Neuroscience and Biobehavioral Reviews 137 (2022) 104651

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Control of complex behavior by astrocytes and microglia

PI Ortinski [a,*,1], KJ Reissner [b,1], J. Turner [c,1], T.A. Anderson [a], A. Scimemi [d,1]

[a] Department of Neuroscience, University of Kentucky, USA
[b] Department of Psychology and Neuroscience, University of North Carolina Chapel Hill, USA
[c] Department of Pharmaceutical Sciences, University of Kentucky, USA
[d] Department of Biology, State University of New York at Albany, USA

A B S T R A C T

Evidence that glial cells influence behavior has been gaining a steady foothold in scientific literature. Out of the five main subtypes of glial cells in the brain, astrocytes and microglia have received an outsized share of attention with regard to shaping a wide spectrum of behavioral phenomena and there is growing appreciation that the signals intrinsic to these cells as well as their interactions with surrounding neurons reflect behavioral history in a brain region-specific manner. Considerable regional diversity of glial cell phenotypes is beginning to be recognized and may contribute to behavioral outcomes arising from circuit-specific computations within and across discrete brain nuclei. Here, we summarize current knowledge on the impact of astrocyte and microglia activity on behavioral outcomes, with a specific focus on brain areas relevant to higher cognitive control, reward-seeking, and circadian regulation.

1. Glial cells: a brief context on cell diversity and behavioral relevance

The term ‘glia’ refers to a heterogeneous population of cell types. These include: oligodendrocytes, that form axon-insulating myelin sheaths, oligodendrocyte progenitors (also called NG2-cells or polydendrocytes), ventricle-lining ependymal glia, astrocytes, and microglial cells (Kandel, 2013). Glia is a contraction of the word ‘neuroglia’ (Nervenkitt) or ‘nerve-glue’, first coined by Rudolf Virchow in 1856, who referred to these cells collectively as the substance “which lies between the proper nervous parts…and gives the whole its form in a greater or less degree”(Virchow, 1856; Parpura and Verkhratsky, 2012). A few years after this statement, the close relationship between glial cells and blood vessels was acknowledged by anatomists, but it was not until 1891 that the term ‘astrocyte’ emerged as a distinct cell type mediating this relationship. It took another 30 years before ‘oligodendrocytes’ and ‘microglia’ were recognized as additional glial cell subtypes (Verkhratsky et al., 2011). Within the broad scientific opinion, the brain glial cells have remained relegated to inert, neuron-supporting roles until about the 1990′s when research into active contributions of glial cells to neuronal activity started to gain ground.

According to recent historical perspectives, oligodendrocytes constitute 45–75% of all glial cells in the human brain, followed by astrocytes (19–40%) and microglial cells (5–10%)(von Bartheld et al., 2016; Pelvig et al., 2008). The frequently cited neuron-to-glia ratios of 1:10 appears to be a mistaken notion that is curiously perpetuated by many textbooks. In the 1960–1980′s, estimates of the number of neurons and glial cells in the human brain indicated that there are 70–85 billion neurons and 40–130 billion glial cells (Blinkov and Glezer, 1968; Haug, 1986), suggesting something close to a 1:1 ratio between neurons and glial cell numbers (von Bartheld et al., 2016). Some studies in the vestibular nuclei of the brainstem did find there were ten times more glial cells than neurons, but these estimates were not backed up by experimental evidence of brain-wide counts (von Bartheld et al., 2016; Brachet and Mirsky, 1959; Hyden and Pigon, 1960; Hyden, 1967; von Bartheld, 2018). Modern techniques, such as isotropic fractionation, flow fractionation and stereological optical fractionation, confirm the estimate of ~1:0.7 ratio between neurons and glial cells that is surprisingly close to the one obtained a long time ago using histological/-stereological approaches (Haug, 1986; Azevedo et al., 2009; Herculano-Houzel and Lent, 2005; Miller et al., 2014). Overall, the emerging picture is that the glial cell density is relatively uniform across species and brain regions, and that the glia-to-neuron ratio is simply higher whenever the size of neurons and their processes, which do vary substantially, is higher and neuronal density is correspondingly lower (Hawkins and Olszewski, 1957; Herculano-Houzel, 2014; Keller et al., 2018).

In the evolutionary context, number of cells and, perhaps more importantly, number of cell types, have been proposed to vary linearly with organismal complexity. Indeed, astrocytes in the human brain are substantially more varied than rodent astrocytes (Oberheim et al., 2006; Oberheim et al., 2009) and some have used this evidence to bolster the

* Corresponding author.
[1] These authors contributed equally

https://doi.org/10.1016/j.neubiorev.2022.104651
Received 14 October 2021; Received in revised form 28 January 2022; Accepted 21 March 2022
Available online 1 April 2022

argument for glial cell role in cognitive processes (Verkhratsky et al., 2011). The anatomical and functional heterogeneity of glia is now beyond doubt and mounting evidence suggests substantial transcriptome diversity (Chai et al., 2017; Morel et al., 2017; Boisvert et al., 2018). The multiple mechanisms by which glial cells may interact with neurons remain a subject of investigation, and it is not currently known whether unique mechanisms map onto specific computations performed by neuronal circuits mediating discrete behaviors. The impact of oligodendrocytes, oligodendrocyte progenitors, and ependymal glia on complex behavior has so far attracted a relatively small share of investigative attention. In the meantime, the role of astrocytes in behavior has been actively pursued and backed by substantial mechanistic insight (Lalo et al., 2021; Semyanov and Verkhratsky, 2021). Microglia contributions to behavior have also been widely recognized as part of a complex interface between neuronal activity and immune system status (Ferro et al., 2021). Given such skewed accumulation of evidence in support of behavioral impact, this review focuses on astrocytes and microglia only. Specifically, here we examine contributions of astrocytes and microglia signals to behaviors thought to arise from activity within three relatively well-established circuits: frontocortical circuits underlying executive function, mesocorticolimbic circuits mediating reward-seeking behaviors, and suprachiasmatic nucleus (SCN) circuits driving circadian homeostasis (Fig. 1).

2. Regulation of activity in frontocortical circuits underlying executive function

Many studies support glial cell contributions to neuropathology of cognitive decline, brain trauma, and neurodegeneration as well as regulation of cognitive function in the healthy brain. In this section, we review the literature that examines astrocytes and microglia in the context of their impact on executive control of behavior by the frontocortical circuits, including cortico-striatal, cortico-hippocampal, and cortico-amygdalar connections (Table 1). We begin with astrocytes and highlight converging evidence that regulation of frontocortical function by these cells involves glutamate recycling, release of transmitter molecules, secretion of inflammatory mediators and other signaling factors in addition to cytoskeletal adaptations that likely impose spatial constraints on neuroglial interactions. We recognize that these aspects of astrocyte activity do not represent an exhaustive list of mechanisms by which astrocytes modulate neuronal transmission and that other functions attributed to astrocytes (e.g., water balance, K^+ buffering, glucose metabolism, etc.) are likely to impact frontocortical-dependent behaviors. Astrocytes represent a regionally heterogeneous population of cells (Chai et al., 2017; Morel et al., 2017; Boisvert et al., 2018; Xin et al., 2019) and it is not yet clear whether any combination of factors (e.g., gene expression, cell morphology, excitability profiles, etc.) can be used to define conserved astrocyte categories regardless of their regional

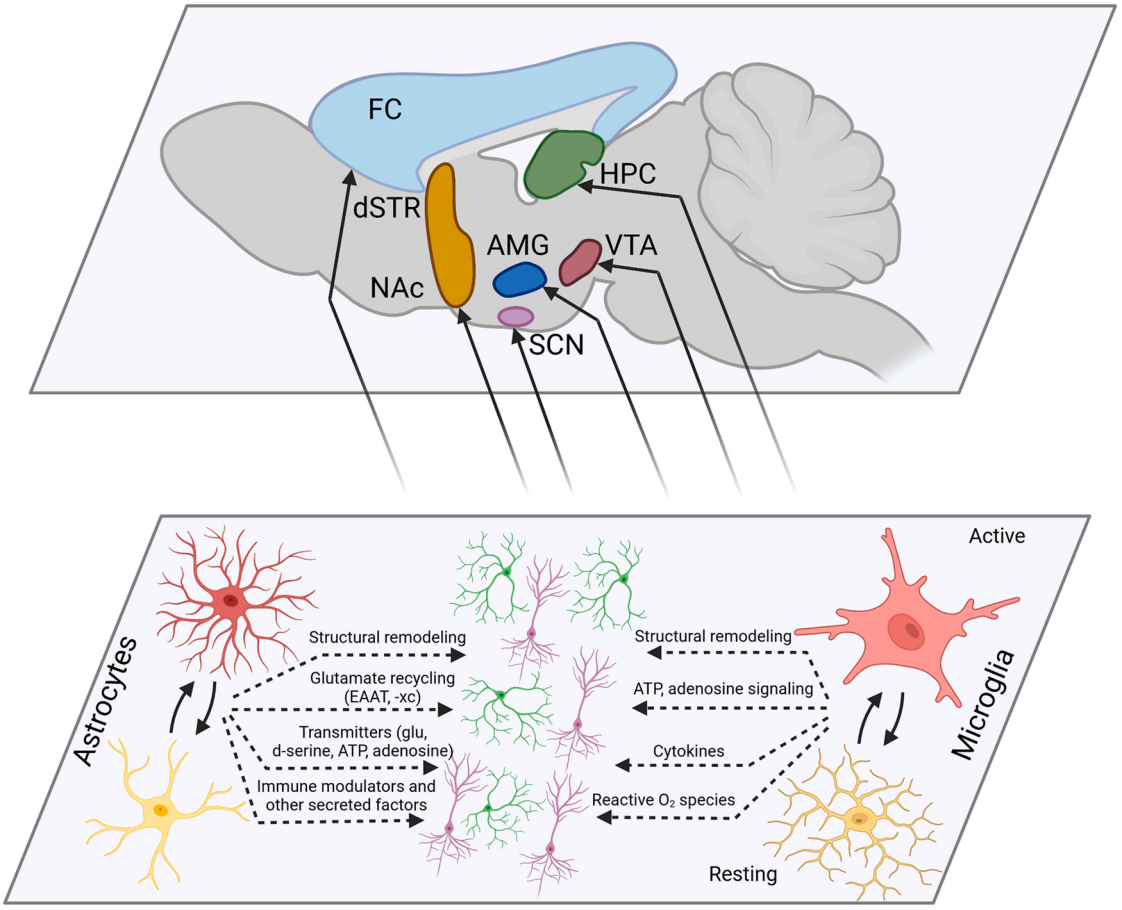

Fig. 1. An outline of the discussed mechanisms underlying glial interactions with neuronal circuitry. *Bottom panel,* astrocytes (left) and microglia (right) display cytoskeletal changes in response to their microenvironment. These changes are linked to molecular signals underlying structural remodeling and a variety of associated functional changes. Note that binary representation of astrocyte and microglia morphologies is overly simplistic and intermediate phenotypes may be possible as discussed in the text for resting and active microglia. Structural and functional adaptations (dashed arrows) influence glial interactions with neuronal networks and impact diverse neuron types (schematized in the middle). Central origin of the dashed arrows indicates that transition between morphologies is not a pre-requisite for functional changes. *Top panel,* discrete brain regionsat the focus of this review, express distinct behaviorally relevant response patterns arising from unique combinations of underlying adaptations. FC, frontal cortex; HPC, hippocampus; dSTR, dorsal striatum (including dorsomedial and dorsolateral striatum), NAc, nucleus accumbens (ventral striatum); AMG, amygdala; VTA, ventral tegmental area; SCN, suprachiasmatic nucleus.

Table 1
The table focuses on those studies where cell-specific manipulations occurred prior to the observed behavioral effects. Studies in which cellular changes were measured after a behavioral manipulation are excluded with a few exceptions. For constitutive gene knock-out models, brain area specificity column indicates brain areas in which cellular changes were measured. Bi-directional effect column lists evidence, if any, that measured behaviors could be either suppressed or enhanced with opposite cellular manipulations.

	Experimental manipulation[REF#]	Brain area specificity	Behavioral impact	Cellular mechanism	Bi-directional effect
Astrocytes					
Cognitive flexibility	L-AAA injection (astrocyte toxicity)(Brockett et al., 2018;Lima et al., 2014)	mPFC	(Brockett et al., 2018)↓cognitive flexibility(set-shifting) Lima et al. (2014)↓texture discrimination ↓reversal learning and working memory	(Brockett et al., 2018)↓ gamma oscillations Lima et al. (2014)Not investigated	Not investigated
	hM3 DREADD activation (Brockett et al., 2018)	mPFC	↑cognitive flexibility (set shifting)	↑Gq signaling in astrocytes	Not investigated
	S100b infusion (Brockett et al., 2018)	mPFC	↑cognitive flexibility (set shifting)	Not investigated	Not investigated
	GFAP & vimentin knockout mice (Wilhelmsson et al., 2019)	Whole brain	↑memory extinction	Not investigated	Not investigated
	Nestin knockout mice (Wilhelmsson et al., 2020)	Whole brain	↑memory extinction	Not investigated	Not investigated
	EAAT1 knockout mice (Karlsson et al., 2009)	Whole brain	↓ visual discrimination learning	↓ astrocyte glutamate reuptake	Not investigated
	Blockade of EAAT2 by dihydrokainate (John et al., 2012)	mPFC	↑ drinking latency & ↓ responding to PFC electrical self-stimulation	↓ astrocyte glutamate reuptake	Not investigated
	IP injections of sub-chronic ketamine (Featherstone et al., 2012)	Hippocampus	↓ extinction of sucrose self-administration	↓ EAAT2 expression	Not investigated
	dnSNARE knockout mice (Sardinha et al., 2017)	PFC, hippocampus	↓ working and spatial memory	↓ theta-cycle synchronization between hippocampus and PFC	Theta coherence and cognitive deficits rescued by D-serine supplementation
	Deletion of astrocyte $GABA_B$ receptors in mice (Mederos et al., 2021)	PFC	Aberrant cortical synchronization and ↓ T-maze alternation performance	astrocytic $GABA_B$ signaling activates mGluRs and recruits PV interneurons	Not investigated
	Urokinase plasminogen activator receptor knockout mice (Bissonette et al., 2010)	orbitofrontal cortex, dorsal striatum	↓ reversal learning	↓ PV interneurons in orbitofrontal cortex and dorsal striatum	Reversal learning deficit rescued by up-regulation of hepatocyte growth factor in astrocytes
	Human Chrdl1 mutations (Webb et al., 2012)	Retina, PFC	↑ executive function	Corneal abnormalities and myelination deficits	Not investigated
	Overexpression of MHC1 in mouse mPFC astrocytes (Caudal et al., 2020)	mPFC	↓ reward-based visual discrimination	↓ dendritic spine density in dorsal striatum	Not investigated
	Chronic expression of IL-6 in transgenic mice (Heyser et al., 1997)	PFC, amygdala	↓ avoidance learning	Loss of synapses and calbindin-containing neurons due to chronic neuroinflammation	Not investigated
Reward seeking	Stimulation of hM3D receptors on astrocytes (Erickson et al., 2021)	PFC	↑ ethanol drinking	Activation of G_q-coupled signaling on astrocytes	Not investigated
	Stimulation of hM3D receptors on astrocytes(Scofield et al., 2015;Bull et al., 2014)	NAc	↓ cocaine reinstatement and motivation to self-administer ethanol (Scofield et al., 2015; Bull et al., 2014)	Stimulation of presynaptic mGluRs before hM3D stimulation (Scofield et al., 2015)	Not investigated
	Optogenetic stimulation of VTA astrocytes (Gomez et al., 2019)	VTA	↑ avoidance behavior, overriding CPP for cocaine	Astrocytes stimulate VTA GABA interneurons, inhibiting dopamine neurons	Glutamate transporter (GLT-1) from VTA astrocytes blocks avoidance behavior and maintains CPP for cocaine
	Optogenetic activation of hippocampal astrocytes (Li et al., 2020)	Hippocampus	↓ consolidation of contextual fear memory	Release of ATP and adenosine	Pharmacological stimulation of A1 receptors elicited similar effects
	hM3D activation of astrocytes (Kang et al., 2020)	Dorsal medial striatum	Shifted behavior from habitual to goal-oriented	hM3D activation reduced sEPSC frequency in D1 MSNs, but increased sEPSC amplitude in D2 MSNs	The effect was not observed in adenosine transporter (ENT1) knockout mice
	Training-induced upregulation of EAAT2/ GLT-1 (Boender et al., 2021)	Dorsal lateral striatum	↑ habit behavior in operant task for chocolate reward	Astrocytes reinforce relative contributions of the DMS and DLS guided behaviors	Inhibition of EAAT2/GLT-1 upregulation promoted goal-directed behavior
	Overexpression of the plasma membrane Ca^{2+}	Dorsal lateral striatum	↑ excessive and compulsive-like self-grooming behavior	Removal of astrocyte Ca^{2+} signaling	Not investigated

