

Glymphatic dysfunction: a unifying hypothesis for delirium

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Abstract

Delirium is a common and severe neuropsychiatric syndrome with lasting cognitive consequences, yet its pathophysiology remains poorly understood. We hypothesize that impaired glymphatic flow represents a central mechanism by which delirium evolves. This hypothesis builds on recent evidence showing that major delirium risk factors, such as ageing, dementia, cardiovascular disease and renal failure, are all associated with reduced glymphatic clearance. Similarly, common delirium triggers, including infection, surgery and sleep deprivation, have been shown to impair glymphatic function. In addition, standard intensive care interventions linked to delirium, such as sedation, opioid administration and noradrenaline, are known to suppress glymphatic clearance. Collectively, these effects could lead to the accumulation of neurotoxic metabolites and pro-inflammatory cytokines, disrupting neural network activity and precipitating delirium. Recognizing glymphatic impairment as a causal contributor to delirium could open new research and therapeutic avenues aimed at preserving brain fluid clearance in critically ill patients.

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Introduction

Changes in mental status are among the most common inpatient consults in neurology¹. These inpatient changes in mentation and arousal are most associated with the intensive care unit (ICU) and postoperative settings but are also frequently noted on general neurological and medical-surgical services. Regardless of its site of presentation, delirium and its associated cognitive impairment present a major challenge, impacting patient comfort and management, length of stay and outcome². Despite considerable advances in delirium screening and treatment, the underlying pathophysiology of delirium remains unclear^{3–5}.

As the most common in-hospital neuropsychiatric syndrome, delirium extends beyond the ICU, affecting nearly a quarter of hospitalized medical and high-risk surgical patients^{3,6}. Delirium in perioperative and general medical settings resembles the syndrome seen in individuals in the ICU, sharing similar risk factors and precipitating triggers, as well as linkage to long-term cognitive impairment and increased mortality^{3,6–8}. The limited efficacy of antipsychotics in the treatment of delirium suggests that its underlying mechanisms differ fundamentally from those of psychosis^{9,10} and points to the need for alternative therapeutic approaches that target the unique pathophysiology of delirium. The need for such approaches is highlighted by the increased mortality¹¹ and long-term morbidity associated with delirium: half of ICU survivors who experienced delirium suffer from cognitive impairments comparable to moderate traumatic brain injury (TBI) or worse, with approximately 25% exhibiting deficits akin to mild Alzheimer disease^{9,12,13}. Furthermore, symptoms are worse in individuals with sustained in-hospital delirium¹¹. An episode of delirium is associated with 30% mortality, compared with 12% in patients in the ICU without delirium, with mortality risk strongly related to delirium duration^{11,14}. Higher disease severity increases the risk for both delirium and mortality, so the pure effect of delirium has been difficult to isolate. The consensus is that delirium is an independent risk factor for death^{11,14}.

In this Perspective, we present a unifying theory of delirium and post-delirium cognitive impairment by proposing that the condition comprises an acute abrogation of fluid flow and waste clearance from the brain. We focus on the role of the glymphatic system, which is a brain-wide homeostatic and waste clearance system that removes extracellular metabolic waste from the brain^{15–17} (Fig. 1). These wastes include neurotoxic proteins such as amyloid- β (A β), tau and cytokines, known to negatively impact brain circuit function¹⁵. Glymphatic function is most active during sleep¹⁸ (Fig. 2), and a broad variety of both premorbid conditions and active diseases impair glymphatic clearance. We posit that the suppression of brain clearance leads to the accumulation of neurotoxic compounds and cytokines, which disrupt synaptic function, impulse synchronization and circuit integrity, ultimately causing the delirium syndrome (Fig. 3).

Delirium — definition, diagnosis and prevalence

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)¹⁹, delirium is an acute syndrome characterized by inattention, a lack of environmental awareness and cognitive disturbance. Delirium develops rapidly and can fluctuate in intensity; it results from an underlying medical condition, and is not explained by pre-existing neurodegenerative disease or another acute neurological disorder. The prevalence of delirium varies depending on the cohort studied and screening methods used³. The condition has been estimated to affect approximately 23% of inpatients on medical wards²⁰, 20% of high-risk surgical patients^{6,21}, 25% of patients with acute stroke^{22,23} and 31% of patients in the ICU²⁴, with the latter rising to 50–70% in individuals requiring mechanical ventilation^{3,11,24–26}. Despite being the most prevalent neuropsychiatric syndrome, delirium remains substantially underdiagnosed, owing to the under-implementation of screening protocols³.

Delirium in the intensive care setting has been an area of intense research for the past 20 years, owing to its high prevalence and severe

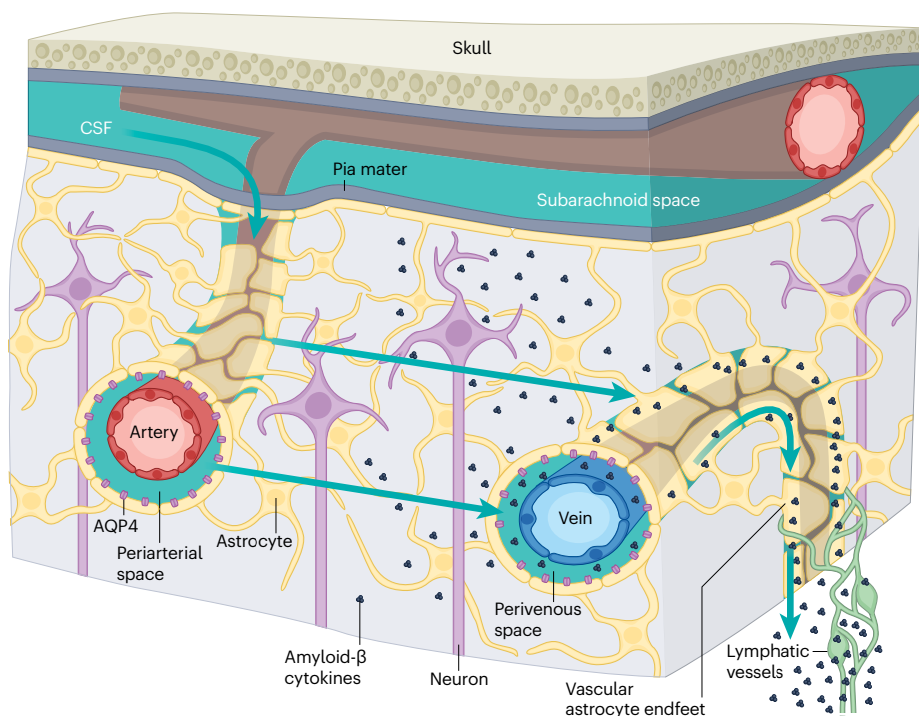


Fig. 1 | The glymphatic system. Brain fluid transport as described by the glymphatic model. Cerebrospinal fluid (CSF) from the subarachnoid space enters the brain along periaxonal spaces, which are formed by astrocytic endfeet that envelop blood vessels throughout the CNS. Arterial pulsatility drives CSF influx, and the process is facilitated by the high expression of water channel aquaporin 4 (AQP4) in the astrocytic endfeet. Within the brain parenchyma, CSF mixes with interstitial fluid and exits along perivenous pathways, as well as along cranial and spinal nerves (not shown). These perivenous outflow routes are connected to meningeal and cervical lymphatic vessels, which return fluid and solutes, including metabolic waste products such as amyloid- β , to the systemic circulation for clearance by the liver. Glymphatic flow is driven by brain pulsation generated by the cardiac cycle and respiratory and vasomotor activity. Initially characterized in rodents, key glymphatic features, including periaxonal-to-perivenous flow, sleep–wake dependency and AQP4-mediated protein clearance, have since been confirmed in humans^{52,117,188,199}. Impaired glymphatic flow is implicated in numerous neurological and systemic diseases.

Perspective

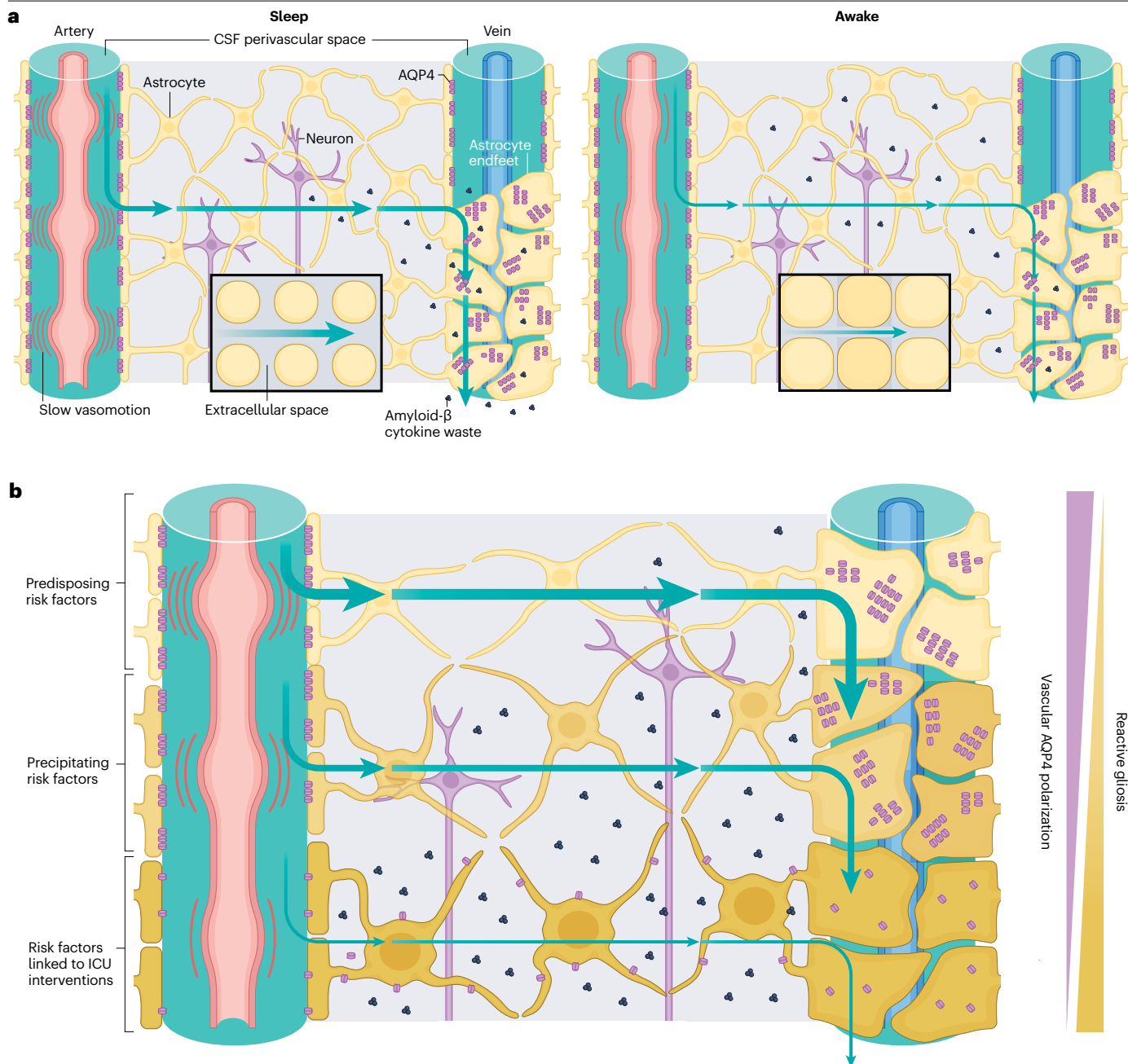


Fig. 2 | Delirium risk factors suppress glymphatic fluid transport.

a, The glymphatic system is most active during sleep and suppressed during wakefulness. This sleep–wake regulation of brain fluid transport is partly owing to an expansion of the extracellular space during sleep, which lowers tissue resistance to cerebrospinal fluid (CSF) inflow and facilitates the clearance of metabolic waste. **b**, Illustrated here is how delirium risk factors converge to impair glymphatic function. Predisposing factors such as ageing and frailty, precipitating events such as acute infections or surgery, and intensive care unit

(ICU)-related intervention including noradrenaline administration and sleep disruption diminish CSF inflow by reducing arterial pulsatility and infra-slow vasomotion during sleep. These factors also promote neuroinflammation and loss of perivascular polarization of aquaporin 4 (AQP4), resulting in impaired glymphatic transport and accumulation of cytokines and potentially neurotoxic waste, including amyloid- β . Elevated noradrenaline levels, sedation and various drugs impair the slow coordinated vasomotion during sleep. Positive-pressure ventilation impairs CSF efflux and compresses perivascular spaces.

consequences. In this hypothesis-driven Perspective, we will discuss delirium in ICU, medical, surgical and aftercare settings, as well as its association with compromise of the glymphatic system. Perioperative

delirium and emergence delirium – a delirious or confusional state that develops after awakening from general anaesthesia – might also be related to glymphatic failure²⁷. However, additional direct

