

Cerebral aqueduct CSF dynamics by diffusion tensor imaging and its association with glymphatic function and cognitive decline in Alzheimer's spectrum

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Abstract

Cerebrospinal fluid (CSF) plays a critical role in maintaining brain homeostasis through the clearance of neurotoxic metabolites, yet the relationship between CSF dynamics and cognitive dysfunction remains unclear. This study examined the diffusion metrics of CSF water molecules in the cerebral aqueduct and their association with cognitive impairment and Alzheimer's disease (AD) pathology, aiming to establish a non-invasive neuroimaging marker of CSF dynamics. A total of 226 participants from the Ruijin Neurobank cohort were included, consisted of cognitively normal individuals, mild cognitive impairment, and AD. Diffusion tensor imaging (DTI) was used to derive fractional anisotropy (FA), mean diffusivity (MD), and the DTI-ALPS index within the aqueduct. Amyloid- β and tau deposition were quantified using 18F-Florbetapir and 18F-MK-6240 PET-MR, and cognitive performance was evaluated by the Mini-Mental State Examination and Auditory Verbal Learning Test. Significant group differences were observed in aqueductal FA metrics, which correlated with amyloid and tau accumulation, cortical thinning, and impaired memory performance. FA and Mes-FA were also associated with the DTI-ALPS index, suggesting a link between CSF dynamics and glymphatic function. Mediation analyses indicated that glymphatic dysfunction mediated the relationship between altered CSF flow and cognitive decline. These findings suggest that impaired CSF dynamics within the cerebral aqueduct may contribute to cognitive deterioration independently of amyloid and tau pathology and highlight DTI-based assessment of CSF flow as a promising translational biomarker for neurodegenerative cognitive disorders.

INTRODUCTION

Cerebrospinal fluid (CSF) continuously circulates surround the brain and spinal cord and provides physical protection, metabolic support for the brain and spinal cord. Recently, the discovery and identification of the glymphatic system further revolutionized our understanding of CSF, and revealed more roles of the CSF in waste removal, neuroinflammation regulation and maintenance of cognitive function.¹ Disruptions of CSF production, flow, and turnover can promote the cognitive impairment under various pathological conditions^{2,3}. Therefore, proper measurements of CSF dynamics may contribute to the assessment of glymphatic function and therefore promote our understanding of disease progression in neurodegenerative diseases like AD.

Two-dimensional (2D) phase-contrast (PC) MRI is a typical method to evaluate CSF dynamics through a single imaging slice, but this approach is limited to unidirectional or planar flow, and does not account for respiration effects.⁴ The 4D flow MRI extended 2D PC-MRI by capturing time-resolved, three-dimensional velocity data across a volumetric region of interest, but at the cost of longer acquisition times, increased motion sensitivity, more complex analysis and limited clinical accessibility.⁵ Diffusion Tensor Imaging (DTI) is also emerging as a potential approach in measuring CSF dynamics. DTI is sensitive to microstructural alteration and fluid movement at molecular level. DTI along perivascular spaces (DTI-ALPS) assesses water diffusivity along perivascular spaces, and is established as a non-invasive biomarker of glymphatic function⁶. However, DTI-ALPS cannot provide direct description of CSF

dynamics. Here we report a novel method assessing CSF dynamics in the aqueduct of Sylvius by DTI, and investigated its correlation with A β and Tau burden, cortical thickness, DTI-ALPS and cognitive function.

METHODS

2.1 Participants and Study Design

This retrospective study analyzed data collected prospectively from the Ruijin NeuroBank of Alzheimer's Disease and Dementia (RJNB-D) cohort between November 2021 and April 2025. The RJNB-D cohort is a prospective cohort that enrolls participants with cognitive complaints from memory clinics and cognitively normal volunteers from the community, as detailed in our previous publication^{7,8}.

In the RJNB-D cohort, participants underwent multimodal MRI scans, A β PET-MR scans, Tau PET-MR scans, neuropsychological testing and blood sample collection. The Neuropsychological assessments included the Mini-Mental State Examination (MMSE, Chinese Version)⁹ and the Auditory Verbal Learning Test (AVLT)¹⁰. Venous blood samples were used for ApoE genotyping. The participants were diagnosed as cognitive normal (CN), mild cognitive impairment (MCI) or Alzheimer's disease (AD) according to the 2016 NIA-AA criteria¹¹.

2.2 MRI Acquisition and Analysis

Multimodal MRI included 3D high-resolution T1-weighted imaging, fluid-attenuated inversion recovery (FLAIR), multi-shell diffusion MRI (dMRI). All MRI data were acquired using a 3.0-T scanner with a 64-channel head coil (uMR 890, United Imaging Healthcare, Shanghai, China). Volumetric analysis was performed using FreeSurfer 7.1.1 (<https://surfer.nmr.mgh.harvard.edu>). White matter hyperintensities (WMH) were assessed using the Brain Intensity AbNormality Classification Algorithm (BIANCA, version 6.0, FMRIB Software Library, Oxford, UK). Diffusion MRI data underwent pre-processing and tensor fitting to generate fractional anisotropy (FA), mean diffusivity (MD), CSF dynamics-related indicators of the aqueduct (Mes-speed, MD-mean, FA-mean, Mes-FA, as detailed below), and to calculate the DTI-ALPS index by FSL (version 6.0.3, <http://www.fmrib.ox.ac.uk/fsl>).

