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ORIGINAL RESEARCH

Glymphatic System in Adolescents with Major Depressive Disorder: No Dysfunction and No Association with Poor Sleep Quality

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Purpose: The purpose of this study was to investigate the relationship between glymphatic function and sleep quality in adolescents with Major Depressive Disorder (MDD). Previous research has linked glymphatic dysfunction to MDD in adults, often associated with sleep disturbances, but the relationship between these factors in adolescents remains unclear.

Patients and Methods: This study utilized Diffusion Tensor Imaging analysis along the perivascular space (DTI-ALPS) to assess glymphatic system function and the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality in adolescents. A total of 138 participants were included: 80 first-episode and medication-naive patients with MDD (total 80: 9 with mild MDD, 28 with moderate MDD, 43 with severe MDD), and 58 healthy controls. Pearson correlation analysis was performed to examine the relationship between sleep quality and glymphatic function.

Results: The results showed adolescents with MDD demonstrated poor sleep quality, whereas healthy controls exhibited normal sleep quality. However, no significant impairment in glymphatic function was observed. Furthermore, no clear correlation was found between sleep quality and glymphatic function in the adolescent MDD group.

Conclusion: This study provides novel insights into the neurobiological mechanisms of adolescent MDD, suggesting that the glymphatic system may not contribute to its pathogenesis in the same way as in adults. However, this cross-sectional study, with its small sample size and single-center design, limits the generalizability of the findings. Future research should adopt longitudinal, multicenter, and larger-scale designs to further investigate these relationships in more depth.

Keywords: major depressive disorder, adolescents, glymphatic system, diffusion tensor imaging analysis along the perivascular space, sleep quality

Introduction

Major Depressive Disorder (MDD) is a severe mental health condition, typically characterized by persistent negative affect, pervasive cognitive distortions, and behavioral impairments, accompanied by somatic symptoms such as fatigue, weight loss, and appetite suppression.[1,2] MDD significantly elevates the risk of self-harm and even suicide, and is currently one of the leading causes of disability worldwide.[3] It is projected to become the leading contributor to global disease burden by 2030.[4] Adolescence is a critical period characterized by significant changes in brain structure and function, particularly in systems involved in emotional regulation, cognitive control, and social behavior. Research indicates that the reorganization of neural circuits during this stage makes adolescents more susceptible to stress and negative emotions, which in turn increases the risk of developing depression.[5] However, most studies examining the biological mechanisms underlying the onset of depression have primarily focused on adult populations, with far fewer studies targeting adolescents.[6] Furthermore, many pharmacological treatments proven effective in adults show limited efficacy in the adolescent population,[7] suggesting potential differences in the underlying pathophysiological mechanisms between these age groups. Therefore, it is crucial to thoroughly investigate the unique pathogenic mechanisms of adolescent MDD and develop tailored therapeutic interventions to address this pressing issue.

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The glymphatic system is a specialized channel network within the brain parenchyma, primarily responsible for facilitating the clearance of harmful substances such as β-amyloid.[8–10] However, research on the human glymphatic system has been limited due to the invasive nature of imaging techniques.[11] To overcome this, a novel method called Diffusion Tensor Imaging analysis along the Perivascular Space (DTI-ALPS) was introduced in 2017. This non-invasive method assesses water diffusion within perivascular spaces to provide an index that reflects glymphatic function. With its non-invasive nature and ease of use, the DTI-ALPS method has significantly advanced the study of human brain lymphatic system function.[12–14]

As research into the glymphatic system has progressed, an increasing body of evidence suggests a relationship between this system and MDD. Previous studies have demonstrated a significant reduction in DTI-ALPS index in adults with MDD, indicating a marked decline in glymphatic system function in these individuals.[15,16] Furthermore, research by Yao[17] revealed that adult depression models in mice exhibited glymphatic dysfunction, which could be ameliorated by improving sleep quality through melatonin treatment, leading to a restoration of glymphatic system function and a significant reduction in depressive behaviors. These findings suggest that a decline in glymphatic system function is closely associated with MDD in adults, and that this dysfunction is particularly linked to poor sleep quality. Modulating glymphatic system function could therefore emerge as a promising therapeutic target for future treatments of MDD.

Despite progress in understanding the relationship between the glymphatic system and adult MDD, the changes in glymphatic system function in adolescent MDD remain unclear. This study seeks to bridge this gap by utilizing the DTI-ALPS index to investigate changes in the glymphatic system in adolescents with MDD and explore the relationship between these changes and sleep quality. The goal is to uncover the patterns of glymphatic system dysfunction in adolescent MDD and analyze its relationship with sleep quality, thereby laying the groundwork for future research on the pathophysiology and personalized treatment strategies for adolescent MDD.