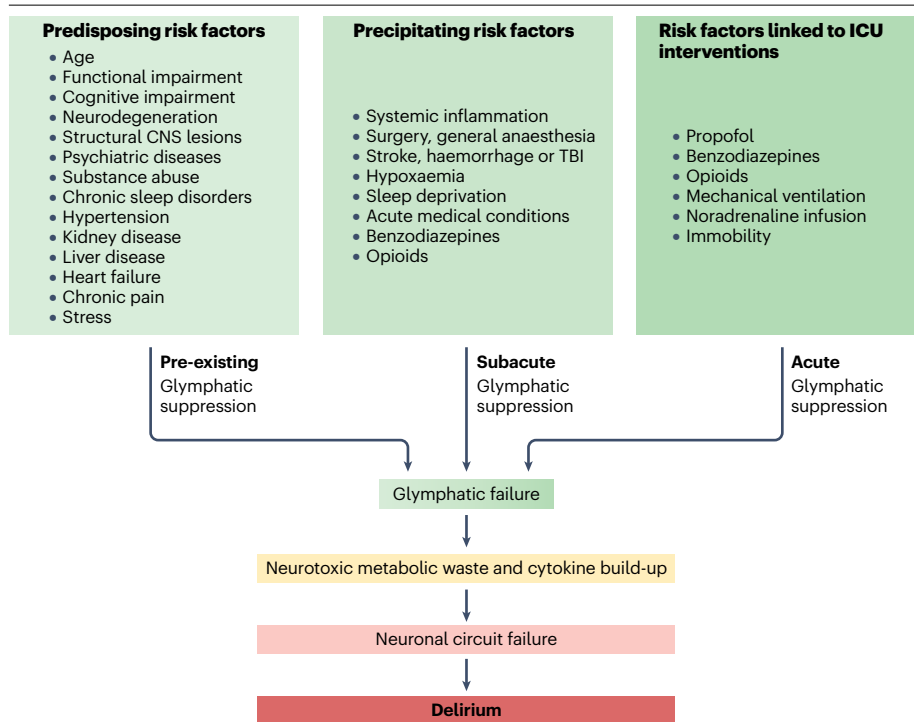


Fig. 3 | Hypothesized model for how stagnation of glymphatic fluid transport leads to delirium. The proposed model is based on the substantial overlap between known risk factors for delirium and factors that suppress glymphatic flow (see Table 1). In this three-hit framework, individuals at increased risk, such as older adults with comorbidities, experience an acute insult, such as an infection, cardiac event or traumatic injury, leading to hospitalization. During treatment, factors such as surgical anaesthesia, immobility and sleep disruption further suppress glymphatic transport. In addition, critically ill patients in the intensive care unit (ICU) are often sedated and mechanically ventilated, and may require noradrenaline for pressor support, all of which can impair glymphatic transport. This stagnation of glymphatic flow results in the accumulation of pro-inflammatory cytokines and metabolic waste. The resulting neuroinflammatory environment disrupts neural circuit function, leading to impaired cognition, confusion and the hallmark symptoms of delirium. TBI, traumatic brain injury.

pharmacological mechanisms, which we do not incorporate into our model, might also be involved, as suggested by the association of delirium with high doses of anaesthetics^{28,29}. Delirium in paediatric patients in the ICU shares similar characteristics with the adult condition, but is beyond the scope of this article. For dedicated reviews on paediatric ICU delirium and emergence delirium, please see refs. 30–34.

Delirium presentation

Delirium is characterized by a highly variable combination of disturbances in attention, awareness, memory and sleep, as well as by the level of arousal of an individual, which might vary from obtunded to severely agitated. The phenotype can range from subsyndromal delirium, with mild episodic memory and attention disturbance, to hypoactive and mixed subtypes, and more rarely a hyperactive form^{2,24,35}. The hypoactive form is the most prevalent^{24,36} and is often mistaken for depression, fatigue, sedation or dementia-associated confusion. In the hyperactive form, patients can become restless, anxious and usually fearful; for example, they might pull out lines and tubes, attempt to leave the bed, or become combative. Relatives are often unrecognized, and affected individuals can misinterpret their surroundings and experience hallucinations. The duration is variable, lasting a few days in most individuals, but can extend to weeks or months³. In all its forms, delirium is frequently associated with short-term memory loss, and often with vivid, realistic delusions, which can be of threatening or frightening character. Individuals usually remember their delusions in detail for years thereafter, which might contribute to PTSD-like symptoms in the aftermath of intensive care^{35,37,38}.

The transition into delirium typically requires both a predisposition and a trigger. The greater the number and severity of predisposing risk factors, including the degree of frailty, the lower the threshold for delirium onset^{7,39}. However, sufficiently severe triggers can induce delirium even in the absence of predisposing factors.

Delirium risk factors are numerous⁴⁰ and include advanced age^{6,29,41–47}, pre-existing cognitive impairment^{6,7,41–43,45,46,48–51}, frailty^{7,46}, neurodegenerative diseases⁴⁸, coexisting medical conditions (for example, chronic heart, liver, kidney or vascular disease)^{7,41,42}, depression^{42,52}, alcohol abuse^{7,41,47,50}, malnutrition and impaired vision or hearing^{7,45,53}. Additionally, structural brain abnormalities seen on MRI or CT, including cerebral atrophy, white matter lesions or sequela from stroke and TBI, also increase vulnerability to delirium^{3,42,54} (Table 1).

Precipitating factors span a wide range of insults, including acute medical illness, trauma, surgery, neurological injury, dehydration and psychological stress⁴⁰. Often more than one trigger is present, presenting multifactorial aetiologies (Table 1). Certain medications, particularly benzodiazepines, opioids and dihydropyridines – a class of calcium channel blockers – are also associated with increased risk^{29,55,56}.

In the ICU setting, acute events such as infections, sepsis, hypoxia, respiratory failure, cardiovascular instability, hypotension, heart failure or metabolic disturbances are the most common triggers. Supportive measures such as opioids, sedation^{25,26,50,57}, mechanical ventilation, vasopressors⁵⁸ and immobilization are also associated with higher risk for delirium^{3,40,41}.

The glymphatic system

The glymphatic system is a brain-wide fluid transport mechanism that facilitates the clearance of metabolic waste products from the brain interstitium, including not only small-molecule metabolites but also larger neurotoxic proteins, such as A β and phosphorylated tau, which are implicated in Alzheimer disease^{15,59} (Fig. 1). Before the first description of the glymphatic system in 2012, the brain – lacking lymphatic vessels – was thought to rely solely on intracellular degradation processes, such as ubiquitination and autophagy, for protein waste clearance. However, since then, a central role has been established for the glymphatic system in both transporting and eliminating neurotoxic waste

Table 1 | Delirium risk factors and glymphatic dysfunction: clinical and preclinical evidence

Factors	Delirium-related clinical effects	Glymphatic effect	
		Clinical data (human studies)	Preclinical data (animal studies)
Delirium risk factors			
Ageing	Strong independent risk factor for delirium in ICU, perioperative and medical patients, rising with advancing age ^{6,29,41–47}	Reduced as a function of ageing ^{85,185–188}	85% reduction in 18-month-old mice ^{75,189}
Cognitive impairment, neurodegeneration, frailty and dementia	Strong risk factors in ICU, perioperative and medical settings Light impairment doubles the risk With diagnosed dementia, the OR rises to 6 (refs. 6,7,41–43,45,46,48–51)	Reduced in all neurodegenerative diseases studied, including AD, PD, HD and ALS ^{91–94,190–197}	20–80% reduction in mouse models of neurodegenerative disease, including AD, PD, HD and ALS ^{77–82,87,198,199}
Functional impairment	Risk factor in medical and perioperative patients ^{7,46}	Not studied	Not studied
Structural CNS lesions	Previous stroke increases the risk of perioperative delirium in patients with CABG Neuroimaging: no clear association between lesions and delirium ^{42,54}	Reduced after stroke, slow recovery ¹⁰⁴ ; reduced in normal pressure hydrocephalus ²⁰⁰	Reduced in a multiple sclerosis mouse model ^{101,105,201}
Chronic sleep disorders	For patients with obstructive sleep apnoea, OR for postoperative delirium is 4.75 (ref. 202)	Reduced glymphatic clearance in poor sleepers, obstructive sleep apnoea and REM sleep behaviour disorder ^{203–207}	20–80% reduction in chronic sleep fragmentation in mice ⁷⁴ Impairs AQP4-dependent glymphatic clearance and accelerates AD-like pathology in mice ^{74,208}
Psychiatric diseases	Depression is a risk factor Limited studies on other psychiatric conditions ^{42,52}	Moderate to severe reduction noted in schizophrenia, psychosis spectrum disorders and depression ^{209–212}	60–70% reduction in a depression mouse model ^{213,214}
Substance abuse	Nicotine use (smoking) associated with increased delirium risk in patients in the ICU ⁵⁰ Alcohol abuse: increased risk in ICU, perioperative and medical patients ^{741,4750}	Methadone treatment in individuals with heroin addiction promotes glymphatic function ²¹⁵	30–35% reduction by acute and chronic alcohol intake in mice ^{216,217} Reduction after cocaine intake in mice ²¹⁸
Visual and hearing impairment	Risk factors in medical and perioperative patients ^{745,53}	Not studied	Not studied
Comorbidities: cardiovascular, liver and kidney diseases	Hypertension, kidney disease, peripheral vascular disease and liver disease are risk factors in ICU, medical and perioperative patients ^{741,42}	Reduction in heart failure, small vessel disease, liver failure and kidney disease ^{219–226}	Disturbance in a heart failure rat model; reduction in hypertension in mice and rats; reduction in liver failure in rats; kidney diseases not studied ^{227–230}
Pain	Association to delirium ²³¹	Reduction in cancer pain; reduction in migraine ^{232,233}	Reduction in a migraine mouse model ²³⁴
Precipitating factors			
Systemic infection and inflammation	The major precipitating factors: increased risk in infections, sepsis, acute surgery, perioperative infections, duration of surgery and time on cardiopulmonary bypass ^{21,25,41,43,110,235}	Not studied	Reduction by acute LPS in a mouse model ^{108,109,236}
Severity of illness	Higher illness-severity scores in ICU and medical patients are associated with increased delirium risk across cohorts and meta-analysis ^{41,45,50}	Not studied	Not studied
Hypoxaemia	Increased risk ²⁵	Not studied	Not studied
Liver disease	Increased ICU delirium risk ²³⁵	Disrupted glymphatic function ²²⁵	Reduction by liver failure in rats ²³⁰
Acute kidney injury	Increased risk in patients in the ICU: 60% prevalence ^{237,238}	Not studied	Not studied
Acute sleep deprivation	72h of sleep deprivation causes delirium-like syndrome Patients in the ICU are sleep-deprived Co-occurrence of sleep deprivation and delirium ^{119–121,124,125,173}	Reduced clearance in poor sleepers, obstructive sleep apnoea and REM sleep behaviour disorder ⁷³	20–80% reduction in chronic sleep fragmentation in mice ⁷⁴
Stroke, TBI and SAH	Stroke: 12–23% delirium rates ^{22,23} TBI: high incidences >50% ^{106,107}	Reduced in subacute stroke ¹⁰⁰ Partial recovery noted post-stroke ¹⁰⁴ Reduced 5 months after TBI ^{99,239,240}	Ischaemic stroke in rodents: acute oedema ^{98,241} ; subsequent reduction ^{103,242,243} ; 60% reduction 1 month after TBI in mice ^{97,174} SAH mouse model: acute reduction ^{244,245}

Table 1 (continued) | Delirium risk factors and glymphatic dysfunction: clinical and preclinical evidence

