



# Astrocytes and human cognition: Modeling information integration and modulation of neuronal activity

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## ABSTRACT

Recent research focusing on the participation of astrocytes in glutamatergic tripartite synapses has revealed mechanisms that support cognitive functions common to human and other mammalian species, such as learning, perception, conscious integration, memory formation/retrieval and the control of voluntary behavior. Astrocytes can modulate neuronal activity by means of release of glutamate, D-serine, adenosine triphosphate and other signaling molecules, contributing to sustain, reinforce or depress pre- and post-synaptic membranes. We review molecular mechanisms present in tripartite synapses and model the cognitive role of astrocytes. Single protoplasmic astrocytes operate as a “Local Hub”, integrating information patterns from neuronal and glial populations. Two mechanisms, here modeled as the “domino” and “carousel” effects, contribute to the formation of intercellular calcium waves. As waves propagate through gap junctions and reach other types of astrocytes (interlaminar, polarized, fibrous and varicose projection), the active astroglial network functions as a “Master Hub” that integrates results of distributed processing from several brain areas and supports conscious states. Response of this network would define the effect exerted on neuronal plasticity (membrane potentiation or depression), behavior and psychosomatic processes. Theoretical results of our modeling can contribute to the development of new experimental research programs to test cognitive functions of astrocytes.

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**Abbreviations:** AC, alternate current; AM, amplitude modulated; AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BBB, blood–brain barrier; BOLD, blood-oxygen-level-dependent; CaMKII, calmodulin-dependent protein kinase subtype II; CTA, conditioned taste aversion; DC, direct current; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; GPCR, G-protein coupled receptor; GABA,  $\gamma$  amino-butyric acid; GFAP, glial fibrillary acidic protein; Glu, glutamate; IP<sub>3</sub>, inositol triphosphate; ITQC, ion-trap quantum computer; LFP, local field potentials; LTP, long-term potentiation; NaFAC, sodium fluoroacetate; NMDAR, N-methyl-D-aspartic acid receptor; NO, nitric oxide; REM, rapid-eye-movement; SIC, slow inward currents; SRR, synaptic reentry reinforcement; STP, short-term potentiation; SWS, slow-wave sleep; TOM, theory of mind; VPA, varicose projection astrocytes.

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## 1. Introduction

Although astrocytes compose at least one half of human brain tissue volume, until two decades ago mostly passive functions were attributed to these glial cells, such as giving structural, metabolic and functional support for neurons. However, a growing number of 'in vitro' and 'in vivo' results support the conception that astrocytes are also excitable cells and play important roles in information processing and modulation of neuronal activity (Perea and Araque, 2005; Haydon and Carmignoto, 2006; Wang et al., 2006b; Fellin et al., 2006; Genoud et al., 2006; Winship et al., 2007; Schummers et al., 2008; Halassa et al., 2009). In an evolutionary approach, Banachlocha states that "in the leech, the astrocyte–neuron ratio is 1:25; in *Caenorhabditis elegans* 1:6; in rats and mice 1:3. In humans, the astrocyte-to-neuron ratio is approximately 3:2. This exponential increase of astrocytes cannot be explained solely on increased glial metabolic support. Alternatively, it is plausible that increasing numbers and organization of astrocytes implicates a role for these cells in the evolution of increasingly complex brain functions" (Banachlocha, 2007). Evidence for this role is an increase in glia-to-neuron ratio in human dorsolateral frontal cortex.

Direct applications of these results for an understanding of human cognition and emotion are beginning to emerge in the fields of neurology and psychiatry. Astrocytes are involved in the etiology of several neurological disorders as epileptic seizures (Willoughby et al., 2003; Silchenko and Tass, 2008; Reyes and Parpura, 2008; Seifert et al., 2009), Alzheimer disease (Fuller et al., 2009; Kuchibhotla et al., 2009), abusive ethanol consumption (González and Salido, 2009) and other drugs (Haydon et al., 2009), schizophrenia (Halassa et al., 2007a; Mitterauer, 2009), depression (McNally et al., 2008) and mood disorders (Lee et al., 2007), among other dysfunctions (Antanitus, 1998; De Keyser et al., 2008). A recent hypothesis about the origin of psychiatric disorders focus on blood–brain barrier (BBB) breakdown and brain astrocyte dysfunction leading to disturbed cognition, mood, and behavior: These events "are initiated by a focal BBB breakdown, and are associated with dysfunction of brain astrocytes, a local inflammatory response, pathological synaptic plasticity, and increased network connectivity" (Shalev et al., 2009).

Other kinds of glial cells – reviewed by Douglas Fields (2009) – have also been shown to be relevant for health and disease, as oligodendrocytes in schizophrenia and microglia in degenerative disorders. In this emerging paradigm, glial cells are envisaged as the main target for new psychiatric drugs. According to Halassa et al. (2009), "These discoveries begin to paint a new picture of brain function in which slow-signaling glia modulate fast synaptic transmission and neuronal firing to impact behavioral output. Because these cells have privileged access to synapses, they may be valuable targets for the development of novel therapies for many neurological and psychiatric conditions".

The name of astrocytes derives from the 'star-like' shape of one kind of these cells – protoplasmic astrocytes – containing bundles of an abundant filamentous component of the cytoskeleton, the glial fibrillary acidic protein (GFAP). In most glutamatergic central synapses, the extremity of a protoplasmic astrocyte process wraps the synaptic cleft. Since astrocytes express membrane receptors to neurotransmitters and can release their own chemical messengers (gliotransmitters), they establish a cross-talk with both pre- and post-synaptic neurons, forming a currently recognized novel functional unit, the tripartite synapse (Araque et al., 1999).

Recent findings by Oberheim et al. (2006, 2009) indicate the existence of other types of astrocytes. They are connected to each other and with protoplasmic astrocytes by gap junctions, forming a brain-wide network: (a) Interlaminar astrocytes: "In layer 1 of the primate cortex...interlaminar astrocytes extend striking long,

frequently unbranched processes throughout the layers of the cortex, terminating in either layer 3 or 4. The cell bodies of these astrocytes...extend two types of processes: three to six fibers that contribute to the astrocytic network near the pial surface, and another one or two that penetrate deeper layers of the cortex" (Oberheim et al., 2006); (b) Polarized astrocytes: "These essentially unipolar cells reside in the deep layers of the cortex, near the white matter (and) extend one or two long (up to 1 mm in length) GFAP-positive processes away from the white matter" (Oberheim et al., 2006); (c) Fibrous astrocytes: These are present in white matter. Their processes "intermingle and overlap" (Oberheim et al., 2006); and (d) Varicose Projection astrocytes: Apparently exclusive to the human brain, these cells present "more spiny processes than exhibited by typical protoplasmic astrocytes and typically extended one to five essentially unbranched, millimeter long fibers within the deep layers of the cortex. The processes of the varicose projection astrocytes...traveled in all directions, piercing and traversing the domains of neighboring protoplasmic astrocytes...the evenly spaced varicosities suggest specialized structures or compartmentalization of cellular elements along the great distance of the fibers" (Oberheim et al., 2009).

The discovery of participation of astrocytes both in local and global integration of information in the brain supports the construction of our model of cognitive functioning, composed of an ensemble of tripartite synapses structurally and functionally connected by the brain's astroglial network. Intracellular calcium waves (the excitable response of astrocytes) are initiated in microdomains of astrocytic processes and, under proper conditions, induce the formation of intercellular waves that putatively mediate large-scale cognitive information processing. This propagation requires a synergy of several factors, such as glutamatergic, cholinergic and purinergic signaling.

We depart from recent experimental results and make a couple of psychophysical theoretical assumptions to develop a model of cognitive and related emotional processes based on astrocyte functions. Our line of reasoning is the following. The protoplasmic astrocyte central to a "synaptic island" (Halassa et al., 2007b) functions as a "Local Hub", integrating the information from thousands of synapses into calcium ion waveforms. The formation of intercellular calcium waves is boosted by the "domino" and "carousel" effects, as defined and discussed below. Under proper conditions, as the activation of "default networks" (Fox et al., 2005), active interconnected astrocytes – including the recently discovered new types – can function as a "Master Hub" that integrates results of local processing from many brain areas. The astrocytic Master Hub, besides integrating neuronal information patterns, also mediates the interactions of blood/cerebrospinal fluid/glia signaling and neuronal systems. Constructive wave interference in the astrocyte network is proposed to produce a state of "satisfaction" or "dissatisfaction" about the states of affair conveyed by information received from neurons. Depending on this response, a positive or negative feedback is exerted on neuronal populations connected to active astrocytes, leading to an effect on plasticity (membrane potentiation or depression), on the resulting behaviors and psychosomatic processes.

## 2. Astrocytes in glutamatergic tripartite synapses

Astrocyte terminations wrap the glutamatergic synaptic cleft, and allow an exchange of transmitters with neurons. Each astrocyte can contact around 140,000 synapses in the rat hippocampus (Bushong et al., 2002) and modulate around 2 million synapses in human cortex (Oberheim et al., 2006). In this condition, astrocytes respond to pre-synaptic input by means of calcium waves and release gliotransmitters that modulate neural activity and synaptic plasticity.