Materials and Methods

Participants

This study was approved by the Ethics Committee of The Third Hospital of Mianyang (2022–18). A total of 80 first-episode and medication-naive patients with MDD from outpatient visits at our institution and included in the MDD group. In parallel, age- and gender-matched healthy controls were recruited via poster advertisements from the same socio-demographic background, and structured clinical interviews (non-patient version) were used to screen the health status of the control participants, ultimately selecting 58 individuals for the HC group. All participants and their parents/legal guardians voluntarily enrolled in the study and provided written informed consent. This declaration of Helsinki was followed in the study.

Inclusion Criteria for the MDD Group

(1) Diagnosis of MDD according to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition);
(2) Age between 12 and 18 years;
(3) A Hamilton Depression Rating Scale (HAMD) score of ≥8;
(4) No pharmacological treatment for at least 14 days prior to MRI scanning.

Exclusion Criteria for the MDD Group

(1) Diagnosis of any other psychiatric disorders (eg, bipolar disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, eating disorders) or a family history of psychiatric disorders;
(2) History of pharmacological treatment or any form of psychotherapy;
(3) Substance use or abuse;
(4) Any significant neurological or systemic medical conditions (eg, epilepsy, traumatic brain injury);
(5) Age outside the 12–18 years range;
(6) Contraindications to MRI scanning.

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The MDD group was further subdivided according to HAMD scores into the following categories: mild MDD (HAMD score: 8–17), moderate MDD (HAMD score: 18–24), and severe MDD (HAMD score ≥25).

Inclusion Criteria for the HC Group

(1) Age between 12 and 18 years;
(2) No history of any psychiatric disorders or medical conditions;
(3) HAMD score <8;
(4) No pharmacological treatment for at least 14 days prior to MRI scanning.

Exclusion Criteria for the HC Group

(1) Age outside the 12–18 years range;
(2) Any history of psychiatric disorders or family history of psychiatric conditions;
(3) Significant neurological or systemic medical conditions;
(4) Substance use or dependency;
(5) Any contraindications to MRI scanning.

Collection of Clinical Data and Sleep Quality Assessment

Demographic variables of all participants, including age, gender, handedness, and educational level (measured in years of education), were recorded within one week before and after MRI scanning. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI),[18] which evaluates various dimensions of sleep, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, daytime dysfunction, and other factors affecting sleep. PSQI scores were categorized as follows: ≤5 indicates good sleep quality, 6–10 indicates mild sleep disturbances, 11–15 indicates moderate sleep disturbances, and 16–21 indicates severe sleep disturbances.

MRI Image Acquisition

MRI data were acquired using a 3.0T MRI scanner (Skyra, Siemens) with an 8-channel head coil at our institution. The imaging modalities included 3D-T1 weighted images, T2 weighted images, and Diffusion Tensor Imaging (DTI). The scanning parameters are as follows:

3D-T1: Repetition time = 2.25 ms, Echo time = 1900 ms, Slice thickness = 1 mm, Field of view = 256×256 cm², Voxel size = 1.0 × 1.0×1.0 mm, Bandwidth = 200 Hz.

DTI: Repetition time = 9200 ms, Echo time = 95 ms, Slice thickness = 2 mm, Field of view = 256×256 cm², Number of directions = 64, Voxel size = 2.0 × 2.0×2.0 mm, Bandwidth =1630Hz/pixel.

DTI-ALPS Index Acquisition

Data Preprocessing and Tensor Fitting

The preprocessing of the DTI data was carried out using Quantitative Susceptibility Imaging Preprocessing (version 0.13.1), which facilitated the correction of head motion and eddy current distortions, while also employing B0 field map correction to rectify magnetic field inhomogeneities. The DTI data were subjected to tensor fitting using the DTI fitting command from FSL, yielding a four-dimensional image file (DTI_tensor.nii.gz) containing six volumes and their corresponding Fractional Anisotropy map. Within the analysis pipeline of this study, diffusion coefficient mappings along the x-axis (right-left, D_{xx}), y-axis (anterior–posterior; D_{yy}), and z-axis (inferior-superior;D_{ZZ}) can be accurately extracted based on this correspondence. The processed diffusion-weighted images were then linearly registered to the individual subject's T1-weighted anatomical space using the FMRIB's Linear Image Registration Tool from FMRIB Software Library (FSL, version 6.0.5), thus providing an anatomical reference for subsequent region of interest (ROI) delineation.

