Association between glymphatic dysfunction and neurocognitive decline in patients with frontal lobe epilepsy

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Background: The glymphatic system is essential for the maintenance of brain homeostasis. It may be impaired in patients with epilepsy, but its association with neurocognitive function remains unknown. In this study, we aimed to elucidate the association between changes in the glymphatic system and neurocognitive function in individuals diagnosed with frontal lobe epilepsy (FLE).

Methods: This retrospective case-control research engaged a group of patients with FLE and age-, sex-, and education-matched healthy volunteers. All participants were subjected to extensive neurocognitive assessments, complemented by structural and diffusion-weighted imaging. The "diffusion tensor imaging analysis along the perivascular space" (DTI-ALPS) index was computed to ascertain differences in glymphatic system function between the groups. Univariate and multivariate analyses were conducted to explore associations between DTI-ALPS, clinical characteristics in patients with FLE, and the neurocognitive test outcomes for both groups.

Results: Twenty-five patients [mean age ± standard deviation (SD): 26.28±8.12 years, 10 females] with FLE and 22 healthy control (HC) participants (average age ± SD: 25.86±6.15 years, 11 females) were included. The average ALPS-index in FLE group was significantly lower than that in HC group (1.387±0.127 *vs.* 1.468±0.114, P=0.026). Further, significant neurocognitive difference was noted in Trail Making Test (TMT), Stroop Color and Word Test (SCWT), Digit Span Test (DST) and similarity test (ST) between the two groups. ALPS-index scores exhibited a negative correlation with disease duration in patients with FLE (r=−0.415, P=0.039), and positive correlations with the Forward Digit Span Test (FDST, r=0.399, P=0.005) and Similarity Test (ST, r=0.395, P=0.006) in both groups. After adjusting for potential confounders, DTI-ALPS maintained a significant independent association with FDST and ST.

Conclusions: The findings of the current study suggest a possible association between impairment in glymphatic function and FLE. Furthermore, results indicate that glymphatic dysfunction, as assessed via DTI-ALPS index, appears to be related to neurocognitive decline in FLE.

Introduction

As the second most prevalent form of focal epilepsy behind temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE) comprises approximately 20–30% of all epilepsy cases (1). Neurocognitive deficits, a primary comorbidity in epilepsy, have emerged as a significant concern, due to their substantial impact on quality of life in individuals with chronic symptoms (2). Unlike TLE, which has shown notable deficits in memory and language (3), the pattern of neurocognitive deficits in FLE is quite heterogeneous, displaying considerable variability in extant literature (4,5). Multiple cognitive impairments and abnormality in motor-related networks have been frequently observed, although instances of preserved cognitive function have also been documented (4,5). The mechanism underlying the alteration of neurocognitive functions in epilepsy remains to be elucidated. Intrinsic epilepsy factors, such as seizure severity (6), age of onset (7), disease duration (8), and the impact of medications (9), are believed to contribute to the observed dysfunction. Moreover, extrinsic factors may also exert influence, particularly in patients who are newly diagnosed with epilepsy and already exhibit neurocognitive alterations (2).

The glymphatic (glial-lymphatic) system, which functions as a cerebral metabolite waste drainage mechanism, is driven by arterial pulsation and flow, facilitated by the astroglial water channel, aquaporin 4 (AQP4). This system enables the exchange of cerebrospinal fluid (CSF) with interstitial fluid (ISF) and facilitates drainage of extracellular soluble proteins and metabolites through perivascular spaces into cervical lymphatic vessels (10,11). Recent research has underscored the role of the glymphatic system in the elimination of neurotoxic compounds, such as excitatory neurotransmitters and protein aggregates. Interestingly, dysfunction of the glymphatic system may also play a part in the pathogenesis of neurodegenerative diseases (12) and epilepsy (13).

