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Evaluating the robustness of DTI-ALPS in clinical context: a meta-analytic parallel on Alzheimer's and Parkinson's diseases

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In recent years, the glymphatic system has received increasing attention due to its possible implications in biological mechanisms associated with neurodegeneration. In the field of human brain mapping, this led to the development of diffusion tensor image analysis along the perivascular space (DTI-ALPS) index. While this index has been repeatedly used to investigate possible differences between neurodegenerative disorders and healthy controls, a comprehensive evaluation of its stability across multiple measurements and different disorders is still missing. In this study, we perform a Bayesian meta-analysis aiming to assess the consistency of the DTI-ALPS results previously reported for 12 studies on Parkinson's disease and 11 studies on Alzheimer's disease. We also evaluated if the measured value of the DTI-ALPS index can quantitatively inform the diagnostic process, allowing disambiguation between these two disorders. Our results, expressed in terms of Bayes' Factor values, confirmed that the DTI-ALPS index is consistent in measuring the different functioning of the glymphatic system between healthy subjects and patients for both Parkinson's disease (Log10(BF10) = 30) and Alzheimer's disease (Log10(BF10) = 10). Moreover, we showed that the DTI-ALPS can be used to compare these two disorders directly, therefore providing a first proof of concept supporting the reliability of taking into consideration this neuroimaging measurement in the diagnostic process. Our study underscores the potential of the DTI-ALPS index in advancing our understanding of neurodegenerative pathologies and enhancing clinical diagnostics.

Keywords Alzheimer's disease, Parkinson's disease, Choroid plexus, Glymphatic, Perivascular space

The glymphatic system is a drainage apparatus of the brain[1]. In particular, it is thought to contribute to the elimination of soluble proteins and metabolites and to the distribution of glucose, lipids, amino acids, and neuromodulators[2]. Its mechanism of functioning is based on the movement of cerebrospinal fluid into the perivascular space[3].

The activity of the glymphatic system has been classically studied through the administration of tracers, therefore limiting the investigation to animal models. In recent years, the brain imaging community has focused on developing MRI methods to study the glymphatic system in humans. Researchers have specifically adapted diffusion tensor imaging (DTI), originally designed to track water molecules along axons, to study liquid flow in this system. This led to the consolidation of a non-invasive method called diffusion tensor image analysis along the perivascular space (DTI-ALPS)[4]. This technique produces a quantitative index by measuring diffusion in three directions (i.e., right-left, front-back, and top-bottom) within three spherical regions of interest (ROIs) located at the lateral ventricle body. This mapping distinguishes the contributions of projection, association, and subcortical fibers, which are orthogonal in this anatomical region. The diffusion values in these three directions within the ROIs are then combined arithmetically to quantify diffusion along the direction of the perivascular space, where glymphatic flow is believed to occur. Since its formulation seven years ago[4], the DTI-ALPS technique has been used to characterize the glymphatic system in a variety of neurodegenerative conditions,

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including Alzheimer's disease (AD), amyotrophic lateral sclerosis, idiopathic normal pressure hydrocephalus, multiple sclerosis, and Parkinson's disease (PD)[4–9]. Different independent efforts have reported significant between-group differences of the index values computed on clinical subjects and healthy controls[10]. However, a comprehensive evaluation of the DTI-ALPS index stability across multiple measurements, as well as between different neurological conditions, has not been realized yet.

In this context, the present meta-analysis had two main objectives: first, to evaluate the consistency of the DTI-ALPS values reported across independent studies investigating the same neurodegenerative disorder. Second, to determine whether the DTI-ALPS index alterations are more strongly associated with a specific clinical condition, thereby supporting its potential inclusion in the diagnostic process. The focus of the present work was on PD and AD. These two disorders share a pathophysiological mechanism involving protein deposition, which leads to neurodegeneration[11]. In the case of PD, protein aggregates may accumulate at the intracellular level, leading to the formation of alpha-synuclein aggregates called Lewy Bodies. In AD, protein sedimentation occurs either at an intracellular level, as with tau neurofibrillary tangles, or at the extracellular level, as with amyloid plaque formation. In both scenarios, the glymphatic system is thought to aid in the removal of these toxic aggregates through its clearance function. This makes studying its role in Alzheimer's disease (AD) and Parkinson's disease (PD) particularly important.