DTI-ALPS Index Calculation

In accordance with prior literature,[11] ROIs were manually delineated in the white matter near the prominent projections and association fibers adjacent to the lateral ventricles. Using the FA image, which was registered to the T1 anatomical space, ROIs for the projection fibers and association fibers were drawn separately on the left and right hemispheres, each ROI having a circular diameter of 5 mm, totaling four ROIs. These ROIs were meticulously positioned on the same plane and aligned horizontally, with efforts made to avoid the ventricular cavities and vascular lumens.

The DTI-ALPS index, as shown in the equation below, is defined as the ratio of the average x-axis diffusivity in the projection area (D_{xxproj}) and the association area ($D_{xxassoc}$) to the average y-axis diffusivity in the projection area (D_{yyproj}) and the z-axis diffusivity in the association area ($D_{zzassoc}$):

$$DTI - ALPS\ index = \frac{mean\left(D_{xxproj}, D_{xxassoc}\right)}{mean\left(D_{yyproj}, D_{zzassoc}\right)}$$

A detailed flowchart of this process is shown in Figure 1.

Statistical Analysis

All statistical analyses were conducted using SPSS 24.0 software. For categorical data, comparisons were performed using the Chi-square test. For quantitative data, normality was first assessed using the Shapiro–Wilk test. If data from all four groups followed a normal distribution, they were expressed as mean ± standard deviation (SD), and one-way analysis of variance (ANOVA) was used for group comparisons. When ANOVA results were significant, Bonferroni post-hoc multiple comparisons were conducted for pairwise comparisons. If the data deviated from normality, they were presented as median and interquartile range (IQR), and the Kruskal–Wallis *H*-test was employed for group comparisons. If the Kruskal–Wallis *H*-test showed significant differences, Dunn's Multiple Comparison Test was applied for pairwise comparisons. To compare differences between the healthy control (HC) group and the MDD group, independent *t*-tests or Mann–Whitney *U*-tests were used, depending on the data distribution. Group comparisons between the HC group and the three MDD sub-groups (mild, moderate, and severe) were then performed using the same statistical methods. Partial correlation analysis was conducted to explore the relationship between sleep scores and DTI-ALPS indices, adjusting for age, gender, and HAMD score as covariates. Correlation values closer to 1 or −1 indicated a stronger linear relationship, while values closer to 0 suggested a weaker linear relationship. A P-value of less than 0.05 was considered statistically significant.

Results

Demographic Data Analysis

The MDD group included 80 participants (18 males, 62 females). The mild MDD group included 9 participants (4 males, 5 females). The moderate MDD group included 28 participants (7 males, 21 females). The severe MDD group included 43 participants (7 males, 36 females). The healthy control (HC) group included 58 participants (21 males, 37 females). No significant differences were found between the HC group and the MDD group, nor between the HC group and any MDD sub-group (mild, moderate, or severe), in terms of age, gender distribution, education level, or handedness (Table 1).

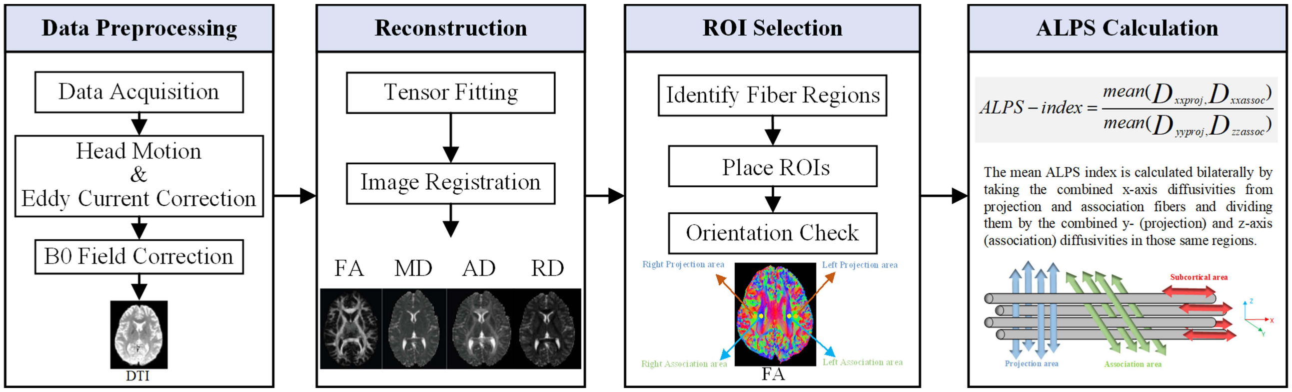

Figure 1 Flowchart of the DTI-Alps data acquisition, preprocessing, and DTI-ALPS index calculation process.