What is the cognitive role of astrocytes in tripartite synapses? To answer this question, we begin with a brief review of mechanisms of membrane potentiation and related cognitive processes. The expression “synaptic plasticity” refers to changes in synaptic strength or efficacy, resulting in potentiation or depression. These processes range from milliseconds and minutes (short-term potentiation) to hours, days and probably longer periods of time (long-term potentiation).

Short-term potentiation (STP) can involve both an increase of pre-synaptic transmitter release (Citri and Malenka, 2007) and post-synaptic sequential glutamate (Glu) binding to alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid receptors (NMDAR), calcium entry and activation of corresponding signal-transduction pathways (Alkon et al., 1998). Both monosynaptic temporal and heterosynaptic spatial input summation can promote potentiation of the membrane of the post-synaptic neuron, supporting basic cognitive processes as sensitization, habituation and stimulus association. Also attention functions, supported by cholinergic mechanisms, guides the onset of STP in the living brain.

Associative learning and memory formation, by means of long-term potentiation (LTP), are classically illustrated at the synaptic level by means of a model composed of two (pre- and post-synaptic) connected neurons, and their respective inter and intracellular signaling pathways. The process of LTP induction shares an initial step with STP. According to a classical view (Bliss and Collingridge, 1993), LTP induction involves signaling from post- to pre-synaptic neuron, by means of retrograde messengers as nitric oxide (NO) and arachidonic acid, leading to an increase of transmitter release at the axon terminal of the pre-synaptic neuron. Post-synaptic effects are essential to LTP consolidation and memory storage. Glutamatergic heterosynaptic converging input to a neocortical or hippocampal neuron opens AMPARs to sodium ions and the resulting depolarization opens NMDARs, promoting calcium ion entry, triggering several intracellular processes that lead to an increase in AMPAR-dependent responses. Potentiation of the post-synaptic neuron membrane involves the activation of calcium-kinase pathways leading to transcriptional regulation increasing the expression of AMPAR at the post-synaptic neuron (Nicoll, 2003).

In LTP processes, the conjoint effect of pre- and post-synaptic events is strengthening synaptic connections. The formation of long-term memories is related to an increase in concentration of ionotropic receptors (as AMPA), caused by signal-transduction processes that reaches the nucleus of the neuron and induces the expression of genes responsible for production of these membrane receptors. In this theoretical context, Joe Tsien and collaborators (Wang et al., 2006a) have argued for the necessity of combining single neuron and systemic approaches to learning and memory. They proposed the NMDAR reactivation-mediated synaptic reentry reinforcement (SRR) model, gathering evidence for the idea that NMDA-CaMKII pathways are repeatedly reactivated to make possible the systemic expression of learning and memory. The reactivation process can occur unconsciously, except when there is a stimulus that elicits the retrieval of the mnemonic pattern at the system level. Therefore, SRR requires a systemic mechanism to promote conjoint reactivation of neuronal populations, producing ensemble representations in neuronal assemblies (Tsien, 2007).

In the classical literature on LTP, the participation of astrocytes in the sequence of neuronal events involved in the process of membrane potentiation/depression and formation of long-term memories has not been taken into consideration. Recent evidence indicates that Glu and D-serine release by astrocytes may be a powerful mechanism promoting neuronal potentiation that serves cognitive functions, including systemic SRR. According to Haydon and Carmignoto (2006, p. 1020), ‘in vitro’ studies showed that the

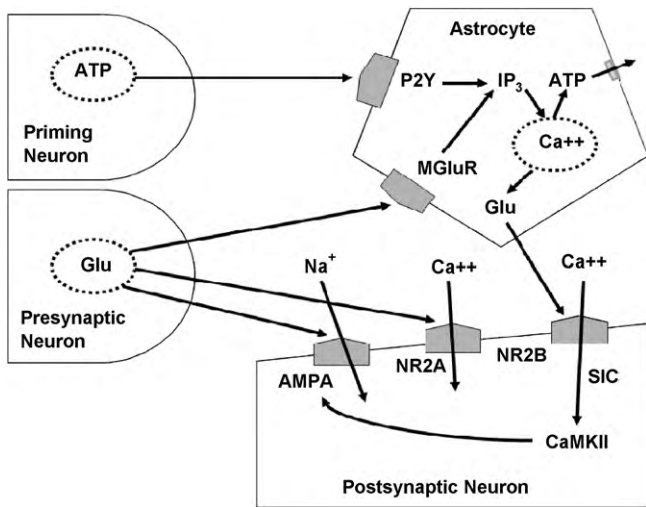
quantity of Glu released by astrocytes may be far greater than neurons: “Astrocyte-evoked NMDAR currents can be extremely large in magnitude. The average current detected is 100 pA. In contrast, the NMDA current due to the fusion of a single vesicle in the synapse is of the order of 2–3 pA”. What would be the function carried by this current ‘in vivo’?

The immediate effect of astroglial Glu binding to neuronal NMDARs is the generation of slow inward currents (SIC; Araque et al., 1998). This current, in turn, has several possible effects. The effect that is most likely to occur in a shorter time scale is the activation of NMDARs connected to CaMKII, as predicted by the SRR model. Additionally, neuronal NMDARs can be activated by Glu and D-serine (in the place of glycine), the latter (D-serine) being released only by astrocytes (Mustafa et al., 2004; Panatier et al., 2006; Henneberger et al., 2010). Several results have confirmed that in shorter time scales (from milliseconds – Haydon and Carmignoto, 2006 – to minutes, up to 2 h – Gardoni et al., 2009) the function of NR2B-containing NMDARs coupled to CamKII is mostly the enhancement of membrane potentiation with corresponding cognitive improvement (Cao et al., 2007), but not membrane depression (Gardoni et al., 2009). Using genetically mutant mice in which the NR2B gene is overexpressed, Wang et al. (2008, 2009) found that it caused enhancement of LTP and memory.

In a later phase, the trafficking of newly synthesized AMPARs to the same synaptic location may be diminished by the same astrocyte-to-neuron signaling pathway. In this phase, activation of NR2B-containing NMDARs may cause neuronal membrane depression (Kim et al., 2005), possibly operating as a habituation mechanism to avoid excessive long-term excitation of a neuronal circuit. This feature illustrates the non-linear (or bell-shaped, as proposed by Zhang et al., 2008) effect of astrocyte activity on neuronal plasticity.

In summary, we distinguish four post-synaptic phases:

- (a) *Excitatory post-synaptic response to pre-synaptic input*: in the glutamatergic synapse, the pre-synaptic-induced post-synaptic response lasts up to 150 ms (Haydon and Carmignoto, 2006), and includes the sequential opening of AMPA and NMDA channels, eliciting several processes that increase the spiking activity of the post-synaptic neuron, and may also take part in STP/LTP processes;
- (b) *Afterpotentiation effects*: following the beginning of the primary post-synaptic response, a variety of excitatory processes occur, generating several afterpotentiation effects. These processes include: pre-synaptic reinforcement by means of retrograde messengers (NO, arachidonic acid) promoted by activation of NMDARs; backpropagation of potentials in each neuron; excitatory modulation of ionotropic receptors by means of metabotropic receptor G-protein pathways, and the opening of voltage-gated ion channels;
- (c) *Meta-potentiation*: afterpotentiation effects trigger a sequence of events that reach a larger neuronal population. Meta-potentiation (Pereira and Furlan, 2007) refers to the participation of astrocytes in tripartite synapses and extrasynaptic transmission. Sustained activity of the tripartite synapse, supported by astroglial release of Glu that binds to NR2B receptors of the post-synaptic neuron, produces SIC of calcium ions into the post-synaptic neurons, which bind preferentially to CamKII, then sustaining previous activity by means of AMPARs phosphorylation (Fig. 1). The same result can be obtained by means of astroglial release of D-serine (Henneberger et al., 2010);
- (d) *Long-term depression*: Astrocyte–neuron signaling pathways involved in meta-potentiation can also activate a slower mechanism that causes membrane depression of post-synaptic neurons.



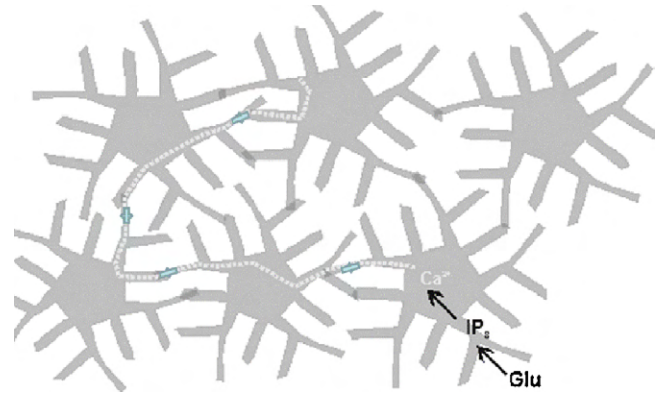
**Fig. 1.** Meta-potential. In the awake state, astrocytes are activated by purinergic transmission mediated by metabotropic receptor (P2Y), GABAergic, cholinergic and other neurotransmissions (not shown). Glutamate (Glu) released by the pre-synaptic neuron binds with both astroglial (MGLuR; possibly also astroglial NMDA receptors, not shown) and post-synaptic neuronal (AMPA and NMDA containing the NR2A subunit) receptors. Synergic action of MGLuR and other astroglial receptors activate the inositol triphosphate (IP<sub>3</sub>) pathway, release calcium ions from internal stores (mitochondria and endoplasmic reticulum) and – when a threshold of activity is crossed – induce calcium waves in adjacent cells, mostly by means of ATP signaling mediation (represented in the figure by an arrow departing from the astrocyte). Astroglial Glu binds mostly with neuronal NMDA receptors containing the NR2B subunit (NR2B), causing calcium ion entry (SIC) and binding to CaMKII, then sustaining the excitatory activity of the neuron by means of AMPA phosphorylation.

