

Review

Glymphatic System Function and Cognition: Converging Evidence from DTI-ALPS Imaging – A Narrative Review

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[Received April 27, 2026; Revised May 23, 2026; Accepted June 1, 2026]

ABSTRACT: The glymphatic system, a brain-wide perivascular network mediating cerebrospinal fluid-interstitial fluid exchange, has emerged as a candidate determinant of cognitive health through its role in clearing metabolic waste, neurotoxic proteins, and neuroactive metabolites. The diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) index provides a non-invasive means to assess glymphatic activity in vivo, yet no synthesis has consolidated what this marker captures, how reliably it predicts cognitive outcomes, and what pathways may account for observed associations. This narrative review, informed by selected principles from the PRISMA 2020 framework but not constituting a formal systematic review, synthesizes evidence linking DTI-ALPS to domain-specific cognitive performance in healthy aging and neurological disease, encompassing the Alzheimer's disease continuum, cerebral small vessel disease, Parkinson's disease, multiple sclerosis, stroke, and HIV-associated neurocognitive disorder. Lower DTI-ALPS values were consistently associated with worse cognitive performance. The strongest associations were observed for memory and global cognition, followed by executive functions and processing speed; evidence for language and visuospatial abilities was less consistent. Longitudinal data indicate that DTI-ALPS decline may precede detectable amyloid pathology, positioning this index as a candidate early prognostic marker. Three mechanistic pathways are discussed: disruption of sleep-dependent waste clearance; compromise of gray matter integrity through neurotoxic metabolite accumulation; and facilitation of amyloid- β and tau pathology via impaired perivascular protein clearance. Limitations include the indirect nature of DTI-ALPS as a clearance measure, predominance of cross-sectional designs, small samples, and absence of sex-stratified analyses despite known hormonal modulation of glymphatic function. Longitudinal studies, randomized trials of glymphatic-targeting interventions, and acquisition protocol standardization represent priority directions for future research.

Keywords: glymphatic system, DTI-ALPS, cognitive function, aging, Alzheimer's disease, neurodegeneration

Introduction

The human brain accounts for just 2% of body mass yet consumes roughly 20% of the body's energy, generating substantial metabolic waste that must be efficiently cleared to maintain neural function and prevent neurotoxic accumulation [1]. The discovery of the

glymphatic system, a brain-wide network facilitating cerebrospinal fluid (CSF) and interstitial fluid exchange, has reshaped our understanding of neural waste clearance and its implications for cognitive health [2].

The glymphatic system operates through aquaporin-4 (AQP4) water channels present in astrocytic endfeet surrounding cerebral blood vessels [3]. CSF enters the

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brain via periarterial Virchow-Robin spaces, which occupy the space between the endothelial basement membrane and the glia limitans surrounding penetrating arteries. From there, fluid traverses the parenchyma driven by AQP4-dependent astrocytic transport and exits via perivenous routes toward subarachnoid CSF efflux pathways, completing the CSF-interstitial fluid (ISF) exchange cycle [4,5]. This fluid movement efficiently removes metabolic waste products, including neurotoxic proteins such as amyloid- β and tau. Convective CSF flow through perivascular spaces is driven by arterial pulsatility, respiratory pressure gradients, and CSF pressure differentials [6,7]. Supporting evidence comes from animal studies in which parenchymal tracer accumulation decreased by approximately 20% following carotid artery ligation and increased by 10 to 40% when pulsatility was pharmacologically augmented [8]. The lateral ventricle walls are particularly rich in perivascular spaces associated with medullary veins, which likely explains the high DTI-ALPS signal detectability in this region [5].

Impaired glymphatic flow leads to accumulation of toxic proteins, disruption of ionic and metabolic homeostasis in the interstitial space, and propagation of neuroinflammatory signals along perivascular pathways. Structural and physiological factors that compromise glymphatic performance include progressive loss of AQP4 polarization in astrocytic endfeet, reduced arterial pulsatility secondary to vascular stiffening, decreased CSF production and pressures, perivascular space enlargement and tortuosity, and sleep disruption [5,7,9].

Several mechanisms may link glymphatic dysfunction to cognitive decline. Impaired clearance of amyloid- β and tau promotes their aggregation and neurotoxicity [4,10]. Reduced glymphatic flow may also compromise clearance of lactate, glutamate, and other metabolites that accumulate during neuronal activity, thereby disrupting synaptic function [11]. Chronic sleep disruption constitutes an additional pathway: glymphatic activity peaks during slow-wave sleep, when the interstitial space expands by approximately 60% and waste clearance capacity increases dramatically [11,12], and impaired sleep may therefore contribute to cognitive decline partly through progressive glymphatic insufficiency. Age-related changes in AQP4 polarization, arterial pulsatility, and perivascular space morphology further reduce glymphatic efficiency over the lifespan [7,9]. Critically, these pathways are not uniform across conditions: in Alzheimer's disease, tau tangles and amyloid- β accumulation are central mediators, whereas in HIV-associated neurocognitive disorder, chronic neuroinflammation and blood-brain barrier disruption dominate. These disease-specific mechanisms are explored in detail in subsequent sections.

Cognitive function encompasses mental processes including memory, attention, executive functions, processing speed, and visuospatial abilities, all of which are fundamental to daily functioning, independence, and quality of life across the lifespan [13]. These abilities rely on the integrity of widespread neural networks and efficient synaptic communication, which in turn depend on optimal cellular homeostasis and metabolic health [14]. The accumulation of metabolic byproducts disrupts neuronal signaling, impairs synaptic plasticity, and compromises cognitive performance [15,16].

Dysfunction of this clearance mechanism has been implicated not only in classical neurodegenerative and cerebrovascular disorders, but also across a broader spectrum of central nervous system conditions, suggesting that glymphatic impairment may represent a transdiagnostic mechanism relevant to multiple forms of brain dysfunction associated with cognitive impairment [17]. Recent reviews and neuroimaging studies have linked altered glymphatic function to depression, schizophrenia, anxiety disorders, trauma-related disorders, substance use disorders, and neurodevelopmental conditions, with proposed mechanisms involving sleep disruption, neuroinflammation, oxidative stress, astrocytic dysfunction, and impaired aquaporin-4 polarization [18–20].

Recent advances in neuroimaging have enabled non-invasive assessment of glymphatic function in living humans through the DTI-ALPS index. This MRI-based biomarker quantifies water diffusivity along perivascular spaces at the level of the lateral ventricle body, capitalizing on the directional properties of water diffusion detected by DTI to provide a proxy measure of glymphatic activity [22,30–32]. DTI-ALPS does not directly measure cerebrospinal fluid-interstitial fluid exchange rates, AQP4-mediated transport, or metabolite clearance capacity. The validity of this index as a surrogate for waste clearance has been questioned on both conceptual and methodological grounds [24], and the fundamental transport mechanisms underlying the signal remain debated. Nevertheless, unlike methods requiring intrathecal contrast agent administration or post-mortem analysis, DTI-ALPS enables repeated, non-invasive assessment, a feature that has proven particularly valuable for large-scale epidemiological and clinical investigations [25]. The index has demonstrated adequate test-retest reliability under controlled acquisition conditions [26] though reliability has been shown to decrease substantially when scanner parameters vary across sessions, a consideration with direct implications for multi-site and longitudinal applications. The index also shows expected associations with factors known to modulate glymphatic function, including sleep and age

[27]. While alternative approaches such as contrast-enhanced MRI and PET imaging exist, DTI-ALPS offers distinct advantages in terms of non-invasiveness, absence of contrast agent requirements, and relative ease of clinical implementation [28]. Important methodological considerations, including anatomical variability, age-related changes in brain structure, and technical factors affecting diffusion measurements, must nonetheless be carefully addressed [29].

Although the DTI-ALPS index, introduced in 2017 [30], has rapidly proliferated across clinical research and is now applied in diverse neurological populations, it has not yet been subjected to a consolidated critical evaluation of what it captures and how reliably it predicts cognitive outcomes. Previous reviews have addressed glymphatic imaging methods [31,32], the role of the glymphatic system in neurodegenerative disease [15,33,34], or the broader biology of perivascular clearance pathways [21,29], but none has specifically focused on the relationship between DTI-ALPS and domain-specific cognitive performance across multiple neurological conditions. This gap carries direct clinical relevance, as identifying modifiable biomarkers of cognitive decline at preclinical stages remains a global priority. The present review therefore aims to integrate evidence across disease states, compare cognitive domains differentially associated with DTI-ALPS, critically evaluate mechanistic interpretations and methodological limitations, and outline translational implications for biomarker development and intervention studies.

