A Neuron-Glial Perspective for Computational Neuroscience

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June 30, 2018

Abstract

There is growing excitement around glial cells, as compelling evidence point to new, previously unimaginable roles for these cells in information processing of the brain, with the potential to affect behavior and higher cognitive functions. Among their many possible functions, glial cells could be involved in practically every aspect of the brain physiology in health and disease. As a result, many investigators in the field welcome the notion of a Neuron-Glial paradigm of brain function, as opposed to Ramon y Cayal's more classical neuronal doctrine which identifies neurons as the prominent, if not the only, cells capable of a signaling role in the brain. The demonstration of a brain-wide Neuron-Glial paradigm however remains elusive and so does the notion of what neuron-glial interactions could be functionally relevant for the brain computational tasks. In this perspective, we present a selection of arguments inspired by available experimental and modeling studies with the aim to provide a biophysical and conceptual platform to computational neuroscience no longer as a mere prerogative of neuronal signaling but rather as the outcome of a complex interaction between neurons and glial cells.

1 Introduction

A decade ago, Ben Barres began his famous review on "The Mystery and Magic of Glia" recalling how he first became interested in the function of glial cells as a young neurologist in training. As he looked at brain sections from various neurological diseases under the microscope, not only he came to realize that at least a half of the brain cells are glial cells – astrocytes, oligodendrocytes and microglial cells – but also that glial cell phenotypes are radically altered in many brain injury and disease (Barres, 2008). These early observations grew in him the wonder of what glial cells normally do, and what their role in the disease is – a question that still lingers, beyond his lifetime achievements and the many other findings by his peers.

Abbreviations. Ado: adenosine; AMPA (AMPAR): α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (receptor); ANLS: astrocyte-to-neuron lactate shuttle; AP: action potential; AQP4: aquaporin channel type 4; cAMP: cyclic adenosine monophosphate; CICR: calcium-induced calcium release; CNS: central nervous system; ECS: extracellular space; GABA: γ-Aminobutyric acid; GGC: glutamate–glutamine cycle; GPCR: G protein-coupled receptor; IP_3: inositol 1,4,5-trisphosphate; ISI: interspike interval; Kir: inwardly rectifying K^+ channel; LC: locus coeroleous; LTD: long-term depression; LTP: long-term potentiation; MCT: monocarboxylate transporter; NA: noradrenaline; NBC: Na^+-HCO_3^- cotransporter; NKP: Na^+/K^+ ATPase pump; NMDA (NMDAR): *N*-Methyl-D-aspartate (receptor); SIC (SOC): slow inward (outward) current; SNR: signal-to-noise ratio; SON: supraoptic nucleus; SSR: steady-state synaptic release; TNFα: tumor necrosis factor alpha; V1: primary visual cortex.

It is almost thirty years since the seminal discovery by Anne Cornell-Bell and colleagues that glutamate evokes calcium concentration rises in astrocytes (Cornell-Bell et al., 1990) – a phenomenon later confirmed in slices (Dani et al., 1992; Porter and McCarthy, 1996; Newman and Zahs, 1997) and *in vivo* (Wang et al., 2006), which could also occur in other glia types (Biber et al., 1999; Alberdi et al., 2002; Butt et al., 2004) – and yet our understanding of the functional role of glial calcium signaling is still very limited. As Ca^{2+} signaling can propagate along astrocytic processes and even between glial cells as waves (Cornell-Bell et al., 1990; Dani et al., 1992; Newman and Zahs, 1997; Hirase et al., 2004; Nimmerjahn et al., 2004), the possibility that glial Ca^{2+} waves might constitute an extraneuronal signaling system in the CNS was raised (Newman and Zahs, 1997). The next step was reached with the demonstration that increases in cytosolic Ca^{2+} concentration of astrocytes could regulate the release of neuroactive molecules (Parpura et al., 1994; Nedergaard, 1994; Jeftinija et al., 1996; Coco et al., 2003; Benz et al., 2004) and hormones (Krzan et al., 2003) or influence ion homeostasis (Price et al., 2002). The possibility that these astrocytic Ca^{2+} transients could influence neurons (Parpura et al., 1994; Nedergaard, 1994) and vascular smooth muscles (Zonta et al., 2003; Mulligan and MacVicar, 2004; Gordon et al., 2007), led to the idea that astrocytes are powerful regulators of neuronal spiking, synaptic plasticity and brain blood flow (Nedergaard et al., 2003; Haydon and Carmignoto, 2006).

The current consensus is that neuronal spiking, synaptic plasticity and the coupling between neurons and the vasculature underpin higher brain functions (Laughlin and Sejnowski, 2003). The recognition that glial cells could be much more than passive bystanders of neurons and their synapses has therefore been welcomed as a revolution of the classical Neuron paradigm of the brain in favor of a more comprehensive Neuron-Glial paradigm (Haydon, 2001). Nonetheless few topics in neuroscience are as controversial as the idea that glia could be an active partner in information processing, and cognitive and behavioral tasks elaborated by neurons. In part, this is due to a lack of definite experimental evidence. But in our opinion, much of the controversy originates form the lack of a theoretical platform whereupon to elaborate the Neuron-Glial paradigm. This perhaps comes without surprise in a context where theoretical studies in neuroscience claim they are able to account for many of the computational tasks performed by our brain by the sole consideration of neurons (Abbott et al., 2016). However, understanding the activity patterns of neural activity that support sensory processing (Ganmor et al., 2015), memory (Buzsáki, 2010), decision-making (Beck et al., 2008) and cognition (Rigotti et al., 2013), remains a major challenge for neuroscience theories. In the following we argue that such theories should also take into account a glial component, as we point out to key mechanisms of computational value that are mediated by glia.

2 Glial codes

When talking about neurons, the term 'neural code' refers to the properties of a single sequence of action potentials (spike trains) or a spike train ensemble to encode, decode and process sensory and/or cognitive information (Perkel and Bullock, 1968). Experimental and theoretical approaches to investigate the neural code are often based on presenting different inputs (stimuli) to an animal, and quantifying various properties of the generated spike patterns (Bialek and Rieke, 1992). Is it possible to think of an analogous code for glial cells?

Because glial cells are notoriously electrically passive (Tasaki and Chang, 1958; Steinhaüser et al., 1992), their code (if any) must rely on mechanisms that are different from the membrane potential, and these mechanisms are likely to be found among the many intracellular signaling pathways occurring within glial cells. Supported by modeling arguments (Kummer et al., 2000; Violin et al., 2008; De Pittà et al., 2009), signals originating from receptors in the glial plasma

membrane could all be potential candidates, as long as they bear strong correlation between the triggering extracellular stimulus and the downstream intracellular events, so as not to loose information about the former. This could be the case for example of second messengers like inositol 1,4,5-trisphospate (IP_3), intracellular calcium or cyclic adenosine monophosphate (cAMP) which result from the activation of a rich panoply of G protein–coupled receptors (GPCRs) expressed by glial cells (Porter and McCarthy, 1997; Káradóttir and Attwell, 2007; Pocock and Kettenmann, 2007). However, the diversity of these receptors, and the fact that they are linked to different signaling cascades – G_q-PCRs to IP_3/Ca^{2+} signaling, and G_s- and $G_{i/o}$-PCRs respectively to stimulation and inhibition of cAMP (Gilman, 1987) – suggest that there might be multiple glial codes at play.

Among the possible glial codes, calcium signaling is the most studied one, arguably because of the availability of indicators to monitor intracellular Ca^{2+} (Rusakov, 2015), as well as for its recognized function as intracellular messenger in a multitude of other cells (Berridge et al., 2000). There are nonetheless further reasons why Ca^{2+} signaling could be an effective code for glial cells. In particular, Ca^{2+} signaling could serve all the four key functions originally proposed by Perkel and Bullock for a candidate neural code: stimulus representation, interpretation, transformation and transmission (Perkel and Bullock, 1968).