In the following sections, we show how cognitive functions, including conscious perception, can be modeled by an ensemble of tripartite synapses connected by astrocytes. The formation of intercellular calcium waves (and the resulting release of astroglial Glu) depends on a synergy of factors. An implication of this necessary synergism is that during the awakening process the individual would take seconds to work consciously (as discussed by Hobson, 1994). After this initial stage, the timing of primed astrocytes to respond to sensory stimulation (around 5% of the astrocyte population in a sensory region, according to Winship et al., 2007) and support cognition becomes compatible with behavioral data on reaction times.

According to a model developed by De Pittà et al. (2008, 2009), astrocytes encode information by means of calcium wave amplitude and/or frequency modulation. Amplitude-modulated (AM) waves are formed when excitation reaches a threshold, corresponding to a fixed point in the temporal dynamics of IP<sub>3</sub> activity. Several neurotransmitters contribute to the “priming” (i.e., activation within a subthreshold level) of the astrocyte. The binding of neuronal Glu with astroglial metabotropic receptors drives the cell towards crossing the threshold, thus eliciting coherent calcium waves. These waves presumably transduce neuronal information into amplitude and frequency-modulated calcium wave patterns in the astrocytic network. The complex dynamics of these waves would then determine the release of astroglial Glu to neurons.

### 3. Formation of intercellular calcium waves

Astrocytes participating in tripartite synapses are coupled by gap junctions forming a network that can support brain large-scale integrative functions, from dynamic glucose delivery (Rouach et al., 2008) to cognitive information processing (Robertson, 2002;



**Fig. 2.** Traditional view of the formation of calcium waves in the astrocytic syncytium. The activation of one astrocyte, by means of the binding of neuronal glutamate with a metabotropic receptor activating the inositol triphosphate (IP<sub>3</sub>) pathway, releases calcium ions from the endoplasmic reticulum, forming calcium waves that propagate in the syncytium (figure adapted from <http://synapses.mcg.edu/>). The propagation of the wave from astrocyte to astrocyte depends on gap junctions (small blue rectangles).

Perea and Araque, 2005). Astroglial calcium waves are formed in response to sensory, cognitive and affective/emotional patterns transmitted from spatially distributed neuronal and glial populations. A traditional view of calcium wave propagation in the astrocytic syncytium is depicted in Fig. 2.

Recently, a consensus emerged that intercellular waves are not the result of calcium ion movement from cell to cell (Haydon and Carmignoto, 2006; Wang and Bordey, 2008; Schummers et al., 2008; Agulhon et al., 2008). Of course, ions can traverse microdomains and gap junctions, but considering temporal and spatial limitations for ionic transportation this way of propagation is not sufficient to support cognitive processes.

Recent findings by Agulhon, Fiacco and McCarthy have further shown that astrocytic G-protein coupled receptors (GPCR) and Ca<sup>2+</sup> signaling activity “are not tied to the release of gliotransmitters affecting synaptic transmission or short and long-term plasticity. Therefore... gliotransmission reflects the pharmacological approaches that were used in previous studies and, at least within the hippocampus, does not occur” (Agulhon et al., 2010). One possible interpretation of being “not tied” is that exclusive astroglial GPCR activation of calcium waves in the hippocampus is not sufficient to elicit the release of astroglial glutamate to the post-synaptic neuron, thus reinforcing the need of a synergistic activation to explain the formation of these waves.

However, the conclusion (drawn by Wiedemann, 2010) that calcium waves in astrocytes – and resulting release of astroglial Glu to post-synaptic neurons – are “pharmacological artifacts” seems to go beyond the results obtained by Agulhon et al. (2010). As long as pharmacological stimulation, in scientifically replicable conditions, is sufficient to produce calcium waves and corresponding post-synaptic potentiation, there are two possible explanations: because this kind of stimulation elicits the synergy of factors necessary to generate the effect, or because it directly generates the effect (the latter being an artifact of the stimulation). The second alternative implies that the pharmacological stimulus targeting the tripartite synapse astrocyte also reaches the post-synaptic neuron. In this case, membrane potentiation would occur without calcium waves and release of astroglial Glu. To certify if this is or is not the case, a better control of pharmacological experiments is required.

In last years, our knowledge about astroglial intercellular communication has considerably increased. While Scemes and Spray (2004) refer to an *Astrocytic Syncytium*, Giaume et al. (2010) refer to an *Astrocytic Network*. The difference lies mostly in the

computational properties ascribed to gap junctions: from “a pathway for direct intercellular exchange of ions, nutrients and signaling molecules” (Scemes and Spray, 2004) into an active computing mechanism, “gap junction channels that are regulated by extra- and intracellular signals and allow exchange of information” (Giaume et al., 2010).

There are 21 kinds of connexins. The Cx30 and Cx43 types are present in astrocyte gap junctions. Their functional properties are dependent on Cx43 permeability to “several endogenous molecules, including second messengers (cyclic AMP, inositol-1,4,5-trisphosphate (InsP3) and  $\text{Ca}^{2+}$ ), amino acids (glutamate, aspartate and taurine), nucleotides (ADP, ATP, CTP and NAD), energy metabolites (glucose, glucose-6-phosphate and lactate), small peptides (glutathione) and RNA (24mer)<sup>51,52</sup>, but not for large molecules, such as nucleic acids, proteins and lipids” (Giaume et al., 2010). Besides controlling gap junction traffic of signaling molecules, connexins form hemichannels, allowing an exchange of these molecules with extracellular medium. Hemichannels are also composed of pannexins, as the recently discovered pannexin 1 (Iglesias et al., 2009; Suadicani et al., 2009).

Astrocyte microdomains are sites of information integration. The effect of multiple transmitters (e.g. glutamate and acetylcholine in the hippocampus) indicates the complexity of the process. The formation of calcium waves in protoplasmic astrocytes requires a synergy of factors to reach a threshold (corresponding to a fixed point in the model proposed by De Pittà et al., 2008). Neuronal glutamate release and activation of astroglial metabotropic receptors are proposed to be necessary for the encoding of information content into the wave, but not sufficient to produce the wave. After such a local integration of information occurs, resulting in the formation of intracellular waves, these can propagate to the whole astrocytic network, forming a large intercellular wave.

Once the spontaneous movement of calcium ions ‘in vivo’ seem to be mostly limited to microdomains, we present two complementary mechanisms to explain astrocyte intercellular signaling and resulting modulation of neuronal activity. First, a “domino effect” (Pereira and Furlan, 2009) produced by means of ATP signaling. Second, a “carousel effect” generated by the synchronization of large populations of neurons in medium to high frequencies (from theta to gamma) and corresponding axonal output to astrocytes.

Calcium waves were conceived as a “saltatory” phenomenon (Roth et al., 1995). A similar “regenerative mechanism” based on ATP mediation was identified by means of computer simulation (MacDonald et al., 2008). This effect ‘in vivo’ also depends, among other factors, on ATP permeability through astroglial gap junctions formed by connexin43 (see Wiencken-Barger et al., 2007), as well as an auxiliary ATP signaling through hemichannels: “astrocyte hemichannels were shown to be permeable to gliotransmitters

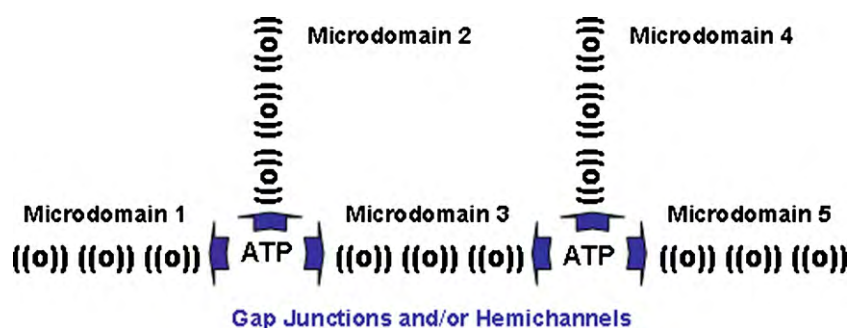
such as glutamate, ATP, glucose and glutathione. Thus, hemichannel activation and ATP release may support the propagation of intercellular  $\text{Ca}^{2+}$  waves” (Giaume et al., 2010). Considering the above possibilities, we propose the “domino effect” (Fig. 3) as an analogical model of formation of large intercellular calcium waves. Local standing waves, limited to one microdomain, elicit ATP signals that elicit calcium waves in other microdomains (for evidence about ATP mediation of calcium waves, see Cornell-Bell et al., 2004; Haydon and Carmignoto, 2006; Di Garbo et al., 2007; MacDonald et al., 2008; Koizumi, 2010). When domains belong to different cells, ATP signaling facilitates intercellular communication through gap junctions.

