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Review

Glymphatic-Related Alterations in Major Depressive Disorder and Treatment-Resistant Depression: Imaging Proxies, Mechanistic Links, and Therapeutic Opportunities

Tommaso Barlattani[1], Chiara D'Amelio[1], Arianna Baschieri[1], Edoardo Trebbi[2], Filippo Trebbi[3], Alessandro Rossi[1], Vassilis Martiadis[4], Valerio Ricci[5], Carmine Tomasetti[6], Domenico De Berardis[6,*], Francesca Pacitti[1]

[1]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, 67100 L'Aquila, Italy
[2]Department of Public Health and Infectious Diseases, "La Sapienza" University of Rome, 00100 Rome, Italy
[3]Psychiatry and Clinical Neurobiology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, 20132 Milano, Italy
[4]Department of Mental Health, Azienda Sanitaria Locale Napoli 1 Centro, 80145 Naples, Italy
[5]Psychiatric Unit, San Luigi Gonzaga University Hospital, 10043 Turin, Italy
[6]Department of Mental Health, Mental Health Center of Giulianova, 64021 Teramo, Italy
*Correspondence: domenico.deberardis@aslteramo.it (Domenico De Berardis)
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Abstract

Major depressive disorder is increasingly conceptualized as a condition involving brain network dysfunction, neuroimmune imbalance, sleep-circadian disruption, hypothalamic-pituitary-adrenal (HPA)-axis dysregulation, monoaminergic arousal instability, and impaired synaptic plasticity. In parallel, the glymphatic system has emerged as a plausible integrative mechanism linking these domains, because it is a glia-dependent pathway supporting cerebrospinal fluid-interstitial fluid exchange and metabolic-waste clearance, with activity strongly modulated by deep non-rapid eye movement (NREM) sleep. This narrative review synthesizes evidence that glymphatic-related magnetic resonance imaging (MRI) proxies, particularly diffusion tensor imaging along the perivascular space (DTI-ALPS), are altered in depression, while emphasizing that DTI-ALPS is an indirect marker of perivascular diffusion rather than a direct measure of glymphatic flow. We define four key research gaps: scarcity of treatment-resistant depression (TRD)-specific cohorts, regional and technical heterogeneity across MRI studies, and uncertainty about causal direction relative to sleep disturbance and inflammation. Altered indices appear to relate to fatigue, psychomotor retardation, cognitive impairment, rumination, suicidality, systemic inflammation, oxidative stress, and HPA-axis dysregulation. We integrate opposite-direction findings, including elevated ALPS in drug-naive somatic depression, into a state- and subtype-dependent working model rather than a unidirectional dysfunction framework. Therapeutic implications are organized by target specificity, including sleep-dependent clearance, perivascular exchange, aquaporin-4 (AQP4) polarization, vascular pulsatility, and neuroimmune modulation. We propose falsifiable predictions and negative-control analyses to distinguish a glymphatic-related model from additive effects of insomnia, inflammation, and vascular risk. Overall, the current evidence supports a cautious translational framework for biomarker-informed trials in TRD-relevant phenotypes rather than a validated diagnostic biomarker.

Keywords: glymphatic system; major depressive disorder; depressive disorder, treatment-resistant; diffusion tensor imaging; sleep; neuroinflammatory diseases

1. Introduction

Despite decades of progress, major depressive disorder (MDD) remains a leading cause of disability worldwide and is associated with recurrent/chronic courses, cognitive impairment, and substantial medical comorbidity [1,2]. Among patients experiencing MDD during their lifetime, about one-third fail to achieve significant and stable clinical improvement after at least two adequate treatment trials, meeting the criteria for treatment-resistant depression (TRD), a condition associated with lower remission rates, poorer long-term outcomes overall, lower social, occupational, and general functioning, and reduced quality of life [3,4]. The dominant neurobiological frameworks, including monoaminergic dysfunction, synaptic plasticity abnormalities, neuroendocrine dysregulation, inflammation, and network-level alterations, are not mutually exclusive [5,6]. However, they do not fully account for the strong and clinically meaningful links between depression, sleep disruption, fatigue, cognitive impairment, and accelerated biological aging [7,8].

In this context, the glymphatic system may offer an integrative lens. Originally described as a glia-dependent "lymphatic-like" clearance pathway [9,10], glymphatic function is shaped by coordinated physiological forces. These include sleep stage-dependent arousal fluctuations [11,12], vascular pulsatility and vasomotion [13], respiratory dynamics, and astroglial water transport (notably

aquaporin-4(AQP4)) arranged around perivascular spaces [14]. Over the last decade, a rapidly expanding neuroimaging literature has reported alterations in magnetic resonance imaging (MRI) glymphatic proxies across psychiatric conditions [15,16], including MDD, with associations with symptom dimensions and biological markers [17,18,19,20]. However, most TRD-relevant inferences still derive from broader MDD cohorts, comorbid insomnia samples, or emerging reports rather than from dedicated TRD imaging studies. A major opportunity is to translate these findings into actionable clinical endpoints: stratification biomarkers, treatment-selection tools, and mechanistically informed interventions [21,22].

To make this framework testable, the present review is organized around four scientific questions: (i) whether glymphatic-related MRI signals differ in non-TRD MDD, insomnia-comorbid depression, and TRD-relevant phenotypes; (ii) whether these signals add incremental explanatory value beyond sleep disturbance, systemic inflammation, vascular risk, and illness chronicity; (iii) whether regional and methodological heterogeneity can explain divergent findings, including opposite-direction along the perivascular space (ALPS) effects; and (iv) which longitudinal changes would support a causal, compensatory, or epiphenomenal interpretation. These questions highlight the core research gaps: the lack of dedicated TRD cohorts, inadequate separation of comorbid insomnia from depression-specific biology, limited harmonization of diffusion tensor imaging along the perivascular space (DTI-ALPS) acquisition/region of interest (ROI) methods, and the absence of longitudinal acute-chronic-remission designs.

In this narrative review, we therefore summarize evidence linking glymphatic-related MRI proxies to MDD and TRD-relevant phenotypes, emphasize where the evidence is direct versus extrapolated, and specify how future studies can test whether these proxies explain symptoms beyond established models of monoaminergic dysfunction, hypothalamic-pituitary-adrenal (HPA)-axis dysregulation, synaptic-plasticity impairment, inflammation, sleep disruption, and vascular risk.