Stimulus representation is broadly defined as the capability to reflect (or encode) extracellular stimuli by detectable changes in the cell activity. Stimulus representation is clearly carried out by Ca^{2+} signaling, which is at the core of our current notion of glial excitability (Zorec et al., 2012). By such notion, we refer to the ability of glial cells to respond to extracellular stimuli by transient increases of their intracellular Ca^{2+} concentration (Butt, 2006; Agulhon et al., 2008; Kettenmann et al., 2011). And accordingly, we dub a glial cell as 'activated' when its intracellular Ca^{2+} dynamics departs from a baseline concentration (Verkhratsky and Kettenmann, 1996; Hoffmann et al., 2003). Because intracellular Ca^{2+} is a simple ion, one expects the associated signal should be encoded in temporal and spatial patterns of intracellular Ca^{2+} concentration (Figure 1, *yellow pathways*), very similar to the use of electric voltage or current signals in information technology (Jaffe, 1993). The ways by which a stimulus could be represented by glial calcium are multiple. The arguably simplest possibly is that the concentration of the extracellular agonist is encoded in the frequency, or amplitude, or a combination thereof, of the sequence of Ca^{2+} elevations ensuing from stimulation (Schuster et al., 2002; De Pittà et al., 2008).

Interpretation refers to the possibility to reliably decode the information on the stimulus carried by the candidate code. In the case of glial Ca^{2+} signaling, decoding is a necessary readout step for any mechanism that uses intracellular Ca^{2+} to perform a downstream action, be it for example, the release of neuroactive molecules (Liu et al., 2006; Frühbeis et al., 2013; Imura et al., 2013; Araque et al., 2014) and myelin-related proteins (Krämer-Albers et al., 2007), the regulation of the blood flow (Haydon and Carmignoto, 2006; Attwell et al., 2010) or the transcription of cellular factors (O'Neill and Kaltschmidt, 1997). All these processes seem to be strongly constrained by intracellular Ca^{2+} dynamics: some of them require intracellular Ca^{2+} concentration to overcome a threshold value in order to occur (Dolmetsch et al., 1997; Parpura and Haydon, 2000; Pasti et al., 2001; Liu et al., 2006), others depend, in magnitude, on intracellular Ca^{2+} concentration (Zonta et al., 2003; Krämer-Albers et al., 2007). Gliotransmitter exocytosis from astrocytes appears to occur preferentially during rising phases of Ca^{2+} elevations (Pasti et al., 1997; Marchaland et al., 2008), hinting a preferential dependence on the frequency rather than the duration of these elevations (De Pittà et al., 2011). Conversely, the activation of transcription factors positively correlates with the amplitude and duration of Ca^{2+} increases (Dolmetsch et al., 1997). Taken together, these observations hint the existence of readout mechanisms that are finely tuned to extract selective features of the Ca^{2+} signal.

Transformation. The Ca^{2+} signal that is generated within glial cells must be manipulated (i.e. transformed) in a controlled way to allow computations of some sort in order to be effectively regarded as a code. Consider for example the formation of a Ca^{2+} wave, that is a range of Ca^{2+} concentration transients traveling through the cytoplasm of a glial cell or a group of glial cells (Leybaert and Sanderson, 2012). One hypothesis states that these waves result from the spatiotemporal summation of short-lived, spatially-confined Ca^{2+} puffs (Marchant and Parker, 2001) whose coordination is possible by inherent cellular properties, like the characteristic distance between Ca^{2+} puff sites and their spatial coupling set by local Ca^{2+} buffers (Skupin et al., 2008). In this exemple, the generation of the wave is a transformation of the local Ca^{2+} signal. The growing recognition of a compartmentation of Ca^{2+} signals within glial cells, like astrocytes in the cortex (Bindocci et al., 2017) or Bergman cells in the cerebellum (Grosche et al., 1999), also supports the hypothesis of a transformation of Ca^{2+} signals by the cellular architecture, based on its control of the genesis, dynamics and extension of the waves.

Transmission. The candidate code must also enable transmission of information between different cells, allowing for the exchange and propagation of information across cell networks. The propagation of intercellular Ca^{2+} waves in astrocyte networks has been observed in the cortex (Nimmerjahn et al., 2004), the hippocampus (Kuga et al., 2011), the retina (Newman, 2001), or the cerebellum (Hoogland et al., 2009). Ca^{2+} waves could as well occur in microglia and oligodendrocytes either independently (Takeda et al., 1995; Wu et al., 2013; Jiang et al., 2017) or in interaction with astrocytes (Verderio and Matteoli, 2001; Schipke et al., 2002; Parys et al., 2010).

Taken together, Ca^{2+} signalling seems to match the four key functions above. There are however several obstacles on the path of the identification of Ca^{2+} signalling as a glial code. First of all, Ca^{2+} signalling is stochastic, a property that has mostly been studied with Ca^{2+} spikes in cultured astrocytes and microglia (Skupin et al., 2008; Thurley and Falcke, 2011; Thurley et al., 2012, 2014). This stochasticity largely complicates the analysis of Ca^{2+} signalling in glial cells. Moreover, at the molecular level, there might be more than a single Ca^{2+} signalling system at play in glial cells and those different systems might be segregated to distinct subparts of the cell (Volterra et al., 2014). The best known example of this anisotropy is provided by astrocytes, in which the main source of Ca^{2+} for the transients is believed to be Ca^{2+} exchange between the endoplasmic reticulum and the cytosol (Scemes and Giaume, 2006; Leybaert and Sanderson, 2012). However, knockout of IP_3R2 receptors – often considered the main channels responsible for endoplasmic reticulum to cytosol Ca^{2+} transport in those cells (Zhang et al., 2014) – indeed abolished nearly all Ca^{2+} transients in the cell soma, but spared roughly half of the Ca^{2+} transients in the cell processes (Srinivasan et al., 2015). The molecular mechanisms for those IP_3R2-independent Ca^{2+} transients in the processes could rely on additional extracellular calcium fluxes from plasma membrane channels (Srinivasan et al., 2015) or on type-1 or type-3 IP_3R (Sherwood et al., 2017), or a combination thereof.

The presence of different mechanisms of Ca^{2+} spiking has also been suggested to account for the variety of the spatiotemporal scales of the Ca^{2+} signals that include fast ($\sim 0.3 - 0.93\,s$) Ca^{2+} events, locally confined in astrocytic processes (Di Castro et al., 2011; Bindocci et al., 2017); as well as large, and longer ($> 5\,s$) Ca^{2+} signals spanning whole processes, and that can invade the whole cell (Volterra et al., 2014; Bindocci et al., 2017). This is reminiscent of the hierarchy of Ca^{2+}induced-Ca^{2+}release (CICR)-mediated Ca^{2+} events that, from blips and puffs – respectively associated with the opening of individual IP_3R receptors or a cluster thereof – can ultimately lead to the generation of cell-wide Ca^{2+} spikes.

There is however evidence that the distribution of intervals between consecutive Ca^{2+} blips or puffs at the astrocyte periphery, maybe different from those reported for CICR-mediated Ca^{2+} events in primary processes and somata (Bindocci et al., 2017). Therefore, a major open

question in the field is to decide wether the different Ca^{2+} signals observed in astrocytes are the result of the spatiotemporal summation of a unique underlying microscopic mechanism or of different microscopic mechanisms, each possibly attached to a specific location in the cell.

3 Oligodendrocytes and regulation of axonal electric conduction

A unique specialization of glia in vertebrates is myelination, that is the ensheathing of axons by myelin (Waehneldt et al., 1986; Zalc et al., 2008). Myelination provides at least two advantages. First, compact lipid-rich myelin provides high membrane electrical resistance and low capacitance, which prevents current loss and enables rapid and efficient action potentiel (AP) conduction. Second, increased conduction velocity allows for computational complexity within a compact nervous system such as that of vertebrates (Fields, 2008).