Materials and methods

Selection of studies

The MEDLINE database was searched to identify all possible experiments performing DTI-ALPS on patients affected by either AD or PD confronting them with healthy controls. The search engine PubMed was used, with the search algorithm consisting of: *(DTI-ALPS) AND ((Parkinson) OR (Alzheimer))*. Moreover, Google Scholar was searched to find articles that could have been missed during the MEDLINE inspection. At the time of the selection phase (January 2024), 104 full-text articles were initially identified by combining the two databases, and screened for eligibility based on the following criteria: (a) articles had to be published in peer-reviewed English-language journals; (b) articles had to measure DTI-ALPS in patients afflicted by either AD or PD and healthy controls. In particular, with respect to criterion b, articles had to report for each experiment the DTI-ALPS index (measured bilaterally and/or on the left and right sides –Alps L and Alps R, respectively) for the clinical group and the control group, their standard deviations, and the number of clinical and healthy subjects.

Bayes factor in the meta-analytic framework

Most of the past and current clinical research, including meta-analytic approaches, applies the classic hypothesis testing that pertains to frequentist statistics. However, in recent years increasing attention has been gained by the use of alternative solutions taken from Bayesian statistics[12–14]. The main advantage of this approach is the shift from the minimization of the probability of obtaining an erroneous result (i.e., the concept behind p-value) to the quantification of the amount of evidence provided by the data in support of the research hypotheses. This has its technical roots in the Bayes' theorem:

$$P(M|D) = \frac{P(D|M)\,P(M)}{P(D)}$$

Where M is the model being evaluated and D are the collected data. The left term of Bayes' theorem, called "posterior probability", expresses that the aim is to find the probability of what is hypothesized (M) given that some values had been observed (D). The data-dependent term $P(D|M)$appearing on the right, called "likelihood", represents the probability of observing those values (D) under the assumption of the validity of what is hypothesized (*M*). The likelihood is indeed the focal point of the Bayesian comparison between different models (or hypotheses), which can be implemented through the computation of the Bayes' Factor (BF), which is essentially a ratio between the competing models (i.e., M1 and M2):

$$BF_{12} = \frac{P(D|M_1)}{P(D|M_2)} = \frac{\int P(\theta_1|M_1)\,P(D|\theta_1, M_1)\,d\theta_1}{\int P(\theta_2|M_2)\,P(D|\theta_2, M_2)\,d\theta_2}$$

As it can be noted, D remains unchanged for both models, taking the role of a normalization constant. In other words, it is the partition function of the inference on the model parameters *M* once obtained the data *D*. In the formula above, θ_1 and θ_2 allow therefore to parametrize the plausibility of the competing models M_1 and M_2 considering the observed data D.

This method had been previously used to run secondary analyses of already published literature using their summary statistics rather than the original raw data[15–17]. However, this approach was so far applied to one experiment at a time. In the present work, the aim is instead to analyze multiple research together, in a meta-analytic framework. It could be thought that a way to address this is to take the posterior probabilities of the first experiment as the prior of the second one, and so on, and then simply compute the product of BF. However, this method would not be correct[18]. To accurately extend the BF to the meta-analytic framework the t-statistics reported as the result in each paper must be thought as the data, while the effect size is modeled as the parameter of interest, δ. In this case, the resulting BF for a single experiment is

$$BF_{10} = \frac{P(D|H_1)}{P(D|H_0)} = \frac{\int P(t|\delta)\,f(\delta)\,d\delta}{P(t|\,\delta = 0)},$$

and the generalization to M-independent experiments is given by

$$BF_{10} = \frac{P\left(D|H_1\right)}{P\left(D|H_0\right)} = \frac{\int \prod_{m=1}^{M} P\left(t|\delta\right) f\left(\delta\right) d\delta}{\prod_{m=1}^{M} P\left(t|\,\delta = 0\right)},$$

where Π indicates the product of terms. The important property of this approach is that while it assumes that the true effect size is constant in each experiment, it does not so for a common variance. Therefore, it is applicable to experiments where the unit of measurement varies among them. The computation of the meta-analytic Bayes factor was here completed using the Bayes Factor package for R software (https://cran.r-project.org/package=BayesFactor).