Beyond these neurological contexts, DTI-ALPS studies have also extended to psychiatric populations, including young adults with acute psychotic episodes [20], schizophrenia [35], schizophrenia compared with bipolar disorder and major depression [36], and across psychosis stages assessed at 7T [37], as well as to sleep disorders, where a recent meta-analysis reported a large pooled reduction in the index that scaled with disease severity and partially normalized after treatment [38]. Although informative, this transdiagnostic literature remains preliminary relative to neurological disease.

This review examines current evidence linking the DTI-ALPS to domain-specific cognitive performance, with a particular focus on age-related changes, disease-specific patterns, and potential therapeutic implications. Evidence is considered spanning healthy aging populations through various disease states, including the Alzheimer's disease continuum, cerebral small vessel disease, and other neurological conditions, with domain-specific associations addressed across memory, executive function, processing speed, language, and visuospatial abilities. Sleep-dependent clearance, gray matter preservation, and protein pathology accumulation are discussed as candidate mediating mechanisms, alongside

alternative glymphatic biomarkers and methodological limitations of current research. Understanding these relationships may ultimately inform novel therapeutic strategies targeting glymphatic enhancement to preserve or restore cognitive function in at-risk populations.

Methods

This work is a narrative review informed by selected principles from the PRISMA 2020 framework but does not constitute a formal systematic review. Literature searches were conducted in PubMed, Scopus, and Web of Science through March 2026 using combinations of terms related to the glymphatic system, DTI-ALPS, cognition, Alzheimer's disease, cerebral small vessel disease, Parkinson's disease, stroke, multiple sclerosis, and related neurological conditions. Additional studies were identified through manual screening of reference lists from relevant reviews and primary articles.

Studies were selected based on relevance to the relationship between glymphatic imaging markers and cognitive outcomes. Priority was given to human studies employing DTI-ALPS methodology and standardized cognitive assessment. Given the narrative design, no formal risk-of-bias assessment or quantitative meta-analysis was performed. Where overall confidence ratings for individual evidence areas are reported in this review (Table 1), they are intended as heuristic narrative judgments based on sample size, study design, depth of cognitive phenotyping, confounder adjustment, imaging standardization, and independent replication. They should not be interpreted as the output of a formal risk-of-bias instrument such as ROBINS-I, QUADAS-2, or the Newcastle-Ottawa Scale, and they do not assign quantitative weights or summary scores to individual studies. Readers are therefore encouraged to interpret these ratings as a transparent indication of where the underlying literature is denser or sparser, rather than as graded recommendations for clinical practice.

Evidence from Healthy Aging Populations

Studies in cognitively healthy older adults provide foundational evidence that DTI-ALPS index is associated with cognitive performance and may reflect the trajectory of age-related cognitive change.

Wang et al. examined 633 community-dwelling older adults (mean age 62.8 ± 8.9 years, 48.2% female) and found that higher DTI-ALPS index values were significantly associated with higher Mini-Mental State Examination (MMSE) scores ($\beta = 0.108$, $p = 0.003$). Critically, this relationship demonstrated longitudinal predictive validity: higher baseline DTI-ALPS conferred protection against cognitive decline over time (odds ratio

= 0.029, $p = 0.007$) [39]. The researchers additionally identified a significant negative correlation between age and DTI-ALPS index, with accelerated decline observed

after age 65. Mediation analysis revealed that a substantial portion of the association between age and cognitive performance was explained by reduced DTI-ALPS.

Table 1. Evidence quality across disease states for the DTI-ALPS – cognition literature.

Disease area	Sample size range	Study designs	Cognitive phenotyping depth	Confounder adjustment	Independent replication	Overall confidence
Alzheimer's disease continuum	~80 to >44,000	Cross-sectional, longitudinal (ADNI, UK Biobank); mediation analyses	Domain-specific batteries plus composite scores; integrated with amyloid PET and CSF biomarkers	Age, sex, education, gray matter volume, amyloid status	East Asian and Western cohorts	Moderate-to-high
Parkinson's disease	~30 to >1,600 (across 2 meta-analyses)	Cross-sectional, prospective 3-year longitudinal; meta-analysis (21 studies)	Composite cognitive scores; PD-MCI/PDD stratification; some plasma biomarker integration	Age, disease duration, Hoehn & Yahr stage; partial	Yes (meta-analysis)	Moderate
Cerebral small vessel disease	~90 to >500	Cross-sectional + 3-year prospective (SCANS)	Domain-specific batteries (AVLT, TMT, SDMT, BNT)	WMH, microbleeds, lacunes, PVS enlargement; vascular risk	Limited; few cohorts	Moderate
Ischemic stroke / PSCI	~50 to 150	Prospective longitudinal (3 and 12 months); systematic review	MoCA/MMSE plus domain-specific tests	Lesion volume, stroke subtype; sleep/inflammation rarely adjusted	Partial	Preliminary-to-moderate
Multiple sclerosis	~30 to ~183	Cross-sectional + 5-year longitudinal; multiple cohorts	Domain-specific battery	Age, disease duration, lesion load	Limited; multiple cohorts emerging	Preliminary-to-moderate
Temporal lobe epilepsy	~25 to ~80 across cohorts	Cross-sectional; multiple cohorts incl. HS vs non-lesional	Domain-specific batteries (memory, verbal fluency, executive)	Limited	Yes; multiple TLE cohorts	Preliminary-to-moderate
HIV-associated neurocognitive disorder	Small (human + primate)	Cross-sectional human + macaque model	HAND screening batteries	Age dissociation reported; limited otherwise	No (author overlap)	Preliminary

ADNI = Alzheimer's Disease Neuroimaging Initiative; AVLT = Auditory Verbal Learning Test; BNT = Boston Naming Test; HAND = HIV-associated neurocognitive disorder; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PD-MCI/PDD = Parkinson's disease with mild cognitive impairment/dementia; PSCI = post-stroke cognitive impairment; PVS = perivascular space; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test; WMH = white matter hyperintensities. Sample sizes are approximate and reflect ranges across the studies cited in this review for each disease area; the Alzheimer's disease range includes the UK Biobank cohort ($n > 44,000$). Overall confidence ratings are heuristic narrative judgments based on the criteria listed in the column headers, not a formal risk-of-bias assessment; they describe the breadth and density of the underlying literature rather than the methodological quality of individual studies.

Siow et al. investigated 84 community-dwelling older adults (mean age 73.3 ± 7.1 years, 56% female) and identified significant associations between the DTI-ALPS index and specific cognitive domains. Higher DTI-ALPS correlated with better language performance ($\beta = -0.59$, $p = 0.04$) as measured by the Everyday Cognition scale —

where higher scores reflect greater functional difficulty, rendering the negative beta coefficient consistent with a beneficial effect of glymphatic function — and with superior memory ($\beta = 6.17$, $p = 0.009$) assessed via the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery [23].

Together, these studies indicate that higher DTI-ALPS values not only correlate cross-sectionally with better cognitive performance but also prospectively predict slower cognitive decline in older adults, consistent with a possible protective role of preserved glymphatic function.

Glymphatic Function in Disease States

Alzheimer's Disease Continuum

Hong et al. examined participants stratified by cognitive status and amyloid burden, finding that DTI-ALPS index values declined progressively across disease stages: cognitively normal amyloid-negative individuals showed the highest values, with successive reductions observed in cognitively normal amyloid-positive, MCI amyloid-positive, and Alzheimer's disease amyloid-positive groups [40]. Mediation analysis demonstrated that DTI-ALPS partially mediates the relationship between amyloid deposition and cognitive impairment. This finding aligns with theoretical models proposing a vicious cycle wherein amyloid accumulation impairs glymphatic function, which in turn reduces amyloid clearance and accelerates pathological progression [41].

A landmark longitudinal investigation by Huang et al. substantially extends these cross-sectional findings, providing the most comprehensive evidence to date that DTI-ALPS index impairment may precede, rather than merely accompany, the Alzheimer's pathological cascade. Drawing on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI; $n = 419$: 47 AD dementia, 137 MCI, 235 cognitively normal controls) and a population-based replication cohort from the UK Biobank ($n = 36,050$), the authors demonstrated that the DTI-ALPS index was significantly reduced not only in overt AD dementia but also at prodromal (MCI) and preclinical stages, with the decrease occurring before CSF amyloid- β 42 (A β 42) reached the established positivity threshold [42]. Critically, lower baseline ALPS index predicted accelerated amyloid PET burden over follow-up, higher risk of A β -positive conversion, progressive brain atrophy in AD-signature regions, and faster rates of cognitive decline, effects that were fully mediated by amyloid PET and structural atrophy. Li et al. conducted a dual-cohort study encompassing an East Asian and a Western sample, demonstrating that the DTI-ALPS index was significantly reduced in individuals with subjective cognitive decline (SCD) relative to cognitively normal controls, with good discriminative accuracy [43]. Participants with lower ALPS values showed higher amyloid burden and a greater risk of clinical progression over follow-up.