Review Scope and Search Approach

This article was designed as a narrative, nonsystematic review rather than a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-based systematic review. Relevant English-language literature was identified through iterative searches of PubMed/MEDLINE and Google Scholar, together with backward citation tracking of key reviews and primary papers, focusing on publications from 2012 through March 2026. Search terms included combinations of “glymphatic”, “perivascular”, “DTI-ALPS”, “major depressive disorder”, “treatment-resistant depression”, “sleep”, “circadian”, “inflammation”, “HPA axis”, “cortisol”, “monoamine”, “synaptic plasticity”, “choroid plexus”, “ketamine”, “repetitive transcranial magnetic stimulation (rTMS)”, and “bright light therapy”. Because this is a rapidly evolving field, early online articles and preprints were screened when they addressed emerging MRI methods or novel clinical findings; when cited, these sources are explicitly labeled as preprints and are not used as the sole basis for established conclusions. For the revised synthesis, we additionally extracted population type, sample-size information when available, effect direction, and whether the study could distinguish TRD from non-TRD MDD or insomnia-comorbid depression.

2. The Glymphatic System as a Sleep- and Glia-Dependent Clearance Pathway

The glymphatic system describes a pathway for cerebrospinal fluid (CSF) influx along periarterial spaces, exchange with interstitial fluid (ISF) through the parenchyma, and efflux along perivenous routes, facilitating clearance of metabolites, proteins, and inflammatory mediators [9,23]. Astrocytes line the perivascular space and express AQP4 water channels enriched at perivascular endfeet, supporting convective and diffusive exchange at the CSF–ISF interface [14,24].

While the system was initially conceptualized as a bulk-flow mechanism, contemporary views emphasize a spectrum of transport modes (diffusion, dispersion, and convective components) that vary across regions, states, and scales.

2.1 Sleep, Arousal, and Noradrenergic Control

Sleep is a major physiological enhancer of glymphatic transport [11]. Deep non-rapid eye movement (NREM) sleep and transitions in arousal state are accompanied by large-scale neural and hemodynamic rhythmic fluctuations that appear to couple to CSF dynamics [12]. Recent work identified tightly synchronized oscillations in norepinephrine (NE), cerebral blood volume, and CSF signals as predictors of glymphatic clearance during NREM sleep; experimental manipulations of locus coeruleus activity and vascular oscillations were consistent with a mechanistic contribution of vasomotion [13]. Complementarily, the same study reported that zolpidem suppressed NE oscillations and glymphatic flow.

These observations are relevant to depression, as hyperarousal, fragmented sleep, and altered NE tone are common, especially in anxious and melancholic phenotypes and in TRD [7,8].

In line with this framework, a recent MRI study in older “poor sleepers” reported widespread reductions in myelin volume fraction and a lower DTI-ALPS index (a noninvasive proxy for impaired perivascular/glymphatic clearance). Mediation analyses suggested that reduced ALPS partly links poor sleep quality to demyelination, and regional myelin vulnerability also tracked spatial variation

in circadian clock gene expression (*CLOCK/CRY/PER*), pointing to an additional circadian layer on sleep–clearance–glial homeostasis [25].

2.2 Vascular, Respiratory, and Meningeal Lymphatic Interfaces

Glymphatic transport appears to be influenced by vascular drivers such as arterial pulsatility and low-frequency vasomotion, although the relative contribution of these mechanisms remains an active area of investigation [13]. Depression and TRD are frequently associated with cardiometabolic risk, vascular aging, and altered endothelial function, which may weaken the mechanical drivers of perivascular exchange [26].

Respiratory dynamics and CO_2 reactivity also modulate CSF movement. This suggests that breathing-related interventions could be explored as adjunctive modulators of clearance physiology, ideally alongside concurrent physiological monitoring and imaging-based readouts. Together, these factors highlight multiple physiological interfaces that can shape clearance processes.

Beyond the parenchyma, meningeal lymphatic vessels provide drainage to the deep cervical lymph nodes [27]. In parallel, the choroid plexus (ChP) is increasingly implicated in depression-related immune-brain communication and has been associated with MRI glymphatic proxies in large datasets [18]. At present, ChP enlargement is better interpreted as a bidirectional marker than as a proven unidirectional cause: it may reflect chronic immune activation and barrier remodeling, yet once established it could further constrain CSF-brain exchange and perpetuate clearance inefficiency.

2.3 Mechanistic Integration With HPA-axis, Monoaminergic, and Synaptic-Plasticity Models

The glymphatic framework should not be treated as an alternative to established depression models. Instead, it provides a mesoscopic interface through which several established mechanisms could converge. HPA-axis dysregulation may affect perivascular exchange through cortisol-related effects on sleep continuity, vascular tone, endothelial permeability, astrocytic reactivity, and AQP4 polarization [28]. A clinically useful prediction is that cortisol rhythm abnormalities should be associated with glymphatic-related MRI signals after adjustment for age, sleep quality, medication exposure, and inflammatory burden, but should not fully explain those signals if a distinct clearance-related pathway is present.

Monoaminergic systems are also directly relevant. Norepinephrine from the locus coeruleus regulates arousal, vasomotion, and sleep-stage transitions, all of which influence CSF dynamics; serotonergic and dopaminergic systems shape sleep architecture, motivation, psychomotor speed, and vascular/neuroimmune tone. This creates a mechanistic bridge between classic monoaminergic hypotheses and symptoms frequently enriched in TRD, including hyperarousal, fatigue, psychomotor retardation, and cognitive slowing.

Finally, synaptic-plasticity models and glymphatic biology are linked through glial function. Astrocytes regulate glutamate homeostasis, neurovascular coupling, inflammatory signaling, and AQP4-dependent water transport. A clearance-informed account is incrementally useful only if it predicts symptom domains or treatment responses not fully explained by monoaminergic, HPA-axis, inflammatory, or network markers alone. The strongest tests will therefore combine DTI-ALPS or alternative fluid-dynamic MRI measures with sleep physiology, cortisol rhythm, inflammatory markers, and cognitive/network outcomes in the same participants.