(*continued on next page*)

Table 1 (*continued*)

	Experimental manipulation[REF#]	Brain area specificity	Behavioral impact	Cellular mechanism	Bi-directional effect
	pump in astrocytes (Yu et al., 2018)				
Circadian rhythms and sleep/ wake cycle	Ca^{2+} imaging of astrocytes in naïve animals(Tsunematsu et al., 2021; Bojarskaite et al., 2020; Ingiosi et al., 2020)	Frontal cortex(Tsunematsu et al., 2021;Ingiosi et al., 2020), hippocampus, hypothalamus, pons, cerebellum (Tsunematsu et al., 2021), barrel cortex (Bojarskaite et al., 2020)	Ca^{2+} levels increase during wakefulness and decrease during REM sleep in several brain areas [(Tsunematsu et al., 2021; Bojarskaite et al., 2020;Ingiosi et al., 2020)]	Not investigated	Not investigated
	Genetic reprogramming of SCN astrocyte clock genes (Brancaccio et al., 2017)	SCN	Altered circadian patterns of locomotion	Astrocyte-derived glutamate and neuronal NMDA receptors in the SCN	Not investigated
	Genetic reprogramming of SCN neurons to have incompetent clock gene expression (Brancaccio et al., 2019)	SCN	Astrocytes reinstate circadian locomotor behavior.	Astrocytes reinstate neuronal clock gene expression via glutamatergic signaling in the SCN	Not investigated
	Experimental manipulation[REF#]	**Brain area specificity**	**Behavioral impact**	**Cellular mechanism**	**Bi-directional effect**
Microglia					
Cognitive flexibility	Chronic unpredictable stressors in mice[(Horchar and Wohleb, 2019;Wohleb et al., 2018)]	mPFC	↓ PFC-dependent temporal object recognition (Horchar and Wohleb, 2019)	↑ CSF1 receptor and complement component mRNA(Horchar and Wohleb, 2019;Wohleb et al., 2018)	Both mRNA and behavior rescued by treatment with RU486 (glucocorticoid antagonist).Horchar and Wohleb (2019)
	7-day restraint stress (Liu et al., 2021)	dmPFC	↓ reversal learning in 4-choice odor discrimination	↑ dmPFC dendritic spine elimination	Not investigated
	Blockade of adenosine$_{2A}$ receptor in prenatal dexamethasone model for anxiety(Duarte et al., 2019; Zhang et al., 2019)	Hippocampus, PFC	↑ cognitive performance in recognition memory task (Zhang et al., 2019)	Normalized frontocortical (Duarte et al., 2019) and hippocampal (Zhang et al., 2019) microglia morphology	Not investigated
	Adolescent social stress model in mice (Zhang et al., 2019)	PFC	↓ cognitive flexibility performance	Activated microglia release TNFα	Cognitive flexibility deficits were rescued by increased TNFα release by ranylcypromine
	Radioligand TSPO distribution PET scan(Li et al., 2018;Rubin et al., 2018;Giridharan et al., 2020;Politis et al., 2011)	PFC	↓ attention (Li et al., 2018) ↓ memory and executive function (Rubin et al., 2018), cognitive decline(Giridharan et al., 2020;Politis et al., 2011)	microglia activation (Li et al., 2018;Rubin et al., 2018; Giridharan et al., 2020;Politis et al., 2011)	Not investigated
Reward seeking	Inhibiting microglia with minocycline in alcohol-dependent mice(Agrawal et al., 2011;Gajbhiye et al., 2018)	Not investigated (IP injection)	↓ withdrawal-induced anxiety(Agrawal et al., 2011;Gajbhiye et al., 2018)	Not investigated	Not investigated
	Depletion of microglia with PLX-5622 (Warden et al., 2021)	Whole brain	Does not change escalation of voluntary alcohol consumption	Not investigated	PLX-5622 does block escalation under conditions of repeated immune activation
	Depletion of microglia with PLX-5622 (Warden et al., 2020)	Whole brain	↓ anxiety during alcohol withdrawal ↓ escalation of alcohol intake	Normalized excitatory and inhibitory synaptic plasticity in central nucleus of the amygdala	Not investigated
	Depletion of microglia with PLX-5622 (Adeluyi et al., 2019)	Whole brain	Normalized performance on marble burying and open field tests after nicotine withdrawal	Elevation of NOX2 release from microglia	Not investigated
	Blockade of TLR4 signaling with LPS-RS or TLR4 knockout mice (Northcutt et al., 2015)	Whole brain	↓ CPP and self-administration of cocaine	Inhibiting TLR4, ↓ extracellular dopamine from cocaine in the NAc by preventing downstream release of IL-1β	Not investigated
	Minocycline treatment(Fujita et al., 2012; Attarzadeh-Yazdi et al., 2014)	Whole brain	↓ both maintenance and reinstatement of methamphetamine-induced CPP	Minocycline ↓ extracellular dopamine from methamphetamine in the NAc	Not investigated
Circadian rhythms and sleep/ wake cycle	Chronic sleep fragmentation model in wild-type mice (Xie et al., 2020)	PFC, hippocampus	↓ spatial learning and memory ↑ aggression and anxiety	↑ intracellular amyloid-β, dysfunction of endosome-autophagosome-lysosome pathway	Not investigated
	Depleting microglia with Cx3cr1 transgenic mice (Sominsky et al., 2021)	SCN, hippocampus	Abnormal circadian body temperature and diurnal rhythms	Disrupted expression of clock genes Per1, Per2, and Bmal1	Not investigated
	Ablation of microglia following PLX-5622	Whole brain, Hippocampus	↑ sleep duration	↓ in light phase-dependent excitatory synaptic	Not investigated

(*continued on next page*)

Table 1 (*continued*)

	Experimental manipulation[REF#]	Brain area specificity	Behavioral impact	Cellular mechanism	Bi-directional effect
	treatment in mice (Corsi et al., 2021)			transmission in CA1 pyramidal neurons	
	Sleep deprivation in rats (Wadhwa et al., 2017)	Whole brain, hippocampus	↑ memory impairments ↓ performance in Morris water maze	Sleep deprivation increases activated microglia activity and minocycline blocks activation of resting microglia	Memory and Morris water maze impairments were rescued by minocycline
	Minocycline treatment in human (Nonaka et al., 1983) and rodents(Wisor and Clegern, 2011;Wisor et al., 2011)	Whole brain	Both ↑ (Nonaka et al., 1983) and ↓(Wisor and Clegern, 2011; Wisor et al., 2011) in sleep quality and episodic memory	minocycline blocks activation of resting microglia(Wadhwa et al., 2017;Nonaka et al., 1983;Wisor and Clegern, 2011;Wisor et al., 2011)	Not investigated

placement in the brain. However, current evidence does indicate unique molecular phenotypes of astrocytes between brain regions and deeper understanding of the importance and role of such phenotypes is beginning to emerge (Khakh and Deneen, 2019; Yu et al., 2020).

2.1. Astrocyte lesions alter cognitive flexibility

Several studies have investigated the impact of lesioning astrocytes in the prefrontal cortex (PFC) on relevant behavioral outcomes. In recent work, bilateral administration of the astrocyte-specific toxin, L-AAA, into the medial PFC (mPFC) impaired cognitive flexibility in an attentional set-shifting task and reduced the power of gamma oscillations in the mPFC without any effects on neuron morphology (Brockett et al., 2018). In contrast, stimulation of astrocyte activity via G_q receptor coupled DREADDs as well as via mPFC infusions of the astrocyte-secreted calcium-binding protein S100β, in the non-L-AAA lesioned groups, improved cognitive performance (Brockett et al., 2018). These observations are consistent with previous work that identified deficits in the ability to discriminate between texture-based, but not odor-based, stimuli, as well as impairments in odor-based reversal learning and working memory after infusions of L-AAA into the mPFC (Lima et al., 2014). The L-AAA lesions of the PFC have also been reported to impair sucrose preference and novelty-suppressed feeding whereas excitotoxic lesioning of neurons by ibotenate did not impact performance on these tasks(Banasr and Duman, 2008; Lee et al., 2013). Consistent with the postulate of a close-knit relationship between local astrocyte function and neuron structure, substantial reductions in dendritic complexity of mPFC neurons have been observed after L-AAA administration (Brockett et al., 2018). In the pre-limbic cortex, L-AAA triggered swelling of neuronal cell bodies, but did not result in measurable neuronal cell death (Banasr and Duman, 2008). The ability of astrocytes to facilitate behavioral dysfunction without an outright neuronal loss has particular relevance to pathophysiology of drug seeking behaviors and depression, conditions characterized more by synaptic reorganization and plasticity rather than extensive neuronal degeneration (Duman, 2009; Luscher and Malenka, 2011). However, results of L-AAA lesioning studies should be interpreted with caution given evidence that L-AAA inhibits glutamate uptake and glutamate metabolism leading to elevated extracellular glutamate levels (McBean, 1994). An additional interpretational caveat of L-AAA studies has to do with findings that L-AAA increases microglial infiltration into the lesioned area (Khurgel et al., 1996) which has clear implications for attribution of the behavioral effects of L-AAA exclusively to astrocytes.

2.2. The role of astrocyte cytoskeleton

Several provocative reports have been published to examine the impact of astrocyte cytoskeletal proteins on behavior. GFAP and vimentin are astrocyte intermediate filament proteins often used for immunohistochemical identification of astrocytes, but also for examination of gross changes in astrocyte morphology. These molecules have been extensively used as markers of reactive gliosis, a phenomenon in which up-regulation of GFAP and vimentin is accompanied by morphological and a wide array of molecular changes (Zamanian et al., 2012). Nestin is another intermediate filament protein that is normally expressed in progenitor cells during development, but is also re-expressed in mature reactive astrocytes, following brain trauma(Lin et al., 1995; Krum and Rosenstein, 1999). With regard to frontocortical function, one investigation found that transgenic mice null for GFAP and vimentin displayed improved extinction of memories linked to location of a food container in a reversal task (Wilhelmsson et al., 2019). While acquisition of place memories relies heavily on the hippocampus, spatial reversal learning implies suppression of existing information and requires additional processing in prefrontal areas (Avigan et al., 2020). GFAP/vimentin null mice maintained surprisingly normal performance on initial acquisition of hippocampus-dependent place memories, highlighting the specific impact on frontocortical processing (Wilhelmsson et al., 2019). Interestingly, mice with constitutive deletion of nestin showed a similar pattern of results: normal memory acquisition, but better extinction of acquired place memories (Wilhelmsson et al., 2020). Although behavioral specificity of GFAP deletion to reversal learning is intriguing, its absence since embryonic stage may have also impacted adult neuron populations or neural circuit interactions since GFAP is expressed in neural progenitor cells. Indeed, there are suggestions that altered cognitive function may be associated with highly local, cell-layer specific regulation of astrocyte number and morphology as found in a post-mortem analysis of GFAP expression in brains of schizophrenia patients (Rajkowska et al., 2002). Pre-clinical studies also support the idea that astrocyte interactions with neurons may be targeted to specific neuronal populations (Martin et al., 2015). Overall, a vast number of reports outside the scope of this review has relied on intermediate filament expression, particularly GFAP, to evaluate astrocyte numbers and morphology throughout the brain. The most parsimonious conclusion from this literature is that astrocyte number is bidirectionally sensitive to and can be correlated with many behavioral antecedents, sequelae, or disease pathologies. However, since GFAP staining does not label fine astrocytic processes that are most likely to contact synapses, research using other markers to evaluate astrocyte plasticity is sorely needed (Lavialle et al., 2011) as neither astrocyte numbers on their own nor GFAP-based gross morphology reports are likely to provide mechanistic insight into behavioral relevance of these cells.

2.3. Astrocytic control of glutamate recycling and GABA synthesis

Astrocytes recycle over 90% of extracellular glutamate (Zhou et al., 2014), with an impact not only on neuronal supply of glutamate, but also on availability of glutamate for GABA synthesis (Ortinski et al., 2010). Among the four major subtypes of glutamate reuptake transporters, two – EAAT1 (GLAST in rodent) and EAAT2 (GLT-1 in rodent) – are abundantly expressed in astrocytes of the CNS. Expression of both EAAT1 and EAAT2 is strongly decreased in schizophrenia and substance

use (Spangaro et al., 2012; Roberts-Wolfe and Kalivas, 2015), disorders known to prominently involve frontocortical activity. A decrease in astrocyte number and EAAT2 expression is also observed in Alzheimer's disease (AD), in humans and in mouse models, where this deficit has been associated with slower clearance of extracellular glutamate (Meeker et al., 2015; Scimemi et al., 2013). Interestingly, overexpression of astrocytic glutamate transport may be beneficial for cognitive function, as suggested, for example, by a post-mortem analysis of entorhinal cortex of AD patients, where overexpression of EAAT2 was found to correlate with the absence of dementia or mild cognitive impairment (Kobayashi et al., 2018). A deficit in visual discrimination learning was reported in mice with constitutive deletion of EAAT1 (Karlsson et al., 2009), suggesting impairment of executive function, although the learning deficit prevented a more direct evaluation of frontocortical control in a reversal task (Karlsson et al., 2009). Reminiscent of the effects of astrocyte lesioning in L-AAA studies, blockade of EAAT2-dependent glutamate uptake by dihydrokainate increased drinking latency in a sucrose preference task and led to near-complete cessation of responding for electrical stimulation of the PFC in an intracranial self-stimulation paradigm (John et al., 2012). In another study, reduced expression of EAAT2 in the mouse hippocampus was observed after treatment with sub-chronic ketamine which was associated with impaired extinction of an operant sucrose self-administration task (Featherstone et al., 2012). These findings were speculated to reflect cognitive deficits characteristic of substance use and resemble data from the PFC of schizophrenic patients (Spangaro et al., 2012). However, extinction of self-administration is not a widely used behavioral indicator of cognitive impairment, and future studies will be needed to more closely examine the impact of astrocytic EAAT2 on frontocortical control of behavior. In the meantime, a repeated observation has been that disrupted glutamate uptake strongly impacts activity of NMDA receptors throughout the brain (Scimemi et al., 2004; Nie and Weng, 2009; Ortinski et al., 2013), with implications for astrocyte control of neuronal output as discussed in the next section.

2.4. Transmitter release by astrocytes

A series of seminal studies used a mouse model of astrocyte-specific deletion of the SNARE protein (dnSNARE mice) that was argued to limit transmitter release (Pascual et al., 2005). Although the specificity of GFAP-driven dnSNARE transgene to astrocytes has been challenged (Fujita et al., 2014), this work formed the foundation for the view that astrocytes may promote synchronous neuronal activity and are instrumental for forms of long-term neuronal plasticity (Durkee et al., 2021). Later studies provided support for this hypothesis by demonstrating that astrocytes regulate sleep patterns and cortical oscillations with implications for cognitive performance (Halassa et al., 2009; Poskanzer and Yuste, 2016). The dnSNARE mice have also been recently used to demonstrate impaired theta-cycle synchronization between the hippocampus and the PFC accompanied by deficits in working and spatial memory, but intact neuronal morphology in both the PFC and the hippocampus (Sardinha et al., 2017). Both the theta coherence and the cognitive deficits could be rescued by supplementation with d-serine (Sardinha et al., 2017). D-serine acts as a co-agonist of NMDA receptors at the glycine site and D-serine release from astrocytes has been argued to impact synaptic long-term potentiation in the hippocampus (Henneberger et al., 2010). Additionally, astrocyte-released ATP and its metabolic product, adenosine, may also influence NMDA receptor expression and signaling via activation of purinergic receptors (Deng et al., 2011). The interaction between ATP/adenosine receptors and neuronal signals in the PFC is supported by experiments in slices indicating that astrocytic P2Y4 receptors are linked to vesicular release of glutamate and activation of neuronal metabotropic glutamate receptors (mGluRs) and NMDA receptors (Wirkner et al., 2007). Altogether, there is substantial support for the view that NMDA receptors represent a critical component of astrocyte interaction with neurons. Particular attention must be paid to a potentially unique contribution of NMDA receptors located at extrasynaptic sites which are posited as primary mediators of neuronal response to astrocyte-released glutamate (Fellin et al., 2004; Henneberger et al., 2020; Ortinski, 2014; O'Donovan et al., 2021).