Taken together with the evidence from Huang et al. [42], these findings point toward a model in which DTI-ALPS index constitutes an early, potentially modifiable predictive factor in the AD cascade, measurable years before objective cognitive deficits emerge. Mediation analyses suggest that DTI-ALPS partially mediates the amyloid-cognition relationship [40,44]

Cerebral Small Vessel Disease

Tang et al. compared cognitively normal and cognitively impaired CSVD patients, finding significantly lower DTI-ALPS index values in the cognitively impaired group [27]. This association remained significant after controlling for traditional CSVD imaging markers including white matter lesions, cerebral microbleeds, lacunes, and perivascular space enlargement. Critically, prospective longitudinal data from the SCANS cohort ($n = 120$, mean age 70.0 years, lacunar stroke with confluent white matter hyperintensities) demonstrated that baseline DTI-ALPS was associated with subsequent changes in global cognition ($\beta = 0.142$, $p = 0.032$), executive function ($\beta = 0.287$, $p = 0.027$), and long-term memory ($\beta = 0.228$, $p = 0.027$) over 5 years, and that DTI-ALPS declined significantly over 3 years of follow-up, providing the strongest longitudinal evidence to date that perivascular dysfunction precedes cognitive deterioration in CSVD [45].

This finding is consistent with the hypothesis that glymphatic dysfunction may contribute to cognitive impairment through mechanisms not fully captured by conventional imaging. Specifically, glymphatic dysfunction in CSVD may impair cognition through at least three pathways: impaired clearance of vasoactive and neuroactive metabolites from deep white matter [34], perivascular space enlargement-associated disruption of CSF flow dynamics [46], and neuroinflammatory signaling propagated along glymphatic pathways [46]. Importantly, the current evidence base in CSVD remains relatively limited and is derived from a small number of cohorts using heterogeneous imaging protocols and cognitive assessments. Although available findings consistently support an association between lower DTI-ALPS values and poorer cognitive performance in CSVD, further replication across independent cohorts and longitudinal designs is required before firm conclusions regarding generalizability and disease-stage specificity can be established.

Other Neurological Conditions

Compared with Alzheimer's disease, Parkinson's disease, and cerebral small vessel disease, where evidence linking DTI-ALPS to cognition has achieved moderate

methodological maturity and partial longitudinal replication, evidence in several other neurological and neuropsychiatric conditions remains preliminary and is frequently based on small single-cohort studies.

Margoni et al. found that reduced DTI-ALPS index was the most important predictor of cognitive impairment in pediatric multiple sclerosis patients using Random Forest analysis (relative importance = 100%, AUC = 0.762) [47]. In adult MS, Jakimovski et al. extended these findings in a larger cohort (n = 183, including 135 people with MS and 48 healthy controls), demonstrating that reduced DTI-ALPS was associated with lower cerebral arterial blood flow and increased mean transit time in normal-appearing white matter, linking DTI-ALPS index to vascular and perfusion abnormalities in MS [48].

In temporal lobe epilepsy (TLE), Wang et al. demonstrated that ipsilateral DTI-ALPS index was significantly lower than the contralateral hemisphere in 38 patients with unilateral TLE, with bilateral indices reduced relative to healthy controls [49]. Semantic verbal fluency correlated negatively with ipsilateral choroid plexus volume but showed only trend-level association with DTI-ALPS after FDR correction. These observations are supported by independent cohorts: the original TLE-HS report by Lee et al. (n = 25 TLE-HS, 26 healthy controls) first established reduced DTI-ALPS in this population [50], and a subsequent larger study by Chen et al. (n = 112 TLE-HS, 73 non-lesional TLE, 55 controls) demonstrated subtype-specific lower DTI-ALPS index with distinct memory-domain correlations between lesional and non-lesional TLE [51]. The proposed mechanism involves disruption of CSF-ISF circulation by seizure-related oxidative stress, glutamate excess, and pro-inflammatory mediators, a pathway distinct from the vascular and protein-aggregation mechanisms predominating in CSVD and AD, respectively, and further illustrating the diversity of routes through which glymphatic dysfunction may impair cognition across disease states.

In Parkinson's disease (PD), a comprehensive systematic review and meta-analysis incorporating 21 primary DTI-ALPS studies (1,678 PD patients, 1,088 healthy controls) demonstrated a consistent and moderate reduction in DTI-ALPS index in PD (Cohen's $d = -0.57$; 95% CI: -0.67 to -0.47 ; $p < 0.001$), with phenotypic analyses revealing a gradient of dysfunction across cognitive strata: the most severe decline was found in PD with dementia, followed by PD with MCI, and PD with normal cognition [52]. Lower DTI-ALPS index was significantly associated with longer disease duration ($\beta = -0.08$, $p = 0.005$) and was particularly pronounced in early-stage PD (Hoehn and Yahr score < 2.5), suggesting that DTI-ALPS may serve as early predictor in the disease course and may constitute a viable target for early

intervention. An independent PRISMA 2020 compliant meta-analysis by Shirbandi et al. (11 studies, $n = 1,462$) corroborated these findings, reporting a similar pooled effect size (SMD = -0.61) and providing methodological replication across distinct study selection criteria [53].

Most compellingly, Zarkali et al. provided longitudinal evidence in a prospectively followed cohort of 98 PD patients (31 with poor outcomes, including dementia, MCI, frailty, or death, and 67 with good outcomes over a 3-year follow-up) and 28 controls [54]. DTI-ALPS was lower in PD patients with poor outcomes compared with those with good outcomes and controls ($p = 0.005$) and showed further longitudinal decline exclusively in the poor-outcome group (group $\times$ time interaction: $\beta = -0.013$, $p = 0.021$). Baseline DTI-ALPS correlated with composite cognitive scores both cross-sectionally ($p = 0.226$, $p = 0.027$) and at 3-year follow-up ($p = 0.25$, $p = 0.014$). Importantly, lower DTI-ALPS was associated with reduced white matter fiber cross-section and altered brain iron distribution (quantitative susceptibility mapping), yet these imaging correlates showed a spatially distinct pattern from white matter changes directly attributable to PD dementia. The absence of correlation between DTI-ALPS and plasma p-tau181 ($p = 0.642$) or neurofilament light ($p = 0.448$) further implies that DTI-ALPS index captures unique variance not reflected in fluid biomarkers, supporting its complementary value in a multimodal biomarker framework for PD. Han et al. reported associations between reduced brain activity-CSF flow coupling, an indirect marker of glymphatic function, and cognitive decline in PD, though direct measurement of alpha-synuclein clearance was not performed [55]. Zhang et al. reviewed evidence from animal models documenting that diabetes mellitus and aging impair glymphatic function, leading to accumulation of metabolic wastes including amyloid- β and subsequent cognitive dysfunction; these findings should be interpreted with caution given their reliance on preclinical models [56]. Traumatic brain injury in mice similarly impairs glymphatic pathway function by approximately 60%, with this impairment persisting for at least one-month post-injury and promoting tau pathology through disruption of CSF-ISF exchange [9].

Post-stroke cognitive impairment (PSCI) affects approximately 40% of stroke survivors, yet its neurobiological determinants remain incompletely characterized. Converging evidence from a systematic review of DTI-ALPS in ischemic stroke synthesizing studies from inception through August 2025 indicates that stroke patients consistently exhibit significantly lower bilateral DTI-ALPS indices than non-stroke populations, with the affected hemisphere showing greater impairment [57]. Wang et al. demonstrated in a prospective

longitudinal design that while DTI-ALPS at early time-points did not predict immediate functional outcome, it correlated significantly with PSCI at 6-month follow-up, and partial recovery of the index was observed following rehabilitation [58]. A complementary study by Chen et al. in chronic stroke patients (3 to 12 months post-stroke; $n = 51$) found that DTI-ALPS in the affected hemisphere remained significantly lower than in controls at 3 months, with partial improvement by 12 months, and that transient cognitive associations observed at 3 months, particularly with language and memory domains, diminished at 1-year follow-up, consistent with stabilization of recovery trajectories [59].

