Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Glymphatic Dysfunction in Early-Onset Schizophrenia: DTI-ALPS Index Reduction Tracks Illness Burden and Is Independently Associated with Cognitive Performance in Treatment-Resistant Patients

Ahmet Oz
Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry
Yesim Saglam
Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry
Kubra Turan
Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry
Ipek Ege Gurel Ficicioglu
Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry
Gul Karacetin
Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry
Umit Haluk Yesilkaya
uyesilka@bidmc.harvard.edu

Beth Israel Deaconess Medical Center

Research Article

Keywords: Cognition, DTI-ALPS, early-onset schizophrenia, glymphatic dysfunction, schizophrenia, treatment resistance

Posted Date: June 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9899666/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Early-onset schizophrenia (EOS) is associated with greater cognitive impairment than adult-onset disease, and many EOS patients also develop treatment resistance. Glymphatic dysfunction has been described in adult schizophrenia but not in EOS, and not in relation to treatment resistance. We used diffusion tensor imaging along the perivascular space (DTI-ALPS) to assess glymphatic function in 30 adolescents with EOS (15 treatment-resistant, TRS; 15 non-treatment-resistant, nTRS) and 29 age- and sex-matched healthy controls (HC). Participants completed a neuropsychological battery covering verbal memory, processing speed, executive function, working memory, and social cognition. ALPS differed across groups ($F(2,56) = 34.66$, $p < 0.001$, $\eta^2 = 0.553$), with values dropping from HC (1.625 ± 0.072) to nTRS (1.501 ± 0.098) to TRS (1.439 ± 0.048); the TRS–nTRS effect was large ($d = 0.81$, $p = 0.066$). Patients showed broad cognitive deficits relative to HC, but nTRS and TRS did not differ on any measure after correction. ALPS was inversely related to the number of psychotic episodes ($\rho = -0.391$, $p = 0.033$) but unrelated to PANSS scores or antipsychotic dose. Within TRS, ALPS independently predicted working memory (KAS: $\beta = +0.74$, $p = 0.003$); a parallel association with categorical fluency ($\beta = +0.92$, $p < 0.001$) was driven in part by an influential observation and is exploratory. No predictive models held in nTRS. Glymphatic dysfunction appears to be a disease-intrinsic feature of EOS, lowest in TRS, linked to cumulative episodes rather than current symptoms, and may contribute to cognitive impairment in treatment-resistant patients.

1. INTRODUCTION

Schizophrenia is a severe and heterogeneous psychiatric disorder with a lifetime prevalence of approximately 0.7%, characterised by positive symptoms, negative symptoms, and pervasive cognitive impairment[1]. Although the modal age of onset occurs in early adulthood, a clinically distinct subgroup presents before the age of 18 years. Early-onset schizophrenia (EOS), defined as onset between 13 and 17 years of age, and very early-onset schizophrenia (VEOS), defined as onset before 13 years, together account for approximately 4–8% of all schizophrenia diagnoses[2]. EOS is associated with more severe clinical presentation, greater neurodevelopmental disruption, higher rates of family loading, and a more malignant long-term course compared with adult-onset illness[3]. The adolescent brain, undergoing active synaptic pruning, myelination, and prefrontal maturation, may be particularly susceptible to the pathological processes underlying schizophrenia, amplifying the neurobiological consequences of each psychotic episode.[4].

Cognitive impairment is now widely recognised as a core feature of schizophrenia rather than a secondary consequence of positive symptoms or medication[5]. Patients with EOS demonstrate deficits of greater magnitude than their adult-onset counterparts across virtually all cognitive domains, including verbal memory, processing speed, executive function, working memory, and social cognition[6], [7]. Meta-analytic estimates indicate that global cognitive impairment in EOS is substantially greater than that typically observed in adult-onset schizophrenia[8]. Crucially, cognitive deficits in EOS are largely established at or before the first psychotic episode and do not fully remit following antipsychotic

treatment, suggesting they reflect an underlying neuropathological process rather than state-dependent symptom effects[8]. While core cognitive deficits are largely established at illness onset, processing speed, executive function, and verbal memory remain vulnerable to further decline with repeated episodes and illness chronicity [8].

Treatment-resistant schizophrenia (TRS), defined as failure of at least two adequate antipsychotic trials of at least 12 weeks, affects approximately 20–30% of adults with schizophrenia [9] and a substantial proportion of EOS patients [10]. TRS is associated with more severe and broader cognitive impairment than treatment-responsive illness, independent of symptom burden[11], and clozapine, the only agent with established efficacy in TRS [12], produces only partial cognitive response in many patients [13]. Its neurobiological basis remains under investigation, with dopamine supersensitivity, glutamatergic dysfunction, and progressive neuroinflammation among the leading hypotheses.[11].

The glymphatic system is a perivascular fluid transport network in which CSF enters the brain parenchyma via periarterial spaces, exchanges with interstitial fluid through aquaporin-4 (AQP4) water channels on astrocytic endfeet, and drains into perivenous spaces.[14]. It clears metabolic waste products including amyloid-β, tau, and lactate during slow-wave sleep, when activity is maximal.[15]. Glymphatic impairment has been implicated in Alzheimer's disease, Parkinson's disease, traumatic brain injury, and, more recently, schizophrenia spectrum disorders.[15], [16] In schizophrenia, slow-wave sleep reduction, altered AQP4 polarisation, and neuroinflammation collectively impair glymphatic efficiency[17], [18]. Impaired clearance of inflammatory mediators and metabolic by-products may in turn, perpetuate the neuroinflammatory and excitotoxic cascades implicated in cognitive decline. Direct in vivo assessment of glymphatic function has historically required invasive or radiotracer-based approaches.

Taoka et al. introduced the ALPS index, a non-invasive DTI-derived metric quantifying water diffusivity along medullary veins and arteries as an indirect surrogate of perivascular fluid dynamics[19]. It is calculated as the mean of Dxx in projection and association fibres divided by the mean of Dyy in projection and Dzz in association fibres, and its correspondence with intrathecal gadolinium-based glymphatic measurements has been evaluated in several imaging studies[20]. Reduced ALPS index has been reported in normal ageing, Alzheimer's disease, Parkinson's disease, and normal pressure hydrocephalus[16], [20].Additionally, in adult schizophrenia, it is significantly lower than in healthy controls, with preliminary evidence of correlation with cognitive impairment.[21]. However, no study to date has examined ALPS index in the EOS population, in which the glymphatic system may be particularly vulnerable given the intersection of developmental neuroplasticity and early psychotic illness. In older adults and patients with neurodegenerative conditions, a lower ALPS index is associated with poorer memory, processing speed, and executive function[15], [16], while in adult-onset schizophrenia, it has been associated with verbal learning, processing speed, and working memory.[21].

Against this background, the present study aimed to investigate glymphatic function, as indexed by the ALPS index, in a clinically well-characterised sample of adolescents with EOS, comparing patients with

TRS and nTRS to healthy controls. We tested the following pre-specified hypotheses: (1) ALPS index would be significantly lower in EOS patients than in healthy controls, and lower in TRS than in nTRS patients, reflecting greater glymphatic impairment with increasing disease severity; (2) ALPS index would be positively correlated with cognitive performance across multiple domains, consistent with glymphatic function as a determinant of cognitive reserve in early psychosis; and (3) the relationship between ALPS index and cognition would be more pronounced within the TRS subgroup, where the cumulative neurobiological burden is greatest.

