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Working memory deficits under high cognitive load in older adults with insomnia disorder: associations with frontoparietal control network connectivity and glymphatic function

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Abstract

Insomnia disorder (ID) is associated with cognitive impairment, but the neuroimaging correlates of high-load working memory deficits in older adults remain unclear. We recruited 80 older adults, including 40 participants with ID and 40 healthy controls (HCs) matched for age, sex, and education. Working memory was assessed using digit span and N-back tasks. Resting-state functional magnetic resonance imaging was used to characterize functional connectivity (FC) within the frontoparietal control network (FPCN). Glymphatic function was assessed using the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) index. We compared groups, examined brain–behaviour associations, and tested whether the DTI-ALPS index moderated the association between functional connectivity within the FPCN and high-load working memory performance. Compared with HCs, participants with ID showed lower backward and total digit-span scores, reduced 2-back accuracy, and longer reaction times during the 1-back and 2-back conditions. They also showed significantly reduced FC between the left lateral prefrontal cortex and the left posterior parietal cortex. In addition, the ID group exhibited a lower DTI-ALPS index, indicating glymphatic dysfunction. Moderation analysis further showed that glymphatic function, as indexed by DTI-ALPS, moderated the association between left lateral prefrontal cortex–left posterior parietal cortex FC and 2-back accuracy. These findings link high-load working memory vulnerability in older adults with ID to altered functional connectivity within the FPCN and lower DTI-ALPS values. This multimodal neuroimaging profile provides a framework for investigating sleep-related cognitive vulnerability.

1. Introduction

Insomnia disorder (ID) is common in later life and has been associated with cognitive decline and dementia risk (Bubu et al., 2017; Endomba et al., 2023; Wennberg et al., 2017). Affected individuals frequently report daytime problems with memory and concentration (Fortier-Brochu et al., 2012). Working memory may be especially vulnerable because it requires the active maintenance, updating, and manipulation of information under sustained task demands (D'Esposito & Postle, 2015). However, the neural basis of high-load working memory impairment in older adults with ID remains insufficiently defined.

Working memory relies on coordinated activity within the frontoparietal control network (FPCN), particularly between lateral prefrontal and posterior parietal regions that support goal maintenance, attentional allocation, and updating of task-relevant information (D'Esposito & Postle, 2015; Wager & Smith, 2003). Frontoparietal coordination becomes increasingly important as memory load increases during N-back tasks (Miri Ashtiani & Daliri, 2023). Resting-state functional connectivity (FC) quantifies statistical associations between BOLD time series across brain regions and can therefore characterize intrinsic network coordination relevant to working memory, rather than local properties of individual regions (Fox & Raichle, 2007). Sleep disturbance has been associated with altered FPCN and other large-scale network connectivity (Dai et al., 2020), but rs-FC alone may not explain individual differences in working memory performance in ID.

Glymphatic-related processes may provide an additional link between sleep disturbance and cognition. The glymphatic system is proposed to facilitate cerebrospinal fluid–interstitial fluid exchange and solute clearance along perivascular pathways (Rasmussen et al., 2018). Experimental studies suggest that these processes are enhanced during sleep (Iliff et al., 2012; Xie et al., 2013). Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) is an indirect MRI marker of water diffusivity along perivascular spaces and is widely used to index glymphatic function (Taoka et al., 2024; Taoka et al., 2017). Lower DTI-ALPS values have been reported in chronic insomnia and obstructive sleep apnea, with lower values also associated with poorer cognition (Jin et al., 2024; Xiong et al., 2024). In ID, DTI-ALPS and subcortical structural–functional coupling jointly mediated the association between sleep quality and backward digit span performance (Lv et al., 2026). Whether DTI-ALPS modifies the association between frontoparietal FC and high-load working memory performance in older adults with ID remains unknown.

This study examined resting-state functional connectivity within FPCN, the DTI-ALPS index, and high-load working memory performance in older adults with ID. We compared these measures between participants with ID and matched healthy controls (HCs). We also assessed associations of DTI-ALPS with global cognition and working memory performance. Finally, we explored whether DTI-ALPS modified the association between frontoparietal FC and 2-back accuracy. We hypothesized that ID would be associated with poorer high-load working memory performance, reduced functional connectivity within FPCN, and lower DTI-ALPS values. We further hypothesized that DTI-ALPS would be associated with cognition and moderate the FC–2-back accuracy association.

2. Materials and Methods

2.1 Participants

This case-control study recruited 145 participants from the Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine and from local communities in Fuzhou, China, between October 2022 and October 2025. Fifty-six participants did not meet eligibility criteria, five because of incomplete neuropsychological assessments, and four because of insufficient image quality. The final sample comprised 40 older adults with ID and 40 HCs, matched for age, sex, and education. The study was approved by the Ethics Committee of the Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine on July 29, 2022 (approval No. 2022KY-024-01). All participants provided written informed consent before participation.

Participants in the insomnia disorder group were older adults with clinically significant insomnia complaints. The inclusion criteria were as follows: (1) meeting the diagnostic criteria for primary insomnia according to the International Classification of Sleep Disorders, third edition (Sateia, 2014); (2) a Pittsburgh Sleep Quality Index (PSQI) score > 6; (3) no history of intracranial cerebrovascular disease, psychiatric disease, brain injury, epilepsy, or neurodegenerative disease; (4) no contraindications to magnetic resonance imaging; (5) right-handedness; and (6) provision of written informed consent. The

exclusion criteria were as follows: (1) major comorbidities that could cause sleep disorders; (2) other cognitive disorders; (3) current use of hypnotic medication; (4) a history of severe head trauma with structural brain abnormalities on conventional MRI; and (5) a history of drug or alcohol abuse.