HIV-associated glymphatic dysfunction represents a mechanistically informative model for dissociating disease-specific from age-related mechanisms. Unlike chronological aging, whose effects on glymphatic function accumulate gradually over decades, HIV disrupts glymphatic clearance from early infection through viral activity at the blood-brain barrier, release of neurotoxic viral proteins, and chronic neuroinflammation in perivascular spaces, thereby impairing CSF-ISF exchange at a stage when age-related decline would not be expected. Crucially, Nguchu et al. demonstrated that DTI-ALPS decline in people living with HIV (PLWH) is statistically independent of age [60]. This dissociation suggests that immune activation and neuroinflammatory mechanisms may substantially contribute to cognitive impairment independently of chronological aging. It should be noted that the evidence base for this section rests on two publications sharing the same first author [60,61], and that one of these studies was conducted in rhesus macaques treated with antiretroviral therapy rather than in human participants. The human and primate findings should therefore not be treated as independent converging evidence; the macaque data are best interpreted as mechanistic support for the neuroinflammatory hypothesis rather than as direct clinical corroboration. Replication in independent human cohorts is needed before the conclusion that neuroinflammation alone is sufficient to disrupt glymphatic clearance and cognition can be considered well-established.

Taken together, these disease-specific patterns suggest that DTI-ALPS may serve as a useful imaging marker for capturing the diverse pathological processes that converge to impair cognition across neurological conditions. The evidence reviewed above is, however, methodologically heterogeneous, and conclusions should be calibrated to the strength of the underlying literature. Considering sample size, study design, depth of cognitive phenotyping, adjustment for established confounders, imaging standardization, and independent replication across cohorts, the evidence base can be broadly graded as follows. Alzheimer's disease continuum represents the

area of greatest methodological maturity, supported by multi-cohort studies including ADNI and UK Biobank, longitudinal designs with mediation analyses, and replication across East Asian and Western samples (overall confidence: moderate-to-high). Parkinson's disease benefits from two independent meta-analyses [52,53] and prospective longitudinal data linking baseline DTI-ALPS to 3-year cognitive outcomes [54], yielding consistent effect sizes across cognitive strata (overall confidence: moderate). Cerebral small vessel disease benefits from both cross-sectional cohorts and a 3-year prospective study (SCANS) [45], with consistent effect directions, mediation evidence relating ALPS to WMH-related cognitive impairment, and adjustment for conventional diffusion metrics and vascular risk factors (overall confidence: moderate). Ischemic stroke evidence has grown rapidly, including systematic review and prospective designs with partial longitudinal recovery data, but cohort sizes remain modest and standardization across post-stroke time-points is incomplete (overall confidence: preliminary-to-moderate). Multiple sclerosis and temporal lobe epilepsy now rest on multiple cohorts, including cross-sectional and longitudinal data in MS [47,48] and replicated subtype-specific findings in TLE [49,51], although cohort sizes remain modest and confounder adjustment is heterogeneous (overall confidence: preliminary-to-moderate). HIV-associated neurocognitive disorder remains the most constrained evidence base, with substantial author overlap and cross-species data from a primate model (overall confidence: preliminary). Across all disease areas, several common limitations recur: predominance of cross-sectional designs, modest sample sizes, heterogeneous cognitive batteries, infrequent adjustment for sleep, head motion, and cerebrovascular confounders, and limited acquisition standardization across centers. These gradings are summarized in Table 1 and are intended as a heuristic framework for the reader rather than as a formal risk-of-bias assessment, which is beyond the scope of this narrative synthesis but is recommended for future systematic reviews and meta-analyses in this rapidly evolving field.

Associations Between DTI-ALPS and Domain-Specific Cognitive Performance

Before reviewing domain-specific findings, a brief interpretive note is warranted. The associations described in the following sections should be understood as relationships between a perivascular diffusion marker (DTI-ALPS) and cognitive outcomes, rather than as direct evidence of impaired glymphatic clearance capacity per se. As discussed in the Introduction and in greater methodological detail in the Limitations section, DTI-

ALPS captures anisotropic water diffusion along periventricular perivascular spaces and is shaped by multiple factors beyond CSF-ISF exchange, including white matter microstructure, partial volume effects, head motion, and cerebrovascular disease.

Memory Function

Memory represents the cognitive domain most consistently and strongly associated with DTI-ALPS across multiple studies and assessment methods. Tang et al. examined 133 patients with cerebral small vessel disease and found that higher DTI-ALPS index correlated significantly with better performance on the Auditory Verbal Learning Test ($p = 0.002$) [27]. Hong et al., studying 133 participants across the Alzheimer's disease continuum, reported one of the strongest observed correlations between DTI-ALPS and memory ($r = 0.470$, $FDR-p < 0.001$) [40].

The consistency of these findings across diverse populations, including healthy older adults, CSVD patients, and individuals with MCI and Alzheimer's disease, link DTI-ALPS to memory processes. Nonetheless, whether the association between DTI-ALPS and verbal learning is consistent across CSVD cohorts using different memory paradigms, such as recognition-based tests or spatial memory measures, remains to be established. The convergence of significant memory associations across methodologically heterogeneous populations lends face validity to the relationship, but direct replication using comparable instruments is lacking.

Executive Functions

The executive functions domain encompasses multiple cognitive processes including planning, cognitive flexibility, inhibitory control, and working memory [62]. Executive functions show associations with DTI-ALPS broadly similar to those observed for memory, though the relationships appear somewhat less robust. Tang et al. documented significant positive correlations between DTI-ALPS and performance on the Verbal Fluency Test ($p = 0.008$) and the Trail Making Test B-A ($p = 0.010$), with better glymphatic function predicting both superior verbal fluency and faster task-switching ability in CSVD patients [27]. Hong et al. corroborated these findings, reporting a significant positive correlation between DTI-ALPS and a composite executive score ($r = 0.358$, $FDR-p = 0.001$) in participants across the Alzheimer's disease continuum [40].

The association between DTI-ALPS and executive abilities appears most robust for cognitive flexibility and verbal fluency, cognitive operations that depend heavily

on prefrontal-striatal circuitry [62], whereas studies examining inhibitory control or working memory specifically in the context of DTI-ALPS remain lacking.

Processing Speed

Processing speed has received less extensive investigation than memory or executive functions, but available evidence suggests a meaningful relationship with DTI-ALPS. Attention is considered jointly in this section given that the primary instrument identified in the reviewed literature, the Symbol Digit Modalities Test, captures both constructs simultaneously and does not permit their independent assessment. Tang et al. found that DTI-ALPS index correlated significantly with performance on the Symbol Digit Modalities Test ($p < 0.001$), a measure reflecting both processing speed and sustained attention, [27].

The relationship between glymphatic function and processing speed may prove particularly significant given that processing speed is among the earliest cognitive abilities to decline with age, with detectable decrements emerging as early as the third decade of life and hypothesized to underlie subsequent deterioration in memory and executive function [63,64]. Whether longitudinal DTI-ALPS measurements predict processing speed trajectories independently of other aging-related factors remains an important open question.

Language and Visuospatial Function

Evidence regarding language and visuospatial abilities is less consistent than for other cognitive domains. Tang et al. found no significant relationship between DTI-ALPS and Boston Naming Test performance ($p = 0.814$) or Rey Complex Figure Test copy scores ($p = 0.526$) [27]. However, Hong et al. reported significant correlations between DTI-ALPS and visuospatial function ($r = 0.223$, $FDR-p = 0.040$) and negative associations between choroid plexus volume, an alternative glymphatic marker where larger volumes suggest glymphatic system dysfunction, and language performance across the Alzheimer's disease continuum [40].

The inconsistent findings for language and visuospatial functions may reflect several factors: relative preservation of these abilities until later stages of cognitive decline, limited measurement sensitivity, or genuinely weaker relationships with DTI-ALPS or other proxies of glymphatic function. Studies using more sensitive language measures or tasks with greater visuospatial complexity may be needed to clarify these domain-specific patterns.

The direction and consistency of associations between DTI-ALPS index and domain-specific cognitive

performance across populations and disease states are summarized in Table 2.

Table 2. DTI-ALPS and Cognitive Function: Evidence Across Populations and Disease States.