Oligodendrocytes are the specialized glial cells responsible both for axon myelination, and for the formation and maintenance of nodal structures and lifelong integrity of axons in the CNS (Nave, 2010). By controlling the structural properties that characterize myelinated axons, oligodendrocytes likely participate to the fine tuning of action potential shape and conduction velocity (Kimura and Itami, 2009; Tomassy et al., 2014; Ford et al., 2015; Hughes et al., 2018). This could be achieved either by changes of myelin thickness or internode length or node geometry, or by a combination thereof (Ullén, 2009; Fields, 2008; Arancibia-Carcamo et al., 2017). For instance, adjustments of conduction speed of myelinated axons can tune propagation times to mediate sound localization (Carr and Konishi, 1990; McAlpine and Grothe, 2003; Seidl et al., 2010; Ford et al., 2015) or promote synchronous neuronal firing (Sugihara et al., 1993; Lang and Rosenbluth, 2003). Together with delays induced by the AP-generation dynamics (Fourcaud-Trocmé et al., 2003) and those rising from synaptic processing (Markram et al., 1997), axonal conduction delays are an important property of neural interactions, which may induce a wealth of dynamical states with different spatiotemporal properties and domains of multistability which could serve different computational purposes (Roxin et al., 2005; Roxin and Montbrió, 2011).

The observation that the tuning of conduction delays by oligodendrocytes continues during adulthood (Dimou et al., 2008; Young et al., 2013) suggests the thought-provoking possibility that these different states could change in an experience-dependent way, i.e. in a manner that depends on neuronal electrical activity (Fields, 2013). The potential functional and computational implications of this two-way regulation of oligodendrocyte-mediated transmission delays and neuronal activity remain to be investigated but we note that the active control of conduction delays of axon ensembles by oligodendrocytes may lead to time-locked patterns of activation of the neurons – a concept known as polychronization which could be of great computational significance (Izhikevich, 2006).

4 Glia morphology and functional specialization

The factors underpinning morphogenesis of neuronal structures remain poorly understood, in particular when one includes neuron-glia interactions into the equation. Experimental studies have identified a combination of transcriptional programs and a battery of molecular signals that seem to be regulated both developmentally and regionally, in a cell-specific manner (Jadhav et al., 2009; Eroglu and Barres, 2010; Götz, 2013; Stassart et al., 2013). A paramount example of this complex combination of factors is provided by astrocytes, the glial cells recognized as key regulators of the neuronal connectome in the cortex and hippocampus (Fields et al., 2015). In the postnatal developing brain, astrocytes are found in spatially distinct domains and

express domain-specific genes that are needed to support formation of specific neural circuits and neuronal subtypes (Molofsky et al., 2014). Astrocytes also secrete a variety of molecules that regulate with spatiotemporal specificity all stages of the genesis of functional neural circuits (Allen, 2013; Clarke and Barres, 2013). This intimate relationship between astrocytes and synapses continues in the adult brain, with the processes of the astrocytes that wrap themselves around synapses (Reichenbach et al., 2010), engaging in a multitude of signals (Figure 1). Eventually, a single astrocyte contacts circa 20–150 thousand synapses in the rodent (Bushong et al., 2002), and $\sim$ 300 thousand to 2 million synapses in the human brain (Oberheim et al., 2009). What are the possible functional impacts of this ensheathing?

One obvious possibility is that astrocytic processes are strategically positioned at synaptic loci to act as physical barriers that constrain and regulate extracellular diffusion of neurotransmitters (Ventura and Harris, 1999). A realistic reconstruction of the extracellular space (ECS) between astrocytic processes and glutamatergic synapses of the hippocampus revealed a strong impact of astrocyte arrangements on glutamate diffusivity (Kinney et al., 2013). The degree of astrocytic ensheathing at glutamatergic synapses also directly dictates the rate of glutamate uptake by glial transporters – the main mechanism of glutamate uptake in the adult brain (Clements, 1996; Danbolt, 2001). The degree of astrocyte ensheathment seems inversely correlated with the size of dendritic spines (Medvedev et al., 2014). This suggests that, in agreement with independent theoretical arguments (Barbour, 2001), smaller synapses are strongly sealed by astrocytic processes whereas larger synapses might exhibit more glutamate spillover (Ventura and Harris, 1999).

An additional element of complexity is that astrocytic processes are highly motile and may undergo structural changes in response to neural activity (Heller and Rusakov, 2015). Activity-dependent plasticity of perisynaptic glial processes has been reported in the rat supraoptic nucleus in relation with parturition (Oliet et al., 2001; Piet et al., 2004b), in the hypothalamic suprachiasmatic nucleus in association with circadian light/dark cycles (Becquet et al., 2008), in the hippocampus (Haber et al., 2006; Verbich et al., 2012) and the cerebellum in correlation with neural activity (Lippman et al., 2008, 2010) and in the somatosensory cortex *in vivo* by sensory stimulation (Bernardinelli et al., 2014b; Perez-Alvarez et al., 2014). Those results suggest that activity-dependent plasticity of perisynaptic glial processes is a brain-wide phenomenon, although its functional consequences are likely region-specific (Khakh and Sofroniew, 2015). At hippocampal excitatory synapses for example, astrocyte processes preferentially colocalize with the postsynaptic element (Rusakov, 2001; Lehre and Rusakov, 2002). Simulations of glutamate diffusion at those synapses suggest that this arrangement favors glutamate spillover to the presynaptic elements (Rusakov, 2001; Lehre and Rusakov, 2002). This could promote activation of presynaptic metabotropic receptors, and account for feedback inhibition mediated by these receptors at mossy fiber-pyramidal cell synapses (Lehre and Rusakov, 2002; Nicoll and Schmitz, 2005; Omrani et al., 2009).

Glial transporters and the degree of glial coverage of synapses have also been implicated in the control of long-term plasticity at excitatory synapses. Astrocytic glutamate transporters gate spike-timing–dependent plasticity in the striatum ex-vivo (Valtcheva and Venance, 2016), as well as rate-coded long-term potentiation (LTP) in the amygdala (Tsvetkov et al., 2004) and in the hippocampus (Katagiri et al., 2001; Lushnikova et al., 2009). LTP induction in the hippocampus correlates with dynamical changes of astrocytic processes at the stimulated synapses (Lushnikova et al., 2009; Bernardinelli et al., 2014b; Perez-Alvarez et al., 2014), and these changes could associate with long-lasting spine formation and remodelling (Lushnikova et al., 2009; Verbich et al., 2012; Bernardinelli et al., 2014b). Taken together, those results pinpoint a key role for activity-dependent, dynamical reshaping of glial ensheathing in the control of synapse morphology, extracellular glutamate homeostasis, and the functionality of

neural circuits (Bernardinelli et al., 2014a).

5 Ion homeostasis and volume regulation

Glial cells express a vast cassette of ion channels, transporters and pumps whereby they can sense and regulate extracellular ion concentrations with important functional consequences on neural activity (Kettenmann and Ransom, 2013; Simard and Nedergaard, 2004). One of the first recognized possible functions of astrocytes was their importance in the maintenance of extracellular K^+ (Figure 1, *blue pathway*) (Hertz, 1965; Orkand et al., 1966). Although traditionally considered in a pathological context including epilepsy and spreading depression (Somjen, 2002), electrophysiological recordings *in vivo* also implicate modulations of extracellular K^+ by astrocytes in the regional control of neuronal excitability in the healthy brain (Amzica et al., 2002; Djukic et al., 2007; Chever et al., 2010). The resting membrane potential of neurons depends on intra- and extracellular concentrations of different ions (by the Goldman-Hodgkin-Katz equation) (Johnston and Wu, 1995), so changes of extracellular K^+ concentration can alter neuronal excitability. Theoretical investigations suggest that the interplay of astrocytic Na^+/K^+ pumps (NKPs) and Kir4.1 channels (Walz, 2000) can promote AP generation in conditions of low neuronal firing (Somjen et al., 2008), thus potentially contributing to the brain basal level of spontaneous neural activity (Deco et al., 2011). Alternatively, depending on the activity level, this could translate into a non-trivial positive feedback on neuronal firing, turning regular spiking dynamics into bursting (Somjen et al., 2008; Øyehaug et al., 2012; Cui et al., 2018).

