Glymphatic Dysfunction: A Bridge Between Sleep Disturbance and Mood Disorders

Tao Yan¹, Yuefeng Qiu², Xinfeng Yu³* and Linglin Yang⁴*

¹Department of Psychiatry, Changxing People’s Hospital, Huzhou, China, ²Department of Psychiatry, Zhejiang Hospital, Hangzhou, China, ³Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, ⁴Department of Psychiatry, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Mounting evidence demonstrates a close relationship between sleep disturbance and mood disorders, including major depression disorder (MDD) and bipolar disorder (BD). According to the classical two-process model of sleep regulation, circadian rhythms driven by the light–dark cycle, and sleep homeostasis modulated by the sleep–wake cycle are disrupted in mood disorders. However, the exact mechanism of interaction between sleep and mood disorders remains unclear. Recent discovery of the glymphatic system and its dynamic fluctuation with sleep provide a plausible explanation. The diurnal variation of the glymphatic circulation is dependent on the astrocytic activity and polarization of water channel protein aquaporin-4 (AQP4). Both animal and human studies have reported suppressed glymphatic transport, abnormal astrocytes, and depolarized AQP4 in mood disorders. In this study, the “glymphatic dysfunction” hypothesis which suggests that the dysfunctional glymphatic pathway serves as a bridge between sleep disturbance and mood disorders is proposed.

Keywords: glymphatic system, depression, sleep, bipolar disorder, astrocyte, aquaporin-4

INTRODUCTION

Mood disorders are a group of complex debilitating psychiatric diseases identified by symptoms centered on markedly disrupted emotions, including major depressive disorder (MDD) and bipolar disorder (BD) (1). Due to their high prevalence, the risk for recurrence and suicide, they remain a serious health concern worldwide (2, 3). However, the exact neurobiological mechanisms underlying mood disorders remain unclear, resulting in unsatisfactory treatment (2, 3).

Sleep disturbance is a common concomitant and prodromal symptom of mood disorders (1, 4, 5). Specifically, both the two processes of sleep regulation—circadian oscillator and sleep pressure—are disrupted in mood disorders (4, 6). On one hand, circadian rhythms are approximately 24-h patterns in physiology and behavior, which are regulated by molecular clocks in the suprachiasmatic nuclei (SCN) of the hypothalamus (7). Mounting evidence suggests that there are abnormalities of the clock genes in mood disorders, such as single nucleotide polymorphisms (SNPs) (8–13), gene expression (14, 15), and gene–gene interactions (8). Excitingly, antidepressants including fluoxetine (16–18), ketamine (19, 20), and agomelatine (21) can reset the circadian clock along with the amelioration of mood symptoms. On the other hand, sleep pressure fluctuates with the sleep–wake cycle (6). Whereas, disturbance of the sleep–wake cycle has often been reported in mood disorders (22–24). Disturbed sleep architecture, especially decreased percentage of stage 3
non-rapid eye movement sleep (NREM III), represents decreased homeostatic drive for sleep (6). Actually, NREM III serves as a deep and recovery sleep, playing a vital role in the operation of the glymphatic system, and clearance of metabolic wastes (25, 26).

The glymphatic system is considered as an effective waste-removal system in the brain, which facilitates the exchange between the cerebrospinal fluid (CSF) and interstitial fluid (ISF), along with the potentially neurotoxic proteins such as amyloid-β (Aβ) (27), tau protein (28), and α-synuclein (29). Therefore, glymphatic impairment caused by sleep disturbance results in protein aggregation and increased risk for neurological diseases, such as Alzheimer’s disease (AD) (30), Parkinson’s disease (PD) (31), stroke (32, 33), and idiopathic normal cranial pressure hydrocephalus (iNPH) (34, 35). The water channel protein aquaporin-4 (AQP-4) is highly expressed on astrocytic endfeet and exerts significant influence in glymphatic transport (36). At present, accumulating evidence suggests the presence of abnormal astrocytes (37–43), depolarized AQP-4 (44–46), and dysfunctional glymphatic system (47, 48) in mood disorders. Therefore, we speculated that glymphatic dysfunction serves as an imperative intermediary factor between sleep disturbance and mood disorders.

In this study, we integrated available data from both animal and human studies regarding sleep in mood disorders and highlighted the core role of the glymphatic system. Furthermore, we discussed the glymphatic system dysfunction in mood disorders and identified the potential therapeutic opportunities for mood disorders based on sleep regulation and the glymphatic pathway.

SLEEP DISTURBANCE AND MOOD DISORDERS

The Model of Sleep Regulation

The classical two-process model of sleep regulation was first proposed by Borbély, and it consists of the process controlled by the circadian oscillator (Process C) and the homeostatic drive for the sleep–wake cycle (Process S). The two processes closely interact with each other but are also relatively independent (6) (Figure 1).

Circadian rhythms (Process C) are approximately 24-h rhythms in physiology and behavior, which are primarily driven by a hierarchy of cellular pacemakers located in the SCN (7). The most common measurements of the circadian rhythm are core body temperature and endogenous melatonin, other than the chronotype or morningness-eveningness (49). In fact, circadian rhythms are generated by a molecular clock in a network of positive and negative feedback loops. At the core of SCN timekeeping, the heterodimeric transcription factors CLOCK/BMAL1 translated from CLOCK and Brain and muscle ARNT-like 1 (BMAL1) genes, activate the Period (PER1–3) and Cryptochrome (CRY1–2) genes and initiate the circadian cycle. In turn, the dimer complex protein PER/CRY inhibit the activity of the CLOCK/BMAL1 proteins (50), exerting dominant effect in the negative feedback. As a critical complementary loop, the BMAL1 transcription is activated by the retinoic acid-related orphan receptor (ROR) protein at night, and repressed by the nuclear receptors REV-ERB α/β (encoded by NR1D1/2 genes) at daytime (51), respectively. In addition, other clock genes also participate in the regulation of circadian rhythms. The neuronal PAS domain protein 2 (NPAS2) functions similarly to CLOCK, while albumin gene D-site binding protein (DBP) acts cooperatively with CLOCK/BMAL1 (52, 53). The casein kinase 1 isofrom δ/ε (CSNK1D/E) regulates levels of PER by phosphorylation-mediated degradation, and thus inhibits the activity of CLOCK/BMAL1 (54). The basic helix-loop-helix family 40/41 (BHLHE40/41), also known as DEC1/2 suppresses PER gene transcription via competing with CLOCK/BMAL1 for e-box element binding (55). The TIMELESS gene is also conceived required for circadian rhythmicity, however, the exact role in human clockwork is still unclear (56). These circadian genes expression rise and fall in rhythm, contributing to the regulation of 24-h physical and behavioral cycles (15).

Process S, also referred to as the sleep pressure gradually accumulates during wakefulness and declines during sleep (6). Especially, as deep sleep (NREM III) dominates in the early phases of sleep and dwindles with decreasing sleep pressure in the late phases. Conversely, sleep deficit such as sleep deprivation results in a longer and deeper NREM III to achieve recovery (57), implying greater sleep pressure. Therefore, NREM III sleep is considered as a representation of sleep pressure (6). Sleep electroencephalogram (EEG) and actigraphy are effective assessments of sleep pressure to detect sleep architecture.

According to the two-process model, proper alignment of Process C and S is essential for recovery sleep. Otherwise, the daytime sleep fails to fulfill the homeostatic sleep drive, manifesting as lighter and lacking of recovery sleep (NREM III) (58). Moreover, the daytime sleep decreases sleep pressure, causing a negative influence on the more effective nighttime sleep.