Factors	Delirium-related clinical effects	Glymphatic effect	
		Clinical data (human studies)	Preclinical data (animal studies)
Precipitating factors (continued)			
General anaesthesia	Same delirium risk as local or spinal anaesthesia ⁶	Not studied	30–80% reduction in inhalation anaesthesia in rodents ^{132,133,246}
Medication	Benzodiazepines, opioids and dihydropyridines associated with delirium ⁵⁵	Reduced in benzodiazepine-use disorders ²⁴⁷	Not studied
ICU interventions			
ICU sedation and mechanical ventilation	Highest prevalence of delirium ^{25,26,50,57}	Not studied	Carbon dioxide levels and anaesthesia agents affect glymphatic flow in rats ¹⁶⁵
Propofol	Associated with increased risk ^{1,127,248}	Not studied	Glymphatic flow reduction (M.N., unpublished data)
Benzodiazepines	Increased risk and duration — across cohorts and meta-analysis ^{7,26,28,29,41,129,130}	Reduced in benzodiazepine-use disorders ²⁴⁷	Zolpidem reduces glymphatic flow in mice ¹¹⁵
Opioids	Increased risk and duration — in patients in the ICU ^{41,55,129,135}	Not studied	Not studied
Noradrenaline infusion	Associated with delirium risk in perioperative and ICU patients Elevated endogenous noradrenaline levels are associated with ICU delirium ^{58,160}	Not studied	Glymphatic flow is reduced by adrenergic agonists and increased by antagonists Reduced by endogenous noradrenaline in mice ^{97,115,162}
Interventions against delirium			
Haloperidol	No effect on duration or incidence in ICU, perioperative or medical patients No effect on cognitive decline ^{9,10,12,249–252}	Not studied	Not studied
Dexmedetomidine	Reduced ICU-delirium risk compared with other sedatives ^{143,147,148,248} Reduced perioperative incidence ^{6,145} Not superior when used as primary sedative for mechanical ventilation or for postoperative delirium prevention in cardiac surgery ^{5,139,146}	Not studied	Glymphatic flow enhancement by dexmedetomidine in mice ^{132,141} Ameliorates consequences of sleep deprivation by restoring glymphatic clearance in mice ¹⁴²
Ketamine infusion	Reduced delirium in patients in the ICU ¹⁴⁹ and in on-pump cardiac surgery ²⁵³ No effect in other perioperative settings ^{254–256}	Not studied	Glymphatic flow enhancement comparable to natural sleep in mice ¹⁵²
Melatonin	Reduced perioperative risk Might reduce the prevalence of ICU delirium ^{6,127,257}	Not studied	Enhance glymphatic flow and restore glymphatic flow in cerebral haemorrhage and ageing in mice ^{157–159}
Exercise or occupational therapy	Occupational therapy shortens delirium in medical patients Can shorten delirium in patients in the ICU ^{258,259}	Long-term exercise increases glymphatic flow ¹⁸⁰	Immediate inhibition but delayed increase in glymphatic activity in mice ¹⁷⁹
Long-term risk after delirium insult			
Cognitive decline	Delirium poses an increased risk of cognitive decline in ICU, perioperative and medical patients ^{8,12,13,26,260–262}	Reduced glymphatic clearance leads to an increase in the risk of cognitive decline ^{185,263}	Not studied
Dementia	Increased dementia risk after delirium ¹⁴	Glymphatic failure involved in prediction of AD ¹⁹⁰	Not studied
Increased mortality	Two to three times increased mortality in medical, ICU and perioperative patients and patients affected by stroke ^{6,211,14,264}	Not studied	Not studied

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; AQP4, aquaporin 4; CABG, coronary artery bypass graft; HD, Huntington disease; ICU, intensive care unit; LPS, lipopolysaccharide; OR, odds ratio; PD, Parkinson disease; REM, rapid eye movement; SAH, subarachnoid haemorrhage; TBI, traumatic brain injury.

products and cytokines, via a riverine network of perivascular channels that converge to leave the brain via its major surface vessels^{15,17,18,60,61}.

Numerous pre-existing and concurrent disease states hinder the efficiency of glymphatic clearance^{17,62–65} (Fig. 2). Ageing reduces the efficiency of glymphatic clearance, with neurodegenerative disorders such

as Alzheimer disease further exacerbating its dysfunction^{66–68}. Additionally, subacute and chronic pathology after stroke, TBI and multiple sclerosis have all been shown to disrupt glymphatic flow^{67,69}. Systemic factors and triggers routinely experienced by patients in the ICU, including prolonged wakefulness and sleep deprivation, anaesthesia and

infections, further suppress glymphatic activity^{18,27,70–74}, highlighting the vulnerability of the system to physiological stressors.

Delirium as glymphatic failure

The multifactorial nature of delirium, combined with its variable clinical presentation, has led to a broad variety of hypotheses to describe its pathogenesis^{3,4}. These hypotheses are based on both the precipitants and the downstream effects of delirium³. These theories have included inflammation, metabolic failure, sleep and circadian dysregulation, neurotransmitter imbalance and, perhaps as a final common pathway, network dysconnectivity³. However, none of the theories have served to adequately provide any unifying theory of pathophysiology. We hypothesize here that the various concomitants and precipitants to delirium converge on a single final common pathway of central glymphatic failure (Box 1); our premise is that accumulation of metabolite waste and cytokines may be both necessary and sufficient for the onset of a delirium syndrome. We propose that glymphatic dysfunction contributes to brain network dysconnectivity by positing that glymphatic failure leads to the accumulation of neurotoxic waste products that impair neural circuits. In the following section, we outline how major delirium risk factors effect glymphatic function and then consider how ICU practices can alter glymphatic transport.

Effects of delirium risk factors on glymphatic activity

Ageing and neurodegenerative diseases. Impaired glymphatic function in ageing has been well documented in mice⁷⁵, with studies showing an 85% reduction in cerebrospinal fluid (CSF) inflow of larger tracers in aged mice compared with young mice independent of sex^{75,76}. However, glymphatic flow is even more markedly suppressed in mice models of Alzheimer disease^{68,77}, and multiple models of amyotrophic lateral sclerosis (ALS)^{78,79} and Huntington disease⁸⁰. Experimental suppression of glymphatic function, achieved either by blocking meningeal or cervical lymphatic vessels or by deleting astrocytic aquaporin 4 (AQP4)

water channels, exacerbates A β , tau or α -synuclein pathology^{81–87}. The age-related decline in glymphatic flow might help explain how impaired clearance drives protein aggregation⁶⁸ – the central pathology in degenerative brain disorders – and why ageing is the greatest risk factor for neurodegenerative diseases. For detailed reviews, we refer readers to refs. 88–90 that highlight the contributions of AQP4 depolarization, low-grade neuroinflammation and reduced CSF production to glymphatic dysfunction during ageing and neurodegeneration. In human MRI studies, reduced glymphatic flow has been reported in Alzheimer disease⁹¹, ALS⁹², age-associated dementia⁹³ and Parkinson disease⁹⁴. The rapidly growing body of literature demonstrates a strong association among ageing, neurodegenerative diseases and suppression of glymphatic flow^{67,75} (Table 1).

In the clinic, even young children can experience delirium when exposed to a sufficient trigger³⁴, but the risk increases markedly with age from 3% in individuals under 65 years to 14% in individuals aged 65–74 years, and up to 36% in individuals over 75 years with medical illness⁴³. Age is, thus, a consistent risk factor across all patient populations^{6,29,41,42,46}. Dementia is identified as the strongest risk factor, with an estimated odds ratio for delirium of 6.5 (ref. 45). Even mild impairment of higher cognitive functions predicts postoperative delirium, with subtle preoperative attention deficits increasing the risk by 4–5-fold⁴⁹, consistent with broader evidence that mild cognitive impairment predicts delirium^{7,42,48,50} (Table 1).

We propose that glymphatic dysfunction associated with ageing and neurodegeneration underlies susceptibility to delirium: greater chronic impairment lowers the threshold for acute suppression, precipitating glymphatic failure and delirium. In turn, substantial evidence links delirium to an increased risk of subsequent dementia⁹⁵, a relationship that might also be mediated by glymphatic dysfunction⁹⁶. If delirium reflects episodes of acutely suppressed glymphatic flow, such suppression could, in some cases, leave longer-lasting deficits that impair the clearance of A β and tau and amplify neuroinflammatory

Box 1 | From research to real-world benefits

Delirium comprises the final common pathway of a variety of triggers. Converging lines of evidence now suggest that delirium is the manifestation of disrupted fluid efflux from the brain. In particular, the clearance of interstitial fluid from the brain is needed to remove waste metabolites and proteins, the accumulation of which might lead to the disordered thought and behaviour that typify delirium. Such fluid clearance occurs largely through the perivascular channels that comprise the glymphatic system of the brain. The patency — and hence clearance function — of this system is negatively regulated by the noradrenergic tone that characterizes the awake state. As a result, the glymphatic system is physically active, with most fluid clearance occurring during sleep. Sleep is thus revealed as critically important in brain homeostasis: it is required for fluid and waste clearance from the brain, without which toxic metabolites as varied as the excitatory amino acids, prostaglandins, and tau and amyloid isoforms will inexorably accumulate. In turn, this accumulation can disrupt neuronal signalling and synchronization, yielding the cognitive and behavioural deterioration that characterize delirium.

Delirium may therefore be best viewed as a pathological state of arousal, permitted and exacerbated by age, disease,

pharmacological intervention and sleep deprivation. As such, the genesis of delirium — regardless of its proximal trigger — can be mechanistically linked to sleep state and the latter's control of brain fluid clearance; delirium is thus not an inherent or inevitable consequence of illness or hospitalization.

Clinically, the sleep deprivation, sedation and sustained adrenergic activation of the typical intensive care unit (ICU) setting may then be viewed as iatrogenic co-contributors to the genesis of delirium in hospitalized patients, including individuals who are acutely ill as well as those recovering postoperatively. Each of these variables — sleep interruption for the assessment of vital signs and neurological function, postoperative sedation, mechanical ventilation and noradrenergic dosing for pressor support — should be minimized to the extent compatible with systemic health and recovery. In particular, the standard practice of awakening patients for vital signs and nursing checks at frequent intervals needs to be reconsidered. Thus, minor changes in standard operating procedures in the ICU could promise real benefits in inpatient length of stay and outcomes. More broadly, recognizing that the preservation of glymphatic function is critical to brain health could present new strategies for mitigating — if not preventing — delirium in critically ill individuals.

signalling. Repeated or prolonged episodes might, therefore, lead to cumulative clearance failure, setting the stage for progressive neurodegeneration and accelerated cognitive decline.

Stroke, TBI and multiple sclerosis. Preclinical and clinical studies demonstrate that sequela from common neurological conditions, including stroke, TBI and multiple sclerosis, all impair glymphatic flow^{97–105}. Contributing pathological factors include neuroinflammation, reactive gliosis, loss of AQP4 vascular polarization, and scar formation, all of which can progressively compromise the waste clearance capacity of the brain⁶⁸.

In the clinical setting, stroke leads to delirium in 25% of patients^{22,23}, with risk depending on stroke size, location and aetiology. In people with TBI referred to the ICU, approximately half experience delirium during their admission, a figure that rises to 75% in individuals >50 years of age^{106,107}.

Impaired glymphatic function in inflammation. Acute bacterial meningitis and systemic inflammation almost completely block glymphatic flow^{108,109}, and chronic neuroinflammation from various diseases also suppresses flow (reviewed by Mogensen et al.¹⁰⁹). So far, no human studies have examined glymphatic function in inflammation.

Overall, systemic infections and inflammation are the most common triggers of delirium, the theory being that pro-inflammatory cytokines, such as IL-6, IL-8 and TNF, have an impact on neural networks involved in attention and cognition¹¹⁰. Sepsis and acute surgery carry high risks of delirium⁶. In open cardiac surgery, the risk of delirium is high, and highly variable, with reported incidences from 3% to 61%. It is widely thought that inflammation and oxidative stress might be triggers, with anaesthesia duration and depth further influencing the risk²¹.

Sleep–wake regulation of glymphatic flow. The glymphatic system is strongly regulated by the sleep–wake cycle¹¹¹. In rodents, wakefulness reduces the influx of CSF into periaxonal spaces and the brain parenchyma by 50–90% compared with natural sleep or ketamine–xylazine anaesthesia^{18,112}. The enhanced influx during sleep coincides with an increase in brain extracellular volume from 13–15% in wakefulness to 22–24% during sleep¹⁸, lowering the resistance to CSF flow. Concurrently, A β CSF concentration falls¹¹³ and clearance doubles during sleep^{18,114}.

The sleep-associated increase in glymphatic activity is enabled by reduced noradrenaline levels, which promote vasodilation, and by pulsatile noradrenaline-mediated infra-slow vasomotion, which facilitates CSF influx and waste removal¹¹⁵. Conversely, the high level of noradrenaline during wakefulness suppresses slow vasomotion and glymphatic function, leading to the accumulation of neurotoxic metabolites. Fragmented sleep impairs glymphatic clearance probably by raising baseline noradrenaline⁷⁴. Human studies using contrast-enhanced MRI confirm that sleep enhances glymphatic clearance⁷³. Brain pulsations from respiratory and slow vasomotion are both major drivers of glymphatic flow and increase during non-rapid eye movement (NREM) sleep¹¹⁶. CSF flow in the fourth ventricle – another MRI indicator for glymphatic flow – is driven by this slow vasomotor activity¹¹⁷.

For people in the ICU, sleep deprivation is one of the most distressing experiences, contributing to anxiety, heightened pain sensitivity, depression, cognitive impairment, respiratory dysfunction, elevated sympathetic activity and immune dysregulation¹¹⁸. Polysomnography studies in patients in the ICU reveal profound sleep fragmentation,

marked by frequent arousals, reduced slow-wave sleep and REM deprivation¹¹⁹. In patients who are moderately ill or have delirium, EEG markers of wakefulness often disappear, replaced by a persistent pathological slow-wave pattern across wakefulness and sleep, termed ‘atypical sleep’ or ‘pathologic wakefulness’, which is linked to increased mortality^{118,120–122}.