Disorder discrimination

The next step is to consider whether a difference in DTI-ALPS index values between the two diseases, as indicated by the previous analysis, would provide informative results. To address this, a Bayesian analysis was conducted, following the "heuristic of space to move" as proposed by Dienes[16]. According to this heuristic, if a theory predicts that A is smaller than B, then if B is greater than the case by a quantity r, then A must lie between the case and r, where r represents the space to move.

In the present work, the application of this heuristic is applied as follows: the meta-analysis computes the DTI-ALPS values for the two diseases along with their respective standard deviations. The means and standard deviations are obtained through the samples from the posterior distribution of the DTI-ALPS values obtained in the meta-analysis, using the Bayes Factor package. A new BF is then computed by considering the case in which the DTI-ALPS value of AD is greater than that of PD. The direction of this comparison was determined based on the obtained meta-analytic results, though the reverse would apply if the outcome were the opposite. The difference between DTI-ALPS values for the two diseases is computed, and a semi-Gaussian distribution is used to model the alternative hypothesis H1, since the case of the AD value being greater than the PD value is considered. This distribution is centered on zero, with a standard deviation equal to half the mean DTI-ALPS for AD. This setup implies that the maximum plausible effect size is twice the standard deviation.

Results

Based on the selection criteria, 23 articles were included in this meta-analysis, amounting to a total of 27 independent experiments: 13 for AD (Table 1) and14 for PD (Table 2), respectively. PRISMA flow chart is reported in Fig. 1. For each selected experiment, a t-value was computed starting from the extracted information. The results of the meta-analytic BF, computed either for the whole-brain, or separately for the left and right hemispheres, are provided in Table 3 for Alzheimer's disease and in Table 4 for Parkinson's disease, respectively.

The strength of the evidence, that here was measured in terms of Ban (i.e., the logarithm of the Bayes factor)[40] was found to be considerable for AD and strong for PD[41]. Notably, a marked lateralization emerged for PD, but not for AD. While the supporting evidence was stronger for PD, the median effect size, i.e. the difference between the DTI-ALPS values measured in the healthy or clinical samples, was slightly greater in AD. Finally, the direct comparison between the two disorders returned evidence of $\mathrm{BF}_{12} = 3.86$.

Discussion

Since its development[4], the DTI-ALPS has been used to investigate the functionality of the glymphatic system in a variety of neurodegenerative conditions. While independent peer-reviewed studies reported a significant difference between the DTI-ALPS values measured in healthy subjects and patients with PD or AD, this is the first attempt to quantitatively assess the consistency of those multiple results.

Based on the meta-analytic Bayesian analysis of 27 experiments, our results first suggested that there is enough strength of evidence to support the thesis that the DTI-ALPS can indeed capture variations in the glymphatic system associated with AD (compared against healthy controls) or PD (compared against healthy controls). In particular, the results of the BF showed that it is 30 times more likely to observe an altered level of functioning of the glymphatic system in PD patients than in healthy controls. In the domain of Bayesian statistics, a BF value of 30 is regarded as strong evidence. Positive evidence was found for AD as well, although slightly less strong (BF = 10). It should be noted that the observed difference is not due to an imbalanced representation of PD and AD experiments, being indeed 14 and 13, respectively. It is also worth noting that the median effect showed an opposite pattern, indicating that the delta in the DTI-ALPS index measured for healthy subjects and clinical subjects is actually wider for AD than PD. This ability to separate the effect size from the strength of the evidence directly results from using the Bayesian framework. Moreover, unlike frequentist statistics, the Bayesian approach offers the advantage of being unaffected by sample size, providing reliable results even with small datasets[14]. This analytic method also enabled us to assess whether the DTI-ALPS index can effectively distinguish between the two disorders, even without direct primary comparative experiments. The evidence of glymphatic system impairment was found to differ between AD and PD, suggesting that the DTI-ALPS index may serve as a potential discriminator between the two disorders.

