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Astrocyte function from information processing to cognition and cognitive impairment

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Astrocytes serve important roles that affect recruitment and function of neurons at the local and network levels. Here we review the contributions of astrocyte signaling to synaptic plasticity, neuronal network oscillations, and memory function. The roles played by astrocytes are not fully understood, but astrocytes seem to contribute to memory consolidation and seem to mediate the effects of vigilance and arousal on memory performance. Understanding the role of astrocytes in cognitive processes may also advance our understanding of how these processes go awry in pathological conditions. Indeed, abnormal astrocytic signaling can cause or contribute to synaptic and network imbalances, leading to cognitive impairment. We discuss evidence for this from animal models of Alzheimer's disease and multiple sclerosis and from animal studies of sleep deprivation and drug abuse and addiction. Understanding the emerging roles of astrocytes in cognitive function and dysfunction will open up a large array of new therapeutic opportunities.

Astrocytes are morphologically complex cells characterized by intricate arborization and by anatomical specializations controlling local interactions with other CNS elements, including neuronal synapses, blood vessels, and other glial cells. Each astrocyte occupies a brain territory distinct from that of other astrocytes, but together they can form dynamic networks via gap-junction connectivity. This anatomical complexity is mirrored by functional complexity. Astrocytes have been implicated in a variety of structural, metabolic, and homeostatic functions, as well as in the control of cerebral blood flow. Since the 90s an additional astrocyte function has emerged that has greatly contributed to our understanding of brain function at the cellular level: the interaction of astrocytes with synapses and neuronal circuits. Key initial observations were that astrocytes sense neuronal activity and respond to it with intracellular Ca^{2+} elevations and that they release transmitters in response to Ca^{2+} elevations and other stimuli. These observations gave rise to the concept of 'tripartite synapses'[1], in which astrocytes were for the first time considered as active participants in synaptic processing.

Animal studies have shown that astrocyte interactions with synaptic circuits are multimodal and multiscale, occur under physiological conditions[2–5], and contribute to behavior[6–8]. Astrocytes express a repertoire of receptors, transporters, and other molecules, enabling them to sense a multitude of synaptic mediators as well as cytokines, prostaglandins, and signals related to changes in local ionic concentrations, pH, and immune or redox state. Moreover, astrocytes possess the machinery to produce a variety of molecules that can act at synapses, including glutamate, the NMDA receptor (NMDAR) co-agonist D-serine, ATP and its catabolic product adenosine, metabolic agents such as L-lactate, and other soluble or contact factors that participate in the formation, stabilization, and elimination of synaptic connections[3].

Evidence of astrocyte–synapse communication exists in so many CNS circuits that it could be considered a universal contributor to synaptic functions. Recently, several rules governing this communication have started to emerge, dictated both by the specific biological properties of astrocytes and by the modalities of their dynamic interaction with individual synapses and neuronal networks. The astrocytic contributions appear to be circuit-specific[9] and stimulus-specific[10], and their outputs are in register with the modalities of their activation[11]. In parallel, improved Ca^{2+} imaging approaches have revealed a spatiotemporal diversity of astrocytic Ca^{2+} signals that may underlie the capacity of astrocytes to encode and process different patterns of activation, accounting for the above properties[12,13].

In this review we discuss the role of astrocytes in cognitive processing, focusing on memory. To start, we will consider the lines of evidence that support a multimodal astrocytic involvement in local synaptic plasticity and in state-dependent oscillations of neuronal networks. Indeed, coordinated network oscillatory activity[14] and plastic remodeling of the underlying synaptic circuits[15] form the basis of memory encoding and other cognitive functions, which are influenced by brain states. We will then describe recent studies that more directly demonstrate the involvement of astrocyte signaling in cognitive processing. Finally, we will discuss data showing that altered astrocyte–synapse or astrocyte-network function in pathological conditions contributes to cognitive disturbances.

Astrocytes influence local synaptic activity and plasticity

Astrocytes contribute to the functional outcome of local synaptic transmission and plasticity in at least two interrelated ways: they undergo plastic rearrangements in coordination with the pre- and postsynaptic elements (morphological plasticity), and they actively control synaptic function via exchange of regulatory signals with the neuronal elements (bidirectional communication).

Morphological plasticity of astrocyte–synapse interactions

Astrocytes have a role in regulating structural remodeling and functional plasticity of synapses. Crucial in this role are the perisynaptic astrocytic processes (PAPs), thin astrocytic lamellae surrounding synapses. PAPs express functionally relevant membrane proteins—such as glutamate transporters, which are essential for removing

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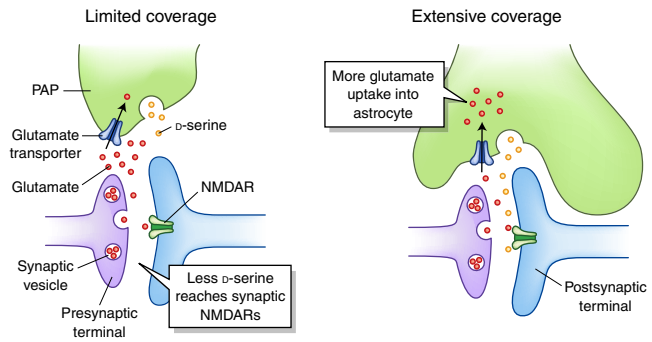

Fig. 1 | Plasticity of structural interactions between synaptic elements and PAPs. Left: reduced PAP coverage of synapses, such as occurs in the supraoptic nucleus during lactation[18], increases glutamate leakage from the synaptic cleft and reduces D-serine availability in the vicinity of postsynaptic NMDA receptors. Less D-serine in the synaptic cleft reduces activation of the NMDA receptors and increases the threshold for LTP induction[18]. Right: extensive PAP coverage, such as induced by connexin-30[24] or ephrin-4[25] knockout, enhances PAP's reuptake of glutamate, which reduces the neurotransmitter availability in the synaptic cleft and impairs LTP expression.

glutamate and terminating its synaptic actions—and contain the machinery for releasing fast transmitters[2]. PAPs ensheath synaptic elements to variable extents, depending on the brain area and circuit. For example, in the cerebellar cortex, PAPs of Bergmann glia (specialized cerebellar astrocytes) cover most synapses completely, whereas in the CA1 region of the hippocampus, PAPs cover about half of the synapses and only partially[16]. The extent to which PAPs ensheath synapses is controlled by their actin-dependent motility and can change over time, including as a function of neuronal activity (Fig. 1). For example, extensive whisker stimulation enhances PAP ensheathment of dendritic spines in the mouse somatosensory cortex, and this effect is accompanied by changes in the location and efficacy of glutamate transporters[17]. By contrast, in the rat hypothalamic supraoptic nucleus, during lactation PAPs retract from synapses, resulting in enhanced extrasynaptic glutamate leakage, reduced synaptic release probability, and decreased availability of astrocyte-released D-serine for NMDAR activation. This leads to a modified glutamatergic input conveying suckling information to oxytocin neurons[18]. In the hippocampus, long-term potentiation (LTP) is associated with altered spatial relations between PAPs and synapses. During LTP induction, more PAPs become proximate to activated synapses[19], a form of local plasticity possibly supported by RNA translation within PAPs[20]. Real-time imaging shows that PAPs, due to actin remodeling, first increase their motility and subsequently enwrap the most enlarged spines more tightly[21,22]. In the amygdala, learning a fear response produces a different plastic change, namely a decrease in the number of large synapses associated with a PAP[23]. Independently of the type of change, anatomical modifications of PAPs are not mere structural correlates of synaptic plasticity; rather, they are active parts of the plasticity mechanisms and can ultimately influence memory. For example, mice lacking the astrocyte gap-junction-related protein connexin-30 show increased PAP coverage of synapses, enhanced astrocytic glutamate uptake, reduced LTP expression, and impaired fear memory[24]. Likewise, mice lacking the neuronal ephrin A4 receptor or its astrocytic ligand, ephrin A3, show increased astrocytic GLT1 glutamate transporter uptake and impaired hippocampal LTP[25], paralleled by altered dendritic spine morphology[26]. In contrast, animals with genetically reduced astrocyte calcium dynamics show reduced PAP ensheathment of synapses, reduced glutamate clearance, and increased NMDAR-mediated excitatory postsynaptic currents[27]; however, the role of astrocyte Ca^{2+} signaling needs further evaluation, because a different genetic-interference strategy (see Table 1 for caveats on the two strategies) led to inconsistent results[28]. In conclusion, astrocytic and synaptic plastic changes occur coordinately and interdependently during synaptic remodeling. Rearrangement of the synaptic ensheathment modifies localization and efficacy