The effect makes possible that a calcium wave inside an astrocyte microdomain propagates to other domains without actual transportation of ions. An increase of calcium concentration in a microdomain leads to ATP signaling to adjacent ones, activating more pathways and reinforcing the propagation of waves into each one. The double role of ATP mediation would then be to allow (unlike domino games) multiplication of waves as well as the reinforcement of the signal—like transformers in electricity transmission lines. As long as there is a message carried by the wave (possibly encoded by means of amplitude modulation), it is broadcasted to the whole network.

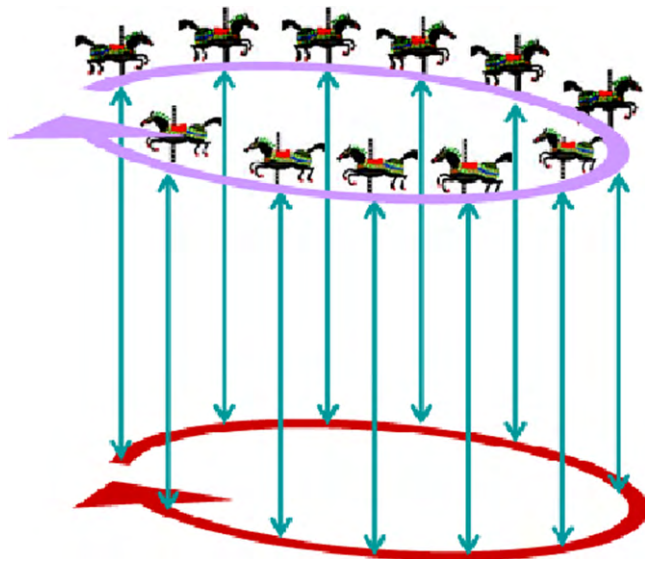
At the systemic level, neuro-astroglial communication involves a synergy of glutamatergic, purinergic and other kinds of neurons co-activating a neighbor astrocyte. We have argued that the readiness of astrocytes to generate calcium waves upon glutamatergic activation requires pre-activation below the threshold necessary to elicit intercellular calcium waves. Astrocyte activity is – in this sense – primed by purinergic (Di Garbo et al., 2007; Verkhrasky et al., 2009), cholinergic (Perea and Araque, 2005; Seigneur et al., 2006),  $\gamma$  amino-butyric acid (GABA) signaling and others. One signal-transduction pathway involved with cholinergic activation is the increase of extracellular potassium caused by the spiking activity of the post-synaptic neuron, leading to calcium influx to the astrocyte at the site of interaction with the neuron (Laming, 2000; Postnov et al., 2007).

The synergy of factors necessary to form an intercellular calcium wave requires, besides the domino effect, some degree of neuronal coordination of astrocyte activity. The synchronization of graded and action potentials of neurons organizes their effects on a spatially distributed population of astrocytes. When neuronal inputs to the astrocyte population are synchronized, the resulting stimulation is more likely to cross the threshold and elicit coherent, amplitude and/or frequency-modulated calcium waves in single astrocytes (Pereira and Furlan, 2009), consequently facilitating the formation of a large wave in the whole astrocyte population.

The spreading and maintenance of high-frequency synchrony, in turn, requires positive feedback from active astrocytes to



**Fig. 3.** The domino effect: Neuronal inputs on astrocytes prompt the release of calcium ions from internal stores (mitochondria and endoplasmic reticulum) and induce calcium waves in astrocyte microdomain 1. This wave prompts ATP signaling through gap junctions or hemichannels, which activates calcium ion waves in microdomains 2 and 3. The latter induces waves in microdomains 4 and 5.



**Fig. 4.** The carousel effect: The red circle represents a cycle of activity of a population of synchronized neurons, while the mauve circle represents an intercellular calcium wave in astrocytes. Each horse corresponds to a small calcium wave inside one astrocyte microdomain. The coordination of smaller waves, generating the large wave, is orchestrated by synchronized neurons and feeds back on them (bidirectional arrows), independently of an actual causal relation between the smaller waves (this causal relation, when it happens, is described by the domino effect).

synchronized neuronal populations (as indicated by results obtained by Fellin et al., 2004; Angulo et al., 2004; Willoughby et al., 2005; Allegrini et al., 2009; Nobili, 2009), as well as the participation of a thalamic pacemaker (found in immature rodents by Parri and Crunelli, 2001; proposed as a general mechanism by Steriade, 2005), to define the frequency of the oscillation, and neuronal electric synapses (Bennett and Zukin, 2004), to provide real-time monitoring of intercellular activity.

We introduce the “carousel effect” analogy to illustrate the effect of synchronized neuronal action potentials on an ensemble of interconnected astrocytes (Fig. 4). This effect, in turn, is sustained by a reverse effect of astrocyte activation on neuronal synchrony. Both combine to support Glu release from neurons, binding with astroglial metabotropic receptors and then transmitting messages by means of activation of the  $IP_3$  pathway. The final step of the process is the formation of large, AM calcium waves in the astrocytic network.

Also quantum entanglement of calcium ions possibly plays a role in intercellular communication (Pereira, 2007; Pereira and Furlan, 2009). When a small wave inside a microdomain is formed, another wave in a spatially distant region of the astrocyte network can be affected, without any particle from the initial wave being actually transported to the second microdomain. However, quantum entanglement cannot explain the formation of waves, since this process requires mechanical causation. The two proposed effects above are intended to explain the formation of waves; after formed, quantum entanglement may occur within them. Considering both effects, the time needed to produce a large intercellular calcium wave is in principle not far greater than the time to form small waves in microdomains.

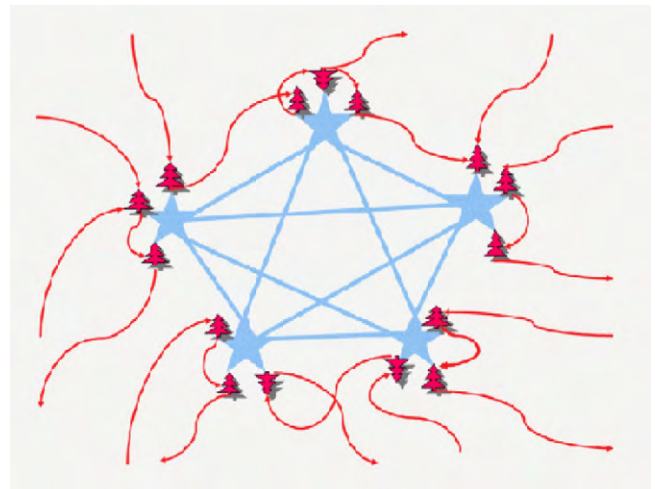
#### 4. Astrocytic network promotes systemic integration

Available data allow a theoretical distinction between astrocytic “Local Hubs”, composed by a single protoplasmic astrocyte connected to a population of neurons, and a “Master Hub”,

composed by the whole active network of astrocytes (of all types) belonging to an individual brain in a given time. Calcium waves generated in one Local Hub interfere with waves generated in others, being further processed – in still unknown ways – by integrative astrocytes (of the interlaminar, fibrous, polarized and varicose projection types).

The composition of the Master Hub changes at each moment, according to the dynamics of brain activity. Depending on neuronal input and respective astroglial responses, as well as possible spontaneous intrinsic oscillations due to homeostatic mechanisms (Parri et al., 2001; De Pittà et al., 2008, 2009), astroglial gap junctions proteins may allow or block the transduction of calcium waves from cell to cell (see Rouach et al., 2000). From a computational perspective, these proteins can be conceived as gates. Their opening and closing define different circuits that support different computational processes. In the perspective of Cognitive Theory, the Master Hub can be viewed as a “Global Workspace” (according to the model presented by Baars, 1997) that integrates patterns from local neuronal assemblies to a brain-wide network (Fig. 5), where it is broadcasted and made accessible to other local assemblies.

The picture that emerges from our theoretical framework is that single neurons are modular and intelligent units, while astrocytes operate collectively, forming an integrated unit. In order to distinguish the operational principles of both kinds of cell, we begin by defining concepts of “digital-like” and “wavelike” computing. The distinction is not absolute, since both result from ionic movement. “Digital-like” computing is based on a binary code corresponding to “homogeneous” classes of ionic activities, as, typically, “firing” (represented by a symbol, for instance “1”) or “not-firing” (represented by “0”). By “homogeneous” we mean that signals (axonal action potentials) have approximately the same amplitude, thus encoding information only in temporal frequency. Of course, in a population of cells operating with this principle it is possible to identify “population codes”, based on the spatial distribution of active cells and on their combined phases (for a review of neuronal codes, see Phillips, 1997; Fotheringham and Young, 1997). The important point to be stressed here is that



**Fig. 5.** A biophysical “Global Workspace” composed of a network of astrocytes. Blue stars represent protoplasmic astrocytes and red trees represent neurons. Each astrocyte participates in a tripartite synapse, being activated by the pre-synaptic neuron and contributing to sustain or reduce the activity of the post-synaptic neuron. When neuronal potentials oscillations synchronize, a large wave is formed in the astroglial network. The radial architecture of interconnected astrocytes promotes wave interference patterns, supporting the integration of information patterns received from neurons. These patterns are further processed by integrative astrocytes (not shown in the figure).

population activity operating with a digital-like principle can only execute combinatorial operations upon the basic homogeneous classes of states. They cannot create a third (or any other) kind of state, and therefore cannot create waveforms analogous to the stimulus being processed. “Wavelike” computing, on the other hand, is based on “heterogeneous” classes of activity. It operates with amplitude-modulated signals, making possible the generation of temporal and spatial waveforms that constitute analog reproductions of properties of stimuli.

