

# Altered cerebrospinal fluid-based clearance mechanisms in aging autistic adults

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# Abstract

## Background.

Autistic adults demonstrate a 4–6-fold increased risk of unspecified dementia compared with the general population; however, the neurobiological substrates underlying this elevated risk remain unexplored. Alterations in cerebrospinal fluid-based mechanisms involved in brain metabolic waste clearance may represent a shared neuropathological pathway between autism spectrum disorder and dementia. Specifically, developmental deviations in cerebrospinal fluid-related imaging markers have been consistently reported in autistic infants, children, and adolescents, and brain amyloid and other metabolic waste accumulation is a hallmark of Alzheimer's disease and related dementias. Despite this overlap, cerebrospinal fluid-based regulatory mechanisms have not been systematically examined in ageing autistic adults. Here, we used a multimodal magnetic resonance imaging approach to quantify structural and diffusion-based markers of cerebrospinal fluid regulation in middle-aged and older autistic adults compared with matched controls.

## Methods.

Forty-nine autistic adults aged 30–73 years and 61 age-, sex-, and intelligence quotient-matched controls underwent T1-, T2-, and diffusion-weighted imaging. Measures included white matter perivascular space volume fraction, count fraction, and mean diameter; diffusion-based indices of fluid movement along perivascular pathways; and volumes of the lateral ventricles and choroid plexus.

## Results.

With increasing age, autistic adults exhibited significantly greater increases in white matter perivascular volume fraction within the left inferior parietal lobule compared with controls. Autistic adults also showed significantly reduced diffusion indices and larger bilateral lateral ventricle and choroid plexus volumes relative to controls. Across both groups, increasing age was associated with higher white matter perivascular volume fraction in the right pars triangularis, reduced diffusion indices, and enlargement of the bilateral lateral ventricles and left choroid plexus.

## Limitations.

First, the cross-sectional design limited our ability to quantify intra-individual variability and capture longitudinal trajectories. Second, the sample primarily comprised cognitively unimpaired autistic adults. Third, participants were predominantly of average or above-average intelligence; thus, findings may not generalize to autistic adults with ID. Finally, health factors

including sleep disturbance, cardiovascular and metabolic disease, polypharmacy, and lifelong medication exposure, may have influenced these findings. Future large-scale studies should systematically evaluate their potential confounding and moderating effects.

## Conclusions.

These findings demonstrate that ageing autistic adults exhibit convergent alterations in cerebrospinal fluid regulatory mechanisms, reflected in perivascular space morphology, diffusion-based fluid dynamics, and ventricular and choroid plexus enlargement. Together, the results link early developmental deviations to later-life vulnerability and highlight cerebrospinal fluid dysregulation as a potential candidate neurobiological substrate contributing to the increased prevalence of dementia in autistic adults.

## Background

Autistic adults exhibit a 4–6-fold increased risk of unspecified dementia relative to the general population.<sup>1–5</sup> This elevated risk persists after adjustment for intellectual disability (ID), psychiatric comorbidities, and lifestyle-related factors, suggesting that autism spectrum disorder (ASD) independently confers a heightened neurobiological vulnerability to pathological brain ageing. While the precise mechanisms underlying this heightened risk have not yet been identified, multiple dementia subtypes—including Alzheimer’s disease, vascular dementia, and frontotemporal dementia—exhibit broad alterations in CSF-based mechanisms critical for brain metabolic waste clearance.<sup>6–9</sup> These alterations include enlarged white matter perivascular spaces (WM-PVS),<sup>10–14</sup> reduced indices of fluid diffusion along perivascular spaces,<sup>15–17</sup> and larger volumes of the lateral ventricles<sup>18–20</sup> and choroid plexus<sup>21–23</sup>. Evidence of dysregulation in CSF-based mechanisms has been reported in middle-aged and older autistic adults, including increased extracellular free-water in frontal lobe transcallosal white matter<sup>24</sup> and enlargement of the cerebral ventricles compared to age-matched neurotypical controls.<sup>25</sup> However, these findings have been derived from single imaging markers rather than from a comprehensive multimodal approach to examine CSF-based mechanisms. Given that ageing neurobiology in ASD remains critically under-researched, the elevated prevalence of dementia in autistic adults underscores the need for systematic investigation of pathological brain ageing processes across middle and later life. Recent work has recognized the pathophysiological overlaps between ASD and Alzheimer’s disease, emphasizing shared alterations among perivascular pathways and brain waste clearance mechanisms.<sup>26</sup> Together, these findings suggest that alterations in CSF-based mechanisms involved in brain metabolic waste clearance may represent an overlapping substrate linking ASD and dementia-related processes, offering insight into shared neurobiological pathways driving this increased prevalence.

Proper functioning of CSF-based mechanisms is necessary for the efficient removal of neurotoxic proteins that may otherwise accumulate within the parenchyma over time.<sup>7,27,28</sup> Brain metabolic waste clearance relies on the bulk fluid exchange between CSF and interstitial

fluid along the perivascular spaces (PVS).<sup>8,27,29</sup> CSF is produced by the choroid plexus, a specialized structure lining the brain's ventricular system,<sup>30,31</sup> and is derived from arterial blood plasma.<sup>31</sup> Beyond CSF production, the choroid plexus also regulates nutrient transport, metabolic exchange between blood and CSF, and triggering neuroimmune responses in the central nervous system.<sup>31-34</sup> The lateral ventricles are the primary compartments that support continuous CSF circulation and maintain homeostasis.<sup>35,36</sup> CSF circulates through the ventricular system and exits into the subarachnoid space as extra-axial CSF (EA-CSF).<sup>37</sup> From here, EA-CSF flows along perivascular pathways that surround penetrating brain arterioles<sup>38,39</sup> and contributes to CSF-interstitial fluid exchange,<sup>27,40,41</sup> facilitating metabolic waste removal throughout the parenchyma.<sup>7,27,28</sup> Structurally, PVS are the fluid-filled compartments bounded internally by the abluminal surface of arterioles and externally by a sheath of astrocytic endfeet,<sup>27,42,43</sup> which are specialized glial processes extending from astrocytes.<sup>27</sup> Cardiac-driven arterial pulsatility offers the mechanical force that propels CSF movement along PVS.<sup>40,44</sup> This rhythmic contraction and relaxation of the arteriole wall promotes CSF-interstitial fluid exchange and enables metabolic waste removal from the surrounding tissue,<sup>27,44</sup> directing collected byproducts toward perivenous drainage pathways.<sup>45</sup> This fluid-based mechanism, commonly referred to as the glymphatic system, is estimated to remove over half of extracellular amyloid- $\beta$  from the brain, underscoring its critical role in minimizing the accumulation of neurodegeneration-promoting products.<sup>8,46</sup>

Developmental alterations in CSF-based mechanisms are well-documented in ASD,<sup>47-56</sup> yet remain largely unexplored in autistic adults. In infants at high risk for ASD, elevated extra-axial CSF<sup>49</sup> and widespread PVS enlargement<sup>52</sup> have been shown to predict later ASD diagnosis. In autistic children aged 1-9 years, increased WM-PVS count and volume fraction have been associated with greater clinical severity of ASD.<sup>47</sup> Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) of deep medullary veins has further revealed lower indices in autistic children aged 2-5 years compared with neurotypical controls, suggesting reduced fluid transport along these pathways.<sup>53</sup> Converging structural MRI studies have also demonstrated enlarged lateral ventricles and choroid plexus in autistic children and adolescents relative to age-matched peers,<sup>54,55,57</sup> suggesting that altered CSF-based mechanisms in ASD are reflected not only in downstream PVS morphology and fluid transport, but also in upstream CSF-handling. Thus, enlargement of the lateral ventricles and choroid plexus implicates abnormalities in structures involved in both CSF handling as well as solute filtration and immune signaling between blood and CSF.<sup>31-34</sup> Despite ample evidence of early-life alterations, little is known about how CSF-based features manifest in ASD after childhood, particularly in middle-aged and older autistic adults. Given the critical role of CSF regulation in brain metabolic waste clearance,<sup>7,27</sup> this knowledge gap limits the development of a mechanistic framework for understanding the heightened vulnerability to dementia in this understudied clinical population.<sup>47</sup>

In this multimodal imaging study, we used structural and diffusion-based MRI approaches to compare WM-PVS count (the total number of PVS lesions), volume (total lesion volume), and diameter (mean diameter of detected PVS) across the frontal, parietal, temporal, and occipital lobes, as well as DTI-ALPS indices and volumes of the lateral ventricles and choroid plexus, between middle-aged and older autistic adults and matched neurotypical controls. To our knowledge, no prior study has jointly examined WM-PVS morphology, DTI-ALPS, and volumes of the lateral ventricles and choroid plexus in ageing autistic adults. Consistent with findings in autistic infants and children,<sup>47,53–55</sup> we predicted that CSF dysregulation would persist beyond early development and hypothesized that autistic adults would exhibit 1) greater WM-PVS volume, count, and diameter; 2) lower DTI-ALPS indices; and 3) increased lateral ventricle and choroid plexus volumes relative to controls. We further hypothesized that age-associated changes in these measures would be more pronounced in autistic adults compared with neurotypical controls, reflecting the life-course neurobiological vulnerability associated with ASD.

## Materials

## Participants

A total of 49 autistic adults and 61 neurotypical controls (NT) participated in this cross-sectional study. The two groups were matched on age, sex, and full-scale IQ (FSIQ), performance IQ (pIQ), and verbal IQ (vIQ) (Table 1). Autistic participants were recruited through the Center for Autism and Related Disabilities (CARD) at the University of Florida, the University of Central Florida, and the University of South Florida, as well as the SPARK Research Match program (<https://www.sfari.org/resource/research-match>). Controls were primarily recruited through local flyers and word of mouth referrals. All study procedures were approved by the Institutional Review Boards (IRB) at the University of Florida (IRB202100659, approved September 23, 2021). In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants after they received a complete description of the study and its procedures.