Box 1 | Genetic models for studying astrocyte signaling in memory processes

Several mouse models have been used to address the contribution of astrocyte signaling to memory processes. For the simplest models, such as the widely used IP3R2-knockout mice[138], the astrocyte-specificity relies on the assumption that the protein is expressed exclusively in astrocytes. This assumption requires convincing evidence, including a demonstration of differential expression of the protein in astrocytes versus other CNS cell populations[140,141]. More specific models are based on strong, astrocyte-specific promoters and controllable transgene expression.

A number of promoters, such as hGFAP, GLAST, GLT1, CX43, and FGF3, are considered selectively active in astrocytes[142]. However, their efficiency can vary greatly between astrocytes and between brain regions[143], and it can be useful to verify their expression for the defined CNS area (for example, using reporters such as GFP) and animal age of interest. Promising in this respect is the recent availability of the AldH1L1 promoter, which seems to have widespread CNS efficiency[144,145]. Another critical aspect of these promoters is that most of them are active in neural stem cells, and therefore, astrocyte-specificity is only guaranteed after development, when stem cells have evolved into their mature progenies.

With regard to controllable transgene expression, both the $Cre^{ERT2/loxP}$[146,147] and the tTA/tetO systems[148] provide temporal control of gene manipulation, which is necessary to overcome the developmental issue. However, gene manipulation may still occur in adult neural stem cells in the subgranular zone of the hippocampus and in the subventricular zone. Consequently, validation of an astrocyte-dependent phenotype in an area that sustains adult neurogenesis requires careful controls, for example by using coherent timing between transgene expression and phenotype[62]. In the future, better understanding of gene expression in adult neural stem cells will enable the use of astrocytic promoters that are not expressed in the precursor cell population[149]. In contrast, in non-neurogenic brain areas, the Cre^{ERT2} system, driven by an astrocytic promoter[143,150] of verified specificity, is highly reliable, and cognitive phenotypes described in these areas can be attributed to astrocyte signaling. The tTA/tetO system resembles the $Cre^{ERT2/LoxP}$ system in allowing for inducible gene manipulation, with the disadvantage of a slower time-course and the advantage of a reversible effect. This is the system used to create the dnSNARE mouse model[35]. Although this model has been recently criticized[139] based on a reported leakage of dnSNARE expression in neurons, several other studies have not observed this leakage[32,33,89]. Further, the dnSNARE mouse colonies used in the critical study[139] were different from those used by the other groups, who all relied on the colony originally described[35]. It is therefore possible that a divergence occurred between colonies, a known and serious problem in mouse genetics.

Regardless of the strategy, the timing of the experiments is also important. For example, protein knockout is efficiently achieved when not only is de novo synthesis of the protein of interest abolished but degradation of the existing protein is also complete[137].

Table 1 | List of mouse lines that target astrocytes, highlighting their caveats and strategies used to circumvent them

Driver	Full construct	Gene manipulation	Comments	References
None	IP3R2$^{-/-}$	Constitutive ubiquitous ablation of IP3R2 and lack of downstream Ca^{2+} signaling	A full KO may induce compensations. IP3R2-KO does not block thapsigargin-induced Ca^{2+} rise. The efficiency in blocking Ca^{2+} rises has not been examined in fine, perisynaptic processes in which recent work suggests the presence of additional sources of Ca^{2+} elevation[4]. The potential presence and role of IP3R2 in non-astrocytic cells has not been evaluated.	27, 52, 134
	GFAP-Srr	Overexpression of serine racemase in GFAP$^+$ cells	Same comments as above. Serine racemase is involved in the biosynthesis of other D-amino acids, involving confounding factors.	135
Cre	GFAP-Cre × IP3R2$^{f/f}$ or A2AR$^{f/f}$	Lack of IP3R2-dependent Ca^{2+} signaling or of A_{2A} receptor in astrocytes	The construct does not enable timed control of recombination. Therefore, recombination may be expected in neurons. The absence of recombination in neurons was evaluated by immunofluorescence in ref. [99] and by PCR on FACS-sorted cells in ref. [102].	28, 99, 102, 136
Cre^{ERT2}	GLAST-Cre^{ERT2} × Adrb2$^{f/f}$ or GluA1-GluA4$^{f/f}$ or Gabbr1$^{f/f}$	Lack of β_2-adrenergic receptors, GluA1 and GluA4 subunits of AMPA receptors, or $GABA_B$ receptors	The efficiency of the inducible KO approach was assessed by qPCR on sorted astrocytes[82]; electrophysiology and immunohistochemistry[137]; and the absence of recombination in neurons was verified by electrophysiology in ref. [72].	72, 82, 137
	GFAP-Cre^{ERT2} × $CB_1R^{f/f}$	Lack of cannabinoid CB1R in astrocytes	CB1R deletion in astrocytes and the absence of recombination in neurons were confirmed by immunoelectron microscopy. CB1R deletion in neurons did not induce a phenotype, supporting the specificity of the phenotype for astrocytic CB1R.	128
	GFAP-Cre^{ERT2} × TNFR1$^{cneo/cneo}$	TNFR1-KO with inducible re-expression of the receptor in astrocytes	The specificity of the construct for astrocytes was examined with immunofluorescence and PCR. Only about 0.7% of recombined cells in the dentate gyrus were neurons, originating from endogenous GFAP$^+$ neural stem cells.	62
	GFAP-Cre^{ERT2} × Srr$^{f/f}$	Suppression of serine racemase in astrocytes	No reporter was used, so the number of targeted astrocytes is unknown. Neuronal or astrocytic knock out of serine racemace did not reduce D-serine brain content, suggesting the existence of a compensatory mechanism.	31
	GLAST-Cre^{ERT2} × STOP$^{f/f}$-iBOT	Expression of a botulinum toxin isoform blocking secretion in astrocytes	The authors[33] found similar effects of dnSNARE mouse (below) and iBOT mouse on adult neurogenesis. Furthermore, the effect of transgene expression on synapse formation was locally restricted to transgene-expressing astrocytes, confirming the astrocytic specificity of the manipulation.	33, 36
tTA-tetO	GFAP-tTA × tetO-MrgA1	Stimulation of Gq-GPCR signaling in astrocytes	Specific expression in astrocytes was verified by immunofluorescence. Long Ca^{2+} events have been assessed in the soma and processes, but it is unclear whether the construct enables fast local Ca^{2+} dynamics in fine processes and gliapil as observed with endogenous Gq-GPCR signaling[4,77].	134, 138
	GFAP-tTA × tetO-Rs1	Chemogenetic activation of astrocyte Gs-coupled signaling	Specific expression in astrocytes was verified by immunofluorescence. About 12% of astrocytes express the synthetic Gs protein.	99
	GLT1-tTA- × tetO-"IP3-sponge"	Attenuation of IP3-dependent Ca^{2+} signaling in astrocytes	Some animals in this study were treated before birth with doxycycline, which may have induced compensations. Due to the expression of the GFAP promoter in neuroblasts, a residual sponge expression in immature neurons is likely. Possible side effects of the sponge were not controlled for.	27
	GFAP-tTA × tetO-dnSNARE	Expression of a dominant-negative VAMP2 that suppresses regulated secretion in astrocytes	Results from ref. [139] suggest possible transgene mRNA transcription in immature neurons, although the effect of this low transcription has not been assessed on protein expression or on vesicular release. See Box 1 above for further discussion.	32, 35, 68, 91, 92, 139
tTA/tetO and Cre^{ERT2}	GFAP-tTA × GFAP-Cre^{ERT2} × tTA-STOP$^{f/f}$-TeNT-GFP	Inducible and reversible expression of tetanus toxin blocking secretion in astrocytes	Blockade of glutamate exocytosis from astrocytes was demonstrated by sniffer cells.	71

KO, knockout; PCR, polymerase chain reaction; qPCR, real-time quantitative PCR; FACS, fluorescence-activated cell sorting.