In addition to glutamate-mediated signaling, astrocytes also release GABA with an impact on inhibitory neurotransmission (Yoon and Lee, 2014). The specific effects of astrocyte-released GABA on behaviorally relevant frontocortical activity remain to be determined. However, a recent publication demonstrated that selective deletion of $GABA_B$ receptors in astrocytes of the mouse PFC resulted in aberrant cortical synchronization and deficits in a T-maze alternation task (Mederos et al., 2021). The study proposed that astrocytic $GABA_B$ signaling facilitates activation of group 1 mGluRs and recruitment of parvalbumin-expressing interneurons, suggesting a link between $GABA_B$ receptor activation and glutamate release from astrocytes. An interaction between astrocytes and parvalbumin positive interneurons has also been reported in the visual cortex, with an effect on orientation to visual stimuli (Perea et al., 2014).

We would like to conclude this section by acknowledging an ongoing debate over astrocytic ability to release transmitter molecules through vesicular (i.e. SNARE-mediated) or non-vesicular release mechanisms all grouped under the general definition of "gliotransmission". The two most prominent aspects of this argument are an unresolved question over the role of astrocyte Ca^{2+} as the mediator of gliotransmitter release and the degree to which *ex vivo* experimental conditions demonstrating astrocyte-mediated release reflect in vivo physiology of these cells (Fiacco and McCarthy, 2018). The contentious nature of the debate is supported by the fact that mechanisms of transmitter release from astrocytes are potentially more diverse and certainly much less understood than in neurons (Fiacco and McCarthy, 2018; Savtchouk and Volterra, 2018). Evaluations of astrocyte Ca^{2+} may, thereofre, require methods distinct from those applied to neuronal Ca^{2+} transients (Khakh and McCarthy, 2015; Semyanov et al., 2020; Neugornet et al., 2021). As a consequence, trying to 'squeeze' gliotransmission into the framework of extensively characterized neuronal release mechanisms may not provide an accurate depiction of transmitter release from astrocytes. Similarly, any answers as to whether astrocyte contributions to neuronal activity align with intact physiology must await further experimentation, given that the overwhelming majority of current knowledge has been generated using astrocyte cultures or *ex vivo* slice preparations.

2.5. Other astrocyte-secreted factors

Astrocytes release a range of neuromodulators that interact with the surrounding neurons and impact behavioral measures of cognition. For example, *Plaur* transgenic mice, that lack urokinase plasminogen activator (uPA) receptors and show a specific loss of parvalbumin positive interneurons in the orbitofrontal cortex and dorsal striatum, display a pronounced deficit in performance on a reversal learning task (Bissonette et al., 2010). This deficit, which does not generalize to a broad learning impairment, can be rescued by up-regulation of the hepatocyte growth factor in GFAP-positive astrocytes (Bissonette et al., 2010). Loss of astrocyte reactivity could play a role in these behavioral outcomes since up-regulation of astrocyte uPA receptors in response to uPA secretion from neurons has been reported to mediate astrocyte activation, as measured by increased GFAP expression, after ischemic injury (Diaz et al., 2017). Another interesting secreted protein is chordin-like 1 (Chrdl1). Chrdl1 acts an antagonist of bone morphogenetic protein, which is critical in CNS development. A human study linked mutations in the *Chrdl1* gene to development of corneal abnormalities and myelination deficits, but strikingly, superior performance on tests of executive function (Webb et al., 2012). In mice, secretion of Chrdl1 from astrocytes is essential for increased developmental expression of Ca^{2+}-impermeable, GluA2 subunit-containing AMPA receptors that impede synaptic plasticity (Blanco-Suarez et al., 2018). Regulated

expression of Ca^{2+}-permeable versus Ca^{2+}-impermeable AMPA receptors has been proposed as one of key characteristics of neuroplasticity within the mesolimbic dopamine reward system associated with cocaine use (Wolf and Tseng, 2012). Related to this, up-regulation of Chrdl1 RNA was demonstrated in cultured astrocytes treated with dopamine (Galloway et al., 2018).

A vast literature supports the notion that astrocytic release of pro- and anti-inflammatory molecules as well as astrocytic response to these molecules has consequences for frontocortical signaling (Sofroniew, 2014). For example, astrocytic overexpression in the mPFC of major histocompatibility complex 1 (MHC1), which is involved in adaptive immune responses, led to decreased neuronal spine density in the dorsal striatum and deficient performance in a reward-based visual discrimination task, despite normal performance in a reversal learning task (Caudal et al., 2020). In another study, mice that constitutively expressed IL-6 in astrocytes showed deficits in avoidance learning that are thought to rely on PFC interactions with the amygdala (Heyser et al., 1997). The inflammatory role of astrocytes has been a prominent area of research on neurodegenerative disease with pathologies that span the gamut of behavioral impairments from memory deficits to dysregulation of executive function to depression, anxiety, etc. Numerous astrocyte-specific targets have been identified across neurodegenerative conditions including Parkinson's disease (Booth et al., 2017), Huntington's disease (Khakh et al., 2017), AD (Carter et al., 2019), multiple sclerosis (Brambilla, 2019), stroke (Pekny et al., 2019), traumatic brain injury (TBI) (Burda et al., 2016) as well as normal aging(Rodriguez-Arellano et al., 2016; Cohen and Torres, 2019). Since it appears unlikely that any one of the behavioral measures in these conditions can be attributed to a single astrocyte-specific factor, a deeper understanding of how combinations of secreted factors impact astrocyte interactions with local neurons and long-range signals between brain regions would be extremely valuable.

2.6. *Microglial contributions to executive function*

Microglia-mediated inflammation has been observed to contribute to frontal cortex dependent behaviors across a range of pathologies, including AD, schizophrenia, TBI, aging, PTSD, depression, neurodegeneration as well as diet-induced inflammation(Veniaminova et al., 2020; Val-Laillet et al., 2020; Bocarsly et al., 2015). Similar to astrocytes, microglial morphology is highly sensitive to a wide range of physiological and pathological stimuli and many studies rely on morphology-based classification of activated microglia as evidence of altered microglial signaling. Indeed, physical appearance of the microglia can be indicative of the neuro-environment (De Biase et al., 2017). For example, resting microglia have long, thin, highly branched processes with a small cell body, and they are primarily in charge of querying the neuronal environment for perturbations to ensure effective communication between neurons. In line with their 'surveillance' role, these cells are regularly tiled throughout the brain to ensure local oversight by at least one microglial cell. However, when microglia detect a potential neuro-insult, these cells are galvanized into an active state, characterized by retraction of their processes and acquisition of a more amoeboid phenotype. Because these cells share a common lineage to macrophages in the peripheral immune system, microglial activation has been similarly described as falling under M1 (pro-inflammatory and expressing markers such as CD86, iNOS, CD16/32, and MHCII) or M2 (anti-inflammatory and expressing markers such as CD206, FIZZ1, and Arginase I) phenotypes. More recently, however, application of M1 and M2 descriptors to microglia has been called into question based on growing support for existence of multiple intermediate and combinative phenotypes (Butovsky and Weiner, 2018).

There is substantial evidence that administration of minocycline, a tetracycline antibiotic that disrupts protein synthesis and prevents microglial activation elicits mild-to-substantial cognitive *improvement* across multiple domains including cognitive symptoms of bipolar disorder (Rosenblat and McIntyre, 2015), HIV (Lin et al., 2021), addiction (Kohno et al., 2019), depression (Bortolato et al., 2016) and psychotic disorders (Jeppesen et al., 2020; Solmi et al., 2017). Pro-cognitive effects of microglia depletion have also been observed after cranial irradiation, often used as a cancer therapy (Acharya et al., 2016). Reducing microglial population in mice by treatment with the colony stimulating factor (CSF)−1 receptor inhibitor, PLX-5622, has been reported to rescue irradiation-induced behavioral deficits on an 'object in place' and contextual fear-conditioning tasks both of which involve frontocortical signaling (Acharya et al., 2016). Interestingly, a recent study reported no effect of minocycline on cognitive decline associated with mild AD in human subjects (Howard et al., 2020), although cognitive benefits have been reported in animal models (Choi et al., 2007). To reconcile such disparate outcomes, some researchers advocate for use of minocycline in combination with other drugs as a strategy to combat cognitive impairment in AD patients(Daulatzai, 2016; Fessel, 2019). It must be noted, however, that similarly to astrocyte depletion with L-AAA, microglia depletion with PLX-5622 or other CSF-1 inhibitors may have off-target effects that involve other cell types (Green et al., 2020).

Consistent with the body of knowledge that stress is both associated with cognitive deficits and promotes systemic inflammation, stress-activated microglia have also been found to facilitate cognitive impairment. Dysregulated stress responsivity within the PFC is thought to be one of core factors leading to emergence of depression and associated cognitive deficits (McEwen and Morrison, 2013; Fogaca and Duman, 2019). For example, a regime of chronic unpredictable stressors led to elevation of CSF1 receptor and complement components C1q and C3 mRNA in the PFC and behavioral deficits in a PFC-dependent temporal object recognition task (Horchar and Wohleb, 2019). In this study, both the mRNA and the behavioral changes could be rescued by treatment with the glucocorticoid receptor antagonist, RU486. Glucocorticoid receptors are known to be expressed by a variety of cell types in the brain including neurons and RU486 treatment was noted to reduce stress-associated morphological remodeling of the PFC microglia as well as to prevent reduction of dendritic spine density in PFC layer V pyramidal cells (Horchar and Wohleb, 2019). These results complement other findings that stress-induced cognitive deficits trigger ramification of microglial processes and increase microglia-neuron contacts in the PFC leading to dendritic spine elimination (Hinwood et al., 2013; Liu et al., 2021; Wohleb et al., 2018). One molecular mechanism that links stress-induced PFC dysfunction with microglial activation has been proposed to involve ATP-gated P2×7 receptor signaling and the downstream release of PGE2 and IL-1β (Furuyashiki, 2012). Extracellular ATP is generally subject to quick hydrolysis to adenosine, predicting a role for adenosine receptors in microglial response to stress. Indeed, blockade of adenosine A_{2A} receptors has been shown to normalize frontocortical microglia morphology in the prenatal dexamethasone model of anxiety in male, but not female rats (Caetano et al., 2017). Using the same model, normalization of microglial morphology by A_{2A} antagonism was observed in the hippocampus of female rats which was further linked to increased synchronization of hippocampal-PFC network and improved cognitive performance (Duarte et al., 2019).

Some evidence suggests that release of TNFα from activated microglia improves cognitive flexibility in an adolescent social stress model and that administration of the monoamine oxidase inhibitor, antidepressant, ranylcypromine, increases the number of microglia and TNFα release in the PFC (Zhang et al., 2019), a finding that suggests microglial activation may rescue, rather than promote, PFC-dependent cognitive impairment in some models and behavioral assays. Notwithstanding such evidence, human studies support deleterious effects of activated microglia on cognitive performance. This work has been greatly facilitated by the availability of radioligands to translocator protein (TSPO), a marker of activated microglia utilized in MRI and PET studies. For example, elevated TSPO distribution in the frontal cortex has been associated with lower attention scores in non-medicated patients with a

major depressive disorder (Li et al., 2018). Similarly, in HIV patients, increased TSPO radioligand binding in the frontal cortex was linked to lower performance on tests of memory and executive function (Rubin et al., 2018). Increased microglial activation reported by TSPO binding has also been reported to predict cognitive decline in a model of experimentally-induced meningitis in rats (Giridharan et al., 2020) and in a population of pre-manifest Huntington's disease patients (Politis et al., 2011). Although a specific role of PFC microglia was not investigated in these studies, they suggest that microglial activation can serve as a useful predictor of clinically manifesting symptoms of cognitive decline.

3. Modulation of reward-seeking behaviors

3.1. Regional heterogeneity of astrocyte responses to drugs of abuse

The role of astrocytes may vary within distinct nodes of the reward circuit, including the PFC, caudate/putamen, nucleus accumbens (NAc), hippocampus, amygdala, and ventral tegmental area (VTA) as most prominent components. Indeed, while our understanding of astrocytes is still in its infancy, accumulating evidence indicates variability exists across brain regions with respect to the basal functional properties and engagement in pathology of these cells (Khakh and Deneen, 2019; Polyzos et al., 2019). While a direct comparison has not been made between cortical and striatal astrocytes, several lines of evidence indicate differential features and expression profiles between striatal and hippocampal astrocytes, supporting other evidence for regional variability of both structure and function (Chai et al., 2017; Khakh and Deneen, 2019; Khakh, 2019; Xin and Bonci, 2018; Batiuk et al., 2020; Clarke et al., 2021). Accordingly, it is not unreasonable to speculate that effects of drug exposure may have dissociable effects within the reward circuitry, and that astrocytes within these regions may differentially influence behavioral responses to drugs.

Early reports reflecting effects of drug self-administration on astrocytes indicated that astrocyte-enriched mediators of glutamate homeostasis, in particular system xC- and EAAT2/GLT-1, are chronically downregulated in the NAc (Baker et al., 2003; Knackstedt et al., 2010; Scofield et al., 2016; Spencer and Kalivas, 2017). It was subsequently revealed that self-administration and extinction of cocaine-seeking led to downregulation of GFAP expression, as well as astrocyte surface area, volume, and colocalization of astrocyte membrane with synapses in the NAc (Scofield et al., 2016;Testen et al., 2018). This decrease in synaptic colocalization has since also been observed following self-administration and extinction from methamphetamine and heroin (Kruyer et al., 2019; Siemsen et al., 2019). The effect of cocaine on astrocytes in the NAc was, in contrast, not observed to extend to the prelimbic PFC or the basolateral nucleus of the amygdala, suggesting regional susceptibility of astrocytes in this model (Testen et al., 2018). However, decreased expression of EAAT1/GLAST and S100β-positive astrocytes has been observed in the SN/VTA following chronic non-contingent delivery of cocaine or methamphetamine (Sharpe et al., 2019). Ethanol consumption in rats exhibits a time-dependent morphological effect on astrocytes in the mPFC, characterized by initial upregulation of GFAP followed by a decrease at 3 weeks of abstinence (Bull et al., 2015; Kim et al., 2018). Likewise, adolescent intermittent ethanol administration results in decreased synaptic colocalization of dorsal hippocampal astrocytes in adulthood (Healey et al., 2020). While many reports have found overall increases in GFAP expression and structural features of astrocytes following ethanol exposure, the general theme of reduced gene expression and structural features following post-administration abstinence has been observed across operant drug paradigms (Kim et al., 2018).

How then do astrocytes affect drug-related behaviors? One prominent line of evidence comes from studies utilizing astrocyte-specific expression of G_q-coupled DREADD (hM3D) constructs. Stimulation of hM3D receptors within the murine PFC promotes ethanol drinking in ethanol-naïve mice in an intermittent access paradigm with free availability of ethanol every other day (Erickson et al., 2021). However, different results are observed in other brain regions. When expressed in the NAc astrocytes, hM3D stimulation opposes cocaine reinstatement and motivation to self-administer ethanol, respectively (Scofield et al., 2015; Bull et al., 2014). In the case of cocaine reinstatement, stimulation of presynaptic inhibitory mGluRs subsequent to hM3D stimulation was shown to be responsible for the observed behavioral effect (Scofield et al., 2015). It is unclear whether these divergent results of DREADDs in the mPFC and NAc reflect heterogeneity of astrocyte signaling or are a function of the stimulation in naïve versus withdrawn, abstinent animals. The parallel between distinct effects on astrocyte morphology and behavioral drug-related output, however, is noteworthy. Moreover, results from the VTA indicate that astrocyte regulation of avoidance behavior is dependent on local circuitry and stimulation of GABAergic neurons (Gomez et al., 2019). Specifically, optogenetic stimulation of VTA astrocytes promotes avoidance behavior which overrides conditioned place preference for cocaine (Gomez et al., 2019). Ventral midbrain astrocytes exhibit distinct gene expression and physiological properties which may contribute to the microcircuit-level outcomes (Xin et al., 2019).