Table 1  
Demographic characteristics between autistic participants (ASD) and neurotypical controls (NT)

|                                                                                                                                                                              |             | ASD         | NT       | $t/\chi^2$ | $p$ |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|----------|------------|-----|
| <b>Sample size (n)</b>                                                                                                                                                       | <b>49</b>   | <b>61</b>   | <b>—</b> | <b>—</b>   |     |
| Age (years) <sup>a</sup>                                                                                                                                                     | 46 ± 11     | 48 ± 12     | 0.65     | 0.52       |     |
| Range                                                                                                                                                                        | 30 – 73     | 30 – 70     | —        | —          |     |
| Sex (M/F)                                                                                                                                                                    | 28/21       | 29/32       | 1.00     | 0.32       |     |
| FSIQ score <sup>a</sup>                                                                                                                                                      | 107 ± 14    | 108 ± 12    | 0.58     | 0.56       |     |
| Range                                                                                                                                                                        | 77 – 143    | 82 – 126    | —        | —          |     |
| vIQ score <sup>a</sup>                                                                                                                                                       | 107 ± 14    | 106 ± 11    | -0.27    | 0.79       |     |
| Range                                                                                                                                                                        | 71 – 136    | 83 – 130    | —        | —          |     |
| pIQ score <sup>a</sup>                                                                                                                                                       | 105 ± 14    | 108 ± 15    | 1.25     | 0.21       |     |
| Range                                                                                                                                                                        | 72 – 142    | 79 – 142    |          |            |     |
| eTIV <sup>a</sup>                                                                                                                                                            | 1545 ± 149  | 1512 ± 157  | -1.15    | 0.25       |     |
| Relative head motion (mm)                                                                                                                                                    | 0.46 ± 1.08 | 0.30 ± 0.67 | 0.09     | 0.38       |     |
| ADOS-2 SA score <sup>b</sup>                                                                                                                                                 | 9 ± 3       | —           | —        | —          |     |
| Range                                                                                                                                                                        | 5 – 18      | —           | —        | —          |     |
| ADOS-2 RRB <sup>b</sup>                                                                                                                                                      | 2 ± 1       | —           | —        | —          |     |
| Range                                                                                                                                                                        | 0 – 6       | —           | —        | —          |     |
| <sup>a</sup> Age, FSIQ, pIQ, vIQ and eTIV shown as mean and standard deviation                                                                                               |             |             |          |            |     |
| <sup>b</sup> ADOS-2 Social Affect (SA) and Restricted and Repetitive Behavior (RRB) are derived from the Module 4 revised algorithm and shown as mean and standard deviation |             |             |          |            |     |

[Insert Table 1 about here]

Screening criteria for participants were consistent with those used in previous studies from our lab and others<sup>58,59</sup>. Autistic adults with a clinical diagnosis of ASD were required to score > 32 on the Autism Spectrum Quotient for Adults (AQ-50)<sup>60</sup> and ≥ 65 on the Social Responsiveness Scale Adult Self-Report (SRS-2)<sup>61</sup> to be invited for a comprehensive in-person diagnostic evaluation using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)<sup>62</sup>. Diagnosis of ASD was confirmed through an integrative review of AQ-50, SRS-2, and ADOS-2

scores, in conjunction with expert clinical judgement by a licensed clinician, following the DSM-5 criteria.<sup>63</sup>

Neurotypical controls were recruited if they scored  $\leq 22$  on the AQ-50 and  $< 60$  on the SRS-2. Exclusion criteria for controls included a family history of ASD or related neurodevelopmental conditions among first- and second-degree relatives.

Exclusion criteria for both groups included: (1) a diagnosis of intellectual disability (including non-specific developmental delay), mild cognitive impairment, or dementia; (2) a current or past major psychiatric condition (e.g., schizophrenia, bipolar disorder, or post-traumatic stress disorder); (3) a current or past illness involving the central nervous system (e.g., brain tumor, thyroid disease, Cushing's disease, or HIV infection); (4) a diagnosed neurological disorder (e.g., Parkinson's disease, cerebellar ataxia, seizure, dystonia, or stroke); (5) a family history of heritable neurological disease (e.g., Huntington's disease, Wilson's disease, or amyotrophic lateral sclerosis); (6) implanted medical devices incompatible with MRI (e.g., cardiac pacemakers, infusion pumps, cochlear implants); (7) current pregnancy; (8) FSIQ  $< 75$  as measured by the Wechsler Abbreviated Scales of Intelligence, Second Edition<sup>64</sup>, or (9) non-English-speaking status.

Medication use and polypharmacy are prevalent in ASD<sup>65</sup>. To allow an ecologically representative sample of autistic adults, routine medication use was not an exclusion criterion in this study. Participants taking psychotropic medication included those prescribed antidepressants (ASD = 25, NT = 4), antipsychotics/neuroleptics (ASD = 4), sedatives/hypnotics/anxiolytics (ASD = 7, NT = 2), stimulants (ASD = 9), and anticonvulsants (ASD = 6, NT = 1).

## MRI data acquisition

MRI scans were acquired using a 3T Siemens Prisma scanner equipped with a 64-channel head coil at the University of Florida McKnight Brain Institute. Participants were screened before scanning, and hearing protection was provided prior to entering the scanner room. Foam padding was securely placed around the head to minimize motion during image acquisition. For T1-weighted imaging, the MPRAGE sequence was acquired with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 2.99 ms, flip angle =  $8^\circ$ , field of view (FOV) =  $256 \times 256$  mm, matrix size =  $320 \times 320$ , 208 sagittal slices, and isotropic voxel size =  $0.8 \times 0.8 \times 0.8$  mm<sup>3</sup>. For T2-weighted imaging, a three-dimensional SPACE sequence was collected with the following parameters: TR = 2500 ms, TE = 370 ms, variable refocusing flip angle, FOV =  $256 \times 256$  mm, matrix size =  $320 \times 320$ , 208 sagittal slices, and isotropic voxel size =  $0.8 \times 0.8 \times 0.8$  mm<sup>3</sup>. Diffusion weighted scans were acquired with an echo-planar imaging sequence with the following parameters: TR = 6400 ms, TE = 58 ms, b-values:  $5 \times 0$  s/mm<sup>2</sup> and  $64 \times 1000$  s/mm<sup>2</sup>, bandwidth = 2442 Hz/pixel, FOV =  $256 \times 256$ , matrix size =  $128 \times 128$ , 69 axial slices, and isotropic voxel size =  $2.0 \times 2.0 \times 2.0$  mm<sup>3</sup>.

[Insert Fig. 1 about here]

## White matter perivascular spaces

T2-weighted images were visually assessed by the team's physician-scientist (GB) for PVS segmentation. Cases with prominent imaging artifacts that significantly compromised accurate PVS quantification were excluded from further analysis ( $ASD = 2$ ). T2-weighted images were rigidly registered to the processed T1-weighted images using a six-degree-of-freedom transformation and boundary-based cost function, as implemented by the *bbregister* command using FreeSurfer version 8.0.0. We segmented MRI-visible WM-PVS using a robust, fully automated pipeline that has been previously validated across multiple independent datasets of healthy aging and neurodegeneration<sup>10</sup> (Fig. 1A). Briefly, we first generated enhanced perivascular contrast (EPC) images for each participant by computing the voxel-wise ratio of T1-weighted to T2-weighted images<sup>66</sup>. Prior work has demonstrated that this approach enhances PVS contrast and increases the sensitivity of both visual detection and automated PVS segmentation<sup>66</sup>. We then applied a multiscale *Frangi vesselness* filter<sup>67</sup> to the white matter mask applied on the EPC images to enhance tubular structures consistent with PVS morphology. We set the filter parameters to  $\alpha = 0.5$  and  $\beta = 0.5$ , with  $c$  defined as half the maximum Hessian norm, in accordance with established recommendations<sup>66</sup>. The *Frangi* filter assigns a *vesselness* value to each voxel based on the eigenvalues of the Hessian matrix, thereby preferentially improving elongated, vessel-like structures while suppressing non-tubular signal.

We applied the *Frangi* filter within 32 bilateral white matter regions generated using FreeSurfer according to the Desikan-Killiany atlas. To minimize contamination from non-PVS pathology, we first segmented white matter lesions unrelated to PVS using a fully automated approach<sup>68</sup> and excluded these lesions from the white matter masks prior to *vesselness* filtering, consistent with prior work<sup>10</sup>. We then automatically derived PVS masks from the resulting *vesselness* maps using a percentile-based thresholding approach that has been previously validated<sup>69</sup>.

For each participant, we quantified PVS metrics including total count, total volume, and mean diameter. Total count and total volume refer to the occurrence and spatial occupancy that visible PVS exhibit in a mask. Mean diameter refers to the average cross-sectional width of detected PVS<sup>69</sup>. We derived these measures using MATLAB's *regionprops3* function applied to the binarized PVS masks. Because both PVS count and volume scale with the volume of the underlying white matter region, we normalized these measures by the corresponding regional white matter mask volume to derive PVS count fraction and PVS volume fraction, respectively<sup>69</sup>.

We grouped white matter masks from the left and right hemisphere by anatomical lobe, consistent with prior studies in autistic children<sup>70</sup>. The frontal lobe comprised 11 masks,

including the superior frontal gyrus, rostral middle frontal gyrus, caudal middle frontal gyrus, pars opercularis, pars orbitalis, pars triangularis, lateral orbitofrontal gyrus, medial orbitofrontal gyrus, precentral gyrus, paracentral lobule, and frontal pole. The parietal lobe consisted of 5 masks encompassing the postcentral gyrus, supramarginal gyrus, superior parietal lobule, inferior parietal lobule, and precuneus regions. The temporal lobe included 8 masks incorporating the entorhinal cortex, parahippocampal gyrus, fusiform gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, transverse temporal gyrus, and temporal pole. Finally, the occipital lobe consisted of 4 masks encompassing the lingual gyrus, pericalcarine cortex, cuneus, and lateral occipital cortex. Across all bilateral regions of interest (ROIs) and PVS metrics, each participant yielded 168 PVS variables (56 ROIs  $\times$  3 PVS metrics).