Considering the three-dimensional tubular geometry of perivascular spaces, water molecule diffusion in these spaces has been hypothesized to be anisotropic. This can be non-invasively assessed using diffusion imaging techniques (14). For instance, Taoka *et al.* (15) introduced the "analysis along the perivascular space" (ALPS) method, employing diffusion tensor imaging (DTI) as a non-invasive tool to evaluate the glymphatic system in humans, with results corroborated by an animal study (16). Various disorders of the central nervous system (CNS), including Alzheimer's disease (AD) (15), mild cognitive impairment (MCI) (17), vascular cognitive impairment (VCI) (18), Parkinson's disease (19), and epilepsy (20-24), exhibit lower diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) indices, which have been significantly associated with the cognitive decline observed in these diseases (15,17,18). However, alteration in glymphatic function and its correlation with neurocognitive function in FLE is not well-defined. Our current study delves into differences in the DTI-ALPS index between patients with magnetic resonance imaging (MRI)-negative FLE and healthy controls (HCs), exploring the association between DTI-ALPS and clinical characteristics in FLE, and examining the neurocognitive performance in both groups. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-375/rc).

Methods

Participants

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and it was approved by institutional ethics committee of the Third Xiangya Hospital (No. I-22254). Informed consent was obtained from all participants and parents of the participants under 18 years old. From January 2019 to December 2020, 58 consecutive patients of FLE were prospectively included from Department of Neurology, the Third Xiangya Hospital, Central South University, Changsha, which is a major epilepsy center and tertiary hospital in China.

Diagnoses were established by expert neurologists through a thorough evaluation of clinical history, 24-hour
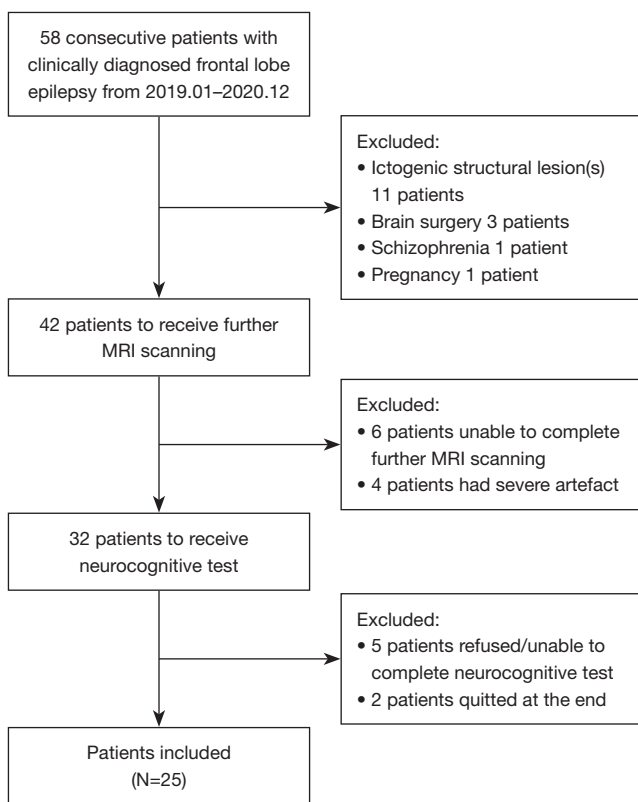
Figure 1 The flowchart of patient inclusion. MRI, magnetic resonance imaging; N, number.

video-electroencephalogram (EEG) recordings, ictal semiology, and routine MRI examinations, adhering to International League Against Epilepsy (ILAE) guidelines (25). The patients underwent 24-hour scalp video-EEG recordings (EEG-1200C, Nihon Kohden, Tokyo, Japan), including overnight sessions. The utilized 16 electrodes placed per the 10–20 international standard, with a sampling rate of 256 Hz. All patients were on anti-epileptic drug (AED) therapy and received regular outpatient follow-up. Exclusion criteria included ictogenic structural abnormality on routine cranial MRI examination, prior brain surgery, alcoholic and drug abuse, pregnancy, patients with any psychiatric and/or systemic disease that affects cognitive functions, and primary sensory or motor impairment that could adversely affect the neurocognitive performance. All participants underwent further MRI examination and thorough neurocognitive tests, and those who refused to and/or were unable to finish the examinations were also excluded. Finally, the current study included 25 patients with FLE (age range, 14–45 years; mean age ± standard deviation (SD): 26.28±8.12 years, 10

females), and the flowchart was shown in *Figure 1*.

A group of 22 HC participants (age range, 17–38 years; average age ± SD: 25.86±6.15 years, 11 females), matched for age, sex, and education, were also recruited. All participants in the HC group had normal routine cranial MRI, without any history of neuro-psychiatric disorders and without alcohol or drug abuse.