Healthy controls were recruited from local communities in Fuzhou and matched to the ID group by age, sex, and years of education. They reported no insomnia or other sleep disorders and had no history of diagnosed mild cognitive impairment, dementia, cerebrovascular disease, psychiatric disease, brain injury, epilepsy, or neurodegenerative disease. All HCs were right-handed and provided written informed consent.

2.2 Sleep and cognitive assessments

All participants completed sleep and neuropsychological assessments. Sleep quality during the preceding month, daytime sleepiness, and depressive symptoms were assessed using the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Chinese 15-item Geriatric Depression Scale (GDS-15), respectively (Buysse et al., 1989; Johns, 1991; Shin et al., 2019). Higher scores indicate poorer sleep quality, greater daytime sleepiness, and more depressive symptoms. Global cognition was assessed using the Fuzhou version of the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), with one additional point awarded to participants with ≤ 12 years of education. Executive function was assessed using Stroop Color-Word Test completion times and Trail Making Test Part B (TMT-B) completion time; longer times indicated poorer performance.

Working memory was assessed using forward and backward digit-span tasks and an N-back task programmed in E-Prime 3.0. Forward, backward, and total digit-span scores were recorded. The N-back task comprised three blocks each of 0-back, 1-back, and 2-back conditions in pseudorandom order. Each block began with a 4,000-ms rule cue followed by a 2,000-ms fixation cross. Digit stimuli were then presented for 1,000 ms, during which participants had 1,000 ms to respond. Blocks were separated by 8-s rest intervals. Each block included 14 trials, including three targets. Participants completed practice trials before testing. In the 0-back condition, participants responded to a prespecified target digit; in the 1-back and 2-back conditions, they responded according to whether the current digit matched the stimulus presented one or two positions earlier, respectively. Accuracy was calculated as the proportion of correct responses per block and averaged across the three blocks within each condition. Mean reaction time was calculated from correct trials only, excluding incorrect responses and responses faster than 100 ms (Owen et al., 2005).

2.3 MRI acquisition

MRI data were acquired on a 3.0-T Siemens Prisma system (Erlangen, Germany) using a 64-channel head/neck coil. All participants underwent structural MRI, resting-state fMRI, and diffusion MRI. During resting-state fMRI, participants were instructed to remain awake, keep still, and not to think of anything in particular. Earplugs and foam cushions were used to reduce scanner noise and minimize head motion, respectively. Resting-state fMRI was acquired using a blood oxygen level-dependent gradient-echo echo-planar imaging sequence. Diffusion MRI was acquired using a diffusion tensor imaging echo-planar

imaging sequence, and structural images were acquired using a three-dimensional T1-weighted magnetization-prepared rapid gradient-echo sequence. Detailed acquisition parameters are provided in Supplementary Table S1.

2.4 Frontoparietal functional connectivity

The resting-state fMRI processing workflow is shown in Fig. 1A. Resting-state fMRI data were processed using the CONN toolbox (version 25.b) and SPM12 (Whitfield-Gabrieli & Nieto-Castanon, 2012). Preprocessing included realignment and unwarping, slice-timing correction, ART-based identification of outlier scans for scrubbing, rigid-body coregistration to the structural image, segmentation, direct normalization to MNI space, and spatial smoothing with an 8-mm full-width at half-maximum Gaussian kernel. During denoising, nuisance effects were regressed from the BOLD time series using five anatomical CompCor components derived separately from eroded white matter and cerebrospinal fluid masks, 12 realignment parameters (six rigid-body motion parameters and their first-order derivatives), participant-specific scrubbing regressors, and the effect-of-rest regressor with its first-order temporal derivative. ART identified outlier scans using thresholds of a scan-to-scan global BOLD-signal change exceeding 5 SD or composite head motion exceeding 0.9 mm. No global signal regression was performed. Linear detrending and temporal band-pass filtering (0.008–0.09 Hz) were applied after nuisance regression. ROI-to-ROI functional connectivity analysis was performed among four predefined ROIs from the CONN frontoparietal control network atlas (networks.nii): left LPFC (− 43, 33, 28), left PPC (− 46, − 58, 49), right LPFC (41, 38, 30), and right PPC (52, − 52, 45). Functional connectivity was defined as the Fisher z-transformed bivariate correlation between denoised ROI time series. Group-level analyses were performed in CONN. Statistical significance was defined as a two-sided connection-level FDR-corrected $P < 0.05$ across the tested ROI-to-ROI connections.

2.5 DTI-ALPS index

The diffusion MRI processing workflow for analysis along the perivascular space (DTI-ALPS) is shown in Fig. 1B. Diffusion MRI data were preprocessed using MRtrix3 (https://www.mrtrix.org/) (Tournier et al., 2019). Raw diffusion-weighted imaging (DWI) data were denoised, corrected for Gibbs ringing artifacts, and corrected for head motion and eddy-current distortions. Brain extraction was then performed on the basis of the b0 images. Diffusion tensor fitting was used to derive fractional anisotropy (FA) maps and diffusivity maps along three principal image axes: Dxx, representing diffusivity along the x axis (left-right direction); Dyy, representing diffusivity along the y axis (anterior-posterior direction); and Dzz, representing diffusivity along the z axis (superior-inferior direction). Individual FA maps were registered to the JHU-ICBM-FA standard template space, and the resulting deformation fields were applied to the corresponding Dxx, Dyy and Dzz maps. To quantify directional diffusivity relevant to the ALPS index, spherical regions of interest with a diameter of 5 mm were placed in projection fibers, namely the superior corona radiata (SCR), and association fibers, namely the superior longitudinal fasciculus (SLF), at the level of the lateral ventricles. According to the JHU-ICBM-DTI-81 white-matter labels atlas, the center coordinates of the ROIs were as follows: left SCR, (116, 110, 99); left SLF, (128, 110, 99); right SCR,

(64, 110, 99); and right SLF, (51, 110, 99) (Liu et al., 2024). Directional diffusivity values along the x, y and z axes were extracted from these ROIs. The ALPS index was calculated as: $ALPS-index=\frac{mean(Dxx_{proj},Dxx_{assoc})}{mean\left(Dyy_{proj},Dzz_{assoc}\right)}$, where Dxx_proj denotes x-axis diffusivity in the projection-fiber ROI, Dxx_assoc denotes x-axis diffusivity in the association-fiber ROI, Dyy_proj denotes y-axis diffusivity in the projection-fiber ROI, and Dzz_assoc denotes z-axis diffusivity in the association-fiber ROI.