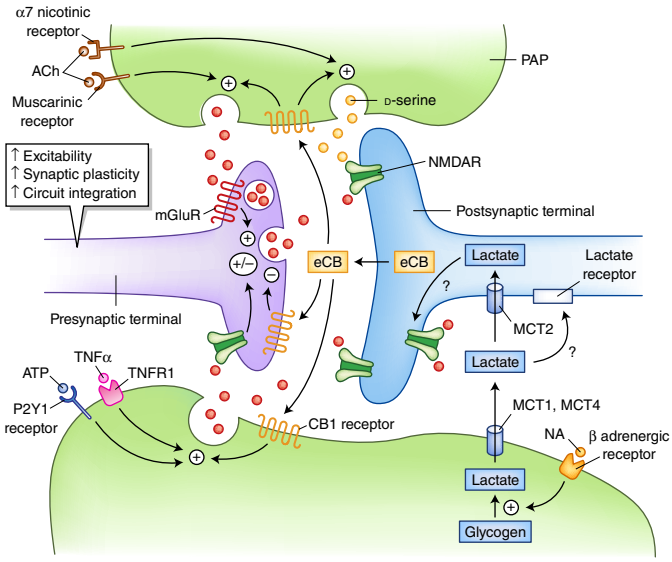

Fig. 2 | Bidirectional signaling between synaptic elements and PAPs controls synaptic function and plasticity. For graphical clarity, the bidirectional signaling is depicted as involving in part the top PAP and in part the bottom PAP. Activity-dependent release of endocannabinoids (eCBs) from postsynaptic neurons stimulates both presynaptic and astrocytic CB1Rs. Activation of presynaptic CB1R exerts an inhibitory effect on synaptic transmitter release, whereas activation of astrocytic CB1R induces release of glutamate (red dots, top and bottom PAPs) and/or D-serine (yellow dots, top PAP). Astrocytic glutamate modulates synaptic transmission and plasticity by activating presynaptic mGluRs, presynaptic NMDAR, and dendritic (extrasynaptic) NMDARs. Depending on the circuit, the effect can be stimulatory or inhibitory[9,45–50]. Astrocyte D-serine potentiates postsynaptic NMDAR activation[18,29,30,32] and increases the synaptic integration of new neurons generated in the adult hippocampus[33]. Activation of cholinergic (top PAP), purinergic and noradrenergic (bottom PAP) receptors on astrocytes induces the release of fast-acting molecules that influence synaptic activity and plasticity via both pre- and postsynaptic mechanisms. In particular, activation of nicotinic α7 or muscarinic receptors by acetylcholine (Ach) induces, respectively, D-serine[32] and glutamate release[52,65] with stimulatory synaptic effects mediated by postsynaptic NMDAR (D-serine) and presynaptic mGluR (glutamate). Activation of purinergic P2Y1 receptors by ATP induces glutamate release and activation of stimulatory presynaptic NMDAR. The P2Y1R-evoked glutamate release is controlled by TNFα via TNFR1 signaling[61] (see also Fig. 4). Activation of β2 adrenoceptors by noradrenaline (NA) increases astrocytic glycogenolysis and production of L-lactate and its shuttling out of the cell by MCT1 or MCT4. L-Lactate can enter the neurons via MCT2 or act on putative membrane receptors[37,82,83], inducing metabolic and/or signaling effects possibly involving control of NMDAR function.

of glutamate transport and astrocyte transmitter (gliotransmitter) release, thereby contributing to changes in the synaptic gain (Fig. 1).

Astrocyte–synapse communication in synaptic plasticity

Astrocytes contribute to synaptic plasticity by releasing fast mediators that directly modify synaptic function[2,4]. This communication appears to play a critical role in various forms of plasticity (Fig. 2). For instance, classical NMDAR-dependent LTP at hippocampal CA1 synapses requires transient D-serine release from the astrocytes[18,29,30]. This D-serine 'boost' appears to increase the occupancy of the NMDAR co-agonist binding site (by about 20–25%) up to a threshold of activation, which then allows the receptor to trigger the downstream signaling pathway that underlies LTP induction. As D-serine may also be produced in neurons[31], some authors have questioned an astrocytic D-serine contribution. However, a recent study showed that activation of astrocytic but not neuronal α7 nicotinic receptors boosts D-serine-mediated occupancy of the NMDAR co-agonist binding site[32] (see below). Astrocyte-released D-serine participates also in another form of synaptic plasticity, the integration of adult-born granule neurons into the hippocampal circuitry[33], a process that is ongoing throughout life and influences local circuit performance in memory processes and mood control (reviewed in ref. [34]). Thus, during synaptic integration, newborn granule neurons display a lower threshold for LTP induction and higher potentiation than mature neurons, thereby maintaining a high degree of network plasticity. The synaptic integration process requires vesicular release of D-serine from astrocytes. Thus, two transgenic mouse lines with selectively suppressed astrocytic release, dnSNARE[35] and iBot mice[36] (see Box 1 and Table 1), showed defective integration of newborn granule cells, with delayed dendritic maturation and reduced excitatory transmission. In addition, the mice had reduced brain D-serine levels (also seen in derived astrocytic cultures), and application of exogenous D-serine could restore synaptic integration and dendritic maturation of new neurons[33].

Another astrocyte-derived molecule, L-lactate, plays a key role in LTP at hippocampal CA1 synapses[37]. During periods of high energy demand, glycogen stored in astrocytes is metabolized to L-lactate and shuttled to neurons[37,38]. Pharmacological inhibition of astrocytic glycogenolysis during LTP induction causes rapid decay of the synaptic potentiation, an effect rescued by co-injection of exogenous L-lactate[37]. Therefore, availability of L-lactate is necessary for maintaining LTP, although whether the agent acts purely as metabolic fuel for the synaptic remodeling or has additional functions is presently unclear. L-lactate can influence neuronal excitability in several ways, for example, by boosting NMDAR activity and by stimulating other neuronal receptors, including the cell-surface lactate receptor GPR81[39–41].

Astrocytes also influence synaptic plasticity via cannabinoid receptor type-1 (CB1R) signaling (Figs. 2 and 4a). CB1R is highly expressed in the CNS (likely the most abundant G-protein-coupled receptor, GPCR)[42], and much evidence has accumulated for a role of its natural ligands, the endocannabinoids, in modulating synaptic function, such as via inhibition of transmitter release at GABAergic and glutamatergic terminals[43]. CB1Rs are also expressed in astrocytes, although at lower levels than in neurons, and they participate in important mechanisms that regulate neuronal activity and ultimately memory performance[44–46]. Initial findings showed that activity-dependent endocannabinoid release from CA1 pyramidal neurons activated astrocytic CB1Rs, inducing astrocytic Ca^{2+} elevation and glutamate release and resulting in NMDAR-dependent postsynaptic slow excitatory currents and mGluR1-dependent heterosynaptic facilitation of presynaptic glutamate release[45,46]. Subsequent studies have shown that astrocyte CB1R signaling participates in long-term synaptic plasticity. Indeed, activation of astrocytic CB1Rs is necessary for induction of spike-timing-dependent long-term depression (LTD) at layer (L) 4–L2/3 cortical synapses, via glutamate release and activation of presynaptic NMDARs that permanently reduce synaptic transmission[47]. A recent study showed that the classical NMDAR-dependent LTP at CA1 hippocampal synapses requires (in addition to astrocyte D-serine[29]) astrocyte CB1Rs[48], as their genetic deletion suppresses LTP, whereas supply of exogenous D-serine in the absence of the receptors restores it[48]. At the same synapses, astrocyte CB1Rs mediate glutamate-dependent heterosynaptic LTP[49], although they can also mediate spike-timing-dependent LTD under specific spike-timing-dependent induction protocols[50].

