Stress, Sleep and the Glymphatic System: A Psychoneuroendocrinoimmunological Perspective on Mental Health

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Abstract. *The glymphatic system offers a perspective on cerebral homeostasis within psychoneuroendocrinoimmunology (PNEI). Cerebrospinal fluid–interstitial exchange involves glial, vascular and sleep-related processes that may be sensitive to stress. This narrative review examines connections between glucocorticoids, noradrenergic regulation, aquaporin-4 and neuroimmune communication, integrating experimental evidence and clinical observations. Animal studies suggest that stress and sleep organization can modify fluid transport; in humans, depression and psychosis have been associated with altered imaging indices. These measures provide indirect information about fluid homeostasis, whose relationship with clearance and symptoms requires longitudinal investigation. The model's contribution to PNEI is to connect brain fluid regulation with stress and immune systems. Clinical perspectives include the integrated study of sleep, hyperarousal, and neuroendocrine and immune signals. The possible involvement of glymphatic mechanisms in the benefits of therapeutic interventions remains an open question for multimodal research.*

Keywords: *glymphatic system; psychoneuroendocrinoimmunology; stress; sleep; neuroinflammation; mental health.*

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An Integrative Perspective on Mental Health

Psychoneuroendocrinoimmunology (PNEI) approaches mental health through the relationships between experience, neural regulation, endocrine signals and immune responses. Within this framework, the glymphatic system provides an opportunity to explore the role of brain fluid homeostasis in these relationships. Reviews by Barlattani and colleagues have outlined this research field, connecting observations across disorders with interactions between sleep, astrocytes and inflammation and integrating them with existing psychopathological models (Barlattani *et al.*, 2024; 2025a).

This article is a focused narrative review of experimental and clinical studies selected for their relevance to interactions between stress, sleep, glial regulation and immunity. Its purpose is to outline a testable hypothesis: in some patients, altered brain fluid dynamics might provide a connection between dysregulated stress systems and psychiatric vulnerability.

From Fluid Homeostasis to Neuroimmune Communication

The glymphatic model describes cerebrospinal fluid–interstitial exchange through perivascular and parenchymal compartments. In animal models, the perivascular distribution of aquaporin-4 (AQP4), a water channel in astrocytic endfeet, contributes to these processes. Foundational studies linked fluid transport to the removal of interstitial solutes, including amyloid-β (Iliff *et al.*, 2012). Assessing these phenomena requires distinguishing water movement, solute transport and actual elimination.

The connection with brain immune interfaces is particularly relevant to PNEI. Experimental studies show that central nervous system antigens carried in cerebrospinal fluid are sampled near the dural sinuses, where antigen-presenting cells interact with T lymphocytes (Rustenhoven *et al.*, 2021). Glymphatic exchange, meningeal lymphatic drainage and immune surveillance are distinct, interconnected processes, each with specific functions in cerebral homeostasis (Hablitz *et al.*, 2020; Rustenhoven *et al.*, 2021).

This organization suggests a possible interpretative framework: fluid dynamics may contribute both to the removal of metabolic products and to communication between the cerebral microenvironment and immune interfaces. The involvement of this communication in persistent psychiatric symptoms represents a hypothesis to be tested through dedicated studies.

The same framework encompasses energy metabolism. The review by Socci and colleagues (2025) examines relationships between metabolic alterations, mitochondrial function and inflammation in mood disorders. Integration with glymphatic

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physiology offers a research perspective on metabolite production, exchange and elimination, with each process characterized through specific measurements. The relationship between peripheral metabolism and brain clearance likewise requires direct assessment of the respective compartments.

Stress and Glucocorticoids: A Connection with Astrocytes

The hypothalamic–pituitary–adrenal axis is a key component of the endocrine stress response. The relationship between stress and inflammation also depends on tissue sensitivity to glucocorticoids: human studies have linked chronic stress to reduced responsiveness to these hormones and less effective regulation of inflammatory responses (Cohen *et al.*, 2012). A PNEI approach therefore considers mediator concentrations together with the organization and responsiveness of the systems on which they act.

A more specific connection with glymphatic physiology emerges from the work of Wei and colleagues (2019). In mouse models, chronic stress altered tracer transport and AQP4 expression and perivascular localization, involving glucocorticoid signalling. These findings suggest that the endocrine stress response can affect the astrocyte–vascular interface. The relevance of this mechanism to depression and its potential therapeutic implications require confirmation in humans.

These findings support the hypothesis of a network of interactions involving persistent stress, disorganized sleep, endocrine signalling and neuroimmune homeostasis. Within this network, altered fluid dynamics could be consequences, maintaining factors or correlates of other processes. Distinguishing these possibilities through longitudinal and experimental studies is essential to clarify the role of glymphatic physiology across clinical profiles.

Sleep, Circadian Rhythms and Noradrenergic Regulation

Sleep provides a particularly relevant interface between neural regulation and fluid dynamics. Xie and colleagues (2013) described increased elimination of selected solutes during sleep in mice. In humans, Fultz and colleagues (2019) observed coordinated oscillations in electrical activity, haemodynamic signals and cerebrospinal fluid. These observations document physiological coupling between brain activity and fluid movement during sleep.