Cognitive Domain	Healthy Aging	AD Continuum (SCD, MCI, Dementia)	Cerebral Small Vessel Disease	Other Neurological Conditions (PD, MS, Stroke, Epilepsy, HIV)
Memory	Lower ALPS → poorer verbal learning, delayed recall (39). Effect independent of gray matter, sleep apnea, age (23).†	Strongest and most replicated. Lower ALPS predicts poorer episodic memory across SCD–MCI–dementia (42,43). Partially mediated by amyloid PET burden, hippocampal atrophy (42).	Higher ALPS → better AVLT ($p = 0.002$) (27).†	PD: poorer composite memory, baseline + 3-y follow-up (54). MS (peds): predicts impairment, AUC = 0.762 (47). Stroke: correlates at 6 mo; memory transient at 3 mo (58,59). TLE: not reported (49).
Executive Functions	<i>Not systematically examined. Domain-specific executive measures not reported in healthy aging DTI-ALPS studies.</i>	Lower ALPS → executive composites (planning, flexibility): $r \approx 0.36$, FDR- $p = 0.001$ (40). Choroid plexus volume complementary negative association.	Higher ALPS → verbal fluency ($p = 0.008$), TMT B–A ($p = 0.010$) (27).†	PD: prefrontal-dependent abilities impaired, strongest in poor-outcome group (54). MS: in composite impairment predictor (47). Stroke: global MoCA only (57,58).
Processing Speed	<i>Not directly examined as an isolated domain in healthy aging cohorts.</i>	<i>Limited evidence. Global instruments (MMSE, CDR) used in most AD continuum studies do not isolate processing speed.</i>	Higher ALPS → SDMT ($p < 0.001$) (27).	<i>Not examined as a distinct domain across other neurological conditions.</i>
Language	Higher ALPS → functional language (Everyday Cognition; $\beta = -0.59$, $p = 0.04$) (23).	Inconsistent. Choroid plexus volume negatively associated with language composites (40).	No association: BNT, $p = 0.814$ (27).	Stroke: language transient at 3 mo, absent at 1 y (59). TLE: trend with choroid plexus only (43).
Visuospatial Function	<i>No studies in healthy aging have assessed visuospatial abilities in relation to DTI-ALPS.</i>	Weak positive: $r \approx 0.22$, FDR- $p = 0.040$ (40); smallest domain effect.	No association: Rey Complex Figure copy, $p = 0.526$ (27).	<i>Not systematically examined across other neurological conditions.</i>
Global Cognition	Higher ALPS → MMSE ($n = 633$; $\beta = 0.108$, $p = 0.003$) (39). Baseline ALPS predicts protection from decline (OR = 0.029, $p = 0.007$).	Strong, replicated. ALPS reduced at all stages incl. preclinical. Predicts global decline, progression, conversion (42). Partially mediated by amyloid + atrophy.	Higher ALPS → MoCA; lower in cognitively impaired vs normal CSVD (27,29).†	PD: lower in poor outcomes; meta-analysis Cohen's $d = -0.57$ (52,54). MS (peds): top predictor, AUC = 0.762 (47). HIV-HAND: independent of age (60). Stroke: ALPS at acute phase ↔ 6-mo outcome; recovery parallels improvement (58).

ALPS = DTI-ALPS index; CSF = cerebrospinal fluid; A β = amyloid- β ; AQP4 = aquaporin-4; NREM = non-rapid eye movement sleep; CBT-I = cognitive behavioural therapy for insomnia; CPAP = continuous positive airway pressure; CSVD = cerebral small vessel disease; HIV = human immunodeficiency virus; PET = positron emission tomography. Evidence categories: Human DTI-ALPS = direct associations between ALPS index and cognitive outcomes in humans; Human other = human studies using alternative glymphatic markers; Animal = preclinical model data; Mechanistic = physiological or pharmacological studies informing pathway biology. Numbers in brackets refer to references in the main manuscript.

Mechanisms Linking Glymphatic Function to Cognition

Glymphatic function, indirectly assessed using the DTI-ALPS index (a proxy of perivascular diffusivity), is associated with sleep-dependent waste clearance, gray matter structural integrity, and the clearance of

pathological proteins such as amyloid- β and tau. Amyloid accumulation may, in turn, impair glymphatic efficiency, suggesting a bidirectional, potentially self-reinforcing mechanism.

Cognitive outcomes most consistently associated with glymphatic function include memory (strongest association), as well as executive functions, processing speed, attention, and global cognition. Associations with language and visuospatial abilities appear weaker or less consistent. Solid arrows indicate relationships supported by consistent evidence, whereas dashed arrows denote limited or inconsistent findings across studies.

Sleep-Dependent Clearance

As outlined in the introduction, glymphatic activity peaks during slow-wave sleep, when interstitial space expansion dramatically increases waste clearance capacity [11,12]. The proposed mechanistic pathways linking glymphatic function to cognitive performance are summarized in Figure 1. Siow et al. examined relationships between sleep architecture, glymphatic function, and cognition in community-dwelling older adults, finding that N2 sleep duration showed positive associations with cognitive performance while sleep apnea severity showed negative

associations. These results suggest that both normal sleep architecture and the absence of sleep-disordered breathing influence cognition partly through effects on glymphatic clearance [23]. This mechanistic understanding provides a physiological basis for epidemiological observations linking poor sleep quality to cognitive decline and dementia risk [25] and suggests that sleep optimization may serve as a behavioral intervention to support cognitive health through enhanced glymphatic function [65]. A key mechanistic advance was provided by Hauglund et al., who identified norepinephrine-mediated slow vasomotion, coordinated low-frequency oscillations in vessel diameter occurring during NREM sleep, as the primary driver of glymphatic clearance in the sleeping brain [66]. This finding substantially refines the earlier mechanistic model by specifying that noradrenergic modulation of arterial pulsatility during slow-wave sleep, rather than passive convection alone, propels glymphatic flow. It also raises the possibility that drugs suppressing vasomotion, including commonly used sleep aids such as zolpidem, may paradoxically impair the very clearance process they might be expected to support, with direct implications for the design of sleep-based glymphatic interventions.

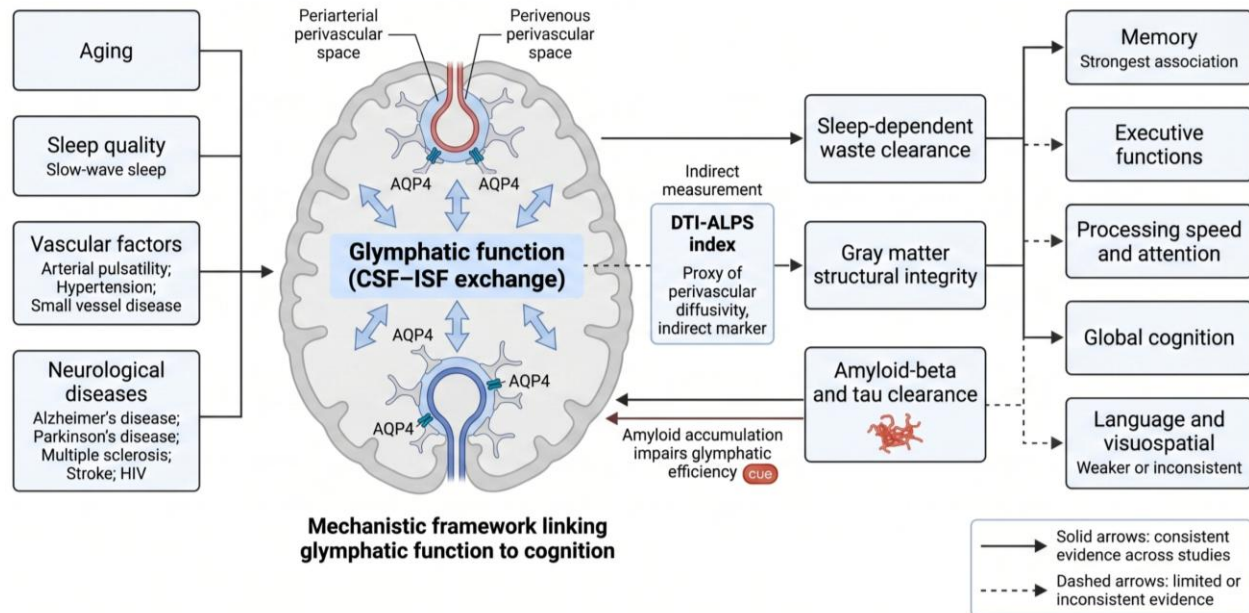


Figure 1. Mechanistic framework linking glymphatic function to cognitive performance. The schematic illustrates the glymphatic system, which mediates cerebrospinal fluid (CSF)-interstitial fluid (ISF) exchange within periarterial and perivenous spaces, facilitated by aquaporin-4 (AQP4) channels. Glymphatic efficiency is influenced by aging, sleep quality (particularly slow-wave sleep), vascular factors (arterial pulsatility, hypertension, small vessel disease), and neurological disorders (including Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, and HIV).

Gray Matter Integrity and Neuronal Health

Chang et al. demonstrated that the association between DTI-ALPS index and cognitive function is mediated by gray matter reserve in brain regions critical for memory and emotional processing. Gray matter reserve refers to the structural capacity of the brain to tolerate age-related or pathological damage before clinical symptoms emerge, with greater baseline gray matter volume providing a buffer against cognitive decline [67]. Siow et al. similarly identified associations between DTI-ALPS index and gray matter volume, further supporting the hypothesis that glymphatic function contributes to structural brain preservation [23].