Central neurons are “integrate and fire” (Abeles, 1991) nanosystems, receiving a multitude of digital-like signals (action potentials) from other neurons, integrating them in wavelike patterns (graded potentials) in their dendritic tree, filtering the result of input summation at the axon hillock and converting it back to a digital-like pattern that is transmitted to other neurons through the axon (neuron “firing”). Since such digital-like signals have approximately the same amplitude, neuronal networks can operate with a binary combinatory principle that consists of sequences of firing and not-firing states. As a result of this neuronal design, a sequence of axonal signals sent from neuron to neuron can reliably transmit information, but an exchange of such signals in neural networks (even with recurrent architectures) cannot integrate the patterns effectively, as required to compose unitary and coherent conscious episodes.

Information integration requires some kind of entanglement (as assumed by Balduzzi and Tononi, 2009) to bind a variety of information patterns into a sequence of unitary and coherent episodes, as experienced by each human individual. This is not necessarily quantum entanglement, but the achievement of a high correlation between bits of information. It can be described as a “quantum-like” macro coherent process. Astrocytes receive digital-like signals from neurons and convert them in wavelike patterns, having calcium ions and ATP signaling as the vehicle for information processing. Contrary to neurons, one astrocyte can directly communicate these wavelike patterns to other astrocytes, allowing large-scale wavelike computing.

The recent proposal (Hameroff, 2010) of a neuro-astroglial gap junction syncytium addresses this issue, but is possibly inflated, because there is no evidence that electric synapses exchange dendritic field information. Electric synapses are fundamental for the onset and maintenance of large-scale fast oscillatory synchrony that prepare the neuro-astroglial system for the operation of integration of distributed patterns to compose conscious episodes, but the integration process itself seems to occur elsewhere. In spite of putting the emphasis on neurons instead of astrocytes, Hameroff’s conception of a “conscious pilot” carried by dendritic fields is similar to our proposal of a dynamical calcium waveform in the astrocytic network supporting conscious processes.

According to the Astrocentric Hypothesis (Robertson, 2002), astrocytes are the final step of conscious information processing in the brain. In a second version of this hypothesis, developed by Pereira (2007) and Pereira and Furlan (2009), information contents that become conscious are first unconsciously instantiated in distributed neuronal local field potentials (LFP). The vehicle for integration, corresponding to the final stage of conscious processing, is the astrocytic calcium wave. Besides receiving chemical signals from neuronal axons in tripartite synapses, astrocytes also possibly receive (by means of ephaptic transmission, as proposed by Banachlocha, 2007) information patterns from neuronal local fields and action potentials, as well as signals from blood and cerebral fluid (both mediated by other types of glial cells). The astrocytic network is presumably in charge of integrating all patterns into coherent episodes, by means of constructive interference of calcium waves. The picture that emerges is that digital-like processes in neurons convey information contents, while wavelike processes in astrocytes generate feelings about the

contents. The result of such an astroglial information processing can be described as an “approval” or “disapproval” of the contents, thus eliciting a positive or negative feedback effect on post-synaptic neurons, causing their membrane potentiation or depression, according to the relevance of the episode for the living individual.

## 5. Modeling calcium waveforms in the astrocytic network

We have proposed (Pereira, 2007; Pereira and Furlan, 2009) that calcium waves in astrocytes might be functionally equivalent to a large-scale Ion-Trap Quantum Computer (ITQC; proposed by Kielbinski et al., 2002). This approximation takes into account the similarity of the ITQC with the dynamics of calcium ions trapped in astrocytic compartments inside hyperpolarized membranes. Once neuronal local field patterns are transduced to astrocytic calcium waves, what would be the mechanism of integration of such patterns in astrocytic networks?

Models of the mechanism of formation of coherent calcium ion waveforms in astrocytic microdomains should be based on physical principles necessary to explain the temporal dynamics of ionic waveforms. State superposition and entanglement, two fundamental quantum phenomena, occur for any system of trapped ions as a result of Coulomb forces, in any temperature. However, they only fully describe the dynamics of quasi-isolated systems in ideal conditions, such as very low temperatures. In order to account for the dynamics of a system as complex as astrocytic calcium waves in a wet and warm medium, they are not sufficient and should be complemented with specifications of relevant initial and boundary conditions.

We previously argued that the operational principle of astrocytic activity is wave computing. This computing has three stages: (a) the transduction of neuronal local field patterns to calcium waveforms in one astrocyte microdomain; (b) intracellular summation of waveforms, and (c) intercellular interference of waveforms, producing a result that impacts brain and body activity, and influences behavior.

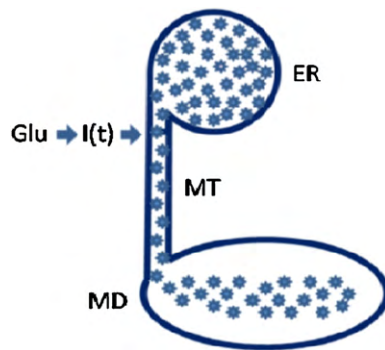
First we present the sketch of a putative mechanism responsible for the induction of calcium waveforms in one astrocyte microdomain (Fig. 6). A population of calcium cations trapped in the endoplasmic reticulum gets entangled, since they repel each other but cannot get away. This situation creates a correlation of states of ions, such that a perturbation of one ion that changes the electronic distribution affects the others’ distribution.

When neuronal Glu binds to astrocytic Glu metabotropic receptors, activating the IP<sub>3</sub> pathway with a given intensity, this chemical energy is transformed into kinetic energy, prompting the release of calcium ions from the reticulum. The ions move along a microtubule and reach one astrocyte microdomain.

Considering other parameters (as spontaneous intracellular calcium oscillations) to be invariant, the resulting dynamical waveform  $C(t)$  is a product of kinetic energy function  $I(t)$  representing the action of IP<sub>3</sub> on the microtubule and a constant  $E$ , representing the degree of entanglement (the degree of cooperativity, or statistical dependence, between the movements of the ions):

$$C(t) = I(t) \cdot E$$

$E$  results from a complex of factors, including the number of ions, their chemical and electronic properties and the size of the cellular compartment where they are trapped.  $C(t)$  is an amplitude-modulated standing wave composed by collective vibrational states of the ions (for more sophisticated models of this process – but without the quantum component – see De Pittà et al., 2009; Postnov et al., 2009).



**Fig. 6.** Mechanism of induction of amplitude-modulated calcium waveforms. Calcium ions trapped in the endoplasmic reticulum of an astrocyte interact and get entangled. Glutamatergic input prompts the movement of ions through a microtubule, towards one astrocytic microdomain where calcium waves are formed, reproducing the pattern of the input. The similarity of this mechanism with the structure of Varicose Projection astrocytes suggests that the varicoses may serve as a reservoir for the ions to get entangled. *Legend:* ER: endoplasmic reticulum; MT: microtubule; MD: astrocyte microdomain;  $I(t)$ : energy function determined by neuronal glutamatergic input.

The second phase begins when microdomains of one astrocyte communicate with each other by means of ATP signaling (for a model composed of one astrocyte and two – one excitatory and one inhibitory – neurons, see Di Garbo, 2009). This process is a convergent and probably resonant one, since the neuronal population connected to one astrocyte is likely to be processing similar information patterns.

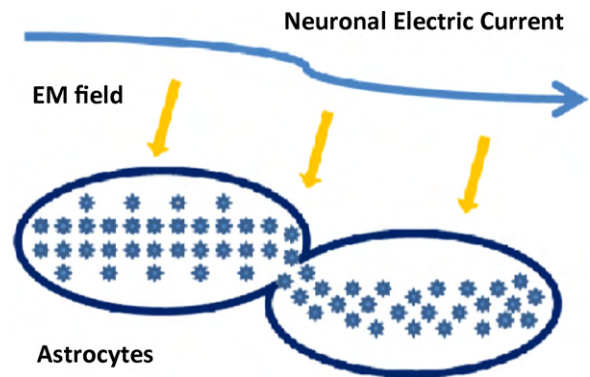
The third phase involves the interference of different waveforms generated in several brain regions, under the influence of surrounding neuronal electromagnetic fields (graded and action potentials). A theory of such a “dialogue” was proposed by Banaclocha (2007), and the hypothesis of an extrasynaptic influence of neuronal action potentials on astrocyte activity by means of the release of extracellular potassium was put forward by Laming (2000) and Postnov et al. (2007). As the activity of Cx30 and Cx43 is voltage-dependent, their functioning can be shaped by neuronal activity (Giaume et al., 2010). This kind of influence is likely to be more effective in fibrous astrocytes interacting with neuronal axons in white matter. This is, of course, a very complex process to model, so we present only a partial and ultra-simplified view of two interfering waveforms (Fig. 7).