Sleep deprivation strongly correlates with delirium, both as a predisposing risk factor and as a direct precipitating trigger^{118,123,124}. Notably, experimental studies in humans show that 72 h of sleep deprivation reliably induces marked alterations in mental state, including complex hallucinations, disordered thinking and delusions, which can progress to a condition characterized by psychotic symptoms, persistent hallucinations and aggression¹²⁵. This state, which shares core features with hyperactive delirium, is reversed by a period of natural sleep¹²⁵.

Although delirium recovery is widely observed to be associated with a period of sleep, this concept remains unproven as polysomnography cannot reliably quantify sleep in patients with delirium¹²⁰. Clinical quantification of sleep time is shown to be inaccurate in ICU and trauma patients, as sleep cannot be distinguished from peaceful rest, sedation or severe hypoactive delirium¹¹⁹.

Clinical practice in the ICU and its effect on glymphatic transport

Sedation and supportive measures

The primary goal of delirium treatment in the ICU is to ensure patient comfort and safety. In patients in the ICU who are unstable or have agitation, securing tracheal tubes and venous lines is critical, sometimes necessitating deep sedation. However, increasing evidence links sedation to delirium and higher mortality, underscoring the need to minimize sedation^{41,57}. Clinical studies support maintenance of light sedation or allowing individuals to remain awake whenever possible^{41,126,127}. When patients are awake, delirium management shifts to address anxiety, agitation, delusions, pain, insomnia and discomfort, especially in individuals with an endotracheal tube. Generally accepted evidence-based recommendations to guide this process are available^{41,127,128}. Despite these guidelines, agitation and insomnia remain challenging in the daily clinic, and effective medical treatments, with evidence for positive effect on outcome, are lacking.

Sedatives

GABA_A agonists, for example, propofol, midazolam and lorazepam, are widely used as sedatives in the ICU, even though sedation depth, sedation time and benzodiazepines are strong risk factors for delirium and are associated with increased mortality^{7,25,26,28,29,41,50,57,129,130}. Moreover, GABA_A agonists reduce slow-wave and REM sleep^{118,131}. Preclinical studies in rodents show that the inhalation anaesthetics isoflurane and sevoflurane and the intravenous anaesthetics pentobarbital and propofol potentially inhibit glymphatic flow^{132–134}, as does the benzodiazepine-like sleep aid zolpidem¹¹⁵. Similar effects on glymphatic function are expected for lorazepam and midazolam based on their similar mechanism of action¹¹⁵.

Opioids

Opioids are frequent adjuncts in ICU sedation, particularly for tolerating endotracheal tubes, but their use considerably increases delirium risk¹³⁵. In medical patients, a systematic review estimates a delirium odds ratio of 2.5 with opioid use⁵⁵. Opioids also suppress slow-wave and REM sleep compared with placebo¹³⁶. Emerging data reveal that morphine reduces glymphatic flow in mice¹³⁷.

Alternative sedation strategies and the role of dexmedetomidine

Given the deliriogenic aspects of benzodiazepines and GABAergic sedatives, alternative sedation strategies such as ‘non-sedation’ or ‘light sedation’ have been explored. Evidence demonstrates that these strategies are associated with shorter ventilation duration and ICU and hospital stays⁴¹.

Dexmedetomidine. Dexmedetomidine, an α_2 agonist, has been widely studied for light-to-moderate sedation: compared with benzodiazepines or propofol, dexmedetomidine reduces delirium, shortens the duration of deep sedation (un arousable state), and facilitates extubation in patients with delirium and agitation¹³⁸. An updated evidence synthesis and guideline suggest using dexmedetomidine over propofol for light sedation in mechanically ventilated adult patients in the ICU, with evidence for a 15% reduction in delirium^{127,139}. The delirium-reducing effect was also found in a meta-analysis of perioperative delirium (relative risk 0.59, low certainty of evidence)⁶, even though one of the sub-studies, a large randomized clinical trial on patients who underwent ‘on-pump cardiac surgery’, has found a higher incidence of delirium in patients receiving dexmedetomidine compared with placebo¹⁴⁰.

In preclinical glymphatic studies, α_2 -adrenergic agonists dexmedetomidine and xylazine, often combined with ketamine, preserve glymphatic clearance to levels comparable to those during NREM sleep^{133,141}. Dexmedetomidine facilitates CSF-mediated drug delivery in the CNS while also inducing sleep-like EEG patterns⁹⁸. In a 2025 study on sleep deprivation in mice treated with dexmedetomidine for 5 days, the negative effects of sleep deprivation were reduced. Furthermore, positive effects were observed on sleep architecture, alongside higher glymphatic influx, improved AQP4 expression, and less neuroinflammation and behavioural symptoms¹⁴². These findings might explain the positive effects of dexmedetomidine in intensive care, highlighting its potential in delirium treatment^{127,138,143–148}.

Ketamine

Ketamine has been studied as an adjunct to reduce opioid requirements. In an ICU study, ketamine infusion (2 mg/kg/h) did not lower remifentanyl use but reduced delirium incidence from 37% to 21% and shortened delirium duration from 5.3 to 2.8 days (ref. 149). The impact on long-term cognitive impairment was not studied and remains unknown.

Antipsychotics

Antipsychotics are commonly used to manage psychotic features in delirium, such as hallucinations and delusions associated with extreme distress, but they have not been shown to reduce the incidence or duration of delirium⁹. Haloperidol, the most frequently used antipsychotic in this setting, is generally considered safe. A large multicentre trial has found that haloperidol provides a significant survival benefit in patients in the ICU who have delirium but does not reduce delirium duration or post-ICU cognitive impairment^{10,12}. Similarly, second-generation antipsychotics have not shown efficacy in modifying these outcomes^{9,150}. The effects of antipsychotics on glymphatic function remain unexplored.

Melatonin

The latest updated review¹⁵¹ on patients in the ICU has reported that melatonin administered to promote sleep might modestly reduce the

prevalence of delirium – although not the delirium duration – and might slightly reduce the ICU length of stay, although the evidence remains limited and inconclusive. While subjective sleep quality can improve, objective sleep duration is often unchanged¹²⁷. Studies on perioperative patients provide stronger evidence that melatonin reduces the incidence of postoperative delirium⁶.

Melatonin is in part released from the pineal gland directly into CSF, resulting in higher concentrations in the third ventricle compared with plasma^{152,153}. Experimental studies^{154–156} demonstrate that melatonin acts as an antioxidant and anti-inflammatory agent and facilitates the clearance of neurotoxic proteins, including A β . Melatonin levels decline markedly with age¹⁵⁷. In mice, melatonin was found to alleviate glymphatic system dysfunction by regulating circadian rhythms and the polarization of AQP4, thereby improving sleep structure and reducing depressive-like behaviours¹⁵⁸. In models of intracerebral haemorrhage, melatonin restored glymphatic transport, facilitated haematoma and oedema clearance, reduced blood–brain barrier disruption, and improved cognitive and behavioural outcomes¹⁵⁹.

Noradrenaline infusion and suppression of glymphatic transport

Intravenous noradrenaline is routinely used in the ICU and operating room to maintain arterial blood pressure, particularly in septic shock and sedation-induced hypotension. Acute sympathetic activation in trauma, inflammation and sepsis elevates noradrenergic and adrenergic activity via both primary sympathetic efferents and the hypothalamic–pituitary–adrenal axis response. Postoperative increases in blood noradrenaline and cortisol have been linked to delirium¹⁶⁰. Regarding sleep, adrenergic catecholamines trigger suppression of REM and slow-wave sleep¹¹⁸, consistent with their role in promoting arousal and vigilance.

The relationship between adrenergic signalling and glymphatic flow is well established¹⁶¹. An early study has shown that cortical application of α_1 -antagonists, α_2 -antagonists and β -receptor antagonists in combination induced sleep-like slow-wave EEG activity and enhanced CSF tracer influx in awake mice¹⁸.

In people with TBI, noradrenaline levels remain elevated for days and weeks after the inciting trauma^{162–164}. In a mouse model of TBI, noradrenaline levels were also elevated, and glymphatic clearance was severely reduced. Notably, systemic pan-adrenergic blockade restored glymphatic flow, reduced brain oedema and improved outcomes, underscoring the role of noradrenaline as a potent glymphatic inhibitor⁹⁷. Furthermore, a 2025 study has revealed that endogenous infra-slow noradrenaline oscillations, released from the locus coeruleus in 20–50-s cycles, drive oscillations in cerebrovascular blood flow, facilitating glymphatic bulk flow during NREM sleep¹¹⁵. The exogenous noradrenaline infusions, given to patients with neurotrauma to support cerebral perfusion pressure and stabilize the general circulation, probably disrupt this process by inducing sustained vasoconstriction and suppressing endogenous infra-slow oscillations, thereby impairing glymphatic clearance.

Mechanical ventilation

Negative pressure during natural breathing facilitates CSF efflux, similar to venous blood flow through the jugular vein⁶¹. By contrast, positive-pressure ventilation increases intrathoracic pressure, reduces venous return and elevates intracranial pressure (ICP), compressing perivascular spaces and impairing CSF circulation and waste

clearance¹⁶⁵. Mechanical ventilation might then be expected to disrupt glymphatic transport.

A 2025 mouse study has reported that positive-pressure mechanical ventilation under isoflurane anaesthesia with opioid sedation suppressed glymphatic transport, promoted brain cytokine accumulation and triggered delirium-like behavioural deficits¹³⁷. By contrast, controls that had isoflurane supplied by a nose cone while being treated with the same opioid doses did not develop glymphatic impairment or delirium-like phenotypes¹³⁷. Notably, mechanical ventilation also caused a rise in ICP compared with nose-cone isoflurane¹³⁷. These findings imply a mechanistic link between positive-pressure ventilation and impaired CSF–interstitial fluid exchange: by blunting respiration-driven intrathoracic pressure swings and/or elevating mean intrathoracic pressure, mechanical ventilation could alter venous outflow dynamics and downstream perivascular CSF circulation¹⁶⁶.

Translationaly, these preclinical observations raise the question of whether positive-pressure ventilation itself contributes to delirium risk in humans. In patients in the ICU on mechanical ventilation, delirium affects as many as 60% overall, but further work is needed to confirm whether this association stems from positive-pressure ventilation itself or confounding factors such as respiratory failure, systemic inflammation or sedatives required for intubation^{25,26}. Additionally, ventilator-induced systemic inflammation and oxidative stress will exacerbate neuroinflammation, further suppressing glymphatic transport^{167–170}.

Discussion

This Perspective aims to (re)introduce the glymphatic system to clinicians and researchers working with delirium, to incorporate an understanding of this system – its neuroanatomy, physiology and pathophysiology – into delirium research. We hypothesize that glymphatic failure could be a unifying mechanism underlying delirium and post-delirium cognitive impairment (Figs. 2 and 3). Our argument is based on the striking findings that multiple risk factors, precipitating events and treatments associated with delirium have now been shown to suppress glymphatic transport (Table 1).

The pathophysiology of delirium remains poorly understood. Yet as noted above, the prevailing theories converge on processes that interfere with glymphatic function, suggesting that glymphatic failure may represent a unifying mechanism precipitating the delirium syndrome. As such, we are proposing that glymphatic dysfunction contributes to the brain network dysconnectivity that characterizes the delirious state^{3,4,171}. The novelty of this hypothesis is that it identifies glymphatic failure as an upstream causal event leading to the accumulation of neurotoxic waste products that disrupt neural circuit function. Strong support for this concept comes from experimental sleep deprivation, which suppresses glymphatic activity⁷¹, increases cytokine accumulation¹⁷² and reliably induces a delirium-like mental state in otherwise healthy individuals^{125,173}. The glymphatic dysfunction hypothesis and its dependence on sleep also provide a framework for understanding why delirium, as a reversible syndrome of variable duration, can resolve with complete remission in some individuals, yet lead to persistent cognitive impairment in others, in light of the role of glymphatic failure in multiple neurodegenerative diseases^{15,174–176}.

As glymphatic activity is suppressed across a broad swathe of neurological diseases⁶⁷, an obvious question is the degree to which glymphatic failure specifically predicts delirium. Specificity with respect to delirium lies in the acute and reversible suppression of

glymphatic clearance that probably occurs during common hospital exposures, such as systemic infection or mechanical ventilation and sedation, particularly in individuals with pre-existing vulnerability owing to already reduced baseline glymphatic function. In this context, the abrupt accumulation of pro-inflammatory cytokines and neuroactive metabolic waste products, including A β , is proposed to transiently disrupt large-scale neural network integrity, impair synaptic signalling, and alter arousal and attentional state regulation. These rapid, state-dependent disturbances in neural network function are characteristic of delirium and distinguish it from chronic neurodegenerative or structural brain disorders, in which glymphatic impairment might contribute to longer-term disease progression rather than acute cognitive–behavioural fluctuations.

Are we inducing glymphatic failure in the ICU?