Sleep Disturbance in Mood Disorders

Disturbed Circadian Rhythms in Mood Disorders

Disruptions of the circadian rhythms are common in people exposed to jet-lag, social jet-lag, shift-work, as well as light
pollution (light exposure at night) (59), and may lead to mood alterations (60, 61). Recently, a large population cross-sectional study (n = 91,105) using a wrist-worn accelerometer reported that lower relative amplitude of the circadian rhythm is associated with the lifetime prevalence of both MDD and BD (4). Individuals with circadian misalignment have higher depressive scores (62, 63). Moreover, a strong correlation between depressive symptoms and advances in dim light melatonin onset (DLMO) has been reported following an adjunctive multimodal chronobiological intervention organically combining psychoeducation, behavioral manipulation, and agomelatine intake (64). Bipolar disorder patients show delayed and decreased melatonin secretion during depressive and euthymic episodes (24, 65), with impaired psychosocial functioning and worse quality of life (24). In addition, manic and mixed episodes present with sustained phase advances, as well as a lower degree of rhythmicity corresponding to the severity of manic symptoms (66, 67). Apart from the daily (solar) cycle mentioned above, the lunar tidal cycles seem to entrain the mood cycles. In patients with rapid cycling BD, the periodicities in mood cycles have been observed to be synchronous with multiples of bi-weekly lunar tidal cycles (68).

The relationship between circadian rhythms and mood disorders is further supported by emerging genomic studies. In depressive cases, genetic association analyses have found SNPs in PER2 (10870), BMAL1 (rs2290035), NPAS2 (S471L), CRY2 (rs10838524), BHLHB2 (rs6442925), CLOCK (rs12504300), CSNK1E (rs135745), and TIMELESS (rs4630333 and rs1082214) (8, 9, 13). Single nucleotide polymorphisms in CSNK1E (rs135745), TIMELESS rs4630333, CRY2 (rs10838524), PER3...
The Unbalanced Homeostatic Drive of Sleep in Mood Disorders

The sleep–wake cycle is significantly affected by mood disorders. Firstly, a disturbed sleep–wake cycle is one of the most common diagnostic criteria for mood disorders. Individuals suffering from manic or hypomanic episodes often show a reduced demand for the sleep, while depressive patients experience insomnia or hypersomnia (1). Delayed sleep–wake phase and evening chronotype is common in patients with mood disorders (24, 71, 72), and strongly associated with the severity of mood symptoms (73). Sleep deficits predict a poor prognosis with a higher risk of suicide (74). Furthermore, both polysomnography and self-reported studies have revealed longer sleep onset latency, a higher percentage of rapid eye movement (REM) sleep, more fragmentation of the sleep/wake rhythm, and daytime dysfunction in patients with mood disorders during the remission state relative to healthy controls (22, 75, 76). More importantly, sleep disturbance often serves as a prodrome of manic or depressive episodes. Several retrospective studies have revealed that sleep disturbance is the most robust early symptom of manic episodes and the sixth most common prodromal symptom of manic episodes (5, 23). Recently, a 10-year prospective study among adolescents and young adults reported that the sleep problem is a risk factor for the development of BD (77). Sleep abnormalities have also been highly related to subsequent depression (23, 78, 79). Moreover, sleep deprivation is reported to trigger manic-like behavior in animal models (80). Thus, some researchers speculate that a disturbed sleep–wake cycle is probably a causal factor triggering mood episodes. However, because of ethical reasons, sleep generally cannot be manipulated in human research and this weakens the causal evidence between the sleep–wake rhythm and mood disorders.

Chronotherapeutic Treatments in Mood Disorders

In response to the vital roles that Process C and S play in the onset and course of mood disorders, chronotherapeutic interventions have been successfully used. Sleep deprivation combined with bright light therapy has been implicated in improving depressive symptoms (72, 81–83), while virtual darkness therapy via blue-light-blocking increases the regularity of sleep and a rapid decline in manic symptoms (84). These treatments exert great influence on mood recovery by resetting the circadian clock. Also, the hormone melatonin (MT) secreted by the pineal gland acts on the circadian clock via MT1 receptors (85, 86), while the MT agonist agomelatine shows important properties for phase shifts of the clock and anti-depressive effects (21). Additionally, agomelatine functions as an antagonist for 5-HT2c receptors and modulates the master SCN clock via 5-HT innervations (87, 88). Similarly, other antidepressants can regulate the expression of the clock genes and thus affect the circadian rhythms (89). Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) can shift electrical rhythms of the SCN and thus affect the behavior rhythm (16–18). Ketamine results in a rapid increase in glutamate level in the SCN and directly acts on NMDA receptors of the circadian clock in the epi-thalamic lateral habenula (LHb) (19, 20), suggesting that the rapid anti-depressive effects of ketamine might also be through the resetting of the circadian system (90). However, the mood stabilizer lithium is considered a clock-modifying drug in that it delays the sleep–wake cycle in healthy human and increase the length of the circadian period in non-human primates (91, 92). At the molecular level, lithium treatment can not only regulate the rhythm period via increasing PER2 mRNA levels, but also significantly augment the oscillation amplitude PER2 and CRY1 protein rhythms via inhibiting the phosphorylation of glycogen synthase kinase 3β (GSK3B) (93, 94). Furthermore, the lithium efficacy is influenced by two GSK3B SNPs (rs334558 and rs3755557) (95). Considering all the above evidence, more pharmacological manipulations targeting the circadian rhythm and sleep drive are increasingly becoming plausible in the treatment of mood disorders.

Taken together, there seems to be a clear link between sleep disturbance and mood disorders, even though the underlying mechanisms remain unclear. The discovery of the glymphatic system provides researchers with insights into sleep-related diseases.

SLEEP AND THE GLYMPHATIC SYSTEM

Overview of the Glymphatic System

The lymphatic system accounts for the clearance of ISF and it is also critical to both hydrostatic and homeostatic maintenance (96). With regard to lymphatic system in central nervous system (CNS), it consists of two interacting system, the glymphatic (glia-lymphatic) system and the meningeal lymphatic vessels (97). The glymphatic system is responsible for exchanging between CSF and ISF, and clearing solutes and metabolites from the brain parenchyma through a unique system of perivascular vessels. More specifically, CSF produced by the choroid plexus and capillary influx is pumped deep into the brain parenchyma via arterial pulsation (36, 98). In the perivascular space (PVS), CSF exchanges with ISF, accompanied by clearance of soluble metabolic waste like Aβ (36). Indeed, large and eccentric PVS provides considerably less hydraulic resistance