2.3 Measurements of CSF dynamics in mesencephalic aqueduct (MA)

The CSF dynamics were calculated from DTI sequence in the MA. The MA mask was first defined in the standard MNI152 space and was then sequentially registered to each subject's T1-weighted image and diffusion MRI b0 image, and finally transformed into the native dMRI/DTI space, yielding a subject-specific MA mask in diffusion space.

Based on diffusion tensor fitting, voxel-wise FA and MD maps were obtained. Mean FA and MD values within the MA were extracted using the subject-specific MA mask in dMRI space, yielding **FA-mean** and **MD-mean**.

The three-dimensional voxel coordinates within each subject-specific MA mask were then calculated in dMRI space and centered by subtracting the mean position. Singular value decomposition was then applied, and the first right singular vector, representing the largest spatial variance, was defined as the MA principal orientation, corresponding to the predominant CSF flow pathway.

For each voxel within the MA, the diffusion tensor was projected onto the MA principal orientation and its two orthogonal directions. A directional diffusion ratio along the MA principal orientation was computed and defined as **Mes-speed**. In addition, a directionally constrained FA metric with respect to the MA principal orientation was calculated and defined as **Mes-FA**¹². Both measurements characterize CSF-related diffusion dynamics along the anatomically defined MA direction. (Fig. 1)

2.4 PET-MRI Acquisition and Analysis

The PET-MR scans included FBP for A β quantification and 18F-MK-6240 for Tau assessment. All PET scans were performed using a 3T whole-body PET/MR scanner (uPMR 790, United Imaging, China). Participants received intravenous injections of FBP for A β and 18F-MK-6240 for tau, as previously described⁸. Cortical standardized uptake value ratios (SUVRs) were calculated by the PETSURFER toolbox in FreeSurfer 7.1.1 (<https://surfer.nmr.mgh.harvard.edu>), using the cerebellum as a reference region.

2.5 Statistical Analyses

Comparisons between CN, MCI and AD groups were performed using ANOVA for continuous variables, followed by post-hoc tests using Bonferroni correction to adjust for multiple comparison. Chi-square tests or Fisher's exact test were used for categorical variables. Bivariate correlations were performed using Spearman's methods. Generalized linear regression was employed to assess the independent contribution of each CSF dynamic markers respectively, adjusted for age, sex and other covariates as specified. Mediation analyses were conducted using PROCESS v3.2 for SPSS (version 25.0, IBM), adjusted for age. All the analyses were conducted using R (version 4.3.3, The R Foundation), SPSS (version 25.0, IBM) or Python 3.9, with statistical significance set at $P < 0.05$ (two-tailed). All analyses were independently performed by two authors (XX and LS).

2.5 Study Approval

This study was approved by the ethics committee at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China. The study adhered to the 1964 Declaration of Helsinki and its amendments. All participants or their caregivers provided written informed consent. The cohort was registered on ClinicalTrials.gov (NCT05623124).

RESULTS

Demographic characteristics of the study participant

This study enrolled participants (n = 226) from the Ruijin Neurobank cognitive cohort (RJNB). The mean age of the participants was 69.68 ± 8.09 years. Among the participants, 136 (60.2%) were female. The participants were further diagnosed as cognitive normal (CN, n = 55), mild cognitive impairment (MCI, n = 71) and Alzheimer's disease (AD, n = 100) according to 2016 NIA-AA criteria. Detailed demographic characteristics were presented in Table 1.

Table 1
Demographic characteristics and aqueduct CSF dynamics measurements

	CN (n = 55)	MCI (n = 71)	AD (n = 100)	p
Age	68.69 ± 7.44	69.94 ± 8.48	70.04 ± 8.19	0.580
Female (n, %)	35 (63.6%)	37 (52.1%)	64 (64.0%)	0.245
Education (years)	11.38 ± 4.17	12.46 ± 3.67	11.81 ± 3.82	0.280
MMSE	29.13 ± 0.72	26.41 ± 1.75	17.02 ± 4.94	< 0.001
AVLT	4.89 ± 2.54	1.23 ± 1.99	0.14 ± 0.47	< 0.001
APOE ϵ 4 carrier (n, %)	14 (25.9%)	41 (61.2%)	60 (63.8%)	< 0.001
A β -PET positivity (n, %)	0 (0%)	71 (100%)	100 (100%)	< 0.001
A β -PET SUVR	0.47 ± 0.47	0.85 ± 0.23	0.94 ± 0.28	< 0.001
Tau-PET positivity (n, %)	0 (0%)	52 (82.5%)	81 (95.3%)	< 0.001
Tau-PET SUVR	1.21 ± 0.40	1.78 ± 0.87	2.45 ± 1.33	< 0.001
DTI-ALPS	1.25 ± 0.16	1.17 ± 0.17	1.10 ± 0.16	< 0.001
Mes_speed	0.57 ± 0.06	0.59 ± 0.07	0.59 ± 0.06	0.093
MD_mean (*10 ³)	0.51 ± 0.07	0.54 ± 0.07	0.54 ± 0.07	0.019
FA_mean	0.21 ± 0.03	0.24 ± 0.04	0.23 ± 0.04	0.001
Mes_FA	0.15 ± 0.03	0.17 ± 0.04	0.17 ± 0.03	0.001

CSF dynamics in MA across AD Spectrum

The measurements of CSF dynamics were compared across CN, MCI and AD by one-way ANOVA (Table 1), and the post hoc analysis showed significant difference between CN and MCI or AD in FA-mean (CN vs MCI: p = 0.002 ; CN vs AD: p = 0.003) and Mes-FA (CN vs MCI: p = 0.009; CN vs AD: p = 0.002), but not Mes-speed (CN vs MCI: p = 0.131 ; CN vs AD: p = 0.181) or MD-mean (CN vs MCI: p = 0.080; CN vs AD: p = 0.019) after Bonferroni multiple-comparison correction (Fig. 2).