Table 1 Comparison of Demographic Characteristics Between Mild, Moderate, and Severe MDD Groups and HC Group

Feature	MDD (n=80)	Mild MDD (n=9)	Moderate MDD (n=28)	Severe MDD (n=43)	HC (n=58)	Effect Size (Cramér's V)	P value
Age	15.11±1.74	14.67±1.12	15.5 (14,17)	15 (14,17)	14 (13,16)	0.110	>0.05[a]
Gender (female, N%)	62,78%	5, 56%	21, 75%	36,84%	37, 64%	0.115	>0.05[b]
Years of Education	9.11±1.74	8.67±1.12	9.5 (8,11)	9 (8,11)	9 (7.75,11)	0.047	>0.05[a]
Handedness (Right-handed, N%)	79,99%	9, 100%	28, 100%	42,98%	57, 98%	0.042	>0.05[b]

Notes: [a] Kruskal–Wallis *H*-test, [b] Chi-square test; No significant differences were observed in age, gender, years of education, and handedness (right-handed) between the MDD, mild MDD, moderate MDD, and severe MDD groups and HC group. Values are presented as mean ± standard deviation (SD) or median (25%, 75% interquartile range), as indicated in the table.

Comparison of DTI-ALPS Index Results

Shapiro–Wilk testing confirmed that the DTI-ALPS indices for all five groups followed a normal distribution.

In the MDD, mild MDD, moderate MDD, severe MDD, and HC groups, the left hemisphere DTI-ALPS indices were 1.60 ± 0.18,1.70 ± 0.20, 1.58 ± 0.18, 1.59 ± 0.17, and 1.63 ± 0.21, respectively. The right hemisphere DTI-ALPS indices were 1.64 ± 0.19,1.74 ± 0.21, 1.64 ± 0.12, 1.62 ± 0.21, and 1.63 ± 0.19, respectively. The whole-brain DTI-ALPS indices were 1.62 ± 0.16,1.72 ± 0.18, 1.61 ± 0.12, 1.61 ± 0.17, and 1.63 ± 0.18, respectively. No significant differences were observed between the HC group and the MDD group (Figure 2A–C), nor between the HC group and the mild, moderate, or severe MDD sub-groups, in terms of the DTI-ALPS indices for the left hemisphere, right hemisphere, and whole brain (Figure 3A–C).

Comparison of PQSI Scores

Shapiro–Wilk testing revealed that the PQSI scores in the HC group did not follow a normal distribution, whereas the PQSI scores in the MDD group and three sub-groups adhered to a normal distribution. The PQSI scores for the MDD, mild MDD, moderate MDD, severe MDD, and HC groups were 12.53 ± 3.65, 11.22 ± 4.55, 12.43 ± 3.71, 12.86 ± 3.43, and 5 (3, 6), respectively. The results of the Kruskal–Wallis *H*-test showed significant differences in PQSI scores between the HC group and the MDD group, as well as between the HC group and the three MDD sub-groups ($p < 0.0001$). Subsequent Dunn's multiple comparisons revealed no significant differences in PQSI scores between the MDD, mild MDD, moderate MDD, and severe MDD groups. However, the HC group showed significantly lower PQSI scores compared to the MDD group and its three sub-groups, with statistically significant differences observed between the HC group and all other groups (HC vs MDD, $p < 0.0001$; HC vs mild MDD, $p < 0.0001$; HC vs moderate MDD, $p < 0.0001$; HC vs severe MDD, $p < 0.0001$) (Figures 2D and 3D).

Correlation Analysis Between DTI-ALPS Indices and PQSI Scores

There was no significant correlation between PQSI scores and the DTI-ALPS indices of the left hemisphere, right hemisphere, or whole brain in the MDD group after controlling for the effects of age, gender and HAMD ($p>0.05$, Figure 4).

Discussion

The results of this study indicate that, compared to the normal sleep quality of age-matched healthy controls, adolescents with MDD exhibit poor sleep quality, while no notable differences were observed in the function of the glymphatic system. These findings suggest that the glymphatic system may not be implicated in the pathogenesis of adolescent MDD, which differs from its potential role in adult MDD. This distinction offers important insights into the divergent pathological mechanisms between adolescent and adult MDD, providing a basis for more tailored and age-specific therapeutic strategies in the future.