Astrocytes also contribute to synaptic modulation and plasticity associated with the activity of long-range cholinergic and noradrenergic fibers[32,51–55] (Fig. 2 and discussed below). Finally, astrocyte signaling to synapses appears to be regulated by immune mediators.

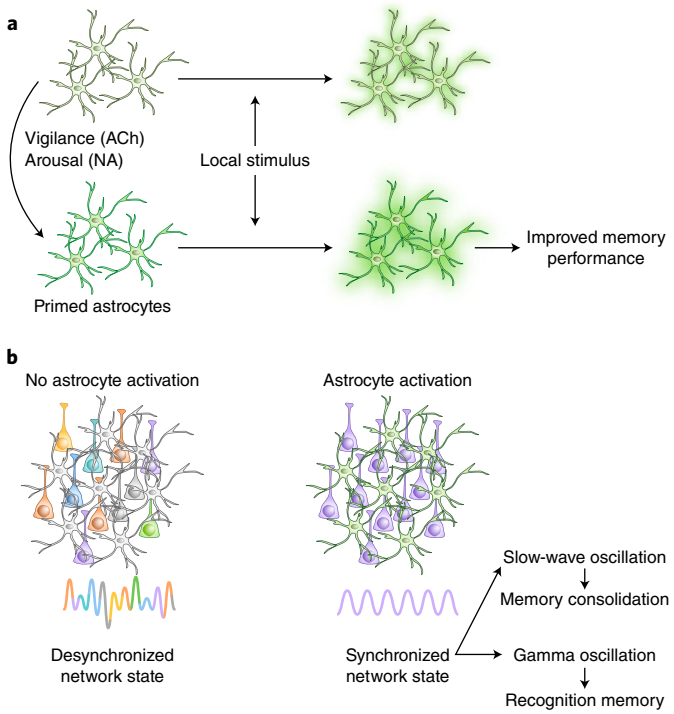

Fig. 3 | Astrocytes modulate neuronal network oscillations and contribute to memory performance. a, Astrocytes stimulated by acetylcholine (during vigilance)[27,32,52,65] or noradrenaline (during arousal)[64] are primed by the brain state and contribute to functional changes, such as long-term plasticity of synaptic networks and enhanced memory performance[51,82,83]. Noradrenergic input from locus coeruleus increases astrocyte responsiveness to local circuit activity in the cortex[64], whereas the septal cholinergic input boosts hippocampal memory through astrocyte activation[32]. Activated astrocytes depicted in green. **b**, Activation of astrocytes drives coordination of the activity of neuronal networks and their switch from desynchronized to oscillatory states, including slow-wave oscillations that are important for memory consolidation[67–69] and gamma oscillations that enhance recognition memory[70–72]. Activated astrocytes depicted in green; desyncronized neurons depicted in different colors corresponding to the different times of their firing; synchronous-firing neurons all depicted in violet, corresponding to their oscillatory up-states.

Until recently, these molecules were thought to be produced mainly during pathological inflammatory reactions. However, they are also present in the healthy brain, albeit at very low levels, and exert regulatory actions at synapses. For example, depending on the circuit, tumor necrosis factor-α (TNFα) can favor membrane insertion or internalization of AMPA receptor subunits at excitatory synapses[56,57]. Through these effects, TNFα contributes to synaptic scaling, a form of homeostatic plasticity by which a population of synapses collectively adjusts its strength to long-term variations in network activity, for example, during plastic rearrangement of sensory circuits[58,59]. TNFα also affects synaptic strength through regulation of astrocyte glutamate release (Figs. 2 and 4c). In the hippocampal dentate gyrus, astrocytic stimulation transiently boosts excitatory synaptic transmission via glutamate release and downstream activation of stimulatory presynaptic NMDARs[60]. Constitutive levels of the cytokine are necessary and sufficient for the astrocytic input to be synaptically effective[61]. However, when TNFα levels increase in pathological conditions, the astrocytic input changes and causes long-lasting increase of synaptic strength[62] (see below). Overall, astrocyte signaling via multiple surface receptor types and released transmitters contributes to the establishment of several forms of synaptic plasticity in various memory-relevant hippocampal and cortical circuits.

Astrocytes sense brain states and modulate neuronal ensembles

So far, we have discussed the involvement of astrocyte signaling in the plasticity of local synapses. However, cognitive functions emerge from more mesoscale processes involving coordinated activity of ensembles of neurons and synaptic circuits[63]. Neuronal network responses to external stimuli are regulated by brain states, and state-dependent excitability of neuronal networks is associated with specific cognitive functions. Neuromodulators, which produce spatially diffuse and slower effects than transmitters at fast excitatory or inhibitory synapses, are implicated in the generation of brain states. Intriguingly, neuromodulators' actions involve activation of the astrocytic networks (Fig. 3a). Arousal, associated with activation of the locus coeruleus and widespread noradrenaline release, activates astrocytes in projection areas. This increases the responsiveness of astrocyte networks to local cortical activity[64], suggesting that arousal increases the gain of such networks to perceive external stimuli and modulate neuronal function. Indeed, activation of astrocytic α1 receptors by noradrenaline triggers the release of D-serine and ATP, which facilitate LTP induction of L2/3 excitatory synapses in the somatosensory cortex[51].

Acetylcholine, which is released during vigilance states by long-range cholinergic fibers (modulating attention and learning), also activates astrocyte networks and promotes astrocyte-mediated neuronal modulation[32,52,53,55,65]. Acetylcholine-activated astrocytes release D-serine at excitatory synapses, including at CA3–CA1 hippocampal synapses[32] and somatosensory synapses[53], to enhance NMDAR activity and NMDAR-dependent functions. Alternatively, they can release glutamate, which excites CA1 pyramidal neurons[65] and inhibits dentate granule cells via intermediary GABAergic interneurons[54]. In addition, cholinergic input to astrocytes can induce LTP of glutamatergic transmission when cholinergic fibers and CA3–CA1 synapses are coincidentally active[52].

Both noradrenaline and acetylcholine regulate brain-wide oscillations, which are hallmarks of synchronization of different brain areas and important for cognitive performance and sensory perception[14]. Interestingly, astrocytes have been recently reported to control neuronal oscillations in several ways (Fig. 3b). At the cortical level, they contribute to the generation of slow-wave oscillations (<1 Hz), which occur prominently during non-rapid eye movement (NREM) sleep and have been associated with memory consolidation[66]. These slow oscillations result in neuronal up- and down-states. Astrocytic Ca^{2+} signaling modulates up-state generation in situ[67], whereas genetic suppression of gliotransmitter release reduces the power of slow-wave oscillations in vivo[68] (see below). Recently, studies using astrocyte-specific optogenetic stimulation have revealed a role for these cells in promoting the transition from high-frequency to low-frequency oscillatory states[69]. Stimulated astrocytes induce a localized increase in extracellular glutamate (likely glia-derived) that increases coactive neuronal firing. Such astrocytic input acts as an instructive synchronizing signal for neuronal ensembles and triggers a switch of the cortical circuit to a slow-wave oscillation-dominated state[69] (Fig. 3b).