3.2. Regional heterogeneity of astrocyte modulation of drug-related behaviors

What is the mechanism by which striatal astrocytes could oppose drug-related, motivated behaviors? As addressed above, one possibility is stimulation of presynaptic, G_α and $G_{i/o}$-coupled metabotropic glutamate receptors (Scofield et al., 2015). In addition, considerable evidence indicates that astrocytes can oppose glutamatergic synaptic transmission via release of ATP/adenosine, acting also on presynaptic inhibitory adenosine A1 receptors (Kofuji and Araque, 2021). For example, optogenetic activation of astrocytes in the hippocampus inhibited consolidation of contextual fear memory via release of ATP and adenosine and pharmacological stimulation of A1 receptors elicited similar effects (Li et al., 2020). In a similar fashion, glutamatergic synapses in the central nucleus of the amygdala can be inhibited by astrocytes via adenosine A1 receptor stimulation, while inhibitory synapses are activated via stimulation of adenosine A2A receptors (Martin-Fernandez et al., 2017). Perhaps most germane, Corkrum et al. (2020) recently showed that Ca^{2+} responses are generated in NAc astrocytes subsequent to dopamine release and amphetamine exposure, resulting in ATP/adenosine release and reduced AMPA receptor-mediated synaptic activity. This effect may be facilitated by increased glutamate-mediated neuroglial coupling in the NAc observed after cocaine self-administration (O'Donovan et al., 2021), although multiple other regulators of AMPA signaling (e.g. Ortinski et al., 2015; Briand et al., 2014; White et al., 2016) could certainly be involved. Independent of drug exposure, Down Syndrome patient-derived induced pluripotent stem cells exhibit increased frequency of spontaneous calcium fluctuations, which inhibit co-cultured neurons via an adenosine-dependent mechanism (Mizuno et al., 2018). This is in keeping with a rich literature on varied effects of astrocytes on potentiation of inhibition of synaptic transmission dependent on subtype of adenosine or glutamate receptors (Pascual et al., 2005; Papouin et al., 2017; Newman, 2003; Koizumi et al., 2003). Thus, while significant evidence indicates that astrocytes can promote and support synaptic transmission (Papouin et al., 2017; Allen and Eroglu, 2017) there is also considerable support for the hypothesis that astrocytes may oppose excitatory drive within the reward circuitry, and relatedly oppose behavioral output associated with drug craving and seeking (Corkrum and Araque, 2021).

3.3. Striatal astrocytes in habit and compulsive behaviors

Striatal astrocytes influence behaviors engaged by drugs beyond seeking. For example, both habit-directed and compulsive behaviors are

associated with protracted drug seeking (Lipton et al., 2019). The transition from recreational drug use to more regulated use and relapse is associated with a shift in cellular activity from the ventral to dorsal striatum (Fouyssac and Belin, 2019). Relatedly, addiction is also associated with a shift from goal-directed, to more habit-based behaviors that are proposed to rely on recruitment of dorsomedial (DMS) and dorsolateral striatum (DLS), respectively (Vandaele and Ahmed, 2021; Everitt and Robbins, 2016).

Recent studies have indicated supportive roles for astrocytes in these processes. For example, chemogenetic hM3D activation of astrocytes in the DMS reduced the frequency of spontaneous neuronal excitatory post-synaptic currents (EPSCs) in D1-receptor expressing medium spiny neurons (MSNs), but increased EPSC amplitude in D2-receptor positive MSNs and shifted behavior from habitual to goal-directed (Kang et al., 2020). The effect of astrocyte G_q stimulation on promoting goal-directed behaviors was dependent on adenosine signaling, as the effect was not observed in adenosine transporter (ENT1) deficient mice. Considerable research has indicated both structural and functional interactions between A1-D1 and A2A-D2 receptors (Fuxe et al., 2010; Ferre et al., 1997; Ferre et al., 1992), underscoring the critical nature of adenosine in the regulation of synaptic and neuronal activity by astrocytes, and providing a mechanism whereby astrocytes may differentially affect different neuronal subtypes within the striatum. Precedent for specific interactions between astrocytes and neuronal subpopulations in the striatum has previously been reported (Martin et al., 2015). In contrast to these findings subsequent to astrocyte hM3D stimulation in the DMS, training-induced upregulation of EAAT2/GLT-1 in the DLS resulted in strengthened habit behavior in an operant task for chocolate reinforcers, and inhibition of EAAT2/GLT-1 upregulation promoted goal-directed behavior (Boender et al., 2021). Collectively, these studies in the dorsal striatum suggest that astrocytes may reinforce the relative contributions of the DMS and DLS to habit and goal-directed behaviors, respectively.

Substance use disorders are characterized by three stages: 1) binge and intoxication, 2) withdrawal and negative affect, and 3) preoccupation and anticipation (Volkow et al., 2016). The third stage is associated with impaired PFC-dependent regulation of behavior and compulsive drug seeking. Accordingly, it is of merit to understand how astrocytes may contribute to compulsive-like behaviors. Removal of astrocyte Ca^{2+} signaling in the DLS via expression of the plasma membrane Ca^{2+} pump resulted in excessive and compulsive-like self-grooming behavior associated with increased GABA transporter, GAT-3, expression in astrocytes and impaired tonic inhibition of medium spiny neurons (Yu et al., 2018). These findings suggest that astrocytes may suppress dopamine release from axon terminals since compulsions manifesting as motor stereotypies are often observed in conditions characterized by excessive dopamine. Importantly, these results also highlight the ability of striatal astrocytes to modulate inhibitory as well as excitatory neuronal signaling echoing the findings in the frontal cortex.

3.4. Microglia and reward-seeking

Microglia interact extensively with the dopamine system (Thomas Broome et al., 2020) and show sensitivity to drugs across a spectrum of substance use disorder models. In alcohol use disorder, ethanol has been found to increase the number of microglia in the hippocampus and the PFC in the absence of astrocyte activation (West et al., 2021). However, another study has found that although ethanol does induce microglial activation, microglial numbers in the hippocampus decrease after a "binge" pattern of exposure, finding that was supported by evidence of microglial dystrophy (Marshall et al., 2020). Microglial activation has also been shown after exposure to psychostimulant drugs, including amphetamine (Marchese et al., 2020), methamphetamine (Thomas et al., 2004) and cocaine (Cotto et al., 2018; Wang et al., 2017; Jarvis et al., 2019; Burkovetskaya et al., 2020; Lewitus et al., 2016). Interestingly, methamphetamine-induced activation of microglia could be prevented by maintaining animals at reduced temperature (10–12 °C), whereas elevated ambient temperature alone (38–40 °C) did not result in microglial activation (Thomas et al., 2004). Additionally, a PET study of human cocaine users using TSPO radioligands found no evidence of activated microglia (Narendran et al., 2014). These somewhat discrepant findings could be reconciled by acknowledging that there is not a binary distinction between activated and resting microglia. For example, while there is converging support for the idea of microglial activation by ethanol using morphological analyses (Melbourne et al., 2019), binge ethanol exposure may result in increase of some, but not other markers of immunoreactive microglia (Marshall et al., 2013). Such observations of partial microglial activation call for a more nuanced classification scheme. Indeed, the need for discriminating between multiple microglia phenotypes has been increasingly recognized and particularly aided by the emergence of rapid and cost-effective gene sequencing techniques (Boche and Gordon, 2021).

In addition to morphological changes and expression of inflammatory markers following drug use, disrupting microglia has also been shown to have an effect on subsequent behavioral read-outs of drug exposure. Alcohol consumption and withdrawal-induced anxiety are both attenuated by inhibiting microglial activation with minocycline (Agrawal et al., 2011; Gajbhiye et al., 2018). Depletion of microglia with PLX-5622 does not change escalation of voluntary alcohol consumption, but does block escalation of intake under conditions of repeated immune activation (Warden et al., 2021). Another study has found that PLX-5622 normalized both excitatory and inhibitory synapse plasticity as well as prevented anxiety during alcohol withdrawal and reduced escalation of alcohol intake (Warden et al., 2020). Consistent with this, microglial depletion normalized behavioral performance on marble burying and open field tests (measures of anxiety) after withdrawal from nicotine, an effect associated with elevation of NOX2, a source of reactive oxygen species expressed predominantly in the microglia (Adeluyi et al., 2019). Inhibition of microglia has also been generally reported to attenuate behavioral effects of psychostimulants. Thus, preventing microglia activation by blockade of toll like receptor 4 (TLR4) signaling and the downstream release of IL-1β attenuated conditioned place preference and self-administration of cocaine (Northcutt et al., 2015). Minocycline treatment has also been reported to attenuate both maintenance and reinstatement of methamphetamine-induced conditioned place preference (Fujita et al., 2012; Attarzadeh-Yazdi et al., 2014) as well as subjective rewarding effects of dextroamphetamine in human subjects (Sofuoglu et al., 2011). Clinical studies generally support the idea that microglial inhibition suppresses behavioral effects of commonly abused drugs (Bachtell et al., 2017), although some results argue against this (Arout et al., 2019). In preclinical work, locomotor sensitization to cocaine appears to break the pattern with findings that sensitization is suppressed by activated rather than inhibited microglia via release of TNFα (Lewitus et al., 2016) and findings that microglial depletion has no effect on cocaine sensitization (Wu and Lai, 2021). It is possible that microglial control of substance-use related behaviors is proportional to the level of stress response that accompanies experimental manipulations. This has been suggested in a recent review (McGrath and Briand, 2019) and is supported by findings that immune activation is required for microglial control of drug-related behavior (Warden et al., 2021).

4. Astrocyte control of circadian rhythmicity

In mammals, a specific nucleus of the hypothalamus, the SCN, acts as the master circadian pacemaker. Its function is required to drive daily rhythms in behavior, and lesions of the SCN abolish rhythms in mammals. Accordingly, in hamsters, transplanting an explant of the SCN into an SCN-lesioned animal restores circadian rhythms (Ralph et al., 1990). Of note, these rhythms have the same period as in the donor, indicating that they arise from cell-autonomous mechanisms present within the SCN (Ralph et al., 1990). This form of cell-autonomous rhythmicity is generated by two interlocking transcription/translation feedback loops

driven by four clock proteins: the activators CLOCK and BMAL1 and the repressors PER and CRY. CLOCK and BMAL1 activate the transcription of the *Per* and *Cry* genes. The proteins PER and CRY inhibit the transcriptional activation of CLOCK and BMAL1. As the proteins PER and CRY are degraded through ubiquitination, the repression of CLOCK and BMAL1 is relieved and the cycle begins again (Buhr and Takahashi, 2013; Partch et al., 2014). The period and phase with which these reactions take place can be modified and reset or entrained by cycles of light and darkness in the environment. Light contributes to reset circadian clocks through the activation of retino-hypothalamic (RHT) glutamatergic inputs to the SCN that, according to studies of changes in the expression of the immediate early gene c-Fos, can activate both neurons and astrocytes (Rea, 1989; Bennett and Schwartz, 1994).

The components of the molecular machinery regulating clock gene expression in mammals were first characterized in hamster neurons. Multiple groups hypothesized that astrocytes may also contribute and perhaps drive circadian rhythmicity in the SCN and experimental evidence showing that astrocytes express clock genes and function as competent circadian oscillators arrived with the use of reporter gene constructs (Prolo et al., 2005; Yagita et al., 2010). The identification of clock genes in astrocytes puts these cells under the spotlight and suggests that these cells are not mere modulators or targets of neuronal pacemakers, but they can act in conjunction with neurons to establish circadian rhythms (Prolo et al., 2005). One should note, however, that the level of expression of clock genes in astrocytes is substantially lower or more diffuse than in neurons, making it perhaps more difficult to detect (Prolo et al., 2005). This might have delayed the due recognition of astrocytes in the circadian pacemaker process, despite the early work demonstrating an essential role of astrocytes for the proper function of the circadian clock (Serviere and Lavialle, 1996; van den Pol et al., 1992; Shinohara et al., 2000; Prosser et al., 1994). There is now a growing awareness that just like the number of a given cell type does not speak to the relevance of its function, the lower expression of clock genes in astrocytes is not a measure of their physiological relevance in the generation and maintenance of circadian rhythms.

How do astrocytes contribute to the pacemaker activity of the SCN? In 1993, Lavialle and Serviere first reported that, in hamsters, there are light-independent (circadian) changes in the spatial distribution of the astrocyte protein GFAP and in astrocyte morphology, suggesting that these cells undergo circadian structural remodeling (Lavialle and Serviere, 1993). Since astrocyte remodeling is associated with changes in glucose consumption (Lavialle and Serviere, 1993; Schwartz and Gainer, 1977), and astrocytes are main sources of glycogen, these findings have been thought to reflect the participation of astrocytes in the regulation of energy metabolism (Lavialle and Serviere, 1993; Brown and Ransom, 2007). However, due to their abundant expression of glutamate transporters (Lehre and Danbolt, 1998), a retraction of astrocyte processes could also imply a longer time for glutamate clearance from the extracellular space (Sweeney et al., 2017). This, in turn, could alter the time course of glutamatergic transmission at RHT synapses onto the SCN without the need for altering glutamate transporter expression in these cells (Beaule et al., 2009). The structural remodeling of astrocytes has been shown to account for circadian changes in the glial coverage of the soma and dendrites of VIP and AVP neurons in the SCN implicated with clock entrainment and pacemaker resetting, respectively (Becquet et al., 2008; Herzog et al., 2017). Despite these findings, there are still uncertainties about the implications that the remodeling of astrocytes in the SCN has for glutamate clearance, synaptic plasticity, and metabolic exchange (Serviere and Lavialle, 1996). What has emerged in recent years, however, is that SCN astrocytes are not mere followers but rather partners in crime with the neuronal circadian pacemaker machinery (Brancaccio et al., 2017). Neurons are metabolically active during circadian daytime. Astrocytes, instead, are active during circadian nighttime and suppress neuronal activity by regulating extracellular glutamate concentration and activation of GluN2C-containing NMDA receptors. More importantly, astrocytes in the SCN can instruct neurons without a competent molecular clock to initiate and sustain circadian patterns of activity (Brancaccio et al., 2019).

4.1. Astrocytes and circadian clocks outside the SCN

The first demonstration that astrocytes are competent circadian oscillators came from luciferase assay studies in rat cultures (Prolo et al., 2005). This work was important for several reasons that we would like to reiterate. *First,* it showed that the circadian period of astrocytes is genetically determined and differs between mice and rats, in parallel with period differences in the locomotor behavior of these species, potentially reconciling experimental differences detected when working with experimental preparations from different rodent species. *Second,* it showed that the expression of clock genes like *Per1* is substantially lower or more diffuse in astrocytes than in neurons, potentially explaining initial difficulties in detectability of clock genes in astrocytes. *Third,* it showed that, in vitro, the circadian rhythms of astrocytes are not detected before the first week of culture. This is in stark contrast with the in vitro developmental timeline of cultured neurons, which display circadian rhythmicity earlier. This finding may provide insights into the different developmental profiles of circadian clocks in neurons and astrocytes in vivo (Welsh et al., 1995). *Last,* and arguably most importantly, the cultured astrocytes used in this work did not derive from the SCN but from the cortex, suggesting that regions of the brain outside the SCN can act as auxiliary, ancillary or accessory circadian oscillators.