2. METHOD

2.1 Participants

A total of 59 individuals (30 patients and 29 healthy controls) were recruited for this study between June 2022 and December 2025. Patients were adolescents diagnosed with a schizophrenia spectrum disorder according to DSM-5 criteria, recruited from outpatient psychiatric clinics, who were able to participate in a clinical interview without symptoms precluding engagement (e.g., psychotic agitation, mutism, or catatonia). Patients were divided into two groups based on current clinical status: 15 patients meeting Andreasen's remission criteria formed the nTRS group (EOS, n = 12; VEOS, n = 3) [22], and 15 patients meeting TRRIP Working Group criteria formed the TRS group (EOS, n = 9; VEOS, n = 6) [9]. Patients were excluded if their psychotic disorder was attributable to a general medical condition or substance use; if they or their caregiver had a comorbid neurodevelopmental disorder (ASD, ADHD, SLD, or intellectual disability); if they had a significant neurological or chronic medical condition, ongoing non-psychiatric medication use, a history of head trauma with loss of consciousness, sensory impairments interfering with cognitive testing, or active substance use or ongoing psychostimulant treatment within the preceding month. Twenty-nine healthy controls matched on age, sex, and BMI were also recruited. Controls were excluded if they carried any DSM-5 psychiatric diagnosis, met patient exclusion criteria 3–8, or had a first-degree relative with a psychotic disorder. Before commencement, all participants were briefed about study procedures, and written consent was obtained only from those willing to partake. Ethical clearance for the study was acquired from the Ethics Committee of [Blinded for Review] (IRB Date/Number: April 04, 2022–2022/120).

2.2 .Imaging Acquisition and DTI-ALPS Processing

2.2.1 Imaging Acquisition

MRI was performed on a 1.5-T Siemens MAGNETOM Aera (Siemens Healthineers, Erlangen, Germany) with a 16-channel head coil at Bakırköy Prof. Dr. Mazhar Osman Hospital. Whole-brain T1-weighted images were acquired with a sagittal 3D MP-RAGE sequence (TR/TE/TI = 1900/3.0/900 ms, flip angle 9°, FOV 256 × 256 mm², matrix 256 × 256, 1.0 mm isotropic voxels, no gap, 160–176 slices) and reoriented to the AC–PC line before processing. DTI used an axial single-shot spin-echo EPI sequence (TR 9200 ms, TE 95 ms, FOV 230 × 230 mm², matrix 128 × 128 or 256 × 256, slice thickness 2 mm, no gap, 60–70

slices), with b = 0 and 1000 s/mm² along 30 non-collinear directions; additional reversed posterior–anterior phase-encoded b0 images were acquired for susceptibility correction.

2.2.2 DTI Processing and ALPS Index Calculation

Preprocessing used FSL 6.0.7 (FMRIB, University of Oxford, UK). Susceptibility-induced EPI distortions were corrected with topup using reversed phase-encoding b0 images[23]. Eddy-current distortions, gradient-dependent spatial distortions, inter-volume and slice-to-volume motion, and movement-by-susceptibility effects were corrected with GPU-accelerated eddy[24], using outlier replacement, quadratic first-level and linear second-level eddy-current models, slice-to-volume motion correction, movement-by-susceptibility estimation, and gradient reorientation. Corrected data were reconstructed in DSI Studio (2021 May), generating FA and direction-specific diffusivity maps (Dxx, Dyy, Dzz along x, y, z). The DTI-ALPS index was calculated using an ROI-based approach on color-coded FA maps. At the level of the lateral ventricular body, projection fibers were identified by their superior–inferior orientation and association fibers by their anterior–posterior orientation. Spherical ROIs were manually placed in both fiber regions bilaterally (four ROIs per subject), where perivascular spaces are assumed to run along the x-axis, perpendicular to both fiber populations; CSF, gray matter, and crossing-fiber regions were avoided to limit partial-volume effects. Mean directional diffusivities were extracted, and the index was computed as the ALPS index **(**Fig. 1**).**

Left- and right-sided ALPS indices were calculated separately, and the mean of the two hemispheric values was used as the global ALPS index. All region-of-interest placements were visually checked on color-coded fractional anisotropy maps to confirm anatomical accuracy and to reduce partial-volume effects or contamination from neighboring fiber tracts.

2.3. Study Design

This study used a cross-sectional design with prospective clinical follow-up to determine treatment resistance status. MRI and neuropsychological assessments were completed within the same week for all participants. Clinical severity was assessed using the Positive and Negative Syndrome Scale (PANSS), administered by a psychiatrist. All neuropsychological assessments were administered by a trained psychologist. The battery assessed verbal memory, processing speed, executive function, working memory, and social cognition, and comprised the Rey Auditory Verbal Learning Test, Digit Span, Digit Symbol Coding, Controlled Oral Word Association Test, Category Fluency, Auditory Consonant Trigrams, Visual Reproduction, Stroop Colour-Word Test, Trail Making Test Parts A and B, and the Reading the Mind in the Eyes Test.

2.4. Statistical Analyses

All statistical analyses were conducted using Python with the scipy and numpy libraries. Group differences in the ALPS index were examined using one-way ANOVA followed by Tukey's HSD post hoc test for the three-group comparison (HC, nTRS, TRS) and the Mann–Whitney U test for the two-group comparison (HC vs EOS). Cognitive performance differences across groups were assessed using

Mann–Whitney U tests. Associations between ALPS index, cognitive variables, PANSS scores, clinical variables, and medication-related factors were examined using Spearman's rank correlation. Effect sizes are reported as eta-squared (η^2) for ANOVA, Cohen's d for pairwise comparisons, and rank-biserial r for Mann–Whitney tests. The Benjamini–Hochberg false discovery rate procedure was applied within each family of tests. To examine whether the ALPS index independently predicted cognitive performance after controlling for age and chlorpromazine-equivalent dose, multiple linear regression was performed with standardised coefficients (β) reported. Given small subgroup sizes (n = 12–15), model stability was assessed using leave-one-out cross-validation (LOO-CV); models with negative LOO-CV R^2 were not interpreted. Model significance was additionally verified using permutation testing (5,000 permutations). Statistical significance was accepted at $p < 0.05$ (two-tailed).

3. RESULTS

3.1 Sample Characteristics

The study included 59 participants: 29 HC, 15 nTRS, and 15 TRS patients (Table 1). Groups were comparable in age and gender (all $p > 0.18$). TRS patients had significantly more hospitalisations (1.6 ± 0.7 vs 0.8 ± 0.4, $p = 0.001$) and episodes (1.9 ± 0.5 vs 1.2 ± 0.4, $p = 0.001$) than nTRS. PANSS Negative scores were significantly higher in TRS (25.5 ± 7.5 vs 16.0 ± 4.6, $p = 0.001$, $q = 0.003$); other PANSS subscales did not differ (all $p > 0.49$).

Table 1
Sociodemographic and clinical characteristics by group

Variable	HC (n = 29)	nTRS (n = 15)	TRS (n = 15)	p value	Test
Sociodemographic characteristics					
Age (years), mean ± SD	16.8 ± 0.8	17.0 ± 1.0	16.5 ± 1.3	0.305	*ANOVA*
Gender — Male, n (%)	15 (52%)	10 (67%)	5 (33%)	0.187	χ^2
Education (years), mean ± SD	11.0 ± 2.1	9.7 ± 1.2	8.6 ± 1.3	< 0.001	*KW*
Smoking, n (%)	0 (0%)	1 (7%)	0 (0%)	0.225	χ^2
Clinical characteristics (patients only)					
Diagnosis: EOS / VEOS	—	12 / 3	9 / 6	—	—
Duration of illness (months)	—	30.5 ± 12.6	38.0 ± 12.9	0.206	*MWU*
No. of hospitalizations	—	0.8 ± 0.4	1.6 ± 0.7	**0.001**	*MWU*
No. of psychotic episodes	—	1.2 ± 0.4	1.9 ± 0.5	**0.001**	*MWU*
CPZ equiv. dose (mg)	—	1019.8 ± 521.1	888.8 ± 412.7	0.443	*MWU*
Family history of psychosis, n (%)	—	1 (7%)	7 (47%)	**0.021**	χ^2
History of ECT, n (%)	—	3 (20%)	5 (33%)	0.683	χ^2
PANSS scores (patients only) (mean ± SD)					
PANSS Positive	—	13.1 ± 5.5	14.1 ± 10.9	0.524	*MWU*
PANSS Negative	—	16.0 ± 4.6	25.5 ± 7.5	**0.003**	*MWU*
PANSS General	—	28.9 ± 8.0	30.3 ± 15.5	0.710	*MWU*
PANSS Total	—	57.9 ± 15.9	63.7 ± 35.2	0.896	*MWU*

HC = healthy control; nTRS = non-treatment-resistant schizophrenia; TRS = treatment-resistant schizophrenia; EOS = early-onset schizophrenia; VEOS = very early-onset schizophrenia; CPZ = chlorpromazine equivalent dose; ECT = electroconvulsive therapy; PANSS Positive and Negative Syndrome Scale; ALPS = along-the-perivascular-space index. Continuous variables: mean ± SD. ANOVA = one-way analysis of variance; KW = Kruskal–Wallis test; MWU = Mann–Whitney U (nTRS vs TRS); χ^2 = chi-square. Bold p values indicate p < 0.05.

