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Glymphatic System Dysfunction Underlying Schizophrenia Is Associated With Cognitive Impairment

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***Background and Hypothesis*: Despite the well-documented structural and functional brain changes in schizophrenia, the potential role of glymphatic dysfunction remains largely unexplored. This study investigates the glymphatic system's function in schizophrenia, utilizing diffusion tensor imaging (DTI) to analyze water diffusion along the perivascular space (ALPS), and examines its correlation with clinical symptoms. *Study Design*: A cohort consisting of 43 people with schizophrenia and 108 healthy controls was examined. We quantified water diffusion metrics along the *x*-, *y*-, and *z*-axis in both projection and association fibers to derive the DTI-ALPS index, a proxy for glymphatic activity. The differences in the ALPS index between groups were analyzed using a 2-way ANCOVA controlling for age and sex, while partial correlations assessed the association between the ALPS index and clinical variables. *Study Results*: People with schizophrenia showed a significantly reduced DTI-ALPS index across the whole brain and within both hemispheres ($F = 9.001$, $P = .011$; $F = 10.024$, $P = .011$; $F = 5.927$, $P = .044$; false discovery rate corrected), indicating potential glymphatic dysfunction in schizophrenia. The group by cognitive performance interaction effects on the ALPS index were not observed. Moreover, a lower ALPS index was associated with poorer cognitive performance on specific neuropsychological tests in people with schizophrenia. *Conclusion*: Our study highlights a lower ALPS index in schizophrenia, correlated with more pronounced cognitive impairments. This suggests that glymphatic dysfunction may contribute to the pathophysiology of schizophrenia, offering new insights into its underlying mechanisms.**

Key words: schizophrenia/glymphatic system/DTI-ALPS/cognitive impairment

Introduction

Schizophrenia is a psychiatric disorder characterized by psychosis, negative symptoms, and cognitive impairment, leading to significant functional disabilities and a reduced quality of life.[1,2] It affects about 1% of the general population and has an enormous impact in terms of suffering, disability, and healthcare costs.[3] This disease has been recognized as a "dysconnectivity" syndrome, indicating a failure to coordinate and process information across different brain regions.[4,5] The pathophysiological mechanisms of this disease remain largely elusive. It is urgent to investigate the underlying neural basis with an aim to develop potential treatment strategies.

The glymphatic system is a well-structured waste clearance pathway that removes soluble proteins from the brain.[6,7] Within the perivascular channels formed by astrocytes, the cerebrospinal fluid enters through the periarterial space, traverses the brain parenchyma with the assistance of aquaporin-4 (AQP4) channels of astrocytic end-feet, which are the most essential part of the glymphatic system, control cerebral water balance, and exchanges with interstitial fluid outflowing toward the perivenous space.[6,8] Consequently, impairment of the glymphatic system has been associated with neurodegenerative disorders characterized by abnormal protein aggregation, such as Alzheimer's disease and Parkinson's disease.[8–11]

Recent evidence implicates an important role for AQP4 in schizophrenia. A schizophrenia-like behavior mouse model shows higher expression of AQP4 channels in the prefrontal cortex and hippocampus.[12] Bioinformatics analyses have revealed alterations in cerebral AQP4 gene expression, and there is a significant correlation between the expression of AQP4 genes and the presence of immune infiltrating cells in individuals with schizophrenia.[13] Wu et al[14] elucidated the correlation between AQP4 gene polymorphisms and schizophrenia in the Southern Han Chinese population.

Most initial studies on human glymphatic drainage have primarily utilized dynamic contrast-enhanced magnetic resonance imaging, which involves the injection of gadolinium-based contrast agents either intrathecally or intravenously.[15–18] However, intrathecal contrast agent injection is an invasive procedure and is restricted in some countries, although it can demonstrate delayed clearance of the agent as an indication of glymphatic dysfunction.[19] Additionally, the administration of gadolinium-based contrast agents into the cerebrospinal fluid or repeated intravenous injections can result in the deposition of gadolinium in the brain.[20,21] Considering these potential risks, it is preferable to assess glymphatic function without the use of contrast agents, especially for people with progressive neurodegenerative and psychiatric diseases.

Herein, we aimed to investigate the function of the glymphatic system in people with schizophrenia using diffusion tensor imaging (DTI) analysis along the perivascular space (ALPS).[22–24] The advantage of DTI-ALPS is that it allows us to assess glymphatic activity without the need for intravenous or intrathecal contrast agent injections. Previous research has demonstrated a correlation between glymphatic function assessed with DTI-ALPS and direct intrathecal tracer-based measurements in humans.[19,25,26] Traditional DTI measures, such as fractional anisotropy (FA) and mean diffusivity, are established indicators of white matter integrity.[27] The DTI-ALPS index distinguishes itself by providing complementary information to these traditional DTI measures. This is particularly useful in enhancing our understanding of neurodegenerative diseases and other conditions where glymphatic dysfunction is implicated.

Given the link between AQP4 and schizophrenia, we hypothesize that changes in glymphatic function, particularly reductions in the DTI-ALPS index, are pivotal in the development of schizophrenia. Thus, our objective was to assess the glymphatic system's performance in people with schizophrenia using the DTI-ALPS index and explore its connection to clinical variables.