3. Decoding Glymphatic-Related Alterations in TRD-Relevant Phenotypes

Treatment-resistant depression can be conceptualized as a "clearance-biology-relevant" phenotype, but this framing remains provisional because it is currently supported mainly by broader MDD, insomnia, inflammatory-depression, and vascular-aging literatures rather than by dedicated TRD imaging cohorts. For this reason, throughout the review we distinguish three levels of inference: direct MDD evidence, comorbid sleep-depression evidence, and TRD-relevant extrapolation. The proposed conceptual framework is summarized in Fig. 1.

Incremental Validity, Boundary Conditions, and Falsifiable Predictions

The framework has incremental validity only if glymphatic-related MRI measures explain clinically relevant variance beyond additive sleep and inflammation effects. A falsifiable prediction is that lower or dysregulated ALPS, impaired cerebrospinal fluid-blood oxygen level-dependent (CSF-BOLD) coupling, or abnormal choroid-plexus/perivascular-space metrics should remain associated with fatigue, psychomotor slowing, cognition, or treatment nonresponse after controlling for objective sleep, C-reactive protein (CRP)/cytokines, HPA-axis markers, vascular risk, and medication exposure. Conversely, if these associations disappear after those covariates are modeled, the glymphatic-related signal should be interpreted as a downstream marker of insomnia, inflammation, or vascular comorbidity rather than a separable mechanism.

A second falsifiable prediction concerns treatment. If an intervention improves depressive symptoms without changing clearance-related physiology, the glymphatic model would not explain that response pathway. If, however, changes in sleep-dependent CSF dynamics, perivascular diffusion, AQP4-relevant glial markers, or vascular pulsatility mediate improvements in fatigue or cognition, then clearance biology may identify a mechanistic subtype within heterogeneous TRD. Such tests require longitudinal

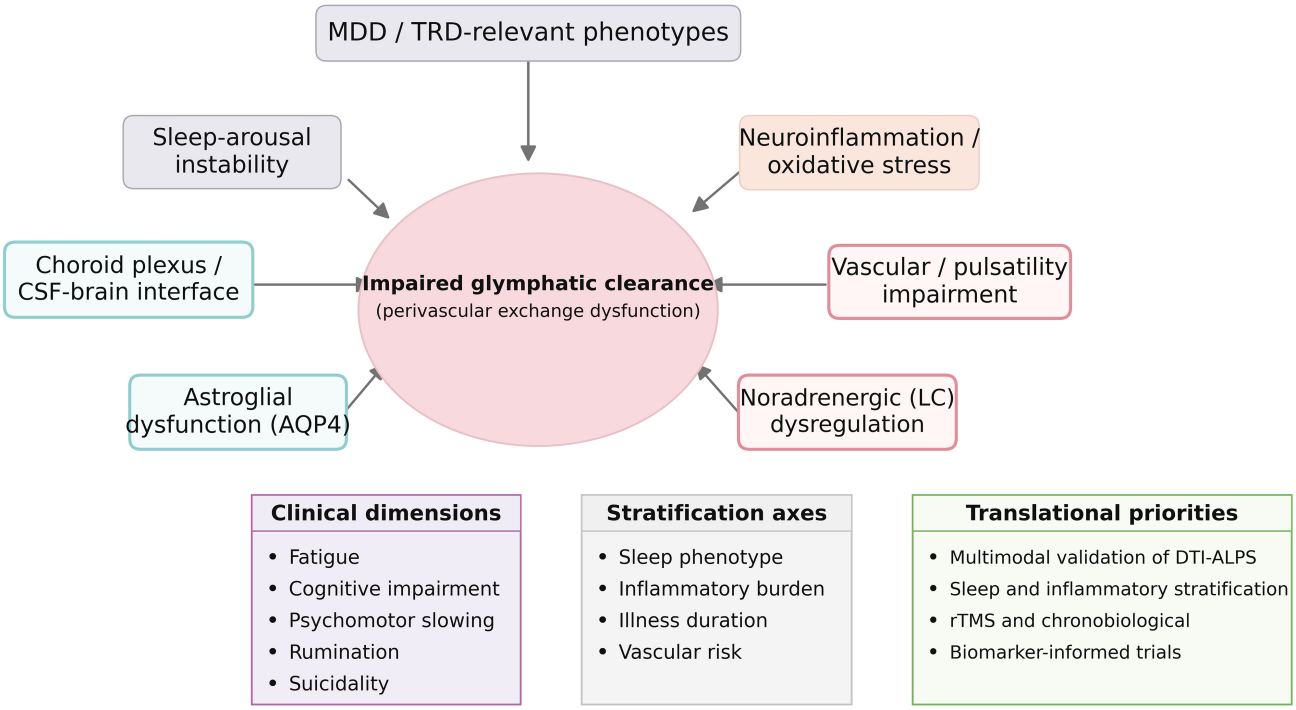

Fig. 1. Conceptual framework of glymphatic dysfunction in MDD and TRD-relevant phenotypes. Multiple TRD-relevant domains, including sleep-arousal instability, neuroinflammation, astroglial dysfunction, vascular impairment, noradrenergic (locus coeruleus) dysregulation, and choroid plexus/CSF-brain interface alterations, converge to impair glymphatic clearance. The framework also integrates clinically relevant symptom dimensions, key stratification axes, and translational priorities for future biomarker-informed studies. MDD, major depressive disorder; TRD, treatment-resistant depression; CSF, cerebrospinal fluid; DTI-ALPS, diffusion tensor imaging along the perivascular space; AQP4, aquaporin-4; LC, locus coeruleus; rTMS, repetitive transcranial magnetic stimulation.

repeated imaging and negative-control outcomes unlikely to depend on glymphatic physiology.

A key candidate driver is the disruption of sleep microarchitecture characteristic of many TRD presentations, including shorter sleep duration, reduced slow-wave activity, chronic insomnia, and persistent hyperarousal, which plausibly limit glymphatic function [7,17]. In this context, the identification of norepinephrine-driven vasomotion as a crucial clearance driver during NREM sleep suggests that dysregulated arousal neuromodulation in depression could weaken the mechanical efficiency of perivascular transport [13].