(rs707467 and rs10462020), RORB (rs1157358, rs7022435, rs3750420, and rs3903529), REV-ERBA (rs2314339) are strongly related to BD (8, 10–12, 69). In particular, CLOCK SNP rs1801260 contribute to the recurrence of mood episodes, while CRY2 SNP rs10838524 is significantly associated to rapid cycling BD (10, 70). Moreover, the arrhythmic expression of circadian genes including BMAL1, PER1–3, REV-ERBA, DBP, and BHLHE40/41, has been observed in postmortem brain tissues of MDD patients (15). Reduced amplitude of rhythmic expression for BMAL1, REV-ERBa, and DBP has been reported in fibroblast cultures of 12 BD patients (14). Recently, Park et al. have explored gene–gene interactions of clock genes using the non-parametric model-free multifactor-dimensionality reduction (MDR) method, and revealed optimal SNP combination models for predicting mood disorders (8). Specifically, the four-locus model differs between MDD (TIMELESS rs4630333, CSNK1E rs135745, BHLHB2 rs2137947, CSNK1E rs2075984) and BD (TIMELESS rs4630333, CSNK1E rs135745, PER3 rs228669, CLOCK rs12649507), supporting the clinical observation of different circadian characteristics in two disorders.
to CSF-ISF flow compared to concentric annular tunnel (99, 100). During the clearance of solutes, convection coexists with diffusion in the glymphatic system (101–103). It is argued that in the brain interstitium, small molecule transport is best explained by diffusion while convection becomes more predominant with increasing molecular size (104). However, the exact contributions of the two processes are highly dynamic and remain controversial, with one of the reasons being that the glymphatic influx and efflux are influenced by arousal state, pulse, respiration, body position, and more (98, 103, 105, 106). Moreover, CSF–ISF and solutes drain from the CNS via meningeal and cervical lymphatic vessels, as well as the cranial and spinal nerve roots (107, 108). Therefore, interference of the lymphatic system, such as ultraviolet photoablation of meningeal lymphatic vessels and ligation of cervical lymphatics, accounts for the stagnation of glymphatic flow and aggregation of metabolic wastes like Aβ (109, 110).

More importantly, the glymphatic system is supported by the water channel AQP4 which is primarily expressed by the astrocytic endfeet (36). Animals lacking AQP4 exhibit slower CSF influx and less interstitial solute clearance (70% reduction) (36, 111, 112). Deletion of the AQP4 in APP/PS1 transgenic mice results in increased interstitial Aβ plaque accumulation, cerebral amyloid angiopathy, as well as loss of synaptic protein and brain-derived neurotrophic factor in the hippocampus and cortex (113). However, it should be noted that the role of AQP4 in glymphatic clearance function are debated (103, 106). Smith et al. have found that AQP4 gene deletion mice exhibited a similar Aβ distribution as wildtype mice, suggesting that AQP4 gene deletion did not impair clearance of Aβ (114).

Sleep-Dependent Glymphatic Cycling
Emerging evidence reveals that the function of the glymphatic system fluctuates daily along with the sleep–wake cycle. A two-photon imaging study reported a 60% increase in the interstitial space and two-fold faster clearance of Aβ in natural sleep or anesthesia mice compared with awake mice (27). A coherent pattern of slow-wave activity and CSF influx has been observed during NREM sleep in humans, supporting the exciting possibility of sleep–regulated glymphatic function (25). However, recent evidence using contrast-enhanced MRI has revealed that the glymphatic system is controlled by the circadian rhythm rather than by the sleep–wake cycle (115, 116). The parenchymal redistribution of contrast agent is lowest during the light phase and highest during the dark phase in fully awake rats, regardless of normal or reversed light–dark cycles (115). The diurnal variation of glymphatic cycling persists even under constant light or anesthesia, suggesting the hypothesis that endogenous circadian oscillations determine glymphatic function (116). The discrepancy may be related to the extreme differences in the circadian rhythm between humans and rodents (117). Rodents are nocturnal animals with opposite circadian phase, and they are also poly-phasic sleepers with relatively low sleep drive (118). Presently, the exact contributions of the light–dark cycle, sleep–wake cycle, and other physiological rhythms remain unknown (116). Further studies are warranted to confirm the circadian control of the glymphatic system in humans.

Surprisingly, the deletion of AQP4 effectively eliminates the circadian rhythm in glymphatic fluid transport (116). A recent genomic study reports that AQP4-haplootype influences sleep homeostasis in NREM sleep and response to prolonged wakefulness (119), providing supporting evidence for the sleep–dependent glymphatic pathway. The high polarization of AQP4 in astrocytic endfeet is under the control of the circadian rhythm, and thus, modulates bulk fluid movement, CSF–ISF exchange, and solutes clearance (116). Conversely, there is also evidence that astrocytes repress SCN neurons and regulate circadian timekeeping via glutamate signaling (120). Thus, astrocytes and AQP4 present a checkpoint for the functional glymphatic system during deep sleep.

Considerable evidence suggests a causal relationship between sleep and regulation of the glymphatic flow, thus modulating protein clearance. Sleep disturbance (including shorter total sleep time, sleep fragmentation, and lack of NREM III) causes suppressed glymphatic function and a decline in the clearance of metabolic waste, hence contributing to the development and progression of various neurological diseases including AD (30), PD (31), stroke (32, 33), and iNPH (34, 35).

Taken together, the glymphatic function is considered as a brain fluid transport with astrocyte-regulated mechanisms, while glymphatic dysfunction is intimately associated with neurological diseases, especially neurodegenerative diseases with cognitive decline (30, 31).

GLYMPHATIC DYSFUNCTION IN MOOD DISORDERS
Abnormalities of Glymphatic Flow, Astrocytes, and AQP4 in Depression
Individuals suffering from depressive episodes always show diverse cognitive decline (1), including attention, memory, response inhibition, decision speed, and so on. Depression has been considered as a prodrome of dementia (121), with increased Aβ deposition reported in an (18) F-florbetapir positron emission tomography (PET) imaging study (122). These observations raise the exciting possibility that wide-spread disruption of the glymphatic system exists in depression. Recent animal studies using chronic unpredictable mild stress (CUMS) model have provided supporting evidence for the glymphatic dysfunction in depression (47, 48) (Table 1). In the CUMS model, animals were exposed to the various stressors randomly for several weeks and injected with fluorescence tracers from cisterna magna to estimate the glymphatic function (47, 48). The CSF tracer penetration in the brain of CUMS-treated mice was significantly decreased, and recovered to the control level after fluoxetine administration or polyunsaturated fatty acid (PUFA) supplementation (47, 48). In parallel with the impaired glymphatic circulation, the increased deposition of Aβ has been observed (47, 48). Amyloid-β accumulation along the blood vessels, in turn, could impair glymphatic function by reducing PVS and increasing hydraulic resistance, and thus result in a more severe parenchymal build-up of Aβ and neuronal death (134). Another plausible explanation of PVS closure induced
by CUMS is the alteration of arterial pulsation and compliance that triggered by neuroinflammation and restored by daily PUFA supplementation (48) (Table 1).

During the neuroinflammatory response, reactive astrocytosis, and AQP4 depolarization have been widely reported in depression (48). Abundant evidence indicated astrocytic abnormalities in patients with depression (Table 2). Golgi-staining of postmortem tissues from depressed suicide cases has revealed reactive astrocytosis within the cingulate cortex (37). Additionally, glial fibrillary acidic protein (GFAP), one of the astrocyte-specific biomarkers, is reduced in depression-associated brain regions including the prefrontal cortex, cingulate cortex (38, 39), hippocampus (40), amygdala (41), locus coeruleus (44), cerebellum (146), thalamus, and caudate nuclei (42). A lower density of S100β-immunopositive astrocytes has been reported in the bilateral hippocampus and locus coeruleus of depressive patients compared to that of healthy controls (44, 135). Downregulated expression of AQP4 has been found in postmortem locus coeruleus and hippocampus in MDD patients (44, 136). More importantly, the reduction in astrocyte density is passed on to offsprings of depressive females via an epigenetic mechanism (123) (Table 1). Nevertheless, there are several contradictory results (Table 2). The density of astrocytes has been observed unchanged in the cingulate cortex and hippocampus of MDD patients (142, 144). A postmortem study using quantitative polymerase chain reaction (qPCR) have observed upregulated expression of GFAP and aldehyde dehydrogenase 1 family member L1 (ALDH1L1) in the basal ganglia of MDD patients (145). Another postmortem study using microarray analysis and qPCR has found upregulated expression of AQP4 in the prefrontal cortex of MDD patients. Obviously, the variety of studied methods involving Glogi-staining, Nissl-staining, qPCR, western blotting, and immunohistochemistry, contributes to the discrepancies.