Clinical information

Comprehensive clinical details were collected for each patient with FLE, including age at epilepsy onset, illness duration, varieties of epileptic seizures experienced, initial and follow-up EEGs, medication strategies, and the frequency of seizure episodes following treatment commencement. Severity of epilepsy was appraised using the National Hospital Seizure Severity Scale (NHS3) (26), which is a measure incorporating seven seizure-related factors, with a scoring range from 1 to 27. Post-treatment seizure attack frequency for each patient was systematically evaluated based on the criteria established by the ILAE scale (27).

Neuropsychological testing

All participants received a thorough neuropsychological evaluation, either during their hospital stay for seizure characterization or in an outpatient setting. Only the initial neuropsychological assessment was utilized for each patient. The evaluation comprised several tests (28): (I) Forward/Backward Digit Span Test (FDST/BDST), which assessed verbal working memory through two subtests; in the FDST, participants repeated a sequence of digits after hearing them, ending when the maximum sequence length was achieved or after two consecutive errors, while the BDST required reciting the digit sequence in reverse. (II) The Visual Recognition Task evaluated visual-spatial memory by having participants recall eight cards from a set of 28, including various graphics, Chinese characters, and mathematical symbols. (III) The Logical Memory Task measured verbal episodic memory, where participants recounted details from two stories immediately after they were read by the experimenter. (IV) The Trail Making Test (TMT), with Trails A (TMT-A) assessing basic speeded sequencing and Trails B (TMT-B) measuring divided visual attention and cognitive flexibility, involved connecting series of numbers and alternating between numbers and letters, respectively. Performance was scored based on

completion time and error count. (V) Stroop Color and Word test (SCWT) assessed cognitive flexibility and the efficiency of the inhibitory process in the frontal lobe by having participants read characters, name colors, and name a color not matching the character as soon as possible, respectively. (VI) The similarity test (ST) examined higher-order executive functions, like abstract thinking and concept formation, requiring participants to identify similarities between pairs of words. Depressive and anxiety symptoms in all participants were assessed using the Beck Depression and Anxiety Inventories, respectively (28). In order to reduce confounding factors, participant with severe intelligence impairment was excluded by a rough estimation of ST and picture completion of Chinese version Wechsler Adult Intelligence Scale (WAIS-RC) (29,30).

Image acquisition

MRI data acquisition was conducted using a 3.0 T MRI scanner (Ingenia, Philips Medical Systems, Netherlands) equipped with a 15-channel receiver array head coil. Participants were instructed to lie still. To enhance image quality, earplugs were provided to reduce scanner noise and foam pads were utilized to limit head movement.

Structural imaging involved a three-dimensional turbo fast echo (3D-TFE) T1WI sequence to capture high-resolution images. The parameters were set as follows: repetition time (TR)/echo time (TE) =9.1/4.5 ms; number of slices =170; slice thickness =1 mm with no gap; flip angle =8°; acquisition matrix =256×256; and field of view (FOV) =240 mm × 240 mm.

For diffusion-weighted imaging, a single-shot gradient echo planar imaging (EPI) sequence was employed with these specific parameters: TR =6,578 ms; TE =85 ms; flip angle =90°; FOV =240 mm × 240 mm; voxel size =2.5×2.5×2.5 mm. The protocol included 32 volumes with noncollinear diffusion directions at a b value of 1,000 s/mm² and one volume with a b value of 0, encompassing a total of 60 slices.

DTI data preprocessing

Careful evaluation of artifacts in all diffusion-weighted images was initially conducted by K.Z. and L.D., two senior neuroradiologists and experienced analysts, focusing on various aspects, such as total geometric distortion, signal loss, and volume motion. Subsequently, the origin positions of all diffusion-weighted images were adjusted to ensure

accuracy. The preprocessing of diffusion-weighted images for all participants was conducted via the FMRIB Software Library (FSL) Package 6.0.1, accessible at (http://www.fmrib.ox.ac.uk/fsl) (31).

During preprocessing, non-brain voxels were removed utilizing the Brain Extraction Tool (BET) within FSL. Further, motion and eddy current corrections were performed using the same software suite. The refined data was then processed through DTI fitting, using FSL's diffusion toolbox, facilitating the generation of fractional anisotropy (FA) and tensor 4D maps.