From the pathophysiological point of view, previous studies have demonstrated that glymphatic dysfunction influences the accumulation of pathological protein aggregates both intracellular and extracellular, triggering neuroinflammation[42,43]. In AD, neurodegeneration is caused by toxic aggregation of extracellular amyloid plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein[44], while PD neuropathology is characterized by the accumulation of misfolded a-synuclein in intracytoplasmic inclusions called Lewy bodies[45]. AD pathologies (i.e., beta amyloid and tau) may act synergistically with a-synuclein pathology to confer a worse prognosis in terms of cognitive and executive impairment in patients with PD[46]. It is also possible to detect

Experiment	Scanner Tesla	Directions	b-Value s/mm^2	Alzheimer's disease			Healthy controls		DTI-ALPS results					
				No. subjects (male)	Age (SD)	MMSE (SD)	No. subjects (male)	Age (SD)	DTI-ALPS AD (SD)	Alps L AD (SD)	Alps R AD (SD)	DTI-ALPS HC (SD)	Alps L HC (SD)	Alps R HC (SD)
Taoka et al., 2017[4]	3.0	30	1000	16 (Na)	75 (Na)	Na	6 (Na)	Na	1.2 (0.19)	1.2 (0.19)	Na	1.4 (0.23)	1.4 (0.23)	Na
Hsu et al., 2022[19]	Na	64	1000	37 (10)	63.2 (4.7)	17.7 (6.7)	13 (4)	61 (7.1)	1.4 (0.2)	1.4 (0.2)	Na	1.5 (0.1)	1.5 (0.1)	Na
Zhang et al., 2024[20]	3.0	104	1000	15 (9)	66.9 (9.5)	9.5 (7.6)	26 (11)	63.4 (7.4)	1.42 (0.16)	1.4 (0.16)	1.45 (0.19)	1.57 (0.16)	1.56 (0.18)	1.59 (0.18)
Ota et al., 2022[21]	3.0	30	1000	21 (7)	71.3 (9.1)	20.8 (3)	36 (15)	64.6 (7.6)	1.19 (0.14)	1.2 (0.15)	1.18 (0.15)	1.39 (1.16)	1.38 (0.19)	1.4 (0.18)
Matsushita et al., 2024[22]	3.0	64	1000	29 (14)	78.3 (6.8)	24.1 (4.4)	29 (14)	78.3 (6.8)	1.3 (0.1)	Na	Na	1.4 (0.1)	Na	Na
Liang et al., 2023[23]	3.0	Na	1000	38 (10)	72.05 (6.95)	17.71 (5.34)	28 (11)	67.75 (6.09)	1.15 (0.07)	1.15 (0.07)	Na	1.44 (0.07)	1.44 (0.07)	Na
Steward et al., 2021[24]	3.0	30	1000	16 (11)	69.13 (Na)	18.7 (Na)	10 (5)	73.8 (Na)	1.47 (Na)	1.58 (0.16)	1.5 (0.14)	1.53 (Na)	1.48 (0.17)	1.6 (0.23)
Zhong et al., 2023[25]	3.0	64	2000	36 (17)	74.8 (8)	14.9 (5.5)	65 (30)	67.9 (6.5)	2.07 (0.22)	Na	Na	2.2 (0.2)	Na	Na
Kamagata et al., 2022[26]	3.0	41	1000	36 (22)	74.28 (8.76)	23.39 (1.96)	31 (14)	73.86 (4.91)	1.24 (0.21)	Na	Na	1.34 (0.11)	Na	Na
Chang et al., 2023[27]	3.0	64	1000	130 (52)	60.15 (3.67)	19.55 (7.77)	130 (60)	58.52 (5.71)	0.99 (0.06)	Na	Na	1.02 (0.05)	Na	Na
Saito et al., 2023[28]	3.0	41	1000	25 (25)	75.4 (6.9)	23.4 (1.9)	29 (29)	73.7 (7.5)	1.47 (Na)	1.5 (0.28)	1.43 (0.22)	1.535 (Na)	1.55 (0.22)	1.52 (0.19)
Saito et al., 2023[28]	3.0	41	1000	11 (11)	75 (6)	23.4 (2.1)	14 (14)	74.9 (7.8)	1.39 (Na)	1.37 (0.19)	1.41 (0.2)	1.55 (Na)	1.56 (0.24)	1.54 (0.19)
Saito et al., 2023[28]	3.0	48	1000	9 (9)	74 (5.5)	23.5 (1.5)	39 (39)	74.2 (7.2)	1.41 (Na)	1.39 (0.17)	1.43 (0.22)	1.525 (Na)	1.52 (0.23)	1.53 (0.21)

Table 1. Experiments included in the meta-analysis of Alzheimer's disease: clinical, socio-demographic, and methodological data. AD = Alzheimer's disease; DTI-ALPS = diffusion tensor image analysis along the perivascular space; HC = healthy controls; L = left; MMSE = Mini-Mental State Examination; Na = data not associated; R = right; SD = standard deviation.