However, emerging animal studies provide powerful evidence implying the pathological alterations of astrocytes and AQP4 in depression. Decreased astrocytes and downregulated AQP4 expression have been reported in various animal models of depression (47, 48, 123, 124, 130) (Table 1), supporting dysfunctional glymphatic transport in depression. Effective antidepressant therapy, such as fluoxetine (47, 124, 125), escitalopram (48), mirtazapine (126), ketamine (127, 128), and repetitive high-frequency transcranial magnetic stimulation (TMS) (129) could benefit the functioning of both astrocytes and AQP4, and hence alleviate depressive-like behaviors. Additionally, the synergistic agents of antidepressant—lithium—can attenuate the reduction of AQP4 and disruption of the neurovascular unit in the hippocampus of CUMS rats (130), resulting in a functioning glymphatic system. These therapeutic effects can be suppressed by AQP4 knockout. More specifically, AQP4 deficiency abolishes fluoxetine treatment-induced hippocampal neurogenesis and behavioral improvement in depressive mice (133). Recent studies indicate that the therapeutic option for depression is via the restoration of astrocytes function, AQP4, and glymphatic system (131, 132), which provide further supporting evidence for the critical role of glymphatic flow in depression.

Abnormalities of Astrocytes and AQP4 in Bipolar Disorders

To date, the role of the glymphatic function in BD has not been widely studied. However, astrocytic dysfunction has undoubtedly been implicated in the development of BD (43). Different from MDD, pictures from human postmortem studies in BD appear to be highly heterogeneous (Table 2). The density of GFAP-positive astrocytes is reported to be significantly increased in Brodmann area (BA) 9 (137) and reduced in BA10 (138), BA24 (38), BA11, and BA 47 (139), while the level of S100β has been reported to be increased in BA40 and reduced in BA9 (140). Other studies on human postmortem tissues from BD exhibit an unchanged density of astrocytes in the frontal cortex (141), cingulate cortex (142), amygdala (41, 143), hippocampus (144), entorhinal cortex (143), basal ganglia (145), dorsal raphe nucleus, and cerebellum (146). The considerable discrepancy is on account of various confounding factors, including phenotype (depressive episode, manic episode, or remission state) (150), cause of death (depressive suicide or physical diseases) (141, 144), comorbidity (150, 151), the methodology used (137, 144), and the brain regions studied (139, 140). Therefore, additional studies regarding diverse phenotypes of BD are essential to investigate state-related abnormalities of astrocytes (152). In patients with bipolar depression, a reduction in S100β-immunopositive astrocytes has been observe, but with no change in GFAP-immunopositive astrocytes (135, 147). As for manic states, in vivo studies have revealed increased serum levels of S100β, suggesting astrocytic activation (148).

Upregulated expression of AQP4 in the prefrontal cortex has been revealed in BD (149). Evaluation of the qualitative alterations of astrocytes (especially AQP4 function) is far much valuable than quantitative alterations. The apparent diffusion coefficient from ultra-high b-values (ADC uh), a parameter of enhanced diffusion-weighted imaging (eDWI), can reflect the function of AQP4 (45). In individuals suffering from bipolar depression, increased ADC uh values in bilateral superior cerebellar peduncles (SCP) and cerebellar hemisphere is positively associated with depressive scores, implying that a positive correlation exists between the upregulated expression of AQP4 and severity of depression (46). A plausible explanation is that increased and depolarized AQP4 impair water homeostasis and glymphatic transport in BD (149). Lithium is a classical mood-stabilizer, and its effect of regulating AQP4 function is discussed above (130). Additionally, other mood-stabilizers such as valproic acid, topiramate, and lamotrigine have been shown to inhibit AQP4 (153), and hence regulate directed glymphatic flow.

Even though direct evidence for glymphatic impairment in mood disorders is lacking, astrocytes and AQP4 abnormalities provide support to the hypothesis that glymphatic dysfunction functions as a bridge between sleep disturbance and mood disorders. Additionally, treatments for mood improvement, including medicines, light therapy, sleep invention, and TMS can
regulate the function of astrocytes and AQP4. Therefore, AQP4dependent glymphatic system may serve as a new therapeutic target in mood disorders.

**CONCLUSION AND OUTLOOK**

Mood symptoms often occur with the onset of sleep disturbance and ameliorate with improved sleep disturbance. Moreover, early-life sleep problems due to jet-lag, social jet-lag, shift-work, or light pollution can significantly increase the lifetime risk of mood disorders (60). In addition, sleep deprivation can directly trigger mania-like symptoms (80). Based on considerable evidence, a causal relationship between sleep disturbance and mood disorders is hypothesized (154). Therefore, how does disrupted sleep affect the development and phenotype of mood disorders? An intriguing possibility has emerged that glymphatic dysfunction serves as a bridge between sleep disturbance and mood disorders. Adequate sleep, especially deep sleep (NREM III), is a key factor in the functioning of the glymphatic system which accounts for the clearance of metabolic wastes. The effects of sleep on the glymphatic system are mainly dependent on the dynamic alterations of astrocytic function and AQP4 distribution (113, 119, 155). Significantly, suppressed glymphatic circulation, astrocytic abnormalities, and AQP4 depolarization are consistently

---

**TABLE 1 | Glymphatic flow, astrocytes, and AQP4 in animal studies.**

| References | Studied cohort | Method | Main findings |
|------------|----------------|--------|---------------|
| Xia et al. (47) | CUMS model mice | Injection of tracers, immunohistochemistry | Impaired glymphatic circulation and increased accumulation of Aβ42, which can be reversed by fluoxetine treatment. Downregulated AQP4 expression in cortex and hippocampus, which can be reversed by fluoxetine treatment. |
| Liu et al. (48) | CUMS model mice | Injection of tracers, immunohistochemistry | Impaired glymphatic circulation and cerebrovascular reactivity, which can be reversed by PUFA supplementation. Decreased Aβ40 clearance, which can be reversed by PUFA supplementation and escitalopram treatment. Decreased astrocytes and AQP4 expression, which can be reversed by PUFA supplementation and escitalopram treatment. |
| Gong et al. (123) | CMS model mice | Immunohistochemistry | Decreased hippocampal astrocyte is passed on to offsprings via an epigenetic mechanism. |
| Czéh et al. (124) | Chronic psychosocial stress mice | Immunohistochemistry | Fluoxetine treatment prevented the stress-induced numerical decrease of astrocytes. |
| Kinoshita et al. (129) | VNUT-knockout mice | Immunochemistry, qPCR | Fluoxetine increased ATP exocytosis and BDNF in astrocytes. |
| Hisaoka-Nakashima et al. (126) | Rat primary astrocytes, C6 astroglia cells | Western blotting, ELISA, western blotting | Mirtazapine treatment increased mRNA expression of GDNF and BDNF in astrocytes. |
| Wang et al. (127) | Mice | Western blotting | Ketamine promotes the activation of astrocyte. Ketamine induced cholesterol redistribution in the plasmalemma of astrocytes. |
| Lasić et al. (128) | Rat primary astrocytes | Structured illumination microscopy and image analysis | Ketamine induced cholesterol redistribution in the plasmalemma of astrocytes. |
| Xue et al. (129) | CUS model rats | Immunochemistry, qPCR | Repetitive TMS at 5 Hz increased the expression of DAGLα and CB1R in hippocampal astrocytes and neurons. |
| Taler et al. (130) | CUMS model rats | Immunochemistry, western blotting, ELISA | Lithium can attenuate the reduction of AQP4 and disruption of the neurovascular unit in hippocampus. |
| Wang et al. (131) | LPS-induced depression model mice | Immunochemistry, qPCR | Inhibition of activated astrocytes ameliorates LPS-induced depressive-like behavior. |
| Portal et al. (132) | Cx43 KD male mice | Immunochemistry, western blotting | Inactivation of astroglial connexin 43 potentiated the antidepressant-like effects of fluoxetine. |
| Kong et al. (133) | CMS model mice | Immunochemistry, western blotting | AQP4 knockout disrupted fluoxetine-induced enhancement of hippocampal neurogenesis, as well as behavioral improvement. |