3.2 ALPS Index Across Diagnostic Groups

A one-way ANOVA revealed a significant group effect on the bilateral ALPS index [$F(2, 56) = 34.66$, $p < 0.001$, $\eta^2 = 0.553$; Fig. 2A-C]. Parametric assumptions were met (Shapiro–Wilk all $p > 0.30$; Levene's $p = 0.063$). Tukey HSD post-hoc tests showed higher ALPS in HC than nTRS ($d = 1.52$, $p < 0.001$) and HC than TRS ($d = 2.87$, $p < 0.001$), with a non-significant trend toward lower ALPS in TRS than nTRS ($d = 0.81$, $p = 0.066$). Group means were HC = 1.625 ± 0.072, nTRS = 1.501 ± 0.098, and TRS = 1.439 ± 0.048. Pooling all patients into a single EOS group, the ALPS index was substantially lower in EOS than HC (1.470 ± 0.082 vs. 1.625 ± 0.072; Mann–Whitney U, $p < 0.001$, $d = 2.01$, rank-biserial $r = 0.84$; Fig. 2D-E), confirmed by an independent-samples t-test [$t(57) = 7.73$, $p < 0.001$].

3.3. Cognitive Performance Across Groups

Both patient groups showed broad cognitive impairment relative to HC (Fig. 3). The most pronounced deficits were in verbal memory (REY learning: $z = -1.9$ nTRS, -2.1 TRS), processing speed (TMT-A: $z = -1.9$ and -3.2), and executive function (Stroop color-word: $z = -1.9$ and -4.2). Mann–Whitney U with FDR correction confirmed significant impairment in 18/23 measures between HC and EOS, 15/23 between HC and nTRS, and 16/23 between HC and TRS (all $q < 0.05$). Critically, no measure differed between nTRS and TRS after FDR correction, indicating that cognitive impairment is largely independent of treatment-resistance status.

3.4 Correlations Between ALPS Index and Cognitive Performance

Spearman correlations between the ALPS index and cognitive performance were examined in the combined EOS sample **(**Fig. 4**)** and separately for each group **(**Fig. 5**).** In HC, no association survived FDR correction. Within nTRS, the only nominally significant association was with WISC-R Digit Span Forward ($\rho = -0.672$, $p = 0.017$), which did not survive correction ($q = 0.384$) and is not interpreted. Within TRS, three measures reached nominal significance: categorical fluency ($\rho = +0.689$, $p = 0.013$), REY learning total ($\rho = +0.657$, $p = 0.015$), and KAS total ($\rho = +0.650$, $p = 0.016$); positive correlations of similar magnitude were also seen for visual reproduction late ($\rho = +0.543$, $p = 0.055$), ACT ($\rho = +0.574$, $p = 0.065$), and RMET ($\rho = +0.475$, $p = 0.140$). None survived FDR correction ($q = 0.135–0.684$), consistent with limited power at $n = 15$, though the uniformly positive direction across domains is consistent. In the

(A) Correlations between the ALPS index and cognitive test scores, grouped by domain. **(B–D)** Scatter plots of the ALPS index against RMET (social cognition), REY learning total (verbal memory), and categorical fluency (language), with nTRS as squares and TRS as triangles.

combined EOS sample, the strongest association was with social cognition (RMET: $\rho = +0.545$, $p = 0.006$, $q = 0.135$; Fig. 4B), followed by verbal learning (REY: $\rho = +0.400$, $p = 0.043$, $q = 0.328$; Fig. 4C) and categorical fluency ($\rho = +0.377$, $p = 0.063$, $q = 0.363$; Fig. 4D); none reached FDR-corrected significance.

3.5 Multiple Linear Regression: ALPS as an Independent Predictor of Cognition

To test whether ALPS predicted cognition independently of age and antipsychotic dose, multiple linear regressions were run with these covariates, validated by LOO-CV and permutation testing (5,000 permutations) (Fig. 6). The association with verbal learning did not survive covariate adjustment (β = +0.153, p = 0.482). Within TRS, two models survived cross-validation: KAS total (β = +0.743, p = 0.003; LOO-CV R^2 = 0.51; perm. p = 0.007) and categorical fluency (β = +0.916, p < 0.001; LOO-CV R^2 = 0.61; perm. p < 0.001), with CPZ dose and age as additional predictors, respectively(Fig. 6A-B**)**. However, the fluency model was sensitive to an influential observation (Cook's D = 1.22, > 1.0 threshold) and should be regarded as exploratory; the KAS model showed no comparable influence. In the combined EOS sample, ALPS showed nominally significant associations with social cognition (β = +0.496, p = 0.037) and categorical fluency (β = +0.467, p = 0.037); however, both models produced negative LOO-CV R^2 values (RMET: −0.104, perm. p = 0.139; categorical fluency: −0.082, perm. p = 0.113), indicating that neither model generalised beyond the current sample(Fig. 6C-D). The nTRS digit span model was nominally significant but overfit (LOO-CV R^2 = −0.235, perm. p = 0.091) and is not interpreted (Fig. 6E**)**.

3.6 ALPS Index, Psychopathology, and Illness Severity

No PANSS subscale correlated significantly with the ALPS index in the EOS sample (all $\rho < 0.21$, all $q > 0.49$; **Supp.** Figure 1). Additionally, the number of prior psychotic episodes showed a negative trend (ρ = −0.391, p = 0.033, q = 0.163), consistent with progressive glymphatic impairment with illness recurrence. Antipsychotic dose (ρ = +0.265, p = 0.157), illness duration (ρ = +0.048, p = 0.812), and, within TRS, actual clozapine dose (ρ = −0.046, p = 0.877) were all unrelated to ALPS(**Supp.** Figure 2**)**.

4. DISCUSSION

To our knowledge, this is the first study to investigate glymphatic function using the DTI-ALPS index in adolescents with early-onset schizophrenia. Our findings revealed significantly reduced ALPS indices in both TRS and nTRS patients relative to healthy controls, with a gradient consistent with increasing disease severity. Within the TRS subgroup, ALPS independently predicted KAS, with a parallel but more tentative association for categorical fluency. In the combined EOS sample, ALPS showed nominal associations with social cognition and language fluency that did not survive cross-validation and should therefore be interpreted cautiously. Neither antipsychotic dose, clozapine dose, nor serum clozapine blood levels were associated with ALPS or any cognitive outcome.

The observed reduction in DTI-ALPS is consistent with findings from adult and first-episode schizophrenia samples. Whole-brain analyses by Tu et al.[21] and bilateral hemispheric examinations by Abdolizadeh et al.[25] consistently demonstrated reduced DTI-ALPS in patients with schizophrenia compared to healthy controls, indicating pan-systemic glymphatic dysregulation. Peng et al. similarly reported significantly lower global and bilateral DTI-ALPS in first-episode schizophrenia patients, with

this impairment persisting even in patients with minimal antipsychotic exposure[26]. Korann et al. further demonstrated that DTI-ALPS reduction in psychosis spectrum disorders was independent of age, metabolic status, and symptom severity[27]. Our data extend these observations to the early-onset population. EOS is associated with greater premorbid neurodevelopmental disruption and a more severe illness trajectory than adult-onset schizophrenia [28], and illness onset during active synaptic pruning and prefrontal maturation may render the perivascular system particularly susceptible to the sleep disruption, neuroinflammatory activation, and astrocytic stress that accompany a first psychotic episode[29], [30]. The standardised effect sizes for ALPS group differences in our sample are larger than those reported in adult and first-episode schizophrenia cohorts, where Hedges' g values of 0.79 and 0.83 have been reported for global and hemispheric indices, respectively[26]. The absolute mean difference between our HC and EOS groups is, however, consistent with what has been reported in the adult literature,[21], [26]and the elevated standardised values reflect the reduced within-group variability characteristic of a strictly phenotyped, single-site, narrow-age-range adolescent sample rather than an unusually large biological effect. Whether this reflects a genuine biological amplification of glymphatic impairment during adolescent brain development or is an artefact of the reduced variability in our strictly phenotyped sample remains an open question that cannot be resolved with the present data. Studies with larger adolescent samples and direct age-matched comparisons across onset groups are needed to address this question. The gradient from healthy controls through nTRS to TRS, while the direct nTRS-TRS comparison did not reach significance, might reflect progressive accumulation of glymphatic impairment as a function of illness burden, though this interpretation should be treated with caution given the limited sample size of the present study.