Experiment	Scanner Tesla	Directions	b-Value s/mm^2	Parkinson's disease			Healthy Controls		DTI-ALPS Results					
				No. subjects (male)	Age (SD)	MMSE (SD)	No. subjects (male)	Age (SD)	DTI-ALPS PD (SD)	Alps L PD (SD)	Alps R PD (SD)	DTI-ALPS HC (SD)	Alps L HC (SD)	Alps R HC (SD)
Bae et al., 2023[29]	3.0	32	1000	54 (23)	68.9 (9.4)	26.5 (3.5)	54 (23)	69 (10.5)	1.5 (0.22)	Na	Na	1.66 (0.2)	Na	Na
Saito et al., 2023[30]	3.0	41	1000	21 (14)	67.5 (5.7)	25 (4.4)	17 (13)	65.4 (6)	1.48 (Na)	1.48 (Na)	1.49 (Na)	1.78 (Na)	1.77 (Na)	1.73 (Na)
Qin et al., 2023[31]	3.0	64	1000	153 (99)	60.97 (9.47)	Na	67(43)	60.1 (10.56)	1.46 (0.24)	1.48 (0.30)	1.44 (0.25)	1.551 (0.24)	1.57 (0.29)	1.53 (0.23)
Gu et al., 2023[32]	3.0	Na	Na	124 (44)	60.97 (9.47)	25.99 (4.99)	106 (40)	60.3 (7)	1.22 (0.18)	1.22 (0.18)	Na	1.34 (0.19)	1.34 (0.19)	Na
Cai et al., 2023[33]	3.0	25	1000	94 (49)	61.87 (8.52)	28 (Na)	42 (19)	61.52 (7.54)	1.16 (0.18)	Na	Na	1.31 (0.18)	Na	Na
Shen et al., 2022[34]	7.0	Na	1000/3000	40 (21)	54.55 (8.34)	26.23 (3.18)	47 (19)	52.22 (8.84)	1.41 (0.26)	1.39 (0.28)	1.42 (0.24)	1.5 (0.22)	1.52 (0.22)	1.48 (0.22)
Shen et al., 2022[34]	7.0	Na	1000/3000	36 (16)	59.72 (10.13)	23.11 (5.54)	31 (11)	57.86 (5.67)	1.36 (0.24)	1.36 (0.27)	1.36 (0.20)	1.5 (0.21)	1.57 (0.19)	1.48 (0.23)
Ruan et al., 2022[9]	3.0	99	2000	28 (18)	66.11 (6.46)	25.3 (3.55)	34 (15)	62.71 (4.12)	1.47 (Na)	Na	Na	1.55 (Na)	Na	Na
Ruan et al., 2022[9]	3.0	99	2000	31 (17)	64.29 (8.2)	25.42 (4.3)	34 (15)	62.71 (4.12)	1.46 (Na)	Na	Na	1.55 (Na)	Na	Na
Si et al., 2022[35]	3.0	30	1000	168 (96)	60.25 (9.88)	26.8 (3.83)	129 (59)	61.96 (7.21)	1.2 (0.17)	1.2 (0.17)	Na	1.31 (0.17)	1.31 (0.17)	Na
Ma et al., 2021[36]	3.0	31	1000	71 (31)	64.68 (8.12)	28.03 (2.15)	36 (18)	62 (6.24)	1.44 (0.16)	1.44 (0.18)	Na	1.53 (0.16)	1.53 (0.16)	Na
Chen et al., 2021[37]	3.0	13	1000	25 (15)	60.08 (10.07)	27.92 (1.78)	47 (15)	61.53 (4.75)	1.35 (Na)	1.35 (Na)	Na	1.44 (Na)	1.44 (Na)	Na
Meng et al., 2023[38]	3.0	30	1000	51 (24)	72.25 (7.82)	Na	50 (24)	70.88 (8)	1.46 (Na)	1.45 (Na)	1.47 (Na)	1.53 (Na)	1.53 (Na)	1.52 (Na)
Bae et al., 2023[39]	3.0	32	1000	20 (12)	72 (Na)	27 (Na)	20 (12)	73 (Na)	1.49 (Na)	Na	Na	1.72 (Na)	Na	Na

Table 2. Experiments included in the meta-analysis of Parkison's disease: clinical, socio-demographic, and methodological data. DTI-ALPS = diffusion tensor image analysis along the perivascular space; HC = healthy controls; L = left; MMSE = Mini-Mental State Examination; Na = data not associated; PD = Parkinson's disease; R = right; SD = standard deviation.