CSF dynamics is associated with global A β burden, cortical thickness and cognitive performance

Spearman's correlation was performed and both FA-mean and Mes-FA showed significant positive association with global AV45 SUVR (FA-mean: $\rho = 0.18$, $p = 0.005$; Mes-FA: $\rho = 0.15$, $p = 0.021$), but not Tau SUVR (FA-mean: $\rho = 0.13$, $p = 0.086$; Mes-FA: $\rho = 0.10$, $p = 0.169$). FA-mean and Mes-FA were also negatively correlated to cortical thickness (FA-mean: $\rho = -0.27$, $p < 0.001$; Mes-FA: $\rho = -0.25$, $p < 0.001$), and cognitive performance by MMSE (FA-mean: $\rho = -0.23$, $p = 0.001$; Mes-FA: $\rho = -0.23$, $p < 0.001$) and AVLT (FA-mean: $\rho = -0.31$, $p < 0.001$; Mes-FA: $\rho = -0.32$, $p < 0.001$). In addition, FA-mean and Mes-FA were related to measurements of glymphatic function, including DTI-ALPS (FA-mean: $\rho = -0.30$, $p < 0.001$; Mes-FA: $\rho = -0.22$, $p = 0.001$) and WMH volume (FA-mean: $\rho = 0.18$, $p = 0.008$; Mes-FA: $\rho = 0.18$, $p = 0.007$). (Fig. 3)

After adjustment for age and sex, the positive association remained significant between AV45 SUVR and FA-mean ($\beta = 1.24$, $p = 0.043$), but not Mes-FA ($\beta = 1.15$, $p = 0.092$). In addition, when adjusted for age, sex, AV45 SUVR and Tau SUVR, FA-mean and Mes-FA remained negatively related with cortical thickness (FA-mean: $\beta = -0.54$, $p = 0.018$; Mes-FA: $\beta = -0.54$, $p = 0.032$). Moreover, after adjustment for age, sex, AV45 SUVR, Tau SUVR and cortical thickness, FA-mean and Mes-FA were still independently associated with declined cognitive performance assessed by AVLT (FA-mean: $\beta = -12.35$, $p = 0.002$; Mes-FA: $\beta = -16.32$, $p < 0.001$), but not MMSE (FA-mean: $\beta = -9.31$, $p = 0.318$; Mes-FA: $\beta = -14.26$, $p = 0.156$). (Fig. 4)

DTI-ALPS mediates the association between CSF dynamics and cognitive performance

Based on the finding that CSF dynamic markers (FA-mean and Mes-FA) were correlated with glymphatic markers and cognitive performance, mediation analysis was performed. After adjustment for age, DTI-ALPS partially mediated the influence of FA-mean (mediation effect = 24.87%; Fig. 5A) and Mes-FA (mediation effect = 18.10%; Fig. 5B) on AVLT, respectively. Meanwhile, full mediation effect of DTI-ALPS was observed on the association between FA-mean (mediation effect = 57.44%; Fig. 5C), Mes-FA (mediation effect = 41.24%; Fig. 5D) and MMSE, respectively, adjusted for age.

DISCUSSION

The present study explored the CSF dynamics in the aqueduct of sylvius by DTI-derived metrics (FA and Mes-FA) in 226 participants across the cognitive continuum, and showed higher anisotropy in MCI/AD than CN after correction for multiple comparisons. We further examined the correlation of these metrics with AD biomarkers (A β and Tau PET SUVRs), cortical atrophy, glymphatic function (by DTI-ALPS and WMH), and neuropsychological performances. And finally, we proved that the influence of DTI-derived CSF metrics on cognitive decline was mediated by DTI-ALPS, suggesting the involvement of glymphatic system.

Despite the important role of CSF dynamics in the maintenance of homeostasis of the brain¹³, there are few noninvasive imaging measures to assess the CSF flow^{14,15}. Previous cohort study in aging population (the Mayo Clinic Study of Aging cohort) found that disproportionately enlarged subarachnoid-space hydrocephalus (DESH) like imaging pattern, derived from T-weighted MRI, is related to cognitive deficit.² However, the DESH-like imaging pattern of structural MRI can only provide indirect assessment of CSF, and A β status is not concerned in the study. Recent MRI measurement of CSF dynamics relies mainly on phase-contrast (PC) MRI. Conventional 2D cine PC MRI has been applied in clinical use, but mainly in CSF circulation disorders like hydrocephalus and normal pressure hydrocephalus (NPH)^{16,17}. Comparative study found that PC MRI derived aqueductal CSF flow elevated in NPH but not AD, which can facilitated the differential diagnosis between HPH and AD³. In the field of dementia with neurodegenerative causes, a cohort study of the elderly found that decreased CSF flow is related to cognitive decline, though the cognitive deficit consists of heterogenous pathological backgrounds including MCI, AD, vascular dementia, dementia with lewy bodies and mixed dementia¹⁸. More recently, 4D flow MRI extends 2D PC to volumetric coverage, allowing simultaneous assessment of CSF velocities in ventricles and subarachnoid space over the cardiac cycle¹⁹. In a recent abstract, the authors calculated root-mean-square (RMS) velocity by 4D flow MRI, and found increased RMS velocity in right ventricle ($P = 0.024$) and spinal canal ($P = 0.048$), but not aqueduct ($P = 0.98$) in A β -positive participants²⁰. The disagreement between 2D cine and 4D flow PC MRI may result from different targets: the aim of the 4D flow abstract is to provide a preliminary attempt to calculate macroscopic CSF flow surrounding the whole CNS, rather than in a certain cerebral region like aqueduct in 2D cine PC analysis. Furthermore, limited spatial resolution of current 4D flow technique, especially in long narrow structure like aqueduct, may also bias the results. Despite the controversy, our study tries to depict CSF dynamics in the aqueduct of sylvius from a new perspective. In this study, DTI based FA and Mes-FA were calculated to represent the direction and velocity of water molecules in the aqueduct, providing description of regional CSF dynamics. This technique requires less acquisition time and post-processing than current PC MRI, which facilitates potential clinical application⁵. Furthermore, the correlation between FA/ Mes-FA and glymphatic biomarkers (DTI-ALPS and WMH) were calculated, and the mediation effect of DTI-ALPS between FA/ Mes-FA and cognitive performance were analyzed, bridging the current findings on CSF dynamics to glymphatic function, revealing substantial underlying mechanism, and indicating the solidity of the metrics.