2.6 Statistical analysis

Statistical analyses of demographic, clinical, and cognitive characteristics were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using Welch's t tests when both groups passed the Shapiro–Wilk normality test; otherwise, Mann–Whitney U tests were used. Categorical variables were compared using chi-square or Fisher's exact tests, as appropriate. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Group differences in the DTI-ALPS index were assessed using linear regression adjusted for age, sex, and education. Resting-state functional connectivity was defined as the Fisher z-transformed Pearson correlation between time series from frontoparietal control-network regions of interest. Six prespecified frontoparietal connections were compared between groups, with Benjamini–Hochberg false discovery rate (FDR) correction at the connection level; FDR-adjusted $q < 0.05$ was considered significant.

Partial correlation analyses were conducted to examine associations of altered frontoparietal functional connectivity and the DTI-ALPS index with measures of global cognition and working memory, adjusting for age, sex, and education. Two-sided $P < 0.05$ was considered statistically significant, and FDR correction was applied for multiple comparisons.

The moderating effect of the DTI-ALPS index on the association between altered frontoparietal functional connectivity and working memory performance was examined using linear regression and the Hayes bootstrap method. As 2-back accuracy was considered an indicator of high-load working memory performance (Halin et al., 2015), an exploratory moderation analysis was conducted using 2-back accuracy as the outcome. The analysis was performed in SPSS version 27.0 using 5,000 bootstrap resamples to derive 95% confidence intervals (CIs). A moderation effect was considered significant when the 95% CI for the interaction term did not include zero.

3. Results

3.1 Participant characteristics and cognitive performance

The clinical and cognitive characteristics of the participants are summarized in Table 1. The ID and HCs groups did not differ in demographic characteristics, lifestyle factors, or mean framewise displacement (all $P > 0.05$). Participants with ID had higher PSQI, ESS, and GDS-15 scores than HCs (all $P \leq 0.05$). The ID group also showed poorer global cognition, longer Stroop completion times, lower backward and total

digit-span scores, lower 1-back and 2-back accuracy, and longer reaction times during the 1-back and 2-back conditions (all $P \leq 0.05$). TMT-B completion time, forward digit span, and 0-back performance did not differ between groups (all $P \geq 0.05$).

Table 1
Demographic and clinical characteristics

Characteristics	HCs	ID	t/Z/χ^2	P
N	40	40		
Age (y)	68.25 ± 3.94	68.78 ± 4.48	-0.556	0.579
Female, N (%)	24 (60.0%)	20 (50.0%)	0.808	0.369
Education (y)	12.00 (12.00, 14.00)	12.00 (11.00, 12.25)	1.647	0.100
Married, N (%)	36 (90.0%)	36 (90.0%)	–	1.000
Current smoking, N (%)	6 (15.0%)	4 (10.0%)	0.457	0.499
Current drinking, N (%)	6 (15.0%)	11 (27.5%)	1.867	0.172
BMI (kg/m²)	23.92 ± 1.77	23.54 ± 2.32	0.822	0.414
Height (m)	1.62 ± 0.08	1.63 ± 0.08	-0.354	0.724
Weight (kg)	63.35 ± 8.12	62.88 ± 9.39	0.241	0.810
PSQI	4.00 (3.00, 6.00)	13.00 (10.75, 15.00)	-7.728	< 0.001
ESS	2.00 (1.00, 3.00)	5.50 (3.75, 10.00)	-5.253	< 0.001
GDS-15	2.00 (1.75, 2.00)	2.00 (2.00, 3.00)	-2.711	0.007
MoCA	28.00 (26.75, 28.25)	25.00 (24.00, 26.00)	6.109	< 0.001
Stroop dot time (s)	14.45 (12.55, 16.77)	17.69 (14.95, 20.57)	-3.580	< 0.001
Stroop word time (s)	18.14 (16.18, 20.21)	24.77 (19.25, 28.07)	-4.138	< 0.001
Stroop color-word time (s)	30.67 ± 9.76	42.89 ± 15.25	-4.271	< 0.001
TMT-B time (s)	154.19 (133.86, 181.62)	160.47 (127.40, 212.26)	-0.693	0.488
Digit span forward	9.00 (8.00, 9.00)	9.00 (8.00, 9.00)	0.356	0.722
Digit span backward	6.00 (5.00, 7.00)	4.00 (3.00, 5.00)	4.543	< 0.001

Note. Values are mean ± SD or median (Q1, Q3) for continuous variables and n (%) for categorical variables. Continuous variables were compared using Welch's t-test when both groups passed Shapiro–Wilk normality tests; otherwise Mann–Whitney U tests were used. Categorical variables were compared using chi-square tests or Fisher's exact tests. HCs, healthy controls; ID, insomnia disorder; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; GDS-15, 15-item Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; TMT-B, Trail Making Test Part B; RT, reaction time; Mean FD, mean framewise displacement.