## DTI-ALPS index

We calculated the DTI-ALPS index using an MNI-space approach <sup>15</sup> (Fig. 1B) and processed diffusion weighted MRI data following pipelines used in previous published work <sup>24</sup>.

Specifically, we performed denoising and Gibbs artefact removal using MRtrix3 <sup>71</sup>. We then generated brain masks directly from the diffusion weighted images using the *dwi2mask* function in MRtrix3 <sup>71</sup>. Next, we corrected for eddy current induced image distortions and head motion, with corresponding adjustment to gradient directions (i.e. b-vectors) using Eddy, a fully automated quality control framework in FSL <sup>72</sup>.

We subsequently reconstructed diffusion tensors using FSL's *dtifit* function to generate fractional anisotropy (FA) images in native subject space. We registered the resulting FA images to the HCP1065 FA template <sup>73</sup> using the symmetric normalization (SyN) algorithm implemented in Advanced Normalization Tools (ANTs) <sup>74</sup>, which applies both an affine transformation and a nonlinear diffeomorphic warp. These registered FA images in MNI space were visually inspected to confirm appropriate data quality, as in our prior work <sup>24</sup>. We then applied the resulting transformation matrices to each of the six unique tensor elements (Dxx, Dxy, Dxz, Dyy, Dyz, and Dzz) to transform the diffusion tensor into MNI space.

To compute the index, we defined four bilateral spherical regions of interest (ROIs; 5mm-diameter) at the level of the lateral ventricles to sample projection and association white matter fibers. We centered projection fiber ROIs at MNI coordinates ( $\pm 25, -20, 28$ ) and association fiber ROIs at ( $\pm 39, -20, 28$ ), based on the HCP1065 1mm FA template and corresponding tensor maps overlaid in RGB to confirm proper orientation. We then calculated the DTI-ALPS index as the ratio of diffusivity along the x-axis to diffusivity perpendicular to the primary fiber direction, defined as:

$$DTI - ALPS = \frac{\text{mean}(D_{xx\_proj}, D_{xx\_assoc})}{\text{mean}(D_{yy\_proj}, D_{zz\_assoc})}$$

where Dxx represents diffusivity along projection and association fibers, Dyy represents perpendicular diffusivity in projection fibers, and Dzz represents perpendicular diffusivity in association fibers. We averaged left and right hemisphere values to obtain a single bilateral ALPS index for each participant. Due to the timing in which individuals were recruited in this study, five participants in our sample were unable to receive the diffusion MRI necessary for DTI-ALPS analysis (ASD = 4; NT = 1).

## Lateral ventricle and choroid plexus volume

We performed quantification of lateral ventricle and choroid plexus volume using FreeSurfer versions 7.2.0 <sup>75</sup> and FSL version 6.0 <sup>72</sup> on a Linux-based computing system. First, T1-weighted images underwent slice-by-slice visual inspection across axial, coronal, and sagittal planes by multiple trained raters. Images that exhibited significant segmentation inaccuracies were corrected using the *Recon Edit* tool in FreeSurfer and subsequently cross-validated by an independent rater to ensure consistency. T1-weighted images that did not meet quality control criteria were excluded from further analysis (ASD = 1). Images that passed quality control were processed for volumetric segmentation and cortical surface reconstruction following the standard *recon-all* pipeline, which includes motion correction, intensity normalization, transformation to Talairach space, skull stripping and brain extraction, white matter segmentation, and cortical surface parcellation. We derived volumes of the left and right lateral ventricles and choroid plexus (Fig. 1C) from T1-weighted MRI scans using automated segmentation outputs generated by FreeSurfer. To account for inter-individual differences in brain size, we normalized these ROIs by the estimated total intracranial volume (eTIV) provided by FreeSurfer.

Participant sample size for each MRI measure was 49 ASD/61 NT for WM-PVS and T1-weighted volume, and 46 ASD/59 NT for DTI-ALPS.

## Statistical analysis

Statistical analysis was conducted in RStudio version 4.4.1. Demographic characteristics between autistic participants and neurotypical controls were compared using independent-sample *t*-tests for continuous variables, including age, FSIQ, pIQ, vIQ, and eTIV. Group differences in sex were assessed using a Chi-square test.

Normality of outcome variables was assessed using the Shapiro-Wilk test, which indicated non-normal distributions for several measures, including lateral ventricle and choroid plexus volumes, and approximately 40% of PVS variables. Given the non-normal distribution properties, linear regression models with 5000 permutations were implemented to examine main effects of group (ASD vs. NT), age, and their interaction (group  $\times$  age). Each MRI metric served as the dependent variable in separate models. Age was mean-centered to improve interpretability of group and group-by-age effects and reduce multicollinearity among predictors.

Bonferroni correction was applied to adjust for multiple comparisons<sup>76</sup>. For WM-PVS, Bonferroni thresholds were set within lobes (frontal, parietal, temporal, and occipital) to control the family-wise error rate while preserving anatomical specificity. Specifically, significance was defined as  $p < 0.00227$  for the frontal lobe (22 masks),  $p < 0.00500$  for the parietal lobe (10 masks),  $p < 0.00313$  for the temporal lobe (16 masks), and  $p < 0.00625$  for the occipital lobe (8 masks). Significance was defined as  $p < 0.025$  for the lateral ventricles and choroid plexus volume, as each consisted of two ROIs (left and right), and  $p < 0.05$  for the DTI-ALPS index.

## Results

### Participant demographics

Table 1 summarizes the demographic characteristics of the groups. Autistic adults and neurotypical controls were matched on age, sex, all IQ scores, and eTIV. Relative head motion also did not differ between groups.

[Insert Table 1 about here]

### White matter perivascular spaces

Autistic adults exhibited significantly steeper age-associated increases in WM-PVS volume fraction within the left inferior parietal lobule compared to controls (Fig. 2). Furthermore, both groups demonstrated significant age-associated increases in WM-PVS volume fraction within the right pars triangularis (Table 2). Multiple lobar patterns in WM-PVS were demonstrated at the uncorrected level ( $p\text{-perm} < 0.05$ ). For example, 1) group effects were most frequent in the temporal lobe (50%), followed by the parietal (25%) and occipital lobes (25%), with no group effect observed in the frontal lobe; 2) group  $\times$  age interaction effects were most frequent in the parietal lobe (62.5%), followed by the temporal (25%) and frontal lobes (12.5%), and no interaction effects observed in the occipital lobe; and 3) age effects were predominantly found in the frontal lobe (55.6%), followed by the parietal (22.2%), temporal (18.5%), and occipital lobes (3.7%). Finally, hemispheric distribution showed that age and group main effects were bilaterally distributed, whereas all group  $\times$  age interaction effects were left-lateralized. No other significant Bonferroni-corrected group, age, or group  $\times$  age effects were observed (Supplementary Tables 1–4).

Table 2  
Linear regression results of p-perm < 0.05 WM-PVS metrics

| Metric                                                                             | Lobe     | Mask                      | Term             | $\beta$       | SE            | $t$         | $p$ -<br><i>perm</i> |  |
|------------------------------------------------------------------------------------|----------|---------------------------|------------------|---------------|---------------|-------------|----------------------|--|
| DM                                                                                 | Frontal  | L-parsopercularis         | Group·Age        | 0.0066        | 0.0030        | 2.21        | 0.029                |  |
| DM                                                                                 |          | L-caudalmiddlefrontal     | Age              | 0.0041        | 0.0016        | 2.62        | 0.010                |  |
| VF                                                                                 |          | L-caudalmiddlefrontal     | Age              | 0.0001        | 0.0001        | 2.48        | 0.017                |  |
| VF                                                                                 |          | L-parsopercularis         | Age              | 0.0002        | 0.0001        | 3.01        | 0.002                |  |
| DM                                                                                 |          | L-parstriangularis        | Age              | 0.0041        | 0.0015        | 2.74        | 0.009                |  |
| VF                                                                                 |          | L-precentral              | Age              | 0.0001        | 0.0000        | 2.30        | 0.025                |  |
| DM                                                                                 |          | L-rostralmiddlefrontal    | Age              | 0.0039        | 0.0012        | 3.15        | 0.003                |  |
| VF                                                                                 |          | L-superiorfrontal         | Age              | 0.0001        | 0.0001        | 1.96        | 0.047                |  |
| DM                                                                                 |          | R-parsopercularis         | Age              | 0.0045        | 0.0020        | 2.22        | 0.029                |  |
| VF                                                                                 | Parietal | R-parsopercularis         | Age              | 0.0001        | 0.0001        | 2.45        | 0.015                |  |
| CF                                                                                 |          | R-parstriangularis        | Age              | 0.0000        | 0.0000        | 2.64        | 0.011                |  |
| DM                                                                                 |          | R-parstriangularis        | Age              | 0.0054        | 0.0018        | 2.98        | 0.005                |  |
| <b>VF</b>                                                                          |          | <b>R-parstriangularis</b> | <b>Age</b>       | <b>0.0002</b> | <b>0.0000</b> | <b>3.75</b> | <b>0.000</b>         |  |
| VF                                                                                 |          | R-precentral              | Age              | 0.0001        | 0.0000        | 2.08        | 0.039                |  |
| DM                                                                                 |          | R-rostralmiddlefrontal    | Age              | 0.0030        | 0.0010        | 2.97        | 0.004                |  |
| VF                                                                                 |          | R-superiorfrontal         | Age              | 0.0001        | 0.0000        | 2.27        | 0.026                |  |
| CF                                                                                 |          | R-inferiorparietal        | Group            | 0.0002        | 0.0001        | 1.98        | 0.048                |  |
| CF                                                                                 |          | R-supramarginal           | Group            | 0.0003        | 0.0001        | 2.41        | 0.019                |  |
| CF                                                                                 |          | L-inferiorparietal        | Group·Age        | 0.0000        | 0.0000        | 2.68        | 0.010                |  |
| DM                                                                                 |          | L-inferiorparietal        | Group·Age        | 0.0069        | 0.0032        | 2.19        | 0.032                |  |
| <b>VF</b>                                                                          |          | <b>L-inferiorparietal</b> | <b>Group·Age</b> | <b>0.0003</b> | <b>0.0001</b> | <b>3.14</b> | <b>0.002</b>         |  |
| DM                                                                                 |          | L-precuneus               | Group·Age        | 0.0061        | 0.0023        | 2.68        | 0.008                |  |
| VF                                                                                 |          | L-precuneus               | Group·Age        | 0.0001        | 0.0001        | 2.07        | 0.046                |  |
| CF                                                                                 |          | L-precuneus               | Age              | 0.0000        | 0.0000        | -2.01       | 0.045                |  |
| Bold indicates significance after Bonferroni correction                            |          |                           |                  |               |               |             |                      |  |
| DM = Diameter mean; VF = volume fraction; CF = count fraction; L = Left; R = Right |          |                           |                  |               |               |             |                      |  |