Astrocytes also modulate oscillatory patterns in other frequency ranges, such as in the gamma range (25–80 Hz). Both inhibitory and stimulatory effects have been reported in the hippocampus. The former was produced by optogenetic activation of astrocytes and involves coordinated control of pyramidal cell and CCK-positive interneuron excitability by astrocyte-released ATP and/or adenosine[70]. The latter was observed in mice with genetically induced suppression of astrocytic exocytosis, which showed reduced electroencephalogram power in the gamma frequency range in vivo; this was associated with impairment of carbachol-induced gamma

oscillations in vitro[71]. The control of such network activity by glia likely depends on astrocytic stimulation by GABAergic interneurons, as astrocyte-specific $GABA_B$-knockout mice show reduced theta and gamma power in vivo[72]. Thus, sustained interneuron firing in the hippocampus induces astrocyte $GABA_B$ signaling, which triggers gliotransmission and thereby controls the oscillatory activity of the neuronal network[72]. Additionally, astrocytes contribute to the coordinated activity across brain regions, as mice with disrupted astrocytic exocytosis exhibit disordered hippocampal–prefrontal theta synchronization[6].

Astrocytes may mediate synchronization of neuronal ensembles in multiple ways. For instance, they can release glutamate simultaneously onto several neighboring neurons and coordinately increase their excitability via activation of extrasynaptic NMDAR[73] and other glutamate receptors[74]. Importantly, direct dendritic recordings from hippocampal CA1 pyramidal neurons show that astrocytic glutamate does target neuronal dendrites and could be the source of dendritic plateau potentials[75] implicated in localized plasticity and spatial memory formation[76]. Astrocytes can also release glutamate onto axons and their terminals and thereby modulate axonal conduction, broaden action potentials[74], or transiently increase presynaptic transmitter release[46,60,77,78]. Since axonal and/or synaptic stimulation is a potent way to synchronize neurons, astrocytes may promote network coordination by acting simultaneously on many afferent fibers or synapses. In addition, they can extend their influence on neuronal domains by forming astrocytic domains via gap-junction connectivity. This astrocytic connectivity seems important for coordinating activation and for synchronizing bursting of the neuronal networks[79]. Overall, astrocytic signaling pathways emerge as relevant contributors to the generation and regulation of various network oscillatory rhythms and, by sustaining the action of neuromodulators, to tuning these rhythms according to brain states.

Astrocyte signaling in memory processes and in the memory function of sleep

Recent studies have linked astrocyte signaling at synaptic or network levels to cognitive performances in animals and have provided direct evidence that cognitive processing requires coordinated activity of synaptic ensembles and astrocytes. Consistent with this notion, chemogenetic activation of astrocytes in relevant circuits can affect memory performance[7,80]. Gq DREAD (designer receptors exclusively activated by designer drugs) activation in astrocytes of the medial central amygdala caused extinction of learned fear memory in a cued fear conditioning task[80]. The effect was ascribed to astrocyte-released adenosine reducing firing of medial central amygdala neurons by joint stimulation of the inhibitory inputs from lateral central amygdala (via A_{2A} receptors) and inhibition of the excitatory inputs from basolateral amygdala (via A_1 receptors). In another study, optogenetic and chemogenetic activation of the Gq astrocytic signaling pathway in the hippocampus were sufficient to enhance memory allocation and cognitive performance[7]. While these data showed that astrocytic activation can drive neuronal circuits to modulate memory performance, they did not prove that astrocytes are activated during physiological memory processes. However, studies using mouse genetics or pharmacological approaches to suppress specific signaling pathways exclusively in astrocytes did provide such evidence (Fig. 4). A first study identified a necessary role for L-lactate in long-term episodic memory by pharmacological inhibition of its production in astrocytes[37]. The manipulation both suppressed CA3–CA1 LTP in vivo (see above) and impaired long-term memory formation in an inhibitory avoidance task, and these effects were rescued by administration of exogenous L-lactate[37]. The same impairment was produced by knockdown of the monocarboxylate transporters (MCTs) that shuttle L-lactate from astrocytes (MCT1 and MCT4) to neurons (MCT2)[37]. One of the neuronal functions requiring L-lactate is the de novo protein synthesis that maintains LTP and fosters memory consolidation[37,39,81]. More recently, noradrenaline acting on β_2 adrenergic receptors was identified as one of the stimuli leading to L-lactate production during memory processing[82,83]. Noradrenaline has long been known to potentiate LTP and hippocampal memory via β receptors, but the recent studies have shown that relevant β_2 adrenoceptors are expressed on astrocytes, not neurons (Fig. 2). Thus, astrocyte-specific knockdown of the receptors[82] prevented memory consolidation, and this effect was rescued by local L-lactate supply in the hippocampus[83]. These data are significant because they link the known positive effect of arousal (and thus noradrenaline release) on memory performance to the finding that a key part of the noradrenergic effect is mediated by astrocytes. Similarly, noradrenaline release during acute stress activates astrocytic β_2 adrenoceptors[84]. Stress stimuli can either enhance or decrease cognitive performance depending on their severity and duration, and it is possible that the type of effect produced reflects the duration and extent of astrocyte activation during stress. A recent study showed that administration of a β_2 agonist over days improves memory performance by upregulating the astrocytic L-lactate export pathway, whereas with longer applications the drug causes internalization of β_2 adrenoceptors and decreases cognitive ability, likely by reducing astrocytic L-lactate supply to neurons[84].

Astrocytes also participate in hippocampus-dependent memory formation by controlling the availability of D-serine for synaptic NMDAR activation[7,32,48] (see above). At least two distinct astrocytic pathways promote this effect, one engaging α7 nicotinic receptors[32], the other CB1Rs[48]. The first pathway depends on the state of vigilance and is mediated by activation of septal cholinergic fibers (see above), which in turn stimulate α7 receptors on hippocampal astrocytes (and not in neurons) to promote D-serine release, thereby boosting NMDAR activation at CA3–CA1 synapses[32]. Indeed, NMDAR co-agonist site occupancy positively correlated with D-serine levels dictated by the wake–sleep cycle, being maximal during wakefulness (dark period for mice). This astrocyte-dependent control of D-serine release had behavioral consequences, as the strength of fear memory in a contextual fear-conditioning task was higher in dark than in light periods[32], suggesting that astrocytes may convey the vigilance input to enhance memory performance (Fig. 3a). In the second pathway, signaling via astrocyte CB1Rs affects hippocampus-dependent memory by boosting D-serine-mediated NMDAR activation at CA3–CA1 synapses (Fig. 4a). Deletion of astrocytic CB1 receptors reduced NMDAR co-agonist binding site occupancy, suppressed CA1 LTP in vivo (see above) and impaired recognition memory; these effects were rescued by administration of exogenous D-serine or pharmacological blockade of D-serine catabolism[48]. Importantly, exogenous D-serine was effective when administered immediately after memory acquisition but not 1 h later, indicating that astrocyte CB1 signaling is engaged in the early phase of memory consolidation[48]. Accordingly, astrocyte-specific optogenetic activation of a light-sensitive Gq-coupled receptor (OptoGq) increased memory acquisition only during the learning phase[7].

Another study confirmed the role of astrocyte signaling in recognition memory[71]. In transgenic mice with inducible tetanus toxin expression selectively in astrocytes (Table 1), the resulting suppression of astrocytic exocytosis impaired gamma frequency oscillations in vivo (see above), as well as performance in the novel-object recognition task. Both effects were reversed by stopping tetanus toxin expression in astrocytes[71]. Similarly, dnSNARE transgenic mice, lacking regulated exocytosis in astrocytes, display both altered hippocampal–prefrontal synchronization and defective spatial learning and reference memory[6].