Methods

Participants

The study utilized data from the University of California, Los Angeles (UCLA) Consortium for Neuropsychiatric Phenomic LA5c Study via OpenNeuro, accession number ds000030.[28] The potential population consisted of 49 people with schizophrenia and 123 healthy controls (HCs). The dataset included a wealth of phenotypic information on neuropsychological assessments and neuroimaging data. Diffusion-weighted imaging (DWI) data were not available for 8 participants (1 person with schizophrenia and 7 HCs). Visual inspection of the DWI revealed that 13 participants (5 people with schizophrenia and 8 HCs) had corrupted volumes and/or ghost images in their DWI data, rendering them unsuitable for further analysis. As a result, the final sample consisted of 43 people with schizophrenia and 108 HCs. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of UCLA. All participants provided written informed consent.

Clinical Assessment

The severity of the clinical symptoms in the schizophrenia group was assessed using the following clinical scales: the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the Young-Mania Rating Scale (YMRS), the Hamilton Psychiatric Rating Scale for Depression (HAMD), and the Brief Psychiatric Rating Scale (BPRS).[29–32] For the BPRS, a 4-factor solution (positive symptoms, negative symptoms, manic-hostility, and anxiety-depression) was used to categorize the symptom items.[33] Cognitive functioning was evaluated using the California Verbal Learning Test-Second edition (CVLT-II) and Wechsler Memory Scale-Revised (WMS-R).[34,35]

MRI Acquisition Parameters

The images were acquired using a Siemens Trio 3T MRI scanner. The parameters for the high-resolution T_1-weighted anatomical scan included: slice thickness = 1 mm; 176 slices; repetition time (TR) = 1900 ms; echo time (TE) = 2.26 ms; matrix = 256 × 256; and field of view = 250 × 250 mm. The parameters of the DWI were as follows: slice thickness = 2 mm; 64 directions; TR/TE = 9000/93 ms; flip angle = 90°; matrix = 96 × 96; axial slices, b = 0 and 1000 s/mm^2.

DTI-ALPS Processing

The DWI data underwent the following preprocessing steps: (1) denoizing using Marčenko-Pastur principal component analysis[36]; (2) Gibbs-ringing artifact removal[37]; (3) motion and distortion artifact correction[38]; and (4) bias field correction. The bias field was first calculated from b = 0 in the DWI image and then utilized to correct all DWI images.[39] Diffusivity maps in the direction of the x-axis (Dxx), y-axis (Dyy), and z-axis (Dzz) and FA were calculated by using MRtrix3 (version 3.0.3).[40] The corona radiata projection and the superior longitudinal

Table 1. Demographic Variables and Clinical Characteristics of All Participants

	SZ, n = 43	HC, n = 108	Statistical Tests	
			t/χ^2	P
Demographic data				
Age (y)	36.53 ± 9.11	31.76 ± 8.87	2.962	.004
Gender [male, n (%)]	32 (74.4%)	53 (49.1%)	8.029	.005
Symptom				
SAPS global score	1.49 ± 0.91			
SANS global score	1.85 ± 0.97			
YMRS total score	8.42 ± 6.41			
HAMD total score	9.58 ± 7.82			
BPRS score				
Positive	2.80 ± 1.15			
Negative	1.80 ± 0.75			
Manic-hostility	1.74 ± 0.71			
Anxiety-depression	2.51 ± 1.28			
CVLT-II				
Trials 1–5 total score	40.36 ± 9.75	56.72 ± 7.82	9.721	<.001
Short-delay free recall	8.09 ± 3.73	12.78 ± 2.31	7.660	<.001
Short-delay cued recall	8.28 ± 3.79	12.78 ± 2.31	7.255	<.001
Long-delay free recall	8.86 ± 3.21	13.14 ± 2.22	8.003	<.001
Long-delay cued recall	9.53 ± 3.24	13.66 ± 1.95	7.787	<.001
Long-delay recognition trial (total hits)	14.00 ± 1.87	15.31 ± 1.14	4.284	<.001
Long-delay recognition trial (total false positives)	5.12 ± 5.62	1.31 ± 2.39	−4.281	<.001
WMS				
Visual Reproduction Total Score	53.05 ± 18.80	70.06 ± 12.48	5.472	<.001
Symbol Search Total Score	16.72 ± 5.50	25.44 ± 6.54	7.707	<.001
Digit Span Total Score	22.56 ± 4.78	30.10 ± 5.92	7.439	<.001

Note: BPRS, Brief Psychiatric Rating Scale; CVLT-II, California Verbal Learning Test—second edition; HAMD, Hamilton Psychiatric Rating Scale for Depression; HC, healthy control; SANS; Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SZ, schizophrenia; YMRS, Young-Mania Rating Scale; WMS, Wechsler Memory Scale.

fasciculus were used to represent the projection and association fibers, respectively, for the ALPS index calculation.[23] The 5–mm-thickness masks were generated at the lateral ventricle body level for both fiber regions, using the JHU atlas (ICBM labels 2 mm).[41] Regions of interest were set on both cerebral hemispheres, and the average values were computed.