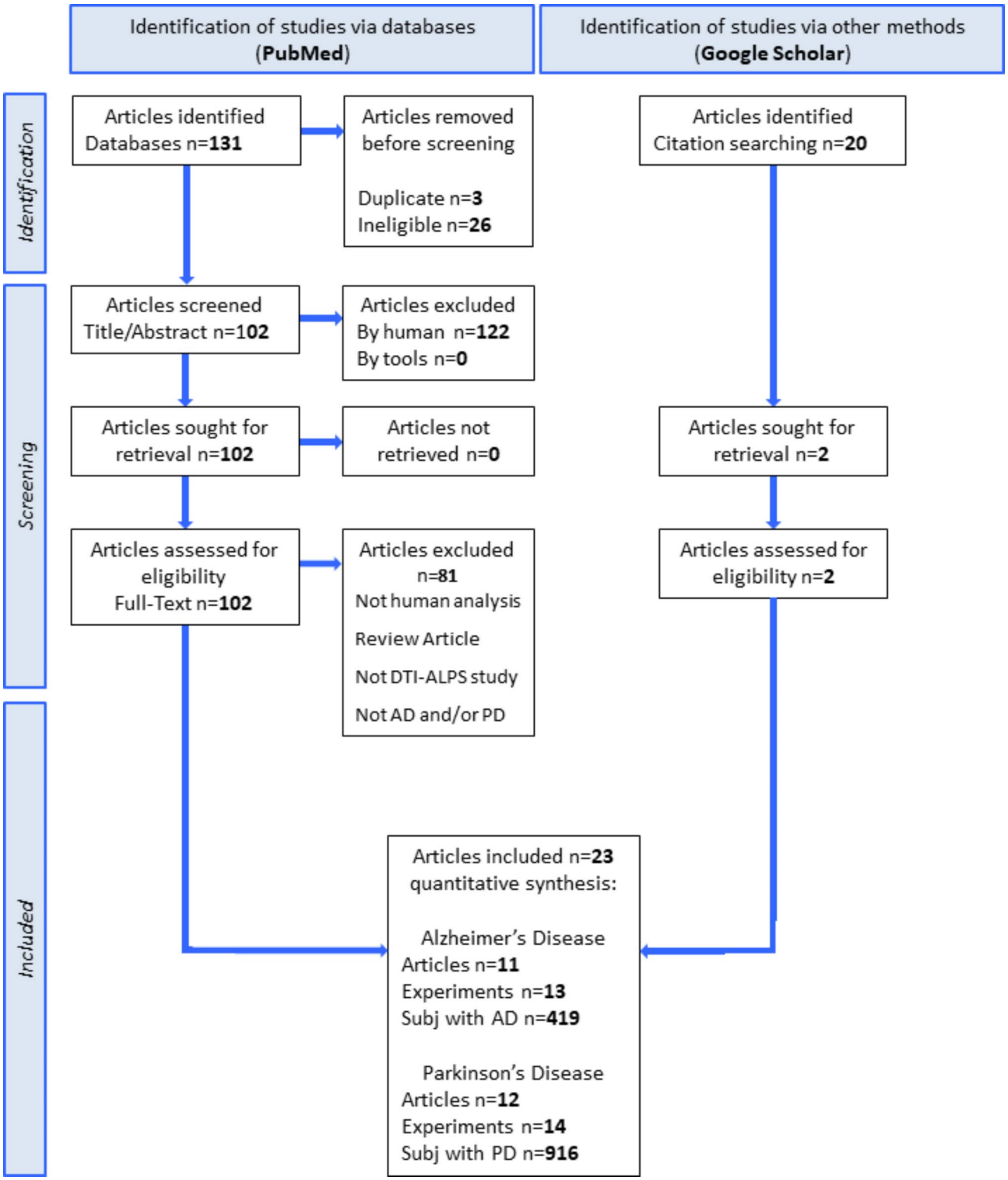

Fig. 1. PRISMA flowchart for data selection in Alzheimer's disease and Parkinson's disease meta-analyses. AD = Alzheimer's disease; DTI-ALPS = diffusion tensor image analysis along the perivascular space; PD = Parkinson's disease; Subj = subjects.

a-synuclein in patients with a biological diagnosis of AD, and a-synuclein was also included as a biomarker of non-AD copathology in the latest criteria for diagnosis of AD[47].