Astrocyte-mediated regulation of extracellular K^+ also affects neuronal excitability by modulating the time course of glutamate at excitatory synapses (Djukic et al., 2007). For each glutamate molecule transported, glial glutamate transporters co-transport 3 Na^+, 1 H^+ and 1 K^+ (Levy et al., 1998). Therefore alteration of extracellular K^+ concentration is expected to change the rate of glutamate uptake, thus modulating the excitatory drive of a neuron and its firing dynamics.

Astrocytes also express a number of transporters involved in pH regulation (Deitmer and Rose, 1996, see also Figure 1, *brown pathway*) that may be affected by alterations of K^+ concentration and glutamate transport rate. The impact of these glial transport/uptake systems on neuronal computation would strongly depend on the stoichiometry of individual transporters and their spatial organisation on the glial plasma membrane along with that of ion channels and pumps. All this can vary depending on the brain region (Kofuji and Newman, 2004; Rose and Chatton, 2016). In the rat optic nerve, for example, extracellular K^+ buffering seems more dependent on NKPs than on Kir channels (Ransom et al., 2000). Similarly, glial K^+ spatial buffering, which ensues from the electrotonic propagation of a K^+ current in glial cells from ECS regions where K^+ is high to others where the concentration of this ion is low (Orkand et al., 1966), may be carried out differently in astrocytes vs. Müller glia, possibly because of the different expression and distribution of Kir channels in these cells (Kofuji and Newman, 2004).

Another specificity of astrocytes in connection with extracellular ion homeostasis is that their volume can change by activity-dependent modulations of extracellular K^+ (Florence et al., 2012; Larsen et al., 2014). Although the molecular mechanisms of astrocytic swelling remain to be elucidated, colocalization of astrocytic Kir4.1 with aquaporin water channels AQP4 strongly supports a role for these channels in this phenomenon (Nagelhus et al., 2004). Compartmental modelling supports a mechanism whereby K^+ influx into astrocytes through Kir4.1 channels, resulting from K^+ buffering of neuronal activity, sets an osmolarity gradient across the astrocyte membrane which drives extracellular water into the astrocyte by AQP4 channels, thus increasing

the cell volume (Østby et al., 2009). Bicarbonate (HCO_3^-) homeostasis also plays a crucial role in physiological astrocyte swelling (Florence et al., 2012), presumably by improving the steepness of the osmolarity gradient (Østby et al., 2009).

6 Gliotransmission

Gliotransmission, that is the active information transfer from astrocytes to neurons (Bezzi and Volterra, 2001) probably bears the widest implications in information processing. There is arguably no other concept that epitomizes the Neuron-Glia paradigm better than the "tripartite synapse", whereby astrocyte is the third active element in synaptic information transfer besides the pre- and postsynaptic terminals, sensing synaptically-released neurotransmitters by a variety of mechanisms, and signaling back to synaptic terminals by gliotransmission (Figure 1, *red pathway*) (Araque et al., 1999, 2014). An emerging view is that gliotransmission is probably not a global, stereotyped On-Off phenomenon, but rather a multifaceted one, dependent on age, circuit, stimulation and the considered synapse (Savtchouk and Volterra, 2018). Indeed, not all synapses are tripartite: $\sim 10\% - 50\%$ of cortical and hippocampal synapses are not adjacent to any astrocytic process (Ventura and Harris, 1999; Witcher et al., 2007; Kasthuri et al., 2015) and that proximity of glial processes to dendritic spines varies depending on the brain area (Ventura and Harris, 1999; Grosche et al., 2002) and on the considered synapse in a given area (Chao et al., 2002). The existence of such bidirectional communication between astrocytes and synapses in physiological conditions is therefore still lively debated (see e.g. Fiacco and McCarthy (2018) and Savtchouk and Volterra (2018)). However consideration of this possibility opens to profound functional implications as it puts astrocytes in the position to actively control synaptic transmission.

Although astrocytes can release a range of gliotransmitters, including glutamate, ATP, GABA and D-serine (Sahlender et al., 2014), the effects of these gliotransmitters can be generalised in terms of modifications of short- and long-term properties of synapses. Consider first short-term synaptic dynamics. An important consequence of this dynamics is that synapses can act as filters of the AP sequence they transmit (Fortune and Rose, 2001). However, the filtering characteristics of a given synapse is not fixed but can be adjusted through modulation of the initial release probability p_0 (Dittman et al., 2000). Depending on receptor type, gliotransmitters may either increase or decrease the value of p_0 at both excitatory and inhibitory synapses (Araque et al., 2014; Angulo et al., 2008), thereby turning high-pass filtering synapses into band-pass filtering ones, or band-pass filtering synapses into low-pass filtering ones, and vice versa (De Pittà et al., 2015). Low-pass filtering synaptic characteristics associates with derivative synaptic coding, that is the transmission of variations (i.e. the derivative) of AP sequences, as opposed to high-pass filtering, which results instead in integrative synaptic coding and carries information on the count of incoming APs (Tsodyks, 2005). Hence, modulation of synaptic filtering by gliotransmitters could make a synapse alternate between these different coding modes (De Pittà and Brunel, 2016).

The modulation of synaptic release probability by gliotransmitters may also occur on multiple time scales (reviewed by De Pittà et al., 2015). It may lasts for tens of seconds up to few minutes, thus affecting synaptic transmission and network computations merely for a transient period of time. But it can become persistent and last for tens of minutes, that is on time scales that could promote long-term plastic changes of the synapse (Bear and Malenka, 1994). This possibility was showed to account for long-term depression (LTD) at glutamatergic synapses between neurons in layers 4 and 2/3 of the barrel cortex (Min and Nevian, 2012). Long-term modulations of synaptic release are expected to substantially alter the recruitment of postsynaptic NMDA receptors, thereby modulating the influx of Ca^{2+} ions (Froemke and Dan, 2002;

Froemke et al., 2006, 2010). Because the time course of postsynaptic Ca^{2+} is believed to control the outcome of spike-timing–dependent plasticity (STDP) – namely whether LTP or LTD is observed (Ismailov et al., 2004; Nevian and Sakmann, 2006; Graupner and Brunel, 2010), the above arguments predict that persistent alterations of synaptic release by gliotransmitters modulate STDP. Computational arguments however hint that this modulation is not straight forward and depends on the timing of gliotransmitter release from perisynaptic astrocytic processes with respect to pre- and postsynaptic APs (De Pittà and Brunel, 2016).