Accordingly, the core circadian molecular machinery of astrocytes has been characterized in several regions of the nervous system (e.g., retina, olfactory bulb and hippocampus) and even outside the brain (e.g., cultured fibroblasts, hepatocytes, leukocytes, adipocytes, and muscle cells) (Tosini and Menaker, 1996; Ruby et al., 1999; Herzog and Huckfeldt, 2003; Izumo et al., 2003; Granados-Fuentes et al., 2004; Granados-Fuentes et al., 2004; Lavery et al., 1999; Arjona and Sarkar, 2005; Du et al., 2005; Durgan et al., 2005; Chalmers et al., 2008). Although cells in these tissues can display intrinsic circadian rhythms, each of them would run at its own pace, desynchronize, and dampen population rhythms without SCN activity. This contrasts with what happens in the SCN, where neurons and astrocytes synchronize to each other (Pando et al., 2002; Balsalobre et al., 2000; Yamazaki et al., 2000; Silver et al., 1996; Aton and Herzog, 2005; Nagoshi et al., 2004; Welsh et al., 2004; Carr and Whitmore, 2005). Several studies have attempted to reveal the identity of paracrine signals capable of synchronizing neuronal and astrocytes rhythms in auxiliary circadian oscillators (i.e., regions that express clock genes, but follow the timekeeping system set by the SCN). One of the first ones to be identified was the peptide hormone VIP, which coordinates circadian rhythms among astrocytes where VIP is released and where its receptor VPAC2R is expressed, like the olfactory bulb, retina, and the neocortex (Marpegan et al., 2009; Gall et al., 1986; Sims et al., 1980; Okamoto et al., 1992). Although the VIP/VPAC2R signaling pathway dominates circadian rhythmicity, other signaling pathways like the AVP/$V1_{a/b}$ and the GRP/ BB2 can also sustain daily cycling (Maywood et al., 2011).

4.2. Astrocytes and circadian clocks in the hippocampus

Clock genes are expressed in the hippocampus, a brain region involved in encoding spatial and episodic memories (Chun et al., 2015). Recent work has shown that not only clock genes, but also a larger set of hippocampal genes (10%) and proteins (11%) are expressed with circadian rhythmicity (cf. 19% in the SCN) (Debski et al., 2020). These oscillations in the molecular landscape of the hippocampus are altered in experimental temporal lobe epilepsy (Debski et al., 2020), which is of particular interest given that seizure onsets within individuals display strong circadian rhythmicity (Quigg et al., 1998).

In vivo behavioral studies indicate that lesioning the SCN eliminates circadian rhythmicity in a passive avoidance task (Stephan and Kovacevic, 1978), and desynchronization of the circadian system impairs

recall of a spatial task (Devan et al., 2001). More specific tests on hippocampal-dependent learning and memory show that these vary between the circadian daytime and nighttime (Gerstner et al., 2009; Ruby et al., 2008; Shimizu et al., 2016; Smarr et al., 2014; Snider et al., 2016; Rawashdeh et al., 2018). The work of Chaudhury et al. is particularly important in this context as it shows that there is a circadian regulation of memory acquisition, recall and extinction in mice tested using a fear conditioning protocol (Chaudhury and Colwell, 2002).

These periodical variations in hippocampal function can also be detected using in vivo electrophysiology recordings, although there are some differences in the results reported in the literature. Early studies in the dentate gyrus showed that the field EPSP and population spike amplitude are larger during the active phase (nighttime for rodents) (Barnes et al., 1977). Potentiation of the field EPSP amplitude, but not of the population spike amplitude, was confirmed in a later study (Caulller et al., 1985). Others also showed that the dentate gyrus is more excitable during the inactive phase (daytime for rodents) (West and Deadwyler, 1980). When reviewing these findings, it is important to keep in mind that the results are sometimes described by comparing two clock times which can be misleading, since circadian rhythmicity is a phenomenon with a sinusoidal profile. The use of two points forces linearization which makes the comparison across datasets collected from different laboratories difficult, if not inaccurate, especially when the two time points are not twelve hours apart from each other (i.e., half the period of a circadian cycle) or when different labs use different reference times. This is important because it can lead to opposite conclusions about whether the described phenomenon increases or decreases during daytime/nighttime.

Perhaps surprisingly, there are circadian changes in hippocampal function that are retained in reduced slice preparations. These show that the incidence and magnitude of long-term potentiation (LTP) varies with opposite phase in the dentate gyrus versus hippocampal area CA1, and may therefore shape in different ways the activity of synapses in different domains of the same brain region (Harris and Teyler, 1983). Until recently, the synaptic mechanisms accounting for this effect remained unknown. What has now emerged is that these circadian changes in synaptic plasticity are differentially regulated by neurons and astrocytes (McCauley et al., 2020). During the nighttime, when LTP is reduced in hippocampal area CA1, pyramidal cells reduce their surface pool of functional NMDA receptors (McCauley et al., 2020). At the same time, glutamate clearance from astrocytes becomes slower, due to a retraction of astrocytic processes enriched with glutamate transporters from synapses, similar to what has also been observed in the SCN (Lavialle and Serviere, 1993). Glutamate inactivates AMPA receptors, and the longer glutamate remains in the extracellular space, the longer it takes for these receptors to recover from inactivation (McCauley et al., 2020). This has implications for synaptic integration of EPSPs, which is impaired during nighttime in CA1 pyramidal cells. The diffusible agent mediating these effects is not D-serine, because there are no detectable circadian changes in the occupancy of the NMDA receptor glycine binding site (McCauley et al., 2020; Papouin et al., 2017). It is likely corticosterone, whose peak production time is during the active phase (i.e., nighttime for mice) (McCauley et al., 2020; Diotel et al., 2018). Accordingly, one can rescue the loss of NMDA receptors and synaptic integration in slices prepared during the nighttime by treating them with antagonists of NR3C1/2 mineralocorticoid and glucocorticoid receptors (McCauley et al., 2020). What is also notable from this work is the fact that the magnitude of the circadian changes in synaptic integration are frequency dependent and are most pronounced for stimulation frequencies that can be detected in vivo during exploratory behaviors (Colgin et al., 2009; Zheng et al., 2016). In other words, circadian rhythms do not alter hippocampal activity as a whole: rather, they modulate hippocampal-dependent learning while preserving memory recall.

Together, these findings suggest that in a subordinate oscillator like the hippocampus, the circadian changes in gene and protein expression may change the rules of synaptic plasticity, but the direction and extent of these changes vary not only across but also within brain regions, in cell-specific ways. On the other hand, different sets of cells can be active to mediate the same behavior at different times (Lamothe-Molina et al., 2020). The ultimate effect of circadian clocks on more complex phenomena and behaviors may be activity-dependent, adding additional levels of complexity. Perhaps, our attempts to draw general rules on the functional properties of the brain, has led us to underestimate how dynamic this organ is and how profoundly our circadian clock can shape what we think we can always do well.

4.3. Astrocytes and sleep/wake cycles

The earliest evidence that astrocyte activity impacts sleep homeostasis came from a 2009 publication showing that mice with astrocytic dnSNARE expression show decreased extracellular accumulation of adenosine, a molecule that in wild type mice promotes sleep and increases sleep pressure, also observed with sleep deprivation (Halassa et al., 2009). These findings implicated astrocyte-derived adenosine and A1 adenosine receptor activation as the factors underlying these behavioral effects, because pharmacological, in vivo blockade of A1 receptors attenuated sleep pressure accumulation in these mice (Halassa et al., 2009). The majority of extracellular adenosine is derived from metabolism of ATP and astrocytes have been recognized as a major source of extracellular ATP (Boison et al., 2010). In addition to these findings, Papouin et al. (2017) showed that D-serine levels oscillate in the hippocampus as a function of wakefulness, not of circadian rhythms (Papouin et al., 2017). This causes saturation of the NMDA receptor glycine binding site during wakefulness, that wanes during sleep. Activation of Ca^{2+}-permeable α7-nicotinic acetylcholine receptors via septal cholinergic afferents to the hippocampus is thought to be the trigger for D-serine release from astrocytes during wakefulness (Papouin et al., 2017). Consistent with these findings, recent Ca^{2+} fiber photometry data show that Ca^{2+} levels in astrocytes increase during wakefulness and decrease during REM sleep in different brain regions including the cortex, hippocampus, hypothalamus, pons and cerebellum(Tsunematsu et al., 2021; Bojarskaite et al., 2020; Ingiosi et al., 2020). However, the magnitude of these oscillations and the detailed Ca^{2+} dynamics change between astrocytes in the: *(i)* cortex and hippocampus; *(ii)* hypothalamus and pons; *(iii)* cerebellum (Tsunematsu et al., 2021). These findings suggest that astrocytes may contribute differently to the regulation of sleep and wakefulness, depending on the brain region (Tsunematsu et al., 2021). The emerging evidence in support of brain region-specific patterns of astrocyte gene expression(Chai et al., 2017; Batiuk et al., 2020; Zeisel et al., 2018; Bayraktar et al., 2020) may help in identification of molecular drivers underlying such divergent functional and behavioral outcomes.

4.4. Microglia involvement in circadian rhythms

Isolated microglia display intrinsic daily fluctuations of circadian clock genes, *Bmal1, Rev-erb, Per1,* and *Per2* (Fonken et al., 2016*)* with inflammatory factors, TNFα, IL-1β, and IL6 oscillating in phase with *Per1* and *Per2* and in anti-phase with *Rev-erb* (Fonken et al., 2015*)*. Dysregulated *Per1* and *Per2* expression in aged animals has been associated with elevated TNFα and IL-1β mRNA expression (Fonken et al., 2016) linking circadian rhythms with evidence of microglial contribution to age-related neurodegeneration (Graykowski and Cudaback, 2021). Moreover, daily microglial cytokine fluctuations may underlie increased sensitivity of neuroinflammatory response to stimulation by lipopolysaccharide during the resting (sleep) phase (Fonken et al., 2015) with the implication that therapeutic efficacy of inflammation-focused treatments may be improved by alignment to daily sleep/wake cycles. The link between microglial immunoreactivity and circadian rhythms is further borne out in studies that reduce or eliminate clock gene expression, although the direction of gene regulation differs between

reports. For example, elevated levels of IL-1β and TNFα have been reported in striatal microglia of *Bmal1* knock-out mice with further elevation after challenge with LPS or treatment with MPTH, a model of Parkinsonian neurodegeneration (Liu et al., 2020). Elevated levels of IL-1β, IL-6 and TNFα have also been reported in the *Rev-erba* knock-out model (Griffin et al., 2019). However, in homogenized brain tissue, *Bmal1* deletion was seen to decrease expression of IL-1β and inflammation-related gene, *Nox2* (Wang et al., 2020), highlighting potential influence of region-specific differences in microglial response to *Bmal1* deletion.

4.5. Microglia involvement in sleep/wake cycles

It is well-documented and, indeed, accepted as common knowledge that disrupted sleep leads to a range of adverse psychological and physiological consequences. Evidence of microglial activation caused by sleep fragmentation (Xie et al., 2020) is consistent with this line of reasoning although it is possible that fragmented sleep may arise secondary to other conditions (e.g., depression, drug use) associated with microglial pathologies. Supporting the former contention, depleting microglia by activating the diphtheria toxin receptor under the Cx3cr1 promoter in a transgenic rat model, resulted in disrupted expression of clock genes *Per1, Per2*, and *Bmal1* in the SCN and the hippocampus, abnormal circadian body temperature, and diurnal rhythm disruptions (Sominsky et al., 2021). Systemic ablation of microglia following PLX-5622 treatment was reported to increase sleep duration and eliminate light phase-dependent difference in synaptic transmission in mouse hippocampal CA1 pyramidal neurons (Corsi et al., 2021). In the healthy brain, microglial morphology fluctuates in rhythm with circadian cycles with longer processes and branching points during wakefulness, phenomena dependent on microglial expression of lysosomal cysteine protease cathepsin S and the adenosine diphosphate, P2Y12 receptors (Nakanishi et al., 2021; Hayashi et al., 2013). Microglial morphology may also be generally sensitive to arousal states with increased arborization of processes and increased process motility observed following anesthesia relative to wakeful conditions (Stowell et al., 2019). Partial activation of microglia during sleep may contribute to synapse elimination, suggesting an intriguing mechanism for the role of sleep in memory consolidation (Choudhury et al., 2020). Indeed, sleep deprivation-induced memory impairments on a Morris water maze could be rescued in rats treated with minocycline (Wadhwa et al., 2017). Minocycline treatment has also been reported to increase slow-wave activity during sleep and improve episodic memory in human subjects (Besedovsky et al., 2017), although others have found sleep disruption by minocycline in both human (Nonaka et al., 1983) and rodent (Wisor and Clegern, 2011; Wisor et al., 2011) studies. Notably, minocycline effects on sleep are unlikely due to its antibiotic activity as ampicillin treatment was not seen to impact sleep homeostasis (Nonaka et al., 1983).

5. Concluding remarks

The emerging picture of structural and functional diversity of glial cells across distinct brain regions suggests co-existence of multiple mechanisms by which glial cells regulate neuronal activity. The diversity of mechanisms likely reflects unique physiological and computational demands placed upon circuits underlying specific behavioral outputs (Table 1). Within brain regions, dynamic glial cell responses to external perturbations, circadian rhythms or other internal changes are echoed by the flexible, adaptive nature of many behaviors. Understanding the functional roles of a molecularly diverse populations of glial cells will advance not only our knowledge of the mechanisms by which these cells control executive function, reward seeking, and circadian function, but will also shed light on phenomenology of a variety of neurodegenerative, substance use, and other disorders. The unique molecular signatures of glial cells make them attractive candidates for development of new therapeutics. Future studies utilizing single cell transcriptomics may shed light on region- and cell-type selective targets for use in both psychiatric and neurological disorders.

Acknowledgements

A.S. NSF, IOS1655365, IOS2011998. P.I.O. NIH, DA04041513, DA053070. J.T. NIH, DA044311, DA053070. K.J.R. NIH, DA041455, DA052447.

References

Kandel, E.R., 2013. Principles of Neural Science, Fifth ed.,. McGraw-Hill, New York, p. 1709.
Virchow, R.R.L.K., Gesammelte Abhandlungen zur Wissenschaftlichen Medicin / von Rudolf Virchow. 1856, University of Glasgow: University of Glasgow.
Parpura, V., Verkhratsky, A., 2012. Neuroglia at the crossroads of homoeostasis, metabolism and signalling: evolution of the concept. ASN Neuro 4 (4), 201–205.
Verkhratsky, A., Parpura, V., Rodriguez, J.J., 2011. Where the thoughts dwell: the physiology of neuronal-glial "diffuse neural net". Brain Res. Rev. 66 (1–2), 133-51.
von Bartheld, C.S., Bahney, J., Herculano-Houzel, S., 2016. The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting. J. Comp. Neurol. 524 (18), 3865–3895.
Pelvig, D.P., et al., 2008. Neocortical glial cell numbers in human brains. Neurobiol. Aging 29 (11), 1754-62.
Hyden, H., Pigon, A., 1960. A cytophysiological study of the functional relationship between oliodendroglial cells and nerve cells of Deiters' nucleus. J. Neurochem 6, 57–72.
Blinkov, S.M.l. and I.i.a.I.. Glezer, The human brain in figures and tables; a quantitative handbook. 1968, New York: Basic Books. xxxii, 482 p.
Haug, H., 1986. History of neuromorphometry. J. Neurosci. Methods 18 (1–2), 1–17.
Brachet, J., Mirsky, A.E., 1959. The cell: biochemistry. Physiology, Morphology. Academic Press, New York.
Hyden, H., 1967. In: Hyden, H. (Ed.), Dynamic aspects of the neuron-glia relationship—A study with microchemical methods., in The Neuron. Elsevier, Netherlands, pp. 179–217.
von Bartheld, C.S., 2018. Myths and truths about the cellular composition of the human brain: a review of influential concepts. J. Chem. Neuroanat. 93, 2–15.
Azevedo, F.A., et al., 2009. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J. Comp. Neurol. 513 (5), 532-41.
Herculano-Houzel, S., Lent, R., 2005. Isotropic fractionator: a simple, rapid method for the quantification of total cell and neuron numbers in the brain. J. Neurosci. 25 (10), 2518–2521.
Miller, D.J., et al., 2014. Three counting methods agree on cell and neuron number in chimpanzee primary visual cortex. Front Neuroanat. 8, 36.
Hawkins, A., Olszewski, J., 1957. Glia/nerve cell index for cortex of the whale. Science 126 (3263), 76–77.
Herculano-Houzel, S., 2014. The glia/neuron ratio: how it varies uniformly across brain structures and species and what that means for brain physiology and evolution. Glia 62 (9), 1377–1391.
Keller, D., Ero, C., Markram, H., 2018. Cell densities in the mouse brain: a systematic review. Front Neuroanat. 12, 83.
Oberheim, N.A., et al., 2006. Astrocytic complexity distinguishes the human brain. Trends Neurosci. 29 (10), 547-53.
Oberheim, N.A., et al., 2009. Uniquely hominid features of adult human astrocytes. J. Neurosci. 29 (10), 3276–3287.
Chai, H., et al., 2017. Neural circuit-specialized astrocytes: transcriptomic, proteomic, morphological, and functional evidence. Neuron 95 (3), 531–549 e9.
Morel, L., et al., 2017. Molecular and functional properties of regional astrocytes in the adult brain. J. Neurosci. 37 (36), 8706–8717.
Boisvert, M.M., et al., 2018. The aging astrocyte transcriptome from multiple regions of the mouse brain. Cell Rep. 22 (1), 269–285.
Lalo, U., et al., 2021. The tripartite glutamatergic synapse. Neuropharmacology 199, 108758.
Semyanov, A., Verkhratsky, A., 2021. Astrocytic processes: from tripartite synapses to the active milieu. Trends Neurosci. 44 (10), 781–792.
Ferro, A., Auguste, Y.S.S., Cheadle, L., 2021. Microglia, cytokines, and neural activity: unexpected interactions in brain development and function. Front Immunol. 12, 703527.
Xin, W., et al., 2019. Ventral midbrain astrocytes display unique physiological features and sensitivity to dopamine D2 receptor signaling. Neuropsychopharmacology 44 (2), 344–355.
Khakh, B.S., Deneen, B., 2019. The emerging nature of astrocyte diversity. Annu Rev. Neurosci. 42, 187–207.
Yu, X., et al., 2020. Context-specific striatal astrocyte molecular responses are phenotypically exploitable. Neuron 108 (6), 1146–1162 e10.
Brockett, A.T., et al., 2018. Evidence supporting a role for astrocytes in the regulation of cognitive flexibility and neuronal oscillations through the Ca2+ binding protein S100beta. PLoS One 13 (4), e0195726.
Lima, A., et al., 2014. Astrocyte pathology in the prefrontal cortex impairs the cognitive function of rats. Mol. Psychiatry 19 (7), 834-41.