These processes enabled the creation of individual diffusivity maps for each participant. Diffusivity maps were generated in three primary directions: the x-axis (right-left, denoted as Dxx), y-axis (anterior-posterior, Dyy), and z-axis (inferior-superior, Dzz), thus providing a comprehensive analysis of diffusion properties across different brain regions.

Total intracranial volume (TIV) was estimated on 3D-TFE T1 data using Statistical Parametric Mapping (SPM)'s three region (gray matter, white matter, and CSF) segmentation, and TIV value was obtained by adding up the volume of gray matter, white matter, and CSF.

ALPS-index calculation

The ALPS index, which is indicative of glymphatic function, is based on water diffusion dynamics in white matter near the lateral ventricle body, primarily from perivascular spaces of medullary veins and white matter fiber tracts (e.g., projection and association fibers), as shown in *Figure 2*. The perpendicular orientation of these medullary veins to both the lateral ventricle wall and fiber tract enables precise analysis of perivascular water diffusivity.

Adhering to methodologies established by Zhang *et al.* (17) and Song *et al.* (18), the DTI-ALPS index was calculated. Diffusivity maps in the x- (Dx), y- (Dy), and z-axis (Dz) were obtained for each subject using FSL, and co-plotted to the standard FA map template in the ICBM DTI-81 Atlas. Given the consistent orientation of medullary veins, region of interest (ROI) placement relied solely on DTI images. Four 5 mm-diameter spherical ROIs were placed on projection and association fibers in the uppermost layer of the lateral ventricle body. ROIs were manually adjusted as necessary to ensure accuracy and avoid non-specific lesions. The ALPS-index, representing the ratio of perivascular space water diffusivity (Dx_projc, Dx_assoc) to diffusivity in non-aligned directions (Dy_proj, Dz_assoc),
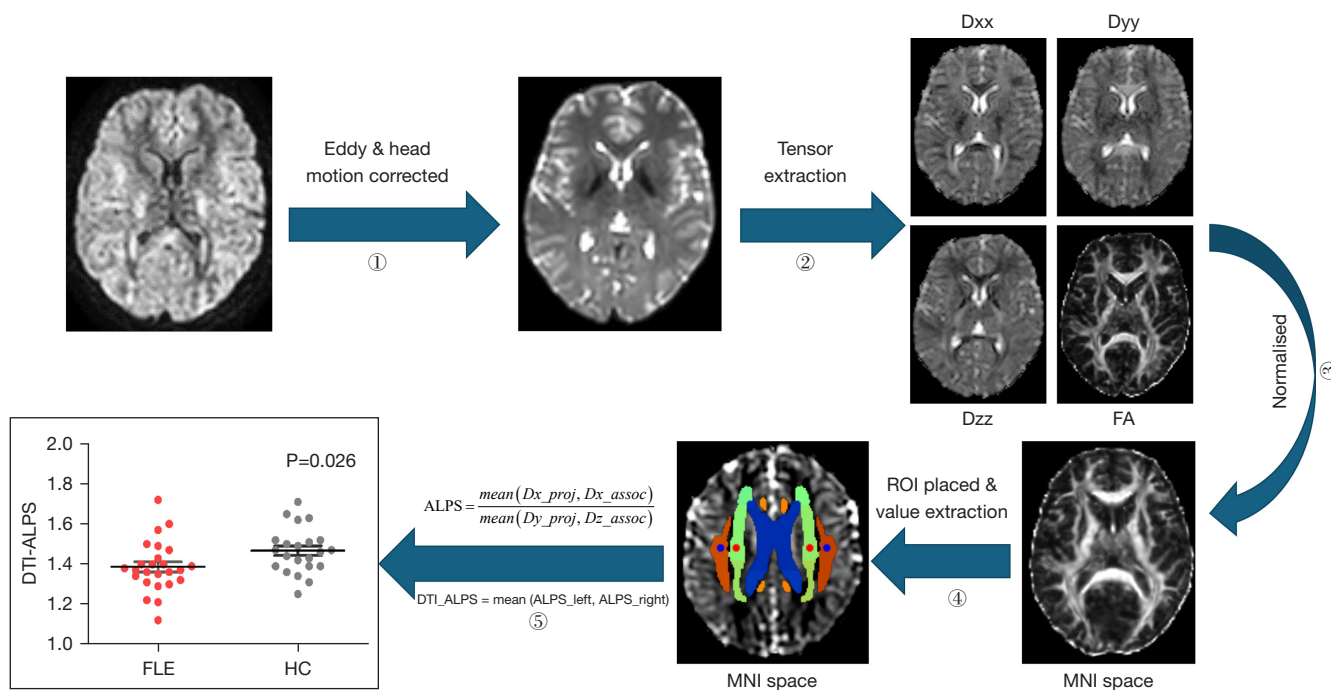
Figure 2 Data processing and DTI-ALPS index calculation process. ① All DTI images were eddy and head motion corrected in FSL toolbox; ② FA maps and diffusivity maps of each subject were then obtained using FSL software in the direction of the x-axis (right-left; Dxx), y-axis (anterior–posterior, Dyy), z-axis (inferior superior, Dzz). ③ The ICBM DTI-81 Atlas was used as a reference to normalize the FA map and triaxial diffusivity to MNI space. ④ Four spherical ROIs were placed on the projection fibers and association fibers in the uppermost layer of the lateral ventricle body. ⑤ The mean of the bilateral DTI-ALPS-index represented the overall glymphatic function of the subjects. FA, fractional anisotropy; MNI, Montreal Neurological Institute; ROI, region of interest; ALPS, analysis along the perivascular space; DTI, diffusion tensor imaging; FLE, frontal lobe epilepsy; HC, healthy control; FSL, FMRIB Software Library.