**Aβ, amyloid-β; AQP4, aquaporin-4; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CB1R, cannabinoid type 1 receptor; CMS, chronic mild stress; CUMS, chronic unpredictable mild stress; CUS, chronic unpredictable stress; Cx43 KD, connexin 43 knock-down; DAGLα, diacylglycerol lipase alpha; ELISA, enzyme-linked immunosorbent assays; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; LPS, lipopolysaccharide; mRNA, messenger RNA; PUFA, polyunsaturated fatty acid; qPCR, quantitative polymerase chain reaction; TMS, transcranial magnetic stimulation; VNUT, vesicular nucleotide transporter.**
#### TABLE 2 | Astrocytes and AQP4 in patients with mood disorder.

| References                        | Studied cohort                  | Tested sample        | Method                                | Main findings                                                                 |
|-----------------------------------|---------------------------------|----------------------|---------------------------------------|-------------------------------------------------------------------------------|
| Torres-Platas et al. (37)         | 10 Depressed suicides, 10HC      | Postmortem tissue    | Golgi-staining                        | Reactive astrocytosis within the cingulate cortex of depressive patients.       |
| Torres-Platas et al. (42)         | 22 Depressed suicides, 22HC      | Postmortem tissue    | Immunohistochemistry, qPCR             | Downregulation of GFAP mRNA and protein in the mediodorsal thalamus and caudate nucleus of depressed suicides. |
| Webster et al. (38)               | 15MDD, 15BD, 15HC               | Postmortem tissue    | In situ hybridization                 | Decreased level of GFAP mRNA in the cingulate cortex of BD patients. Decreased level of GFAP mRNA in the cingulate cortex of MDD patients (not significantly). |
| Gittins et al. (39)               | 5MDD, 2BD, 9HC                  | Postmortem tissue    | Immunohistochemistry                  | Decreased GFAP protein in the anterior cingulate cortex of patients with mood disorders. |
| Cobb et al. (40)                  | 17MDD, 17HC                     | Postmortem tissue    | Immunohistochemistry                  | Decreased GFAP-positive astrocytes in the left hippocampus of depressive patients. |
| Alshuler et al. (41)              | 11MDD, 10BD, 14HC               | Postmortem tissue    | Immunohistochemistry                  | Decreased GFAP-positive astrocytes in the amygdala of depressive patients. Unchanged GFAP-positive astrocytes in the amygdala of BD patients. |
| Bernard et al. (44)               | 12MDD, 6BD, 9HC                 | Postmortem tissue    | In situ hybridization                 | Downregulated expression of GFAP, S100B and AQP4 in locus coeruleus of MDD patients. |
| Gos et al. (135)                  | 9MDD, 6BD, 13HC                 | Postmortem tissue    | Immunohistochemistry                  | Decreased S100β-immunopositive astrocytes in the bilateral hippocampus of depressive patients. |
| Medina et al. (136)               | 13MDD, 10HC                     | Postmortem tissue    | Microarray analysis, qPCR              | Downregulated AQP4 mRNA expression in hippocampus of MDD patients. |
| Feresten AH et al. (137)          | 34BD, 36HC                      | Postmortem tissue    | Western blotting                      | Increased GFAP expression in nBA9 of BD patients. Unchanged levels of vimentin and ALDH1L1 in nBA9 of BD patients. |
| Johnston-Wilson et al. (138)     | 19MDD, 23BD, 23HC               | Postmortem tissue    | Western blotting                      | Decreased GFAP-positive astrocytes in nBA10 of BD patients.                  |
| Toro et al. (139)                 | 15MDD, 15BD, 15HC               | Postmortem tissue    | Immunohistochemistry                  | Decreased GFAP-positive astrocytes in nBA11/47 of BD patients.               |
| Dean et al. (140)                 | 8BD, 20HC                       | Postmortem tissue    | Western blotting, qPCR                | Increased S100β in nBA40 of BD patients. Decreased S100β in nBA9 of BD patients. |
| Hercher et al. (141)              | 20BD, 20HC                      | Postmortem tissue    | Immunohistochemistry                  | Unchanged density of astrocytes in the frontal cortex of BD patients.         |
| Williams et al. (142)             | 20MDD, 16BD, 20HC               | Postmortem tissue    | Immunohistochemistry                  | Unchanged density of astrocytes in the cingulate cortex of patients with mood disorder. |
| Pantazopoulos et al. (143)        | 11BD, 15HC                      | Postmortem tissue    | Immunohistochemistry                  | Unchanged density of astrocytes in the amygdala and entorhinal cortex of BD patients. |
| Malchow et al. (144)              | 8MDD, 8BD, 10HC                 | Postmortem tissue    | Nissl-staining                        | Unchanged density of astrocytes in the hippocampus of patients with mood disorder. |
| Barley et al. (145)               | 14MDD, 14BD, 15HC               | Postmortem tissue    | qPCR                                  | Upregulated expression of GFAP and ALDH1L1 the basal ganglia of MDD patients. Upregulated expression of GFAP and ALDH1L1 the basal ganglia of BD patients (not significantly). |
| Fatemi et al. (146)               | 15MDD, 15BD, 15HC               | Postmortem tissue    | Western blotting                      | Decreased GFAP in the cerebellum of patients with mood disorders.            |
| Steiner et al. (147)              | 9MDD, 5BD, 10HC                 | Postmortem tissue    | Immunohistochemistry                  | No change in GFPA-immunopositive astrocytes of patients with mood disorder.   |
| da Rosa et al. (148)              | 52 manic BD, 52HC               | Serum                | meta-analysis                         | Increased S100β levels in serum of patients with manic episodes.             |
| Zhao et al. (46)                  | 50BD II, 43HC                   | eDWI                 | ADCuh                                | Increased ADCuh values in bilateral SCP and cerebellar hemisphere, which positively associated with depressive scores. |
| Iwamoto et al. (149)              | 11MDD, 11BD, 15HC               | Postmortem tissue    | Microarray analysis, qPCR              | Upregulated expression of AQP4 in the prefrontal cortex of patients with mood disorders. |

AQP4, aquaporin-4; ADCuh, apparent diffusion coefficient from ultra-high b-values; ALDH1L1, aldehyde dehydrogenase 1L1; BA, Brodmann area; BD, bipolar disorder; eDWI, enhanced diffusion-weighted imaging; GFAP, glial fibrillary acidic protein; HC, health control; mRNA, messenger RNA; qPCR, quantitative polymerase chain reaction; SCP, superior cerebellar peduncles.
reported in mood disorders, providing support for the posited hypothesis.