Transformation matrices were derived between the Montreal Neurological Institute (MNI)-152 spaces and individual 3D T1WI images, and between 3D T1WI and FA images. The combined transformation matrix was used to convert the MNI-152 spaces (JHU atlas masks) into FA native spaces. With this combined matrix, diffusivity values were registered in the x, y, and z directions for projection fibers and association fibers, labeled as Dxxproj, Dyyproj, Dzzproj, Dxxassoc, Dyyassoc, and Dzzassoc. The ALPS index was computed as ([mean(Dxxproj + Dxxassoc)/mean(Dyyproj + Dzzassoc)]).[23] We calculated the ALPS indices for both the left and right hemispheres, as well as the mean ALPS index for each hemisphere.

Statistical Analysis

Statistical analyses were conducted using R software (version 3.0.2). To assess the normality of distribution, we employed the Shapiro-Wilk test. For between-group comparisons, we utilized the 2-sample independent t-test or the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, as deemed appropriate. To examine the effects of group, cognitive performance, and their interactions in ALPS, 2-way ANOVA was used. Group (schizophrenia vs HCs), cognitive performance served as factors, and age and sex served as covariates. Multiple comparison correction was performed using the false discovery rate (FDR) method. Additionally, exploratory partial correlation analyses were undertaken to investigate the relationship between the ALPS index and various clinical parameters, with adjustments made for age and sex (uncorrected). Significance was set at P values less than .05 (2-sided).

Results

Clinical Characteristics

Demographic and clinical data characteristics of people with schizophrenia and HCs are provided in table 1. People with schizophrenia displayed significantly older age (t = 2.96, P = .004) and a higher proportion of males (χ^2 = 8.03, P = .005) compared with

HCs. The people with schizophrenia recalled fewer words correctly than HCs on CVLT-II trials 1–5 total score (40.4 ± 9.75 vs 56.7 ± 7.82, $t = 9.721$, $P < .001$). Similarly, the people with schizophrenia showed lower levels of short-delay free recall, short-delay cued recall (8.1 ± 3.73 vs 12.8 ± 2.31, $t = 7.660$, $P < .001$; 8.3 ± 3.79 vs 12.8 ± 2.31, $t = 7.255$, $P < .001$) and long-delay free recall, long-delay cued recall (8.9 ± 3.21 vs 13.1 ± 2.22, $t = 8.003$, $P < .001$; 9.5 ± 3.24 vs 13.7 ± 1.95, $t = 7.787$, $P < .001$). People with schizophrenia performed significantly worse than HCs on the long-delay recognition trial (14.0 ± 1.87 vs 15.3 ± 1.14, $t = 4.284$, $P < .001$). All 3 indices of the WMS-R were significantly lower in people with schizophrenia than in HCs (Visual Reproduction Total Score: 53.1 ± 18.80 vs 70.1 ± 12.48, $t = 5.472$, $P < .001$; Symbol Search Total Score: 16.7 ± 5.50 vs 25.4 ± 6.54, $t = 7.707$, $P < .001$; Digit Span Total Score: 22.6 ± 4.78 vs 30.1 ± 5.92, $t = 7.439$, $P < .001$).

Main Effects of Group Factor

As shown in table 2 and Figure 1, the DTI-ALPS index of the left hemisphere, right hemisphere, and whole brain was significantly lower in people with schizophrenia compared with controls after controlling for age and sex ($F = 9.001$, $P = .011$; $F_{(1,148)} = 10.024$, $P = .011$; $F_{(1,148)} = 5.927$, $P = .044$, FDR corrected, respectively). The diffusivities along the *x*-axis of the projection fiber in the left hemisphere were lower in people with schizophrenia than that in HCs ($F = 9.155$, $P = .011$, FDR corrected).

Group × Cognitive Performance Interaction Effects

As shown in table 3, we did not observe significant interaction effects between group status and cognitive performance on the DTI-ALPS index.

Correlation Between the DTI-ALPS Index and Clinical Characteristics

We found that the global ALPS index demonstrated significant correlations with cognitive performance measures, specifically the Symbol Search and Digit Span Total Scores, with correlation coefficients of 0.311 ($P = .048$) and 0.345 ($P = .031$), respectively. Furthermore, when focusing on the right hemisphere, the DTI-ALPS index showed significant associations not only with the aforementioned cognitive tests but also with the trials 1–5 total score, yielding correlation coefficients of 0.311 ($P = .034$), 0.323 ($P = .039$), and 0.311 ($P = .048$), respectively (table 4 and figure 2). Initially, our exploratory correlation analyses between DTI-ALPS metrics and clinical indicators did not apply a multiple comparison correction; we subsequently applied the FDR correction to these analyses. Unfortunately, after this adjustment, the results did not reach statistical significance ($P > .05$).

We did not observe a significant correlation between age and the DTI-ALPS index when analyzing the schizophrenia and HC groups separately. However, upon combining the data from both groups, a negative correlation emerged, suggesting that the DTI-ALPS index decreases with age across the entire study population ($r = -.215$, $P = .008$, table 5).

Discussion

In the present investigation, we utilized the DTI-ALPS index, derived from a noninvasive diffusion-based methodology, to evaluate glymphatic function in individuals with schizophrenia, who exhibit various levels of sleep disturbances and cognitive deficits. Our findings reveal a reduced glymphatic function in these individuals compared to HCs. Interestingly, we found no significant interaction effects between group status and cognitive performance on the DTI-ALPS index.