Neuroimmune and oxidative stress pathways, which are prominent in inflammatory TRD subgroups, may further contribute to impaired clearance physiology. Elevated inflammatory markers, such as CRP, and cytokine patterns have been linked with debilitating symptom dimensions such as anhedonia and psychomotor slowing [5,6]. Reports of choroid plexus hypertrophy and reduced DTI-ALPS indices are consistent with the possibility that chronic immune activation disrupts the CSF-brain interface and constrains perivascular transport pathways. ChP remodeling may therefore be both a consequence of sustained inflammation and a potential amplifier of clearance inefficiency [18,29].

Astrocytes represent another plausible nexus. Astroglial aquaporin-4 (AQP4) polarization is a key determinant of solute transport at the CSF-ISF interface [14], and evidence implicating glial dysfunction in TRD provides conceptual continuity between impaired synaptic plasticity models and emerging clearance-based models. This supports prioritizing glial markers as candidate therapeutic targets, even though direct glymphatic measures in TRD remain limited [21].

Finally, TRD is frequently associated with vascular aging and cardiometabolic comorbidities. In these patients, increased arterial stiffness, endothelial dysfunction, and impaired vasomotion may weaken perivascular pumping mechanisms essential for fluid movement. This may be particularly relevant in late-life depression, where reduced arterial pulsatility could further attenuate clearance-related driving forces [13,26].

4. Glymphatic-Related MRI Alterations in Depression: Clinical Neuroimaging Evidence

A growing set of studies suggests that depression is associated with alterations in glymphatic-related MRI measures. In the following sections, the term “glymphatic-related” is used deliberately: DTI-ALPS and related indices index perivascular diffusion or CSF-coupled physi-

ology and should not be equated with direct *in vivo* measurement of solute clearance. The direction and magnitude of effects vary by subtype, illness stage, comorbidity (especially insomnia), medication exposure, and technical factors relevant to DTI-ALPS interpretation.

4.1 Core Findings: Reduced Glymphatic-Related Diffusion in MDD

Multiple DTI-ALPS studies in MDD report lower ALPS indices than in healthy controls, often linking these reductions to fatigue severity, cognitive symptoms, or white matter abnormalities [30,31]. Large-scale evidence also points to involvement of the immune-CSF interface: in a large sample, MDD was associated with increased ChP volume and reduced DTI-ALPS, and these measures were related to systemic inflammation and oxidative stress markers, supporting a coupled immune-CSF-clearance axis in depression [18,29]. At present, ChP enlargement is best viewed as a bidirectional marker rather than a proven primary cause: it may reflect chronic peripheral immune signaling and barrier remodeling, yet persistent ChP abnormalities could themselves constrain CSF-brain exchange and become therapeutically relevant.

Endocrine regulation is another emerging dimension. One study reported associations between MRI glymphatic proxies and cortisol dysregulation in MDD, consistent with the notion that HPA-axis alterations may affect astroglial polarization, vascular tone, and sleep architecture, each of which is relevant to perivascular exchange [19].

4.2 Inflammation, Psychomotor Slowing, and Network Coupling

Beyond total symptom severity, MRI-derived glymphatic indices appear linked to specific dimensions. One study examined inflammation and psychomotor retardation (PMR), suggesting that lower perivascular diffusion may moderate the relationship between inflammatory markers and motor-network effects, consistent with a pathway in which impaired clearance could amplify inflammation-linked motor slowing [32].

Multimodal work combining DTI-ALPS with functional connectivity adds a network-level layer. In insomnia with comorbid depression, measures of the default mode network (DMN) and glymphatic indices appear to covary, consistent with a shared physiological substrate in which sleep microarchitecture and global arousal may shape both functional connectivity and CSF dynamics [33]. This may be relevant to TRD, where DMN hyperconnectivity and ruminative processes are often prominent.

4.3 State/Stage Heterogeneity: Somatic Depression and Possible Compensation

Not all studies find lower glymphatic indices. In drug-naive somatic depression, higher DTI-ALPS indices have been reported alongside thalamic structural vulnerability [34]. One possible interpretation is state/stage dependency: early illness, medication-naive status, or somatic symptom predominance may be associated with transient increases in perivascular diffusivity before chronic insomnia, inflammation, vascular aging, and white-matter injury reduce clearance efficiency.

A second explanation is methodological. Because DTI-ALPS is an indirect surrogate, changes in crossing fibers, extracellular water, edema, ventricular geometry, and region-of-interest placement can shift the index independent of true glymphatic flow. The practical implication is that future biomarker studies-especially in TRD-should stratify participants at minimum by insomnia severity/objective sleep measures, inflammatory burden (e.g., CRP or cytokine profile), illness duration/chronicity, medication exposure, and cardiometabolic risk, rather than expecting a uniform "lower ALPS" signature.

The elevated ALPS finding in drug-naive somatic depression therefore becomes informative rather than anomalous. It suggests at least three competing working models: an early compensatory model, in which perivascular diffusivity increases before chronic sleep/inflammatory/vascular injury reduces clearance efficiency; a subtype model, in which somatic depression has a different arousal-autonomic-thalamic profile than melancholic/anxious or chronic TRD presentations; and a measurement model, in which apparent ALPS elevation reflects extracellular water, edema, fiber geometry, or ROI placement rather than enhanced clearance. These alternatives are empirically distinguishable only with longitudinal designs, objective sleep monitoring, harmonized ROIs, and orthogonal fluid-dynamic measures.

4.4 Rumination and Cognition: Toward Mechanistic Symptom Biomarkers

Rumination is a key cognitive process in depression and a strong predictor of persistence and TRD. A recent study reported associations between lower DTI-ALPS and rumination and integrated static and dynamic functional connectivity with neurotransmitter-related maps to propose a "glymphatic-rumination" link [35]. While preliminary, this line of work is best considered a mechanistic hypothesis generator rather than definitive biomarker evidence.

4.5 Adolescence, Suicidality, and Bipolar Depression

Findings in adolescents are mixed. Some work in adolescents with MDD reports no clear glymphatic dysfunction and no significant association with sleep quality [36]. In contrast, other multimodal investigations highlight abnormal coupling between glymphatic activity and structure–function patterns in depressed adolescents with suicidality [37]. In bipolar depression, associations between glymphatic dysfunction and personality trait alterations have been reported in individuals with a history of suicide attempts, suggesting that MRI glymphatic proxies may relate

not only to diagnosis but also to risk-relevant phenotypes across mood disorders [38].