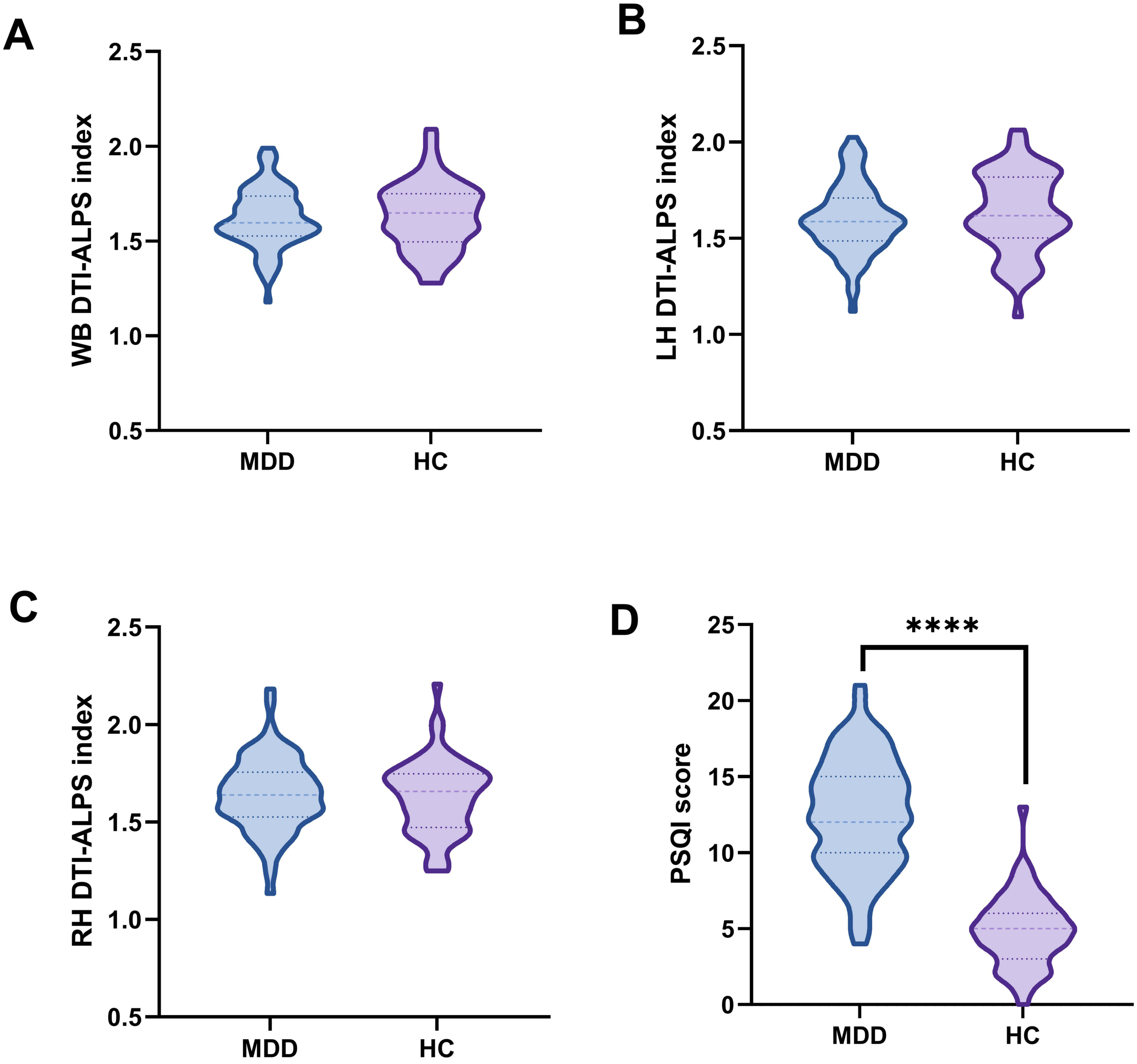

Figure 2 Comparison of DTI-Alps index results and PQSI scores between MDD and HC groups. (**A–C**) No significant differences for the left hemisphere DTI-ALPS index, right hemisphere DTI-ALPS index, and whole-brain DTI-ALPS index between MDD and HC groups. (**D**) HC group demonstrated significantly lower PQSI scores compared to MDD group. ****$p < 0.0001$.