Table 2. Group Comparisons of ALPS Index

	SZ, $n = 43$	HC, $n = 108$	Statistical Tests		
			F	*P*	*P* (FDR Corrected)
ALPS	1.33 (0.11)	1.46 (0.18)	9.001	0.003	.011
ALPS_L	1.32 (0.12)	1.46 (0.19)	10.024	0.002	.011
ALPS_R	1.34 (0.13)	1.45 (0.20)	5.927	0.016	.044
x_projection_L ($\times 10^{-3}$ mm^2/s)	0.58 (0.04)	0.62 (0.07)	9.155	0.003	.011
x_association_L ($\times 10^{-3}$ mm^2/s)	0.69 (0.06)	0.73 (0.07)	4.953	0.028	.051
y_projection_L ($\times 10^{-3}$ mm^2/s)	0.56 (0.06)	0.53 (0.07)	0.759	0.385	.423
z_association_L ($\times 10^{-3}$ mm^2/s)	0.41 (0.05)	0.40 (0.05)	0.931	0.336	.411
x_projection_R ($\times 10^{-3}$ mm^2/s)	0.59 (0.04)	0.62 (0.06)	4.997	0.027	.051
x_association_R ($\times 10^{-3}$ mm^2/s)	0.69 (0.06)	0.72 (0.07)	3.441	0.066	.103
y_projection_R ($\times 10^{-3}$ mm^2/s)	0.56 (0.06)	0.52 (0.07)	1.371	0.244	.335
z_association_R ($\times 10^{-3}$ mm^2/s)	0.40 (0.04)	0.40 (0.05)	0.011	0.917	.917

Note: ALPS, along the perivascular space; FDR, false discovery rate; HC, healthy control; L, left; R, right; SZ, schizophrenia.

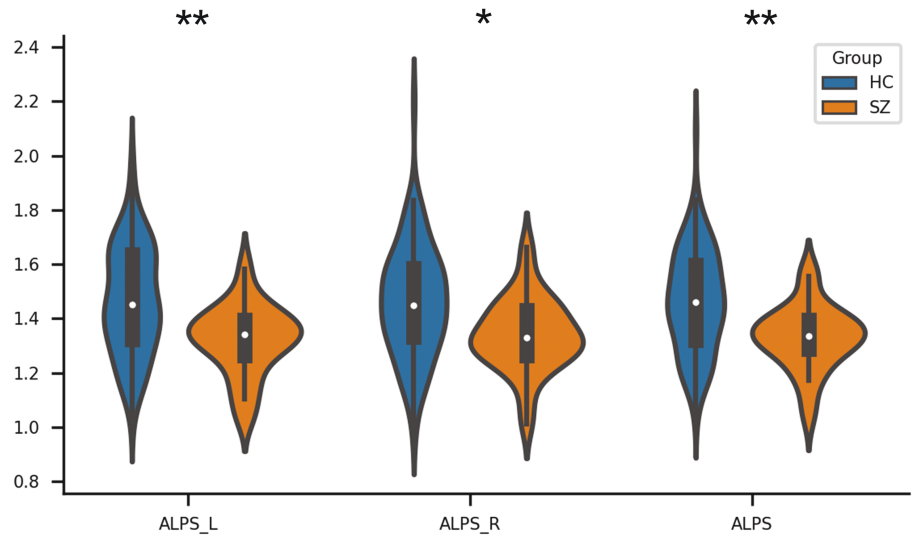

Fig. 1. Comparisons of the DTI-ALPS index. Comparisons of the DTI-ALPS index between the schizophrenia and HC groups in the left/right hemisphere and whole brain. *P<.05; **P<.01. *Note*: ALPS, along the perivascular space; DTI, diffusion tensor imaging; HC, healthy control.

Table 3. Group × Cognitive Performance Interaction Effects on ALPS

	Clinical Variables	F	P
ALPS	Group × Symbol Search Total Score	2.253	.135
ALPS	Group × Digit Span Total Score	2.82	.095
ALPS_R	Group × Symbol Search Total Score	2.895	.091
ALPS_R	Group × Digit Span Total Score	3.268	.072
ALPS_R	Group × Trials 1–5 total score	0.003	.957

Note: ALPS, along the perivascular space; L, left; R, right.

Table 4. Relationships Between ALPS and Clinical Variables in People With Schizophrenia

	Clinical Variables	r	P
ALPS	BPRS negative symptom subscales	−.33	.032
ALPS_L	BPRS negative symptom subscales	−.39	.010
ALPS_L	SANS global score	−.35	.023
ALPS	Long-delay free recall	.32	.039
ALPS_L	Trials 1–5 total score	.34	.025
ALPS	Trials 1–5 total score	.34	.027
ALPS_L	Symbol Search Total Score	.36	.017
ALPS_R	Symbol Search Total Score	.37	.018
ALPS	Symbol Search Total Score	.37	.015
ALPS	Digit Span Total Score	.30	.049

Note: ALPS, along the perivascular space; BPRS, Brief Psychiatric Rating Scale; L, left; R, right; SANS, Scale for the Assessment of Negative Symptoms.

Moreover, our analysis identified a correlation between the DTI-ALPS index and impaired cognitive performance across different domains, highlighting the DTI-ALPS index as a valuable noninvasive tool for detecting and quantifying alterations in glymphatic function in schizophrenia.