Characteristics	HCs	ID	t/Z/χ^2	P
Digit span total	14.25 ± 2.01	12.10 ± 2.71	4.034	< 0.001
0-back accuracy	0.95 (0.90, 0.98)	0.95 (0.90, 0.98)	0.257	0.797
1-back accuracy	0.88 (0.83, 0.93)	0.79 (0.69, 0.86)	3.045	0.002
2-back accuracy	0.64 (0.59, 0.77)	0.57 (0.52, 0.62)	3.669	< 0.001
0-back RT (ms)	648.98 (620.41, 668.64)	646.98 (604.04, 721.69)	-0.423	0.672
1-back RT (ms)	842.65 ± 117.76	903.19 ± 147.08	-2.032	0.046
2-back RT (ms)	925.62 ± 144.38	1005.05 ± 125.78	-2.624	0.010
Mean FD Power (mm)	0.20 ± 0.08	0.18 ± 0.07	1.405	0.164

Note. Values are mean ± SD or median (Q1, Q3) for continuous variables and n (%) for categorical variables. Continuous variables were compared using Welch's t-test when both groups passed Shapiro–Wilk normality tests; otherwise Mann–Whitney U tests were used. Categorical variables were compared using chi-square tests or Fisher's exact tests. HCs, healthy controls; ID, insomnia disorder; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; GDS-15, 15-item Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; TMT-B, Trail Making Test Part B; RT, reaction time; Mean FD, mean framewise displacement.

3.2 Frontoparietal network functional connectivity

Compared with HCs, participants with ID showed lower resting-state functional connectivity between the left LPFC and left PPC (0.69 ± 0.21 vs 0.88 ± 0.20; t(78) = − 4.19, $P < 0.001$, FDR q < 0.001; Fig. 2A). The other three connections shown in Fig. 2A exhibited nominal group differences (all uncorrected $P < 0.05$), but none remained significant after FDR correction (all FDR $q > 0.05$). After adjustment for age, sex, and education, higher left LPFC–left PPC connectivity was associated with higher 1-back accuracy (partial r = 0.46, FDR $q < 0.001$; Fig. 2B), higher 2-back accuracy (partial r = 0.31, FDR $q = 0.014$; Fig. 2C), and shorter 1-back reaction time (partial r = − 0.33, FDR $q = 0.010$).

3.3 Glymphatic function

After adjustment for age, sex, and education, the DTI-ALPS index was lower in the ID group than in HCs ($P < 0.001$; Fig. 3A). Higher DTI-ALPS values were associated with higher MoCA scores (partial r = 0.33, $P = 0.004$, FDR $q = 0.024$; Fig. 3B) and greater 2-back accuracy (partial r = 0.28, $P = 0.012$, FDR $q = 0.037$; Fig. 3C). No other associations between DTI-ALPS and cognitive measures survived FDR correction.

3.4 Moderation analysis

After adjustment for age, sex, education, and group, the DTI-ALPS index significantly moderated the association between left LPFC–left PPC functional connectivity and 2-back accuracy (interaction B = − 0.0259, SE = 0.0122, t(72) = − 2.12, $P = 0.038$, 95% percentile bootstrap CI [− 0.0477, − 0.0022]; ΔR^2 =

0.0437, F(1, 72) = 4.48, *P* = 0.038; Fig. 4.). Simple-slope analyses showed a positive association between left LPFC–left PPC functional connectivity and 2-back accuracy at lower DTI-ALPS values (16th percentile; B = 0.0378, SE = 0.0163, t(72) = 2.32, *P* = 0.023), but not at median or higher DTI-ALPS values.

4. Discussion

This study links high-load working memory performance with frontoparietal functional connectivity and the DTI-ALPS index in older adults with ID. Compared with HCs, participants with ID showed poorer high-load working memory performance, lower left LPFC–left PPC functional connectivity, and lower DTI-ALPS values. Across the full sample, left LPFC–left PPC connectivity was associated with working memory measures, whereas DTI-ALPS was associated with MoCA scores and 2-back accuracy. The exploratory analysis further suggested that the connectivity–2-back accuracy association varied according to DTI-ALPS.

Reduced left LPFC–left PPC functional connectivity may represent a network-level feature relevant to working memory impairment in older adults with ID. The LPFC contributes to goal maintenance and top-down control, whereas the PPC supports attentional allocation and task-relevant information representation (D'Esposito & Postle, 2015; Wager & Smith, 2003). Functional coupling between these regions may facilitate the maintenance and updating of information as task demands change. More broadly, the frontoparietal control network functions as a flexible hub that coordinates cognitive control across task contexts (Cole et al., 2013; Gazzaley et al., 2004). Previous studies have reported reduced prefrontal and parietal recruitment during working memory tasks after sleep deprivation (Mu et al., 2005), as well as altered frontal-control and frontoparietal connectivity in ID (Zheng et al., 2023). In this context, the lower resting-state left LPFC–left PPC FC observed in the ID group, together with its associations with working memory performance, is consistent with less coordinated frontoparietal communication being related to poorer working memory performance.

The lower DTI-ALPS index observed in the ID group, together with its positive association with 2-back accuracy, suggests that altered glymphatic function may be relevant to high-load working memory deficits in older adults with ID. Sleep supports cerebrospinal fluid–interstitial fluid exchange and the clearance of metabolic solutes from the brain (Iliff et al., 2012; Xie et al., 2013). DTI-ALPS is an indirect MRI marker of diffusivity along perivascular spaces and has been proposed to reflect aspects of glymphatic function (Taoka et al., 2024). Impaired perivascular fluid transport could disrupt extracellular homeostasis and thereby affect neuronal signalling and large-scale network coordination (Buzsáki & Draguhn, 2004; Fries, 2015; Friston et al., 1993). Such effects may be particularly consequential during high-load working memory processing, which requires sustained and coordinated activity across distributed cortical systems (D'Esposito & Postle, 2015; Gazzaley et al., 2004; Miller & Cohen, 2001). The positive associations of DTI-ALPS with MoCA scores and 2-back accuracy are consistent with this account.