However, several limitations exist in this study. First, much of the existing evidence on the glymphatic system has been conducted in rodents and only a few in humans. Although sleep is an evolutionarily conserved physiological behavior, the reversed circadian rhythms and polyphasic sleep which reduces sleep pressure in rodents make it less representative. Most of the current human studies use invasive methods such as intrathecal injection of contrast agents, while the ADCv value obtained from the emerging eDWI fails to identify the distribution of AQP4. Therefore, non-invasive methods to explore the glymphatic system in humans are necessary for future studies. Secondly, there is a lack of evidence of known metabolic wastes that fail to be cleared by the glymphatic system and trigger or exacerbate mood symptoms, such as Aβ in AD and α-synuclein in PD. Exploring the excessive metabolic wastes in mood disorders is warranted, and can provide promising biomarkers for indicating the occurrence and severity of mood disorders.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TY, YQ, and LY defined the research questions and aims of the study. TY and YQ carried out the literature search, selected and interpreted relevant articles, and wrote the first draft of the manuscript. XY made the original figure and tables. LY and XY critically appraised the texts, figure and tables, corrected them, and made suggestions for further improvement. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by National Natural Science Foundation of China (81901319 and 81901706).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM). 5th edition. Washington, DC: American Psychiatric Publishing (2013).

2. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet (London, England). (2016) 387:1561–72. doi: 10.1016/S0140-6736(15)00241-X

3. O’Leary OF, Dinan TG, Cryan JF. Faster, better, stronger: towards new antidepressant therapeutic strategies. Eur J Pharmacol. (2015) 753:32–50. doi: 10.1016/j.ejphar.2014.07.046

4. Lyall LM, Wyse CA, Graham N, Ferguson A, Lyall DM, Cullen B, et al. Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91,015 participants from the UK Biobank. Lancet Psychiatry. (2018) 5:507–14. doi: 10.1016/S2215-0366(18)30139-1

5. Jackson A, Cavanagh J, Scott J. A systematic review of manic and depressive prodromes. J Affect Disord. (2003) 74:209–14. doi: 10.1016/S0165-0327(02)00266-5

6. Borbély AA, Montaruli E, Amador X, Amin A, Al-Sairafi H, Al-Saadi S, et al. Reverse circadian rhythms and polyphasic sleep which reduces sleep pressure in rodents make it less representative. J Sleep Res. (2016) 25:131–9. doi: 10.1111/jsr.12371

7. Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, Ueda M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. Science. (2000) 288:682–5. doi: 10.1126/science.288.5466.688

8. Park P, Kim SA, Yee J, Shin J, Lee KY, Joo EJ. Significant role of gene-gene interactions of clock genes in mood disorder. J Affect Disord. (2019) 257:510–7. doi: 10.1016/j.jad.2019.06.056

9. Lavebratt C, Sjöholm LK, Soronen P, Paunio T, Tawter MP, Bunney WE, et al. CRY2 is associated with depression. PLoS ONE. (2010) 5:e9407. doi: 10.1371/journal.pone.0009407

10. Sjöholm LK, Backlund L, Cheteh EH, Ek IR, Friisen L, Schalling M, et al. CRY2 is associated with rapid cycling in bipolar disorder patients. PLoS ONE. (2010) 5:e12632. doi: 10.1371/journal.pone.0012632

11. Brasil Rocha PM, Campos SB, Neves FS, da Silva Filho HC. Genetic association of the PERIOD3 (Per3) clock gene with bipolar disorder. Psychiatry Investig. (2017) 14:674–80. doi: 10.43036/pi.2017.14.5.674

12. McGrath CL, Glatt SJ, Sklar P, Le-Niculescu H, Kuczenski R, Doyle AE, et al. Evidence for genetic association of RORB with bipolar disorder. BMC Psychiatry. (2009) 9:70. doi: 10.1186/1471-244X-9-70

13. Partonen T, Treutlein J, Alpman A, Frank J, Johansson C, Depner M, et al. Three circadian clock genes Per2, Arntl, and Npas2 contribute to winter depression. Ann Med. (2007) 39:229–38. doi: 10.1080/07853907012787975

14. Yang S, Van Dongen HP, Wang K, Berrettini W, Bučan M. Assessment of circadian function in fibroblasts of patients with bipolar disorder. Mol Psychiatry. (2009) 14:143–55. doi: 10.1038/mp.2008.10

15. Li JZ, Bunney BG, Meng E, Hagenauer MH, Walsh DM, Vawter MP, et al. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proc Natl Acad Sci USA. (2013) 110:9950–5. doi: 10.1073/pnas.1305811110

16. Horikawa K, Yokota S, Fuji K, Akiyama M, Moriya T, Okamura H, et al. Nonphotic entrainment by 5-HT1A/7 receptor agonists accompanied by reduced Per1 and Per2 mRNA levels in the suprachiasmatic nuclei. J Neurosci. (2000) 20:5867–73. doi: 10.1523/JNEUROSCI.20-15-05867.2000

17. Horikawa K, Shibata S. Phase-resetting response to (+)-OH- DPAT, a serotonin 1A/7 receptor agonist, in the mouse in vivo. Neurosci Lett. (2004) 368:130–4. doi: 10.1016/j.neulet.2004.06.072

18. Shibata S, Tsuneyoshi A, Hamada T, Tominaga K, Watanabe S. Phase-resetting effect of 8-OH-DPAT, a serotonin1A receptor agonist, on the circadian rhythm of firing rate in the rat suprachiasmatic nuclei in vitro. Brain Res. (1992) 582:353–6. doi: 10.1016/0006-8993(92)90156-4

19. Orozco-Solis R, Montellier E, Aguilar-Argul L, Sato S, Vawter MP, Bunney BG, et al. A circadian genomic signature common to ketamine and sleep deprivation in the anterior cingulate cortex. Biol Psychiatry. (2017) 82:351–60. doi: 10.1016/j.biopsych.2017.02.1176

20. Cui Y, Hu S, Hu H. Lateral habenular burst firing as a target of the rapid antidepressant effects of ketamine. Trends Neurosci. (2019) 42:179–91. doi: 10.1016/j.tins.2018.12.002

21. de Bodinat C, Guardiola-Lemaitre B, Mocaer E, Renard P, Muñoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat Rev Drug Discov. (2010) 9:628–42. doi: 10.1038/nrd3140

22. Jones SH, Hare DJ, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. Bipolar Disord. (2005) 7:176–86. doi: 10.1111/j.1399-5618.2005.00187.x

23. Jaussent I, Bouyer J, Ancelin ML, Akbaraly T, Péris K, Ritchie K, et al. Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. Sleep. (2011) 34:1103–10. doi: 10.5656/SLEEP.1170

24. Bradley AJ, Webb-Mitchell R, Hatz A, Slater N, Middleton B, Gallagher P, et al. Sleep and circadian rhythm disturbance in bipolar disorder. Psychol Med. (2017) 47:1678–89. doi: 10.1017/S0033291717000186
Yan et al. Glymphatic Dysfunction in Mood Disorders

63. Murray JM, Sletten TL, Magee M, Gordon C, Lovato N, Bartlett DJ, et al. Prevalence of circadian misalignment and its association with depressive symptoms in delayed sleep phase disorder. Sleep. (2017) 40:zsw002. doi: 10.1093/sleep/zsw002

64. Robillard R, Carpenter JS, Fields KS, Hermes DF, White D, Naismith SL, et al. Parallel changes in mood and melatonin rhythm following an adjunctive multimodal chronobiological intervention with geomagnetite in people with depression: a proof of concept open label study. Front Psychiatry. (2018) 9:624. doi: 10.3389/fpsyg.2018.00624