Impaired clearance of A β from CNS plays a vital role in the pathogenesis of AD, leading to accumulation of the aberrant neurotoxic proteins in brain.²¹ Previous *in vivo* human lumbar CSF sampling study has measured the rate of A β production and clearance in healthy participants, which consisted of a delicate balance of 7.6% production and 8.3% clearance per hour.²² With the current acknowledgement of the glymphatic system, the role of CSF mediated clearance in gaining increasing research interest.²³ The glymphatic system is a CSF–interstitial fluid (ISF) exchange network in the brain that facilitate the clearance of metabolic waste such as amyloid- β , tau²⁴. Proper function of the glymphatic clearance depend on aquaporin-4 (AQP4), a water channel enriched on the perivascular endfeet of astrocytes.

Previous study found that perivascular AQP4 is reduced in frontal cortical gray matter of subjects with AD in post mortem human tissue, whereas deletion of *Snta1* gene in Tg2576 AD mice which anchors AQP4 at the perivascular endfeet.²⁵ In rodent studies, single-nucleus analysis found that the protein kinase RNA-like ER kinase (PERK) pathway was over-activated in AD mouse, and chronic PERK activation disrupts AQP4 localization and impedes glymphatic clearance in AD models, whereas selective deletion of PERK in astrocytes restores AQP4 localization, enhances glymphatic clearance, reduces A β and Tau pathology, and improves cognitive performance in mice²⁶. Moreover, non-invasive life-style modulation and multisensory audio-visual stimulation can promote glymphatic A β removal through astrocytic AQP4-related glymphatic clearance. Previous study suggested that high-intensity interval training in rodent AD models was proven to enhance clearance of A β and Tau by restoring polarized astrocytic AQP4-dependent glymphatic drainage to the kidney²⁷. And a recent study published in *Nature* proved that 40 Hz multisensory audio-visual gamma stimulation in 5XFAD AD mice can enhance glymphatic removal of A β via CSF-ISF exchange by restoring AQP4 polarization.²⁸ In human *in vivo* studies, diminished CSF clearance AD was also confirmed by dynamic PET imaging studies, using two distinct PET tracers (¹⁸F-THK5117 for Tau and ¹¹C-PiB for A β)^{14,29}. Consistently, our study also demonstrated elevated global A β accumulation with increased aqueductal CSF FA, supporting impaired CSF A β clearance in AD pathology.

Furthermore, our data revealed that FA and Mes-FA elevations in the aqueduct of Sylvius are independently related to brain atrophy and cognition decline, after adjustment for global A β and Tau burden. This finding was consistent with prior reports that CSF flow alters in aging and correlates to cognitive decline regardless of A β status^{2,30}, and echoes previous study that found decreased CSF flow in dementia with heterogeneous neurodegenerative causes including aging, MCI, AD, vascular dementia, dementia with Lewy bodies and mixed dementia^{2,18}. The findings that altered CSF dynamics can independently lead to cognitive decline suggested more potential underlying mechanism which can outreach to other forms of dementia in addition to AD, indicating a broader potential for clinical application.

Although our study provides novel insights into CSF dynamics assessed via DTI-derived metrics, several limitations should be considered. First, the cross-sectional design precludes causal inference regarding the relationship between aqueductal CSF dynamics, glymphatic function, and cognitive decline. Longitudinal studies are needed to determine whether altered CSF dynamics precede or result from neurodegenerative changes. Second, the DTI-based approach, though innovative, provides an indirect measure of CSF flow and may not fully capture the complexity of CSF flow compared to phase-contrast or 4D flow MRI. Third, the study population was drawn from a single-center cohort, which may limit generalizability to broader populations. Finally, while we adjusted for key AD biomarkers (A β and Tau), other factors such as vascular burden, sleep patterns, or systemic comorbidities that may influence glymphatic function were not comprehensively accounted for.