Abbreviations: LH DTI-ALPS index, left hemisphere DTI-ALPS index; RH DTI-ALPS index, right hemisphere DTI-ALPS index; WB DTI-ALPS index, whole-brain DTI-ALPS index.

Previous research has demonstrated that the function of the glymphatic system varies significantly across different age groups. Compared to both young and elderly mice, juvenile mice exhibit a more efficient clearance rate of the brain's glymphatic system.[19] A recent multicenter study by Dai[20] collected and analyzed brain DTI-ALPS indices from a healthy population aged 20 to 87 years. The results revealed that the average DTI-ALPS index for the young group (20–39 years) ranged from 1.58 to 1.62, for the middle-aged group (40–59 years) it ranged from 1.32 to 1.52, and for the elderly group (60–87 years), the DTI-ALPS index ranged from 1.32 to 1.48. These findings suggest that the DTI-ALPS index in the younger population is significantly higher compared to the middle-aged and elderly groups. Research by Yang[16] indicated that the average whole-brain DTI-ALPS index in healthy adults (with a median age of 55 years) was 1.57, while in adults with MDD (with a median age of 53 years), the DTI-ALPS index decreased to 1.45. Our findings show that the average whole-brain DTI-ALPS index for both adolescent healthy individuals and those with MDD is approximately between 1.6