Efficient waste clearance likely protects neurons from toxic protein accumulation, oxidative stress, and inflammatory mediators. By preserving gray matter volume and neuronal health, an intact glymphatic system may maintain the structural substrate necessary for cognitive processes [15].

Amyloid and Tau Pathology

The most methodologically rigorous longitudinal evidence linking DTI-ALPS to amyloid pathology and cognitive decline comes from the ADNI-based study by Huang et al. [42], who demonstrated that ALPS-indexed glymphatic impairment not only correlates with amyloid burden cross-sectionally but predicts future accumulation, suggesting temporal precedence of DTI-ALPS decline over detectable A β pathology. Within this framework,

two studies have examined relationships between DTI-ALPS index, protein pathology, and cognition, yielding partially divergent findings. Hsu et al. found that DTI-ALPS index correlated negatively with both amyloid and tau accumulation while showing positive correlations with cognitive scores [44].

Inflammatory and Vascular Factors

The association between glymphatic function and cognition likely involves inflammatory and vascular components. Aquaporin-4 expression and perivascular space integrity depend on intact neurovascular coupling and healthy cerebrovascular function [33], and conditions affecting vascular health, including hypertension, diabetes, and cerebral small vessel disease, impair both cerebrovascular function and glymphatic clearance [68]. Inflammatory processes may further compromise glymphatic function through effects on astrocyte morphology, aquaporin-4 polarization, and blood-brain barrier integrity. The multi-factorial nature of glymphatic dysfunction highlights the complex interplay between vascular health, inflammation, protein pathology, and cognitive decline [31]. Empirical studies directly linking inflammatory and vascular biomarkers to DTI-ALPS index values and cognitive outcomes within the same cohort are currently lacking and represent an important direction for future research.

Key mechanistic pathways, supporting evidence, and hypothesis-generating intervention targets are summarized in Table 3.

Table 3. Mechanistic pathways linking glymphatic dysfunction to cognitive impairment: evidence synthesis and hypothesis-generating intervention targets.

Mechanistic Pathway	Key Evidence	Hypothesis-generating intervention targets
Sleep-Dependent Waste Clearance	Human DTI-ALPS: N2 sleep duration $\uparrow$ associated, sleep apnea severity $\downarrow$ associated with ALPS (23). Mechanistic: NE-mediated slow vasomotion during NREM identified as primary driver of clearance (66); vasomotion-suppressing hypnotics (e.g., zolpidem) may paradoxically reduce clearance. Human other: CSF tau varies with sleep-wake cycle; SWS deprivation acutely elevates CSF tau (10).	CBT for insomnia (CBT-I) CPAP treatment for obstructive sleep apnea Sleep hygiene optimisation Avoidance of vasomotion-suppressing hypnotics
Gray Matter Structural Integrity	Human DTI-ALPS: gray matter volume mediates the ALPS–cognition association in healthy aging and AD (23,40). Human other: free water in white matter (interstitial fluid) negatively correlates with cognition (41). Animal: paravascular clearance impairment yields progressive cortical and hippocampal volume loss (9).	Physical exercise (enhances cerebrovascular pulsatility and glymphatic flow) Vascular risk factor control (preserves arterial pulsatility) Interventions targeting AQP4 polarisation restoration

Amyloid-β and Tau Pathology	Human DTI-ALPS + PET: ALPS decline precedes CSF A β 42 positivity; ALPS predicts amyloid PET accumulation; ALPS–cognition fully mediated by amyloid PET + atrophy (42). Human DTI-ALPS: ALPS negatively correlated with amyloid and tau burden; partially mediates amyloid–cognition (44).	Glymphatic enhancement as adjunct to anti-amyloid therapy Targeting the lymphatic–meningeal lymphatic axis to accelerate A β removal Sleep optimisation to reduce A β accumulation rate
Neuroinflammation and Vascular Factors	Human DTI-ALPS: ALPS independently predicts cognitive impairment in CSVD beyond conventional imaging (27,29); glymphatic impairment in HIV independent of age (60); ALPS reduced in diabetes (56). Human other: enlarged PVS and WMH co-occur with reduced glymphatic markers in vascular disease (45). Limitation: direct studies linking inflammatory/vascular biomarkers to ALPS and cognition within the same cohort are absent.	Blood pressure control Anti-inflammatory strategies Glycaemic management in diabetes Treatment of HIV-associated neuroinflammation

ALPS = DTI-ALPS index; AD = Alzheimer’s disease; SCD = subjective cognitive decline; MCI = mild cognitive impairment; CSVD = cerebral small vessel disease; PD = Parkinson’s disease; MS = multiple sclerosis; PSCI = post-stroke cognitive impairment; TLE = temporal lobe epilepsy; HIV-HAND = HIV-associated neurocognitive disorder; TMT = Trail Making Test; AVLT = Auditory Verbal Learning Test; OR = odds ratio. Bold text indicates strength of association. “Not examined” indicates absence of relevant published data, not absence of an effect. Numbers in brackets refer to references in the main manuscript. Effect sizes and statistical parameters reported in cells are illustrative of the strongest published associations for each domain; full study designs, sample characteristics, and confounder adjustments are detailed in the corresponding sections of the main text.

Alternative Glymphatic Markers

While DTI-ALPS remains the most widely used glymphatic biomarker in cognitive research, its inherent methodological limitations, including sensitivity to scanner parameters, anatomical variability, and indirect nature of the measurement, have motivated exploration of complementary approaches. Three alternative markers have been examined in relation to cognitive outcomes in the studies reviewed here.

Hong et al. examined choroid plexus volume as an indirect indicator of glymphatic dysfunction. Enlarged choroid plexus volume may reflect compensatory upregulation of CSF production in response to impaired parenchymal clearance, or alternatively may indicate inflammatory processes affecting CSF dynamics; these two mechanisms carry distinct pathophysiological implications and their relative contributions remain unclear. Enlarged choroid plexus volume showed significant negative associations with both memory (r approximately -0.315, FDR- p approximately 0.007) and executive functions (r approximately -0.321, FDR- p approximately 0.007), suggesting that this structural marker captures aspects of glymphatic dysfunction relevant to cognitive performance [40].

Kamagata et al. examined free water fraction in white matter as a third alternative marker. Free water, quantified using bi-tensor DTI models, reflects extracellular fluid that diffuses freely without restriction from tissue boundaries and may therefore index interstitial fluid accumulation secondary to impaired glymphatic clearance. Increased free water showed significant negative correlations with cognitive performance ($r_s = -$

0.47), consistent with the hypothesis that interstitial fluid accumulation reflecting impaired clearance is cognitively detrimental [41].

The convergence of cognitive associations across these methodologically distinct approaches strengthens confidence in the link between glymphatic function and cognition, as consistent findings across multiple measurement strategies reduce concerns about measurement artifacts specific to any single technique. Nonetheless, each marker captures a somewhat different aspect of glymphatic biology: DTI-ALPS indexes perivascular water diffusivity, choroid plexus volume reflects structural adaptation of the CSF production system, gadolinium clearance provides a direct functional measure of fluid transport, and free water fraction indexes interstitial fluid accumulation. No study to date has directly compared these markers within the same cohort, which represents an important methodological gap.

Despite its limitations, DTI-ALPS currently remains the most extensively studied and clinically accessible MRI-based proxy of glymphatic function in human cognitive research. Compared with contrast-enhanced MRI approaches requiring intrathecal tracer administration, DTI-ALPS is fully non-invasive, feasible in large-scale cohorts, and compatible with routine diffusion MRI acquisitions. These practical advantages largely explain its predominance in the current literature despite ongoing debate regarding its physiological specificity.

Clinical Implications

The DTI-ALPS index has potential as a prognostic biomarker for identifying individuals at risk of cognitive decline, particularly at preclinical stages when intervention may prove most effective. Wang et al. demonstrated that baseline DTI-ALPS index predicts subsequent cognitive decline, supporting the prognostic utility of this measure [39]. Integration of glymphatic markers with established biomarkers, including amyloid and tau PET, structural MRI, and CSF analysis, could enhance risk stratification and improve prediction of disease progression; Hong et al. showed that DTI-ALPS provides information complementary to amyloid status in predicting cognitive outcomes [40].

From a therapeutic standpoint, several behavioral and pharmacological strategies targeting glymphatic enhancement warrant investigation as potential cognitive interventions. Sleep optimization protocols, circadian rhythm stabilization, vascular risk factor management, and physical exercise programs have each been proposed as candidate approaches based on their known effects on glymphatic function. Randomized controlled trials testing these interventions with cognitive outcomes as primary endpoints would provide much stronger evidence for causal relationships and clarify whether improvements in glymphatic clearance translate to measurable cognitive benefits. However, several methodological prerequisites must be addressed before glymphatic-targeting randomized controlled trials can be meaningfully designed and interpreted. These include standardization of DTI-ALPS acquisition and analysis protocols, harmonization of region-of-interest placement across centers, establishment of normative reference values across demographic groups, validation of longitudinal test-retest reliability, identification of clinically meaningful change thresholds, and integration with complementary biomarkers including amyloid PET, plasma biomarkers, and structural MRI. Consensus regarding optimal cognitive endpoints and adjustment for vascular and sleep-related confounders will additionally be necessary to improve interpretability across studies.