Astrocytes also contribute to the memory function of sleep. Sleep promotes memory consolidation (reviewed in ref. [85]), particularly during early-night NREM phases, which are rich in cortical slow-wave oscillations. This consolidation refines memory

engrams by establishing long-lasting forms of synaptic potentiation for memories to be retained, while simultaneously reducing less-relevant memories via synaptic depression and downscaling of established synapses[86,87]. Sleep deprivation impairs memory consolidation by interfering with the above processes. During prolonged wakefulness the need to sleep increases due to a progressive increase in adenosine, a sleep-inducing molecule (reviewed in ref. [88]). If the wake period is excessively long, adenosine levels in the following sleep period decay more slowly than normal. Adenosine was long believed to be produced by neurons, but recent work[35] using dnSNARE transgenic mice challenged this idea and suggested instead an astrocytic origin. These mice lack regulated exocytosis in astrocytes[35], including release of the adenosine precursor ATP[89] (see above; see Table 1 and Box 1 for a discussion on the model validity). When sleep-deprived, dnSNARE mice showed no adenosine accumulation, as measured in hippocampal slices[90], and exhibited much milder phenotypes than control mice, with little alteration of slow-wave cortical oscillations and cognitive performance[91,92]. Therefore, astrocyte-released adenosine may underlie impaired cognitive function upon sleep deprivation.

A recent study showed that another astrocyte-released molecule, L-lactate, has the opposite role of adenosine, helping maintain normal sleep architecture and, therefore, preserving cognitive performance by supporting the activity of wake-producing orexin neurons in the lateral hypothalamus[40]. Overall, studies involving selective activation or suppression of given astrocytic signaling pathways have revealed participation of astrocytes in specific types or phases of memory processes. Likewise, astrocyte signaling has a role in the memory function of sleep as well as in the detrimental consequences of sleep deprivation.

Astrocytic control of cognitive function goes awry in pathological brain conditions

The role of astrocytes in synaptic and network processing appears to be plastic and subject to perturbations. In pathological conditions, astrocyte–neuron interactions can undergo dramatic changes, with strong impact on brain circuits supporting memory formation and cognitive function. This is the case in Alzheimer's disease (AD), a pathology characterized by progressive impairment of memory and other cognitive functions such as abstract thinking, judgment, language, and recognition. The notion that astrocytes surrounding β-amyloid (Aβ) deposits are altered in AD stems from the original description of AD pathology by Alois Alzheimer in 1911. Only recently have the anatomical descriptions been complemented by functional studies. These studies showed increased expression of several receptors in astrocytes surrounding Aβ sites in both AD mouse models and postmortem human AD brains, likely affecting the downstream signaling and its synaptic function[93]. Upregulated receptors included α7 nicotinic Ach receptors[94], Ca^{2+}-permeant ligand-gated channels whose upregulation causes abnormal astrocytic Ca^{2+} elevations and massive glutamate release[95,96]; mGlu5 receptors[97] and P2Y1 receptors[98], whose enhanced G_q-IP_3-dependent Ca^{2+} signaling can similarly contribute to astrocytic Ca^{2+} alteration; and A_{2A} adenosine receptors[99], which instead signal via G_s-cAMP. A_{2A} receptors normally promote 'active forgetting', a process that removes irrelevant memories during sleep[100]. However, when excessively activated in AD[99], A_{2A} receptors may accentuate the 'forgetting' pathway, resulting in reduced memory performance. In line with this, transgenic mice lacking the A_{2A} receptor or AD mice treated with an A_{2A} antagonist[101] show increased memory (but see ref. [102]), whereas mice in which astrocyte G_s signaling is selectively stimulated (Table 1) show the opposite[99]. Another signaling aberration seen in reactive astrocytes surrounding Aβ deposits consists in an enhanced synthesis and release of GABA[103–105], which increases tonic inhibition of dentate granule cells with a negative impact on memory processing.

AD patients and AD mouse models display excitation–inhibition circuit imbalances that affect the oscillatory patterns underlying cognitive processing[106,107]. In mouse models, neurons within the vicinity of Aβ deposition are often hyperexcitable, possibly due to an altered local microenvironment. This could be explained by Aβ-mediated disruptions of glutamate uptake[108], glutamate release[109], and GABAergic inhibition[110]. Interestingly, astrocytes in apposition to Aβ deposits are also hyperactive and display higher resting Ca^{2+} levels, more frequent and larger Ca^{2+} elevations, long-range coordinated Ca^{2+} waves that are never seen in control mice[95,98,111], and increased gliotransmission[112]. These abnormalities could be due to a direct action of Aβ on astrocytes[113], as well as to an enhanced receptor-mediated Ca^{2+} signaling (see above), and are likely to affect the neuronal network, for example, by extending the areas of functional alteration and abnormal synchronization. Preventing excessive Ca^{2+} increase and transmitter release from astrocytes might therefore represent a promising strategy for AD therapy. In keeping with this idea, the acetylcholinesterase inhibitor donepezil, which is approved for symptomatic AD treatment, appears to reduce astrocyte Ca^{2+} signaling[114]. Moreover, P2Y1R antagonists or genetic suppression of IP3R2-dependent astrocyte Ca^{2+} signaling reduce neuron–astrocyte network hyperactivity and ameliorate spatial learning and memory deficits in AD mice[115].

AD, along with many other CNS pathologies, is characterized by the presence of local intraparenchymal inflammation. It has been proposed that astrocytic modulation of network activity and cognition undergo deleterious transformation in such inflammatory states. An example of this was observed in the experimental autoimmune encephalitis (EAE) model of multiple sclerosis, in which abnormal TNFα-dependent signaling by astrocytes causes cognitive deficits resembling those seen in patients[62] (Fig. 4d). In particular, in EAE mice, a local inflammatory focus in dorsal hippocampus caused TNFα increases, long-lasting modification of excitatory neurotransmission, and impaired contextual memory. These effects depend on enhanced TNFα signaling via its astrocytic type-1 receptor (TNFR1), which hijacked the regulatory mechanism controlling astrocytic glutamate release (see above) and caused long-lasting potentiation of excitatory synapses. This synaptic and behavioral phenotype was abolished in global TNFR1-knockout EAE mice and could be restored by inducing re-expression of the receptor solely in astrocytes (Table 1), demonstrating that astrocytes mediate the deleterious action of TNFα on memory function in EAE mice[62].

Based on the role of TNFα in promoting inflammation-induced memory impairment, substantial efforts have aimed at developing TNFα inhibitors for treating CNS diseases. Several such agents have been or are currently being tested for disorders including multiple sclerosis and AD, with both success and failures having been reported[58]. Selective blockade of TNFR1 function may be a more promising therapeutic strategy with increased mechanistic specificity[116]. Accordingly, new TNFR1 antagonists with CNS action were effective in reversing enhanced glutamatergic transmission in an AD mouse model[117].

Recently, astrocytes have been implicated in the development of drug addiction. The astrocytic role in addiction appears to involve altered D-serine and L-lactate signaling, which in turn perturbs physiological synaptic plasticity and memory. Hence, instalment of the addictive behavior occurs via formation of 'maladaptive memories' in the mesocorticolimbic reward circuitry—ventral tegmental area and nucleus accumbens (NAc)—that take over the normal memory processes activated by natural rewards. For example, cocaine alters glutamatergic function in the NAc by modifying the AMPA receptor/NMDA receptor currents ratio and by impairing LTP and LTD[118]. As astrocytes influence glutamatergic transmission in the NAc[118,119], they could participate in these changes. Consistently, cocaine treatment leads to reduced D-serine levels in NAc, which could explain the reduced NMDAR-dependent synaptic