The adolescent null study is especially important for boundary-setting. It included 80 first-episode, medication-naive adolescent MDD patients and 58 healthy controls and found no significant ALPS impairment or ALPS-sleep association. This result argues against a universal depression-associated ALPS deficit, but it does not rule out smaller effects, adult or late-life effects, chronicity-dependent changes, TRD-specific alterations, or effects detectable only during sleep or with multimodal CSF-dynamic measures. Future null findings should report confidence intervals, detectable effect sizes, scanner/ROI details, and whether the study was powered for subgroup analyses; otherwise, Type II error remains difficult to interpret.

4.6 Technical Limitations of DTI-ALPS and the Need for Multimodal Validation

DTI-ALPS remains the most widely used MRI proxy in psychiatric studies, but it does not directly measure glymphatic flow. The index is derived from diffusion anisotropy in white matter regions adjacent to the lateral ventricles and can be influenced by factors not specific to perivascular transport, including crossing fibers, white-matter degeneration, edema, ventricular enlargement, motion, and region-of-interest placement [39,40]. Physiological state variables-time of day, recent sleep, hydration, respiration, vascular pulsatility, and medication exposure-may further alter the measurement.

These limitations are especially important for multisite and TRD studies, in which reproducibility across scanners and processing pipelines cannot be assumed. Dedicated harmonization of acquisition parameters, motion correction, and ROI definition is therefore essential. Where feasible, DTI-ALPS should be complemented by more direct or orthogonal readouts, such as CSF-BOLD coupling during sleep, volumetric/perivascular-space analyses, perfusion measures, velocity-spectrum or velocity-selective MRI approaches, and invasive contrast-based methods only in appropriately justified settings [39,40,41,42,43].

Technical heterogeneity should be treated as an analytic variable, not merely a limitation. Minimum reporting should include scanner field strength, diffusion directions, b-values, voxel size, eddy/motion correction, tensor-fitting software, ROI template versus manual placement, laterality, free-water correction, ventricular size adjustment, and whether participants were scanned at a standardized time of day after standardized sleep and caffeine/medication conditions. Without this information, between-study differences in ALPS may reflect acquisition and processing rather than biology.

4.7 A Transdiagnostic Approach for TRD

In line with broader scoping reviews [15], a 2026 preprint systematic review and meta-analysis of diffusion MRI studies using DTI-ALPS across psychiatric disorders reported an overall transdiagnostic reduction in DTI-ALPS compared with controls, with a reduction also present in the mood-disorders subgroup (k = 10; pooled standardized mean difference (SMD) approximately –0.69), albeit with substantial heterogeneity [16]. Because this synthesis is currently available as a preprint, its quantitative estimates should be treated as provisional. Nonetheless, it supports the view that reduced perivascular diffusion may reflect a shared vulnerability factor rather than a depression-specific marker. For TRD, this is both a challenge (limited specificity) and an opportunity (shared biology that could be targeted transdiagnostically).

4.8 Systematic Comparison of TRD, Comorbid Depression, and Non-TRD MDD Evidence

The current evidence base is uneven. Non-TRD or unspecified MDD samples provide the strongest direct clinical imaging evidence. Insomnia-comorbid depression samples provide mechanistic leverage for sleep-dependent clearance but cannot isolate depression-specific effects. TRD-specific evidence remains largely inferential, derived from symptom dimensions and treatment contexts rather than cohorts defined by failure of two or more adequate treatments. Therefore, TRD should be treated as a priority stratum for future studies rather than as an established glymphatic-imaging phenotype (Table 1).

4.9 Acute, Chronic, and Remission-Phase Hypotheses

Illness phase is a critical missing variable. In acute episodes, sleep fragmentation, hyperarousal, cytokine activation, and cortisol abnormalities may transiently alter perivascular diffusivity. In chronic or recurrent depression, persistent insomnia, vascular risk, white-matter injury, and astroglial dysregulation may reduce the efficiency of clearance-related processes. During remission, normalization of sleep and inflammatory tone might partly restore glymphatic-related measures, whereas persistent abnormalities could identify residual vulnerability, cognitive impairment, fatigue, or relapse risk. A decisive test would measure the same participants across acute illness, treatment response, remission, and relapse while collecting objective sleep and inflammatory data.

5. Treatments, Glymphatic Modulation, and Implications for TRD: Distinguishing Evidence Tiers

A central translational question is whether glymphatic-related dysfunction is primarily a disease correlate or a modifiable contributor to symptoms and disability. Emerging work suggests that selected interventions can influence clearance-relevant physiology, but the evidence remains heterogeneous across study designs, populations, and measurement approaches. For clarity, the available therapeutic literature can be grouped

Table 1. Evidence strata distinguishing direct MDD findings, insomnia-comorbid depression evidence, opposite-direction subtype findings, adolescent null findings, and TRD-relevant extrapolation.

Evidence stratum	Representative evidence	Main inference	Key unresolved issue
Non-TRD or unspecified MDD	Cross-sectional adult MDD DTI-ALPS, ChP, cortisol, inflammation, fatigue, PMR, and rumination studies	Supports associations between glymphatic-related MRI proxies and depression-relevant symptoms/biology	Cannot determine treatment resistance, causality, or phase effects
Comorbid insomnia/depression	CID +/- MDD multimodal MRI and sleep-glymphatic physiology literature	Supports sleep-arousal and DMN/CSF-dynamic coupling as a plausible pathway	May reflect insomnia effects rather than depression-specific or TRD-specific biology
Drug-naive somatic depression	Higher ALPS with thalamic vulnerability in somatic depression	Challenges a unidirectional deficit model and supports subtype/state heterogeneity	Requires longitudinal confirmation and orthogonal fluid measures
Adolescent first-episode MDD	Null ALPS findings in first-episode medication-naive adolescents	Defines boundary conditions and suggests adult/chronic/TRD findings may not generalize developmentally	Power for subtle or subgroup effects and sleep-state measures remain limited
TRD-defined cohorts	Direct glymphatic imaging studies remain scarce	TRD relevance is currently inferred from insomnia, inflammation, fatigue, cognition, psychomotor slowing, and treatment studies	Need prospective cohorts stratified by resistance, subtype, sleep, inflammation, and vascular risk

ChP, choroid plexus; PMR, psychomotor retardation; CID, chronic insomnia disorder; ALPS, along the perivascular space; MRI, magnetic resonance imaging; DMN, default mode network.

into four evidence tiers: randomized human trials, early clinical/open-label or pre-post imaging studies, preclinical animal data, and explicitly hypothesis-generating mechanisms (Table 2). Direct TRD-specific studies with glymphatic endpoints remain rare, and interventions should be interpreted according to their putative target: sleep-dependent clearance, perivascular exchange, AQP4 polarization, vascular pulsatility, neuroimmune tone, or synaptic/network remodeling.