Gliotransmitters may also modulate the probability of activation of postsynaptic receptors, either by the release of D-serine from astrocytes, which is a co-agonist for NMDA receptors with synaptically-released glutamate (Oliet and Mothet, 2009), or by slow depolarizing and hyperpolarizing currents (De Pittà and Brunel, 2016), respectively mediated by extrasynaptic NMDA and GABA receptors (Kozlov et al., 2006; Jiménez-González et al., 2011; Chen et al., 2012; Le Meur et al., 2012; Martín et al., 2015). How could gliotransmission affect learning via modulation of synaptic plasticity? Although this topic remains to be investigated, few theoretical studies offer some enticing insights into the question. Porto-Pazos and collaborators investigated the performance of an astrocyte-inspired learning rule to train deep learning networks in data classification and found that the trained neuron-glial networks were able to outperform identical networks without astrocytes in all discrimination tasks they implemented (Porto-Pazos et al., 2011; Alvarellos-González et al., 2012; Mesejo et al., 2015). Although those investigators do not provide any explanation for the possible mechanism whereby astrocyte-mediated plasticity could improve network learning and performance, a significant feature of their learning rule is that, for successful training, potentiation by astrocytes must be weaker than depression resulting from astrocyte inactivity (Alvarellos-González et al., 2012; Mesejo et al., 2015). In their model, this amounts to putting the threshold between LTP and LTD under the control of astrocyte activity. There is circumstantial evidence that astrocytes could modify the threshold for LTD vs. LTP induction, such as in the supraoptic nucleus – where astrocytic coverage of synapse is reduced during lactation (Panatier et al., 2006).

Philips et al. (2017) devised a modified version of the BCM rule (Bienenstock et al., 1982; Gerstner and Kistler, 2002) where the threshold rate of postsynaptic firing for induction of LTD vs. LTP varies proportionally with astrocyte activation, and investigated how this rule affects development of orientation preference maps (OPMs) in a self-organizing network model of the primary visual cortex (V1) (Stevens et al., 2013). This choice not only allows reproducing map orientation experimentally observed in V1, but also reveals that, upon reduction of astrocytic radius, the periodicity of OPMs increases while the width of individual hypercolumns decreases (Philips et al., 2017). Since astrocyte size varies across species (Oberheim et al., 2009; López-Hidalgo et al., 2016), these results predict a causal link between astrocytic radius and the different hypercolumn widths observed in different species (Kaschube et al., 2010).

7 Resource management

Glucose is the almost exclusive energetic fuel of the mammalian brain and can completely sustain neural activity acting as a substrate for the synthesis of lipids and amino acids, as well as of neurotransmitters like glutamate, GABA or acetylcholine (Dienel, 2012; Mergenthaler et al., 2013). Cerebral glucose fuels neural activity by glycolysis which converts glucose into pyruvate by the concomitant production of two molecules of ATP. Pyruvate may then either enter mitochondria, where it is oxidized by Krebs cycle, or be temporarily converted to lactate in the cytoplasm for later use. Moreover, lactate produced in one cell can also be released into the ECS and be used by other cells (Simpson et al., 2007). Glucose supply to the brain is mainly either through the interstitial fluid by blood circulation or by metabolism of intracellular glycogen

– the only glucose store. Multiple mechanisms ensure neurovascular coupling whereby local energy supply, together with the cerebral blood flow, is finely adjusted to variations of the neuronal activity to allow normal neuronal function (Magistretti and Allaman, 2015). Astrocytes have been implicated in all aspects of this coupling. They can regulate cerebral blood flow, by dilating or constricting blood vessels through multiple Ca^{2+}-dependent pathways (Figure 1, *magenta pathway*) (Iadecola and Nedergaard, 2007; Attwell et al., 2010). In parallel, they can actively supply glucose through glycogen and by production of lactate – possibly triggered by the energy demand of excitatory synaptic activity (Magistretti and Allaman, 2015).

The proposal of an astrocyte-to-neuron lactate shuttle (ANLS) was originally formulated by Pellerin and Magistretti (1994) and envisages the generation of lactate at excitatory synapses by astrocytes, and its export to neurons where it is converted to pyruvate for ATP generation in mitochondria (Pellerin and Magistretti, 2012). This scheme could regulate the energy supplied to neurons in response to their activity, since glutamate released by active neurons could promote lactate production in astrocytes by stimulating glycolytic ATP generation to power astrocytic uptake of glutamate in a positive feedback loop (Figure 1, *purple pathway*). However, it is not clear under what circumstances of neuronal activation the ANLS could occur, as well as if it could be a brain-wide signaling pathway, or rather depend on the architecture of local neuron-glial circuits (Vaishnavi et al., 2010; Bélanger et al., 2011; Magistretti and Allaman, 2015). Actually, the only evidence *in vivo* for the ANLS at present, sees it implicated in hippocampal LTP maintenance (Suzuki et al., 2011) and spatial working memory (Newman et al., 2011).

Astrocytes are also mediators of the glutamate–glutamine cycle (GGC) (Danbolt, 2001; Hertz, 2013), whereby synaptically released glutamate is taken up by astrocytic transporters and converted to glutamine by glutamine synthase – an enzyme exclusively found in astrocytes (Figure 1, *turquoise pathway*). Glutamine is then released to the ECS, where it is sequestered by neurons and reconverted to glutamate, and by this latter, possibly to GABA too (Rothman et al., 2003; Hertz, 2013). The GGC can continuously supply neurotransmitters to neurons to sustain synaptic transmission, both at excitatory and at inhibitory synapses. At cortical and hippocampal excitatory synapses however, neurotransmitter supply by GGC was proven necessary to sustain synaptic release for prolonged, high-frequency stimulations, but appeared dispensable in conditions of low synaptic activity (Tani et al., 2014).

8 Microglia in neuronal and astrocytic signaling

Microglial cells roughly constitute 5% to 15% of the brain's cellular elements, representing the most numerous glial population in the brain after astrocytes and oligodendrocytes (Lawson et al., 1990; Pelvig et al., 2008). Although they are traditionally described to comprise the main component of the brain's innate immune system by responding to any pathological insult, experimental observations over the past two decades also suggest an involvement of these cells in the genesis and function of neural circuits in the healthy brain (Kettenmann et al., 2013).

Microglial processes in the somatosensory and visual cortex make brief, repetitive contacts with synapses at a frequency of about once per hour (Nimmerjahn et al., 2005; Wake et al., 2009). The nature of these contacts is synapse-specific and varies with neuronal activity and brain region. Visual deprivation shifts the preferential association of V1 microglial processes to small dendritic spines that transiently grow, to a subset of bigger spines that persistently shrink (Tremblay et al., 2010). Reduction of spontaneous neuronal activity correlates with retraction of microglial processes in the visual cortex (Wake et al., 2009), but not in the somatosensory cortex (Nimmerjahn et al., 2005).

Besides a role in structural synaptic plasticity (Stevens et al., 2007; Schafer et al., 2012; Kettenmann et al., 2013), microglia could also participate in several forms of functional synaptic

plasticity (Kettenmann et al., 2013; Wake et al., 2013). This could be achieved either directly, by release from microglia of plasticity-inducing molecules, or indirectly, through the modulation of gliotransmission-mediated pathways of plasticity (Section 6). In the latter scenario in particular, microglia could either promote (Pascual et al., 2011) or amplify glutamate release from astrocytes (Bezzi et al., 2001) (Figure 2, schemes A and E), with the potential to modulate excitatory synaptic transmission and neuronal excitability in a variegated fashion.

The proinflammatory cytokine tumor necrosis factor alpha (TNFα) is tightly related to microglia. Brain TNFα production can be stimulated by neuronal activity (Churchill et al., 2008), and the cytokine can be released into the ECS both by astrocytes and by microglia (Habbas et al., 2015; Lewitus et al., 2016). TNFα is found in low concentrations in the ECS in physiological conditions (Santello and Volterra, 2012), where it seems necessary for normal glutamatergic gliotransmission (Bezzi et al., 2001; Stellwagen et al., 2005; Domercq et al., 2006; Santello et al., 2011; Pribiag and Stellwagen, 2013) and regulation of homeostatic synaptic plasticity mechanisms, like synaptic scaling (Steinmetz and Turrigiano, 2010). The implication of TNFα in synaptic scaling may be important during competition with Hebbian plasticity, for instance for ocular dominance plasticity (Kaneko et al., 2008).