To further understand the relationship between glymphatic function and psychotic symptoms, we conducted a partial correlation analysis examining the association between the BPRS subscales and the DTI-ALPS index, taking into account potential confounding factors such as age and sex. The BPRS, known for its efficacy in evaluating the severity of psychotic symptoms, especially under severe conditions like schizophrenia, comprises 5 subfactors: anxiety and depression, lack of vitality, thinking disorder, activation, and hostile

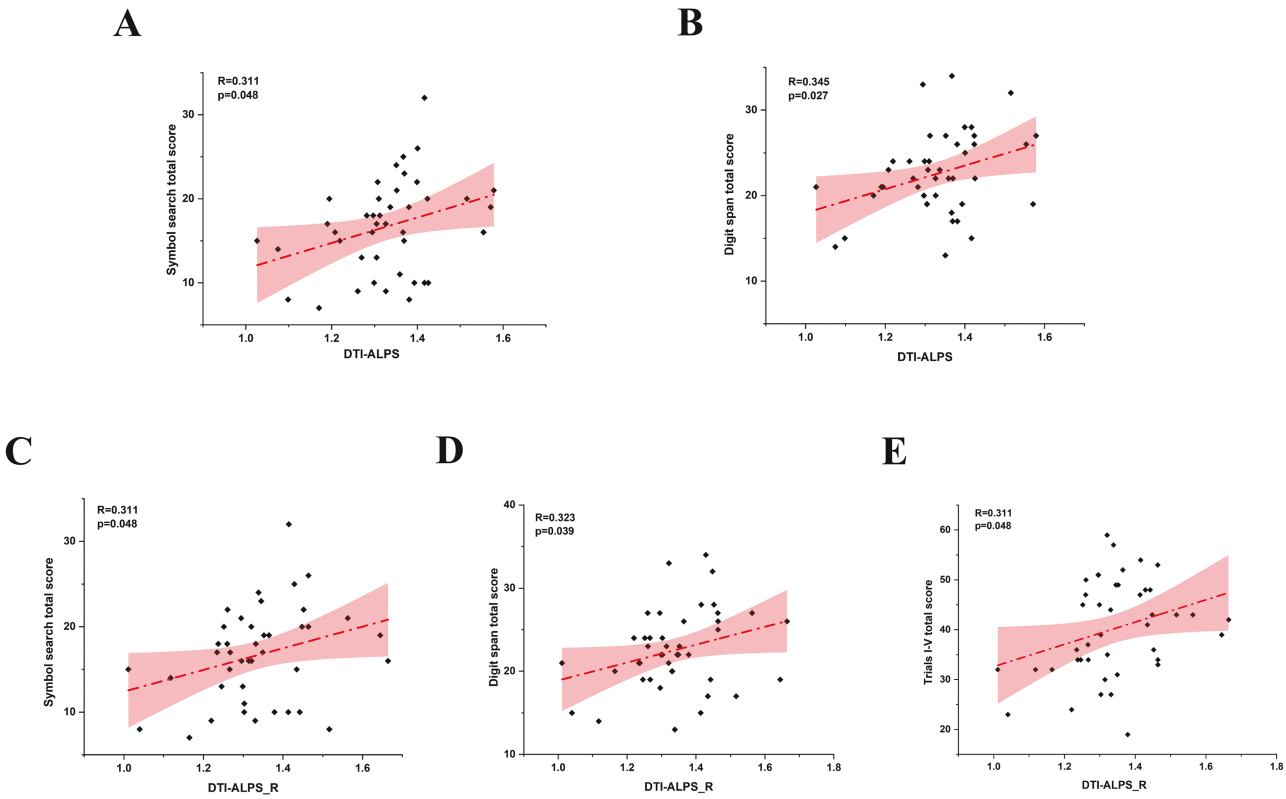

Fig. 2. The relationships between the DTI-ALPS index and cognitive performance in the schizophrenia group. (A) Correlation of the whole-brain DTI-ALPS index with Symbol Search Total Scores; (B) correlation of the DTI-ALPS index with Digit Span Total Scores; (C) correlation of the right DTI-ALPS with Symbol Search Total Scores; (D) correlation of the right DTI-ALPS index with Digit Span Total Scores; and (E) correlation right DTI-ALPS index with trials 1–5 total score. Partial correlation analyses were used for all the above. *Note*: ALPS, along the perivascular space; DTI, diffusion tensor imaging.

Table 5. Relationships Between ALPS and Age

	Clinical Variables	*r*	*P*
ALPS_L	Age (Total *n* = 151)	−.215	.008
ALPS_R	Age (Total *n* = 151)	−.147	.072
ALPS	Age (Total *n* = 151)	−.192	.018
ALPS_L	Age (HC *n* = 108)	−.115	.236
ALPS_R	Age (HC *n* = 108)	−.093	.339
ALPS	Age (HC *n* = 108)	−.11	.257
ALPS_L	Age (SZ *n* = 43)	−.284	.065
ALPS_R	Age (SZ *n* = 43)	−.068	.666
ALPS	Age (SZ *n* = 43)	−.191	.22

Note: ALPS, along the perivascular space; HC, healthy control; L, left; R, right; SZ, schizophrenia.

suspicion.[42] However, our analysis indicated no significant correlations between the DTI-ALPS index and any BPRS subscales, suggesting that glymphatic function alterations, as quantified by the DTI-ALPS index, may not be directly linked to the symptomatic dimensions assessed by the BPRS in our study population (supplementary table S1).