quantifies glymphatic function.

$$ALPS\text{-}index = \frac{mean(Dx\_proj, Dx\_assoc)}{mean(Dy\_proj, Dz\_assoc)} \qquad [1]$$

The bilateral ALPS-index average served as a composite measure, representing the overall glymphatic function across subjects.

Statistical analyses

SPSS Statistics version 23.0 (IBM Corporation) was used to analyze data. Quantitative variables were expressed as mean ± standard deviation. Categorical variables were expressed as percentages [n (%)]. In order to measure inter-group difference, two-sample t-tests, Mann-Whitney U tests, and Fisher's/chi-square tests were used for normally distributed quantitative, non-normally distributed quantitative, and categorical variables, respectively. False discovery rate

(FDR) correction was performed for between-group two-tailed comparison of neurocognitive test results. Pearson's and Spearman's correlations were used to assess variable relationships for normally- and non-normally distributed variables respectively. A linear regression model with forward selection was used to evaluate associations with multiple cognition variables, including those significant in univariate logistic regression ($P<0.1$) or otherwise clinically relevant. Variance inflation factors (VIF) confirmed no multicollinearity (VIF <3). Statistical significance was set at $P<0.05$.

Results

Clinical characteristics and neurocognitive test results

Table 1 presents a detailed demonstration of the demographic information and neurocognitive test outcomes for all participants. The mean disease duration among the enrolled

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Table 1 Demographic, clinical, and neuropsychological test differences between FLE and HC groups

Clinical characteristics	FLE patients (n=25)	HC (n=22)	P value
Age at examination/year, mean ± SD	26.28±8.12	25.86±6.15	0.853
Sex: male, N [%]	15 [60]	11 [50]	0.487
Education (year), mean ± SD	12.72±2.70	14.23±2.94	0.074
Disease duration (year), mean ± SD	6.24±5.89		
Localization (left/right/bilateral/unknown), n	3/6/16/0		
Seizure frequency (grade 0/1/2/3), n	6/12/0/7		
Medication (mono/multi-medication), n	20/5		
Neurocognitive test[†], mean ± SD			
TMT-A time (sec)	41.24±16.06	39.50±17.85	0.283
TMT-A error	0.12±0.33	0.09±0.43	0.268
TMT-B time (sec)	106.48±34.52	82.91±27.82	0.035*
TMT-B error	0.80±1.38	0.14±0.35	0.028*
SCWT average time (sec)	49.69±20.37	37.59±10.78	0.027*
SCWT average error	1.48±2.81	1.00±2.14	0.057
FDST	8.20±1.55	9.36±1.05	0.025*
BDST	5.48±1.74	6.23±1.69	0.080
ST	9.60±2.96	11.50±2.50	0.029*
Visual recognition	9.96±2.85	11.18±3.19	0.089
Logical memory task	8.54±2.82	9.91±2.53	0.056
Beck anxiety inventory	30.12±7.75	29.02±8.02	0.271
Beck depression inventory	9.16±5.84	6.68±7.49	0.096