9 Glia in higher brain functions

A popular argument, often raised to wow the audience, is that Albert Einstein's brain, when first inspected, did not look statistically significantly different from that of other individuals with normal cognitive ability, except for a higher glia/neuron ratio, leading to speculate that the larger number of glial cells could partly have accounted for Einstein's exceptional intelligence (Diamond et al., 1985). The further observation that Einstein's corpus callosum – the largest bundle of myelinated fibers in the brain that connects the two cerebral hemispheres – was thicker in several subregions than in elderly and younger individuals certainly added to the popularity of the argument (Men et al., 2014). Although the studies at the origin of those sensational results have been strongly opposed because of methodological issues or interpretation biases (Fields, 2009), the implication of glia in higher brain functions is still an hypothesis that cannot be rejected.

From an evolutionary point of view, glia emergence coincides with the appearance of the centralized nervous systems (Hartline, 2011), and later on, with the birth of radial glial cells which hallmark the development of nervous systems of chordates and vertebrates, and are precursors of astrocytes in the adult brain of these animals (Sild and Ruthazer, 2011). In parallel, the evolution of myelin reduced the energy required for neuronal communication and boosted the speed of impulse propagation, allowing complex nervous systems to operate quickly and efficiently (Zalc and Colman, 2000). Oligodendrocytes also provide trophic support for the axons they myelinate, thus allowing for longer axons and, ultimately, greater vertebrate size (Nave, 2010). As nervous systems increase in complexity, a trend in increased complexity is also observed for astrocytes (Verkhratsky and Nedergaard, 2016). Human and primate astrocytes are larger and more branched than rodent ones, with humans astrocytes generally being the largest (Oberheim et al., 2009). Moreover, human astrocytes morphologies are more divers, with some morphologies that are not observed in other species (Colombo and Reisin, 2004; Oberheim et al., 2009). A landmark study by Maiken Nedergaard's group considered the injection of human glial progenitor cells into the ventricles of newborn mice (Han et al., 2013). As those progenitors cells differentiated into mature astrocytes and oligodendrocytes, the adult engrafted animals were found to outperform their littermates that did not receive human glial progenitor grafts, on multiple cognition tests, including novel object recognition and fear conditioning. Overall, these observations provide direct evidence that human astrocytes boost cognitive abilities of

mice, possibly by increasing neural plasticity (Han et al., 2013).

Several lines of evidence in humans and in other animal models link glia function with the development and maturation of multiple cognitive and motor skills (Fields, 2008; Oliveira et al., 2015). Beyond motor performance, sensory processing is of great importance for appropriate evaluation of behavior. The development and function of cortical maps seem coupled with astrocytic signaling (López-Hidalgo and Schummers, 2014). In the primary visual cortex for example, astrocytes are integral components of OPMs, as they are both visually responsive and capable of modulating visually driven responses in close register with receptive fields of individual neurons (Schummers et al., 2008). In addition, astrocytes, either individually or in association with microglia, could control OPM formation during developmental plasticity (Sections 6 and 8), as well as during adulthood (López-Hidalgo and Schummers, 2014). Gliotransmission has also been implicated in the sensory modulation of rhythmic activity of the central pattern generators responsible for breathing and chewing (Kadala et al., 2015; Del Negro et al., 2018). Stimulation of glutamatergic sensory fibers that project onto the trigeminal sensory-motor circuit for mastication can indeed activate astrocytes, triggering Ca^{2+}-dependent release of the astrocyte-specific Ca^{2+}-binding protein S100β. In turn, this results in a reduction of Ca^{2+} in the ECS which promotes rhythmic bursting at frequencies that are compatible with those observed for voluntary chewing (Morquette et al., 2015; Condamine et al., 2018). In addition, medial basal hypothalamic astrocytes can control feeding behavior bidirectionally by purinergic gliotransmission, regulating appetite under both favorable and unfavorable conditions (Yang et al., 2015). Thus, astrocytes critically regulate food intake which is a crucial behavior for energy homeostasis, preventing energy deficits or surfeit.

In the general framework of neuronal network theory, glia-mediated variations of network activity may ultimately be linked to modulations of the balance between excitation (E) and inhibition (I). This possibility arises by the analysis of the few currently available models of neuron-glia network dynamics which come in different flavors, as a result of the combination of different E–I network configurations with different choices of neuronal (and synaptic) models and astrocytic signaling pathways (Savin et al., 2009; Ullah et al., 2009; Volman et al., 2013; Savtchenko and Rusakov, 2014; Garnier et al., 2016). Nonetheless, all these models eventually envisage an effect of glial signaling in terms of a modulation of synaptic drive, either at excitatory (Savin et al., 2009; Savtchenko and Rusakov, 2014) or at excitatory and inhibitory synapses (Ullah et al., 2009; Volman et al., 2013; Garnier et al., 2016), which accounts for emergence of a variety of network activities. Similar observations may also be made by other models which consider different scenarios of gliotransmission, such as short-term modulation of E-to-I synaptic connections by glutamatergic or purinergic gliotransmission (Savtchenko and Rusakov, 2014), or homeostatic upregulation of excitation by glial TNFα, although the latter scenario could also account for emergence of paroxysmal activity in various pathological conditions (Volman et al., 2013). Significantly, these models identify the spatial extent of gliotransmission as a key factor for the regulation of glia-mediated episodes of increased network activity (Volman et al., 2013; Savtchenko and Rusakov, 2014). In these models, the transient depression of synapses within an astrocytic anatomical domain correlates with a decrease of neuronal firing and synchronization, which is larger for larger astrocytic domains (Savtchenko and Rusakov, 2014). In the context of oscillatory network dynamics, this could then account for reductions of specific frequencies of oscillation with possibly multiple functional and behavioral consequences (Buzsáki and Draguhn, 2004). For example, selective, inducible inhibition of vesicular release from brain-wide astrocytic domains was shown to reduce the power spectrum of gamma frequency oscillations ($\sim$25–80 Hz) in living mice and, ultimately a performance deficit in novel object recognition tasks (Lee et al., 2014)(Lee et al., 2014). Another possible pathway that has indeed been linked with memory consolidation during fear conditioning is gliotransmitter

release by connexin 43 (Cx43) hemichannels (Stehberg et al., 2012).

Another illustration is the putative involvement of glia in sleep regulation. Many factors involved in the regulation of sleep are still unknown, yet mounting evidence indicate glia as integral component of the neurobiological substrate underpinning circadian and homeostatic mechanisms believed to regulate sleep (Halassa and Haydon, 2010; Jackson, 2011; Petit and Magistretti, 2016). In the suprachiasmatic nucleus of the hypothalamus where the main circadian clock resides, neuron-glial networks undergo rhythmic structural reorganization during the 24 h light/day cycle, which is deemed necessary for appropriate adjustment of the circadian clock to this cycle (Becquet et al., 2008). Gene transcription analysis revealed that several genes that control diverse aspects of glial morphology and function are differentially expressed during sleep vs. wakefulness, independently of the behavioral state (Cirelli et al., 2004; Bellesi et al., 2013, 2015). In parallel, compelling evidence also link astrocytes with homeostatic mechanisms of sleep. Extracellular accumulation during wakefulness of adenosine originating from astrocytic ATP, has been implicated in the progressive need of sleep (also dubbed "sleep pressure") (Pascual et al., 2005; Schmitt et al., 2012; Bjorness et al., 2016), as well as in cognitive impairment associated with prolonged periods of sleep deprivation (Halassa et al., 2009; Florian et al., 2011). Spatially-confined extracellular glutamate increases that correlate with astrocytic Ca^{2+} activation could also promote putative sleep states at the level of individual brain regions, triggering there slow wave activity characteristic of non-random eye movement (NREM) sleep (Nir et al., 2011; Vyazovskiy et al., 2011; Poskanzer and Yuste, 2016).