The glymphatic system is a key component of the central nervous system's solutes clearance and water transport network, and its impairment creates a facilitatory environment for waste product accumulation, with relevant implications in proteinopathies[48]. Proposed mechanisms for the impairment of brain fluid homeostasis

DTI-ALPS	$log_{10}(BF_{20})$	Median effect
Whole-brain	10	0.53
Left hemisphere	6.57	0.51
Right hemisphere	3.42	0.47

Table 3. The meta-analytic BF for Alzheimer's disease. Each row represents a measured condition. All means the whole brain DTI-ALPS. Left and Right are the DTI-ALPS measured in the two sides of the brain. Results are expressed as the log_{10}, that is the logarithm of the Bayes factor which measures the strength of the evidence of the measured effect size. The last column is the dimension of the effect for the different pathologies is also provided and measured in the whole and lateralized brain.

DTI-ALPS	$log_{10}(BF_{10})$	Median effect
Whole-brain	30	0.42
Left hemisphere	20	0.38
Right hemisphere	4	0.27

Table 4. The meta-analytic BF for Parkinson's disease. Each row represents a measured condition. All means the whole brain DTI-ALPS. Left and Right are the DTI-ALPS measured in the two sides of the brain. Results are expressed as the log_{10}, that is the logarithm of the Bayes factor which measures the strength of the evidence of the measured effect size. The last column is the dimension of the effect for the different pathologies is also provided and measured in the whole and lateralized brain.

mediated by glymphatic drainage include dilated or increased perivascular spaces and blood-brain barrier disruption. Another key factor is the impairment of aquaporin-4 (AQP-4) water channels, which mediate the flow from periarterial spaces to the brain parenchyma[48]. The role of AQP4 in neurodegeneration is a potential link between glymphatic disorders and neuroinflammation, triggered by the accumulation of toxic protein aggregates. Studies in an animal model of AD have shown that in APP/PS1 transgenic mice, AQP4 deletion exacerbates cognitive deficits and is associated with an increase in beta-amyloid accumulation[49]. Another study in an animal model of PD showed that the impairment of the glymphatic system through the deletion of the AQP4 gene reduced the clearance of injected alpha-synuclein from the brain[5]. It is interesting to note that the glymphatic system appears to interact with various mechanisms involved in neurodegeneration, in general, and not in a disease-specific way. In particular, neuroinflammation via AQP-4 impact renders AQP4 a promising target for further research and a potential avenue for therapeutic interventions in both AD and PD.

An additional aspect worth considering is the speculation that sleep deprivation and circadian rhythm disruptions may be associated with increased accumulation of beta-amyloid, tau and alpha-synuclein levels in humans. Sleep disturbances are widely prevalent both in AD and PD[50]. In AD, they tend to co-occur with other cognitive and behavioral symptoms from the very early stages of the disease[51], and it was observed that shorter sleep duration and poor sleep quality were associated with increased beta-amyloid accumulation[52]. Among alpha-synucleinopathies, REM-sleep behavior disorder (RBD) is recognized as one of the most promising markers of prodromal PD[53]. A large prospective multicenter trial found that the overall conversion rate from idiopathic RBD to an overt neurodegenerative syndrome was 6.3% per year, with 73.5% of subjects with idiopathic RBD converting after 12-year follow-up[54]. Research in mice indicates that interstitial clearance is most effective during REM sleep. Specifically, an increase in water diffusivity during sleep was positively correlated with the REM sleep stage and negatively correlated with the non-REM sleep stage[55]. It has also been shown that DTI-ALPS values in RBD demonstrated a more severe reduction of glymphatic activity in individuals with phenoconversion to alpha synucleinopathies[39]. The suggested greater impairment of the glymphatic system in PD could thus be traced back to a *time effect*, with a prolonged duration of sleep-associated disorder[39]. However, it should also be noted that PD is characterized by a greater involvement of deep brain regions (i.e., basal ganglia) that are close to the ROI localization used for DTI-ALPS calculation[56].