The exploratory interaction between the DTI-ALPS index and left LPFC–left PPC functional connectivity is consistent with emerging evidence linking glymphatic-related measures, brain-network organization, and cognition. DTI-ALPS has been associated with working memory performance and structural–functional coupling in ID (Lv et al., 2026), and ALPS has been reported to moderate the association between network connectivity and cognition in amnestic mild cognitive impairment (Li et al., 2025). In the present study, the positive association between left LPFC–left PPC functional connectivity and 2-back accuracy was evident at lower DTI-ALPS levels but attenuated at higher DTI-ALPS levels. One possible explanation is that, when glymphatic-related function is relatively compromised, stronger frontoparietal coupling may reflect greater network recruitment to sustain performance under high cognitive load. Task-based studies in older adults have similarly suggested that greater network integration may support working memory performance under demanding conditions (Crowell et al., 2020).

Limitations

While this study provides insight into the relationships among frontoparietal functional connectivity, glymphatic function, and working memory performance in older adults with ID, several limitations should be considered. First, the sample size was modest, and larger multicenter cohorts are needed to improve the generalizability of the findings. Second, although ID was diagnosed clinically according to ICSD-3 criteria, polysomnography was not performed. Third, DTI-ALPS is an indirect imaging marker of glymphatic function and may be influenced by white-matter microstructure and fiber geometry; it does not directly measure glymphatic transport or solute clearance. In addition, the exploratory moderation analysis was based on a connection selected from the observed group differences and requires independent replication. Finally, the cross-sectional design precludes causal inference, and resting-state fMRI cannot capture load-dependent network recruitment. Future longitudinal studies integrating polysomnography, task-based fMRI, and more direct measures of glymphatic transport should further clarify these relationships.

5. Conclusion

In conclusion, older adults with ID showed poorer working memory performance under higher cognitive load, reduced left LPFC–left PPC functional connectivity, and a lower DTI-ALPS index. Exploratory moderation analysis further suggested that the association between left LPFC–left PPC functional connectivity and 2-back accuracy varied according to the DTI-ALPS index. Together, these findings suggest that frontoparietal network alterations and DTI-ALPS–indexed glymphatic-related function may be jointly associated with high-load working memory vulnerability in ID.

Declarations

Declaration of competing interest

The authors declare that they have no competing interests.

Ethics approval

The study was approved by the Ethics Committee of the Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine on July 29, 2022 (approval No. 2022KY-024-01).

Consent to participate

All participants provided written informed consent before participation.

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Author Contribution

K.X. drafted the manuscript and contributed to methodology, investigation, formal analysis, and data curation. X.W. and Y.S. contributed to investigation and data curation. H.L. contributed to data curation. L.B., Z.G., and L.Z. contributed to investigation. Z.L. contributed to conceptualization, methodology, visualization, supervision, resources, and funding acquisition. All authors reviewed and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Bubu, O. M., Brannick, M., Mortimer, J., Umasabor-Bubu, O., Sebastião, Y. V., Wen, Y., Schwartz, S., Borenstein, A. R., Wu, Y., Morgan, D., & Anderson, W. M. (2017). Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. *Sleep*, *40*(1). https://doi.org/10.1093/sleep/zsw032
2. Buysse, D. J., Reynolds, C. F. 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4
3. Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science*, *304*(5679), 1926–1929. https://doi.org/10.1126/science.1099745
4. Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, *16*(9), 1348–1355. https://doi.org/10.1038/nn.3470
5. Crowell, C. A., Davis, S. W., Beynel, L., Deng, L., Lakhlani, D., Hilbig, S. A., Palmer, H., Brito, A., Peterchev, A. V., Luber, B., Lisanby, S. H., Appelbaum, L. G., & Cabeza, R. (2020). Older adults benefit from more widespread brain network integration during working memory. *Neuroimage*, *218*, 116959. https://doi.org/10.1016/j.neuroimage.2020.116959
6. D'Esposito, M., & Postle, B. R. (2015). The cognitive neuroscience of working memory. *Annu Rev Psychol*, *66*, 115–142. https://doi.org/10.1146/annurev-psych-010814-015031
7. Dai, C., Zhang, Y., Cai, X., Peng, Z., Zhang, L., Shao, Y., & Wang, C. (2020). Effects of Sleep Deprivation on Working Memory: Change in Functional Connectivity Between the Dorsal Attention, Default Mode, and Fronto-Parietal Networks [Original Research]. *Frontiers in Human Neuroscience*, *Volume 14–2020*. https://doi.org/10.3389/fnhum.2020.00360
8. Endomba, F. T., Tchebegna, P. Y., Chiabi, E., Angong Wouna, D. L., Guillet, C., & Chauvet-Gélinier, J. C. (2023). Epidemiology of insomnia disorder in older persons according to the Diagnostic and Statistical Manual of Mental Disorders: a systematic review and meta-analysis. *European Geriatric Medicine*, *14*(6), 1261–1272. https://doi.org/10.1007/s41999-023-00862-2
9. Fortier-Brochu, E., Beaulieu-Bonneau, S., Ivers, H., & Morin, C. M. (2012). Insomnia and daytime cognitive performance: a meta-analysis. *Sleep Medicine Reviews*, *16*(1), 83–94. https://doi.org/10.1016/j.smrv.2011.03.008
10. Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–711. https://doi.org/10.1038/nrn2201
11. Fries, P. (2015). Rhythms for Cognition: Communication through Coherence. *Neuron*, *88*(1), 220–235. https://doi.org/10.1016/j.neuron.2015.09.034
12. Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. (1993). Functional connectivity: the principal-component analysis of large (PET) data sets. *Journal Of Cerebral Blood Flow And Metabolism*, *13*(1), 5–14. https://doi.org/10.1038/jcbfm.1993.4