*, P<0.05 was considered statistically significant; [†], for between-group comparison of neurocognitive test results, FDR correction was performed. FLE, frontal lobe epilepsy; HC, healthy control; SD, standard deviation; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; SCWT, Stroop Color Word Test; FDST, Forward Digit Span Test; BDST, Backward Digit Span Test; ST, similarity test; FDR, false discovery rate.

patients was recorded at 6.24±5.89 years, with a predominant manifestation of bilateral scalp EEG anomalies. When examining the neurocognitive performance disparities between the groups, it was noted that the scores in both the ST and FDST were significantly lower in the FLE group. Comparing to HC group, time to complete TMT-B was significantly longer with slightly but significantly more errors Moreover, the FLE group exhibited a substantial increase in the average completion time for the SCWT, although there was no marked difference in accuracy between the two groups. Furthermore, analysis revealed no significant divergence in levels of anxiety, depression, visual recognition abilities, or performance on the TMT-A

between patients with FLE and HCs.

Difference in DTI-ALPS index between FLE and HC groups

A statistically significant difference was evident with the DTI-ALPS index averaging 1.387±0.127 in the FLE group, in contrast to 1.468±0.114 in HCs (P=0.026). The 95% confidence interval for this disparity ranged from 0.010 to 0.151, with the test statistic t-value being 2.299, as illustrated in *Figure 3*. In addition, TIV was not significantly different between the two groups (mean ± SD: 1,493±138 mL in FLE *vs.* 1,481±164 mL in HCs group, two-tailed
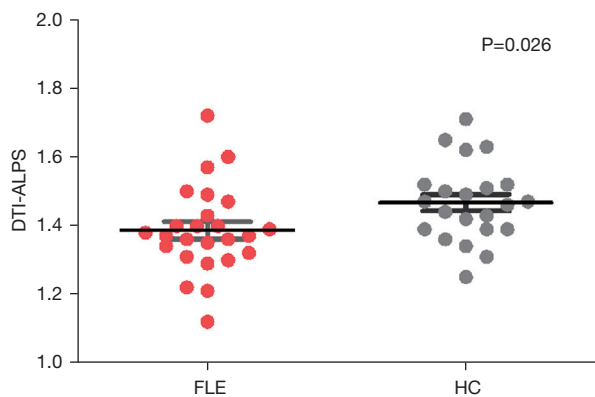
Figure 3 Comparison of DTI-ALPS index between FLE and HC groups. The error bars indicated standard deviation. DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; FLE, frontal lobe epilepsy; HC, healthy control.

P=0.79).

Association of DTI-ALPS with clinical and neurocognitive results

DTI-ALPS index demonstrated a significant correlation with disease duration in the FLE group (r=−0.415, P=0.039), as depicted in *Figure 4A*. Furthermore, this index was also significantly associated with performance in the ST (r=0.395, P=0.006) and FDST (r=0.399, P=0.005), across both groups, as illustrated in *Figure 4B,4C*. In the multivariate analysis, after adjusting for age, sex, education level, total cerebral volume, and disease duration, the DTI-ALPS index was found to be significantly related to the FDST and ST scores in both groups, as detailed in *Table 2*.