In the ICU, respiratory and circulatory failure are routinely managed with oral intubation, positive-pressure ventilation, opioid analgesia and sedation with agents such as propofol, midazolam or dexmedetomidine. In septic shock or hypotension, noradrenaline infusion and intravenous fluids are standard therapies. Sleep deprivation is nearly universal. However, emerging preclinical evidence suggests that these life-saving interventions might unintentionally harm brain function, compromising glymphatic clearance, the primary waste removal system of the brain^{72,170}. This raises the unsettling possibility that standard ICU therapies can trigger, exacerbate or sustain glymphatic dysfunction, potentially contributing to ICU delirium and post-ICU cognitive impairment.

Limitations of the proposed hypothesis

The hypothesis linking glymphatic dysfunction to delirium is necessarily limited by the current lack of direct human evidence demonstrating a causal relationship between impaired glymphatic flow and delirium onset, severity or resolution. Moreover, glymphatic impairment is increasingly recognized as a non-specific feature shared across a broad range of neurological and systemic conditions, including ageing, neurodegenerative disease, stroke, TBI, infection-related encephalopathy and generalized sickness behaviour. Accordingly, the present framework does not propose glymphatic failure as a delirium-exclusive mechanism, but rather as a shared vulnerability pathway that could be acutely and reversibly engaged under specific clinical circumstances.

A key limitation is the incomplete delineation of why transient glymphatic suppression would preferentially manifest as delirium rather than other encephalopathic syndromes. We posit that delirium reflects a state-dependent disruption of large-scale neural network function driven by rapid accumulation of neuroactive metabolites and cytokines, as documented in the above-mentioned experimental study on isoflurane anaesthesia and positive-pressure ventilation (see the section ‘Mechanical ventilation’)¹³⁷. Finally, the absence of validated delirium-specific or glymphatic-related biomarkers of delirium limits mechanistic resolution. However, one experimental study has shown that clinically relevant manipulation of glymphatic flow, including sleep deprivation and CSF sampling, suppressed or eliminated TBI-induced increases in blood biomarkers, including S100, GFAP and neuron-specific enolase¹⁷⁷. Translationally, these studies suggest searching for a reduction in serum markers during delirium, with a transition to elevated levels following effective treatment modalities or delirium resolution.

Nevertheless, the hypothesis should be viewed as explanatory and hypothesis-generating, providing a framework to guide future

experimental and clinical studies rather than a definitive mechanistic account.

Preserving glymphatic flow in the ICU

Glymphatic principles might already be applicable in intensive care. Optimization of the ICU environment and the choice of medications to support sleep, tailoring mechanical ventilation strategies and minimizing opioid and sedation use, are already known to enhance patient outcomes. Although these interventions align with current ICU best practices, their link to glymphatic health remains unrecognized; realization of their impact on glymphatic function could further inform clinical practice and research. This paradigm shift in viewing glymphatic support as part of organ protection could open new therapeutic avenues for preserving neurological function in delirious and critically ill patients.

Interventions to prevent delirium, including promoting awake, spontaneously breathing and mobile patients with focus on pain relief, sleep support and lighter sedation, have been grouped into a process of care named the 'A2F-bundle', being the best documented anti-delirium strategy in clinical use¹²⁸. Although preliminary, the preclinical and clinical research on the glymphatic system presented here would be consistent with the positive effects of the A2F-bundle, as the interventions included are theoretically expected to preserve glymphatic function: reducing the use of sedatives that suppress glymphatic activity, shifting to α_2 -agonists and promoting physical exercise have all been documented to enhance glymphatic clearance^{133,141,178–180}. In addition, analgesic and non-pharmacological interventions that lower noradrenergic tone are expected to further support glymphatic function (Table 1).

Dexmedetomidine and melatonin are proven to be clinically feasible. They have positive effects on the glymphatic system and are now recommended in clinical use¹²⁷, but in clinical cases wherein deeper sedation is needed, for example, owing to agitation^{41,181}, they are often not sufficient on their own. For this purpose, ketamine sedation, preclinically shown to spare glymphatic clearance¹³², might be promising and should be tested clinically. To address the negative effects of opioids, prolonged endotracheal local analgesia should be tested as a sedation-sparing intervention.

Advancing strategies to address glymphatic failure in the ICU

Research is urgently needed to determine which and to what extent ICU interventions induce glymphatic failure, and how to mitigate this process to preserve cognitive function and improve outcomes. Identification of patients with impaired glymphatic flow requires a fast, low-cost and reliable diagnostic test. Although MRI-based methods are available, they remain largely restricted to research settings¹⁸². Several wireless devices for monitoring glymphatic function have been developed, based on either mapping dynamic changes in brain infrared signals or measuring brain electrical resistance; however, these approaches have not yet been validated for clinical research^{183,184}. The refining and validation of such bedside tools should therefore be a priority, both to advance research on glymphatic function in disease and to enable the design of therapeutic strategies. Further research is particularly important to establish when and how glymphatic inhibition occurs in critically ill patients, especially in the postoperative and intensive care settings, and to clarify its role in delirium.

Equally important is the development of experimental models that faithfully replicate clinical delirium. For instance, as noted

previously, an ICU-relevant murine paradigm has established that mechanical ventilation under anaesthesia is sufficient to induce delirium-like behaviour, accompanied by acute glymphatic dysfunction¹³⁷; such studies provide compelling platforms for further mechanistic and therapeutic studies.

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References

- Misulis, K. E. & Murray, E. L. (eds) in *Essentials of Hospital Neurology* Ch. 5 (Oxford Univ. Press, 2017).
- Williams, S. T., Dhesi, J. K. & Partridge, J. S. L. Distress in delirium: causes, assessment and management. *Eur. Geriatr. Med.* **11**, 63–70 (2020).
- Wilson, J. E. et al. Delirium. *Nat. Rev. Dis. Primers* **6**, 90 (2020).
- Maldonado, J. R. Delirium pathophysiology: an updated hypothesis of the etiology of acute brain failure. *Int. J. Geriatr. Psychiatry* **33**, 1428–1457 (2018).
- Vasunilashorn, S. M. et al. Preclinical and translational models for delirium: recommendations for future research from the NIDUS Delirium Network. *Alzheimers Dement.* **19**, 2150–2174 (2023).
- Aldecoa, C. et al. Update of the European Society of Anaesthesiology and Intensive Care Medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. *Eur. J. Anaesthesiol.* **41**, 81–108 (2024).
- Inouye, S. K., Westendorp, R. G. & Saczynski, J. S. Delirium in elderly people. *Lancet* **383**, 911–922 (2014).
- Marcantonio, E. R. Delirium in hospitalized older adults. *N. Engl. J. Med.* **377**, 1456–1466 (2017).
- Mart, M. F. et al. Long-term outcomes after treatment of delirium during critical illness with antipsychotics (MIND-USA): a randomised, placebo-controlled, phase 3 trial. *Lancet Respir. Med.* **12**, 599–607 (2024).
- Andersen-Ranberg, N. C. et al. Haloperidol for the treatment of delirium in ICU patients. *N. Engl. J. Med.* **387**, 2425–2435 (2022).
- Shehabi, Y. et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit. Care Med.* **38**, 2311–2318 (2010).
- Mortensen, C. B. et al. Long-term outcomes with haloperidol versus placebo in acutely admitted adult ICU patients with delirium. *Intensive Care Med.* **50**, 103 (2024).
- Estrup, S. et al. Cognitive function 3 and 12 months after ICU discharge — a prospective cohort study. *Crit. Care Med.* **46**, e1121 (2018).
- Witlox, J. et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* **304**, 443–451 (2010).
- Iliff, J. J. et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci. Transl. Med.* **4**, 147ra111 (2012).
- Jessen, N. A., Munk, A. S. F., Lundgaard, I. & Nedergaard, M. The glymphatic system: a beginner's guide. *Neurochem. Res.* **40**, 2583–2599 (2015).
- Hablitz, L. M. & Nedergaard, M. The glymphatic system: a novel component of fundamental neurobiology. *J. Neurosci.* **41**, 7698 (2021).
- Xie, L. et al. Sleep drives metabolite clearance from the adult brain. *Science* **342**, 373–377 (2013).
- American Psychiatric Association & American Psychiatric Association DSM-5 Task Force. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (DSM-5) (American Psychiatric Association, 2013).
- Gibb, K. et al. The consistent burden in published estimates of delirium occurrence in medical inpatients over four decades: a systematic review and meta-analysis study. *Age Ageing* **49**, 352–360 (2020).
- Pang, Y. et al. Effects of inflammation and oxidative stress on postoperative delirium in cardiac surgery. *Front. Cardiovasc. Med.* **9**, 1049600 (2022).
- Shaw, R. C., Walker, G., Elliott, E. & Quinn, T. J. Occurrence rate of delirium in acute stroke settings: systematic review and meta-analysis. *Stroke* **50**, 3028–3036 (2019).
- Oldenbeuving, A. W. et al. Delirium in the acute phase after stroke: incidence, risk factors, and outcome. *Neurology* **76**, 993–999 (2011).
- Krewulak, K. D., Stelfox, H. T., Leigh, J. P., Ely, E. W. & Fiest, K. M. Incidence and prevalence of delirium subtypes in an adult ICU: a systematic review and meta-analysis. *Crit. Care Med.* **46**, 2029–2035 (2018).
- Zhang, H. et al. Development and validation of a predictive score for ICU delirium in critically ill patients. *BMC Anesthesiol.* **21**, 37 (2021).
- Pandharipande, P. P. et al. Long-term cognitive impairment after critical illness. *N. Engl. J. Med.* **369**, 1306–1316 (2013).
- Ren, X. et al. Dysfunction of the glymphatic system as a potential mechanism of perioperative neurocognitive disorders. *Front. Aging Neurosci.* **13**, 659457 (2021).
- van Gelder, T. G. et al. The risk of delirium after sedation with propofol or midazolam in intensive care unit patients. *Br. J. Clin. Pharmacol.* **90**, 1471–1479 (2024).
- Pandharipande, P. et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* **104**, 21–26 (2006).
- Urits, I. et al. Emergence delirium in perioperative pediatric care: a review of current evidence and new directions. *Adv. Ther.* **37**, 1897–1909 (2020).