Several pathophysiological mechanisms may account for the glymphatic impairment observed in EOS. The glymphatic system depends on polarised AQP4 expression at astrocytic endfeet to drive CSF flow through the brain parenchyma and facilitate interstitial waste clearance, and disruption of this system leads to accumulation of neurotoxic metabolites, including amyloid-β, tau, and inflammatory mediators[31], [32]. Slow-wave sleep, during which glymphatic transport is maximally active[33], is markedly and persistently reduced in schizophrenia, and experimental data confirm that chronic sleep disruption impairs glymphatic transport and promotes accumulation of neurotoxic waste products[34]. Neuroinflammation, which is well documented in schizophrenia spectrum disorders,[35], [36] disrupts astrocytic function and impairs glymphatic clearance, establishing a self-reinforcing cycle in which accumulated inflammatory mediators further compromise perivascular fluid transport.[35]. Moreover, Genome-wide association studies have additionally identified genetic overlap between DTI-ALPS index and neuropsychiatric disorders, including schizophrenia, providing convergent biological support for a disease-intrinsic glymphatic vulnerability in this population[37]. The recent observation that glymphatic dysfunction moderates the association between neuroinflammation and psychomotor symptoms[38] further supports the view that the glymphatic system serves as a critical interface between molecular-level abnormalities and clinical manifestations in schizophrenia spectrum disorders.

Both patient groups demonstrated extensive cognitive impairment relative to healthy controls across verbal memory, processing speed, executive function, and working memory, consistent with the

established neuropsychological profile of schizophrenia[7], [11]. Notably, nTRS and TRS patients did not differ significantly on any cognitive measure, despite clear differences in PANSS Negative scores and ALPS indices. This dissociation suggests that broad cognitive impairment is established early in EOS and does not worsen straightforwardly with treatment resistance. Peng et al. similarly observed that DTI-ALPS distinguished patient subgroups in first-episode schizophrenia where cognitive differences were not apparent, suggesting that perivascular imaging may be sensitive to neurobiological burden that standard assessments do not capture[26]. Glymphatic function, however, did distinguish the two groups, suggesting that DTI-ALPS may capture neurobiological differences between nTRS and TRS that current cognitive assessments do not detect. The association between ALPS and cognitive performance was observed within the TRS subgroup, while no significant associations were found in nTRS patients or healthy controls. Associations between DTI-ALPS and neuropsychological performance have been reported in adult schizophrenia by Tu et al.[21], However, to our knowledge, the moderation of this relationship by treatment resistance status has not previously been investigated. TRS is associated with more advanced and treatment-refractory neurobiological abnormalities[9], and it may be against this background of greater disease burden that glymphatic impairment exerts a more pronounced influence on cognitive function. The ALPS-social cognition association in the combined EOS sample warrants attention. Social cognitive deficits are a core feature of schizophrenia that respond poorly to available pharmacological treatments[11] and are associated with impaired real-world psychosocial functioning[39]. An association between ALPS and social cognition independently of antipsychotic dose suggests that glymphatic dysfunction may contribute to social cognitive impairment through mechanisms not addressed by current antipsychotic treatments.

No significant associations were observed between the ALPS index and any PANSS subscale, a finding now consistent across independent cohorts[25]–[27], and supports the interpretation of DTI-ALPS as a trait neurobiological marker rather than a state measure of current psychopathological severity. The negative association between episode recurrence and ALPS index suggests that cumulative illness burden, rather than current symptom intensity, drives glymphatic impairment. Antipsychotic dosage showed no significant association with ALPS, consistent with findings across cohorts with varying degrees of medication exposure[26], [27]. Actual clozapine serum blood levels, which account for individual variation in drug absorption and metabolism and therefore provide a more definitive pharmacological control than dose data alone, were equally unrelated to ALPS and all cognitive outcomes across a clinically wide concentration range. Taken together, these findings indicate that the glymphatic impairment observed in this sample reflects the disease process rather than its pharmacological treatment.

Several limitations of this study warrant consideration. The within-group analyses were conducted in subgroups of twelve to fifteen patients, which limits statistical power and precludes definitive inference. The cross-sectional design does not allow causal inferences regarding the temporal relationship between glymphatic impairment and cognitive decline, and longitudinal studies are needed to clarify this. Objective sleep assessment and peripheral inflammatory biomarkers were not available from healthy controls, leaving the proposed mechanistic pathways untested. Finally, while the DTI-ALPS index

provides a non-invasive surrogate measure of perivascular fluid dynamics[19], [20], it does not directly capture glymphatic clearance capacity and may be influenced by factors beyond true glymphatic diffusivity, including axonal changes in adjacent white matter tracts.

Our study provides the first evidence of glymphatic dysfunction in EOS, demonstrating that reduced DTI-ALPS is a disease-intrinsic feature that tracks illness burden, is independent of antipsychotic exposure at both the dose and pharmacokinetic level, and predicts cognitive performance in treatment-resistant patients. The associations with social cognition and language fluency suggest that glymphatic dysfunction may contribute to cognitive impairments that remain unaddressed by current pharmacological treatments, and that interventions targeting perivascular fluid dynamics, such as sleep optimisation, neuroinflammatory reduction, or AQP4 modulation, deserve investigation in this population.

Declarations

Acknowledgments

None

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

U.H.Y. and G.K. conducted the study. U.H.Y. performed the statistical analyses. A.O. processed the MRI data and calculated the ALPS index. U.H.Y. and A.O. wrote the manuscript. Y.S., I.E.G.F., and K.T. collected all participants' data. All authors provided feedback on and gave final approval of the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this

article

Informed Consent

Written informed consent was obtained from the patients who agreed to take part in the study.

References

1. M. J. Owen, A. Sawa, and P. B. Mortensen, “Schizophrenia,” *Lancet*, vol. 388, no. 10039, pp. 86–97, 2016, doi: 10.1016/S0140-6736(15)01121-6.