| <b>Metric</b>                                                                      | <b>Lobe</b> | <b>Mask</b>          | <b>Term</b> | <b><math>\beta</math></b> | <b>SE</b> | <b><i>t</i></b> | <b><i>p</i>-<br/><i>perm</i></b> |
|------------------------------------------------------------------------------------|-------------|----------------------|-------------|---------------------------|-----------|-----------------|----------------------------------|
| DM                                                                                 |             | L-supramarginal      | Age         | 0.0040                    | 0.0018    | 2.19            | 0.028                            |
| DM                                                                                 |             | R-inferiorparietal   | Age         | 0.0048                    | 0.0020    | 2.37            | 0.023                            |
| VF                                                                                 |             | R-postcentral        | Age         | 0.0001                    | 0.0000    | 2.28            | 0.026                            |
| DM                                                                                 |             | R-precuneus          | Age         | 0.0029                    | 0.0015    | 1.96            | 0.048                            |
| VF                                                                                 |             | R-supramarginal      | Age         | 0.0001                    | 0.0000    | 2.46            | 0.019                            |
| CF                                                                                 | Temporal    | L-entorhinal         | Group       | -0.0004                   | 0.0002    | -2.13           | 0.037                            |
| DM                                                                                 |             | L-parahippocampal    | Group       | -0.4256                   | 0.1644    | -2.59           | 0.011                            |
| CF                                                                                 |             | R-transversetemporal | Group       | 0.0009                    | 0.0004    | 2.48            | 0.014                            |
| VF                                                                                 |             | R-transversetemporal | Group       | 0.0034                    | 0.0015    | 2.32            | 0.021                            |
| DM                                                                                 |             | L-fusiform           | Group·Age   | 0.0050                    | 0.0024    | 2.11            | 0.038                            |
| VF                                                                                 |             | L-inferiortemporal   | Group·Age   | 0.0001                    | 0.0001    | 2.39            | 0.021                            |
| DM                                                                                 |             | L-inferiortemporal   | Age         | 0.0027                    | 0.0012    | 2.27            | 0.024                            |
| CF                                                                                 |             | L-middletemporal     | Age         | 0.0000                    | 0.0000    | 2.07            | 0.041                            |
| VF                                                                                 |             | L-middletemporal     | Age         | 0.0001                    | 0.0000    | 2.23            | 0.028                            |
| VF                                                                                 |             | R-inferiortemporal   | Age         | 0.0001                    | 0.0000    | 2.06            | 0.040                            |
| VF                                                                                 |             | R-middletemporal     | Age         | 0.0001                    | 0.0000    | 2.36            | 0.021                            |
| DM                                                                                 | Occipital   | L-lingual            | Group       | -0.3454                   | 0.1623    | -2.13           | 0.036                            |
| VF                                                                                 |             | L-pericalcarine      | Group       | -0.0016                   | 0.0008    | -1.98           | 0.048                            |
| DM                                                                                 |             | L-lingual            | Age         | -0.0198                   | 0.0093    | -2.13           | 0.037                            |
| Bold indicates significance after Bonferroni correction                            |             |                      |             |                           |           |                 |                                  |
| DM = Diameter mean; VF = volume fraction; CF = count fraction; L = Left; R = Right |             |                      |             |                           |           |                 |                                  |

[Insert Table 2]

## DTI-ALPS index

Autistic adults showed significantly lower DTI-ALPS indices compared to controls (Fig. 2). Both groups showed significant age-associated decreases in DTI-ALPS indices, although no group  $\times$  age interaction was observed (Table 3).

Table 3  
Linear regression results of DTI-ALPS index

| <b>Metric</b>                                           | <b>Term</b>  | <b><math>\beta</math></b> | <b>SE</b>     | <b><i>t</i></b> | <b><i>p-perm</i></b> |
|---------------------------------------------------------|--------------|---------------------------|---------------|-----------------|----------------------|
| DTI-ALPS index                                          | <b>Group</b> | <b>-0.0624</b>            | <b>0.0282</b> | <b>-2.21</b>    | <b>0.029</b>         |
|                                                         | Group·Age    | 0.0025                    | 0.0025        | 1.01            | 0.322                |
|                                                         | <b>Age</b>   | <b>-0.0043</b>            | <b>0.0016</b> | <b>-2.63</b>    | <b>0.011</b>         |
| Bold indicates significance after Bonferroni correction |              |                           |               |                 |                      |

[Insert Table 3]

## Lateral ventricle and choroid plexus volumes

Autistic adults showed significantly larger lateral ventricle volumes in both the left and right hemispheres relative to controls (Fig. 2). Significant age-associated increases in left and right lateral ventricle volumes were observed in both groups; however, no significant group  $\times$  age interactions were identified (Table 4). Autistic adults also demonstrated significantly larger left and right choroid plexus volume compared to controls, and both groups showed age-associated volume increases in the left choroid plexus. No significant group  $\times$  age effect was observed in either the left or right choroid plexus.

Table 4  
Linear regression results of lateral ventricles and choroid plexus volumes

| <b>Metric</b>                                           | <b>Term</b>  | <b><math>\beta</math></b> | <b>SE</b>     | <b><i>t</i></b> | <b><i>p-perm</i></b> |
|---------------------------------------------------------|--------------|---------------------------|---------------|-----------------|----------------------|
| L-Lateral ventricle                                     | <b>Group</b> | <b>0.0018</b>             | <b>0.0006</b> | <b>2.76</b>     | <b>0.010</b>         |
|                                                         | Group*Age    | 0.0000                    | 0.0001        | 0.33            | 0.751                |
|                                                         | <b>Age</b>   | <b>0.0001</b>             | <b>0.0000</b> | <b>2.97</b>     | <b>0.003</b>         |
| R-Lateral ventricle                                     | <b>Group</b> | <b>0.0018</b>             | <b>0.0006</b> | <b>3.09</b>     | <b>0.001</b>         |
|                                                         | Group*Age    | 0.0001                    | 0.0001        | 1.48            | 0.142                |
|                                                         | <b>Age</b>   | <b>0.0001</b>             | <b>0.0000</b> | <b>2.35</b>     | <b>0.018</b>         |
| L-Choroid plexus                                        | <b>Group</b> | <b>0.0000</b>             | <b>0.0000</b> | <b>2.38</b>     | <b>0.021</b>         |
|                                                         | Group*Age    | 0.0000                    | 0.0000        | -0.08           | 0.939                |
|                                                         | <b>Age</b>   | <b>0.0000</b>             | <b>0.0000</b> | <b>2.37</b>     | <b>0.018</b>         |
| R-Choroid plexus                                        | <b>Group</b> | <b>0.0000</b>             | <b>0.0000</b> | <b>2.73</b>     | <b>0.008</b>         |
|                                                         | Group*Age    | 0.0000                    | 0.0000        | 1.18            | 0.242                |
|                                                         | Age          | 0.0000                    | 0.0000        | 0.97            | 0.341                |
| Bold indicates significance after Bonferroni correction |              |                           |               |                 |                      |
| L = Left; R = Right                                     |              |                           |               |                 |                      |

## Discussion

Our study examined CSF-based mechanisms critical for brain metabolic waste clearance using multimodal imaging in ageing autistic adults and neurotypical controls. We report several novel findings. First, autistic adults exhibited an age-associated increase in WM-PVS volume fraction in the left inferior parietal lobule that was not observed in controls. Second, autistic adults demonstrated lower DTI-ALPS indices compared to controls. Third, autistic adults showed larger left and right lateral ventricles compared to controls. Fourth, autistic adults showed larger left and right choroid plexus volumes relative to controls. Fifth, both groups demonstrated greater WM-PVS volume fraction in the right pars triangularis, reduced DTI-ALPS indices, and increased bilateral lateral ventricle and left choroid plexus volumes with increasing age. Collectively, these findings provide evidence for a mechanistic overlap between CSF-based alterations observed in ageing autistic adults and those reported across multiple subtypes of dementia. Therefore, CSF-based alterations evident from early development through middle and older adulthood may support the framework of a lifelong neurobiological vulnerability contributing to increased dementia risk in ASD.