65. Robillard R, Naismith SL, Rogers NL, Scott EM, Ip TK, Hermes DF, et al. Sleepwake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. Eur Psychiatry. (2013) 28:412–6. doi: 10.1016/j.eurpsy.2013.04.001

66. Salvatore P, Ghidini S, Zita G, De Panfilis C, Lambertini S, Maggini C, et al. Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. Bipolar Disord. (2008) 10:256–65. doi: 10.1111/j.1399-5618.2007.00565.x

67. Gonzalez R, Tamminga CA, Tohen M, Suppes T. The relationship between affective state and the rhythmicity of activity in bipolar disorder. J Clin Psychiatry. (2014) 75:e317–22. doi: 10.4088/JCP.13m08506

68. Wehr TA. Bipolar mood cycles and lunar tidal cycles. Mol Psychiatry. (2018) 23:923–6. doi: 10.1038/mp.2016.263

69. Kripke DF, Nievergelt CM, Joo E, Shekhtman T, Kelsoe JR. Circadian polymorphisms associated with affective disorders. J Circadian Rhythms. (2009) 7:2. doi: 10.1186/1744-8069-7-2

70. Lee KY, Song JY, Kim SH, Kim SC, Joo EJ, Ahn YM, et al. Association between CLOCK 3111T/C and preferred circadian phase in Korean patients with bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. (2010) 34:1196–201. doi: 10.1016/j.pnpbp.2010.06.010

71. Drennan MD, Klauzer MR, Kripke DF, Goyette LM. The effects of depression and age on the Horne-Ostberg morningness-eveningness score. J Affect Disord. (1991) 23:93–8. doi: 10.1016/0165-0378(91)90096-B

72. Maruani J, Geoffroy PA. Bright light as a personalized precision treatment of mood disorders. Front Psychiatry. (2019) 10:85. doi: 10.3389/fpsyt.2019.00085

73. Park H, Lee HK, Lee K. Chronotype and suicide: the mediating effect of depressive symptoms. Psychiatry Res. (2018) 269:316–20. doi: 10.1016/j.psychres.2018.08.046

74. Stange JP, Kleinman EM, Sylvia LG, Magalhães PV, Berk M, Nierenberg AA, et al. Specific mood symptoms confer risk for subsequent suicidal ideation in bipolar disorder with and without suicide attempt history: multi-wave data from step-BD. Depress Anxiety. (2016) 33:464–72. doi: 10.1002/da.22464

75. Cretu JB, Culver JL, Goffin KC, Shah S, Ketter TA. Sleep, residual mood symptoms, and time to relapse in recovered patients with bipolar disorder. J Affect Disord. (2016) 190:162–6. doi: 10.1016/j.jad.2015.09.076

76. Wichniak A, Skrede S, Fasmer OB, Hamre B, Grønli J, Lund A. Blocking blue light during mania - markedly increased regularity of sleep and rapid improvement of symptoms: a case report. Bipolar Disord. (2014) 16:894–8. doi: 10.1111/bdi.12265

77. Cretu JB, Culver JL, Delagrange P, Piggins HD. Electrophysiological effects of melatonin on mouse Per1 and non-Per1 suprachiasmatic nuclei neurons in vitro. J Neuroendocrinol. (2010) 22:1148–56. doi: 10.1111/j.1365-2826.2010.02063.x

78. Antle MC, Ogilvie MD, Pickard GE, Milstberger RE. Response of the mouse circadian system to serotonin 1A/27 agonists in vivo: surprisingly little. J Biol Rhythms. (2003) 18:145–58. doi: 10.1172/JBR.2003.304321805

79. Dudley TE, DiNardo LA, Glass JD. Endogenous regulation of serotonin release in the hamster suprachiasmatic nucleus. J Neurosci. (1998) 18:5045–52. doi: 10.1523/JNEUROSCI.18-13-05045.1998

80. Spencer J, Falcon E, Kumar J, Krishnan V, Mukherjee S, Birnbaum SG, et al. Circadian genes Period 1 and Period 2 in the nucleus accumbens regulate anxiety-related behavior. Eur J Neurosci. (2013) 37:242–50. doi: 10.1111/jen.12010

81. Duncan WC Jr., Slonena E, Hejazi NS, Brutsche N, Yu KC, Park L, et al. Motor-activity markers of circadian timekeeping are related to ketamine's rapid antidepressant properties. Biol Psychiatry. (2017) 82:361–9. doi: 10.1016/j.biopsych.2017.03.011

82. Kripke DF, Judd LL, Hubbard B, Janowsky DS, Huey LY. The effect of lithium carbonate on the circadian rhythm of sleep in normal human subjects. Biol Psychiatry. (1979) 14:545–8

83. Welsh DK, Moore-Edé MC. Lithium lengthens circadian period in a diurnal primate, Saimiri sciureus. Biol Psychiatry. (1990) 28:117–26. doi: 10.1016/0006-3223(90)90629-G

84. Li J, Lu WQ, Beeley S, Loudon AS, Meng QJ. Lithium impacts on the amplitude and period of the molecular circadian clockwork. PLoS ONE. (2012) 7:e33292. doi: 10.1371/journal.pone.0033292

85. Schnell A, Sandrelli F, Ranc V, Ripperger JA, Brai E, Alberi L, et al. Mice lacking circadian clock components display different mood-related behaviors and do not respond uniformly to chronic lithium treatment. Chronobiol Int. (2015) 32:1075–83. doi: 10.1080/07420528.2015.1062024

86. Iwahashi K, Nishizawa D, Narita S, Numajiri M, Murayama O, Yoshihara A, et al. Haplotypic analysis of GSK-3β gene polymorphisms in bipolar disorder lithium responders and nonresponders. Clin Pharmacol. (2014) 37:108–10. doi: 10.1097/WNP.0000000000000039

87. Aukland K, Reed RK. Intestinal-lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev. (1993) 73:1–78. doi: 10.1152/physrev.1993.73.1.1

88. Louveau A, Plog BA, Antila S, Alitalo K, Nedergaard M, Kipnis JM. Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. J Clin Invest. (2017) 127:3210–. doi: 10.1172/JCI90603

89. Mestre H, Tifhøf J, Du T, Song W, Peng W, Sweeney AM, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nat Commun. (2018) 9:4788. doi: 10.1038/s41467-018-07318-3

90. Roy J, Sarmimarontan M. Pulsatile flow drivers in brain parenchyma and perivascular spaces: a resistance network model. Fluids Barriers CNS. (2015) 12:205. doi: 10.1186/s12987-015-0105-6

91. Tifhøf J, Kelley DH, Mestre H, Nedergranad M, Thomas JH. Hydraulic resistance of perivascular spaces in the brain. Fluids Barriers CNS. (2019) 16:19. doi: 10.1186/s12987-019-0140-y

92. Koundal S, Elkin R, Nadeem S, Xue Y, Constantinou S, Sanggaard S, et al. Optimal mass transport with Lagrangian workflow reveals advective and
diffusion driven solute transport in the sympathetic system. Sci Rep. (2020) 10:1990, doi: 10.1038/s41598-020-59045-9

102. Thomas JH. Fluid dynamics of cerebrospinal fluid flow in perivascular spaces. J R Soc Interface. (2019) 16:20190572. doi: 10.1098/rsif.2019.0572

103. Mestre H, Mori Y, Nedergaard M. The brain’s sympathetic system: current controversies. Trends Neurosci. (2020) 43:458-66. doi: 10.1016/j.tins.2020.04.003