5.1 Antidepressant Pharmacotherapy: Predominantly Preclinical and Early Clinical Evidence

Overall, preclinical and early clinical data do not support a straightforward class effect of antidepressants on glymphatic function. An illustrative animal example comes from a chronic stress model in which polyunsaturated fatty acid (PUFA) supplementation improved depression-like behaviors and cognitive impairment while restoring vascular function, AQP4 polarization, and glymphatic transport. In contrast, escitalopram improved depressive-like behavior without restoring glymphatic function or cognitive deficits [44]. This pattern is consistent with the possibility that symptom improvement can occur without full restoration of clearance physiology and that cognition- or fatigue-related dimensions may be more closely linked to clearance recovery.

Early clinical interventional evidence is also emerging. In an 8-week pre-post study, vortioxetine improved glymphatic-related MRI measures, functional connectivity, and cognitive performance in MDD [45]. While replication and TRD-specific testing are needed, multimodal designs combining glymphatic proxies, connectivity, and cognition offer a useful model for TRD trials, in which cognitive impairment and network dysfunction often contribute substantially to disability.

5.2 Chronobiological Interventions: Randomized Human Evidence and Circadian Stabilization

Chronobiological strategies are clinically relevant both for non-seasonal depression and as augmentation approaches in TRD. A 2026 randomized, placebo-controlled trial in subthreshold depression reported that bright light therapy influenced glymphatic-related indices and CSF-related measures. If replicated, these findings would strengthen the case for scalable interventions that directly target circadian alignment, an important determinant of sleep quality and arousal stability [46].

In TRD, where circadian disruption and insomnia are common, chronobiological strategies with potential relevance to glymphatic physiology may include appropriately timed light exposure, structured sleep scheduling, and, where appropriate (e.g., bipolar-spectrum presentations), dark-therapy principles, as well as potentially melatonin-ergic approaches, although direct glymphatic endpoints remain understudied [47].

5.3 Neuromodulation: Early Human Evidence and Mechanistic Rationale

Although rTMS is an established treatment option for TRD, its mechanisms-spanning synaptic plasticity, neuroimmune shifts, network reconfiguration, and sleep effects-remain debated. Nonetheless, glymphatic modula-

Table 2. Intervention-target mapping for TRD-relevant glymphatic hypotheses.

Intervention class	Primary clearance-relevant target	TRD subtype most relevant	Critical test
Chronobiological strategies	Slow-wave sleep stability, circadian alignment, sleep-dependent CSF dynamics	Insomnia/hyperarousal, circadian-delay, seasonal or atypical features	Improved ALPS/CSF-BOLD coupling should track sleep physiology and fatigue/cognition
rTMS/neuromodulation	Network reconfiguration, cortical excitability, autonomic/vascular regulation, possible glial signaling	Cognitive slowing, rumination/DMN dominance, fatigue, sleep-fragmented TRD	Clearance-related change should mediate symptom domains beyond mood score change
Anti-inflammatory/vascular strategies	Endothelial function, vasomotion, immune-CSF interface, oxidative stress	High-CRP/cytokine, cardiometabolic, late-life or vascular-risk TRD	Effects should persist after controlling for sleep and medication exposure
AQP4/glial or PUFA/melatoninergic mechanisms	Astrocytic endfeet polarity, neurovascular coupling, water transport	Cognitive/fatigue-predominant or glial-inflammatory phenotypes	Preclinical AQP4 restoration should translate to human multimodal biomarkers
Ketamine/esketamine and rapid-acting antidepressants	Synaptic plasticity and network effects; possible bidirectional clearance effects	Severe TRD, suicidality, anhedonia; cognitive outcomes may vary	Separate antidepressant response from possible adverse or beneficial CSF-dynamic effects

This mapping is intended to prevent overgeneralization: a treatment may improve mood through monoaminergic, plasticity, or network mechanisms without normalizing clearance-related physiology. Conversely, glymphatic-related change may be most clinically meaningful for fatigue, cognition, psychomotor slowing, and relapse vulnerability rather than for total depression severity alone. CSF-BOLD, cerebrospinal fluid–blood oxygen level-dependent; CRP, C-reactive protein; AQP4, aquaporin-4; PUFA, polyunsaturated fatty acid.

tion represents a plausible contributing mechanism for several reasons. First, rTMS can alter sleep architecture and cortical excitability, potentially shifting slow-wave dynamics relevant to metabolic waste clearance [11,22]. Second, rTMS may influence autonomic and vascular regulation, thereby affecting perivascular fluid movement [13,48]. Third, rTMS can affect astrocyte and microglial signaling pathways relevant to AQP4 polarization, a key determinant of glymphatic function [14,49].

An editorial in *SLEEP* proposed that the neuroprotective effects of rTMS in chronic insomnia may involve glymphatic system modulation, providing a conceptual bridge to depression, given the high insomnia–MDD overlap [22]. A clinical study in older adults further demonstrated that TMS can modulate glymphatic-related measures, supporting the feasibility of assessing glymphatic indices before and after neuromodulation [48].

For TRD, a priority is to test whether standard antidepressant rTMS protocols, such as left dorsolateral prefrontal cortex (DLPFC) high-frequency stimulation, right low-frequency stimulation, bilateral approaches, or intermittent theta burst stimulation (iTBS), produce measurable changes in DTI-ALPS or other glymphatic-related indices, and whether such changes are preferentially associated with improvements in fatigue, sleep quality, and cognition.