2. A. Vourdas, R. Pipe, R. Corrigall, and S. Frangou, “Increased developmental deviance and premorbid dysfunction in early onset schizophrenia,” *Schizophr. Res.*, vol. 62, no. 1–2, pp. 13–22, 2003.
3. R. Nicolson and J. L. Rapoport, “Childhood-onset schizophrenia: rare but worth studying,” *Biol. Psychiatry*, vol. 46, no. 10, pp. 1418–1428, 1999.
4. I. Feinberg, “Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence?,” *J. Psychiatr. Res.*, vol. 17, no. 4, pp. 319–334, 1982.
5. M. F. Green, “What are the functional consequences of neurocognitive deficits in schizophrenia?,” *Am. J. Psychiatry*, vol. 153, no. 3, pp. 321–330, 1996.
6. S. Frangou, M. Hadjulis, and A. Vourdas, “The Maudsley early onset schizophrenia study: cognitive function over a 4-year follow-up period,” *Schizophr. Bull.*, vol. 34, no. 1, pp. 52–59, 2008.
7. T. K. Rajji, Z. Ismail, and B. H. Mulsant, “Age at onset and cognition in schizophrenia: meta-analysis,” *Br. J. Psychiatry*, vol. 195, no. 4, pp. 286–293, 2009.
8. E. Bora and R. M. Murray, “Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis?,” *Schizophr. Bull.*, vol. 40, no. 4, pp. 744–755, 2014.
9. O. D. Howes *et al.*, “Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology,” *Am. J. Psychiatry*, vol. 174, no. 3, pp. 216–229, 2017.
10. F. Iasevoli *et al.*, “Relationships between early age at onset of psychotic symptoms and treatment resistant schizophrenia,” *Early Interv. Psychiatry*, vol. 16, no. 4, pp. 352–362, 2022.
11. R. A. McCutcheon, J. H. Krystal, and O. D. Howes, “Dopamine and glutamate in schizophrenia: biology, symptoms and treatment,” *World Psychiatry*, vol. 19, no. 1, pp. 15–33, 2020.
12. Y. H. Balcioglu, H. Gokcay, and U. H. Yesilkaya, “One Plus One Sometimes Equals More Than Two: Long-acting Injectable Aripiprazole Adjunction in Clozapine-Resistant Schizophrenia,” *Clin. Neuropharmacol.*, 2020.
13. J. Kane, G. Honigfeld, J. Singer, and H. Meltzer, “Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine,” *Arch. Gen. Psychiatry*, vol. 45, no. 9, pp. 789–796, 1988.
14. M. Nedergaard, “Garbage truck of the brain,” *Science (80-.).*, vol. 340, no. 6140, pp. 1529–1530, 2013.
15. M. K. Rasmussen, H. Mestre, and M. Nedergaard, “The glymphatic pathway in neurological disorders,” *Lancet Neurol.*, vol. 17, no. 11, pp. 1016–1024, 2018.
16. K. Kamagata *et al.*, “Association of MRI indices of glymphatic system with amyloid deposition and cognition in mild cognitive impairment and Alzheimer disease,” *Neurology*, vol. 99, no. 24, pp. e2648–e2660, 2022.
17. M. S. Keshavan *et al.*, “Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data,” *Arch. Gen. Psychiatry*, vol. 55, no. 5, pp. 443–448, 1998.

18. T. Barlattani *et al.*, “Glymphatic system and psychiatric disorders: a rapid comprehensive scoping review,” *Curr. Neuropharmacol.*, vol. 22, no. 12, pp. 2016–2033, 2024.
19. T. Taoka *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.*, vol. 35, no. 4, pp. 172–178, 2017.
20. T. Taoka and S. Naganawa, “Glymphatic imaging using MRI,” *J. Magn. Reson. Imaging*, vol. 51, no. 1, pp. 11–24, 2020.
21. Y. Tu, Y. Fang, G. Li, F. Xiong, and F. Gao, “Glymphatic system dysfunction underlying schizophrenia is associated with cognitive impairment,” *Schizophr. Bull.*, vol. 50, no. 5, pp. 1223–1231, 2024.
22. N. C. Andreasen, W. T. Carpenter, J. M. Kane, R. A. Lasser, S. R. Marder, and D. R. Weinberger, “Remission in schizophrenia: Proposed criteria and rationale for consensus,” *Am. J. Psychiatry*, vol. 162, no. 3, pp. 441–449, 2005, doi: 10.1176/appi.ajp.162.3.441.
23. J. L. R. Andersson, S. Skare, and J. Ashburner, “How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging,” *Neuroimage*, vol. 20, no. 2, pp. 870–888, 2003.
24. J. L. R. Andersson and S. N. Sotiropoulos, “An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging,” *Neuroimage*, vol. 125, pp. 1063–1078, 2016.
25. A. Abdolizadeh *et al.*, “Evaluation of the glymphatic system in schizophrenia spectrum disorder using proton magnetic resonance spectroscopy measurement of brain macromolecule and diffusion tensor image analysis along the perivascular space index,” *Schizophr. Bull.*, vol. 50, no. 6, pp. 1396–1410, 2024.
26. S. Peng *et al.*, “Dual glymphatic roles in first-episode schizophrenia and clinical high-risk for psychosis: Evidence from diffusion tensor image analysis along the perivascular space index,” *Schizophr. Res.*, vol. 288, pp. 26–34, 2026.
27. V. Korann *et al.*, “The Dysregulation of the Glymphatic System in Patients with Psychosis Spectrum Disorders Minimally Exposed to Antipsychotics: La dérégulation du système glymphatique en présence de troubles psychotiques chez des patients peu exposés à des antipsychotiques,” *Can. J. Psychiatry*, vol. 70, no. 3, pp. 260–270, 2025.
28. T. K. Rajji, Z. Ismail, and B. H. Mulsant, “Age at onset and cognition in schizophrenia: Meta-analysis,” *Br. J. Psychiatry*, vol. 195, no. 4, pp. 286–293, 2009, doi: 10.1192/bjp.bp.108.060723.
29. M. R. Basso, H. A. Nasrallah, S. C. Olson, and R. A. Bornstein, “Cognitive deficits distinguish patients with adolescent-and adult-onset schizophrenia,” *Cogn. Behav. Neurol.*, vol. 10, no. 2, pp. 107–112, 1997.
30. S. Grover, S. Sahoo, and R. Nehra, “A comparative study of childhood/adolescent and adult onset schizophrenia: does the neurocognitive and psychosocial outcome differ?,” *Asian J. Psychiatr.*, vol. 43, pp. 160–169, 2019.

31. J. J. Iliff *et al.*, “A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β,” *Sci. Transl. Med.*, vol. 4, no. 147, pp. 147ra111-147ra111, 2012.
32. M. Nedergaard and S. A. Goldman, “Glymphatic failure as a final common pathway to dementia,” *Science (80-.).*, vol. 370, no. 6512, pp. 50–56, 2020.
33. N. L. Hauglund and M. Nedergaard, “Is glymphatic clearance the secret to restorative sleep?,” *Brain*, p. awaf453, 2025.
34. L. Xie *et al.*, “Sleep drives metabolite clearance from the adult brain,” *Science (80-.).*, vol. 342, no. 6156, pp. 373–377, 2013.
35. S. Gu, Y. Li, Y. Jiang, J. H. Huang, and F. Wang, “Glymphatic dysfunction induced oxidative stress and neuro-inflammation in major depression disorders,” *Antioxidants*, vol. 11, no. 11, p. 2296, 2022.
36. X. He *et al.*, “Chronic colitis exacerbates NLRP3-dependent neuroinflammation and cognitive impairment in middle-aged brain,” *J. Neuroinflammation*, vol. 18, no. 1, p. 153, 2021.
37. S. Y. Huang *et al.*, “Genome-wide association study unravels mechanisms of brain glymphatic activity,” *Nat. Commun.* , vol. 16, no. 1, pp. 1–17, 2025, doi: 10.1038/s41467-024-55706-9.
38. Q. Liang *et al.*, “Inflammation and psychomotor retardation in depression: The moderating role of glymphatic system,” *Brain. Behav. Immun.*, vol. 127, pp. 387–395, 2025.
39. M. F. Green, W. P. Horan, and J. Lee, “Nonsocial and social cognition in schizophrenia: current evidence and future directions,” *World psychiatry*, vol. 18, no. 2, pp. 146–161, 2019.