CONCLUSION

This study demonstrates that DTI-derived metrics of CSF dynamics (FA and Mes-FA) in the cerebral aqueduct are elevated in individuals with MCI and AD compared to cognitively normal controls. These metrics are correlated with global A β burden, and are associated with cortical atrophy and cognitive performance independent of A β and Tau accumulation. Furthermore, the association between aqueductal CSF dynamics and cognitive decline is mediated by glymphatic function, as measured by the DTI-ALPS index. These findings support the role of CSF and glymphatic system dysfunction in the pathophysiology of AD and related cognitive impairment. The DTI-based method offers a clinically feasible, non-invasive approach to assess regional CSF dynamics, bridging macroscopic flow with microstructural fluid movement. Future longitudinal and multimodal imaging studies are warranted to validate these metrics and explore their potential in early diagnosis, disease monitoring, and therapeutic targeting of glymphatic function in neurodegenerative disorders.

Declarations

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China. The study adhered to the 1964 Declaration of Helsinki and its amendments. All participants or their caregivers provided written informed consent. The cohort was registered on ClinicalTrials.gov (NCT05623124).

ADDITIONAL INFORMATION

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AUTHOR CONTRIBUTIONS

LS, XY and XX processed and analyzed the imaging data. XX wrote the manuscript. LK, YD, and WX collected clinical data and blood samples. LS and BL conducted the MRI procedure and acquired the imaging data. BL and XX designed the study and revised the manuscript. The authors read and approved the final manuscript.

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Figures

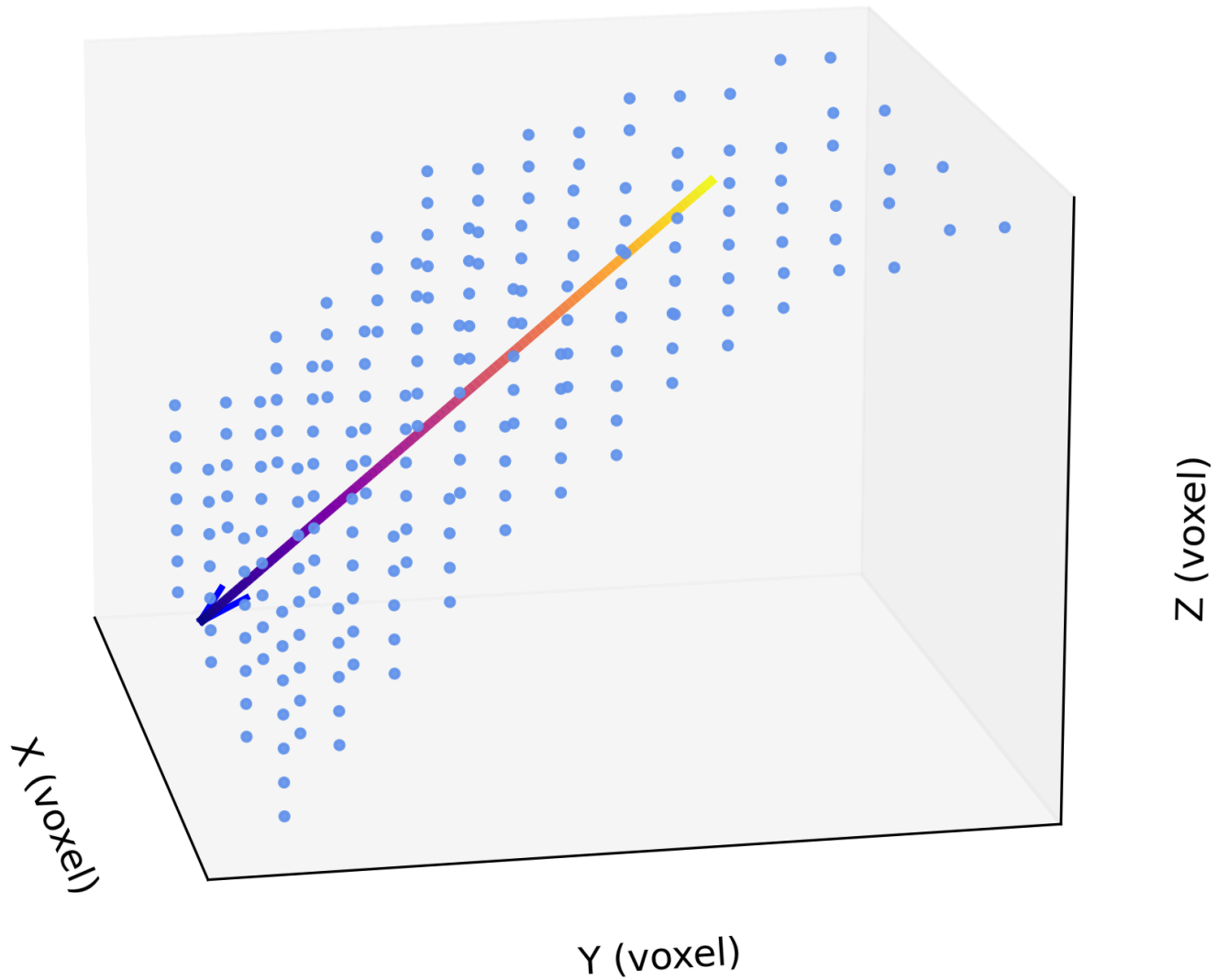


Figure 1

MA mask and principal orientation. Three-dimensional reconstruction of the MA mask (blue points) showing the spatial distribution of voxels. The principal axis of the MA, calculated by singular value decomposition, is indicated by the blue gradient line, with the arrow representing the main direction. The plot highlights the overall orientation and shape of the MA for illustrative purposes.