Additionally, our study uncovered a decreased diffusion coefficient along the *x*-direction in the projection fiber regions of individuals with schizophrenia compared with HCs. This suggests a potential disruption in the integrity of these fibers, which could impair the efficient transmission of motor and sensory information. Such disruptions could contribute to the motor and sensory integration deficits often observed in schizophrenia, including altered sensory processing and impaired motor coordination.[43,44] The significance of these findings lies in their potential to enhance our understanding of the structural changes in schizophrenia, particularly in the context of white matter pathways. By elucidating the specific alterations in projection fibers, we can better comprehend the neural underpinnings of the motor and sensory deficits in schizophrenia.

Schizophrenia has been linked to dysregulation of neurotransmitters, such as dopamine, norepinephrine, and serotonin.[45,46] Norepinephrine has been identified as the primary neurotransmitter responsible for suppressing the glymphatic system during wakefulness by inhibiting the flow of cerebrospinal fluid in the choroid plexus.[6] Additionally, dopaminergic signaling plays a crucial role in regulating arousal.[47] Consequently, disruptions in dopamine metabolism may result in difficulties in regulating sleep and wakefulness, potentially impacting the function of the glymphatic system.[48]

The pivotal discovery of our study underscores a significant correlation between the DTI-ALPS index and

cognitive performance among people with schizophrenia. Cognitive impairment remains a hallmark characteristic of schizophrenia, afflicting over 70% of individuals with the condition. Echoing the findings from extant research, our study reveals a notable decrement in certain facets of cognitive functioning, as measured by the CVLT-II and the WMS-R in people with schizophrenia.[49–52] This correlation not only enriches our understanding of the cognitive deficits associated with schizophrenia but also highlights the DTI-ALPS index as a potential biomarker for cognitive performance in this population.

Previous studies have reported that ALPS-index levels were decreased, and correlated with cognitive function in people with Alzheimer's disease, small vessel disease, behavioral variant frontotemporal dementia, and metabolic syndrome.[53–56] Similar to the neurodegenerative diseases with cognitive deficit, our study demonstrated that the ALPS index was lower in people with schizophrenia than HCs, and it was correlated with their cognitive function in schizophrenia. Notably, a lower DTI-ALPS index was correlated with worse cognition, suggesting that these cognitive domains are more susceptible to glymphatic impairment. We propose that improving glymphatic function could represent a novel therapeutic approach for schizophrenia, such as the preservation of cognitive function.

Sleep-onset and maintenance insomnia are common in people with schizophrenia, regardless of their medication or the phase of the disorder. While antipsychotic drugs can help improve sleep disturbances in people with schizophrenia, they do not always guarantee better sleep.[57] The glymphatic system clears the cerebral protein waste products, and is mostly active during sleep[58]; thus, sleep disturbances might compromise glymphatic function in pathological conditions. In line with our findings, Siow et al[59] reported significant associations between sleep problems and glymphatic dysfunction in community-dwelling older adults. Recently, a study conducted by Cai et al[60] discovered a negative association between the ALPS index and sleep disruptions in Parkinson's disease (PD). The impaired arousal state or sleep disturbances may be somewhat related to the reduced activity of the glymphatic system. Importantly, our findings propose that improved sleep may play a pivotal role in the treatment of schizophrenia.[61]

A recent investigation led by Wang et al[62] elucidated a decrement in the DTI-ALPS index concomitant with aging across a robust cohort of 693 participants. This decline is thought to reflect the reduced efficiency of glymphatic clearance mechanisms, which play a crucial role in the removal of brain waste products and, thus, are implicated in the aging process.[63] In our study, when analyzing the schizophrenia and HCs groups separately, we did not observe a significant correlation between age and the DTI-ALPS index. However, upon combining the data from both groups, a negative correlation emerged, suggesting that the DTI-ALPS index decreases with age across the entire study population. We speculated that the lack of significant findings within each group individually could be attributed to the relatively smaller sample sizes, which may limit the statistical power necessary to detect such associations.

This study had some limitations. First, the sample size was relatively small. Second, our study was unable to analyze the causal relationship between cognitive deficit and glymphatic function. It is possible that cognitive deficits and glymphatic dysfunction have bidirectional roles in neuropsychiatric disorders, potentially forming a vicious cycle. Therefore, we propose that future research should incorporate longitudinal studies. Third, all individuals with schizophrenia in our study had a history of antipsychotic medication use, often with exposure to multiple drugs. The variability in antipsychotic medication among people with schizophrenia in our study introduces a significant confounding factor, necessitating a cautious interpretation of our findings.