10 Conclusions

The variety of experimental and theoretical arguments presented in the previous sections outlines a role for glial cells in the control of multiple mechanisms underpinning information processing by the brain. Although this role can in principle extend to the whole brain, in its many spatial and temporal scales of activity, the biophysical considerations made here also support the idea of a strong regional specialization for neuron-glial interactions and function, ensuing from evolutionary, developmental and environmental (activity-dependent) factors (Sections 2 and 4). The multiplicity of chemical signals that glial cells can sense and generate in response to neuronal activity also make these cells potential signaling hubs in the neuropil. Accordingly, glial cells could sense different aspects of neuronal activity, such as electrical signals, synaptic neurotransmitters, structural changes, energy demands and vascular metabolites, thanks to a rich cassette of membrane receptors, channels, transporters, and pumps (Sections 4 and 5). In turn, they can release multiple molecules with different, and potentially multiple signaling roles. Gliotransmitters like ATP and glutamate for example, could also be involved both in metabolic (Section 7) and in inflammatory processes (Section 8). Conversely, glial release of the proinflammatory cytokine TNFα could be permissive towards gliotransmission and homeostatic mechanisms of plasticity (Section 8). While signaling multiplexing may be guaranteed by spatially and temporally distinct scales of action of different signals impinging on and mediated by glial cells, it should be emphasized that these different signals could also be interdependent, with potential for emergence of nontrivial correlations in the neural code (Section 9).

It may be objected that the majority of the arguments exposed here link glial signaling to neurobiological mechanisms that are generally regarded to underpin computations performed by the brain but for which a definitive experimental connection with higher brain functions is still missing (Section 10). This however does not weaken the original motivation of our hitherto discussion, that is the conceptualization of a Neuron-Glial paradigm of the brain; rather it should prompt readers to revise our knowledge of the literature from a different, potentially deeper perspective, inclusive of glial signaling. We indeed predict that many contradicting

results in neuroscience and poorly understood signaling pathways of the brain could benefit from novel investigations driven by a theoretical understanding of the possible functional relevance of neuron-glial interactions in brain physiology.

Figure captions

Figure 1. Interaction of astrocytes with neuropil and vasculature. Simplified illustration of the main pathways of interaction of astrocytes with neurons at glutamatergic synapses. (*Yellow pathway*) *Calcium signaling.* Glutamate (Glu) spillover from the synaptic cleft targets metabotropic receptors (mGluR) on perisynaptic astrocytic processes which trigger inositol 1,4,5-trisphosphate (IP_3)-mediated calcium (Ca^{2+}) release from the cell's endoplasmic reticulum (ER). IP_3 can also diffuse intra- and inter-cellularly by gap junction channels (GJCs), allowing regenerative propagation of Ca^{2+} signaling to other regions of the cell or neighboring astrocytes. Intracellular Ca^{2+} transients in astrocytic processes can also occur by spontaneous opening of transient receptor potential channels $TRPA_1$ (Shigetomi et al., 2013), or by neurotransmitter-gated ionotropic receptor channels (iRCs) such as AMPA and NMDA channels and purine-bound P2X channels (Newman, 2005; Suadicani et al., 2006; Hamilton et al., 2008; Palygin et al., 2010; Lind et al., 2013). Excess Ca^{2+} is pumped out of the cell by the sodium Na^+/Ca^{2+} exchanger (NCX) or into the ER by (sarco)endoplasmic reticulum Ca^{2+}/ATPase (SERCA) pumps. (*Red pathway*) *Gliotransmission.* Transient cytosolic Ca^{2+} increases may trigger release of neuroactive molecules (or "gliotransmitters") from astrocytes by multiple pathways. These pathways include glutamate release by exocytosis or by bestrophin-1 (Best-1) ion channels (Sahlender et al., 2014), and release of ATP by vesicular exocytosis (not shown) or by purine-permeable channels (PPCs) (Stout et al., 2002; Suadicani et al., 2006; Bowser and Khakh, 2007). Extracellular ATP rapidly degraded into adenosine (Ado) which, along with glutamate of astrocytic origin, can target different receptors on presynaptic and postsynaptic elements, thereby modulating synaptic transmission and neuronal excitability (Savtchouk and Volterra, 2018). Either with glutamate (not shown) or independently, astrocytes can also release D-serine (D-ser), which is the main co-agonist (with glutamate) of postsynaptic NMDA receptors at many synapses (Mothet et al., 2000; Henneberger et al., 2010; Papouin et al., 2012). (*Green pathway*) (*Cytokine signaling*) Among possible signals mediated by astrocytes is also the release of cytokine tumor necrosis factor alpha (TNFα) by Ca^{2+}-dependent TNFα-converting enzyme (TACE) (Bezzi et al., 2001). This cytokine – which is also present in the extracellular milieu at constitutive concentrations $< 100 - 200$ pM –, may target both astrocytic and synaptic TNF receptors (TNFR1). In the astrocyte this modulates glutamatergic gliotransmission (via a yet-unresolved pathway) (Santello and Volterra, 2012); at synapses it modulates instead insertion (endocytosis) of postsynaptic AMPA (GABA) receptors (not shown) (Stellwagen et al., 2005; Pribiag and Stellwagen, 2013; Lewitus et al., 2014). (*Turquoise pathway*) *Glutamate–glutamine cycle.* Astrocytic excitatory amino acid transporters (EAATs) are responsible for the uptake of a large fraction of glutamate at the synapse. Glutamate is converted into glutamine by glutamine synthetase (GS) and shuttled back to neurons by Na^+-coupled neutral amino acid transporters (SNATs) (Mackenzie and Erickson, 2004). Once in the neuron, glutamine is reconverted to glutamate by phosphate-activate glutaminase (PAG), and the ensuing glutamate may either be (transiently) consumed by oxidative metabolism of mitochondria, or be used to refill synaptic vesicles. The whole process is coupled with ammonia (NH_3) homeostasis and also accounts for GABA synthesis from glutamate at inhibitory synapses (not shown), possibly in association with astrocytic uptake by GABA transporter 3 (GAT3) (Rothman et al., 2003; Hertz, 2013). Significantly, expression of astrocytic EAATs and GATs may be modulated by intracellular Ca^{2+} (*dashed yellow pathways*) (Mashimo et al., 2010; Shigetomi et al., 2012; Devaraju et al., 2013). (*Blue pathway*) *Potassium buffering.* Astrocytes buffer excess potassium (K^+) released into the extracellular space as a result of neuronal activity. Excess extracellular K^+ is taken up mostly by inwardly rectifying K^+ channels (Kir4.1) in conjunction with Na^+/K^+-ATPase (NKP) pumps and Na^+–K^+–$2Cl^-$ cotransporters (NKClC), all of which are richly expressed on perisynaptic