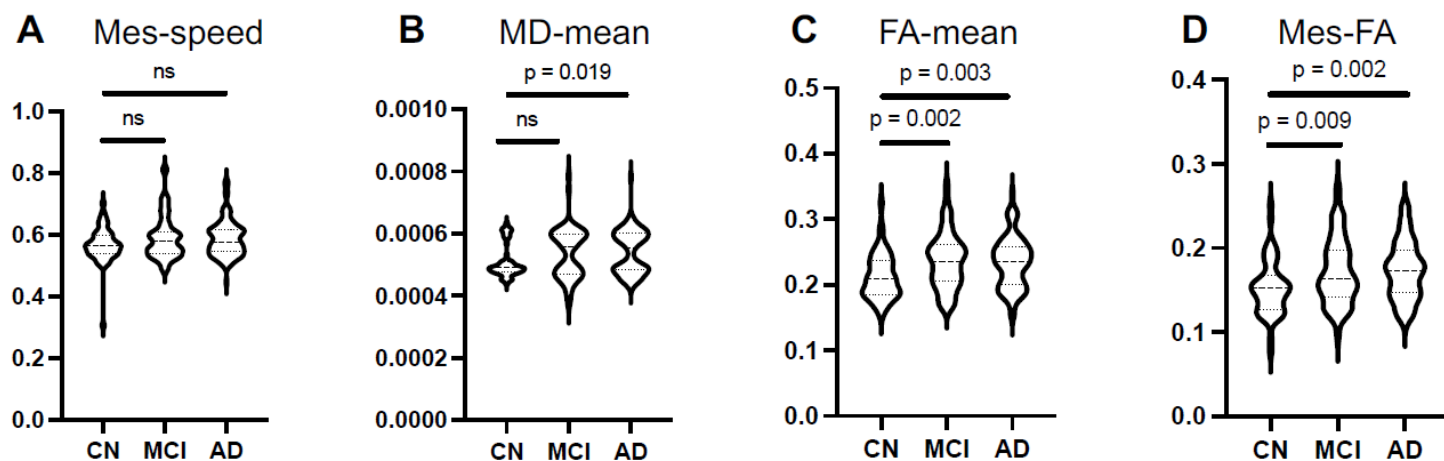


Figure 2

CSF dynamic metrics (Mes-speed, MD-mean, FA-mean and Mes-FA) compared across CN, MCI and AD by one-way ANOVA and post hoc analysis with Bonferroni multiple-comparison correction. (A) Mes-speed comparison between CN, MCI and AD (CN vs MCI: $p = 0.131$; CN vs AD: $p = 0.181$). (B) MD-mean comparison between CN, MCI and AD (CN vs MCI: $p = 0.080$; CN vs AD: $p = 0.019$). (C) FA-mean comparison between CN, MCI and AD (CN vs MCI: $p = 0.002$; CN vs AD: $p = 0.003$). (D) Mes-FA (CN vs MCI: $p = 0.009$; CN vs AD: $p = 0.002$).