In conclusion, our study underscores the pivotal role of glymphatic dysfunction in the etiology of schizophrenia. Moreover, our research sheds light on the intricate link between glymphatic deficits and cognitive impairments observed in schizophrenia, offering novel insights into their association. Importantly, our study posits that augmenting glymphatic functionality presents a viable therapeutic avenue for schizophrenia, suggesting a novel paradigm in treatment strategies.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Acknowledgments

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull.* 2000;26(1):119–136.
2. Rassovsky Y, Horan WP, Lee J, Sergi MJ, Green MF. Pathways between early visual processing and functional outcome in schizophrenia. *Psychol Med.* 2011;41(3):487–497.
3. Chong HY, Teoh SL, Wu DB, Kotirum S, Chiou CF, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. *Neuropsychiatr Dis Treat.* 2016;12:357–373.
4. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci.* 1995;3(2):89–97.
5. Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a

dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull.* 1998;24(2):203–218.
6. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. *Neurochem Res.* 2015;40(12):2583–2599.
7. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. *Lancet Neurol.* 2018;17(11):1016–1024.
8. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med.* 2012;4(147):147ra111.
9. Sundaram S, Hughes RL, Peterson E, et al. Establishing a framework for neuropathological correlates and glymphatic system functioning in Parkinson's disease. *Neurosci Biobehav Rev.* 2019;103:305–315.
10. Hablitz LM, Nedergaard M. The glymphatic system: a novel component of fundamental neurobiology. *J Neurosci.* 2021;41(37):7698–7711.
11. Harrison IF, Ismail O, Machhada A, et al. Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. *Brain.* 2020;143(8):2576–2593.
12. Ericek OB, Akillioglu K, Saker D, et al. Distribution of Aquaporin-4 channels in hippocampus and prefrontal cortex in MK-801-treated Balb/c mice. *Ultrastruct Pathol.* 2022;46(1):63–79.
13. Li Z, Li X, Jin M, et al. Identification of potential biomarkers and their correlation with immune infiltration cells in schizophrenia using combinative bioinformatics strategy. *Psychiatry Res.* 2022;314:114658.
14. Wu YF, Sytwu HK, Lung FW. Polymorphisms in the human aquaporin 4 gene are associated with schizophrenia in the Southern Chinese Han population: a case-control study. *Front Psychiatry.* 2020;11:596.
15. Taoka T, Naganawa S. Glymphatic imaging using MRI. *J Magn Reson Imaging.* 2020;51(1):11–24.
16. Manava P, Eckrich C, Luciani F, Schmidbauer J, Lell MM, Detmar K. Glymphatic system in ocular diseases: evaluation of MRI findings. *AJNR Am J Neuroradiol.* 2022;43(7):1012–1017.
17. Ringstad G, Vatnehol SAS, Eide PK. Glymphatic MRI in idiopathic normal pressure hydrocephalus. *Brain.* 2017;140(10):2691–2705.
18. Eide PK, Ringstad G. Delayed clearance of cerebrospinal fluid tracer from entorhinal cortex in idiopathic normal pressure hydrocephalus: a glymphatic magnetic resonance imaging study. *J Cereb Blood Flow Metab.* 2019;39(7):1355–1368.
19. Lee MK, Cho SJ, Bae YJ, Kim JM. MRI-based demonstration of the normal glymphatic system in a human population: a systematic review. *Front Neurol.* 2022;13:827398.
20. Nguyen NC, Molnar TT, Cummin LG, Kanal E. Dentate nucleus signal intensity increases following repeated gadobenate dimeglumine administrations: a retrospective analysis. *Radiology.* 2020;296(1):122–130.
21. McDonald RJ, Kallmes DF. Signal intensity changes at MRI following GBCA exposure: incidental finding or cause for concern? *Radiology.* 2020;296(1):131–133.
22. Barisano G, Lynch KM, Sibilia F, et al. Imaging perivascular space structure and function using brain MRI. *Neuroimage.* 2022;257:119329.
23. Taoka T, Masutani Y, Kawai H, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. *Jpn J Radiol.* 2017;35(4):172–178.
24. Kamagata K, Andica C, Takabayashi K, et al.; Alzheimer's Disease Neuroimaging Initiative. Association of MRI indices of glymphatic system with amyloid deposition and cognition in mild cognitive impairment and Alzheimer disease. *Neurology.* 2022;99(24):e2648–e2660.
25. Zhang W, Zhou Y, Wang J, et al. Glymphatic clearance function in patients with cerebral small vessel disease. *Neuroimage.* 2021;238:118257.
26. Taoka T, Ito R, Nakamichi R, et al. Reproducibility of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating interstitial fluid diffusivity and glymphatic function: CHanges in Alps index on Multiple conditiON acquIsition eXperiment (CHAMONIX) study. *Jpn J Radiol.* 2022;40(2):147–158.
27. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics.* 2007;4(3):316–329.
28. Poldrack RA, Congdon E, Triplett W, et al. A phenome-wide examination of neural and cognitive function. *Sci Data.* 2016;3:160110.
29. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry Suppl.* 1989;10(7):49–58.
30. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133:429–435.
31. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry.* 1988;45(8):742–747.
32. Lukoff D, Liberman RP, Nuechterlein KH. Symptom monitoring in the rehabilitation of schizophrenic patients. *Schizophr Bull.* 1986;12(4):578–602.
33. Ventura J, Nuechterlein KH, Subotnik KL, Gutkind D, Gilbert EA. Symptom dimensions in recent-onset schizophrenia and mania: a principal components analysis of the 24-item Brief Psychiatric Rating Scale. *Psychiatry Res.* 2000;97(2–3):129–135.
34. Bornstein RA, Chelune GJ. Factor structure of the Wechsler memory scale-revised in relation to age and educational level. *Arch Clin Neuropsychol.* 1989;4(1):15–24.
35. Stone WS, Mesholam-Gately RI, Braff DL, et al. California Verbal Learning Test-II performance in schizophrenia as a function of ascertainment strategy: comparing the first and second phases of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophr Res.* 2015;163(1–3):32–37.
36. Veraart J, Novikov DS, Christiaens D, Ades-Aron B, Sijbers J, Fieremans E. Denoising of diffusion MRI using random matrix theory. *Neuroimage.* 2016;142:394–406.
37. Kellner E, Dhital B, Kiselev VG, Reisert M. Gibbs-ringing artifact removal based on local subvoxel-shifts. *Magn Reson Med.* 2016;76(5):1574–1581.
38. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage.* 2016;125:1063–1078.
39. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med Imaging.* 2010;29(6):1310–1320.
40. Tournier JD, Smith R, Raffelt D, et al. MRtrix3: a fast, flexible and open software framework for medical image processing and visualisation. *Neuroimage.* 2019;202:116137.
41. Mori S, Oishi K, Jiang H, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage.* 2008;40(2):570–582.

