segmentation method cannot distinguish between hippocampal PVS and hippocampal sulcus remnant cysts. Given the exploratory nature of this study and the relatively limited sample size, uncorrected p-values ($p < 0.05$) were reported for partial correlation analyses. These results should therefore be interpreted as preliminary associations, which require confirmation in larger cohorts. Nevertheless, consistent patterns observed across related clinical variables suggest biologically plausible relationships between altered perivascular fluid dynamics and sleep–related markers. Recent studies have highlighted the need for increased coherence between measurements and interpretation of glymphatic activity [7,69].

Future investigations should prioritize the development of robust methodologies for assessing glymphatic function, possibly through the integration of multiple complementary indices [17]. Such a multimodal framework has the potential not only to delineate associations between specific symptom constellations and glymphatic activity but also to advance our understanding of how discrete components of sleep contribute to neurofluid transport in general. Recently, the introduction of a novel MRI method (CSF-Selective T2-prepared REadout with Acceleration and Mobility-encoding) has created new opportunities to examine CSF-mediated clearance mechanisms in sleep disorders [70]. Furthermore, the use of large-scale sleep disorder cohorts such as ENIGMA-Sleep will be of particular importance [71], as they provide the statistical power and data richness necessary to apply advanced machine learning approaches capable of detecting generalizable complex non-linear patterns in glymphatic-sleep interactions that may remain obscured under conventional frequentist analyses. Finally, longitudinal studies should examine changes in glymphatic function under the influence of established therapeutic interventions for sleep disorders, such as CPAP and cognitive behavioral therapy for insomnia, in order to elucidate potential treatment-related effects on glymphatic dynamics.

5. Conclusion

By integrating complementary non-invasive MRI indices with both objective and subjective sleep measures of common sleep disorders, our findings reveal differential alterations in neurofluid-transport markers in OSA and ID. Notably, enlarged PVSVF emerged as a prominent feature specific to OSA, whereas no group differences were detected in DTI-ALPS. It is important to emphasize that these findings reflect

associations with indirect proxy indices of neurofluid transport rather than direct measurements of CSF-ISF flow. Future research should incorporate multimodal, longitudinal, and large-scale approaches to clarify the roles of neurofluid transport and the glymphatic system in individuals with sleep disorders.

CRediT authorship contribution statement

Masoumeh Rostampour: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Daryna Apter:** Writing – review & editing, Writing – original draft. **Ali Rostampour:** Visualization, Methodology, Formal analysis. **Shayesteh Khosravi-Bayangani:** Investigation, Data curation. **Jorik D. Elberse:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Amir Sharafkhaneh:** Writing – review & editing. **Habibolah Khazaie:** Writing – review & editing, Supervision, Data curation. **Masoud Tahmasian:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Data sharing and data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Masoumeh Rostampour, Habibolah Khazaie reports financial support was provided by National Institute for Medical Research Development. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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