104. Ray L, Iliff JJ, Heys JJ. Analysis of convective and diffusive transport in the brain interstitium. Fluids Barriers CNS. (2019) 166. doi: 10.1186/s12874-019-0126-9

105. Kiviniemi V, Wang X, Korhonen V, Keinänen T, Tuovinen T, Autio J, et al. Ultra-fast magnetic resonance encephalography of physiological brain activity - glymphatic pulsation mechanisms? J Cereb Blood Flow Metab. (2016) 36:1033–45. doi: 10.1038/jcbfm.2016.22047

106. Christensen J, Yamakawa GR, Shultz SR, Mychasiuk R. Is the sympathetic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties. Prog Neurobiol. (2021) 198:101917, doi: 10.1016/j.pneurobio.2020.101917

107. Ma Q, Ries M, Decker Y, Müller A, Riner C, Bücke A, et al. Rapid lymphatic efflux limits cerebrospinal fluid flow to the brain. Acta Neuropathol. (2019) 137:151–65. doi: 10.1007/s00401-018-1916-x

108. Ahn HJ, Cho H, Kim JH, Kim SH, Ham JS, Park I, et al. Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid. Nature. (2019) 572:62–6. doi: 10.1038/s41586-019-1415-9

109. Wang L, Zhang Y, Zhao Y, Marshall C, Wu T, Xiao M. Deep cervical lymphnode ligation aggravates AD-like pathology of APP/PS1 mice. Brain Pathol. (2019) 29:176–92. doi: 10.1111/bpa.12656

110. Da Mesquita S, Louveau A, Vaccari A, Cornellis RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer’s disease. Nature. (2018) 560:185–91. doi: 10.1038/s41586-018-0368-8

111. Mestre H, Hablitz LM, Xavier AI, Feng W, Zou W, Pu T, et al. Aquaporin-4-dependent glymphatic solute transport in the rodent brain. Elife. (2017) 6:e04070. doi: 10.7554/eLife.04070

112. Tarasso-CONWAY JM, Carare RO, Osorio RS, Głowidz L, Butler T, et al. Clearance systems in the brain-implications for Alzheimer disease. Nat Rev Neurol. (2015) 11:457–70. doi: 10.1038/nrneurol.2015.119

113. Xu Z, Xiao N, Chen Y, Huang H, Marshall C, Gao J, et al. Deletion of aquaporin-4 in APP/PS1 mice exacerbates brain Aβ accumulation and memory deficits. Mol Neurodegener. (2015) 10:58. doi: 10.1186/s13204-015-0056-1

114. Smith AJ, Yao X, Dix JA, Jin BJ, Verkman AS. Test of the...
138. Johnston-Wilson NL, Sims CD, Hofmann JP, Anderson L, Shore AD, Torrey EF, et al. Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder. The Stanley Neuropathology Consortium. Mol Psychiatry. (2000) 5:142–9. doi: 10.1038/sj.mp.4000696

139. Toro CT, Hallak JE, Dunham JS, Deakin JF. Gial fibrillary acidic protein and glutamine synthetase in subregions of prefrontal cortex in schizophrenia and mood disorder. Neurosci Lett. (2006) 404:276–81. doi: 10.1016/j.neulet.2006.05.067

140. Dean B, Gray L, Scarr E. Regionally specific changes in levels of cortical S100beta in bipolar 1 disorder but not schizophrenia. Aust N Z J Psychiatry. (2006) 40:217–24. doi: 10.1111/j.1440-1614.2006.01777.x

141. Hercher C, Chopra V, Beasley CL. Evidence for morphological alterations in prefrontal white matter glia in schizophrenia and bipolar disorder. J Psychiatry Neurosci. (2014) 39:376–85. doi: 10.1503/jpn.130277

142. Williams MR, Hampton T, Pearce RKB, Hirsch SR, Ansorge O, Thom M, et al. Astrocyte decrease in the subgenual cingulate and callosal genu in schizophrenia. Eur Arch Psychiatry Clin Neurosci. (2013) 263:41–52. doi: 10.1007/s00406-012-0328-5

143. Pantazopoulos H, Woo T-UW, Lim MP, Berretta S. Extracellular matrix-glial abnormalities in the amygdala and entorhinal cortex of subjects diagnosed with schizophrenia. Arch Gen Psychiatry. (2010) 67:155–66. doi: 10.1001/archgenpsychiatry.2009.196

144. Malchow B, Strocka S, Frank F, Bernstein H-G, Schneider-Axmann T, et al. Stereological investigation of the posterior hippocampus in affective disorders. J Neural Transm (Vienna). (2015) 122:1019–33. doi: 10.1007/s00702-014-1316-x

145. Barley K, Dracheva S, Byrne W. Subcortical oligodendrocyte- and astrocyte-associated gene expression in subjects with schizophrenia, major depression and bipolar disorder. Schizophr Res. (2009) 112:54–64. doi: 10.1016/j.schres.2009.04.019

146. Fatemi SH, Laurence JA, Araghi-Niknam M, Stary JM, Schulz SC, Lee S, et al. Gial fibrillary acidic protein is reduced in cerebellum of subjects with major depression, but not schizophrenia. Schizophr Res. (2004) 69:317–23. doi: 10.1016/j.schres.2003.08.014

147. Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res. (2008) 42:151–7. doi: 10.1016/j.jpsychires.2006.10.013

148. da Rosa MI, Simon C, Grande AJ, Barichello T, Oses JP, Quevedo J. Serum S100B in manic bipolar disorder patients: systematic review and meta-analysis. J Affect Disord. (2016) 206:210–5. doi: 10.1016/j.jad.2016.07.030

149. Iwamoto K, Kakuuchi C, Bundo M, Ikeda K, Kato T. Molecular characterization of bipolar disorder by comparing gene expression profiles of postmortem brains of major mental disorders. Mol Psychiatry. (2004) 9:406–6. doi: 10.1038/sj.mp.4001437

150. Woo T-UW, Walsh JP, Benes FM. Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. Arch Gen Psychiatry. (2004) 61:649–57. doi: 10.1001/archpsyc.61.7.649

151. Seredenina T, Sorce S, Herrmann FR, Ma Mulone XJ, Plastre O, Aguzzi A, et al. Decreased NOX2 expression in the brain of patients with bipolar disorder: association with valproic acid prescription and substance abuse. Transl Psychiatry. (2017) 7:e1206. doi: 10.1038/tp.2017.175

152. Harrison PJ, Geddes JR, Tunbridge EM. The emerging neurobiology of bipolar disorder. Trends Neurosci. (2018) 41:18–30. doi: 10.1016/j.tins.2017.10.006

153. Huber VJ, Tujjita M, Kwee IL, Nakada T. Inhibition of aquaporin 4 by antiepileptic drugs. Bioorg Med Chem. (2009) 17:418–24. doi: 10.1016/j.bmc.2007.12.038

154. Morton E, Murray G. An update on sleep in bipolar disorders: presentation, comorbidities, temporal relationships and treatment. Curr Opin Psychol. (2020) 34:1–6. doi: 10.1016/j.copsyc.2019.08.022

155. Zeppenfeld DM, Simon M, Haswell JD, D’Abreo D, Murchison C, Quinn J, et al. Association of perivascular localization of aquaporin-4 with cognition and alzheimer disease in aging brains. JAMA Neurol. (2017) 74:91–9. doi: 10.1001/jamaneurol.2016.4370

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Yan, Qiu, Yu and Yang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.