31. Mason, K. P. Paediatric emergence delirium: a comprehensive review and interpretation of the literature. *Br. J. Anaesth.* **118**, 335–343 (2017).
32. Smith, H. A., Brink, E., Fuchs, D. C., Ely, E. W. & Pandharipande, P. P. Pediatric delirium: monitoring and management in the pediatric intensive care unit. *Pediatr. Clin. N. Am.* **60**, 741–760 (2013).
33. Calandriello, A., Tylka, J. C. & Patwari, P. P. Sleep and delirium in pediatric critical illness: what is the relationship? *Med. Sci.* **6**, 90 (2018).
34. Smith, H. A. B. et al. 2022 Society of Critical Care Medicine clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr. Crit. Care Med.* **23**, e74–e110 (2022).
35. Page, V. & Ely, E. W. (eds) in *Delirium in Critical Care Core Critical Care 27–43* (Cambridge Univ. Press, 2015).
36. la Cour, K. N. et al. Distribution of delirium motor subtypes in the intensive care unit: a systematic scoping review. *Crit. Care* **26**, 53 (2022).
37. Kooken, R. W. J., Tilburgs, B., Slooter, A. J. C. & van den Boogaard, M. Determinants of ICU memories and the impact on the development and trajectory of post-traumatic stress symptoms: a multicenter longitudinal cohort study. *Intensive Care Med.* **51**, 2021–2030 (2025).
38. Jones, C., Griffiths, R. D., Humphris, G. & Skirrow, P. M. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Crit. Care Med.* **29**, 573–580 (2001).
39. Sanchez, D. et al. Frailty, delirium and hospital mortality of older adults admitted to intensive care: the Delirium (Del) in ICU study. *Crit. Care* **24**, 609 (2020).
40. Ormseth, C. H. et al. Predisposing and precipitating factors associated with delirium: a systematic review. *JAMA Netw. Open* **6**, e2249950 (2023).
41. Devlin, J. W. et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit. Care Med.* **46**, e825–e873 (2018).
42. Greaves, D. et al. Risk factors for delirium and cognitive decline following coronary artery bypass grafting surgery: a systematic review and meta-analysis. *J. Am. Heart Assoc.* **9**, e017275 (2020).
43. Pendlebury, S. T. et al. Observational, longitudinal study of delirium in consecutive unselected acute medical admissions: age-specific rates and associated factors, mortality and re-admission. *BMJ Open* **5**, e007808 (2015).
44. Marquetand, J. et al. Risk factors for delirium are different in the very old: a comparative one-year prospective cohort study of 5,831 patients. *Front. Psychiatry* **12**, 655087 (2021).
45. Ahmed, S., Leurent, B. & Sampson, E. L. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. *Age Ageing* **43**, 326–333 (2014).
46. Smith, T. O. et al. Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis. *Int. J. Geriatr. Psychiatry* **32**, 386–396 (2017).
47. Smith, P. J., Attix, D. K., Weldon, B. C., Greene, N. H. & Monk, T. G. Executive function and depression as independent risk factors for postoperative delirium. *Anesthesiology* **110**, 781–787 (2009).
48. Davis, D. H. J. et al. Worsening cognitive impairment and neurodegenerative pathology progressively increase risk for delirium. *Am. J. Geriatr. Psychiatry* **23**, 403–415 (2015).
49. Lowery, D. P., Wesnes, K. & Ballard, C. G. Subtle attentional deficits in the absence of dementia are associated with an increased risk of post-operative delirium. *Dement. Geriatr. Cogn. Disord.* **23**, 390–394 (2007).
50. Van Rompaey, B. et al. Risk factors for delirium in intensive care patients: a prospective cohort study. *Crit. Care* **13**, R77 (2009).
51. Wilson, K., Broadhurst, C., Diver, M., Jackson, M. & Mottram, P. Plasma insulin growth factor-1 and incident delirium in older people. *Int. J. Geriatr. Psychiatry* **20**, 154–159 (2005).
52. Huang, C. et al. Delirium in psychiatric settings: risk factors and assessment tools in patients with psychiatric illness: a scoping review. *BMC Nurs.* **23**, 464 (2024).
53. Morandi, A. et al. Visual and hearing impairment are associated with delirium in hospitalized patients: results of a multisite prevalence study. *J. Am. Med. Dir. Assoc.* **22**, 1162–1167.e3 (2021).
54. Nitchingham, A., Kumar, V., Shenkin, S., Ferguson, K. J. & Caplan, G. A. A systematic review of neuroimaging in delirium: predictors, correlates and consequences. *Int. J. Geriatr. Psychiatry* **33**, 1458–1478 (2018).
55. Clegg, A. & Young, J. B. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing* **40**, 23–29 (2011).
56. Foley, K. A. & Djaiani, G. Update of the European Society of Anaesthesiology and Intensive Care Medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. *Eur. J. Anaesthesiol.* **42**, 86–87 (2025).
57. Shehabi, Y. et al. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a multinational prospective longitudinal cohort study. *Crit. Care Med.* **46**, 850–859 (2018).
58. Yasuda, Y. et al. Relationship between serum norepinephrine levels at ICU admission and the risk of ICU-acquired delirium: secondary analysis of the melatonin evaluation of lowered inflammation of ICU trial. *Crit. Care Explor.* **2**, e0082 (2020).
59. Nedergaard, M. Neuroscience. Garbage truck of the brain. *Science* **340**, 1529–1530 (2013).
60. Keil, S. A., Jansson, D., Braun, M. & Iliff, J. J. Glymphatic dysfunction in Alzheimer's disease: a critical appraisal. *Science* **389**, eadv8269 (2025).
61. Rasmussen, M. K., Mestre, H. & Nedergaard, M. Fluid transport in the brain. *Physiol. Rev.* **102**, 1025–1151 (2022).
62. Ringstad, G. et al. Brain-wide glymphatic enhancement and clearance in humans assessed with MRI. *JCI Insight* **3**, e121537 (2018).
63. Liu, X. et al. MRI free water mediates the association between diffusion tensor image analysis along the perivascular space and executive function in four independent middle to aged cohorts. *Alzheimers Dement.* **21**, e14453 (2025).
64. Eide, P. K. et al. Impact of subarachnoid hemorrhage on human glymphatic function: a time-evolution magnetic resonance imaging study. *Stroke* **56**, 678–691 (2025).
65. Naganawa, S., Taoka, T., Ito, R. & Kawamura, M. The glymphatic system in humans: investigations with magnetic resonance imaging. *Invest. Radiol.* **59**, 1–12 (2024).
66. Beschorner, N. & Nedergaard, M. Glymphatic system dysfunction in neurodegenerative diseases. *Curr. Opin. Neurol.* **37**, 182–188 (2024).
67. Rasmussen, M. K., Mestre, H. & Nedergaard, M. The glymphatic pathway in neurological disorders. *Lancet Neurol.* **17**, 1016–1024 (2018).
68. Nedergaard, M. & Goldman, S. A. Glymphatic failure as a final common pathway to dementia. *Science* **370**, 50–56 (2020).
69. Ding, Z. et al. The glymphatic system: a new perspective on brain diseases. *Front. Aging Neurosci.* **15**, 1179988 (2023).
70. Lohela, T. J., Lilius, T. O. & Nedergaard, M. The glymphatic system: implications for drugs for central nervous system diseases. *Nat. Rev. Drug Discov.* **21**, 763–779 (2022).
71. Vinje, V. et al. Human brain solute transport quantified by glymphatic MRI-informed biophysics during sleep and sleep deprivation. *Fluids Barriers CNS* **20**, 62 (2023).
72. Gakuba, C. et al. General anesthesia inhibits the activity of the “glymphatic system”. *Theranostics* **8**, 710–722 (2018).
73. Eide, P. K., Vinje, V., Pripp, A. H., Mardal, K. A. & Ringstad, G. Sleep deprivation impairs molecular clearance from the human brain. *Brain J. Neurol.* **144**, 863–874 (2021).
74. Deng, S. et al. Chronic sleep fragmentation impairs brain interstitial clearance in young wildtype mice. *J. Cereb. Blood Flow Metab.* **44**, 1515–1531 (2024).
75. Kress, B. T. et al. Impairment of paravascular clearance pathways in the aging brain. *Ann. Neurol.* **76**, 845–861 (2014).
76. Giannetto, M. et al. Biological sex does not predict glymphatic influx in healthy young, middle aged or old mice. *Sci. Rep.* **10**, 16073 (2020).
77. Peng, W. et al. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. *Neurobiol. Dis.* **93**, 215–225 (2016).
78. Hirose, M. et al. Stagnation of glymphatic interstitial fluid flow and delay in waste clearance in the SOD1-G93A mouse model of ALS. *Neurosci. Res.* **171**, 74–82 (2021).
79. Zamani, A. et al. Impaired glymphatic function in the early stages of disease in a TDP-43 mouse model of amyotrophic lateral sclerosis. *Transl. Neurodegener.* **11**, 17 (2022).
80. Liu, H. et al. Glymphatic influx and clearance are perturbed in Huntington's disease. *JCI Insight* **9**, e172286 (2024).
81. Cui, H. et al. Decreased AQP4 expression aggravates α -synuclein pathology in Parkinson's disease mice, possibly via impaired glymphatic clearance. *J. Mol. Neurosci.* **71**, 2500–2513 (2021).
82. Xu, Z. et al. Deletion of aquaporin-4 in APP/PS1 mice exacerbates brain $A\beta$ accumulation and memory deficits. *Mol. Neurodegener.* **10**, 58 (2015).
83. Da Mesquita, S. et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature* **560**, 185–191 (2018).
84. Wang, L. et al. Deep cervical lymph node ligation aggravates AD-like pathology of APP/PS1 mice. *Brain Pathol.* **29**, 176–192 (2019).
85. Zhou, Y. et al. Impairment of the glymphatic pathway and putative meningeal lymphatic vessels in the aging human. *Ann. Neurol.* **87**, 357–369 (2020).
86. Ishida, K. et al. Glymphatic system clears extracellular tau and protects from tau aggregation and neurodegeneration. *J. Exp. Med.* **219**, e20211275 (2022).
87. Harrison, I. F. et al. Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. *Brain J. Neurol.* **143**, 2576–2593 (2020).
88. Lopes, D. M., Llewellyn, S. K. & Harrison, I. F. Propagation of tau and α -synuclein in the brain: therapeutic potential of the glymphatic system. *Transl. Neurodegener.* **11**, 19 (2022).
89. Formolo, D. A. et al. Leveraging the glymphatic and meningeal lymphatic systems as therapeutic strategies in Alzheimer's disease: an updated overview of nonpharmacological therapies. *Mol. Neurodegener.* **18**, 26 (2023).
90. Gao, Y., Liu, K. & Zhu, J. Glymphatic system: an emerging therapeutic approach for neurological disorders. *Front. Mol. Neurosci.* **16**, 1138769 (2023).
91. Zhang, X. et al. Glymphatic system impairment in Alzheimer's disease: associations with perivascular space volume and cognitive function. *Eur. Radiol.* **34**, 1314–1323 (2024).
92. Sharkey, R. J. et al. Longitudinal analysis of glymphatic function in amyotrophic lateral sclerosis and primary lateral sclerosis. *Brain J. Neurol.* **147**, 4026–4032 (2024).
93. Liang, T. et al. Evaluation of glymphatic system activity by diffusion tensor image analysis along the perivascular space (DTI-ALPS) in dementia patients. *Br. J. Radiol.* **96**, 20220315 (2023).
94. Cai, X. et al. Diffusion along perivascular spaces provides evidence interlinking compromised glymphatic function with aging in Parkinson's disease. *CNS Neurosci. Ther.* **29**, 111–121 (2023).
95. Goldberg, T. E. et al. Association of delirium with long-term cognitive decline: a meta-analysis. *JAMA Neurol.* **77**, 1373–1381 (2020).
96. Chen, K., Du, X., Chao, M. A., Xie, Z. & Yang, G. Surgery impairs glymphatic activity and cognitive function in aged mice. *Mol. Brain* **18**, 7 (2025).