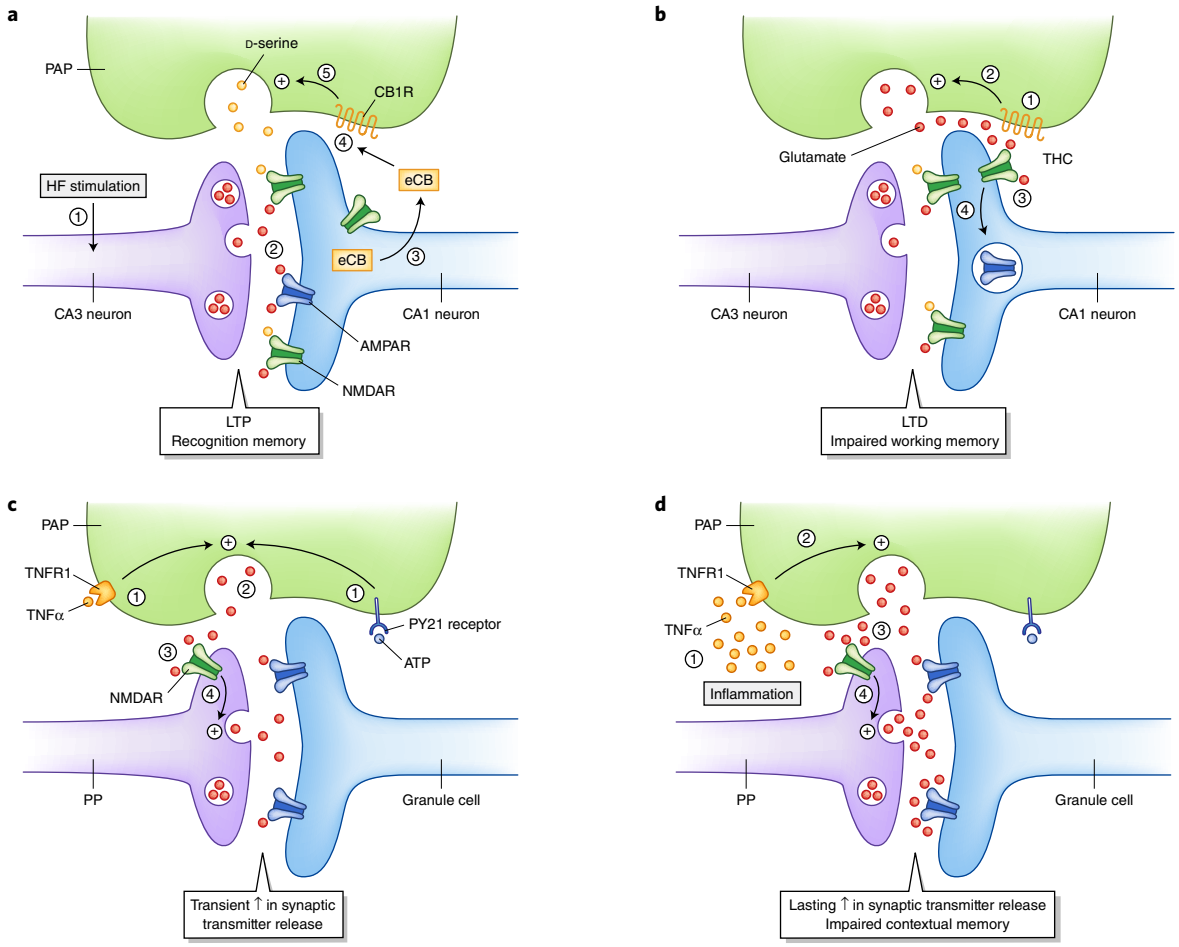

Fig. 4 | Effects of astrocyte signaling on hippocampus-dependent memory pathways in physiological and pathological conditions. a, During the induction of LTP via high-frequency stimulation at CA3–CA1 synapses (1, 2), eCBs are released in an activity-dependent manner from postsynaptic neurons (3). eCBs activate CB1Rs on astrocytes (4) and induce d-serine release (5), which is necessary for NMDAR-dependent LTP of the synapses[48]. Appropriate recognition memory performance requires such astrocyte signaling[48]. HF, high-frequency. **b**, In a pathology-related setting, injection of THC causes activation of astrocyte CB1Rs (1), but in this case the downstream signaling activated is different and leads to LTD of CA3–CA1 synapses and impaired working memory[44]. This effect seems to involve astrocyte glutamate release (2), activation of extrasynaptic NR2B-containing NMDARs (3) and, eventually, internalization of AMPA receptors (AMPARs) (4). **c**, Astrocytes control synaptic transmitter release probability at perforant path-granule cell synapses in the dentate gyrus[61], a key pathway for context discrimination. Activity of these excitatory synapses leads to stimulation of P2Y1Rs on astrocytes (possibly by synaptically co-released ATP) (1), which induce glutamate release (2) via a processes controlled by constitutive TNFα signaling via TNFR1 (1). Astrocytic glutamate acts on presynaptic NR2B-containing NMDAR (3) to transiently upregulate synaptic transmitter release (4) and increase frequency of AMPAR-mediated synaptic events[60]. Studies in TNFα- and TNFR1-knockout mice indicate that cytokine signaling is necessary for appropriate hippocampus-dependent memory[58]. **d**, During brain inflammation, however, massive increase in TNFα released by activated microglia and/or infiltrated immune cells and overstimulation of astrocyte TNFR1 (1) leads to excess glutamate release (even in the absence of P2Y1R stimulation) (2) and presynaptic NMDAR activation (3). The final effect is a long-lasting enhancement of synaptic transmitter release (4) resulting in impaired contextual memory[62].

plasticity associated with cocaine treatment (both LTP and LTD[119,120]). In keeping with this, exogenous D-serine treatment reverts the impaired plasticity and reduces a number of behavioral manifestations associated with cocaine addiction, including cocaine-induced place preference[121,122], reinstatement of cocaine self-administration (relapse)[123], and locomotor sensitization to cocaine[120,121]. Furthermore, the facts that D-serine treatment can reduce compulsive alcohol intake[124] and that D-serine participates in the mechanisms of morphine addiction[125] suggest a role for altered D-serine signaling in the establishment of addictive behavior at large. Therefore, compounds acting on D-serine metabolism hold promise for the treatment of addictions[118]. Astrocyte signaling via L-lactate likewise appears involved in the formation of maladaptive memories and reinstatement of drug addiction. Accordingly, pharmacological inhibition of astrocyte L-lactate release prevents cocaine relapse by persistently disrupting cocaine-induced conditioned place preference[126,127].

Cannabis-induced disruption of working memory also appears to be astrocyte-mediated (Fig. 4b). Specifically, systemic treatment with Δ^9-tetrahydrocannabinol (THC, the main active compound of marijuana), causes LTD of CA3–CA1 hippocampal synapses and impaired working memory in vivo[44]. Strikingly, parallel tests conducted on astrocyte-specific and neuron-specific CB1R-knockout mice (Table 1) demonstrated that astrocytic, not neuronal, CB1Rs are essential mediators of both the plasticity and behavioral memory effects of THC[44]. These findings demonstrate not only that astrocyte-dependent LTD underlies THC-induced working memory impairment, but also that THC 'hijacks' the astrocyte CB1 signaling pathway normally involved in CA3–CA1 LTP and memory formation[48].