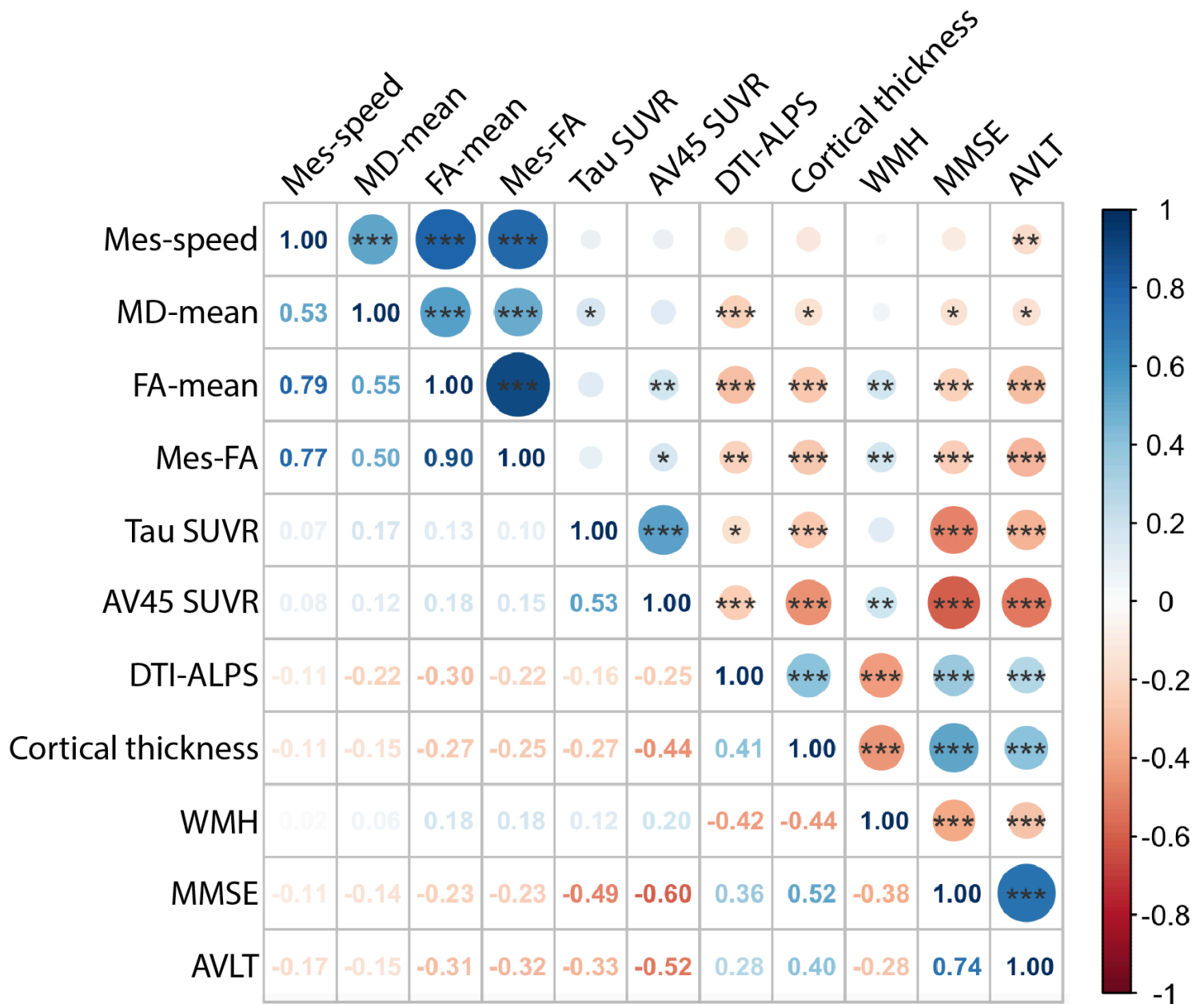


Figure 3

Spearman's correlation was performed between CSF dynamic metrics (Mes-speed, MD-mean, FA-mean and Mes-FA), AD PET-imaging markers (AV45 SUVR and Tau SUVR), MRI markers (DTI-ALPS, cortical thickness and WMH) and cognitive performance (MMSE and AVLT), respectively. The ρ -values and significances were presented correspondingly (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$).