5.4 Rapid-Acting Antidepressants: Predominantly Preclinical Ketamine Data

Ketamine is central to contemporary TRD care, but direct glymphatic evidence remains predominantly preclinical. In an animal study, ketamine administration disrupted glymphatic function and was accompanied by cognitive impairment [50]. Other work suggests that timing, dose, and baseline neuroimmune state may influence whether ketamine-related effects support or disrupt clearance-relevant physiology [51].

For TRD trials, this implies that glymphatic endpoints could help distinguish beneficial network or plasticity effects from potentially unfavorable clearance-related effects in some contexts and may help explain heterogeneity in cognitive outcomes after ketamine or esketamine.

5.5 Hypnotics and Sleep Aids: Sedation Is Not Necessarily Clearance Restoration

The demonstration that zolpidem suppressed NE oscillations and glymphatic flow during NREM sleep suggests that some hypnotics may blunt physiological clearance dynamics [13]. A glymphatic-informed approach would prioritize interventions that restore stable slow-wave sleep rather than simply increasing time asleep [52].

Clinical relevance for TRD is also suggested by a randomized comparison reporting antidepressant effects of dexmedetomidine relative to electroconvulsive therapy (ECT) in treatment-resistant depression [53]. Although this study was not designed to test glymphatic endpoints, it highlights noradrenergic and arousal-related mechanisms that may intersect with clearance-relevant physiology and can be prioritized in future biomarker-informed designs.

5.6 Psychedelics and Metabotropic Targets: Explicitly Hypothesis-Generating Mechanisms

Direct empirical evidence linking psychedelic interventions to glymphatic modulation is currently absent. Accordingly, this section should be read as hypothesis-

Table 3. Representative studies linking glymphatic-related MRI features to depression phenotypes and treatment-relevant dimensions, with sample-size/effect-direction notes and selected limitations.

Study	Design	Population	Modality	Main glymphatic-related finding (effect direction)	Key correlates/implications and selected limitations
Yang et al., 2024 [30]	Cross-sectional	MDD vs controls	DTI-ALPS + DTI	Lower ALPS in MDD; linked to white-matter alterations	N = 35 MDD/23 HC; cross-sectional adult MDD sample, not TRD-defined; limited power for subtype, phase, and regional heterogeneity analyses.
Bao et al., 2025 [31]	Cross-sectional	MDD vs controls	DTI-ALPS	Lower ALPS in MDD	N = 46 MDD/55 HC; right ALPS difference reported with fatigue mediation; single-site, non-TRD sample; effect-size reporting and replication are needed.
Gong et al., 2025 [18]	Cross-sectional (large sample)	Large MDD sample vs controls	DTI-ALPS + ChP volumetry + blood indices	Increased ChP volume and decreased ALPS in MDD	N = 665 MDD/338 HC; large cross-sectional sample supports immune-CSF-clearance association, but causal direction and treatment-resistance status remain unresolved.
Chen et al., 2025 [19]	Cross-sectional/ correlational	MDD cohort	DTI-ALPS + cortisol	ALPS-cortisol coupling in MDD	N = 164 depressed/46 HC; supports HPA-glymphatic coupling; cortisol timing, medication exposure, sleep, and chronicity need prospective control.
Liang et al., 2025 [32]	Cross-sectional	MDD vs controls	DTI-ALPS + hsCRP + network measures	Lower ALPS moderates the inflammation–PMR association	N = 67 MDD/67 HC; moderation model links inflammation to PMR; replication in larger TRD cohorts is required to reduce Type II/overfitting concerns.
Deng et al., 2025 [34]	Cross-sectional	Drug-naive somatic depression (vs controls)	DTI-ALPS + VBM	Higher ALPS (especially in somatic depression)	N = 272 total across somatic depression, psychiatric depression, and HC groups; higher ALPS challenges a unidirectional dysfunction model and requires state/subtype and technical explanations.
Tao et al., 2025 [33]	Cross-sectional (multimodal)	Chronic insomnia disorder (CID) ± MDD vs controls	DTI-ALPS + rs-fMRI	DMN alterations parallel ALPS changes in CID+MDD	N = 60 CID+MDD/52 CID-only/56 HC; useful comorbid-insomnia comparison, but does not isolate TRD-specific biology.
Guo et al., 2025 [45]	Interventional (pre- and post–treatment)	MDD treated with vortioxetine	Glymphatic-related MRI + connectivity	Vortioxetine improved glymphatic-related measures and connectivity	Early pre-post clinical design; mechanistic template for trials, but without randomization/TRD stratification, biomarker changes may reflect practice, medication, or regression effects.
Chen et al., 2026 [46]	Randomized, placebo-controlled trial	Subthreshold depression	Bright light therapy trial with glymphatic-related readouts	Bright light therapy influenced glymphatic-related indices/metrics	Randomized evidence in subthreshold depression; not MDD/TRD, so generalization to resistant phenotypes remains uncertain.
Ma et al., 2026 [35]	Cross-sectional	MDD	DTI-ALPS; RRS/HAMD; static & dynamic FC; PET maps	Glymphatic–rumination relationship in MDD	N = 51 MDD/45 HC; preprint and hypothesis-generating; should not be used as definitive biomarker evidence before peer-reviewed replication.
Ranti et al., 2022 [57]	Cross-sectional	MDD (7T MRI)	7T MRI + semi-automated PVS segmentation; trauma assessment (TLEQ)	Higher PVS burden associated with trauma in MDD	7T PVS segmentation rather than DTI-ALPS; trauma-related PVS burden may represent vascular/stress effects rather than direct glymphatic flow.
Zhang et al., 2025 [36]	Cross-sectional	First-episode, medication-naive adolescent MDD vs controls	DTI-ALPS + PSQI	No significant ALPS impairment and no ALPS-sleep association	N = 80 adolescent MDD/58 HC; important null finding. Interpretable as a boundary condition, but subtle effects, phase effects, and TRD-specific effects remain vulnerable to Type II error.

Effect direction is summarized in the "Main glymphatic-related finding" column, and the final column now emphasizes sample size, effect-size/power interpretation, and whether each study can distinguish TRD, comorbid insomnia/depression, and non-TRD MDD. VBM, voxel-based morphometry; HAMD, Hamilton Depression Rating Scale; FC, functional connectivity; PET, positron emission tomography; PVS, perivascular spaces; PSQI, Pittsburgh Sleep Quality Index; 7T MRI, 7-Tesla magnetic resonance imaging; CID, chronic insomnia disorder; RRS, ruminative response scale.

generating only. Potential intersections include DMN reconfiguration, glial/neuroimmune signaling, and metabotropic effects on astrocytic calcium dynamics and sleep-wake regulation [33,54,55,56].