A realistic modeling should take into consideration the three phases of the process. Small waves generated in a population of billions of astrocyte microdomains communicate and interfere with each other and with neuronal electromagnetic fields, generating a large wave that is proposed to correspond to actual conscious states and processes. The philosophical position we assume here is Double-Aspect Monism: neuro-astroglial calcium waves and their conscious information contents are thought to be two aspects of the same underlying reality (for a defense of this position, see Velmans, 2008).

## 6. Astrocyte calcium waves and conscious processing

Conscious processing, conceived as composed of potentially reportable patterns experienced by living individuals (Pereira and Ricke, 2009), is the “tip of the iceberg” of a complex cycle of perceptual/cognitive/affective/emotional processes involving the brain, body and environment of living individuals. Some of the properties commonly attributed to conscious processes are:

- (a) Most of brain/body experiences are unconscious; the “flux of consciousness” has “limited capacity” (Baars, 1997). Only a



**Fig. 7.** Interference of waves in two interconnected astrocytes, under the influence of a neuronal electromagnetic field. Two independently generated calcium (star-like figures) waves meet at the astrocytic gap junction mediated by ATP signaling (this mechanism is not shown in the picture). Besides the intrinsic form of each wave, the boundary conditions of the process – containing EM fields caused by sodium and potassium ion movements in neuronal axons – may also influence the resulting waveform.

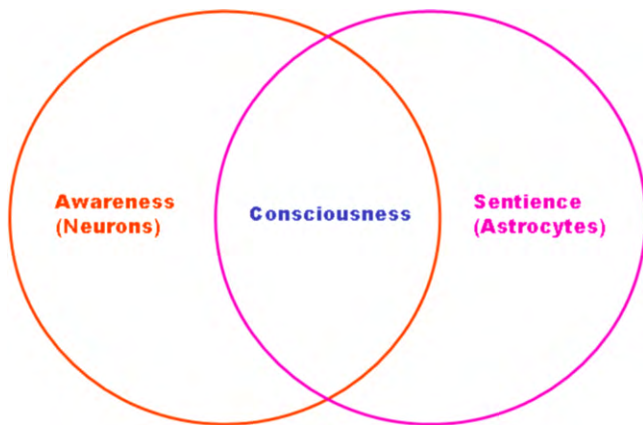
part of the information processed by the brain that “crosses a threshold” (Del Cul et al., 2009; Changeux and Dehaene, 2009) becomes conscious. We interpret this threshold as being a fixed point for the generation of coherent AM intercellular calcium waves, as suggested by Agulhon et al. (2008) and defined by De Pittà et al. (2008);

- (b) Influential proponents of scientific theories of consciousness agree about the necessity of information integration to construct coherent and unitary conscious episodes (see Tononi and Koch, 2008; Balduzzi and Tononi, 2009), although diverging about the nature of this integrative process;
- (c) Conscious processes involve the experience of a “here and now”. According to the classic work on time perception by Husserl (1964), the conscious present is like the tail of a comet, including “retention” of the past and also “protension” towards the future. Also James (1890) conceives the “specious present” as an extended “here and now” of each individual’s flux of consciousness.

It may be useful to paraphrase the title of Damásio’s book, “The Feeling of What Happens” (Damasio, 1999), by suggesting that the division of work in the brain is such that the astrocytic network conveys “The Feeling”, while neuronal networks carry information about “What Happens”. In this context, we make the following terminological definitions. Possession of information without consciousness is called “Awareness”. The capacity of integrating information contents and generating a feeling about them is called “Sentience”. Consciousness is conceived as “The Feeling of What Happens”: the intersection of awareness with sentience. These conceptual relations are illustrated in Fig. 8.

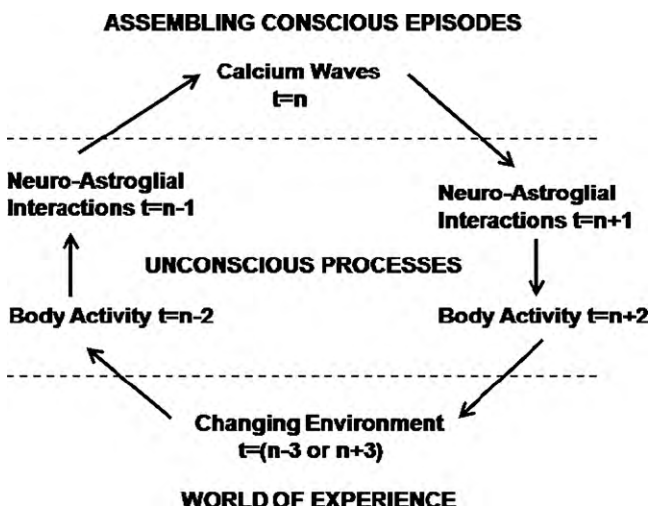
We also consider the possibility of astrocytes integrating somatic processes communicated to the brain by means of blood flow and cerebrospinal fluid signaling, mediated by other glial cells. Different types of glial cells possibly form a “panglial syncytium” (Rash et al., 1997) that controls the concentration of water and ions in the brain (a central factor in health and several diseases; see Rash, 2010). The convergence of both kinds of processes – body signals mediated by blood flow/cerebrospinal fluid/panglia and neuronal information – leading to the activation of coherent calcium waves in the astrocytic network is claimed to correspond to conscious episodes experienced by the living individual (Fig. 9).





**Fig. 8.** Consciousness as “The Feeling” (astroglial sentience) of “What Happens” (neuronal awareness). Awareness and sentience of information patterns can occur unconsciously, but when they occur together the informational content becomes conscious. This conception is consistent with the Astrocentric Hypothesis, since consciousness of contents occurs only when they are integrated by means of wavelike computing in the astrocytic network. The process of integration includes the formation of a feeling about the content of an episode.

Somatic self-regulatory processes impact on the astrocytic network by means of arterial blood flow and cerebrospinal fluid signaling mediated by – respectively – endothelial and ependymal cells (e.g., cytokine signaling in inflammatory processes). These signals include small molecules, as hormones and neuropeptides. Gliotransmitters (as neurotrophins) and neuromodulators are diffused in these mediums. The importance of blood signaling has been neglected in most attempts of formulating a scientific theory of brain information processing supporting cognition (an exception is Moore and Cao, 2008). In an earlier work, Tauber (1994) argued that the unconscious Self – a mental entity – is influenced by the activity of the immune system (e.g., eliciting creativity and hallucination during a period of high fever). Another kind of cell,



**Fig. 9.** The place and time of conscious episodes. According to our development of the astrocentric hypothesis, conscious episodes at time  $n$  (corresponding to the “specious present”) are generated by the interference of perceptual, cognitive, affective and emotional patterns when transduced to intercellular astrocytic calcium waves. Astrocytes receive these patterns from pre-synaptic neurons and sustain activity of their respective tripartite synapses in time  $n - 1$ , sending reinforcement or veto signals to post-synaptic neurons in time  $n + 1$ . The formation of conscious episodes in the astrocytic network can modulate neuronal transmission, influencing the resulting behavior of the individual in the environment.

the tanycyte, mediates communication of astrocytes and neurons with cerebrospinal fluid. There are four types of tanycytes, expressing important functional molecules, “such as glucose and glutamate transporters; a series of receptors for neuropeptides and peripheral hormones; secretory molecules such as transforming growth factors, prostaglandin E(2), and the specific protein P85; and proteins of the endocytic pathways” (Rodríguez et al., 2005).

Astrocytes are in an adequate position to integrate all these signals, modulate neuronal processes and feedback on the body (e.g., by means of the release of neuropeptides carried by blood). Considering the strategic position of astrocytes in the brain, mediating blood/cerebrospinal fluid/panglia and neuron signaling (for details see Abbott et al., 2006; Wang and Bordey, 2008), the astrocentric hypothesis of consciousness is – relatively to neurocentric approaches – on an advantageous standpoint to explain the interaction of several kinds of signaling in the brain and body of the living individual.

## 7. The human brain’s Master Hub

We use the term “Master Hub” to refer to a large and morphologically specialized astrocytic network that covers both cerebral hemispheres and permeates white matter in the corpus callosum, allowing whole-brain integration (with possible exceptions due to anatomical insulation, as in the case of the cerebellum) by means of calcium waves prompted by synergic factors and propagated (or not) according to the opening and closing of astroglial gap junctions.

The Master Hub is potentially connected to all Local Hubs by means of structural connections (gap junctions) that may become functional depending on patterns of brain activation. It constitutes a large-scale communication network supplementary to neuronal connections. Groundbreaking work by Oberheim et al. (2006, 2009) led to the identification of five kinds of astrocytes with different morphologies (and, possibly, different functions) in the human brain. This typology fits well with our proposed distinction of cognitive functions of astrocytes: integrating synaptic and whole-brain activities.