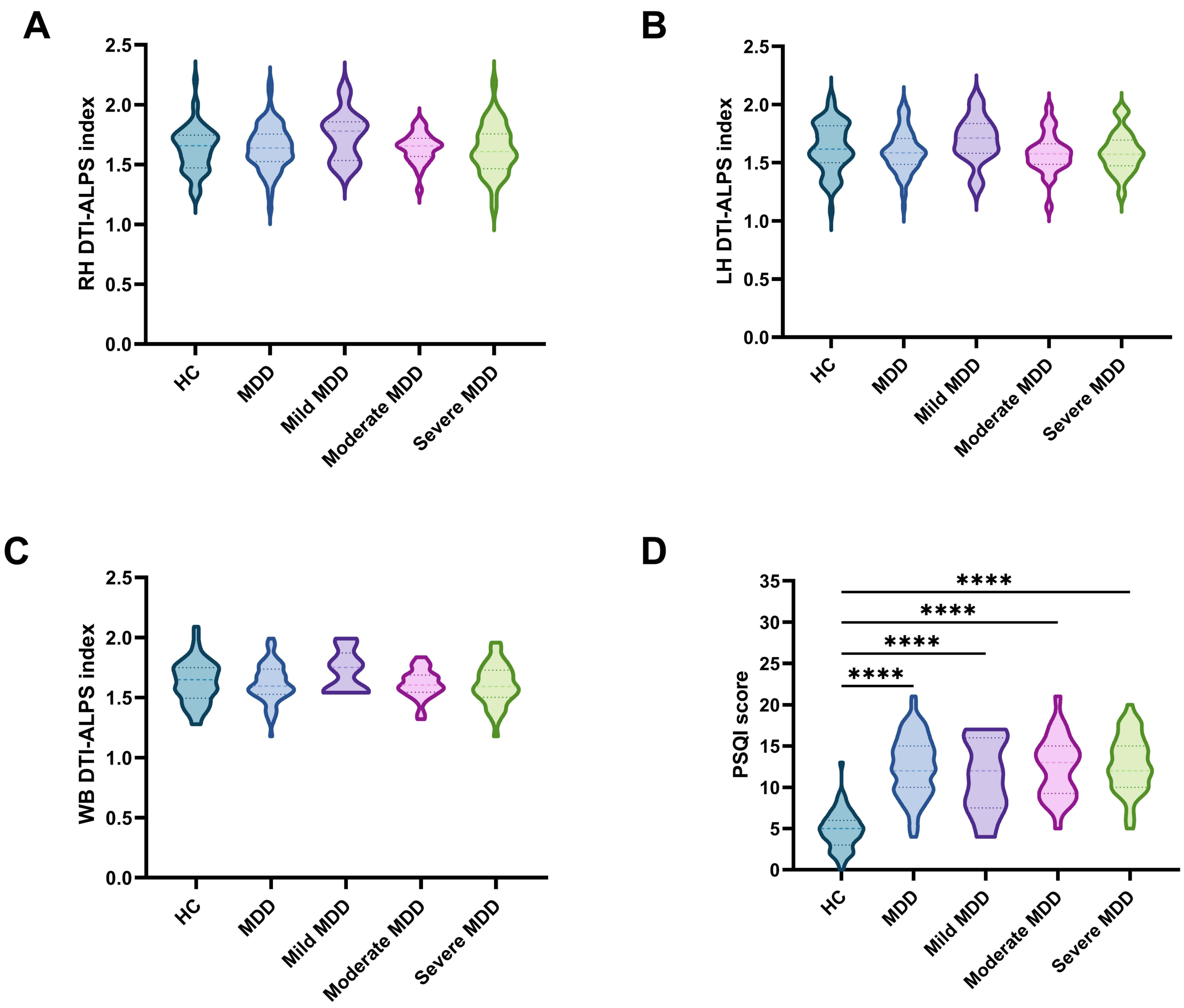

Figure 3 Comparison of DTI-Alps index results and PQSI scores between mild MDD, moderate MDD, severe MDD, and HC groups. (**A–C**) No significant differences for the left hemisphere DTI-ALPS index, right hemisphere DTI-ALPS index, and whole-brain DTI-ALPS index between mild MDD, moderate MDD, severe MDD, and HC groups. (**D**) HC group demonstrated significantly lower PQSI scores compared to mild MDD, moderate MDD, severe MDD groups, respectively. No significant differences in PQSI scores between mild MDD, moderate MDD, and severe MDD groups. ****p < 0.0001.

Abbreviations: LH DTI-ALPS index, left hemisphere DTI-ALPS index; RH DTI-ALPS index, right hemisphere DTI-ALPS index; WB DTI-ALPS index, whole-brain DTI-ALPS index.

and 1.7, suggesting that the function of the glymphatic system in both adolescent healthy and depressed populations remains within normal functional parameters.

The PQSI scores indicated that adolescent patients with MDD exhibit sleep disturbances, which is consistent with findings in adult MDD research.[21] Sleep disorders are a significant factor in the onset and progression of various psychiatric disorders, including MDD.[22] The relationship between sleep disturbances and MDD is multifaceted and reciprocal,[23] with sleep disorders not only serving as a symptom of MDD but also potentially exacerbating depressive symptoms.[24] Moreover, sleep status is one of the primary factors influencing the function of the glymphatic system. Glymphatic system activity is inhibited during wakefulness and significantly enhanced during sleep.[10] Research has demonstrated that during sleep or general anesthesia, the spatial structure of the glymphatic system expands, and its clearance efficiency increases several-fold compared to the wakeful state.[25]

Despite our findings showing that adolescents with MDD experience a poor sleep quality, there was no significant alteration in the function of the glymphatic system, and no clear correlation was observed between these two factors. This

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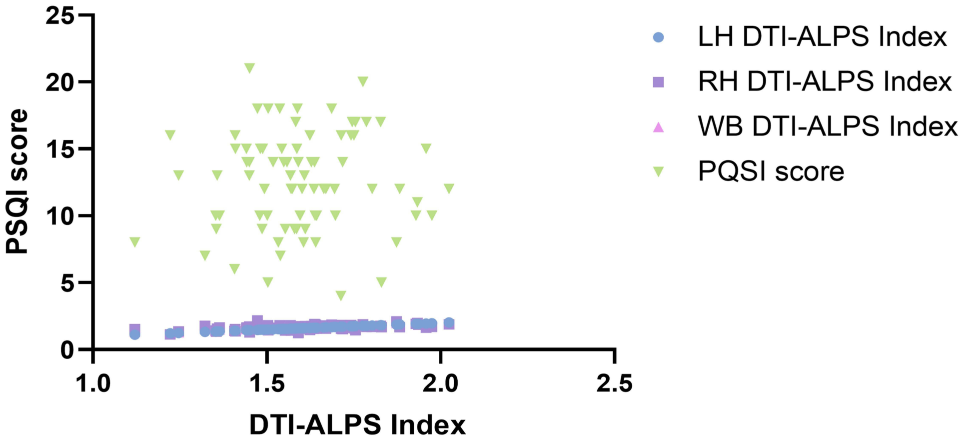

Figure 4 Correlation analysis between DTI-Alps indices and PQSI scores. No significant correlation between PQSI scores and the left hemisphere DTI-ALPS index, right hemisphere DTI-ALPS index, and whole-brain DTI-ALPS index in MDD group.
Abbreviations: LH DTI-ALPS index, left hemisphere DTI-ALPS index; RH DTI-ALPS index, right hemisphere DTI-ALPS index; WB DTI-ALPS index, whole-brain DTI-ALPS index.