Compared to controls, autistic adults demonstrated an age-associated increase in WM-PVS volume fraction localized to the left inferior parietal lobule. The inferior parietal lobule is a densely vascularized region within the default mode network and serves as a major hub for sensory integration<sup>77</sup>, language<sup>78</sup>, and motor processes<sup>78</sup> through long-range connectivity across multiple cortical networks<sup>79</sup>. Lateralized alterations of the left inferior parietal lobule have been reported in autistic children and adolescents in MRI studies of brain structure and functional connectivity, and have been strongly associated with clinical severity<sup>80,81</sup>. Our finding extends this regional atypicality into middle and older adulthood, suggesting increased susceptibility of this integrative association cortex to perivascular burden with aging in ASD. As a metabolically demanding region, the inferior parietal lobule is particularly sensitive to vascular alterations that influence perivascular fluid dynamics, processes that are strongly modulated by arterial stiffness and pulsatility<sup>82</sup>. Notably, the inferior parietal lobule is also recognized as an early site of vascular and metabolic dysfunction in Alzheimer's disease, as evidenced by hypoperfusion, hypometabolism, and volume atrophy<sup>83-85</sup>. Volumetric reductions of the left inferior parietal lobule have been shown to differentiate Alzheimer's disease from normal cognition, with left-lateralized cortical thinning in this region identified as a prominent marker of early neurodegeneration<sup>85</sup>. Although region-specific assessments of WM-PVS in Alzheimer's disease remain limited, increased WM-PVS burden has been consistently documented<sup>13,69</sup>. Taken together, these findings highlight a shared neurobiological substrate involving the left inferior parietal lobule and underscore its heightened vulnerability to pathological brain aging in autistic adults, warranting further investigation to clarify the mechanistic linkage between perivascular dysfunction and neurodegenerative risk in ASD.

Autistic adults exhibited lower DTI-ALPS indices relative to controls. The deep medullary veins, medullary arteries, and their associated perivascular spaces run predominantly in the x-direction (left-right orientation) at the level of the lateral ventricles. DTI-ALPS indices serve as a proxy measure of CSF-mediated fluid diffusivity along the perivascular pathways, supporting bulk CSF transport into and out of the brain parenchyma, capturing fluid movement toward both the brain surface and the ventricular system<sup>15,86</sup>. Our findings indicate that reduced perivascular fluid diffusivity in ASD persists beyond childhood<sup>70</sup> and extends into middle and older adulthood. Lower DTI-ALPS indices have been reported across the dementia spectrum, including Alzheimer's disease<sup>15,86</sup>, vascular dementia<sup>87</sup>, and Lewy body disease<sup>88</sup>. In middle-aged adults, reduced DTI-ALPS indices predict future cognitive impairment and increased risk of dementia<sup>89,90</sup>, highlighting the downstream consequences of chronically impaired fluid diffusivity. In Alzheimer's disease, lower DTI-ALPS indices have been associated with increased cerebral amyloid- $\beta$  deposition and worsened clinical outcomes, consistent with a disrupted capacity to regulate the accumulation of neurotoxic species<sup>91</sup>. As a diffusion-based metric, DTI-ALPS indices may also reflect contributions from white matter microstructure alterations and vascular changes that are not specific to perivascular clearance<sup>15</sup>. Nevertheless, reduced perivascular fluid diffusivity in ASD from early life<sup>50</sup> through older adulthood reflect enduring alterations in perivascular fluid regulation that may present lifelong altered clearance of neurotoxic byproducts along major medullary vessels within the brain parenchyma. This impairment aligns with converging evidence of central neuroimmune activation observed in the CSF<sup>92</sup> and brain tissue<sup>93</sup> of autistic children and adults. These findings emphasize functionally relevant alterations in perivascular fluid dynamics in aging autistic adults that may overlap with established biological vulnerabilities associated with dementia progression and coincide with observed differences in WM-PVS.

Autistic adults also demonstrated larger left and right lateral ventricle volumes relative to controls. This finding is consistent with prior studies reporting enlarged lateral ventricles in autistic children<sup>55</sup>, adolescents<sup>54</sup>, and adults<sup>58</sup>, indicating that ventricular enlargement represents a persistent neurodevelopmental vulnerability in ASD across the lifespan. Expansion of the cerebral ventricles—particularly in cohorts in which ventriculomegaly is evident early in development—has been interpreted as reflecting compromised CSF homeostasis due to altered circulation, distribution, or resorption dynamics<sup>31</sup>. This interpretation is particularly plausible in ASD, as ventricular enlargement has been observed very early in life, well before the typical onset of aging-related neurodegenerative processes. In parallel, ventricular enlargement has also been linked to broader structural alterations within surrounding brain regions<sup>58</sup> and has been observed in Alzheimer's disease<sup>18</sup>, frontotemporal dementia<sup>94</sup>, and Lewy body disease<sup>95</sup>. Prior work from our group identified significant associations between enlarged ventricle volumes and reduced volumes in adjacent subcortical hippocampus and amygdala beginning in middle adulthood in ASD, but not during early development, highlighting accelerated structural deviations involving ventricular expansion and neighboring tissue volume reduction later in life<sup>58</sup>. Notably, none of the autistic adults in the current study had a clinical diagnosis of mild

cognitive impairment or dementia. Ventricular expansion observed in this cohort may reflect a persistent vulnerability in brain morphogenesis that may confer increased susceptibility to aging-related neurodegeneration rather than dementia-specific pathology in ASD<sup>54,55</sup>. Future longitudinal studies are needed to disentangle the combined effects of early developmental vulnerability and aging-associated structural dynamics on ventricular enlargement in ASD.

Finally, autistic adults showed larger left and right choroid plexus compared to controls. This finding of choroid plexus enlargement is consistent with early childhood and adolescent studies of ASD<sup>55,56</sup>, in which early brain overgrowth<sup>55</sup> and neuroimmune dysregulation<sup>56</sup> have been proposed as potential underlying mechanisms. Enlargement of the choroid plexus has also been commonly reported in aging-related neurodegenerative disorders, including Alzheimer's disease<sup>21</sup>, vascular dementia<sup>96</sup>, and frontotemporal dementia<sup>97</sup>, implicating compromised CSF production, nutrient transport, metabolic exchange, neuroimmune signaling, and clearance of neurotoxic peptides between the blood and CSF compartments. Our finding in autistic adults suggests that choroid plexus enlargement is observable across middle and older adulthood, and may align with longstanding disruptions in CSF production, homeostasis and neuroimmune signaling contributing to increased vulnerability to aging-related neurodegeneration in autistic adults.

Age-associated patterns were observed in both groups across multiple neuroimaging markers. The age-associated increase in WM-PVS volume fraction in the right pars triangularis across both groups suggests that perivascular morphology within this region is particularly sensitive to aging independent of diagnosis. Furthermore, the presence of age-associated reductions in DTI-ALPS demonstrates that decreased fluid diffusivity along perivascular pathways represents a general feature of aging for both groups. The age-associated increases in left and right lateral ventricle volumes we observed in both groups is consistent with studies of neurobiological aging in the general population showing bilateral ventricular enlargement as a common feature of advancing age<sup>98</sup>. Finally, both groups demonstrated a lateralized age-associated volume increase in the left choroid plexus, suggesting an asymmetric susceptibility to enlargement in this CSF-producing and immune-signaling region with increasing age.<sup>31</sup>

## Limitations

Our findings should be interpreted alongside several considerations. First, the cross-sectional design limited our ability to quantify intra-individual variability and capture longitudinal trajectories<sup>99</sup>. Therefore, age- and group-by-age-associated CSF-based alterations should be interpreted cautiously. Longitudinal studies spanning the lifespan are needed to clarify the role of CSF-based mechanisms in neurobiological vulnerability contributing to increased dementia risk in ASD. Second, the sample primarily comprised cognitively unimpaired autistic adults. While this allowed characterization of predisposed CSF-related vulnerability in middle and older adulthood, it limited our ability to disentangle neurodevelopmental from neurodegenerative processes contributing to pathological aging in ASD. Studies including

autistic adults across the dementia spectrum will be essential to address this gap. Third, participants were predominantly of average or above-average intelligence; thus, findings may not generalize to autistic adults with ID. Although ID modifies dementia risk in ASD<sup>2</sup>, our results suggest that ASD itself—independent of ID—may be associated with altered CSF-related neurobiology linked to pathological brain aging. Finally, health factors including sleep disturbance, cardiovascular and metabolic disease, polypharmacy, and lifelong medication exposure, may have influenced these findings. Future large-scale studies should systematically evaluate their potential confounding and moderating effects.

## Conclusions

This study represents the first multimodal MRI investigation of CSF-based markers in ageing autistic adults. We identified convergent impairments of CSF-based clearance mechanisms in ASD, including region-specific alterations in white matter perivascular spaces, reduced perivascular fluid diffusivity, and lateral ventricular enlargement. Considered alongside prior findings in autistic children,<sup>54,57</sup> these results support a lifelong pattern of altered CSF regulation that extends into the pathologically vulnerable periods of middle and older adulthood. Collectively, these findings establish a conceptual foundation for future research aimed at disentangling lifelong neurobiological vulnerabilities that may contribute to increased dementia risk in ASD.

## Declarations

### **Ethics approval**

The study protocols were approved by the Institutional Review Boards (IRB) at UF (IRB201801378; approval date: July 26, 2022).

### **Consent for publication**

All authors have read and approved the submission.

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#### Conflicts of interest

All authors declare that they have no competing interests.

#### Consent statement

All authors have read and consented to the submission of this manuscript.