The evolution of astrocyte morphology seems to be closely related with mammalian and primate evolution. Cognitive roles of glia can be traced back to *C. elegans* (Bacaj et al., 2008). The astrocyte function of mediating blood flow and neuronal activity parallels the evolution of vertebrates (Bundgaard and Abbott, 2008). In primates, particularly in the human brain, astrocytes assumed increasingly complex cognitive functions. According to Oberheim et al. (2006), “the ability of astrocytes to sense neuronal activity and in turn release gliotransmitters creates a new dimension of communication that might participate in processing of local activity independent of synaptic transmission”.

Cáceres et al. (2007) relate the evolution of the human brain with changes in the expression of a neuropil protein (thrombospondin) that regulates synaptogenesis and dendrite growth. These changes largely affect the cortex but not the cerebellum. In a commentary to this finding, Premack remarks that “the areas found to have enhanced thrombospondin expression have larger neuropil space and thus more room for synaptic connections. Virtually all the newly discovered human singularities are located in areas associated with either complex social cognition [theory of mind (TOM)] or language. But the reorganization of the human brain has not been without cost. In addition to advancing language and TOM, it brought about neurodegenerative disease: schizophrenia, autism, Alzheimer’s, etc. These diseases are as unique to humans as is advanced cognitive function” (Premack, 2007).

Comparing human with rodent protoplasmic astrocytes, Oberheim et al. found that the first are “remarkably larger and more complex... their processes span 100–200  $\mu$ m, giving them a

27-fold greater volume than their rodent counterparts. On average, human astrocytes extend 40 large GFAP-positive processes radially and symmetrically in all directions from the soma" (Oberheim et al., 2006). They conclude that "it seems unlikely that the increased functional competence of the human brain can be attributed to any discrete aspect of neuronal number, form or function. In that context, the highly conserved morphological and electrophysiological properties of neurons throughout evolution present a stark contrast to the remarkable increase in complexity and size of human protoplasmic astrocytes. On that basis, we propose here that the domain encompassed by a cortical protoplasmic astrocyte creates and defines a glioneuronal functional unit, the complexity and functional importance of which has increased with mammalian evolution" (Oberheim et al., 2006)

While Oberheim et al. (2006) made a remark that "it is unclear whether a higher level of organization among astrocytic domains exists within functionally defined regions, such as within the barrel cortex", new findings (including a fifth type of human astrocyte) by a larger team (also first-authored by Oberheim), reported in a 2009 paper, suggest that large-scale coordination do exist. Oberheim et al. (2009) report the existence of varicose projection astrocytes (VPA), apparently exclusive to the human brain, presenting "more spiny processes than exhibited by typical protoplasmic astrocytes and typically extended one to five essentially unbranched, millimeter long fibers within the deep layers of the cortex. The processes... did not respect the domain organization, because they traveled in all directions, piercing and traversing the domains of neighboring protoplasmic astrocytes. Their process morphology was also intriguing; the evenly spaced varicosities suggest specialized structures or compartmentalization of cellular elements along the great distance of the fibers... We hypothesize based on their distinct morphology that these cells are specialized for long-distance communication across cortical layers or even between gray and white matter" (Oberheim et al., 2009).

They also make a suggestion about the function of interlaminar astrocytes: "In light of the length of interlaminar fibers and the large numbers of cells that each fiber may contact in its cortical path, their capacity to respond to both purinergic and glutamnergic stimulation with calcium elevation, and thence to propagate calcium waves, is of potential importance. Of note, the calcium increases in interlaminar cells could be triggered independently in both the cell bodies and fibers... these traits suggest that they may provide a network for the long-distance coordination of intracortical communication thresholds". This suggestion reinforces our proposed concept of a Master Hub as vehicle for whole-brain integration of information and support for the formation of conscious episodes.

## 8. The Master Hub and default networks

An approximate picture of how the dynamics of astrocytic waves influence whole-brain neurodynamics was presented in the thalamocortical loop model (Crunelli et al., 2002). The reverse view (neuronal dynamics influencing global astrocyte activity) was discussed by Aguado et al. (2002). Reciprocal influences and several kinds of neuron-astrocyte loops have been recently discussed (Giaume et al., 2010; Hamilton and Atwell, 2010). Since the maintenance of activity of the Master Hub 'in vivo' requires the synergy of several factors, there should exist a neuro-astroglial arrangement that supports its functionality during awake and dreaming states, and shuts down in dreamless slow-wave sleep. We suggest that this arrangement corresponds to "default networks" in the human brain; more precisely, to the components of such networks that are active only in the conscious state, as described in the Slow Cortical Potential hypothesis presented by He and Raichle (2009).

Using blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signals, Fox et al. (2005) identified "two diametrically opposed, widely distributed brain networks on the basis of both spontaneous correlations within each network and anticorrelations between networks", one consisting of "regions routinely exhibiting task-related activations" (including intra-parietal sulcus and inferior parietal lobule, medial temporal cortex, frontal eye fields, dorsolateral prefrontal cortex and insula) and the other of "regions routinely exhibiting task-related deactivations" (including the posterior cingulate, precuneus, lateral parietal and medial prefrontal cortex). According to the authors "this intrinsic organization, featuring the presence of anticorrelated networks in the absence of overt task performance, provides a critical context in which to understand brain function" (Fox et al., 2005).

The authors stress that this finding adds, in relation to oscillatory synchrony, a new dimension to brain integration mechanisms supporting conscious processing: "Although our current results share important theoretical properties with synchrony and coherence reported across different temporal and spatial scales, they extend this thinking in a critical way, suggesting that anticorrelations may be as important as correlations in brain organization" (Fox et al., 2005). What is then the role of anticorrelated regions and circuits in cognitive processing? How is it related to astrocyte activity?

The default network's involvement in conscious processing was recently discussed by He and Raichle (2009), who noted that "not all brain networks contribute to consciousness equally...the anterior cingulate and anterior insular cortices, in addition to the default network, might be more pivotal than the sensory and motor networks and maybe even the dorsal attention network (including the dorsal visual stream and frontal eye field)". The authors compared brain activations during slow-wave sleep (SWS) with wakefulness and rapid-eye-movement (REM) sleep, concluding that "whereas the sensory and motor regions and the dorsal attention network are as active in SWS as in wakefulness; the anterior cingulate, anterior insular and the midline regions of the default network are deactivated in SWS and reactivated in both REM sleep and wakefulness...this conjecture is also consistent with existing data from persistent vegetative patients, blindsight patients and from manipulations of momentary conscious perception" (He and Raichle, 2009). The part of the human default network that is active only in conscious states was called "Slow Cortical Potential". Based on the conjecture raised by the authors, we suggest that the sub-network they identified as being critical to conscious processing is closely related to the astrocytic Master Hub.

One intriguing feature of default networks is that the excitation of some brain regions and circuits is always accompanied by the inhibition of others. What would be the functionality of such an arrangement, or better, what is the use of keeping some regions and circuits inhibited during conscious activities? One possible, straightforward answer, is that these regions and circuits are not necessary for conscious processing, but possibly serve to unconscious processing (e.g. supporting unconscious motor activity). However, as neurons belonging to these regions and circuits are kept hyperpolarized, they cannot generate action potentials to support motor or any other activity. Therefore, there may be another function for the inhibited regions.

What would be, in general, the role of inhibition for cognitive and emotional processing? Is inhibition just limiting excitation, or does it also have a constructive role? For instance, the inhibition of pain is part of the mechanisms that generate pleasure. However, pleasure is more than the absence of pain. Do inhibitory mechanisms also generate the very sensation of pleasure? Or is it dependent on excitatory mechanisms? Leknes and Tracey (2008)

indicate “extensive similarities in the anatomical substrates of painful and pleasant sensations (such as) the important role of the opioid and dopamine systems in modulating both pain and pleasure”, pointing to the importance of “understanding the mutually inhibitory effects that pain and reward processing have on each other, and the neural mechanisms that underpin such modulation”.

How does inhibition impact on BOLD fMRI signals? Is there a role for astrocytes in this kind of process? As pointed out by Douglas Fields, “the brain and blood were somehow communicating. Now we know they communicate using astrocytes as interpreters” (Douglas Fields, 2009; see also evidence gathered by Schummers et al., 2008). GABAergic transmission generates neuronal electric fields, corresponding to the excitation of an inhibitory neuron and membrane hyperpolarization of a target excitatory neuron. The hyperpolarized neuron, although generating an electric field, does not contribute to BOLD fMRI signals, because blood flow is controlled by astrocytes in such a way that an increase in arterial blood supply occurs to regions where neurons display higher excitatory activity (increase of amplitude and/or frequency of local electric fields, but not necessarily spiking activity, as shown by Logothetis and Pfeuffer, 2004). Therefore, the cognitive role of inhibition is not likely to depend on hyperpolarization of the target neuron, but on another effect of GABA release.

A solution to the puzzle comes from research on astrocytes. Astrocytes metabolize GABA, and GABA<sub>B</sub> receptors operate in cooperation with astroglial NMDARs, which do not depend on temporal coincidence of inputs to prompt calcium entry. Possibly astroglial NMDA and GABA receptors are modulated by the concentration of extracellular ATP, thus contributing to the onset of astroglial calcium waves (Lalo et al., 2009). Astrocyte calcium waves can be induced by neuronal release of GABA and binding to astroglial GABA receptors, as indicated from results of ‘in vitro’ experimentation by Kang et al. (1998) and from ‘in vivo’ response to gamma-hydroxybutyrate (Molnár et al., 2009). Another possibility is a concerted action of glial Glu and GABA transporters, operating as a negative feedback loop that contributes to the balance of excitation and inhibition (Genoud et al., 2006; Héja et al., 2009). In any case, the conclusion seems to be that the same GABAergic transmission that silences neurons can also modulate astrocyte activity, then causing cognitive and emotional effects.