Figures

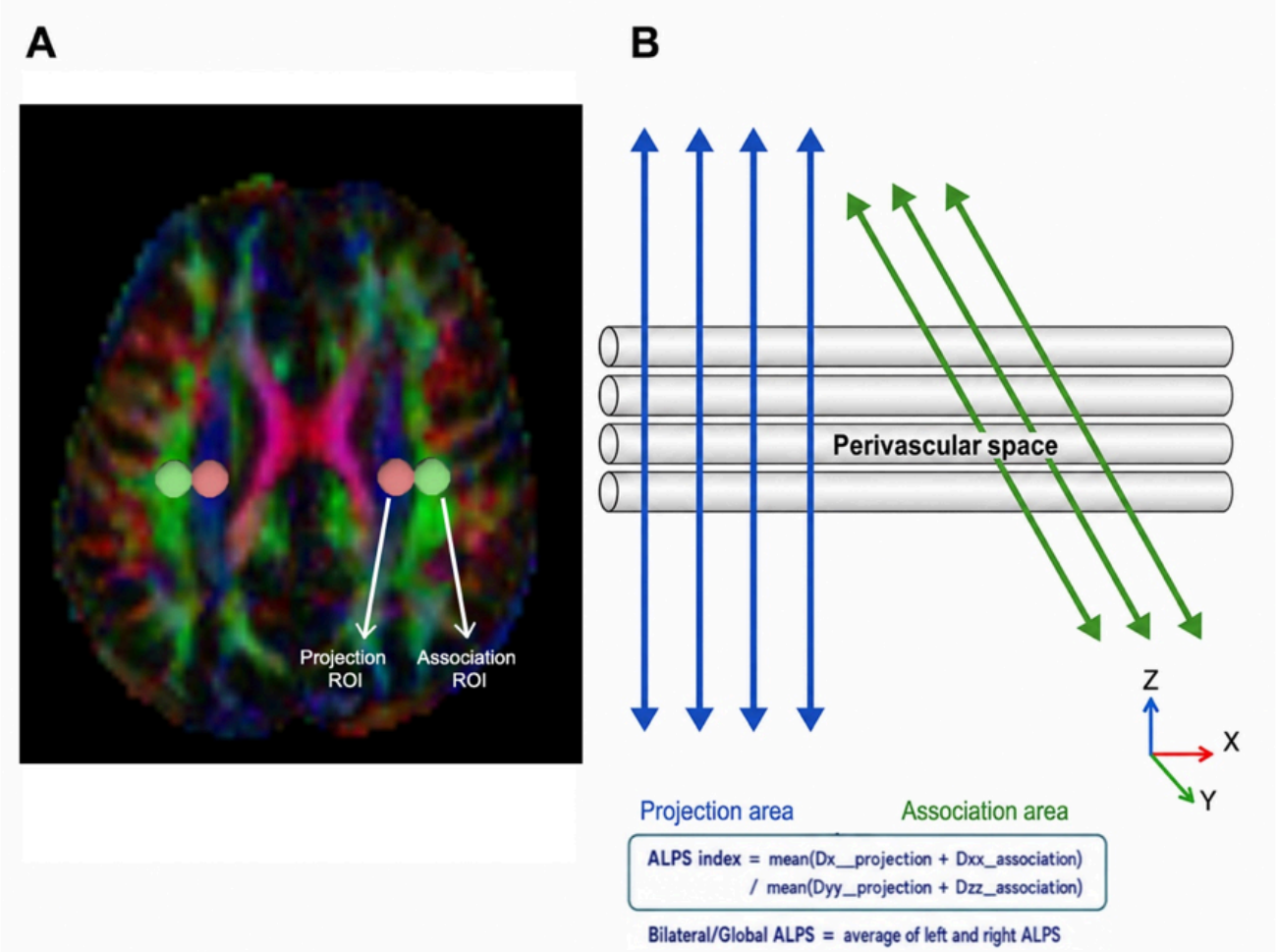


Figure 1

DTI-ALPS analysis. ALP index (**A**) Color-coded FA map showing ROI placement in projection (blue), association (green), and subcortical (red) fiber regions at the lateral ventricular body. (**B**) Schematic of the perivascular space (gray), running along the x-axis perpendicular to projection (Z), association (Y), and subcortical (X) fibers. The ALPS index reflects diffusivity along the x-axis relative to the perpendicular axes.

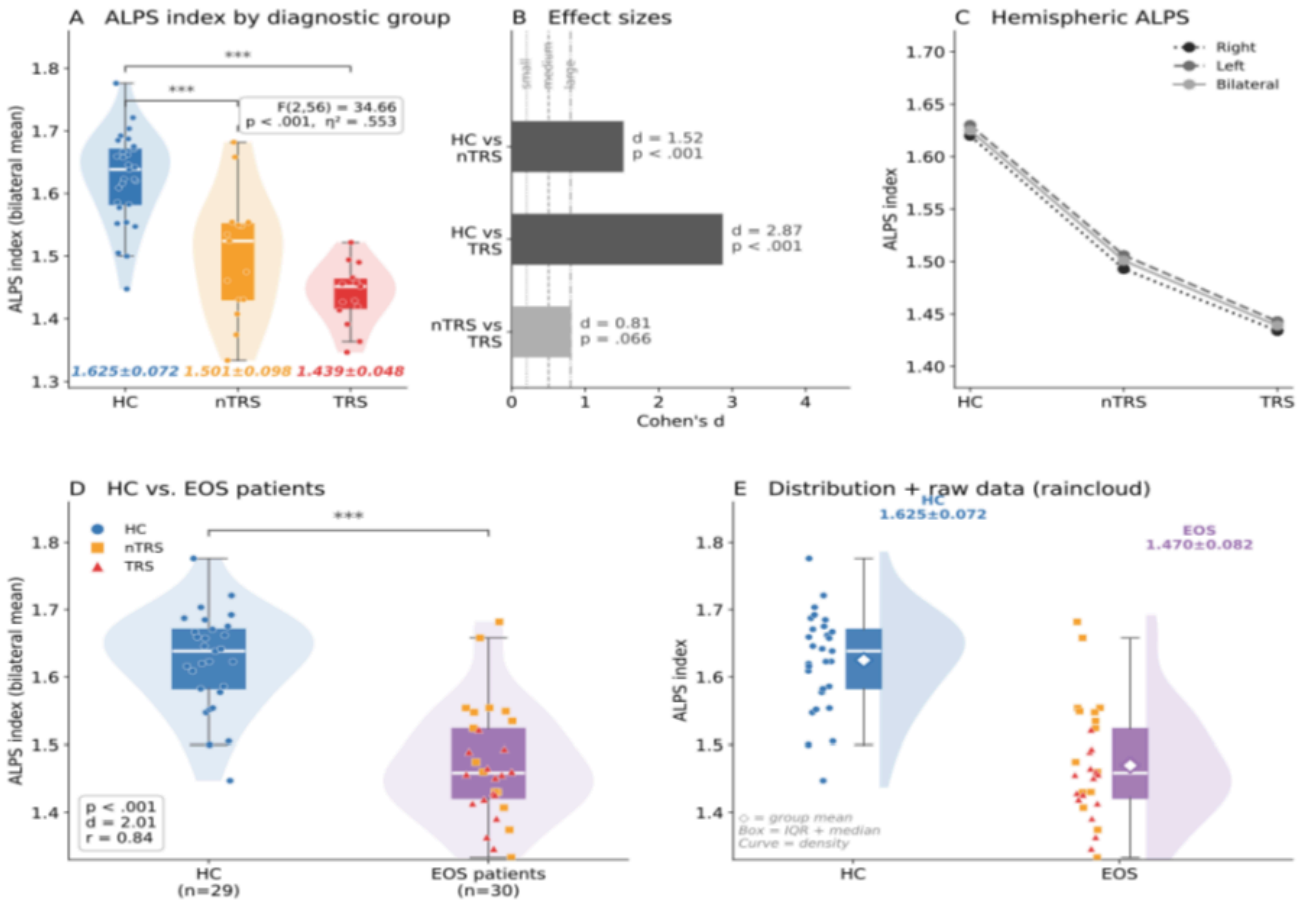


Figure 2

ALPS index in healthy controls and patients with early-onset schizophrenia. (A) Bilateral ALPS index across the three diagnostic groups (HC, nTRS, TRS), shown as violin and box plots with individual data points. **(B)** Pairwise effect sizes between the three groups; dashed lines mark small, medium, and large thresholds. **(C)**Mean ALPS index for the right, left, and bilateral measures across groups. **(D)**Bilateral ALPS index comparing HC and pooled EOS patients (nTRS shown as squares, TRS as triangles). **(E)** Raincloud plot showing the distribution, raw data, and group mean for HC and EOS. HC = healthy controls; nTRS = non-treatment-resistant schizophrenia; TRS = treatment-resistant schizophrenia; EOS = early-onset schizophrenia (nTRS + TRS); *** p < .001.