## References

1. Vivanti G, Tao S, Lyall K, Robins DL, Shea LL (2021) The prevalence and incidence of early-onset dementia among adults with autism spectrum disorder. *Autism Res* 14:2189–2199. <https://doi.org/10.1002/aur.2590>
2. Vivanti G et al (2025) Prevalence of Dementia Among US Adults With Autism Spectrum Disorder. *JAMA Netw Open* 8:e2453691. <https://doi.org/10.1001/jamanetworkopen.2024.53691>
3. Chang Z et al (2025) Association between autism and dementia across generations: evidence from a family study of the Swedish population. *Mol Psychiatry* 30:4605–4612. <https://doi.org/10.1038/s41380-025-03045-6>
4. Shea L et al (2025) Examining Dementia Subtypes in a National Sample of Autistic Medicaid and Medicare Enrollees. *Alzheimers Dement* 21. [https://doi.org/10.1002/alz70860\\_100521](https://doi.org/10.1002/alz70860_100521)
5. Gautam A, Kaelber D, Davis P, Terebuh P, Xu R (2025) Increased Dementia Risk in Higher-Functioning Adults with Autism Spectrum Disorder: Insights from 21,648 Adults with Autism Spectrum Disorder. *Alzheimers Dement* 21:e108233. [https://doi.org/10.1002/alz70861\\_108233](https://doi.org/10.1002/alz70861_108233)
6. Tarasoff-Conway JM et al (2015) Clearance systems in the brain-implications for Alzheimer disease. *Nat Rev Neurol* 11:457–470. <https://doi.org/10.1038/nrneurol.2015.119>
7. Nedergaard M, Goldman SA (2020) Glymphatic failure as a final common pathway to dementia. *Science* 370:50–56. <https://doi.org/10.1126/science.abb8739>
8. Benveniste H et al (2019) The Glymphatic System and Waste Clearance with Brain Aging: A Review. *Gerontology* 65:106–119. <https://doi.org/10.1159/000490349>
9. Li Y et al (2022) Decreased CSF clearance and increased brain amyloid in Alzheimer's disease. *Fluids Barriers CNS* 19:21. <https://doi.org/10.1186/s12987-022-00318-y>

10. Leone R et al (2025) Alterations in MRI-visible perivascular spaces precede dementia diagnosis by 18 years in autosomal dominant Alzheimer's disease. *Alzheimers Dement* 21:e70588. <https://doi.org/10.1002/alz.70588>
11. Wang ML et al (2022) Associations of MRI-visible perivascular spaces with longitudinal cognitive decline across the Alzheimer's disease spectrum. *Alzheimers Res Ther* 14:185. <https://doi.org/10.1186/s13195-022-01136-y>
12. Nagaraja N et al (2023) Imaging features of small vessel disease in cerebral amyloid angiopathy among patients with Alzheimer's disease. *NeuroImage: Clin* 38:103437. <https://doi.org/10.1016/j.nicl.2023.103437>
13. Banerjee G et al (2017) MRI-visible perivascular space location is associated with Alzheimer's disease independently of amyloid burden. *Brain* 140:1107–1116. <https://doi.org/10.1093/brain/awx003>
14. Kim HJ et al (2021) MRI-Visible Perivascular Spaces in the Centrum Semiovale Are Associated with Brain Amyloid Deposition in Patients with Alzheimer Disease-Related Cognitive Impairment. *AJNR Am J Neuroradiol* 42:1231–1238. <https://doi.org/10.3174/ajnr.A7155>
15. Taoka T et al (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* 35:172–178. <https://doi.org/10.1007/s11604-017-0617-z>
16. Schirge PM et al (2025) Perivascular space and white matter hyperintensities in Alzheimer's disease: associations with disease progression and cognitive function. *Alzheimers Res Ther* 17:62. <https://doi.org/10.1186/s13195-025-01707-9>
17. Zhang Q et al (2025) Association of magnetic resonance imaging glymphatic function with gray matter volume loss and cognitive impairment in Alzheimer's disease: a diffusion tensor image analysis along the perivascular space (DTI-ALPS) study. *Quant Imaging Med Surg* 15:6160–6174. <https://doi.org/10.21037/qims-2025-96>
18. Nestor SM et al (2008) Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain* 131:2443–2454. <https://doi.org/10.1093/brain/awn146>
19. Carmichael OT et al (2007) Ventricular volume and dementia progression in the Cardiovascular Health Study. *Neurobiol Aging* 28:389–397. <https://doi.org/10.1016/j.neurobiolaging.2006.01.006>
20. Chou YY et al (2009) Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. *NeuroImage* 46:394–410. <https://doi.org/10.1016/j.neuroimage.2009.02.015>
21. Jiang J et al (2024) Choroid plexus volume as a novel candidate neuroimaging marker of the Alzheimer's continuum. *Alzheimer's Res Ther* 16:149. <https://doi.org/10.1186/s13195-024-01520-w>

22. Lin W et al (2025) Multimodal MRI reveals impaired glymphatic function with choroid plexus enlargement and cerebrospinal fluid expansion in alzheimer's disease. *Sci Rep* 15:30409. <https://doi.org/10.1038/s41598-025-15923-8>
23. Choi JD et al (2022) Choroid Plexus Volume and Permeability at Brain MRI within the Alzheimer Disease Clinical Spectrum. *Radiology* 304:635–645. <https://doi.org/10.1148/radiol.212400>
24. Shin YS et al (2025) Transcallosal white matter and cortical gray matter variations in autistic adults aged 30–73 years. *Mol Autism* 16:16. <https://doi.org/10.1186/s13229-025-00652-6>
25. Christensen D et al (2025) Subcortical brain volume variations in autistic individuals across the lifespan. *Mol Autism* 16:46. <https://doi.org/10.1186/s13229-025-00673-1>
26. Phillips WT, Sheesley AP, Schwartz JG (2026) Pathophysiologic similarities between autism spectrum disorder and Alzheimer's disease: therapeutic possibilities. *Front Neurosci* 19–2025. <https://doi.org/10.3389/fnins.2025.1737007>
27. Iliff JJ et al (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid  $\beta$ . *Sci Transl Med* 4:147ra111. <https://doi.org/10.1126/scitranslmed.3003748>
28. Xie L et al (2013) Sleep drives metabolite clearance from the adult brain. *Science* 342:373–377. <https://doi.org/10.1126/science.1241224>
29. Mestre H et al (2018) Aquaporin-4-dependent glymphatic solute transport in the rodent brain. *eLife* 7, e40070 <https://doi.org/10.7554/eLife.40070>
30. Spector R, Robert Snodgrass S, Johanson CE (2015) A balanced view of the cerebrospinal fluid composition and functions: Focus on adult humans. *Exp Neurol* 273:57–68. <https://doi.org/10.1016/j.expneurol.2015.07.027>
31. Damkier HH, Brown PD, Praetorius J (2013) Cerebrospinal fluid secretion by the choroid plexus. *Physiol Rev* 93:1847–1892. <https://doi.org/10.1152/physrev.00004.2013>
32. Bitanhirwe BKY, Lizano P, Woo T-UW (2022) Deconstructing the functional neuroanatomy of the choroid plexus: an ontogenetic perspective for studying neurodevelopmental and neuropsychiatric disorders. *Mol Psychiatry* 27:3573–3582. <https://doi.org/10.1038/s41380-022-01623-6>
33. Solár P, Zamani A, Kubíčková L, Dubový P, Joukal M (2020) Choroid plexus and the blood–cerebrospinal fluid barrier in disease. *Fluids Barriers CNS* 17:35. <https://doi.org/10.1186/s12987-020-00196-2>
34. el Courtney Y, Hochstetler A, Lehtinen MK (2025) Choroid Plexus Pathophysiology. *Annu Rev Pathol* 20, 193–220 <https://doi.org/https://doi.org/10.1146/annurev-pathmechdis-051222-114051>
35. MacAulay N, Keep RF, Zeuthen T (2022) Cerebrospinal fluid production by the choroid plexus: a century of barrier research revisited. *Fluids Barriers CNS* 19:26. <https://doi.org/10.1186/s12987-022-00323-1>

36. Yamada S, Mase M (2023) Cerebrospinal Fluid Production and Absorption and Ventricular Enlargement Mechanisms in Hydrocephalus. *Neurol Med Chir (Tokyo)* 63:141–151. <https://doi.org/10.2176/jns-nmc.2022-0331>
37. Johanson C et al (2011) The Distributional Nexus of Choroid Plexus to Cerebrospinal Fluid, Ependyma and Brain: Toxicologic/Pathologic Phenomena, Periventricular Destabilization, and Lesion Spread. *Toxicol Pathol* 39:186–212. <https://doi.org/10.1177/0192623310394214>
38. Le RFD, Karmonik C, Regnier-Golanov AS, Golanov EV, Britz GW (2025) Quantitative evaluation of normal cerebrospinal fluid flow in Sylvian aqueduct and perivascular spaces of middle cerebral artery and circle of Willis using 2D phase-contrast MRI imaging. *Front Neurosci* 19–2025. <https://doi.org/10.3389/fnins.2025.1622351>
39. Rasmussen MK, Mestre H, Nedergaard M (2022) Fluid transport in the brain. *Physiol Rev* 102:1025–1151. <https://doi.org/10.1152/physrev.00031.2020>
40. Iliff JJ et al (2013) Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J Neurosci* 33:18190–18199. <https://doi.org/10.1523/jneurosci.1592-13.2013>
41. Wardlaw JM et al (2020) Perivascular spaces in the brain: anatomy, physiology and pathology. *Nat Rev Neurol* 16:137–153. <https://doi.org/10.1038/s41582-020-0312-z>
42. Bown CW, Carare RO, Schrag MS, Jefferson AL (2022) Physiology and Clinical Relevance of Enlarged Perivascular Spaces in the Aging Brain. *Neurology* 98:107–117. <https://doi.org/10.1212/wnl.00000000000013077>
43. Ineichen BV et al (2022) Perivascular spaces and their role in neuroinflammation. *Neuron* 110:3566–3581. <https://doi.org/10.1016/j.neuron.2022.10.024>
44. Mestre H et al (2018) Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat Commun* 9:4878. <https://doi.org/10.1038/s41467-018-07318-3>
45. Zhao L, Tannenbaum A, Bakker E, Benveniste H (2022) Physiology of Glymphatic Solute Transport and Waste Clearance from the Brain. *Physiol (Bethesda)* 37:0. <https://doi.org/10.1152/physiol.00015.2022>
46. Uchida K (2022) Waste clearance in the brain and neuroinflammation: a novel perspective on biomarker and drug target discovery in Alzheimer's disease. *Cells* 11. <https://doi.org/10.3390/cells11050919>
47. Sotgiu S et al (2025) Enlarged perivascular spaces under the dorso-lateral prefrontal cortex and severity of autism. *Sci Rep* 15:8142. <https://doi.org/10.1038/s41598-025-92913-w>
48. Sotgiu MA et al (2023) Brain perivascular spaces and autism: clinical and pathogenic implications from an innovative volumetric MRI study. *Front Neurosci* 17–2023. <https://doi.org/10.3389/fnins.2023.1205489>
49. Shen MD et al (2017) Increased Extra-axial Cerebrospinal Fluid in High-Risk Infants Who Later Develop Autism. *Biol Psychiatry* 82:186–193.