13. Gazzaley, A., Rissman, J., & D'Esposito, M. (2004). Functional connectivity during working memory maintenance. *Cognitive, Affective & Behavioral Neuroscience*, *4*(4), 580–599. https://doi.org/10.3758/cabn.4.4.580
14. Halin, N., Marsh, J. E., & Sörqvist, P. (2015). Central load reduces peripheral processing: Evidence from incidental memory of background speech. *Scandinavian Journal of Psychology*, *56*(6), 607–612. https://doi.org/10.1111/sjop.12246
15. Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., Benveniste, H., Vates, G. E., Deane, R., Goldman, S. A., Nagelhus, E. A., & Nedergaard, M. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Science Translational Medicine*, *4*(147), 147ra111. https://doi.org/10.1126/scitranslmed.3003748
16. Jin, Y., Zhang, W., Yu, M., Li, J., Du, Y., Wang, W., Chen, G., Ding, X., & Ding, J. (2024). Glymphatic system dysfunction in middle-aged and elderly chronic insomnia patients with cognitive impairment evidenced by diffusion tensor imaging along the perivascular space (DTI-ALPS). *Sleep Medicine*, *115*, 145–151. https://doi.org/10.1016/j.sleep.2024.01.028
17. Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*, *14*(6), 540–545. https://doi.org/10.1093/sleep/14.6.540
18. Li, L. L., Ma, J., Wu, J. J., Xue, X., Zheng, M. X., Hua, X. Y., Guo, Q. H., & Xu, J. G. (2025). Impact of effective connectivity within the Papez circuit on episodic memory: moderation by perivascular space function. *Alzheimer'S Research & Therapy*, *17*(1), 66. https://doi.org/10.1186/s13195-025-01717-7
19. Liu, X., Barisano, G., Shao, X., Jann, K., Ringman, J. M., Lu, H., Arfanakis, K., Caprihan, A., DeCarli, C., Gold, B. T., Maillard, P., Satizabal, C. L., Fadaee, E., Habes, M., Stables, L., Singh, H., Fischl, B., van der Kouwe, A., Schwab, K., & Wang, D. J. J. (2024). Cross-Vendor Test-Retest Validation of Diffusion Tensor Image Analysis along the Perivascular Space (DTI-ALPS) for Evaluating Glymphatic System Function. *Aging Dis*, *15*(4), 1885–1898. https://doi.org/10.14336/ad.2023.0321-2
20. Lv, Z., Zhang, H., Yang, Y., Wei, Y., & Lei, X. (2026). DTI-ALPS and subcortical structural-functional coupling mediate the impact of sleep quality on working memory in insomnia disorder. *Psychological Medicine*, *56*, e201. https://doi.org/10.1017/s0033291726104188
21. Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review Of Neuroscience*, *24*, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167
22. Miri Ashtiani, S. N., & Daliri, M. R. (2023). Identification of cognitive load-dependent activation patterns using working memory task-based fMRI at various levels of difficulty. *Scientific Reports*, *13*(1), 16476. https://doi.org/10.1038/s41598-023-43837-w
23. Mu, Q., Nahas, Z., Johnson, K. A., Yamanaka, K., Mishory, A., Koola, J., Hill, S., Horner, M. D., Bohning, D. E., & George, M. S. (2005). Decreased Cortical Response to Verbal Working Memory Following Sleep Deprivation. *Sleep*, *28*(1), 55–67. https://doi.org/10.1093/sleep/28.1.55

24. Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal Of The American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x
25. Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 46–59. https://doi.org/10.1002/hbm.20131
26. Rasmussen, M. K., Mestre, H., & Nedergaard, M. (2018). The glymphatic pathway in neurological disorders. *Lancet Neurology*, *17*(11), 1016–1024. https://doi.org/10.1016/s1474-4422(18)30318-1
27. Sateia, M. J. (2014). International classification of sleep disorders-third edition: highlights and modifications. *Chest*, *146*(5), 1387–1394. https://doi.org/10.1378/chest.14-0970
28. Shin, C., Park, M. H., Lee, S. H., Ko, Y. H., Kim, Y. K., Han, K. M., Jeong, H. G., & Han, C. (2019). Usefulness of the 15-item geriatric depression scale (GDS-15) for classifying minor and major depressive disorders among community-dwelling elders. *Journal Of Affective Disorders*, *259*, 370–375. https://doi.org/10.1016/j.jad.2019.08.053
29. Taoka, T., Ito, R., Nakamichi, R., Nakane, T., Kawai, H., & Naganawa, S. (2024). Diffusion Tensor Image Analysis ALong the Perivascular Space (DTI-ALPS): Revisiting the Meaning and Significance of the Method. *Magnetic Resonance In Medical Sciences : Mrms : An Official Journal Of Japan Society Of Magnetic Resonance In Medicine*, *23*(3), 268–290. https://doi.org/10.2463/mrms.rev.2023-0175
30. Taoka, T., Masutani, Y., Kawai, H., Nakane, T., Matsuoka, K., Yasuno, F., Kishimoto, T., & Naganawa, S. (2017). Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. *Jpn J Radiol*, *35*(4), 172–178. https://doi.org/10.1007/s11604-017-0617-z
31. Tournier, J. D., Smith, R., Raffelt, D., Tabbara, R., Dhollander, T., Pietsch, M., Christiaens, D., Jeurissen, B., Yeh, C. H., & Connelly, A. (2019). MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *Neuroimage*, *202*, 116137. https://doi.org/10.1016/j.neuroimage.2019.116137
32. Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory. *Cognitive Affective & Behavioral Neuroscience*, *3*(4), 255–274. https://doi.org/10.3758/CABN.3.4.255
33. Wennberg, A. M. V., Wu, M. N., Rosenberg, P. B., & Spira, A. P. (2017). Sleep Disturbance, Cognitive Decline, and Dementia: A Review. *Seminars In Neurology*, *37*(4), 395–406. https://doi.org/10.1055/s-0037-1604351
34. Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, *2*(3), 125–141. https://doi.org/10.1089/brain.2012.0073
35. Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D. J., Nicholson, C., Iliff, J. J., Takano, T., Deane, R., & Nedergaard, M. (2013). Sleep drives metabolite

clearance from the adult brain. *Science*, *342*(6156), 373–377. https://doi.org/10.1126/science.1241224