Banasr, M., Duman, R.S., 2008. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. Biol. Psychiatry 64 (10), 863–870.
Lee, Y., et al., 2013. Glutamine deficiency in the prefrontal cortex increases depressive-like behaviours in male mice. J. Psychiatry Neurosci. 38 (3), 183–191.
Duman, R.S., 2009. Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: stress and depression. Dialog-. Clin. Neurosci. 11 (3), 239–255.
Luscher, C., Malenka, R.C., 2011. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron 69 (4), 650-63.
McBean, G.J., 1994. Inhibition of the glutamate transporter and glial enzymes in rat striatum by the gliotoxin, alpha aminoadipate. Br. J. Pharm. 113 (2), 536–540.
Khurgel, M., Koo, A.C., Ivy, G.O., 1996. Selective ablation of astrocytes by intracerebral injections of alpha-aminoadipate. Glia 16 (4), 351–358.
Zamanian, J.L., et al., 2012. Genomic analysis of reactive astrogliosis. J. Neurosci. 32 (18), 6391-410.
Lin, R.C., et al., 1995. Re-expression of the intermediate filament nestin in reactive astrocytes. Neurobiol. Dis. 2 (2), 79–85.
Krum, J.M., Rosenstein, J.M., 1999. Transient coexpression of nestin, GFAP, and vascular endothelial growth factor in mature reactive astroglia following neural grafting or brain wounds. Exp. Neurol. 160 (2), 348–360.
Wilhelmsson, U., et al., 2019. The role of GFAP and vimentin in learning and memory. Biol. Chem. 400 (9), 1147–1156.
Avigan, P.D., Cammack, K., Shapiro, M.L., 2020. Flexible spatial learning requires both the dorsal and ventral hippocampus and their functional interactions with the prefrontal cortex. Hippocampus 30 (7), 733–744.
Wilhelmsson, U., et al., 2020. Nestin null mice show improved reversal place learning. Neurochem Res. 45 (1), 215–220.
Rajkowska, G., et al., 2002. Layer-specific reductions in GFAP-reactive astroglia in the dorsolateral prefrontal cortex in schizophrenia. Schizophr. Res 57 (2–3), 127-38.
Martin, R., et al., 2015. Circuit-specific signaling in astrocyte-neuron networks in basal ganglia pathways. Science 349 (6249), 730–734.
Lavialle, M., et al., 2011. Structural plasticity of perisynaptic astrocyte processes involves ezrin and metabotropic glutamate receptors. Proc. Natl. Acad. Sci. USA 108 (31), 12915–12919.
Zhou, Y., et al., 2014. EAAT2 (GLT-1; slc1a2) glutamate transporters reconstituted in liposomes argues against heteroexchange being substantially faster than net uptake. J. Neurosci. 34 (40), 13472-85.
Ortinski, P.I., et al., 2010. Selective induction of astrocytic gliosis generates deficits in neuronal inhibition. Nat. Neurosci. 13 (5), 584-91.
Spangaro, M., et al., 2012. Cognitive dysfunction and glutamate reuptake: effect of EAAT2 polymorphism in schizophrenia. Neurosci. Lett. 522 (2), 151–155.
Roberts-Wolfe, D.J., Kalivas, P.W., 2015. Glutamate transporter GLT-1 as a therapeutic target for substance use disorders. CNS Neurol. Disord. Drug Targets 14 (6), 745–756.
Meeker, K.D., Meabon, J.S., Cook, D.G., 2015. Partial loss of the glutamate transporter GLT-1 alters brain akt and insulin signaling in a mouse model of Alzheimer's disease. J. Alzheimers Dis. 45 (2), 509-20.
Scimemi, A., et al., 2013. Amyloid-beta1-42 slows clearance of synaptically released glutamate by mislocalizing astrocytic GLT-1. J. Neurosci. 33 (12), 5312–5318.
Kobayashi, E., et al., 2018. Activated forms of astrocytes with higher GLT-1 expression are associated with cognitive normal subjects with Alzheimer pathology in human brain. Sci. Rep. 8 (1), 1712.
Karlsson, R.M., et al., 2009. Assessment of glutamate transporter GLAST (EAAT1)-deficient mice for phenotypes relevant to the negative and executive/cognitive symptoms of schizophrenia. Neuropsychopharmacology 34 (6), 1578-89.
John, C.S., et al., 2012. Blockade of astrocytic glutamate uptake in the prefrontal cortex induces anhedonia. Neuropsychopharmacology 37 (11), 2467–2475.
Featherstone, R.E., et al., 2012. Subchronic ketamine treatment leads to permanent changes in EEG, cognition and the astrocytic glutamate transporter EAAT2 in mice. Neurobiol. Dis. 47 (3), 338–346.
Scimemi, A., et al., 2004. NR2B-containing receptors mediate cross talk among hippocampal synapses. J. Neurosci. 24 (20), 4767–4777.
Nie, H., Weng, H.R., 2009. Glutamate transporters prevent excessive activation of NMDA receptors and extrasynaptic glutamate spillover in the spinal dorsal horn. J. Neurophysiol. 101 (4), 2041-51.
Ortinski, P.I., Turner, J.R., Pierce, R.C., 2013. Extrasynaptic targeting of NMDA receptors following D1 dopamine receptor activation and cocaine self-administration. J. Neurosci. 33 (22), 9451–9461.
Pascual, O., et al., 2005. Astrocytic purinergic signaling coordinates synaptic networks. Science 310 (5745), 113–116.
Fujita, T., et al., 2014. Neuronal transgene expression in dominant-negative SNARE mice. J. Neurosci. 34 (50), 16594-604.
Durkee, C., et al., 2021. Astrocyte and neuron cooperation in long-term depression. Trends Neurosci. 44 (10), 837–848.
Halassa, M.M., et al., 2009. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61 (2), 213–219.
Poskanzer, K.E., Yuste, R., 2016. Astrocytes regulate cortical state switching in vivo. Proc. Natl. Acad. Sci. USA 113 (19), E2675–E2684.
Sardinha, V.M., et al., 2017. Astrocytic signaling supports hippocampal-prefrontal theta synchronization and cognitive function. Glia 65 (12), 1944–1960.
Henneberger, C., et al., 2010. Long-term potentiation depends on release of D-serine from astrocytes. Nature 463 (7278), 232–236.
Deng, Q., et al., 2011. Astrocytic activation of A1 receptors regulates the surface expression of NMDA receptors through a Src kinase dependent pathway. Glia 59 (7), 1084–1093.
Wirkner, K., et al., 2007. Modulation of NMDA receptor current in layer V pyramidal neurons of the rat prefrontal cortex by P2Y receptor activation. Cereb. Cortex 17 (3), 621-31.
Fellin, T., et al., 2004. Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors. Neuron 43 (5), 729-43.
Henneberger, C., et al., 2020. LTP induction boosts glutamate spillover by driving withdrawal of perisynaptic astroglia. Neuron 108 (5), 919–936 e11.
Ortinski, P.I., 2014. Cocaine-induced changes in NMDA receptor signaling. Mol. Neurobiol. 50 (2), 494–506.
O'Donovan, B., et al., 2021. Cocaine experience induces functional adaptations in astrocytes: Implications for synaptic plasticity in the nucleus accumbens shell. Addict. Biol., e13042
Yoon, B.E., Lee, C.J., 2014. GABA as a rising gliotransmitter. Front Neural Circuits 8, 141.
Mederos, S., et al., 2021. GABAergic signaling to astrocytes in the prefrontal cortex sustains goal-directed behaviors. Nat. Neurosci. 24 (1), 82–92.
Perea, G., et al., 2014. Optogenetic astrocyte activation modulates response selectivity of visual cortex neurons in vivo. Nat. Commun. 5, 3262.
Fiacco, T.A., McCarthy, K.D., 2018. Multiple lines of evidence indicate that gliotransmission does not occur under physiological conditions. J. Neurosci. 38 (1), 3–13.
Savtchouk, I., Volterra, A., 2018. Gliotransmission: beyond black-and-white. J. Neurosci. 38 (1), 14–25.
Khakh, B.S., McCarthy, K.D., 2015. Astrocyte calcium signaling: from observations to functions and the challenges therein. Cold Spring Harb. Perspect. Biol. 7 (4), a020404.
Semyanov, A., Henneberger, C., Agarwal, A., 2020. Making sense of astrocytic calcium signals - from acquisition to interpretation. Nat. Rev. Neurosci. 21 (10), 551–564.
Neugornet, A., O'Donovan, B., Ortinski, P.I., 2021. Comparative effects of event detection methods on the analysis and interpretation of Ca(2+) imaging data. Front Neurosci. 15, 620869.
Bissonette, G.B., et al., 2010. Astrocyte-mediated hepatocyte growth factor/scatter factor supplementation restores GABAergic interneurons and corrects reversal learning deficits in mice. J. Neurosci. 30 (8), 2918–2923.
Diaz, A., et al., 2017. A cross talk between neuronal urokinase-type plasminogen activator (uPA) and astrocytic uPA receptor (uPAR) promotes astrocytic activation and synaptic recovery in the ischemic brain. J. Neurosci. 37 (43), 10310–10322.
Webb, T.R., et al., 2012. X-linked megalocornea caused by mutations in CHRDL1 identifies an essential role for ventroptin in anterior segment development. Am. J. Hum. Genet 90 (2), 247-59.
Blanco-Suarez, E., et al., 2018. Astrocyte-secreted chordin-like 1 drives synapse maturation and limits plasticity by increasing synaptic GluA2 AMPA receptors. Neuron 100 (5), 1116–1132 e13.
Wolf, M.E., Tseng, K.Y., 2012. Calcium-permeable AMPA receptors in the VTA and nucleus accumbens after cocaine exposure: when, how, and why? Front Mol. Neurosci. 5, 72.
Galloway, A., et al., 2018. Dopamine triggers CTCF-dependent morphological and genomic remodeling of astrocytes. J. Neurosci. 38 (21), 4846–4858.
Sofroniew, M.V., 2014. Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. Neuroscientist 20 (2), 160–172.
Caudal, L.C., et al., 2020. The paradox of astroglial Ca(2 +) signals at the interface of excitation and inhibition. Front Cell Neurosci. 14, 609947.
Heyser, C.J., et al., 1997. Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain. Proc. Natl. Acad. Sci. USA 94 (4), 1500–1505.
Booth, H.D.E., Hirst, W.D., Wade-Martins, R., 2017. The role of astrocyte dysfunction in Parkinson's disease pathogenesis. Trends Neurosci. 40 (6), 358–370.
Khakh, B.S., et al., 2017. Unravelling and exploiting astrocyte dysfunction in Huntington's disease. Trends Neurosci. 40 (7), 422–437.
Carter, S.F., et al., 2019. Astrocyte biomarkers in Alzheimer's disease. Trends Mol. Med. 25 (2), 77–95.
Brambilla, R., 2019. The contribution of astrocytes to the neuroinflammatory response in multiple sclerosis and experimental autoimmune encephalomyelitis. Acta Neuropathol. 137 (5), 757–783.
Pekny, M., et al., 2019. Astrocyte activation and reactive gliosis-a new target in stroke? Neurosci. Lett. 689, 45–55.
Burda, J.E., Bernstein, A.M., Sofroniew, M.V., 2016. Astrocyte roles in traumatic brain injury. Exp. Neurol. 275 (Pt 3), 305–315.
Rodriguez-Arellano, J.J., et al., 2016. Astrocytes in physiological aging and Alzheimer's disease. Neuroscience 323, 170–182.
Cohen, J., Torres, C., 2019. Astrocyte senescence: evidence and significance. Aging Cell 18 (3), e12937.
Veniaminova, E., et al., 2020. Prefrontal cortex inflammation and liver pathologies accompany cognitive and motor deficits following Western diet consumption in non-obese female mice. Life Sci. 241, 117163.
Val-Laillet, D., et al., 2020. A maternal Western diet during gestation and lactation modifies offspring's microglial cell density and morphology in the hippocampus and prefrontal cortex in Yucatan minipigs. Neurosci. Lett. 739, 135395.
Bocarsly, M.E., et al., 2015. Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. Proc. Natl. Acad. Sci. USA 112 (51), 15731–15736.
De Biase, L.M., et al., 2017. Local cues establish and maintain region-specific phenotypes of basal ganglia microglia. Neuron 95 (2), 341–356 e6.
Butovsky, O., Weiner, H.L., 2018. Microglial signatures and their role in health and disease. Nat. Rev. Neurosci. 19 (10), 622–635.