- <https://doi.org/10.1016/j.biopsych.2017.02.1095>
50. Shen MD (2018) Cerebrospinal fluid and the early brain development of autism. *J Neurodev Disord* 10:39. <https://doi.org/10.1186/s11689-018-9256-7>
  51. Shen MD et al (2018) Extra-axial cerebrospinal fluid in high-risk and normal-risk children with autism aged 2–4 years: a case-control study. *Lancet Psychiatry* 5:895–904. [https://doi.org/10.1016/s2215-0366\(18\)30294-3](https://doi.org/10.1016/s2215-0366(18)30294-3)
  52. Garic D et al (2023) Enlarged Perivascular Spaces in Infancy and Autism Diagnosis, Cerebrospinal Fluid Volume, and Later Sleep Problems. *JAMA Netw Open* 6:e2348341–e2348341. <https://doi.org/10.1001/jamanetworkopen.2023.48341>
  53. Li X et al (2022) Children with autism spectrum disorder present glymphatic system dysfunction evidenced by diffusion tensor imaging along the perivascular space. *Med (Baltim)* 101:e32061. <https://doi.org/10.1097/md.00000000000032061>
  54. Prigge MBD et al (2021) A 16-year study of longitudinal volumetric brain development in males with autism. *NeuroImage* 236:118067. <https://doi.org/10.1016/j.neuroimage.2021.118067>
  55. Levman J et al (2018) Regional volumetric abnormalities in pediatric autism revealed by structural magnetic resonance imaging. *Int J Dev neuroscience: official J Int Soc Dev Neurosci* 71:34–45. <https://doi.org/10.1016/j.ijdevneu.2018.08.001>
  56. Tezcan ME, Ataş AE, Ferahkaya H (2025) Can optic nerve morphology in children with autism spectrum disorder be associated with atypical visual-sensory behaviors? *Front Psychiatry* 16–2025. <https://doi.org/10.3389/fpsy.2025.1639695>
  57. Turner AH, Greenspan KS, van Erp TGM (2016) Pallidum and lateral ventricle volume enlargement in autism spectrum disorder. *Psychiatry Res Neuroimaging* 252:40–45. <https://doi.org/10.1016/j.psychresns.2016.04.003>
  58. Christensen D et al (2025) Subcortical brain volumetric variations in autistic individuals across the lifespan. *Molecular Autism*., In press
  59. Walsh MJM et al (2022) Preliminary findings of accelerated visual memory decline and baseline brain correlates in middle-age and older adults with autism: The case for hippocampal free-water. *Front Aging Neurosci* 14:1029166. <https://doi.org/10.3389/fnagi.2022.1029166>
  60. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E (2001) The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Males and Females, Scientists and Mathematicians. *J Autism Dev Disord* 31:5–17
  61. Constantino JN (2012) Social Responsiveness Scale–Second Edition (SRS-2): Adult self-report. Western Psychological Services
  62. Lord C et al (2012) Autism Diagnostic Observation Schedule, Second Edition (ADOS-2). Western Psychological Services
  63. Association AP (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing

64. Wechsler D (2011) Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II). Pearson Education
65. Buck TR et al (2014) Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *J Autism Dev Disord* 44:3063–3071. <https://doi.org/10.1007/s10803-014-2170-2>
66. Sepehrband F et al (2019) Image processing approaches to enhance perivascular space visibility and quantification using MRI. *Sci Rep* 9:12351. <https://doi.org/10.1038/s41598-019-48910-x>
67. Frangi AF, Niessen WJ, Vincken KL, Viergever MA in *Med Image Comput Comput Assist Interv.* (eds William M. Wells, Alan Colchester, & Scott Delp) 130–137 (Springer Berlin Heidelberg)
68. Puonti O, Iglesias JE, Van Leemput K (2016) Fast and sequence-adaptive whole-brain segmentation using parametric Bayesian modeling. *NeuroImage* 143, 235–249 <https://doi.org/https://doi.org/10.1016/j.neuroimage.2016.09.011>
69. Barisano G et al (2025) Robust, fully-automated assessment of cerebral perivascular spaces and white matter lesions: a multicentre MRI longitudinal study of their evolution and association with risk of dementia and accelerated brain atrophy. *eBioMedicine* 111. <https://doi.org/10.1016/j.ebiom.2024.105523>
70. Sotgiu S et al (2025) Enlarged perivascular spaces under the dorso-lateral prefrontal cortex and severity of autism. *Sci Rep* 15:8142. <https://doi.org/10.1038/s41598-025-92913-w>
71. Tournier JD et al (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>
72. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012) FSL *Neuroimage* 62:782–790. <https://doi.org/10.1016/j.neuroimage.2011.09.015>
73. Yeh FC et al (2018) Population-averaged atlas of the macroscale human structural connectome and its network topology. *NeuroImage* 178:57–68. <https://doi.org/10.1016/j.neuroimage.2018.05.027>
74. Avants BB, Epstein CL, Grossman M, Gee JC (2008) Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* 12:26–41. <https://doi.org/10.1016/j.media.2007.06.004>
75. Fischl B, FreeSurfer. (2012) *NeuroImage* 62:774–781. <https://doi.org/10.1016/j.neuroimage.2012.01.021>
76. Koolschijn PC, Geurts HM (2016) Gray Matter Characteristics in Mid and Old Aged Adults with ASD. *J Autism Dev Disord* 46:2666–2678. <https://doi.org/10.1007/s10803-016-2810-9>
77. Porada DK, Regenbogen C, Freiherr J, Seubert J, Lundström JN (2021) Trimodal processing of complex stimuli in inferior parietal cortex is modality-independent. *Cortex* 139:198–210. <https://doi.org/https://doi.org/10.1016/j.cortex.2021.03.008>

78. Hill VB et al (2019) A Practical Review of Functional MRI Anatomy of the Language and Motor Systems. *AJNR Am J Neuroradiol* 40:1084–1090. <https://doi.org/10.3174/ajnr.A6089>
79. Williams KA et al (2024) Inhibition of the inferior parietal lobe triggers state-dependent network adaptations. *Heliyon* 10:e39735. <https://doi.org/https://doi.org/10.1016/j.heliyon.2024.e39735>
80. Lee Y, Park B-y, James O, Kim S-G, Park H (2017) Autism Spectrum Disorder Related Functional Connectivity Changes in the Language Network in Children, Adolescents and Adults. *Front Hum Neurosci* 11–2017. <https://doi.org/10.3389/fnhum.2017.00418>
81. Wymbs NF, Nebel MB, Ewen JB, Mostofsky SH (2021) Altered Inferior Parietal Functional Connectivity is Correlated with Praxis and Social Skill Performance in Children with Autism Spectrum Disorder. *Cereb Cortex* 31:2639–2652. <https://doi.org/10.1093/cercor/bhaa380>
82. Mitchell GF (2008) Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol* (1985) 105:1652–1660. <https://doi.org/10.1152/japplphysiol.90549.2008>
83. Johnson NA et al (2005) Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology* 234:851–859. <https://doi.org/10.1148/radiol.2343040197>
84. Weise CM et al (2018) Left lateralized cerebral glucose metabolism declines in amyloid-beta positive persons with mild cognitive impairment. *Neuroimage Clin* 20:286–296. <https://doi.org/10.1016/j.nicl.2018.07.016>
85. Greene SJ, Killiany RJ (2010) Subregions of the inferior parietal lobule are affected in the progression to Alzheimer's disease. *Neurobiol Aging* 31:1304–1311. <https://doi.org/10.1016/j.neurobiolaging.2010.04.026>
86. Taoka T et al (2024) Diffusion Tensor Image Analysis ALong the Perivascular Space (DTI-ALPS): Revisiting the Meaning and Significance of the Method. *Magn Reson Med Sci* 23:268–290. <https://doi.org/10.2463/mrms.rev.2023-0175>
87. Liu X et al (2025) MRI free water mediates the association between diffusion tensor image analysis along the perivascular space and executive function in four independent middle to aged cohorts. *Alzheimers Dement* 21:e14453. <https://doi.org/10.1002/alz.14453>
88. Firbank MJ et al (2025) Changes in DTI-ALPS index and its associations with neuronal damage in Lewy body disease. *Parkinsonism Relat Disord* 140:108014. <https://doi.org/10.1016/j.parkreldis.2025.108014>
89. Wang J et al (2023) Glymphatic function plays a protective role in ageing-related cognitive decline. *Age Ageing* 52. <https://doi.org/10.1093/ageing/afad107>
90. Bao C et al (2025) Poor glymphatic function is associated with mild cognitive impairment and its progression to Alzheimer's disease: A DTI-ALPS study. *J Prev Alzheimers Dis* 12:100156. <https://doi.org/10.1016/j.tjpad.2025.100156>
91. Taoka T, Naganawa S (2020) Glymphatic imaging using MRI. *J Magn Reson Imaging* 51:11–24. <https://doi.org/10.1002/jmri.26892>

92. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol* 57:67–81. <https://doi.org/10.1002/ana.20315>
93. Li X et al (2009) Elevated immune response in the brain of autistic patients. *J Neuroimmunol* 207:111–116. <https://doi.org/10.1016/j.jneuroim.2008.12.002>
94. Manera AL, Dadar M, Collins DL, Ducharme S (2022) Ventricular features as reliable differentiators between bvFTD and other dementias. *NeuroImage: Clin* 33:102947. <https://doi.org/https://doi.org/10.1016/j.nicl.2022.102947>
95. Barber R, Ballard C, McKeith IG, Gholkar A, O'Brien (2000) J. T. MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. *Neurology* 54:1304–1309. <https://doi.org/10.1212/wnl.54.6.1304>
96. Lu W et al (2025) An exploratory study of the diffusion tensor imaging analysis along perivascular spaces (DTI-ALPS) index combined with quantitative analysis of choroid plexus volume and perivascular spaces in different cognitive stages of cerebral small vessel disease. *Quant Imaging Med Surg* 15:8173–8188. <https://doi.org/10.21037/qims-2025-733>
97. Assogna M et al (2023) Association of Choroid Plexus Volume With Serum Biomarkers, Clinical Features, and Disease Severity in Patients With Frontotemporal Lobar Degeneration Spectrum. *Neurology* 101:e1218–e1230. <https://doi.org/doi:10.1212/WNL.0000000000207600>
98. Missori P et al (2016) In normal aging ventricular system never attains pathological values of Evans' index. *Oncotarget* 7:11860–11863. <https://doi.org/10.18632/oncotarget.7644>
99. Wang J, Christensen D, Coombes SA, Wang Z (2024) Cognitive and brain morphological deviations in middle-to-old aged autistic adults: A systematic review and meta-analysis. *Neurosci Biobehav Rev* 105782. <https://doi.org/10.1016/j.neubiorev.2024.105782>

## Figures

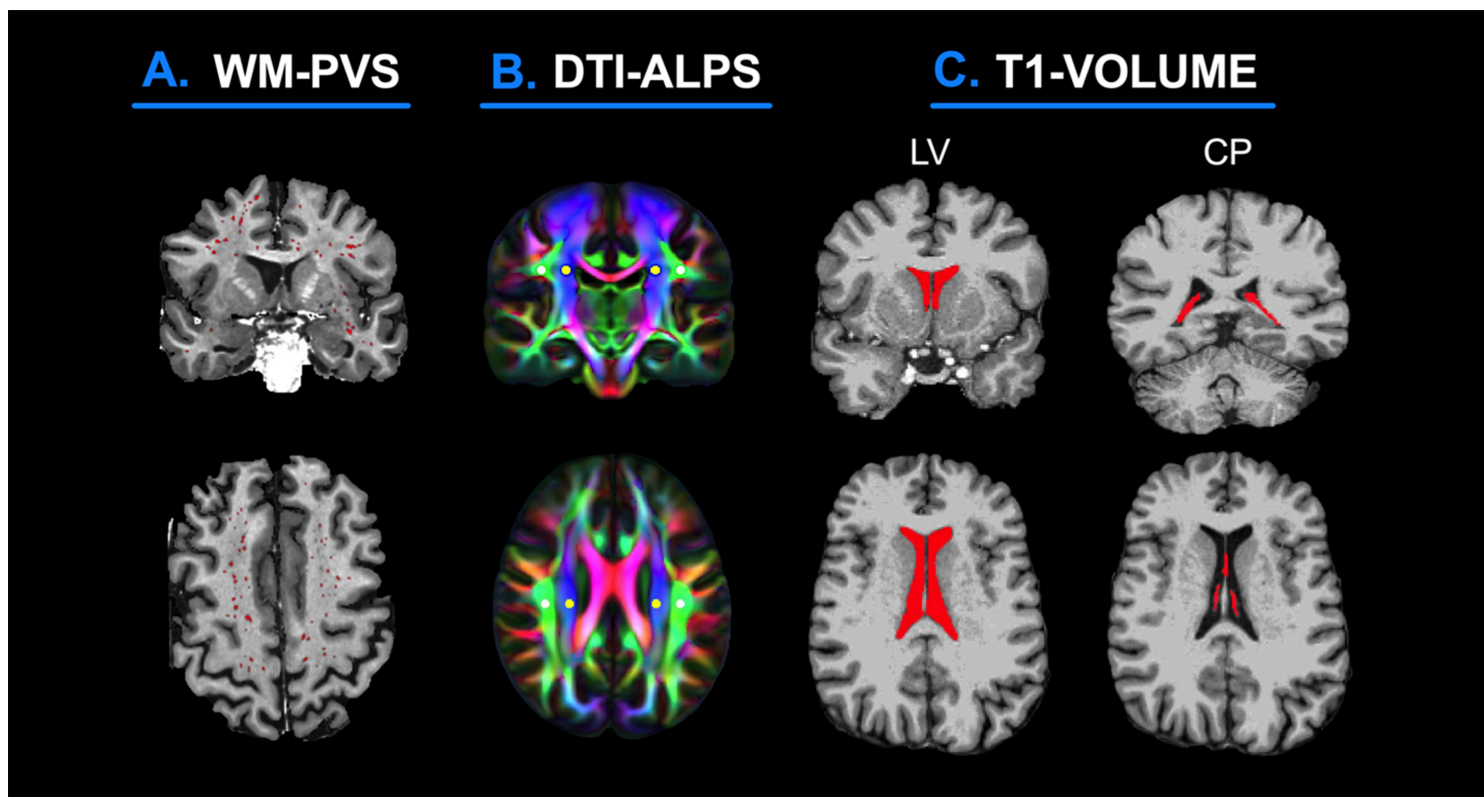


Figure 1

**Coronal and axial MRI depictions of multimodal methods used in this study to examine CSF-based mechanisms.** (A) Automated segmentation of white matter perivascular spaces (WM-PVS). (B) Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS). (C) Volumetric segmentation of the lateral ventricles (LV) and choroid plexus (CP).

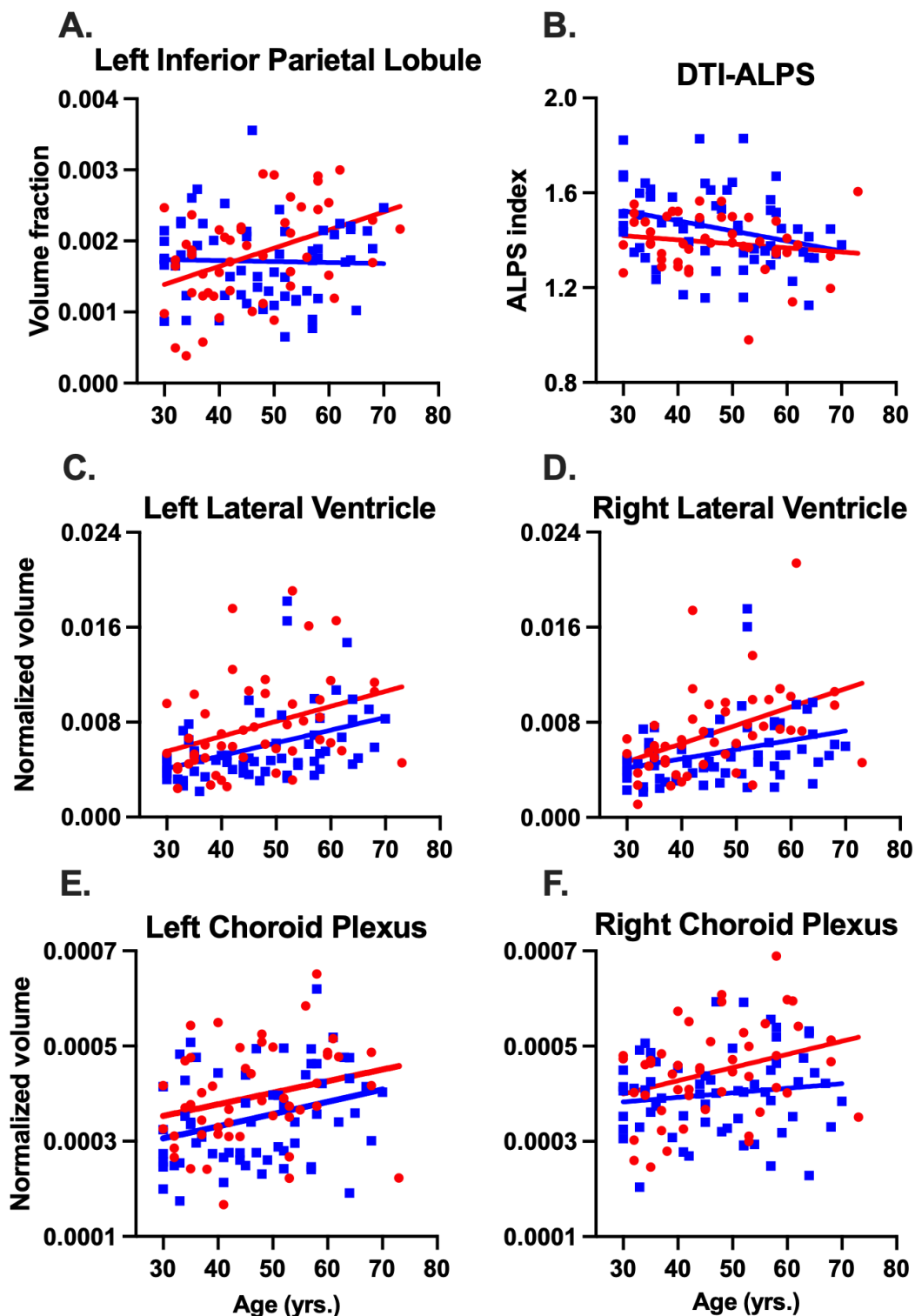


Figure 2

Scatterplots of significant group and group-by-age interactions across CSF-based mechanisms. Scatterplot of white matter perivascular space volume fraction in the left inferior parietal lobule with age (A). Autistic adults exhibited significantly steeper age-associated increases in WM-PVS volume fraction in the left inferior parietal lobule compared with neurotypical controls. Scatterplot of diffusion tensor imaging analysis along the perivascular space with age

**(B)**. Autistic adults exhibited significantly lower DTI-ALPS indices relative to neurotypical controls across middle and older adulthood. Scatterplots show normalized volumes of the left lateral ventricle **(C)**, right lateral ventricle **(D)**, left choroid plexus **(E)**, and right choroid plexus **(F)** with age. Autistic adults exhibited significantly larger left and right lateral ventricle and choroid plexus volumes compared to neurotypical controls.

## Supplementary Files

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