Methodological Considerations and Limitations

Study Design and Sample Characteristics

The current literature is predominantly cross-sectional in nature, which fundamentally limits causal inference regarding the relationship between glymphatic function and cognitive performance. While Wang et al. provided valuable longitudinal data, the majority of investigations assessed single time points, precluding determination of whether glymphatic dysfunction precedes, accompanies, or follows cognitive decline [39]. Prospective longitudinal studies with repeated glymphatic

assessments and cognitive testing at multiple time points are critically needed to establish temporal relationships and test mechanistic hypotheses. The complete absence of interventional studies represents a particularly significant gap; trials testing glymphatic-enhancing strategies with cognitive outcomes as endpoints would provide much stronger evidence for causality.

Sample sizes ranged widely from 24 to 633 participants, with the majority of studies examining fewer than 150 individuals. These modest sample sizes limit statistical power to detect moderate effect sizes and preclude adequately powered subgroup analyses examining whether glymphatic-cognitive relationships vary by age, sex, disease severity, or other clinically relevant factors. Several studies also provided incomplete demographic characterization, with information on age distribution, sex, education level, and relevant comorbidities frequently underreported. Given that age, biological sex, cardiovascular risk factors, and sleep quality all influence both glymphatic function and cognitive performance, incomplete demographic reporting substantially limits interpretation and assessment of potential confounding. Study populations have furthermore predominantly consisted of patients with existing cognitive impairment or neurological conditions; studies in cognitively healthy adults across the lifespan are needed to establish normative glymphatic function and its contribution to typical cognitive aging.

Cognitive assessments varied considerably across studies, ranging from comprehensive neuropsychological batteries to brief screening instruments such as the MMSE or MoCA. This heterogeneity complicates cross-study comparisons and may partially explain inconsistent findings across cognitive domains. Standardization of cognitive assessment protocols, including specification of which instruments best capture glymphatic-related cognitive changes, would facilitate systematic comparison and enable meta-analytic synthesis.

A further unaddressed variable across the reviewed literature is biological sex. Glymphatic function has been proposed to be modulated by sex hormones: preclinical evidence indicates that estrogen may upregulate aquaporin-4 expression and enhances AQP4 polarization in perivascular astrocytic endfeet, while estrogen withdrawal following menopause has been hypothesized, on the basis of animal and indirect human data, to be associated with reductions in glymphatic efficiency; direct DTI-ALPS evidence in human peri-menopausal cohorts remains lacking. Sex differences in sleep architecture, particularly in slow-wave sleep duration and susceptibility to sleep-disordered breathing, provide an additional pathway through which biological sex may moderate the glymphatic-cognition relationship. Despite this, none of the studies reviewed in this manuscript

reported sex-stratified DTI-ALPS analyses, and several did not report sex distribution at all. This represents a significant gap: if glymphatic function declines differentially by sex across the lifespan, pooled estimates of the ALPS-cognition association may obscure clinically meaningful heterogeneity. Future studies should routinely report and where feasible analyze DTI-ALPS data stratified by biological sex and should consider hormonal status as a covariate in postmenopausal cohorts. Menopausal transition may represent a particularly important period of glymphatic vulnerability due to estrogen decline and associated alterations in AQP4 polarization, sleep architecture, cerebrovascular regulation, and inflammatory signaling. Hormonal transitions may therefore act not merely as demographic confounders but as biologically meaningful moderators of the glymphatic-cognition relationship, with direct implications for the design and interpretation of future glymphatic-targeting intervention trials.

Limitations of the DTI-ALPS Index

A fundamental limitation insufficiently acknowledged in many primary studies is that DTI-ALPS is an indirect proxy of glymphatic function, not a validated measure of waste clearance. The index reflects anisotropic water diffusion along perivascular spaces at the level of the lateral ventricle body but does not directly quantify CSF-ISF exchange rates, AQP4-mediated transport, or clearance of specific metabolites such as amyloid- β [32,30]. Without validation studies directly comparing DTI-ALPS to gold-standard glymphatic measures such as intrathecal gadobutrol clearance kinetics, the assertion that DTI-ALPS differences between groups reflect differences in waste clearance capacity remains inferential. Correlational associations between DTI-ALPS and cognitive performance should therefore be interpreted as evidence of a relationship between a diffusion-derived imaging marker and cognition, with glymphatic function as one plausible but not definitively established mediating mechanism.

Several confounders may systematically bias DTI-ALPS values independently of true glymphatic function. Age-related white matter degeneration reduces fractional anisotropy in adjacent fibers, potentially inflating DTI-ALPS through changes in reference fiber diffusivity rather than perivascular water movement [5]. Partial volume effects at the periventricular region are substantial, as the region of interest overlaps with CSF spaces where cerebrospinal fluid contamination can elevate radial diffusivity measurements. Head motion during diffusion acquisition represents an additional important confounder, particularly in cognitively impaired and elderly populations, because even subtle motion artifacts

can systematically alter diffusion anisotropy measures and thereby influence calculated DTI-ALPS values. Cerebrovascular disease independently alters diffusion metrics through white matter hyperintensities, microstructural damage, and perivascular space enlargement, all of which co-occur in the same populations being studied [29]. Region-of-interest placement variability across centers and lack of standardized acquisition protocols regarding b-values, gradient directions, and voxel size introduce measurement noise that is rarely quantified [26,69]. Standardization of acquisition and analysis pipelines across research centers would improve reproducibility and facilitate cross-study comparisons.

There is additionally ongoing debate regarding the fundamental transport mechanism underlying the DTI-ALPS signal. Computational models and experimental data suggest that interstitial solute transport may be diffusion-dominant rather than convection-driven, with Peclet numbers well below 1 even under physiological pressure gradients, a finding that challenges the convective flow assumptions underlying some interpretations of the index [5]. This does not invalidate DTI-ALPS as a marker of perivascular space integrity, but it complicates the inference from diffusion anisotropy to glymphatic waste clearance capacity. Alternative measures including choroid plexus volume, enlarged perivascular space ratings, and contrast agent clearance kinetics each carry their own limitations and require further validation; development of more direct and physiologically specific glymphatic measurement techniques represents a critical priority for advancing the field.

Unresolved Findings

Several findings in the current literature remain difficult to interpret. The inconsistent findings regarding language and visuospatial functions require reconciliation through systematic investigation of potential moderating factors such as disease stage, specific tests employed, and regional variability in glymphatic dysfunction.

The relative contributions of glymphatic dysfunction versus other concurrent pathological processes, including protein aggregation, neuroinflammation, vascular dysfunction, and synaptic loss, to cognitive impairment remain incompletely characterized. While several studies have demonstrated glymphatic-cognitive associations independent of established biomarkers, whether glymphatic dysfunction represents a primary driver of cognitive decline, a consequence of other pathological processes, or part of a complex bidirectional relationship remains unresolved. Multimodal biomarker studies integrating glymphatic markers with amyloid PET, tau

imaging, and inflammatory measures within the same cohorts would help clarify these mechanistic relationships.

Future Directions

Several key questions warrant systematic investigation to advance understanding of the relationship between glymphatic function and cognition.

Longitudinal Trajectories and Early Detection

Fundamental questions regarding the temporal dynamics of glymphatic decline remain unanswered. How does glymphatic function change over time in healthy aging compared to neurodegenerative disease, and how early in the disease process does dysfunction appear? What rate of decline predicts subsequent cognitive impairment, and can detection at preclinical stages enable earlier intervention? Longitudinal studies should examine whether the rate of DTI-ALPS decline predicts MCI onset independently of established screening measures such as the MMSE, and what minimum cohort size and follow-up duration are needed to detect clinically meaningful differences. Preliminary support for this hypothesis is provided by Huang et al. [42], who demonstrated in the ADNI cohort that lower baseline ALPS index prospectively predicted clinical conversion from non-demented status to AD, with effects mediated through amyloid accumulation and structural neurodegeneration. Crucially, ALPS decline was detectable before CSF A β 42 reached the positive threshold, establishing a temporal window in which glymphatic biomarkers may offer earlier detection than established fluid biomarkers. Expanding such longitudinal designs to include repeated DTI-ALPS measurements alongside plasma biomarkers (p-tau181, amyloid- β 42/40 ratio) and multimodal cognitive assessments across the SCD-MCI-dementia continuum represents a tractable and high-priority research agenda.