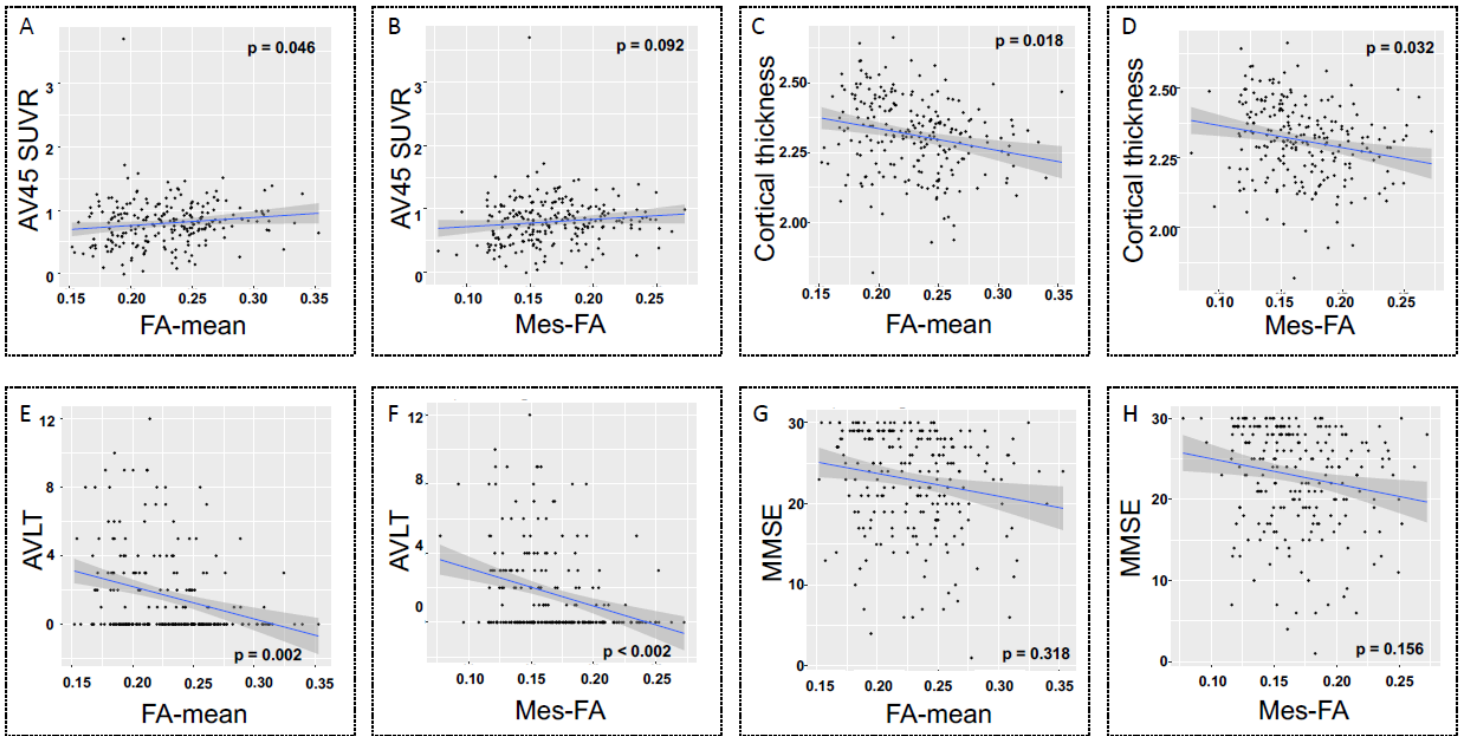


Figure 4

Generalized linear regression between AD PET-imaging marker (AV45 SUVR), MRI marker (cortical thickness), cognitive performance (MMSE and AVLT), and CSF dynamic metrics (FA-mean and Mes-FA), respectively. (A-B) Generalized linear regression between AV45 SUVR and FA-mean ($\beta = 1.24$, $p = 0.043$) and Mes-FA ($\beta = 1.15$, $p = 0.092$), adjusted for age and sex. (C-D) Generalized linear regression between cortical thickness and FA-mean ($\beta = -0.54$, $p = 0.018$) and Mes-FA ($\beta = -0.54$, $p = 0.032$), adjusted for age, sex, AV45 SUVR and Tau SUVR. (E-F) Generalized linear regression between AVLT and FA-mean ($\beta = -12.35$, $p = 0.002$) and Mes-FA ($\beta = -16.32$, $p < 0.001$), adjusted for age, sex, AV45 SUVR, Tau SUVR and cortical thickness. (G-H) Generalized linear regression between MMSE and FA-mean ($\beta = -9.31$, $p = 0.318$) and Mes-FA ($\beta = -14.26$, $p = 0.156$), adjusted for age, sex, AV45 SUVR, Tau SUVR and cortical thickness.

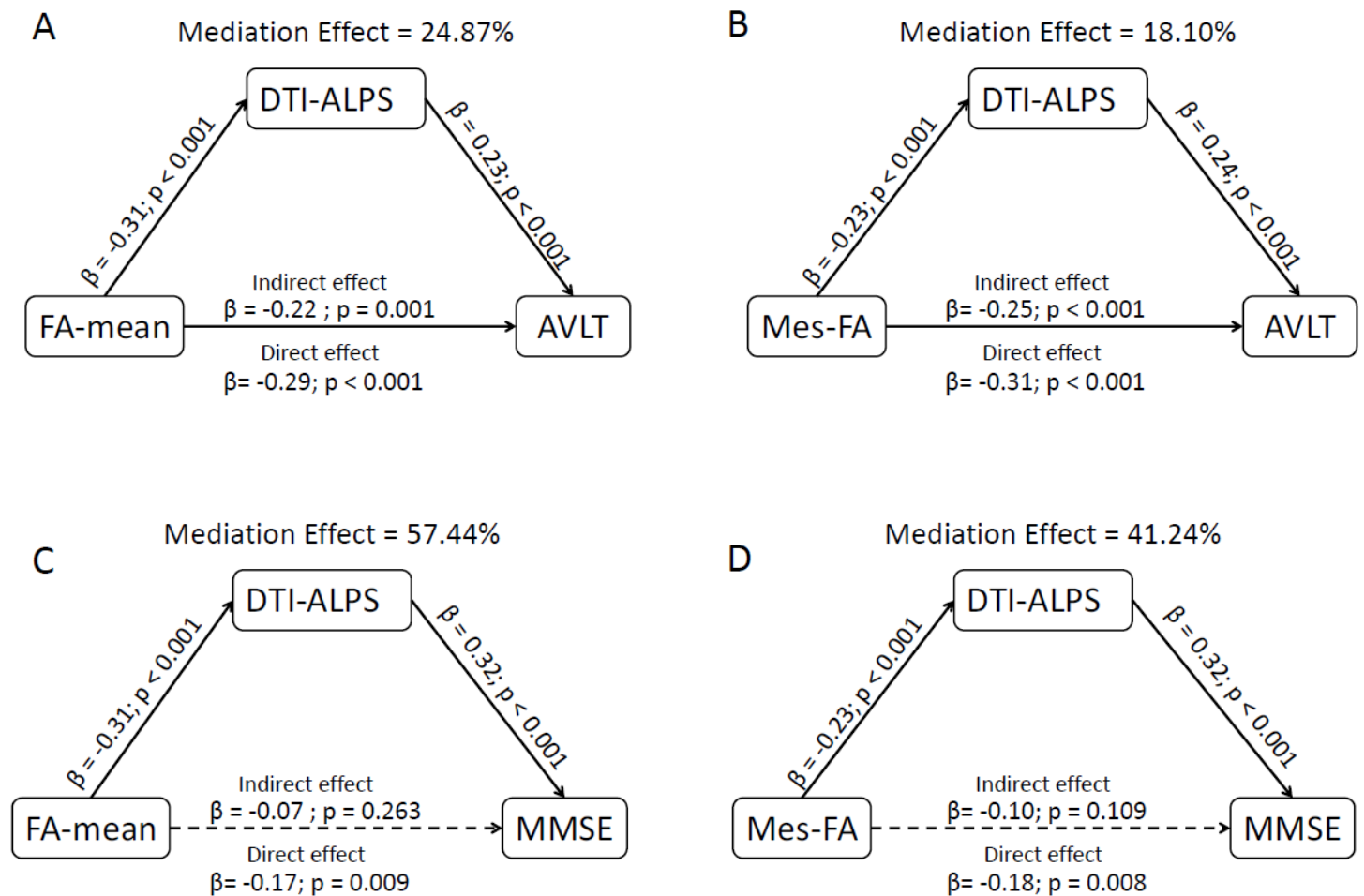


Figure 5

Mediation analysis of CSF dynamics and cognitive performance. (A) DTI-ALPS partially mediates the influence of FA-mean on AVLT (mediation effect = 24.87%). (B) DTI-ALPS partially mediates the influence of Mes-FA on AVLT (mediation effect = 18.10%). (C) DTI-ALPS fully mediates the influence of FA-mean on MMSE (mediation effect = 57.44%). (D) DTI-ALPS fully mediates the influence of Mes-FA on MMSE (mediation effect = 41.24%). All the mediation analyses are adjusted for age.