A plausible-but untested-bridge is DMN modulation: because altered DMN-glymphatic coupling has been reported in insomnia with depression, interventions that reduce maladaptive DMN dominance might secondarily influence arousal microarchitecture and CSF dynamics [12,33,35,55].

Metabotropic glutamate receptor modulation on glial cells is another speculative avenue, given links with astrocytic signaling, neurovascular coupling, and neuroimmune regulation [14,54]. However, no direct human glymphatic data are yet available.

Therefore, future work should treat psychedelics and related metabotropic strategies as early mechanistic hypotheses to be tested with pharmacodynamic readouts such as DTI-ALPS, CSF-BOLD coupling, or velocity-spectrum MRI, rather than as evidence-based glymphatic interventions [42,43].

6. A Practical Translational Roadmap for Depression and TRD

To move from correlational findings to actionable biology, depression and TRD research can adopt several concrete design principles (see Table 3 (Ref. [18,19,30,31,32,33,34,35,36,45,46,57]).

6.1 Harmonize Acquisition and Processing

DTI-ALPS studies should harmonize diffusion acquisition parameters, region-of-interest placement rules, motion correction procedures, and confound adjustment, including age, sex, sleep quality, vascular risk, intracranial volume, medication exposure, and time of day. Multisite harmonized pipelines are particularly important for adequately powered TRD trials [39,40].

6.2 Stratify by Sleep–Arousal Phenotype and Inflammation

Rather than treating MDD and TRD as monolithic conditions, future biomarker studies should prioritize at least four stratification axes: (i) insomnia severity and objective sleep/arousal measures, such as actigraphy or polysomnography where feasible; (ii) inflammatory burden, especially CRP/cytokine profiles; (iii) illness duration/chronicity and episode burden; and (iv) medication exposure together with cardiometabolic/vascular risk [7,18,26]. Existing evidence links glymphatic-related indices to fatigue, psychomotor retardation, inflammatory markers, cortisol patterns, and choroid plexus volume, suggesting that these dimensions represent biologically meaningful axes of heterogeneity [18,19,31,32].

6.3 Use Multimodal Endpoints

Future mechanistic trials should combine DTI-ALPS with arterial spin labelling for perfusion, resting-state functional MRI to assess default mode network dynamics, choroid plexus volumetry, and blood-based inflammatory and oxidative markers [33,58]. Emerging MRI approaches, including velocity-spectrum imaging and related velocity-selective methods, may provide more direct indices of fluid dynamics and could be incorporated into early-phase studies [42,43].

6.4 Prioritize Interventions Most Likely to Modify Glymphatic Function

Based on current evidence, the most plausible modifiable drivers include sleep stabilization [47], circadian alignment through appropriately timed light and dark exposure, vascular fitness through physical exercise [13], neuroimmune modulation using anti-inflammatory or antioxidant strategies where clinically appropriate [29], and neuromodulation approaches targeting sleep architecture and large-scale network dynamics [22,48].

6.5 Falsification and Negative-Control Analyses

Future studies should predefine conditions that would weaken the framework. These include: (i) no association between glymphatic-related MRI measures and TRD-relevant symptoms after adjustment for sleep, inflammation, cortisol, and vascular risk; (ii) no change in clearance-related measures despite objective sleep restoration; (iii) symptom response to a putatively clearance-targeting intervention without biomarker change; (iv) equivalent ALPS effects in depression and nondepressed insomnia after sleep variables are modeled; and (v) inconsistent results across harmonized acquisition/processing pipelines. Negative-control outcomes and regions not expected to depend on perivascular exchange should be included to detect nonspecific white-matter or motion artifacts.

7. Conclusions

Research on glymphatic-related function in depression has progressed from hypothesis and analogy to a growing empirical neuroimaging literature. Across mood disorders, altered diffusion-based indices may reflect a transdiagnostic vulnerability potentially relevant to TRD; however, most available human evidence still comes from broader MDD, insomnia-comorbid, or mixed mood-disorder samples rather than cohorts defined by formal treatment resistance.

Important limitations should temper interpretation. First, the literature remains dominated by cross-sectional MDD studies rather than TRD-specific cohorts. Second, several emerging sources remain preprints or early online reports. Third, DTI-ALPS is an indirect surrogate susceptible to physiological and technical confounding and should not be equated with a direct measure of glymphatic flow.

Fourth, opposite-direction and null findings indicate that subtype, illness phase, age, medication exposure, and technical heterogeneity are not secondary details but central determinants of interpretation.

Accordingly, the current literature supports a cautious, falsifiable working framework rather than a validated disease-specific biomarker model. Glymphatic-related abnormalities have been reported in major depression and have been associated with symptoms and domains highly prevalent in TRD, including insomnia, fatigue, cognitive impairment, psychomotor retardation, inflammation, cortisol dysregulation, and rumination, but a definitive TRD-specific signature has not yet been established [18,19,30,31,32,34,59].

The near-term priority is not to overinterpret causality, but to incorporate glymphatic-related biomarkers into rigorously designed, adequately powered, longitudinal trials of rTMS, ketamine-based interventions, chronobiological strategies, and vascular/neuroimmune interventions. Such studies should pair DTI-ALPS with orthogonal measures of sleep physiology, vascular pulsatility, CSF dynamics, choroid-plexus/perivascular-space structure, inflammatory markers, and HPA-axis measures. Only if these biomarkers show incremental validity, phase-sensitive change, and treatment-linked mediation beyond sleep and inflammation should they be considered mechanistically actionable in TRD.

Author Contributions

TB conceived and designed the review. TB, CDA, AB, ET, FT, AR, VM, VR, CT, DDB, and FP contributed to the literature search, interpretation of the evidence, and manuscript preparation. TB drafted the initial manuscript. CDA, AB, ET, FT, AR, VM, VR, CT, DDB, and FP critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

Domenico De Berardis is serving as one of the Editorial Board members of this journal. We declare that Domenico De Berardis had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Drozdstoy Stoyanov and Bettina Platt.

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