97. Hussain, R. et al. Potentiating glymphatic drainage minimizes post-traumatic cerebral oedema. *Nature* **623**, 992–1000 (2023).
98. Mestre, H. et al. Cerebrospinal fluid influx drives acute ischemic tissue swelling. *Science* **367**, eaax7171 (2020).
99. Butler, T. et al. Glymphatic clearance estimated using diffusion tensor imaging along perivascular spaces is reduced after traumatic brain injury and correlates with plasma neurofilament light, a biomarker of injury severity. *Brain Commun.* **5**, fca4134 (2023).
100. Qin, Y. et al. DTI-ALPS: an MR biomarker for motor dysfunction in patients with subacute ischemic stroke. *Front. Neurosci.* **17**, 1132393 (2023).
101. Alghanimy, A., Work, L. M. & Holmes, W. M. The glymphatic system and multiple sclerosis: an evolving connection. *Mult. Scler. Relat. Disord.* **83**, 105456 (2024).
102. Hagiwara, A. et al. Glymphatic system dysfunction in myelin oligodendrocyte glycoprotein immunoglobulin G antibody-associated disorders: association with clinical disability. *Am. J. Neuroradiol.* **45**, 66–71 (2023).
103. Gaberel, T. et al. Impaired glymphatic perfusion after strokes revealed by contrast-enhanced MRI: a new target for fibrinolysis? *Stroke* **45**, 3092–3096 (2014).
104. Toh, C. H. & Siow, T. Y. Glymphatic dysfunction in patients with ischemic stroke. *Front. Aging Neurosci.* **13**, 756249 (2021).
105. Alghanimy, A. A. et al. Is multiple sclerosis a glymphaticopathy? *Mult. Scler. Relat. Disord.* **80**, 105141 (2023).
106. Roberson, S. W. et al. Challenges of delirium management in patients with traumatic brain injury: from pathophysiology to clinical practice. *Curr. Neuropharmacol.* **19**, 1519–1544 (2021).
107. Maneewong, J. et al. Delirium after a traumatic brain injury: predictors and symptom patterns. *Neuropsychiatr. Dis. Treat.* **13**, 459–465 (2017).
108. Manouchehrian, O., Ramos, M., Bachiller, S., Lundgaard, I. & Deierborg, T. Acute systemic LPS-exposure impairs perivascular CSF distribution in mice. *J. Neuroinflamm.* **18**, 34 (2021).
109. Mogensen, F. L., Delle, C. & Nedergaard, M. The glymphatic system (en)during inflammation. *Int. J. Mol. Sci.* **22**, 7491 (2021).
110. McGrane, S. et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. *Crit. Care* **15**, R78 (2011).
111. Hablitz, L. M. et al. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat. Commun.* **11**, 4411 (2020).
112. Miyakoshi, L. M. et al. The state of brain activity modulates cerebrospinal fluid transport. *Prog. Neurobiol.* **229**, 102512 (2023).
113. Kang, J. E. et al. Amyloid- β dynamics are regulated by orexin and the sleep-wake cycle. *Science* **326**, 1005–1007 (2009).
114. Hauglund, L., Pavan, C. & Nedergaard, M. Cleaning the sleeping brain — the potential restorative function of the glymphatic system. *Curr. Opin. Physiol.* **15**, 1–6 (2020).
115. Hauglund, N. L. et al. Norepinephrine-mediated slow vasomotion drives glymphatic clearance during sleep. *Cell* **188**, 606–622.e17 (2025).
116. Helakari, H. et al. Effect of sleep deprivation and NREM sleep stage on physiological brain pulsations. *Front. Neurosci.* **17**, 1275184 (2023).
117. Fultz, N. E. et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science* **366**, 628–631 (2019).
118. Showler, L., Ali Abdelhamid, Y., Goldin, J. & Deane, A. M. Sleep during and following critical illness: a narrative review. *World J. Crit. Care Med.* **12**, 92–115 (2023).
119. Andersen, J. H., Boesen, H. C. & Skovgaard Olsen, K. Sleep in the intensive care unit measured by polysomnography. *Minerva Anesthesiol.* **79**, 804–815 (2013).
120. Boesen, H. C., Andersen, J. H., Bendtsen, A. O. & Jennum, P. J. Sleep and delirium in unsedated patients in the intensive care unit. *Acta Anaesthesiol. Scand.* **60**, 59–68 (2016).
121. Watson, P. L. et al. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit. Care Med.* **41**, 1958–1967 (2013).
122. Boyko, Y. et al. Atypical sleep in critically ill patients on mechanical ventilation is associated with increased mortality. *Sleep Breath.* **23**, 379–388 (2019).
123. Watson, P. L., Ceriana, P. & Fanfulla, F. Delirium: is sleep important? *Best Pract. Res. Clin. Anaesthesiol.* **26**, 355–366 (2012).
124. Trompeo, A. C. et al. Sleep disturbances in the critically ill patients: role of delirium and sedative agents. *Minerva Anesthesiol.* **77**, 604–612 (2011).
125. Waters, F., Chiu, V., Atkinson, A. & Blom, J. D. Severe sleep deprivation causes hallucinations and a gradual progression toward psychosis with increasing time awake. *Front. Psychiatry* **9**, 303 (2018).
126. Strøm, T., Stylsvig, M. & Toft, P. Long-term psychological effects of a no-sedation protocol in critically ill patients. *Crit. Care* **15**, R293 (2011).
127. Lewis, K. et al. A focused update to the Clinical Practice Guidelines for the Prevention and Management of Pain, Anxiety, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit. Care Med.* **53**, e711–e727 (2025).
128. Pun, B. T. et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. *Crit. Care Med.* **47**, 3–14 (2019).
129. Pisani, M. A. et al. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit. Care Med.* **37**, 177–183 (2009).
130. Zaal, I. J. et al. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med.* **41**, 2130–2137 (2015).
131. Plante, D. T. et al. Effects of oral temazepam on slow waves during non-rapid eye movement sleep in healthy young adults: a high-density EEG investigation. *Int. J. Psychophysiol.* **101**, 25–32 (2016).
132. Hablitz, L. M. et al. Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. *Sci. Adv.* **5**, eaav5447 (2019).
133. Benveniste, H. et al. Anesthesia with dexmedetomidine and low-dose isoflurane increases solute transport via the glymphatic pathway in rat brain when compared with high-dose isoflurane. *Anesthesiology* **127**, 976–988 (2017).
134. Benveniste, H., Heerdt, P. M., Fontes, M., Rothman, D. L. & Volkow, N. D. Glymphatic system function in relation to anesthesia and sleep states. *Anesth. Analg.* **128**, 747–758 (2019).
135. Duprey, M. S. et al. Opioid use increases the risk of delirium in critically ill adults independently of pain. *Am. J. Respir. Crit. Care Med.* **204**, 566–572 (2021).
136. Dimsdale, J. E., Norman, D., DeJardin, D. & Wallace, M. S. The effect of opioids on sleep architecture. *J. Clin. Sleep Med.* **3**, 33–36 (2007).
137. Liu, G. et al. Mechanical ventilation suppresses glymphatic function in parallel with delirium-like symptoms in mice. Preprint at *bioRxiv* <https://doi.org/10.64898/2025.12.12.694005> (2025).
138. Reade, M. C. et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. *JAMA* **315**, 1460–1468 (2016).
139. Shehabi, Y. et al. Early sedation with dexmedetomidine in critically ill patients. *N. Engl. J. Med.* **380**, 2506–2517 (2019).
140. Turan, A. et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet* **396**, 177–185 (2020).
141. Lilius, T. O. et al. Dexmedetomidine enhances glymphatic brain delivery of intrathecally administered drugs. *J. Control. Release* **304**, 29–38 (2019).
142. Sun, X. et al. Engineering near-infrared-II nanoprobes reveal dexmedetomidine potentiating brain waste clearance in healthy and sleep-restricted mice. *ACS Nano* **19**, 34830–34846 (2025).
143. Riker, R. R. et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* **301**, 489–499 (2009).
144. Pandharipande, P. P. et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* **298**, 2644–2653 (2007).
145. Maagaard, M. et al. Dexmedetomidine for the prevention of delirium in adults admitted to the intensive care unit or post-operative care unit: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Acta Anaesthesiol. Scand.* **67**, 382–411 (2023).
146. Huet, O. et al. Prevention of post-operative delirium using an overnight infusion of dexmedetomidine in patients undergoing cardiac surgery: a pragmatic, randomized, double-blind, placebo-controlled trial. *Crit. Care* **28**, 64 (2024).
147. Pereira, J. V., Sanjanwala, R. M., Mohammed, M. K., Le, M. L. & Arora, R. C. Dexmedetomidine versus propofol sedation in reducing delirium among older adults in the ICU: a systematic review and meta-analysis. *Eur. J. Anaesthesiol.* **37**, 121–131 (2020).
148. Skrobik, Y., Duprey, M. S., Hill, N. S. & Devlin, J. W. Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. *Am. J. Respir. Crit. Care Med.* **197**, 1147–1156 (2018).
149. Perbet, S. et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: a randomised double-blind control trial. *Anaesth. Crit. Care Pain Med.* **37**, 589–595 (2018).
150. Nikoobe, R. et al. Antipsychotics for treating delirium in hospitalized adults: a systematic review. *Ann. Intern. Med.* **171**, 485–495 (2019).
151. Tang, B. H. Y. et al. Melatonin use in the ICU: a systematic review and meta-analysis. *Crit. Care Med.* **53**, e1714–e1724 (2025).
152. Tricoire, H., Locatelli, A., Chemineau, P. & Malpaux, B. Melatonin enters the cerebrospinal fluid through the pineal recess. *Endocrinology* **143**, 84–90 (2002).
153. Leston, J. et al. Melatonin is released in the third ventricle in humans. A study in movement disorders. *Neurosci. Lett.* **469**, 294–297 (2010).
154. Feng, Z., Qin, C., Chang, Y. & Zhang, J. T. Early melatonin supplementation alleviates oxidative stress in a transgenic mouse model of Alzheimer's disease. *Free Radic. Biol. Med.* **40**, 101–109 (2006).
155. Pappolla, M. A. et al. Melatonin treatment enhances A β lymphatic clearance in a transgenic mouse model of amyloidosis. *Curr. Alzheimer Res.* **15**, 637–642 (2018).
156. O'Neal-Moffitt, G., Delic, V., Bradshaw, P. C. & Olcese, J. Prophylactic melatonin significantly reduces Alzheimer's neuropathology and associated cognitive deficits independent of antioxidant pathways in A β PP(swe)/PS1 mice. *Mol. Neurodegener.* **10**, 27 (2015).
157. Reiter, R. J. et al. Melatonin in ventricular and subarachnoid cerebrospinal fluid: its function in the neural glymphatic network and biological significance for neurocognitive health. *Biochem. Biophys. Res. Commun.* **605**, 70–81 (2022).
158. Yao, D. et al. Melatonin alleviates depression-like behaviors and cognitive dysfunction in mice by regulating the circadian rhythm of AQP4 polarization. *Transl. Psychiatry* **13**, 310 (2023).
159. Chen, Y. et al. Melatonin regulates glymphatic function to affect cognitive deficits, behavioral issues, and blood-brain barrier damage in mice after intracerebral hemorrhage: potential links to circadian rhythms. *CNS Neurosci. Ther.* **31**, e70289 (2025).
160. Deiner, S., Lin, H. M., Bodansky, D., Silverstein, J. & Sano, M. Do stress markers and anesthetic technique predict delirium in the elderly? *Dement. Geriatr. Cogn. Disord.* **38**, 366–374 (2014).