Rosenblat, J.D., McIntyre, R.S., 2015. Are medical comorbid conditions of bipolar disorder due to immune dysfunction? Acta Psychiatr. Scand. 132 (3), 180–191.
Lin, S.P., et al., 2021. Clinical treatment options and randomized clinical trials for neurocognitive complications of HIV Infection: combination antiretroviral therapy, central nervous system penetration effectiveness, and adjuvants. Curr. Top. Behav. Neurosci.
Kohno, M., et al., 2019. Neuroinflammation in addiction: a review of neuroimaging studies and potential immunotherapies. Pharm. Biochem Behav. 179, 34–42.
Bortolato, B., et al., 2016. Cognitive remission: a novel objective for the treatment of major depression? BMC Med. 14, 9.
Jeppesen, R., et al., 2020. Efficacy and safety of anti-inflammatory agents in treatment of psychotic disorders - a comprehensive systematic review and meta-analysis. Brain Behav. Immun. 90, 364–380.
Solmi, M., et al., 2017. Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia. CNS Spectr. 22 (5), 415–426.
Acharya, M.M., et al., 2016. Elimination of microglia improves cognitive function following cranial irradiation. Sci. Rep. 6, 31545.
Howard, R., et al., in Minocycline 200 mg or 400 mg versus placebo for mild Alzheimer's disease: the MADE Phase II, three-arm RCT. 2020: Southampton (UK).
Choi, Y., et al., 2007. Minocycline attenuates neuronal cell death and improves cognitive impairment in Alzheimer's disease models. Neuropsychopharmacology 32 (11), 2393–2404.
Daulatzai, M.A., 2016. Pharmacotherpy and Alzheimer's disease: the M-drugs (melatonin, minocycline, modafinil, and memantine) approach. Curr. Pharm. Des. 22 (16), 2411–2430.
Fessel, J., 2019. Prevention of Alzheimer's disease by treating mild cognitive impairment with combinations chosen from eight available drugs. Alzheimers Dement 5, 780–788.
Green, K.N., Crapser, J.D., Hohsfield, L.A., 2020. To kill a microglia: a case for CSF1R Inhibitors. Trends Immunol. 41 (9), 771–784.
McEwen, B.S., Morrison, J.H., 2013. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79 (1), 16–29.
Fogaca, M.V., Duman, R.S., 2019. Cortical GABAergic dysfunction in stress and depression: new insights for therapeutic interventions. Front Cell Neurosci. 13, 87.
Horchar, M.J., Wohleb, E.S., 2019. Glucocorticoid receptor antagonism prevents microglia-mediated neuronal remodeling and behavioral despair following chronic unpredictable stress. Brain Behav. Immun. 81, 329–340.
Hinwood, M., et al., 2013. Chronic stress induced remodeling of the prefrontal cortex: structural re-organization of microglia and the inhibitory effect of minocycline. Cereb. Cortex 23 (8), 1784–1797.
Liu, T., et al., 2021. Stress induces microglia-associated synaptic circuit alterations in the dorsomedial prefrontal cortex. Neurobiol. Stress 15, 100342.
Wohleb, E.S., et al., 2018. Stress-induced neuronal colony stimulating factor 1 provokes microglia-mediated neuronal remodeling and depressive-like behavior. Biol. Psychiatry 83 (1), 38–49.
Furuyashiki, T., 2012. Roles of dopamine and inflammation-related molecules in behavioral alterations caused by repeated stress. J. Pharm. Sci. 120 (2), 63–69.
Caetano, L., et al., 2017. Adenosine A2A receptor regulation of microglia morphological remodeling-gender bias in physiology and in a model of chronic anxiety. Mol. Psychiatry 22 (7), 1035–1043.
Duarte, J.M., et al., 2019. Region-specific control of microglia by adenosine A2A receptors: uncoupling anxiety and associated cognitive deficits in female rats. Glia 67 (1), 182–192.
Zhang, Y., et al., 2019. Deficiencies of microglia and TNFalpha in the mPFC-mediated cognitive inflexibility induced by social stress during adolescence. Brain Behav. Immun. 79, 256–266.
Li, H., Sagar, A.P., Keri, S., 2018. Microglial markers in the frontal cortex are related to cognitive dysfunctions in major depressive disorder. J. Affect Disord. 241, 305–310.
Rubin, L.H., et al., 2018. Microglial activation is inversely associated with cognition in individuals living with HIV on effective antiretroviral therapy. AIDS 32 (12), 1661–1667.
Giridharan, V.V., et al., 2020. Neuroinflammation trajectories precede cognitive impairment after experimental meningitis-evidence from an in vivo PET study. J. Neuroinflamm. 17 (1), 5.
Politis, M., et al., 2011. Microglial activation in regions related to cognitive function predicts disease onset in Huntington's disease: a multimodal imaging study. Hum. Brain Mapp. 32 (2), 258-70.
Polyzos, A.A., et al., 2019. Metabolic reprogramming in astrocytes distinguishes region-specific neuronal susceptibility in huntington mice. Cell Metab. 29 (6), 1258–1273 e11.
Khakh, B.S., 2019. Astrocyte-neuron interactions in the striatum: insights on identity, form, and function. Trends Neurosci. 42 (9), 617–630.
Xin, W., Bonci, A., 2018. Functional astrocyte heterogeneity and implications for their role in shaping neurotransmission. Front Cell Neurosci. 12, 141.
Batiuk, M.Y., et al., 2020. Identification of region-specific astrocyte subtypes at single cell resolution. Nat. Commun. 11 (1), 1220.
Clarke, B.E., et al., 2021. Regionally encoded functional heterogeneity of astrocytes in health and disease: a perspective. Glia 69 (1), 20–27.
Baker, D.A., et al., 2003. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. Nat. Neurosci. 6 (7), 743–749.
Knackstedt, L.A., Melendez, R.I., Kalivas, P.W., 2010. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. Biol. Psychiatry 67 (1), 81–84.
Scofield, M.D., et al., 2016. The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharm. Rev. 68 (3), 816–871.
Spencer, S., Kalivas, P.W., 2017. Glutamate transport: a new bench to bedside mechanism for treating drug abuse. Int J. Neuropsychopharmacol. 20 (10), 797–812.
Scofield, M.D., et al., 2016. Cocaine self-administration and extinction leads to reduced glial fibrillary acidic protein expression and morphometric features of astrocytes in the nucleus accumbens core. Biol. Psychiatry 80 (3), 207–215.
Testen, A., et al., 2018. Region-specific reductions in morphometric properties and synaptic colocalization of astrocytes following cocaine self-administration and extinction. Front Cell Neurosci. 12, 246.
Kruyer, A., et al., 2019. Heroin cue-evoked astrocytic structural plasticity at nucleus accumbens synapses inhibits heroin seeking. Biol. Psychiatry 86 (11), 811–819.
Siemsen, B.M., et al., 2019. Effects of methamphetamine self-administration and extinction on astrocyte structure and function in the nucleus accumbens core. Neuroscience 406, 528–541.
Sharpe, A., Trzeciak, M., Douglas, P., Beckstead, MJ., Repeated treatment with cocaine or methamphetamine increases CRF2 and decreases astrocytic markers in the ventral tegmental area and substantia nigra, in bioRxiv. 2019.
Bull, C., et al., 2015. Differential response of glial fibrillary acidic protein-positive astrocytes in the rat prefrontal cortex following ethanol self-administration. Alcohol Clin. Exp. Res. 39 (4), 650–658.
Kim, R., et al., 2018. Astroglial correlates of neuropsychiatric disease: From astrocytopathy to astrogliosis. Prog. Neuropsychopharmacol. Biol. Psychiatry 87 (Pt A), 126–146.
Healey, K.L., et al., 2020. Enduring alterations in hippocampal astrocytesynaptic proximity following adolescent alcohol exposure: reversal by gabapentin. Neural Regen. Res 15 (8), 1496–1501.
Erickson, E.K., et al., 2021. Cortical astrocytes regulate ethanol consumption and intoxication in mice. Neuropsychopharmacology 46 (3), 500–508.
Scofield, M.D., et al., 2015. Gq-DREADD selectively initiates glial glutamate release and inhibits cue-induced cocaine seeking. Biol. Psychiatry 78 (7), 441–451.
Bull, C., et al., 2014. Rat nucleus accumbens core astrocytes modulate reward and the motivation to self-administer ethanol after abstinence. Neuropsychopharmacology 39 (12), 2835-45.
Gomez, J.A., et al., 2019. Ventral tegmental area astrocytes orchestrate avoidance and approach behavior. Nat. Commun. 10 (1), 1455.
Kofuji, P., Araque, A., 2021. G-protein-coupled receptors in astrocyte-neuron communication. Neuroscience 456, 71–84.
Li, Y., et al., 2020. Activation of astrocytes in hippocampus decreases fear memory through adenosine A1 receptors. Elife **9**.
Martin-Fernandez, M., et al., 2017. Synapse-specific astrocyte gating of amygdala-related behavior. Nat. Neurosci. 20 (11), 1540–1548.
Corkrum, M., et al., 2020. Dopamine-evoked synaptic regulation in the nucleus accumbens requires astrocyte activity. Neuron 105 (6), 1036–1047 e5.
Ortinski, P.I., et al., 2015. Cocaine-seeking is associated with PKC-dependent reduction of excitatory signaling in accumbens shell D2 dopamine receptor-expressing neurons. Neuropharmacology 92, 80–89.
Briand, L.A., et al., 2014. Disruption of glutamate receptor-interacting protein in nucleus accumbens enhances vulnerability to cocaine relapse. Neuropsychopharmacology 39 (3), 759-69.
White, S.L., et al., 2016. A critical role for the GluA1 accessory protein, SAP97, in cocaine seeking. Neuropsychopharmacology 41 (3), 736–750.
Mizuno, G.O., et al., 2018. Aberrant calcium signaling in astrocytes inhibits neuronal excitability in a human down syndrome stem cell model. Cell Rep. 24 (2), 355–365.
Papouin, T., et al., 2017. Astrocytic control of synaptic function. Philos. Trans. R. Soc. Lond. B Biol. Sci. 372, 1715.
Newman, E.A., 2003. Glial cell inhibition of neurons by release of ATP. J. Neurosci. 23 (5), 1659-66.
Koizumi, S., et al., 2003. Dynamic inhibition of excitatory synaptic transmission by astrocyte-derived ATP in hippocampal cultures. Proc. Natl. Acad. Sci. USA 100 (19), 11023–11028.
Allen, N.J., Eroglu, C., 2017. Cell biology of astrocyte-synapse interactions. Neuron 96 (3), 697–708.
Corkrum, M., Araque, A., 2021. Astrocyte-neuron signaling in the mesolimbic dopamine system: the hidden stars of dopamine signaling. Neuropsychopharmacology 46 (11), 1864–1872.
Lipton, D.M., Gonzales, B.J., Citri, A., 2019. Dorsal striatal circuits for habits, compulsions and addictions. Front Syst. Neurosci. 13, 28.
Fouyssac, M., Belin, D., 2019. Beyond drug-induced alteration of glutamate homeostasis, astrocytes may contribute to dopamine-dependent intrastriatal functional shifts that underlie the development of drug addiction: a working hypothesis. Eur. J. Neurosci. 50 (6), 3014–3027.
Vandaele, Y., Ahmed, S.H., 2021. Habit, choice, and addiction. Neuropsychopharmacology 46 (4), 689–698.
Everitt, B.J., Robbins, T.W., 2016. Drug addiction: updating actions to habits to compulsions ten years on. Annu Rev. Psychol. 67, 23–50.
Kang, S., et al., 2020. Activation of astrocytes in the dorsomedial striatum facilitates transition from habitual to goal-directed reward-seeking behavior. Biol. Psychiatry 88 (10), 797–808.
Fuxe, K., et al., 2010. Adenosine-dopamine interactions in the pathophysiology and treatment of CNS disorders. CNS Neurosci. Ther. 16 (3), e18–e42.
Ferre, S., et al., 1997. Adenosine-dopamine receptor-receptor interactions as an integrative mechanism in the basal ganglia. Trends Neurosci. 20 (10), 482–487.
Ferre, S., et al., 1992. Adenosine-dopamine interactions in the brain. Neuroscience 51 (3), 501–512.
Boender, A.J., et al., 2021. Striatal astrocytes shape behavioral flexibility via regulation of the glutamate transporter EAAT2. Biol. Psychiatry 89 (11), 1045–1057.

Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic advances from the brain disease model of addiction. N. Engl. J. Med. 374 (4), 363-71.
Yu, X., et al., 2018. Reducing astrocyte calcium signaling in vivo alters striatal microcircuits and causes repetitive behavior. Neuron 99 (6), 1170–1187 e9.
Thomas Broome, S., et al., 2020. Dopamine: an immune transmitter. Neural Regen. Res. 15 (12), 2173–2185.
West, R.K., Rodgers, S.P., Leasure, J.L., 2021. Neural perturbations associated with recurrent binge alcohol in male and female rats. Alcohol Clin. Exp. Res 45 (2), 365–374.
Marshall, S.A., et al., 2020. Microglia dystrophy following binge-like alcohol exposure in adolescent and adult male rats. Front Neuroanat. 14, 52.
Marchese, N.A., et al., 2020. Angiotensin II modulates amphetamine-induced glial and brain vascular responses, and attention deficit via angiotensin type 1 receptor: Evidence from brain regional sensitivity to amphetamine. Eur. J. Neurosci. 51 (4), 1026–1041.
Thomas, D.M., et al., 2004. Methamphetamine neurotoxicity in dopamine nerve endings of the striatum is associated with microglial activation. J. Pharm. Exp. Ther. 311 (1), 1–7.
Cotto, B., et al., 2018. Cocaine-mediated activation of microglia and microglial MeCP2 and BDNF production. Neurobiol. Dis. 117, 28–41.
Wang, Z.J., et al., 2017. Activin A is increased in the nucleus accumbens following a cocaine binge. Sci. Rep. 7, 43658.
Jarvis, R., et al., 2019. Cocaine self-administration and extinction inversely alter neuron to glia exosomal dynamics in the nucleus accumbens. Front Cell Neurosci. 13, 581.
Burkovetskaya, M.E., et al., 2020. Cocaine self-administration differentially activates microglia in the mouse brain. Neurosci. Lett. 728, 134951.
Lewitus, G.M., et al., 2016. Microglial TNF-alpha suppresses cocaine-induced plasticity and behavioral sensitization. Neuron 90 (3), 483–491.
Narendran, R., et al., 2014. Cocaine abuse in humans is not associated with increased microglial activation: an 18-kDa translocator protein positron emission tomography imaging study with [11C]PBR28. J. Neurosci. 34 (30), 9945-50.
Melbourne, J.K., et al., 2019. Its complicated: The relationship between alcohol and microglia in the search for novel pharmacotherapeutic targets for alcohol use disorders. Prog. Mol. Biol. Transl. Sci. 167, 179–221.
Marshall, S.A., et al., 2013. Microglial activation is not equivalent to neuroinflammation in alcohol-induced neurodegeneration: the importance of microglia phenotype. Neurobiol. Dis. 54, 239-51.
Boche, D., Gordon, M.N., 2021. Diversity of transcriptomic microglial phenotypes in aging and Alzheimer's disease. Alzheimers Dement.
Agrawal, R.G., et al., 2011. Minocycline reduces ethanol drinking. Brain Behav. Immun. 25 (Suppl 1), S165–S169.
Gajbhiye, S.V., et al., 2018. Minocycline in alcohol withdrawal induced anxiety and alcohol relapse in rats. Curr. Clin. Pharm. 13 (1), 65–72.
Warden, A.S., et al., 2021. Microglia depletion and alcohol: transcriptome and behavioral profiles. Addict. Biol. 26 (2), e12889.
Warden, A.S., et al., 2020. Microglia control escalation of drinking in alcohol-dependent mice: genomic and synaptic drivers. Biol. Psychiatry 88 (12), 910–921.
Adeluyi, A., et al., 2019. Microglia morphology and proinflammatory signaling in the nucleus accumbens during nicotine withdrawal. Sci. Adv. 5 (10), eaax7031.
Northcutt, A.L., et al., 2015. DAT isn't all that: cocaine reward and reinforcement require Toll-like receptor 4 signaling. Mol. Psychiatry 20 (12), 1525–1537.
Fujita, Y., et al., 2012. The antibiotic minocycline prevents methamphetamine-induced rewarding effects in mice. Pharm. Biochem Behav. 101 (2), 303–306.
Attarzadeh-Yazdi, G., Arezoomandan, R., Haghparast, A., 2014. Minocycline, an antibiotic with inhibitory effect on microglial activation, attenuates the maintenance and reinstatement of methamphetamine-seeking behavior in rat. Prog. Neuropsychopharmacol. Biol. Psychiatry 53, 142–148.
Sofuoglu, M., et al., 2011. Minocycline attenuates subjective rewarding effects of dextroamphetamine in humans. Psychopharmacology 213 (1), 61–68.
Bachtell, R.K., et al., 2017. Glial and neuroinflammatory targets for treating substance use disorders. Drug Alcohol Depend. 180, 156–170.
Arout, C.A., et al., 2019. Minocycline does not affect experimental pain or addiction-related outcomes in opioid maintained patients. Psychopharmacology 236 (10), 2857–2866.
Wu, C.M., Lai, T.W., 2021. Microglia depletion by PLX3397 has no effect on cocaine-induced behavioral sensitization in male mice. Brain Res. 1761, 147391.
McGrath, A.G., Briand, L.A., 2019. A potential role for microglia in stress- and drug-induced plasticity in the nucleus accumbens: a mechanism for stress-induced vulnerability to substance use disorder. Neurosci. Biobehav Rev. 107, 360–369.
Ralph, M.R., et al., 1990. Transplanted suprachiasmatic nucleus determines circadian period. Science 247 (4945), 975–978.
Buhr, E.D., Takahashi, J.S., 2013. Molecular components of the Mammalian circadian clock. Handb. Exp. Pharm. 217, 3–27.
Partch, C.L., Green, C.B., Takahashi, J.S., 2014. Molecular architecture of the mammalian circadian clock. Trends Cell Biol. 24 (2), 90–99.
Rea, M.A., 1989. Light increases Fos-related protein immunoreactivity in the rat suprachiasmatic nuclei. Brain Res. Bull. 23 (6), 577-81.
Bennett, M.R., Schwartz, W.J., 1994. Are glia among the cells that express immunoreactive c-Fos in the suprachiasmatic nucleus? Neuroreport 5 (14), 1737-40.
Prolo, L.M., Takahashi, J.S., Herzog, E.D., 2005. Circadian rhythm generation and entrainment in astrocytes. J. Neurosci. 25 (2), 404–408.
Yagita, K., et al., 2010. Real-time monitoring of circadian clock oscillations in primary cultures of mammalian cells using Tol2 transposon-mediated gene transfer strategy. BMC Biotechnol. 10, 3.
Serviere, J., Lavialle, M., 1996. Astrocytes in the mammalian circadian clock: putative roles. Prog. Brain Res. 111, 57–73.
van den Pol, A.N., Finkbeiner, S.M., Cornell-Bell, A.H., 1992. Calcium excitability and oscillations in suprachiasmatic nucleus neurons and glia in vitro. J. Neurosci. 12 (7), 2648–2664.
Shinohara, K., et al., 2000. Circadian release of excitatory amino acids in the suprachiasmatic nucleus culture is Ca(2+)-independent. Neurosci. Res 36 (3), 245–250.
Prosser, R.A., et al., 1994. A possible glial role in the mammalian circadian clock. Brain Res. 643 (1–2), 296–301.
Lavialle, M., Serviere, J., 1993. Circadian fluctuations in GFAP distribution in the Syrian hamster suprachiasmatic nucleus. Neuroreport 4 (11), 1243–1246.
Schwartz, W.J., Gainer, H., 1977. Suprachiasmatic nucleus: use of 14C-labeled deoxyglucose uptake as a functional marker. Science 197 (4308), 1089-91.
Brown, A.M., Ransom, B.R., 2007. Astrocyte glycogen and brain energy metabolism. Glia 55 (12), 1263-71.
Lehre, K.P., Danbolt, N.C., 1998. The number of glutamate transporter subtype molecules at glutamatergic synapses: chemical and stereological quantification in young adult rat brain. J. Neurosci. 18 (21), 8751–8757.
Sweeney, A.M., et al., 2017. PAR1 activation induces rapid changes in glutamate uptake and astrocyte morphology. Sci. Rep. 7, 43606.
Beaule, C., et al., 2009. Circadian modulation of gene expression, but not glutamate uptake, in mouse and rat cortical astrocytes. PLoS One 4 (10), e7476.
Becquet, D., et al., 2008. Ultrastructural plasticity in the rat suprachiasmatic nucleus. Possib. Involv. Clock Entrain. Glia 56 (3), 294–305.
Herzog, E.D., et al., 2017. Regulating the suprachiasmatic nucleus (SCN) circadian clockwork: interplay between cell-autonomous and circuit-level mechanisms. Cold Spring Harb. Perspect. Biol. 9, 1.
Brancaccio, M., et al., 2017. Astrocytes control circadian timekeeping in the suprachiasmatic nucleus via glutamatergic signaling. Neuron 93 (6), 1420–1435 e5.
Brancaccio, M., et al., 2019. Cell-autonomous clock of astrocytes drives circadian behavior in mammals. Science 363 (6423), 187–192.
Welsh, D.K., et al., 1995. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. Neuron 14 (4), 697–706.
Tosini, G., Menaker, M., 1996. Circadian rhythms in cultured mammalian retina. Science 272 (5260), 419–421.
Ruby, N.F., Burns, D.E., Heller, H.C., 1999. Circadian rhythms in the suprachiasmatic nucleus are temperature-compensated and phase-shifted by heat pulses in vitro. J. Neurosci. 19 (19), 8630–8636.
Herzog, E.D., Huckfeldt, R.M., 2003. Circadian entrainment to temperature, but not light, in the isolated suprachiasmatic nucleus. J. Neurophysiol. 90 (2), 763-70.
Izumo, M., Johnson, C.H., Yamazaki, S., 2003. Circadian gene expression in mammalian fibroblasts revealed by real-time luminescence reporting: temperature compensation and damping. Proc. Natl. Acad. Sci. USA 100 (26), 16089-94.
Granados-Fuentes, D., et al., 2004. The suprachiasmatic nucleus entrains, but does not sustain, circadian rhythmicity in the olfactory bulb. J. Neurosci. 24 (3), 615–619.
Granados-Fuentes, D., et al., 2004. Olfactory bulb neurons express functional, entrainable circadian rhythms. Eur. J. Neurosci. 19 (4), 898–906.
Lavery, D.J., et al., 1999. Circadian expression of the steroid 15 alpha-hydroxylase (Cyp2a4) and coumarin 7-hydroxylase (Cyp2a5) genes in mouse liver is regulated by the PAR leucine zipper transcription factor DBP. Mol. Cell Biol. 19 (10), 6488–6499.
Arjona, A., Sarkar, D.K., 2005. Circadian oscillations of clock genes, cytolytic factors, and cytokines in rat NK cells. J. Immunol. 174 (12), 7618-24.
Du, Y.Z., et al., 2005. Circadian expression of clock and screening of clock-controlled genes in peripheral lymphocytes of rat. Biochem Biophys. Res Commun. 336 (4), 1069–1073.
Durgan, D.J., et al., 2005. The intrinsic circadian clock within the cardiomyocyte. Am. J. Physiol. Heart Circ. Physiol. 289 (4), H1530–H1541.
Chalmers, J.A., et al., 2008. Vascular circadian rhythms in a mouse vascular smooth muscle cell line (Movas-1). Am. J. Physiol. Regul. Integr. Comp. Physiol. 295 (5), R1529–R1538.
Pando, M.P., et al., 2002. Phenotypic rescue of a peripheral clock genetic defect via SCN hierarchical dominance. Cell 110 (1), 107-17.
Balsalobre, A., Marcacci, L., Schibler, U., 2000. Multiple signaling pathways elicit circadian gene expression in cultured Rat-1 fibroblasts. Curr. Biol. 10 (20), 1291–1294.
Yamazaki, S., et al., 2000. Resetting central and peripheral circadian oscillators in transgenic rats. Science 288 (5466), 682–685.
Silver, R., et al., 1996. A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. Nature 382 (6594), 810–813.
Aton, S.J., Herzog, E.D., 2005. Come together, right.now: synchronization of rhythms in a mammalian circadian clock. Neuron 48 (4), 531–534.
Nagoshi, E., et al., 2004. Circadian gene expression in individual fibroblasts: cell-autonomous and self-sustained oscillators pass time to daughter cells. Cell 119 (5), 693–705.
Welsh, D.K., et al., 2004. Bioluminescence imaging of individual fibroblasts reveals persistent, independently phased circadian rhythms of clock gene expression. Curr. Biol. 14 (24), 2289–2295.
Carr, A.J., Whitmore, D., 2005. Imaging of single light-responsive clock cells reveals fluctuating free-running periods. Nat. Cell Biol. 7 (3), 319–321.
Marpegan, L., Krall, T.J., Herzog, E.D., 2009. Vasoactive intestinal polypeptide entrains circadian rhythms in astrocytes. J. Biol. Rhythms 24 (2), 135–143.
Gall, C., Seroogy, K.B., Brecha, N., 1986. Distribution of VIP- and NPY-like immunoreactivities in rat main olfactory bulb. Brain Res. 374 (2), 389-94.
Sims, K.B., et al., 1980. Vasoactive intestinal polypeptide (VIP) in mouse and rat brain: an immunocytochemical study. Brain Res. 186 (1), 165–183.

Okamoto, S., et al., 1992. Localization of vasoactive intestinal peptide (VIP) messenger RNA (mRNA) in amacrine cells of rat retina. Curr. Eye Res. 11 (7), 711–715.
Maywood, E.S., et al., 2011. A diversity of paracrine signals sustains molecular circadian cycling in suprachiasmatic nucleus circuits. Proc. Natl. Acad. Sci. USA 108 (34), 14306-11.
Chun, L.E., et al., 2015. Variations in phase and amplitude of rhythmic clock gene expression across prefrontal cortex, hippocampus, amygdala, and hypothalamic paraventricular and suprachiasmatic nuclei of male and female rats. J. Biol. Rhythms 30 (5), 417-36.
Debski, K.J., et al., 2020. The circadian dynamics of the hippocampal transcriptome and proteome is altered in experimental temporal lobe epilepsy. Sci. Adv. 6, 41.
Quigg, M., et al., 1998. Temporal distribution of partial seizures: comparison of an animal model with human partial epilepsy. Ann. Neurol. 43 (6), 748–755.
Stephan, F.K., Kovacevic, N.S., 1978. Multiple retention deficit in passive avoidance in rats is eliminated by suprachiasmatic lesions. Behav. Biol. 22 (4), 456–462.
Devan, B.D., et al., 2001. Circadian phase-shifted rats show normal acquisition but impaired long-term retention of place information in the water task. Neurobiol. Learn Mem. 75 (1), 51–62.
Gerstner, J.R., et al., 2009. Cycling behavior and memory formation. J. Neurosci. 29 (41), 12824-30.
Ruby, N.F., et al., 2008. Hippocampal-dependent learning requires a functional circadian system. Proc. Natl. Acad. Sci. USA 105 (40), 15593–15598.
Shimizu, K., et al., 2016. SCOP/PHLPP1beta mediates circadian regulation of long-term recognition memory. Nat. Commun. 7, 12926.
Smarr, B.L., et al., 2014. A time to remember: the role of circadian clocks in learning and memory. Behav. Neurosci. 128 (3), 283–303.
Snider, K.H., et al., 2016. Modulation of learning and memory by the targeted deletion of the circadian clock gene Bmal1 in forebrain circuits. Behav. Brain Res 308, 222-35.
Rawashdeh, O., Parsons, R., Maronde, E., 2018. Clocking In Time to Gate Memory Processes: The Circadian Clock Is Part of the Ins and Outs of Memory. Neural Plast. 2018, 6238989.
Chaudhury, D., Colwell, C.S., 2002. Circadian modulation of learning and memory in fear-conditioned mice. Behav. Brain Res. 133 (1), 95–108.
Barnes, C.A., et al., 1977. Circadian rhythm of synaptic excitability in rat and monkey central nervous system. Science 197 (4298), 91–92.
Cauller, L.J., Boulos, Z., Goddard, G.V., 1985. Circadian rhythms in hippocampal responsiveness to perforant path stimulation and their relation to behavioral state. Brain Res. 329 (1–2), 117-30.
West, M.O., Deadwyler, S.A., 1980. Circadian modulation of granule cell response to perforant path synaptic input in the rat. Neuroscience 5 (9), 1597–1602.
Harris, K.M., Teyler, T.J., 1983. Age differences in a circadian influence on hippocampal LTP. Brain Res. 261 (1), 69–73.
McCauley, J.P., et al., 2020. Circadian modulation of neurons and astrocytes controls synaptic plasticity in hippocampal area CA1. Cell Rep. 33 (2).
Papouin, T., et al., 2017. Septal cholinergic neuromodulation tunes the astrocyte-dependent gating of hippocampal NMDA receptors to wakefulness. Neuron 94 (4), 840–854 e7.
Diotel, N., et al., 2018. Steroid transport, local synthesis, and signaling within the brain: roles in neurogenesis, neuroprotection, and sexual behaviors. Front. Neurosci. 12, 84.
Colgin, L.L., et al., 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. Nature 462 (7271), 353–357.
Zheng, C., et al., 2016. Fast gamma rhythms in the hippocampus promote encoding of novel object-place pairings. eNeuro 3, 2.
Lamothe-Molina, P., Franzelin, A., Auksutat, L., Laprell, L., Alhbeck, J., Kneussel, M., Engel, AK., Morellini, F., Oertner, TG, cFos ensembles in the dentate gyrus rapidly segregate over time and do not form a stable map of space, in bioRxiv. 2020.
Boison, D., Chen, J.F., Fredholm, B.B., 2010. Adenosine signaling and function in glial cells. Cell Death Differ. 17 (7), 1071–1082.
Tsunematsu, T., et al., 2021. Region-specific and state-dependent astrocyte Ca(2+) dynamics during the sleep-wake cycle in mice. J. Neurosci. 41 (25), 5440–5452.
Bojarskaite, L., et al., 2020. Astrocytic Ca(2+) signaling is reduced during sleep and is involved in the regulation of slow wave sleep. Nat. Commun. 11 (1), 3240.
Ingiosi, A.M., et al., 2020. A role for astroglial calcium in mammalian sleep and sleep regulation. Curr. Biol. 30 (22), 4373–4383 e7.
Zeisel, A., et al., 2018. Molecular architecture of the mouse nervous system. Cell 174 (4), 999–1014 e22.
Bayraktar, O.A., et al., 2020. Astrocyte layers in the mammalian cerebral cortex revealed by a single-cell in situ transcriptomic map. Nat. Neurosci. 23 (4), 500–509.
Fonken, L.K., et al., 2016. Diminished circadian rhythms in hippocampal microglia may contribute to age-related neuroinflammatory sensitization. Neurobiol. Aging 47, 102–112.
Fonken, L.K., et al., 2015. Microglia inflammatory responses are controlled by an intrinsic circadian clock. Brain Behav. Immun. 45, 171–179.
Graykowski, D., Cudaback, E., 2021. Don't know what you got till it's gone: microglial depletion and neurodegeneration. Neural Regen. Res. 16 (10), 1921–1927.
Liu, W.W., et al., 2020. BMAL1 regulation of microglia-mediated neuroinflammation in MPTP-induced Parkinson's disease mouse model. FASEB J. 34 (5), 6570–6581.
Griffin, P., et al., 2019. Circadian clock protein Rev-erbalpha regulates neuroinflammation. Proc. Natl. Acad. Sci. USA 116 (11), 5102–5107.
Wang, X.L., et al., 2020. Deficiency of the circadian clock gene Bmal1 reduces microglial immunometabolism. Front Immunol. 11, 586399.
Xie, Y., et al., 2020. Chronic sleep fragmentation shares similar pathogenesis with neurodegenerative diseases: endosome-autophagosome-lysosome pathway dysfunction and microglia-mediated neuroinflammation. CNS Neurosci. Ther. 26 (2), 215–227.
Sominsky, L., et al., 2021. Microglial ablation in rats disrupts the circadian system. FASEB J. 35 (2), e21195.
Corsi, G., et al., Microglia modulate hippocampal synaptic transmission and sleep duration along the light/dark cycle. Glia, 2021.
Nakanishi, H., et al., 2021. Microglial circadian clock regulation of microglial structural complexity, dendritic spine density and inflammatory response. Neurochem Int 142, 104905.
Hayashi, Y., et al., 2013. The intrinsic microglial molecular clock controls synaptic strength via the circadian expression of cathepsin S. Sci. Rep. 3, 2744.
Stowell, R.D., et al., 2019. Noradrenergic signaling in the wakeful state inhibits microglial surveillance and synaptic plasticity in the mouse visual cortex. Nat. Neurosci. 22 (11), 1782–1792.
Choudhury, M.E., et al., 2020. Phagocytic elimination of synapses by microglia during sleep. Glia 68 (1), 44–59.
Wadhwa, M., et al., 2017. Inhibiting the microglia activation improves the spatial memory and adult neurogenesis in rat hippocampus during 48h of sleep deprivation. J. Neuroinflamm. 14 (1), 222.
Besedovsky, L., et al., 2017. Signs of enhanced sleep and sleep-associated memory processing following the anti-inflammatory antibiotic minocycline in men. J. Psychopharmacol. 31 (2), 204–210.
Nonaka, K., Nakazawa, Y., Kotorii, T., 1983. Effects of antibiotics, minocycline and ampicillin, on human sleep. Brain Res. 288 (1–2), 253–259.
Wisor, J.P., Clegern, W.C., 2011. Quantification of short-term slow wave sleep homeostasis and its disruption by minocycline in the laboratory mouse. Neurosci. Lett. 490 (3), 165–169.
Wisor, J.P., Schmidt, M.A., Clegern, W.C., 2011. Evidence for neuroinflammatory and microglial changes in the cerebral response to sleep loss. Sleep 34 (3), 261-72.