astrocytic processes. Potassium ions then travel down their concentration gradient through the astrocyte's cytoplasm, or through gap junction channels to other cells, where they are released at sites of lower extracellular K^+ concentration or shunted to the vascular system (Kofuji and Newman, 2004; Simard and Nedergaard, 2004). The pathway is coupled with the cell's water homeostasis by aquaporin channels (AQP4), as well as with glutamate uptake, since intracellular K^+ controls astrocytic transporters' stoichiometry together with extracellular Na^+ and H^+(Section 5). (*Purple pathway*). *Lactate shuttle.* Glutamate uptake is accompanied by Na^+ influx into the astrocyte which is counteracted by the action of NKPs. The resulting increase in ADP/ATP ratio triggers anaerobic glucose utilization in astrocytes by glycolysis which may be associated with glycogenolysis and/or with glucose uptake from the circulation by glucose transporter GLUT1. Lactate dehydrogenase (LDH) catalyzes the interconversion of pyruvate (Pyr) from glycolysis into lactate (and vice versa) with concomitant interconversion of NADH and NAD^+. Lactate (Lac) is then shuttled to neurons through monocarboxylate transporters (mainly MCT1 in astrocytes and MCT2 in neurons), where it can be used as an energy substrate after its reconversion to pyruvate (Allaman et al., 2011). (*Brown pathway*). *pH buffering.* Abundant carbonic anhydrase (CA) in astrocytes converts CO_2 resulting from cellular metabolism (plus H_2O) into H^+ and HCO_3^-. Two HCO_3^- are transported into the extracellular space along with one Na^+ via the Na^+-coupled bicarbonate transporter (NBC), thereby increasing the extracellular buffering power. The efflux of HCO_3^- induces extracellular alkalinization and also occurs by activation of $GABA_A$ channels as well as by Cl^-/HCO_3^- exchanger (ClBX). Excess H^+ in astrocytes is extruded via Na^+-H^+ exchanger (NHX). Chloride and bicarbonate homeostasis are also intimately related to cell volume regulation (Section 5). (*Orange pathway*) *Glutathione metabolism.* Astrocytes release glutathione (GSH) in the extracellular space where it is cleaved by the astrocytic ectoenzyme γ-glutamyl transpeptidase (γGT) to produce cysteinylglycine (CysGly). In turn, CysGly is cleaved by neuronal ectoaminopeptidase N (ApN), forming cysteine (Cys) and glycine (Gly), which serve as precursors for neuronal GSH synthesis (Aoyama et al., 2008). In the astrocyte the reduced form of glutathione (i.e. GSH) is obtained by multiple pathways including recycling of extracellular CysGly, *de novo* synthesis from intracellular glutamate, or precursors of it like glutamine for example (*dashed orange arrow*), or by oxidized glutathione (GSSG) via NADPH-dependent glutathione reductase (GR) (Dringen, 2000). Astrocytic GSSG ensues from oxidative metabolism but may also be linked with the ANLS via $NADP^+$-dependent ascorbic acid/vitamin C recycling (not shown, see Castro et al. (2009)). NADPH/$NADP^+$ can instead be modulated by NADH/NAD^+ either in the cytoplasm or in mitochondria (Ying, 2008), although astrocytic NADPH production seems strongly dependent on pentose phosphate pathway-mediated metabolism of glucose 6-phosphate (glucose-6P) (Dringen, 2000) – the main available form of intracellular glucose obtained from uptake from blood and by glycogenolysis. Shuttling of GSH between astrocytes and neurons is essential in providing precursors for neuronal GSH synthesis and makes astrocytes key players in neuroprotection against oxidative stress. (*Magenta pathway*) *Vascular coupling.* Ca^{2+} rise in the astrocyte may also stimulate generation of arachidonic acid (AA) from phospholipase A_2 (PLA_2), which is converted to prostaglandins (PGs) and epoxyeicosatrieonic acids (EETs) (by cyclooxygenases) to dilate blood vessels through astrocytic endfeet – which are specialized astrocytic processes contacting blood vessels. Alternatively, astrocytic AA passes via endfoot to the smooth muscle surrounding capillaries, and there it is converted into 20-hydroxy-eicosatetraenoic acid (20-HETE) (by ω-hydroxylase) which constricts vessels (Attwell et al., 2010). ClC: chloride channel; NAD^+ (NADH): oxidized (reduced) nicotinamide adenine dinucleotide; $NADP^+$ (NADPH): oxidized (reduced) nicotinamide adenine dinucleotide phosphate; GPhos: glycogen phosphorylase; GGS/PTG: glycogen synthase/UTP–glycogen–phosphate uridylyltransferase; SAClC: swell-activated chloride channel; VGCC: voltage-gated Ca^{2+} channel; VGKC: voltage-gated K^+ channel; VGNC: voltage-gated Na^+ channel.

Figures

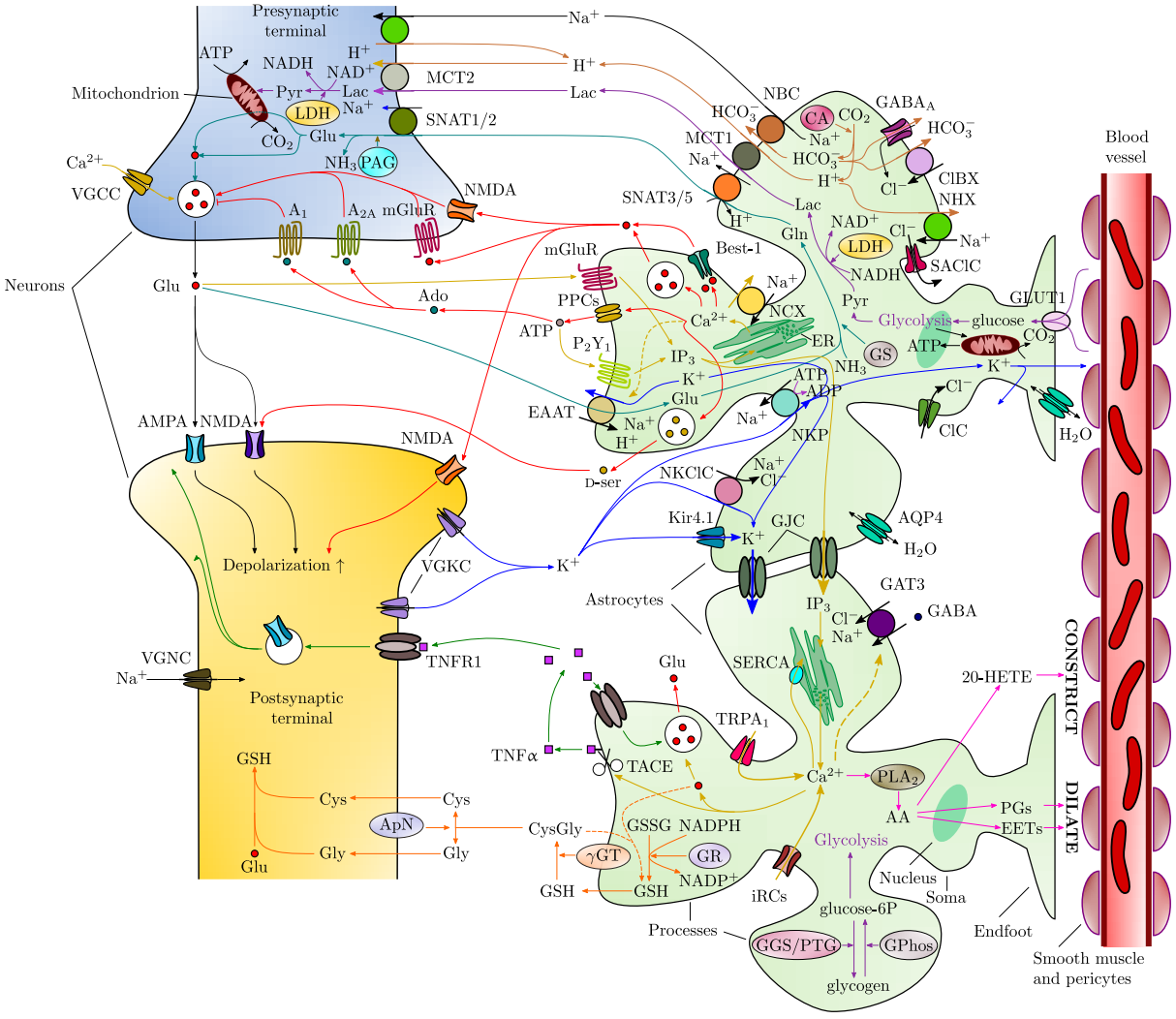

Figure 1. Interaction of astrocytes with neuropil and vasculature.

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