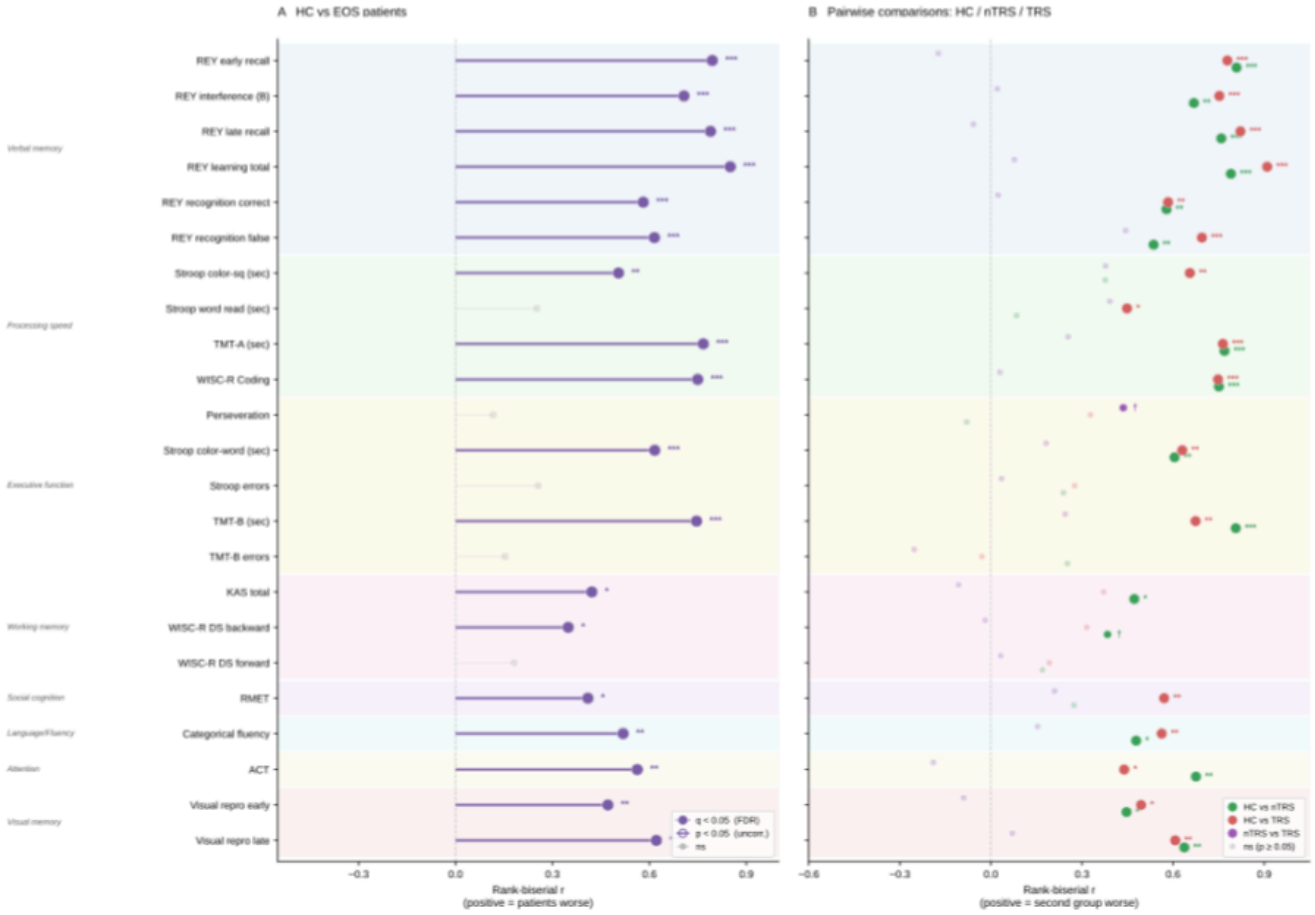


Figure 3

Cognitive performance comparisons across diagnostic groups. **(A)** Comparison between healthy controls (HC) and EOS patients across cognitive tests, grouped by domain. Positive values indicate worse performance in patients. **(B)** Pairwise comparisons between HC, nTRS, and TRS for the same tests, with positive values indicating worse performance in the second group of each pair. Across all panels: HC = healthy controls; nTRS = non-treatment-resistant schizophrenia; TRS = treatment-resistant schizophrenia; EOS = early-onset schizophrenia (nTRS + TRS); † p < .10; * p < .05; ** p < .01; *** p < .001.

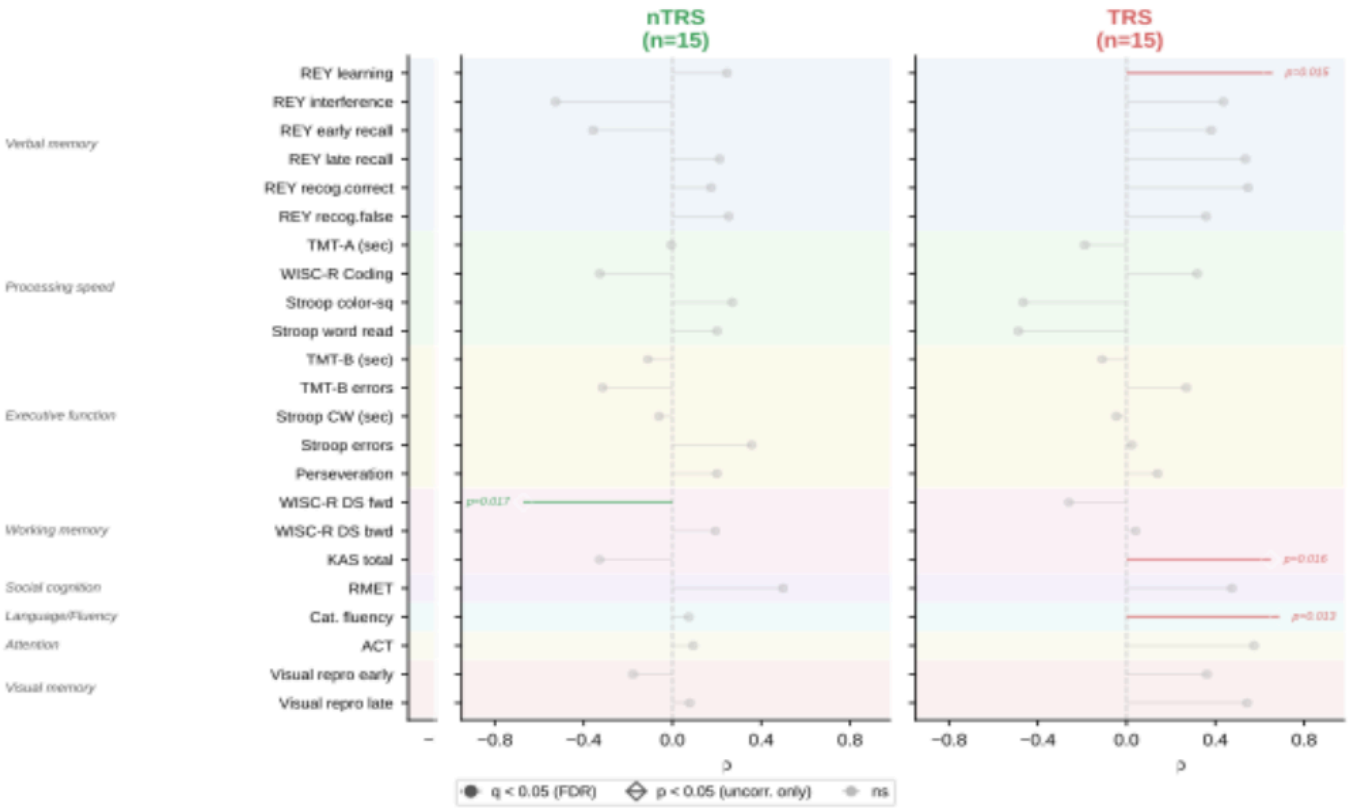


Figure 4

Associations between the ALPS index and cognitive performance in EOS patients

(A) Correlations between the ALPS index and cognitive test scores, grouped by domain. **(B–D)** Scatter plots of the ALPS index against RMET (social cognition), REY learning total (verbal memory), and categorical fluency (language), with nTRS as squares and TRS as triangles.