36. Xiong, Z., Bai, M., Wang, Z., Wang, R., Tian, C., Wang, L., Nie, L., & Zeng, X. (2024). Resting-state fMRI network efficiency as a mediator in the relationship between the glymphatic system and cognitive function in obstructive sleep apnea hypopnea syndrome: Insights from a DTI-ALPS investigation. *Sleep Medicine*, *119*, 250–257. https://doi.org/10.1016/j.sleep.2024.05.009
37. Zheng, H., Zhou, Q., Yang, J., Lu, Q., Qiu, H., He, C., & Yan, H. (2023). Altered functional connectivity of the default mode and frontal control networks in patients with insomnia. *CNS Neuroscience & Therapeutics*, *29*(8), 2318–2326. https://doi.org/10.1111/cns.14183

Figures

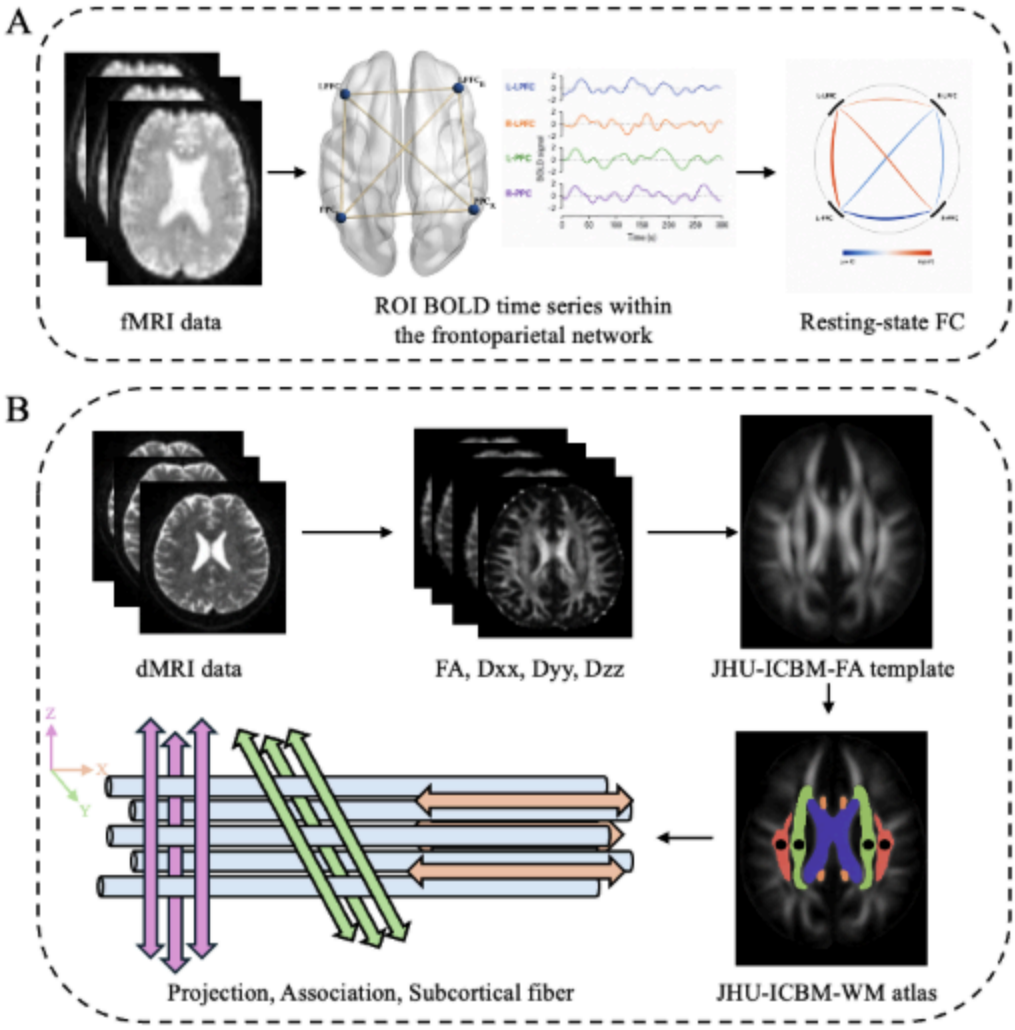


Figure 1

Pipelines for data processing. **A.** Functional connectivity. Resting-state functional MRI (fMRI) data were used to extract regional blood oxygen level-dependent (BOLD) time series within the frontoparietal

network and resting-state functional connectivity (FC) was then calculated. L-LPFC, left lateral prefrontal cortex; L-PPC, left posterior parietal cortex; R-LPFC, right lateral prefrontal cortex; R-PPC, right posterior parietal cortex. **B.**DTI-ALPS index. Diffusion MRI (dMRI) data were used to derive fractional anisotropy (FA) and directional diffusivity maps along the x-, y-, and z-axes (Dxx, Dyy, and Dzz). The FA image was registered to the Johns Hopkins University International Consortium for Brain Mapping FA template (JHU-ICBM-FA template), and the deformation matrix was applied to all diffusivity maps. White matter regions were defined using the JHU-ICBM white matter atlas, including projection, association, and subcortical fibers, for analysis along the perivascular space (ALPS). BOLD, blood oxygen level-dependent; FC, functional connectivity; FA, fractional anisotropy; ALPS, analysis along the perivascular space.