Noradrenergic signalling contributes to the dynamic organization of these processes. In mice, Hauglund and colleagues (2025) showed that slow norepinephrine oscillations coordinate vascular changes and cerebrospinal fluid movement during non-rapid eye movement (NREM) sleep. In the same study, zolpidem attenuated

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these oscillations and glymphatic flow. Translation of these findings into clinical practice requires human studies specifically assessing medication effects on sleep and fluid dynamics.

Biological timing also matters. Hablitz and colleagues (2020) demonstrated circadian regulation of glymphatic and lymphatic transport in mice. For clinical research, this suggests recording acquisition time, sleep–wake regularity and vigilance state, so that imaging measures can be interpreted within their temporal and physiological context.

Findings vary across experimental paradigms. Miao and colleagues (2024) observed reduced clearance during sleep and anaesthesia using a different measurement approach. Comparing these studies highlights the importance of distinguishing tracer entry, redistribution and actual elimination. An accurate account of the relationship between sleep and clearance therefore requires attention to the characteristics of each measure and the experimental conditions.

A link with psychological functioning is illustrated by Socci and colleagues (2024), who documented poorer sleep quality and altered emotional reactivity in patients with borderline personality disorder. Across the whole sample, sleep quality was associated with measures of emotional dysregulation. Focusing on the clinical dimensions of sleep and affect, the study supports investigating emotional experience and physiological processes together. The potential contribution of glymphatic dynamics to these relationships could be explored through dedicated measurements.

Depression and Psychosis: Clinical Signals and Measurement Limitations

In major depressive disorder, Chen and colleagues (2025) studied 164 patients and 46 controls, identifying a lower DTI-ALPS (diffusion tensor imaging analysis along the perivascular space) index and a higher free-water fraction in patients. Within the subgroup undergoing hormone assessment, cortisol was positively associated with free water. This cortisol–free-water association is relevant to PNEI because it connects an endocrine measure with a brain parameter; its causal significance and relationship with clearance remain subjects for further investigation.

The review focusing on major depressive disorder and treatment-resistant depression (TRD) highlights heterogeneous findings, few TRD-specific cohorts and uncertainty about the causal direction of associations (Barlattani *et al.*, 2026). This heterogeneity encourages the investigation of distinct clinical and biological profiles. Within a PNEI framework, sleep, endocrine activation and neuroimmune signals might help characterize these profiles, which require longitudinal assessment in relation to treatment response.

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In psychosis research, a pilot study involving nine young adults hospitalized for an acute psychotic episode and twelve controls found lower ALPS values in patients. Associations with subjective sleep, cognition and thought disorganization were statistically nonsignificant (Barlattani *et al.*, 2025b). The small sample, demographic differences, acute illness and medication exposure require an exploratory interpretation. These findings motivate larger studies to clarify the clinical relevance of the index and its relationships with stress, sleep and inflammation.

DTI-ALPS compares directional components of water diffusion in specific white matter regions and provides an indirect indicator of interest for investigating perivascular exchange. Fibre geometry can affect its value independently of such exchange (Schilling *et al.*, 2025). Free water and blood oxygen level-dependent (BOLD)–cerebrospinal fluid coupling characterize different aspects of fluid organization and dynamics (Chen *et al.*, 2025; Fultz *et al.*, 2019). Their combined use requires clarification of the physiological meaning of each measure; quantification of clearance and diagnostic applications require further validation studies.



Fig. 1. ***Glymphatic system and mental health: schematic representation of the possible links between alterations in glymphatic function, sleep disorders, dysregulation of circadian rhythms, neuroinflammation, astrocyte dysfunction and increased oxidative stress. (Original elaboration by the Authors)***

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Clinical Implications: Targeting Systems, Testing Mechanisms

Sleep quality and stress regulation have a central clinical role within this perspective. In a randomized trial involving older adults with insomnia, cognitive behavioural therapy and tai chi modified selected cellular and genomic indicators of inflammation (Irwin *et al.*, 2015). These findings illustrate the relationship between behavioural interventions and immune responses. The possible contribution of brain clearance to the observed benefits is a question to be addressed using specific measurements.

The practical implication is to include sleep quality and regularity, hyperarousal and stressful circumstances in a comprehensive clinical assessment, while keeping treatment decisions grounded in established clinical indications. The glymphatic model informs research into the possible biological mechanisms of interventions. Treatment selection remains based on clinical assessment, while the use of glymphatic indices for therapeutic purposes requires dedicated validation.

A study design consistent with PNEI should combine repeated clinical assessments with objective sleep measurements, temporal cortisol profiles, inflammatory indicators and multimodal imaging. Age, vascular characteristics, medications, head motion and acquisition time should be controlled, distinguishing indicators of peripheral inflammation from central neuroinflammatory processes. The decisive question would be whether a biological change precedes and mediates clinical improvement or represents a correlate. This methodological proposal aims to clarify the temporal sequence and clinical significance of the observed associations.

Conclusions

The glymphatic system provides PNEI with a research domain in which brain fluids, astrocytes, endocrine regulation and immune communication can be investigated together. Its value lies in making new connections between systems testable and in relating cerebral physiology to experience, stress and biological rhythms. In psychiatry, the aim is to translate imaging associations into a more precise understanding of clinically relevant mechanisms through longitudinal and experimental studies capable of assessing their therapeutic potential.

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