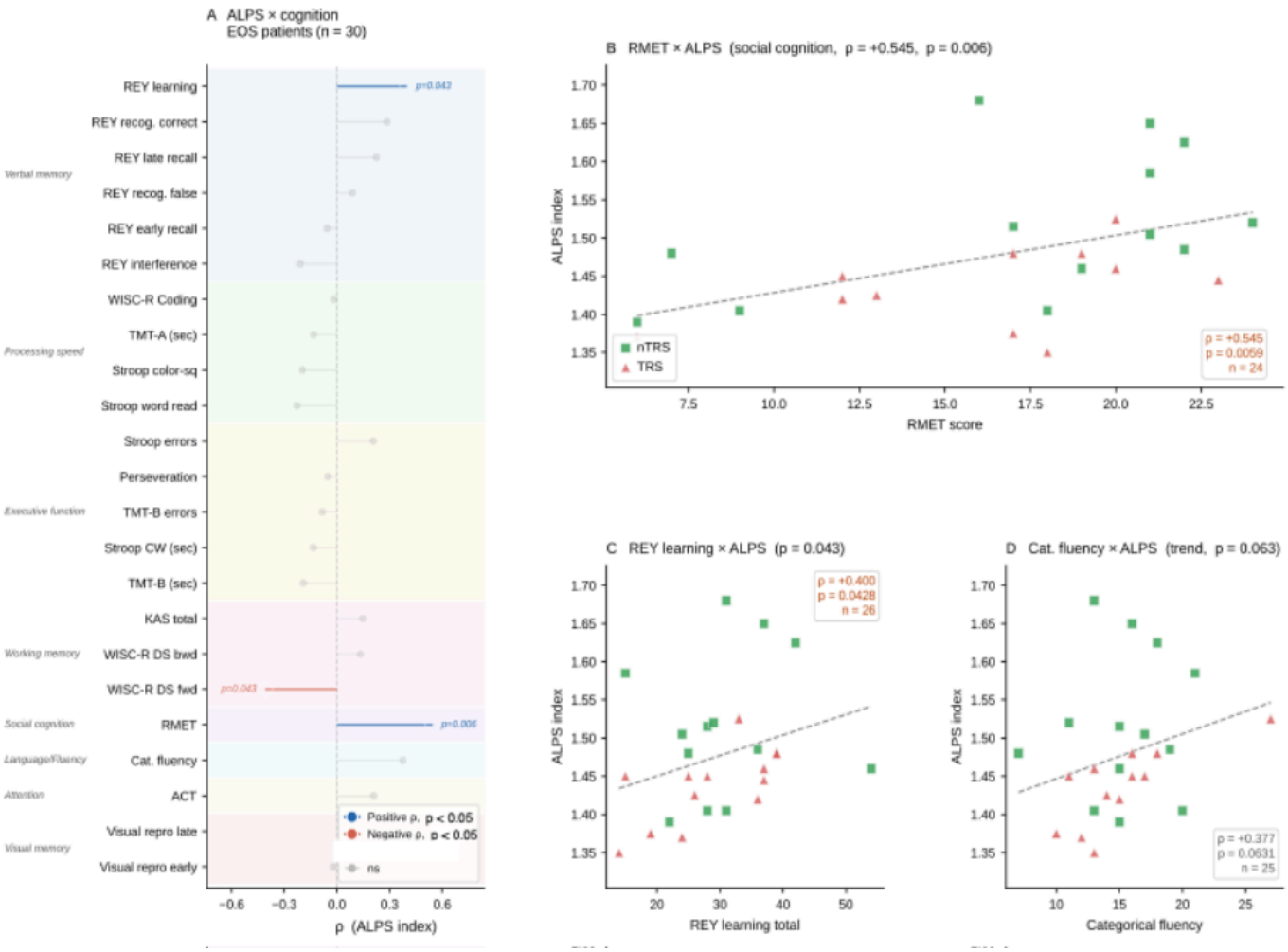


Figure 5

Associations between the ALPS index and cognitive performance in nTRS and TRS patients.

Spearman correlations between the ALPS index and cognitive test scores, shown separately for non-treatment-resistant (nTRS) and treatment-resistant (TRS) schizophrenia, grouped by cognitive domain. Bars extending to the right indicate positive correlations (higher ALPS with better cognitive performance); bars to the left indicate negative correlations. Coloured bars mark p < .05 (green for nTRS, red for TRS); grey bars are non-significant.

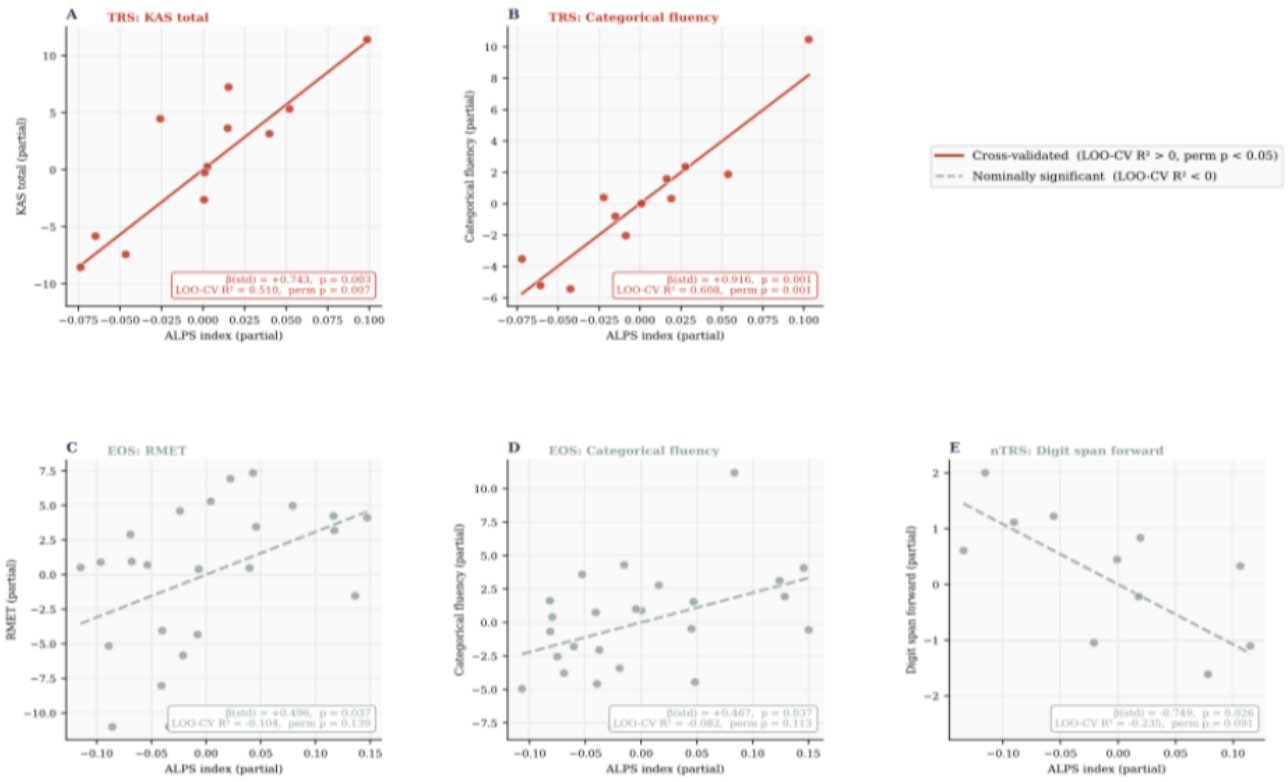


Figure 6

ALPS index as an independent predictor of cognitive performance. Partial regression plots showing associations between DTI-ALPS and cognitive outcomes, adjusted for age and antipsychotic dose. **Panels A–B** show cross-validated models within TRS: KAS total and categorical fluency. **Panels C–E** show nominally significant associations that did not survive cross-validation: RMET and categorical fluency in the combined EOS sample, and digit span forward in nTRS. Solid red lines indicate models surviving (LOO-CV $R^2 > 0$, perm $p < 0.05$); dashed grey lines indicate nominally significant models that did not generalise. Standardised β, p-values, LOO-CV R^2, and permutation p-values are shown within each panel.