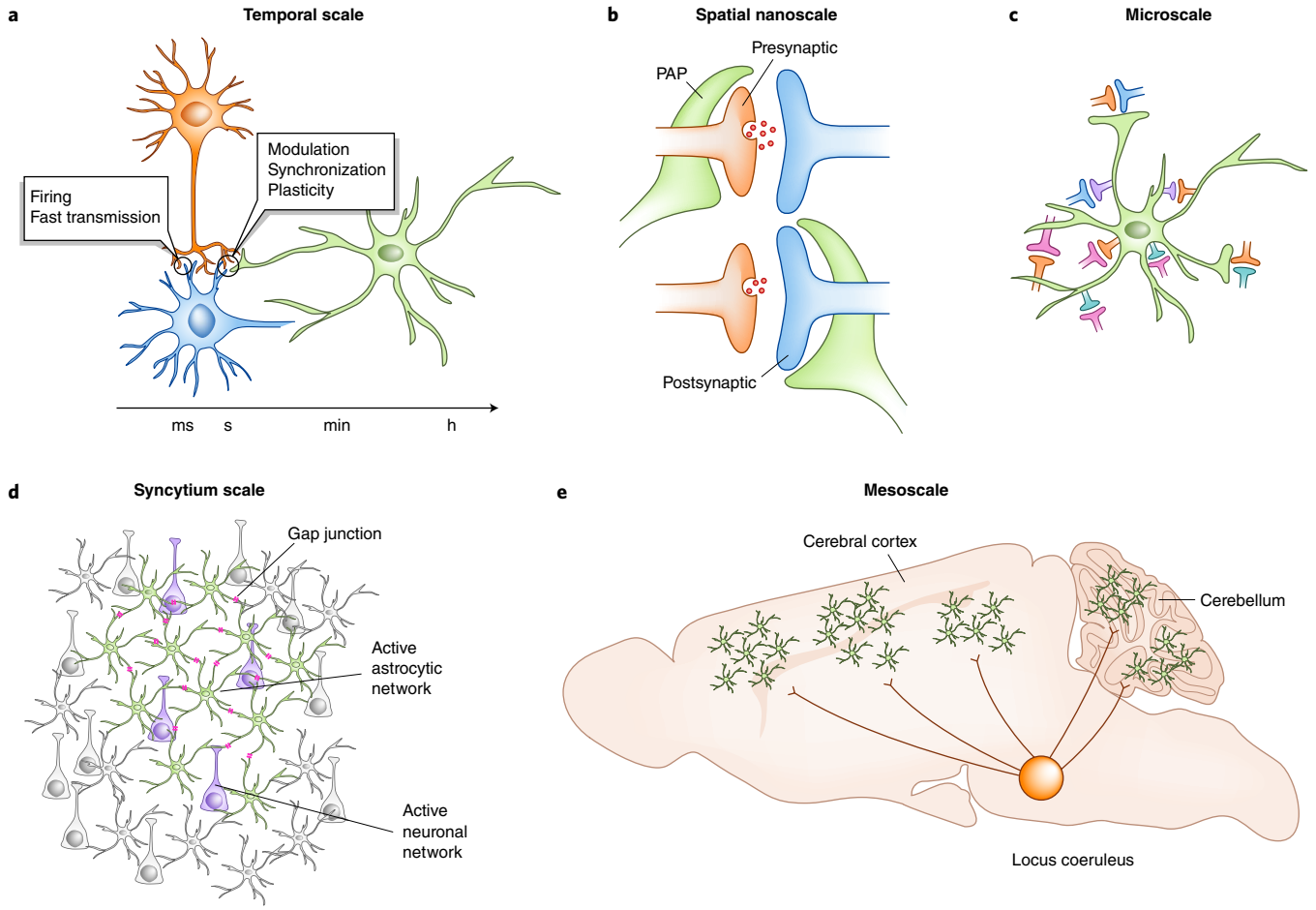

Fig. 5 | Multiscale spatiotemporal integration of astrocytes with synaptic and neuronal networks. a, Communication between neurons and astrocytes occurs on temporal scales (seconds to minutes) distinct from those of neuronal firing and fast excitatory or inhibitory synaptic transmission (which function on millisecond timescales) and likely serves different functions, such as tuning synaptic outputs, inducing long-term changes in synaptic gain, and promoting network synchronicity. **b**, At the spatial nanoscale, local signaling in astrocytic PAPs can target presynaptic terminals to change synaptic transmitter release probability or can target postsynaptic ones to change neuronal excitability. **c**, At the microscale level, an individual active astrocyte can affect coordinately multiple synapses sitting in its territory (different colors denote that synapses belong to different neurons), for example, by simultaneous multisite release of modulatory transmitters. **d**, At a syncytium scale, groups of astrocytes can form dynamic networks (green) via gap-junction connectivity (rose) to match domains of highly active neurons (violet) and support or regulate their function. **e**, At the mesoscale level, populations of astrocytes in different brain areas can respond in concert to activity of long-range neuronal projections, such as noradrenergic fibers from locus coeruleus, to mediate the influence of brain state on complex behaviors, including cognitive performance.

In summary, various astrocytic signaling pathways, some of which play recently identified roles in synaptic, network, and memory functions, undergo profound changes in CNS disorders characterized by cognitive alterations. Their mechanistic contributions to specific conditions are starting to be unraveled, notably via mouse genetics studies.

Conclusions

We here presented evidence that astrocytes are actively involved in normal memory functions as well as in the abnormal processes leading to cognitive impairment in pathological conditions. In many of the presented cases, our understanding of the astrocytic involvement is still incomplete, and more work is required to confirm these findings and better elucidate the specific role played by astrocytes and the precise targets and mechanisms of their action. The notion that astrocytes integrate neuronal functions at synaptic and network levels to influence behavior is rather new, particularly because these cells have long been thought to be largely unable of communication and computing. Only recent findings using state-of-the-art approaches with an ad hoc design to study astrocytes paint a different picture. For example, dynamic cellular imaging work[12,13] reveals an unexpected functional complexity of astrocytes and an intimacy of their interactions with neurons, while astrocyte-targeted mouse genetics boosts the case for astrocyte participation in memory processes, as reviewed here. While leading to these breakthroughs, the technical advances also highlight the incompleteness of our comprehension of astrocyte biology, also illustrated by numerous ongoing controversies in the field[2,4,5]. This calls for development of even better astrocyte-specific investigation tools, techniques, and experimental designs to resolve these controversies and bridge the current gaps in our knowledge.

How may astrocyte interactions with synapses and networks influence neuronal activity and memory performance? Considering the spatiotemporal properties of astrocyte signaling as we currently understand them, there appear to be at least four possible spatial scales of interaction (Fig. 5): first, a nanoscale, at which astrocytes signal in ‘nanodomains’ and may influence local synaptic computations and remodeling[1,12,21,77,128]; second, a microscale, on the order of a single astrocyte, at which the entire cell activates and may exert a coordinated influence on synaptic ensembles residing in its

territory[29,129]; third, a syncytium scale, at which groups of astrocytes form functional domains (via dynamic gap-junction connectivity) matching domains of neuronal activity and may coordinate the excitability of the functional neuronal ensembles and support their energetic demands[40,79]; and fourth, a mesoscale, at which astrocytes from multiple brain regions respond in concert to the activity of long-range neuronal fibers and may thereby contribute to the generation of brain states. At the temporal scale, astrocytes are currently thought to be unable to modulate synapses at the timescale of synaptic events and instead are thought to exert slower influences, by tuning basal synaptic properties like transmitter release probability[77,128] and postsynaptic excitability (Fig. 5a)[2,73]. These slow temporal properties of astrocytes could be essential during induction of synaptic plasticity for maintaining the history of past activity and to initiate plastic changes[47]. Intuitively, a multiscale spatiotemporal astrocytic integration with the neuronal network should produce higher-order organization of the information processing[130]. This is what computational models predict, i.e., that integration of astrocytes improves network performance[131]. In particular, astrocytes would increase firing synchronicity and synaptic coordination[132] and would better tune the networks to oscillatory rhythms underlying memory processing[133].

Specific roles of astrocytes are currently largely speculative. For example, the requirement for L-lactate during long-term memory consolidation could be in support of the additional metabolic needs of the structural remodeling involved in this process. This way, the active metabolic function of astrocytes would be an integral element of brain cognitive function[41]. The fact that L-lactate cannot be substituted in this function by equicaloric glucose[37] hints, however, at additional nonmetabolic functions for this molecule. The need for D-serine in the early phases of memory formation and the fact that, by controlling its availability, astrocytes control synaptic NMDAR function according to the sleep–wake cycle, suggests that astrocytes link vigilance state to memory formation. The same may apply to their activation during arousal, which is known to enhance cognitive performance. Along this line, astrocytes might use cytokine signaling to tune cognitive processing to immune states and, furthermore, by integrating non-neuronal inputs and checking metabolic, redox, pH, immune or other environmental states, astrocytes could perform their own computations, eventually resulting in instructive signals sent to neurons.

Integration of astrocytic signaling in cognitive processing has implications for understanding the basis of cognitive alterations in pathological conditions. We presented several examples in which altered astrocytic signaling affects synapses, networks, and ultimately cognitive performance. These findings suggest that targeting astrocyte pathways may represent an important new therapeutic opportunity to fight against cognitive alterations or decline in many CNS diseases.

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Competing interests

The authors declare no competing interests.

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