In AD, both beta-amyloid and tau accumulation predominantly affect cortical areas far from the ROIs, with a progressive and hierarchical spreading. Beta-amyloid spreads from the frontotemporal cortices to neocortical areas and medial temporal structures, while tau spreads from the transentorhinal and entorhinal cortices to adjacent medial temporal structures, and subsequently to more distant association and primary cortices[57]. PD begins as a synucleinopathy in non-dopaminergic structures of the lower brainstem or in the olfactory bulb, with alpha-synuclein deposition progressing rostrally to affect the substantia nigra, then the basal ganglia, the amygdala, the thalamus, and reaching the neocortex only in the latest stages of the disease[58].

The sensitivity of the DTI-ALPS method to microstructural changes may be influenced by proximity, particularly regarding neurodegenerative processes in the basal ganglia and thalamus. In a previous study, Chung et al[59]. showed that a high number of enlarged perivascular spaces (another imaging marker of glymphatic dysfunction) in the basal ganglia was associated with more severely decreased striatal dopamine transporter availability.

Methodological considerations and future directions

The current findings should be interpreted considering several limitations, primarily arising from the meta-level approach used. First, we observe a non-negligible between- and within-experiment heterogeneity of some sociodemographic, clinical, and methodological variables (i.e., age at scan session, sample size, sex distribution, DTI diffusion/encoding directions, and MMSE scores). Inevitably, this issue may contribute to the variability of the published results meta-analyzed and makes it challenging to discriminate possible differences related to specific subpopulations. At the same time, it is important to note that the meta-analytic approach offers significant advantages in this context. In fact, in conjunction with the substantial statistical power provided by the quantitative synthesis[60,61], the neuroimaging meta-level approach tends to afford more robust and reliable results in terms of generalization for the population of interest[62,63]. Second, although systematic search criteria were employed to query the literature, it is possible that some relevant studies may have been missed. Additionally, meta-analytic findings could be influenced by file-drawer problems or publication bias, a primary literature bias relating to null or contra evidence results that are unpublished[64]. However, it should be noted that Bayesian statistics allows to update results as further literature becomes available, without p-value related issues as in the case of frequentist statistics.

Irrespective of the meta-analytic level, the DTI-ALPS itself has intrinsic limitations. In particular, it aims to represent the state of a whole-brain system through an extremely coarse and circumscribed sampling. Nevertheless, it has repeatedly been shown to correlate with clinical features, and the present work also supports the reliability and informativity of the method. Future research will be instrumental in investigating the relationship between the value measured in the ROIs and the rest of the glymphatic system. The understanding of the human glymphatic system itself is still in its infancy, and much remains to be learned about its role and variability along the lifespan even in healthy conditions. In particular, a better comprehension of the glymphatic-sleep relationship could allow to correctly model a possible relevant co-factor of several disorders. Finally, it is noteworthy that the proposed method can be readily applied to any disorder supposed to affect the brain, offering a further clue of the actual involvement of the glymphatic system across different diseases.

Conclusion

The present research aimed at evaluating the coherence among the increasing corpus of studies reporting an alteration of the human glymphatic system in AD and PD. Results suggest that considerable strong evidence supports the actual capability of the DTI-ALPS technique to quantify the level of functioning of this brain apparatus. The straightforward replicability of the proposed approach could open the way to a systematic investigation of glymphatic impairment across neurological and neurodegenerative disorders.

Data availability

The data that support the findings of this study are available in the tables of the manuscript. Any further request can be addressed to Prof. Tommaso Costa.

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TC: Conceptualization, Methodology, Investigation, Formal Analysis, Software, Resources, Data curation, Writing - original draft, Writing - review & editing, Project administration, Funding acquisition. JM: Methodology, Investigation, Writing - original draft, Writing - review & editing. EP: Methodology, Writing - original draft, Writing - review & editing. IM: Writing - original draft, Writing - review & editing; LL: Data curation, Writing - original draft, Writing - review & editing. CBL: Data curation, Writing - original draft, Writing - review & editing. FC: Writing - review & editing. SD: Writing - review & editing; DL: Methodology, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization.

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Declarations

Competing interests
The authors declare no competing interests.

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