161. Persson, N. D. A., Uusalo, P., Nedergaard, M., Lohela, T. J. & Lilius, T. O. Could dexmedetomidine be repurposed as a glymphatic enhancer? *Trends Pharmacol. Sci.* **43**, 1030–1040 (2022).
162. Hussain, R. & Nedergaard, M. Managing noradrenaline after traumatic brain injury. *Clin. Transl. Med.* **14**, e1562 (2024).
163. Clifton, G. L., Ziegler, M. G. & Grossman, R. G. Circulating catecholamines and sympathetic activity after head injury. *Neurosurgery* **8**, 10–14 (1981).
164. Rizoli, S. B. et al. Catecholamines as outcome markers in isolated traumatic brain injury: the COMA-TBI study. *Crit. Care* **21**, 37 (2017).
165. Persson, N. D. A. et al. Anesthesia blunts carbon dioxide effects on glymphatic cerebrospinal fluid dynamics in mechanically ventilated rats. *Anesthesiology* **141**, 338–352 (2024).
166. Kipnis, J. et al. Resolving the mysteries of brain clearance and immune surveillance. *Neuron* **113**, 3908–3923 (2025).
167. Machado-Junior, P. A. et al. A short duration of mechanical ventilation alters redox status in the diaphragm and aggravates inflammation in septic mice. *Respir. Physiol. Neurobiol.* **331**, 104361 (2025).
168. Joelsson, J. P. et al. Ventilator-induced lung injury results in oxidative stress response and mitochondrial swelling in a mouse model. *Lab. Anim. Res.* **38**, 23 (2022).
169. Pinheiro de Oliveira, R., Hetzel, M. P., dos Anjos Silva, M., Dallegre, D. & Friedman, G. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. *Crit. Care* **14**, R39 (2010).
170. Chen, C. et al. Prolonged mechanical ventilation-induced neuroinflammation affects postoperative memory dysfunction in surgical mice. *Crit. Care* **19**, 159 (2015).
171. van Montfort, S. J. T. et al. Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis. *NeuroImage Clin.* **23**, 101809 (2019).
172. Zhu, B. et al. Sleep disturbance induces neuroinflammation and impairment of learning and memory. *Neurobiol. Dis.* **48**, 348–355 (2012).
173. Farasat, S. et al. Sleep and delirium in older adults. *Curr. Sleep Med. Rep.* **6**, 136–148 (2020).
174. Iliff, J. J. et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J. Neurosci.* **34**, 16180–16193 (2014).
175. Lopes, D. M. et al. The influence of the glymphatic system on α -synuclein propagation: the role of aquaporin-4. *Brain J. Neurol.* **148**, 4519–4531 (2025).
176. Jia, L. et al. The glymphatic system in neurodegenerative diseases and brain tumors: mechanistic insights, biomarker advances, and therapeutic opportunities. *Acta Neuropathol. Commun.* **14**, 19 (2025).
177. Plog, B. A. et al. Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. *J. Neurosci.* **35**, 518–526 (2015).
178. He, X. F. et al. Voluntary exercise promotes glymphatic clearance of amyloid beta and reduces the activation of astrocytes and microglia in aged mice. *Front. Mol. Neurosci.* **10**, 144 (2017).
179. von Holstein-Rathlou, S., Petersen, N. C. & Nedergaard, M. Voluntary running enhances glymphatic influx in awake behaving, young mice. *Neurosci. Lett.* **662**, 253–258 (2018).
180. Yoo, R. E. et al. Long-term physical exercise facilitates putative glymphatic and meningeal lymphatic vessel flow in humans. *Nat. Commun.* **16**, 3360 (2025).
181. Ozaki, M. et al. Safety and efficacy of dexmedetomidine for long-term sedation in critically ill patients. *J. Anesth.* **28**, 38–50 (2014).
182. Taoka, T. & Naganawa, S. Glymphatic imaging using MRI. *J. Magn. Reson. Imaging* **51**, 11–24 (2020).
183. Ferdinando, H., Moradi, S., Korhonen, V., Kiviniemi, V. & Myllyla, T. Altered cerebrovascular-CSF coupling in Alzheimer's disease measured by functional near-infrared spectroscopy. *Sci. Rep.* **13**, 22364 (2023).
184. Dagum, P. et al. A wireless device for continuous measurement of brain parenchymal resistance tracks glymphatic function in humans. *Nat. Biomed. Eng.* **9**, 1656–1676 (2025).
185. Wang, J. et al. Glymphatic function plays a protective role in ageing-related cognitive decline. *Age Ageing* **52**, afad107 (2023).
186. Ozsahin, I. et al. Diffusion tensor imaging along perivascular spaces (DTI-ALPS) to assess effects of age, sex, and head size on interstitial fluid dynamics in healthy subjects. *J. Alzheimers Dis. Rep.* **8**, 355–361 (2024).
187. Han, G. et al. Age- and time-of-day dependence of glymphatic function in the human brain measured via two diffusion MRI methods. *Front. Aging Neurosci.* **15**, 1173221 (2023).
188. Zeppenfeld, D. M. et al. Association of perivascular localization of aquaporin-4 with cognition and Alzheimer disease in aging brains. *JAMA Neurol.* **74**, 91–99 (2017).
189. Li, L. et al. Aging-related alterations of glymphatic transport in rat: in vivo magnetic resonance imaging and kinetic study. *Front. Aging Neurosci.* **14**, 841798 (2022).
190. Huang, S.-Y. et al. Glymphatic system dysfunction predicts amyloid deposition, neurodegeneration, and clinical progression in Alzheimer's disease. *Alzheimers Dement.* **20**, 3251–3269 (2024).
191. Kamagata, K. et al. Association of MRI indices of glymphatic system with amyloid deposition and cognition in mild cognitive impairment and Alzheimer disease. *Neurology* **99**, e2648–e2660 (2022).
192. Zhou, C. et al. Glymphatic system dysfunction and risk of clinical milestones in patients with Parkinson disease. *Eur. J. Neurol.* **31**, e16521 (2024).
193. Jungwon, J., Lee, J. H., Choi, C. H. & Lee, J. DTI-ALPS index as a predictor of cognitive decline over 1 year. *Neuroradiology* **67**, 163–170 (2024).
194. Liu, S. et al. Glymphatic dysfunction in patients with early-stage amyotrophic lateral sclerosis. *Brain J. Neurol.* **147**, 100–108 (2024).
195. Si, X. et al. Neuroimaging evidence of glymphatic system dysfunction in possible REM sleep behavior disorder and Parkinson's disease. *NPJ Parkinsons Dis.* **8**, 54 (2022).
196. Taoka, T. 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.* **35**, 172–178 (2017).
197. Steward, C. E. et al. Assessment of the DTI-ALPS parameter along the perivascular space in older adults at risk of dementia. *J. Neuroimaging* **31**, 569–578 (2021).
198. Zhang, Y. et al. Interaction between the glymphatic system and α -synuclein in Parkinson's disease. *Mol. Neurobiol.* **60**, 2209–2222 (2023).
199. Simon, M. et al. Loss of perivascular aquaporin-4 localization impairs glymphatic exchange and promotes amyloid β plaque formation in mice. *Alzheimers Res. Ther.* **14**, 59 (2022).
200. Bae, Y. J. et al. Altered glymphatic system in idiopathic normal pressure hydrocephalus. *Parkinsonism Relat. Disord.* **82**, 56–60 (2021).
201. Fournier, A. P. et al. Reduced spinal cord parenchymal cerebrospinal fluid circulation in experimental autoimmune encephalomyelitis. *J. Cereb. Blood Flow Metab.* **39**, 1258–1265 (2019).
202. Fadayomi, A. B., Ibalá, R., Bilotta, F., Westover, M. B. & Akeju, O. A systematic review and meta-analysis examining the impact of sleep disturbance on postoperative delirium. *Crit. Care Med.* **46**, e1204–e1212 (2018).
203. Ma, J. et al. Effects of sleep on the glymphatic functioning and multimodal human brain network affecting memory in older adults. *Mol. Psychiatry* **30**, 1717–1729 (2024).
204. Wang, J. et al. Impaired glymphatic drainage underlying obstructive sleep apnea is associated with cognitive dysfunction. *J. Neurol.* **270**, 2204–2216 (2023).
205. Lee, H.-J., Lee, D. A., Shin, K. J. & Park, K. M. Glymphatic system dysfunction in obstructive sleep apnea evidenced by DTI-ALPS. *Sleep Med.* **89**, 176–181 (2022).
206. Roy, B. et al. Impaired glymphatic system actions in obstructive sleep apnea adults. *Front. Neurosci.* **16**, 884234 (2022).
207. Lee, D. A., Lee, H. J. & Park, K. M. Glymphatic dysfunction in isolated REM sleep behavior disorder. *Acta Neurol. Scand.* **145**, 464–470 (2022).
208. Vasciaveo, V. et al. Sleep fragmentation affects glymphatic system through the different expression of AQP4 in wild type and 5xTAD mouse models. *Acta Neuropathol. Commun.* **11**, 16 (2023).
209. Abdolizadeh, A. 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.* **50**, 1396–1410 (2024).
210. Tu, Y., Fang, Y., Li, G., Xiong, F. & Gao, F. Glymphatic system dysfunction underlying schizophrenia is associated with cognitive impairment. *Schizophr. Bull.* **50**, 1223–1231 (2024).
211. Korann, V. 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* **70**, 260–270 (2024).
212. Bao, W. et al. Lower DTI-ALPS index in patients with major depressive disorder: correlation with fatigue. *Behav. Brain Res.* **478**, 115323 (2025).
213. Xia, M., Yang, L., Sun, G., Qi, S. & Li, B. Mechanism of depression as a risk factor in the development of Alzheimer's disease: the function of AQP4 and the glymphatic system. *Psychopharmacology* **234**, 365–379 (2017).
214. Liu, X. et al. Polyunsaturated fatty acid supplement alleviates depression-incident cognitive dysfunction by protecting the cerebrovascular and glymphatic systems. *Brain Behav. Immun.* **89**, 357–370 (2020).
215. Wang, L. et al. Glymphatic-system function is associated with addiction and relapse in heroin dependents undergoing methadone maintenance treatment. *Brain Sci.* **13**, 1292 (2023).
216. Lundgaard, I. et al. Beneficial effects of low alcohol exposure, but adverse effects of high alcohol intake on glymphatic function. *Sci. Rep.* **8**, 2246 (2018).
217. Liu, Q. et al. Experimental alcoholism primes structural and functional impairment of the glymphatic pathway. *Brain Behav. Immun.* **85**, 106–119 (2020).
218. Chen, W. et al. Cocaine-induced structural and functional impairments of the glymphatic pathway in mice. *Brain Behav. Immun.* **88**, 97–104 (2020).
219. Wang, M.-L. et al. Associations of ischemic heart disease with brain glymphatic MRI indices and risk of Alzheimer's disease. *J. Prev. Alzheimers Dis.* **12**, 100045 (2025).
220. Yang, J. et al. Association of glymphatic clearance function with imaging markers and risk factors of cerebral small vessel disease. *J. Stroke Cerebrovasc. Dis.* **34**, 108187 (2025).
221. Xu, J. et al. Glymphatic dysfunction correlates with severity of small vessel disease and cognitive impairment in cerebral amyloid angiopathy. *Eur. J. Neurol.* **29**, 2895–2904 (2022).
222. Yu, T. et al. Impaired glymphatic system as evidenced by low diffusivity along perivascular spaces is associated with cerebral small vessel disease: a population-based study. *Stroke Vasc. Neurol.* **8**, e002191 (2023).
223. Heo, C. M. et al. Glymphatic system dysfunction in patients with early chronic kidney disease. *Front. Neurol.* **13**, 976089 (2022).
224. Xu, S. et al. Cognitive impairment in chronic kidney disease is associated with glymphatic system dysfunction. *Kidney Dis.* **9**, 384–397 (2023).
225. Shu, K. et al. Altered brain glymphatic function at diffusion-tensor MRI in pre-cirrhotic metabolic dysfunction-associated fatty liver disease. *Acad. Radiol.* **31**, 4946–4954 (2024).
226. Capasso, G. et al. Drivers and mechanisms of cognitive decline in chronic kidney disease. *Nat. Rev. Nephrol.* **21**, 536–552 (2025).

227. Mestre, H. et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat. Commun.* **9**, 4878 (2018).
228. Kritsilis, M. et al. Loss of glymphatic homeostasis in heart failure. *Brain J. Neurol.* **148**, 985–1000 (2024).
229. Mortensen, K. N. et al. Impaired glymphatic transport in spontaneously hypertensive rats. *J. Neurosci.* **39**, 6365–6377 (2019).
230. Hadjihambi, A. et al. Impaired brain glymphatic flow in experimental hepatic encephalopathy. *J. Hepatol.* **70**, 40–49 (2019).
231. Sampson, E. L., West, E. & Fischer, T. Pain and delirium: mechanisms, assessment, and management. *Eur. Geriatr. Med.* **11**, 45–52 (2020).
232. Wang, A. B. et al. Evaluation of the glymphatic system with diffusion tensor imaging-along the perivascular space in cancer pain. *Front. Neurosci.* **16**, 823701 (2022).
233. Wu, C. H. et al. Impaired glymphatic and meningeal lymphatic functions in patients with chronic migraine. *Ann. Neurol.* **95**, 583–595 (2024).
234. Huang, W. B. et al. Glymphatic dysfunction in migraine mice model. *Neuroscience* **528**, 64–74 (2023).
235. Denk, A. et al. Liver diseases as a novel risk factor for delirium in the ICU — delirium and hepatic encephalopathy are two distinct entities. *PLoS ONE* **17**, e0276914 (2022).
236. Healy, D. et al. Susceptibility to acute cognitive dysfunction in aged mice is underpinned by reduced white matter integrity and microgliosis. *Commun. Biol.* **7**, 105 (2024).
237. Jackel, M. et al. Incidence and predictors of delirium on the intensive care unit in patients with acute kidney injury, insight from a retrospective registry. *Sci. Rep.* **11**, 17260 (2021).
238. Siew, E. D. et al. Acute kidney injury as a risk factor for delirium and coma during critical illness. *Am. J. Respir. Crit. Care Med.* **195**, 1597–1607 (2017).
239. Joseph, C. R. et al. Identifying delay in glymphatic clearance of labeled protons post-acute head trauma utilizing 3D ASL MRI (arterial spin labeling): a pilot study. *Sci. Rep.* **14**, 6188 (2024).
240. Yang, D. X. et al. Associations of MRI-derived glymphatic system impairment with global white matter damage and cognitive impairment in mild traumatic brain injury: a DTI-ALPS study. *J. Magn. Reson. Imaging* **59**, 639–647 (2024).
241. Ji, C. et al. The role of glymphatic system in the cerebral edema formation after ischemic stroke. *Exp. Neurol.* **340**, 113685 (2021).
242. Lin, L. et al. Impaired glymphatic system in secondary degeneration areas after ischemic stroke in rats. *J. Stroke Cerebrovasc. Dis.* **29**, 104828 (2020).
243. Lv, T., Zhao, B., Hu, Q. & Zhang, X. The glymphatic system: a novel therapeutic target for stroke treatment. *Front. Aging Neurosci.* **13**, 689098 (2021).
244. Pu, T. et al. Persistent malfunction of glymphatic and meningeal lymphatic drainage in a mouse model of subarachnoid hemorrhage. *Exp. Neurol.* **28**, 104–118 (2019).
245. Hou, C. et al. Dynamic evolution of the glymphatic system at the early stages of subarachnoid hemorrhage. *Front. Neurol.* **13**, 924080 (2022).
246. Sigurdsson, B. et al. A SPECT-based method for dynamic imaging of the glymphatic system in rats. *J. Cereb. Blood Flow Metab.* **43**, 1153–1165 (2023).
247. Zhou, Y. et al. Enlarged choroid plexus related to atrophy of hippocampal subfield volumes and glymphatic dysfunction in benzodiazepine use disorder. *Br. J. Clin. Pharmacol.* <https://doi.org/10.1111/bcp.16328> (2024).
248. Lewis, K. et al. Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials. *Intensive Care Med.* **48**, 811–840 (2022).
249. van den Boogaard, M. et al. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE randomized clinical trial. *JAMA* **319**, 680–690 (2018).
250. Khan, B. A. et al. Preventing postoperative delirium after major noncardiac thoracic surgery — a randomized clinical trial. *J. Am. Geriatr. Soc.* **66**, 2289–2297 (2018).
251. Nikooye, R. et al. Antipsychotics for treating delirium in hospitalized adults. *Ann. Intern. Med.* **171**, 485–495 (2019).
252. Girard, T. D. et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N. Engl. J. Med.* **379**, 2506–2516 (2018).
253. Hudetz, J. A. et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. *J. Cardiothorac. Vasc. Anesth.* **23**, 651–657 (2009).
254. Avidan, M. S. et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Lancet* **390**, 267–275 (2017).
255. Ma, C. B. et al. Effect of low-dose esketamine on postoperative delirium in elderly patients undergoing total hip or knee arthroplasty: a randomized controlled trial. *Drug Des. Dev. Ther.* **18**, 5409–5421 (2024).
256. Wu, T. T., Ko, S., Kooker, R., van den Boogaard, M. & Devlin, J. W. Exploring ketamine analgesation use and its effect on incident delirium in critically ill adults. *Crit. Care Explor.* **3**, e0544 (2021).
257. Siddiqi, N. et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst. Rev.* **3**, CD005563 (2016).
258. Lozano-Vicario, L. et al. Effects of exercise intervention for the management of delirium in hospitalized older adults: a randomized clinical trial. *J. Am. Med. Dir. Assoc.* **25**, 104980 (2024).
259. Schweickert, W. D. et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* **373**, 1874–1882 (2009).
260. Girard, T. D. et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir. Med.* **6**, 213–222 (2018).
261. Saczynski, J. S. et al. Cognitive trajectories after postoperative delirium. *N. Engl. J. Med.* **367**, 30–39 (2012).
262. Girard, T. D. et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit. Care Med.* **38**, 1513–1520 (2010).
263. Tang, J. et al. The association between glymphatic system dysfunction and cognitive impairment in cerebral small vessel disease. *Front. Aging Neurosci.* **14**, 916633 (2022).
264. Ely, E. W. et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* **291**, 1753–1762 (2004).

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Competing interests

The authors declare no competing interests.

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