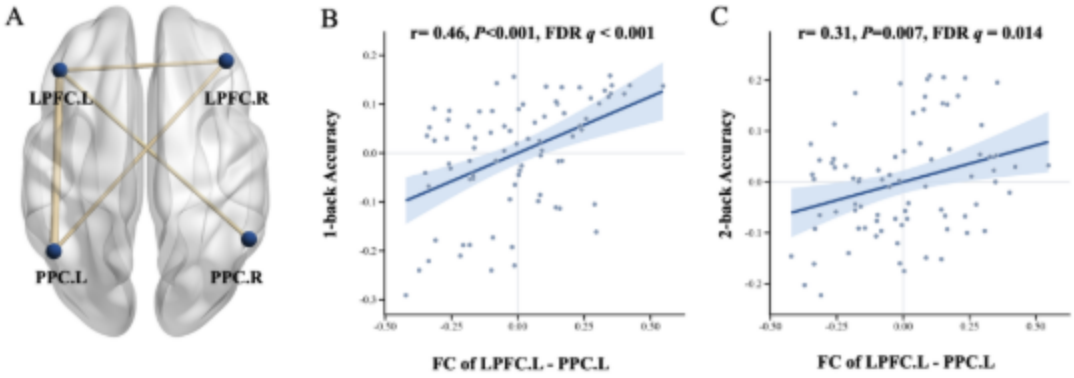


Figure 2

Frontoparietal functional connectivity and its associations with working memory performance. **A.** Schematic representation of functional connectivity among four regions of interest in the frontoparietal control network: the left lateral prefrontal cortex (LPFC.L), right lateral prefrontal cortex (LPFC.R), left posterior parietal cortex (PPC.L), and right posterior parietal cortex (PPC.R). The highlighted connection remained significant after FDR correction, whereas the thin connections showed nominal group differences only. **B.** Scatter plot of the association between left LPFC.L–PPC.L functional connectivity and 1-back accuracy. **C.** Scatter plot of the association between left LPFC.L–PPC.L functional connectivity and 2-back accuracy. Shaded areas represent 95% confidence intervals.

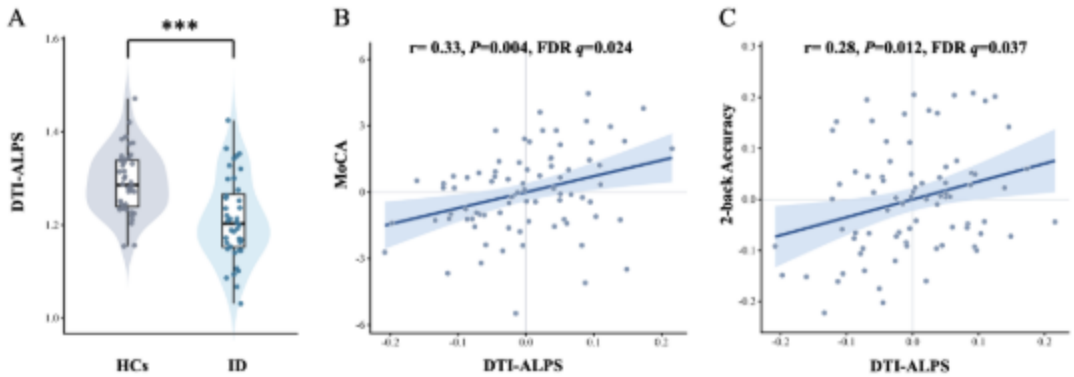


Figure 3

DTI-ALPS index in the ID and HCs groups and its associations with cognitive performance. **A.** Violin and box plots of DTI-ALPS index values in HCs and participants with ID. **B.**Scatter plot of DTI-ALPS index and Montreal Cognitive Assessment (MoCA) scores. **C.** Scatter plot of DTI-ALPS index and 2-back accuracy. Shaded areas indicate 95% confidence intervals. ***$P < 0.001$; DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; MoCA, Montreal Cognitive Assessment; HCs, healthy controls; ID, insomnia disorder.

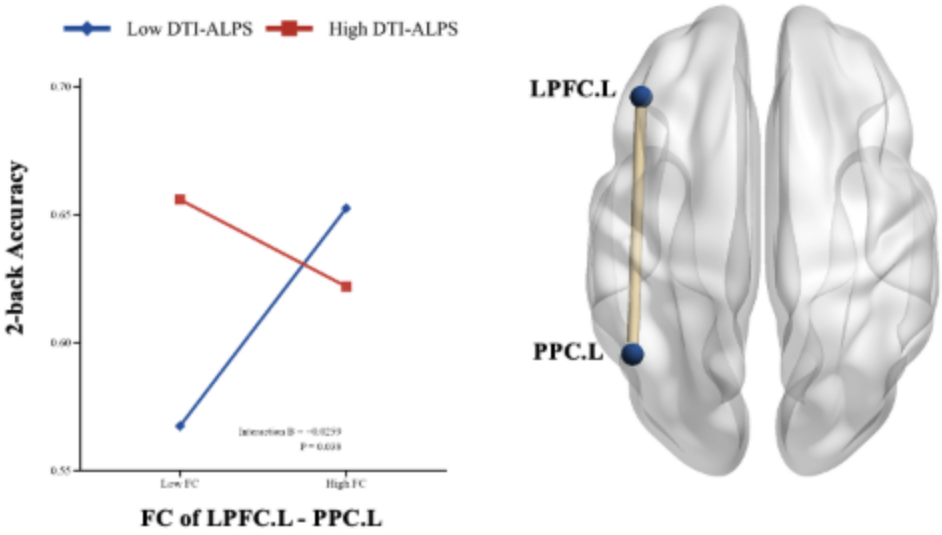


Figure 4

Moderating effect of DTI-ALPS on the association between left LPFC-left PPC functional connectivity and 2-back accuracy. FC, functional connectivity; LPFC.L, left lateral prefrontal cortex; PPC.L, left posterior parietal cortex; DTI-ALPS, diffusion tensor imaging analysis along the perivascular space.

Supplementary Files

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