Discussion

The current study investigated differences in glymphatic function, as indicated by the DTI-ALPS index, and cognitive capabilities between patients with FLE and a group of age-, sex-, and education-matched HCs. Our findings revealed that the FLE group exhibited a significantly reduced ALPS-index and lower scores in tests of neurocognitive function when compared to the HC group. Additionally, the ALPS-index showed a significant correlation with the results of neurocognitive tests in both groups, particularly with FDST and ST scores. These results suggest that the functionality of the glymphatic system may be a contributing factor to cognitive dysfunction
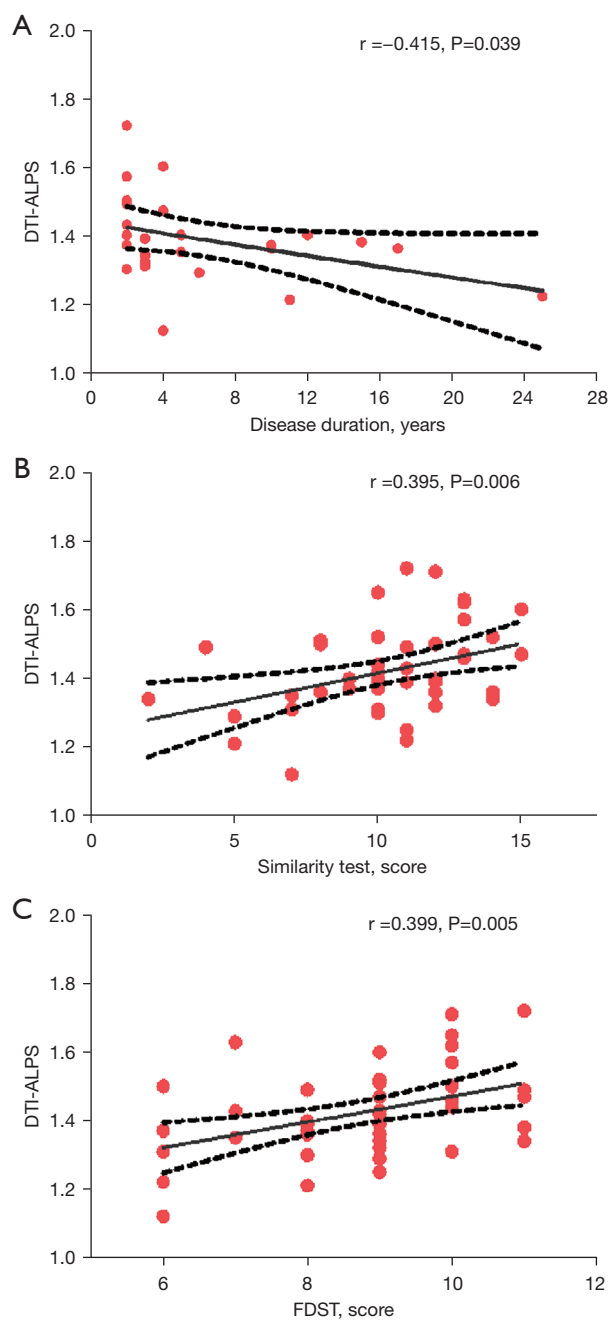

Figure 4 Correlation between DTI-ALPS index and clinical or neuropsychological test scores. DTI-ALPS index was significantly correlated with (A) disease duration, (B) similarity test and (C) FDST. DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; FDST, Forward Digit Span Test.

in patients with FLE.

Compared to tracer methodologies, the DTI-ALPS technique, developed by Taoka *et al.* (15), enables a non-

Table 2 Univariate and multivariate linear regression analyses of the association between DTI-ALPS index and neurocognitive function

DTI-ALPS	Model 1			Model 2			Model 3		
	R^2	Beta	P	R^2	Beta	P	R^2	Beta	P
ST	0.148	0.385	0.008	0.362	0.279	0.042	0.276	0.525	0.007
FDST	0.186	0.431	0.003	0.270	0.285	0.044	0.254	0.534	0.006

Model 1, unadjusted; Model 2, adjusted for age, sex, education, TIV; Model 3, adjusted for age, sex, education. DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; ST, similarity test; FDST, Forward Digit Span Test; TIV, total intercranial volume.

invasive examination of glymphatic clearance function without the need for contrast administration. This method has gained widespread use for the study of diverse neurological disorders (17-23). However, findings regarding glymphatic function impairment in epilepsy, as indicated by the ALPS-index, have been inconsistent. A decrease in ALPS has been observed in generalized (20) and focal (22) epilepsy, as well as status epilepticus (23), while improvements have been observed in surgically treated individuals with TLE and a favorable prognosis (21). Conversely, some study has reported no significant differences in ALPS metrics (24) in newly diagnosed focal epilepsy compared to HCs. In our study, a markedly lower ALPS was observed in patients with FLE, and ALPS index scores were significantly correlated with disease duration, but not with attack frequency or NHS3 score. This discrepancy in findings could be attributed to variations in patient selection, suggesting that disease duration in epilepsy may contribute to glymphatic impairment.