result contrasts with the glymphatic system dysfunction typically seen in adults with MDD. This discrepancy may be attributed to the unique physiological and metabolic mechanisms inherent to adolescents. Research has shown that the distribution of aquaporin-4 (AQP-4) in the adolescent brain is more optimized compared to that in adults, with AQP-4 playing a pivotal role in cerebrospinal fluid circulation and the clearance of metabolic waste.[26] This enhanced distribution of AQP-4 may enable adolescents to maintain efficient waste clearance even in the face of reduced sleep quality. Furthermore, adolescents exhibit more pronounced arterial pulsatility compared to adults, a physiological feature that facilitates fluctuations in cerebral blood flow,[27] thereby promoting the movement of cerebrospinal fluid. This, in turn, augments the glymphatic system's capacity to eliminate waste. Such mechanisms may allow adolescents to preserve normal glymphatic function despite experiencing poor sleep quality. On the other hand, the sleep architecture in adolescent depression diverges notably from that of adults. Studies[28] have revealed that adolescents with depression display distinct sleep spindle activity and cyclic alternating patterns, contrasting with the increased rapid eye movement (REM) sleep and shortened REM latency typically observed in adult depression. These differential patterns of sleep disturbances may exert disparate effects on the glymphatic system, potentially contributing to the maintenance of a normally functioning glymphatic system in adolescents with depression.

While adolescents with MDD maintain normal glymphatic function, adults exhibit impaired glymphatic function. This age-related difference provides novel insights into the pathophysiological mechanisms underlying MDD. Previous studies have established a strong association between MDD and neuroinflammation.[29,30] As a vital conduit for the clearance of neurotoxic substances from the brain,[10] glymphatic system dysfunction may lead to the accumulation of inflammatory mediators,[31] thereby potentiating the pathophysiology of MDD. In adolescent MDD patients, the glymphatic system appears to maintain its functional integrity, enabling efficient clearance of inflammatory cytokines and thereby mitigating the neuroinflammatory response and alleviating clinical symptoms. Therefore, the treatment of adult MDD may require a heightened focus on restoring the function of the lymphatic system to eliminate neurotoxic substances, alleviate neuroinflammation, and facilitate the brain's natural repair processes. In contrast, in adolescent MDD patients, neuroinflammation may not be linked to glymphatic system, thereby necessitating the exploration of alternative treatment approaches grounded in different biological mechanisms.

This study has several limitations. Chief among them is the absence of longitudinal data, which hinders the ability to assess long-term outcomes and establish causal relationships. Moreover, the relatively small sample size in the mild MDD group (only 9 patients) may compromise statistical power, increase the likelihood of random error and thereby limit the robustness of the findings. The study is also susceptible to selection bias, as participants were drawn from a single institution, which may not accurately reflect the broader population. Additionally, the single-center design restricts the external validity of the results, as they may not be generalizable to other clinical settings. Future research should aim to address these limitations by employing larger sample sizes, multicenter collaborations, and longitudinal follow-up to validate the findings, minimize biases, and enhance the generalizability of the conclusions.

Nevertheless, the findings suggest that, in contrast to adults, glymphatic system dysfunction does not significantly manifest in adolescent MDD patients. This discrepancy may stem from age-related differences in glymphatic system functionality, as well as distinct variations in sleep patterns between adolescent and adult MDD patients. Further investigation is warranted to clarify the underlying mechanisms that allow the glymphatic system to remain functional in adolescents with MDD. The divergent glymphatic system function between adolescent and adult MDD patients is critical for the development of age-tailored therapeutic strategies for MDD.

Data Sharing Statement

The data supporting the results of this study are available upon request from the corresponding author.

Author Contributions

Ruohan Feng: Conceptualization, Writing – Original Draft, Writing – Review & Editing. Jie Zhang: Investigation (Subject Recruitment), Data Curation (MRI Scanning), Formal Analysis (Data Analysis), Writing – Original Draft. Xingxiong Zou: Investigation (Subject Recruitment), Data Curation (MRI Scanning), Formal Analysis (Data Analysis), Writing – Original Draft. Xianjie Cai: Writing – Review & Editing, Formal Analysis (Data Analysis). Menghong Zou: Writing – Review & Editing, Formal Analysis (Data Analysis). Hongwei Li: Writing – Review & Editing, Formal Analysis (Data Analysis). Jie Zhang and Xingxiong Zou contributed equally to this work.

All authors agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; and agree to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors declare that they have no financial interests that could be perceived as a conflict of interest.

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