Intervention Studies

No randomized controlled trial has yet examined whether interventions targeting glymphatic function produce measurable cognitive benefits in humans. A priority direction is to test whether sleep optimization interventions — combining cognitive behavioral therapy for insomnia with sleep hygiene education — produce measurable changes in DTI-ALPS index and improve memory composite scores in older adults with insomnia. Future trials should specify DTI-ALPS change as a primary endpoint alongside domain-specific neuropsychological performance and subjective sleep

quality. Beyond sleep, vascular risk factor management and physical exercise programs represent additional candidate interventions warranting evaluation in this framework. Importantly, direct evidence that these interventions improve cognition specifically through DTI-ALPS-measured glymphatic enhancement remains lacking, and current proposals should be regarded as hypothesis-generating rather than as evidence-based clinical recommendations. Operationalization of glymphatic-targeting strategies as clinical trial endpoints will additionally require standardized DTI-ALPS acquisition and analysis protocols, validated minimal clinically important differences for the index, and head-to-head comparisons with established glymphatic measures such as intrathecal gadobutrol clearance.

Biomarker Development and Validation

More direct, sensitive, and physiologically specific glymphatic markers are needed. How do existing markers compare in terms of reliability, validity, and clinical utility? A direct head-to-head comparison of DTI-ALPS against plasma p-tau181, amyloid PET, and CSF amyloid- β 42/40 ratio in predicting two-year cognitive decline is currently absent from the literature and would help establish the incremental and complementary value of glymphatic imaging in clinical risk stratification.

Causal Mechanisms and Individual Differences

The precise mechanisms through which glymphatic dysfunction affect specific cognitive domains remain poorly characterized. Do different cognitive domains show differential vulnerability to particular aspects of glymphatic impairment, and if so, what are the underlying neurobiological explanations? Relatedly, substantial inter-individual variability in glymphatic function is observed even within age-matched cohorts, yet the genetic, lifestyle, and demographic factors that explain this variability are largely unknown. Identifying determinants of individual differences in glymphatic efficiency could help stratify risk and guide targeted preventive strategies.

Emerging Measurement Technologies

Beyond longitudinal and interventional priorities, advances in measurement technology will be essential to overcoming the fundamental limitations of DTI-ALPS identified throughout this review. Current glymphatic assessment relies predominantly on DTI-ALPS, which captures only one aspect of perivascular fluid dynamics. Several emerging approaches may enable more comprehensive and direct measurement. Advanced MRI

sequences including arterial spin labeling and phase-contrast imaging could provide complementary information about CSF flow dynamics and neurovascular coupling, potentially addressing the indirect nature of diffusion-based markers; ASL in particular monitors water permeability across the blood-brain barrier, which may determine CSF-ISF flow and waste clearance in the glymphatic system [69]. Development of PET tracers specifically targeting components of glymphatic pathways could enable direct visualization of clearance mechanisms *in vivo*; albumin-binding radiotracers allowing visualization of CSF flow with PET have recently been developed and show promise for tracking CSF dynamics in preclinical models, though no validated tracer is currently available for routine human use [69]. Wearable sensors enabling continuous monitoring of sleep architecture and autonomic physiological parameters relevant to glymphatic function, including heart rate variability and respiratory patterns, could facilitate investigation of real-world factors influencing glymphatic activity over timescales inaccessible to single-session MRI assessments; consumer wearables combining accelerometer and photoplethysmography data show improving performance for sleep staging, though their reliability across specific sleep stages requires further validation before use as research-grade instruments [70]. Multimodal approaches integrating DTI-ALPS with complementary markers within the same cohorts may offer more comprehensive characterization of glymphatic status than any single measure alone. One recent study demonstrated tri-modal integration of choroid plexus volume, CSF volume, and DTI-ALPS to model CSF circulation dynamics in Alzheimer's disease, providing the first evidence that CSF volume mediates the relationship between choroid plexus enlargement and glymphatic dysfunction [71]. However, a critical appraisal of DTI-ALPS has noted that the validity of this index as a marker of glymphatic brain clearance remains highly questionable, particularly because the hypothesis that water movement along white matter perivascular spaces can serve as a surrogate for cortical clearance of larger solutes such as amyloid- β and tau lacks foundation in existing knowledge [24].

Clinical Translation

Moving from research findings to clinical application requires several steps that remain largely unaddressed. Standardization of glymphatic assessment protocols is a prerequisite for comparison across centers, yet consensus on acquisition parameters, region-of-interest placement, and analysis pipelines has not been achieved; this issue is discussed in detail in the Methodological Considerations section above. The challenges associated with conducting

multisite studies, including variability in MRI systems and acquisition parameters, have been highlighted in recent methodological reviews, with harmonization methods such as the combined association test (ComBat) proposed as a potential solution to enhance standardization and statistical power [69]. Establishment of normative reference values across age ranges, sexes, and populations is equally necessary before glymphatic markers can be interpreted clinically in individual patients. Validation of glymphatic markers against hard clinical outcomes, including longitudinal cognitive decline trajectories and dementia diagnosis, in large prospective cohorts is needed to establish their prognostic utility beyond the cross-sectional associations reviewed here.

Cost-effectiveness analyses will ultimately be required to determine appropriate clinical contexts for glymphatic assessment, particularly given the resource intensity of MRI-based protocols relative to plasma biomarker alternatives. Development of clinical practice guidelines specifying indications, interpretation criteria, and recommended follow-up intervals for glymphatic biomarker use would facilitate responsible implementation as evidence matures.

Conclusions

This review provides a consolidated synthesis of evidence linking the DTI-ALPS index to domain-specific cognitive performance across the aging spectrum and multiple neurological conditions. The available data support the conclusion that DTI-ALPS index is meaningfully and consistently associated with cognitive health, with the strongest relationships observed for memory, global cognition, and executive functions. These associations persist across methodologically heterogeneous studies and remain significant after controlling for established cognitive risk factors and neurodegeneration biomarkers. Importantly, the strength of this evidence is not uniform across conditions. As summarized in Table 1, confidence in the DTI-ALPS - cognition association ranges from moderate-to-high in the Alzheimer's disease continuum, where multi-cohort longitudinal data and mediation analyses are available, through moderate in Parkinson's disease and cerebral small vessel disease, to preliminary in HIV-associated neurocognitive disorder and several other emerging areas. Conclusions drawn from this synthesis should therefore be calibrated to these differential levels of evidence rather than treated as uniformly established. Because this is a narrative rather than systematic review, the confidence ratings shown in Table 1 reflect a qualitative heuristic appraisal of the available literature and should not be read as outputs of a

formal risk-of-bias assessment or as graded clinical recommendations.

Mechanistically, the reviewed evidence points to three converging pathways through which glymphatic impairment may translate to cognitive decline: disruption of sleep-dependent waste clearance, compromise of gray matter structural integrity, and facilitation of amyloid- β and tau accumulation. These pathways are not mutually exclusive and likely operate synergistically across disease states, with their relative contributions varying by condition and disease stage. The parallel dysfunction observed across Alzheimer's disease, Parkinson's disease, cerebral small vessel disease, multiple sclerosis, ischemic stroke, temporal lobe epilepsy, and HIV-associated neurocognitive disorder suggests that glymphatic failure may represent a shared downstream mechanism through which diverse pathological processes converge to impair cognition.

Important caveats temper these conclusions. The DTI-ALPS index remains an indirect and insufficiently validated proxy of glymphatic clearance, the predominance of cross-sectional designs precludes causal inference, and the evidence base is limited by modest sample sizes and heterogeneous assessment methods. Whether glymphatic dysfunction precedes and drives cognitive decline, represents a consequence of other pathological processes, or participates in a bidirectional vicious cycle with protein aggregation and neuroinflammation remains unresolved.

Advancing this field requires longitudinal studies with repeated glymphatic and cognitive assessments, multimodal biomarker integration within shared cohorts, standardization of DTI-ALPS acquisition and analysis protocols, and ultimately randomized controlled trials testing whether glymphatic-targeting interventions—including sleep optimization, vascular risk factor management, and physical exercise—produce measurable cognitive benefits. At present, DTI-ALPS should be regarded primarily as a research biomarker reflecting perivascular diffusion characteristics rather than a clinically validated measure of glymphatic clearance capacity or an established prognostic tool for individual patients. If these research priorities are addressed, glymphatic biomarkers may ultimately contribute to improved preclinical risk stratification, multimodal biomarker integration, and development of mechanistically informed interventions for cognitive aging and neurodegeneration.

Conflicts of Interest

None.

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