Our study also identified a mild, yet significant decline in both executive function and memory in FLE patients, as shown by significantly lower FDST and ST scores, along with higher duration and error counts in the TMT-B test in the FLE group. Consistent with previous studies (4,5,32,33), these outcomes indicate that FLE patients may experience impairments across multiple neurocognitive domains, including basic and complex attention, working memory, semantic memory, and executive function. However, we found that the ALPS index was significantly associated only with FDST and ST scores in both FLE and HC groups. The DST assesses aspects of working memory maintenance, while the ST is an effective measure of memory performance, possibly due to its semantic encoding strategy, which enhances memory retention compared to simpler repetition strategies (34). Both tests are also effective in evaluating attention, which is closely linked to memory performance. Hence, we speculate that a decrease in the DTI-ALPS index may contribute to memory impairments

in FLE.

Memory impairment has been observed in both pediatric and adult patients with FLE (32,33), ranging from mild encoding and retrieval difficulties in working memory, to more significant long-term memory issues; however, these memory difficulties have been observed less consistently in individuals with FLE than in individuals with TLE. Memory-task functional magnetic resonance imaging (fMRI) studies (35,36) have also revealed divergent activation patterns in patients with FLE, suggesting memory reliance on a network encompassing both the temporal and frontal lobes, rather than confined to specific brain structures, such as the medial temporal lobes. However, the heterogeneity in memory impairment patterns implies additional mechanisms beyond seizure propagation from the focal seizure onset area(s) and/or remote functional deficit zone(s). Given that short-term memories necessitate increased pre-synaptic glutamate release and changes in postsynaptic glutamatergic receptor activity (37,38), mediated by covalent modifications of existing proteins at preexisting synapses (39,40), glymphatic dysfunction could interfere with neurotransmitter clearance and associated neurocognition processes. In addition, neurocognitive adverse events related to anti-seizure medication (ASM) was also reported (41), and epilepsy duration and ASM administration duration may be the major risk factor (42). Thus, we postulate that glymphatic clearance system may also play a role in maintaining neurocognitive function in patients with FLE, but this certainly warrants further research for validation.

DTI-ALPS calculation is based on FA values. Previous studies (43,44) have shown that a decrease in FA in frontal and extra-frontal regions is significantly associated with cognitive alterations. Combined with our findings, it is plausible that a decrease in FA may indicate impairment in both white matter fiber integrity and in the micro-environment of the interstitial space. However, since the periventricular region of the glymphatic system, measured

by DTI-ALPS, is predominantly located in the frontal lobe, it remains unclear whether DTI-ALPS is more susceptible to changes in frontal lobe function and whether glymphatic system function in other regions would also be associated. Additionally, the potential impact of sampling bias cannot be excluded, as the majority of participants in our study exhibited bilateral EEG abnormalities, suggesting either more extensive involvement of epileptogenic foci, or a greater propensity for bilateral propagation of epileptiform discharges.

The current study possesses some limitations that warrant discussion. First, the relatively small sample size and the cross-sectional nature of the data do not allow for the establishment of a causal relationship between lower DTI-ALPS and cognitive decline in FLE. This aspect may be more effectively explored in future studies. Additionally, as all participants were drawn from the same region within Changsha, China, the potential for sampling bias necessitates caution when generalizing the current findings. Second, while DTI-ALPS effectively isolates perivascular glymphatic diffusivity, the measurement is predominantly based on diffusion alterations parallel to the x-axis in frontoparietal region. It does not directly reflect glymphatic flow along other axes or glymphatic alterations in other brain regions, such as the nigrostriatal pathway. Therefore, future research with a larger sample size and multimodal assessment approaches should be conducted in epilepsies of other pathologies. Specifically, advances in MRI technology may eventually enable noninvasive glymphatic measurements across various anatomical structures, further enriching our understanding of this complex system.

Conclusions

Results of the current investigation revealed that the functionality of the glymphatic system may be compromised in individuals diagnosed with FLE, as evidenced by alterations in the DTI-ALPS index. Furthermore, a substantial correlation was established between DTI-ALPS index and diminished neurocognitive function. This finding suggests that glymphatic clearance mechanisms may be integral to the understanding of neurocognitive impairments associated with epilepsy. Consequently, the DTI-ALPS index is beginning to emerge as a pivotal biomarker, potentially playing a crucial role in the future exploration and understanding of the interplay between epilepsy and neurocognitive function.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-375/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-375/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of the Third Xiangya Hospital (No. I-22254) and informed consent was taken from all participants and parents of the participants under 18 years old.

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