42. Chen S, Xia X, Deng C, et al. The correlation between metabolic syndrome and neurocognitive and social cognitive performance of patients with schizophrenia. *Psychiatry Res.* 2020;288:112941.
43. Vrtunski PB, Simpson DM, Weiss KM, Davis GC. Abnormalities of fine motor control in schizophrenia. *Psychiatry Res.* 1986;18(3):275–284.
44. Doniger GM, Silipo G, Rabinowicz EF, Snodgrass JG, Javitt DC. Impaired sensory processing as a basis for object-recognition deficits in schizophrenia. *Am J Psychiatry.* 2001;158(11):1818–1826.
45. Maki-Marttunen V, Andreassen OA, Espeseth T. The role of norepinephrine in the pathophysiology of schizophrenia. *Neurosci Biobehav Rev.* 2020;118:298–314.
46. Kraguljac NV, McDonald WM, Widge AS, Rodriguez CI, Tohen M, Nemeroff CB. Neuroimaging biomarkers in schizophrenia. *Am J Psychiatry.* 2021;178(6):509–521.
47. Oishi Y, Lazarus M. The control of sleep and wakefulness by mesolimbic dopamine systems. *Neurosci Res.* 2017;118:66–73.
48. Wisor JP. Dopamine and wakefulness: pharmacology, genetics, and circuitry. *Handb Exp Pharmacol.* 2019;253:321–335.
49. Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry.* 2006;67(10):e12.
50. Shmukler AB, Gurovich IY, Agius M, Zaytseva Y. Long-term trajectories of cognitive deficits in schizophrenia: a critical overview. *Eur Psychiatry.* 2015;30(8):1002–1010.
51. Koshiyama D, Fukunaga M, Okada N, et al. Subcortical association with memory performance in schizophrenia: a structural magnetic resonance imaging study. *Transl Psychiatry.* 2018;8(1):20.
52. Hill SK, Beers SR, Kmiec JA, Keshavan MS, Sweeney JA. Impairment of verbal memory and learning in antipsychotic-naive patients with first-episode schizophrenia. *Schizophr Res.* 2004;68(2–3):127–136.
53. Andica C, Kamagata K, Takabayashi K, et al. Neuroimaging findings related to glymphatic system alterations in older adults with metabolic syndrome. *Neurobiol Dis.* 2023;177:105990.
54. Hsu JL, Wei YC, Toh CH, et al. Magnetic resonance images implicate that glymphatic alterations mediate cognitive dysfunction in Alzheimer disease. *Ann Neurol.* 2023;93(1):164–174.
55. Jiang D, Liu L, Kong Y, et al.; Frontotemporal Lobar Degeneration Neuroimaging Initiative. Regional glymphatic abnormality in behavioral variant frontotemporal dementia. *Ann Neurol.* 2023;94(3):442–456.
56. Xu J, Su Y, Fu J, et al. Glymphatic dysfunction correlates with severity of small vessel disease and cognitive impairment in cerebral amyloid angiopathy. *Eur J Neurol.* 2022;29(10):2895–2904.
57. Monti JM, BaHammam AS, Pandi-Perumal SR, et al. Sleep and circadian rhythm dysregulation in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;43:209–216.
58. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science.* 2020;370(6512):50–56.
59. Siow TY, Toh CH, Hsu JL, et al. Association of sleep, neuropsychological performance, and gray matter volume with glymphatic function in community-dwelling older adults. *Neurology.* 2022;98(8):e829–e838.
60. Cai X, Chen Z, He C, et al. Diffusion along perivascular spaces provides evidence interlinking compromised glymphatic function with aging in Parkinson's disease. *CNS Neurosci Ther.* 2023;29(1):111–121.
61. Waite F, Sheaves B, Isham L, Reeve S, Freeman D. Sleep and schizophrenia: from epiphenomenon to treatable causal target. *Schizophr Res.* 2020;221:44–56.
62. Wang J, Zhou Y, Zhang K, et al. Glymphatic function plays a protective role in ageing-related cognitive decline. *Age Ageing.* 2023;52(7):1–8.
63. Benveniste H, Liu X, Koundal S, Sanggaard S, Lee H, Wardlaw J. The glymphatic system and waste clearance with brain aging: a review. *Gerontology.* 2019;65(2):106–119.