### 9. Astrocytic network induces neuronal plasticity

Once an integrated cognitive state is formed in the brain’s astrocytic network, the result can feedback on brain activity, inducing effects on perceptual, cognitive, endocrine and motor systems. Such a feedback is carried from astrocytes to post-synaptic neurons by means of at least seven pathways, with different effects on neuronal membranes (see Haydon and Carmignoto, 2006, except for the fourth and seventh alternatives below):

- (a) Glu release by astrocytes activating synaptic NR2A subtype NMDA receptors, causing membrane potentiation by promoting AMPARs transport to the post-synaptic density;
- (b) Glu release by astrocytes activating extrasynaptic NR2B, causing membrane depression by means of inhibition of AMPARs transporters;
- (c) D-serine release by astrocytes potentiating NR2A neuronal NMDARs in the presence of pre-synaptic Glu release (Henneberger et al., 2010);
- (d) D-serine release by astrocytes depressing NR2A neuronal NMDARs in the absence of pre-synaptic Glu release (Zhang et al., 2008);

- (e) ATP release and binding to neuronal purinergic receptors (Pascual et al., 2005), and
- (f) ATP release in extracellular space and degradation into adenosine, causing depolarizations that impact on brain activity and behavior (Halassa et al., 2009);
- (g) The release of cytokines that mediate pain sensations (Zhu et al., 2009; for a review, see Miller et al., 2009).

In the above list, for the sake of simplicity we did not mention astrocytic homeostatic control of ionic concentrations in perisynaptic intercellular fluid, because it is too general and does not seem to convey information patterns to neurons (for a review, see Deitmer and Rose, 2010).

The double role of astrocytes for neuronal plasticity – leading to non-linear responses to drugs that perturb their metabolism – is the result of the interplay of above pathways. For instance, a reduction of ATP production and/or availability can have non-linear effects, promoting neuronal membrane potentiation by means of binding to neuronal receptors and reducing the availability of adenosine, or blocking it by means of reducing calcium waves and the consequent release of astroglial Glu and D-serine to neurons.

According to Fellin and co-authors, “by providing local feedback excitation mediated by glutamate, astrocytes provide a source of neuronal activation that may be critical in controlling the synchronous depolarization of groups of pyramidal neurons. At the same time, by providing distant feedforward actions that are mediated by purines, the astrocyte suppresses synaptic transmission. Through these coordinated actions, the astrocyte provides balanced excitation and inhibition mediated by two distinct transmitter systems... Any displacement of this equilibrium between excitation and inhibition has the potential to lead to disorders of the nervous system” (Fellin et al., 2006)

What determines whether astroglial influences on neuronal pre- and post-synaptic activity will cause membrane potentiation or depression? Gielen et al. (2009), although recognizing that “the molecular basis for this profound difference in activity between NMDAR subtypes is unknown”, attempt to “provide a proof of concept for a drug-based bidirectional control of NMDAR activity by using molecules acting either as... ‘closers’ or ‘openers’ promoting receptor inhibition or potentiation, respectively”. Would this control be exerted by astrocytes? We have suggested that astrocytic networks mediate the interactions of metabolic signals (carried by blood, cerebrospinal fluid and panglial pathways) with neuronal information processing. By integrating this variety of signals, the astrocytic network finds a result, then reinforcing (potentiating) the synapses that processed the received patterns, if they generate a state of satisfaction, or vetoing (depressing) them, if they generate dissatisfaction and/or if they were habituated.

In anthropomorphic terms, the astroglial network compares the information conveyed by neurons with signals received from the body, making a “judgment” of “good” or “bad”. This kind of “judgment” also has a possible role in the determination of which patterns are more likely to form new memories that can be retrieved later. When a cognitive pattern is reinforced by astrocytic glutamatergic output, the chance to form long-term memories retrievable in the future obviously increases. Correspondingly, the chance decreases if the pattern is “vetoed” by means of membrane depression. Post-synaptic neuronal membrane potentiation or depression are thus conceived as possibilities of conscious processing having an effect on memory and behavior. Also the consolidation of long-term memories involves an interplay between cortical and hippocampal tripartite synapses during sleep, when positively selected cortical patterns are reinforced by means of hippocampal activation of entorhinal cortical units, while negatively selected patterns are discarded.

An illustration of such a complex soma-haemo-neuroglial scenario is provided by experimental data resulting from the usage of drugs that perturb astrocyte metabolism. Different doses of fluoracetate or its metabolite, fluorocitrate, an inhibitor of astrocyte production of ATP, have different effects on cognition. In non-lethal doses, fluorocitrate partially perturbs the tricarboxylic acid cycle, leading to a reduction of aconitase production, with two main effects: an increase in citrate, possibly causing calcium chelation, and a reduction in the production of glutamine, a precursor of both Glu and GABA (Fonnum et al., 1997). A dose administered by means of cerebrospinal fluid enhances, while a slightly higher dose impairs working memory (Lei et al., 2009).

One of the possible explanations of this non-linear effect is that impairment of production of glutamine can have opposite post-synaptic effects, such as spreading depression or focal epileptiform discharges with secondary generalized seizures, depending on the impact on the production of – respectively – Glu or GABA, according to the specific characteristics of brain circuits (Willoughby et al., 2003). Similar recent findings show a non-linear, bell-shaped effect of perturbations of astrocyte activity on mnemonic processes. Gibbs and Bowser (2009) showed that astroglial GABA receptors can contribute to memory processing in the young chick hippocampus: “The GABA<sub>B</sub> antagonist, phaclofen, and the inhibitor of astrocytic oxidative metabolism, fluoroacetate, inhibited memory when injected between 2.5 and 30 min. Paradoxically, a high dose of the GABA<sub>B</sub> agonist, baclofen, also inhibited memory, but a low dose promoted memory consolidation” (Gibbs and Bowser, 2009), while Zhang et al. (2008) found that “sodium fluoroacetate (NaFAC) reduced the magnitude of long-term depression, which could be restored by exogenous D-serine... (that) enhanced spatial memory retrieval in the Morris water maze in a bell-shaped dose-dependent manner and rescued the NaFAC-induced impairment of memory retrieval”.

## 10. Astrocytic network supports mnemonic functions

Currently, there are several proposals of possible contributions of the astrocytic network to memory formation, consolidation and storage. Information processing supporting memory formation was one of the main tenets of the astrocentric hypothesis (Robertson, 2002). Some – but not all – mnemonic functions, like working memory, are implicit in the consciousness-supporting role of astrocytes. Their involvement in memory formation is further supported by several lines of evidence. As a functional partner in the tripartite synapse, astrocytes modulate both excitatory and inhibitory transmission between neurons, thus mediating Hebbian learning (Fellin, 2009). Astrocytic release of Glu (Perea and Araque, 2007) and/or D-serine (Henneberger et al., 2010), when coupled to post-synaptic depolarization, leads to long-term potentiation. Laming (2000) proposed that memory formation is based on the activation of astrocytes following release of potassium ions from neuronal activity. They also function as a “gatekeeper” by decreasing the transfer of information carried by spikes after a period of high-frequency pre-synaptic stimulation (Volman et al., 2007). Another auxiliary function of astrocytes would be supporting memory consolidation, as shown by Gibbs et al. (2008).

Some proposals ascribe to astrocytes the role of information storage supporting memory functions. Caudle (2006) argues that ion channels located in astrocytes and their syncytium can store information for long periods of time, more efficiently than neuronal synapses. A related version is Banaclocha's hypothesis of a magnetic engram: “local astrocytes integrate information from multiple neuronal axonic and dendritic magnetic fields arranged in their proximity... Repetition (iteration) of this spatiotemporal integration results in a permanent modification of astrocytic magnetic fields... (that) constitute the central mechanism for

memory and neurocomputation in the human neocortex” (Banaclocha, 2007). The structure of the information storage system would be the following: “magnetic storage of information can be accomplished through astrocytic parcellation of the cortical neuropil into small cellular domains. These cellular domains can work in a similar way than those drawn from other physical systems, such as artificial magnetic memory storage devices. These systems work by reorienting permanent magnetic domains (dipoles), which are stuck to tape substrate” (Banaclocha, 2007).

In our view, the study of information storage capabilities of astrocytes should not be assumed as a heuristic priority, since there are good evidences that neurons do store long-term memories. Although there is no evidence against a possible participation of astrocytes in this kind of process, there is competing evidence that storage is made by neurons. Shema et al. (2007) found that “in the rat cortex, long-term associative memories vanished rapidly after local application of an inhibitor of the protein kinase C isoform... In the neocortex, which is assumed to be the repository of multiple types of long-term memory, persistence of memory is thus dependent on ongoing activity of a protein kinase long after that memory is considered to have consolidated into a long-term stable form”.

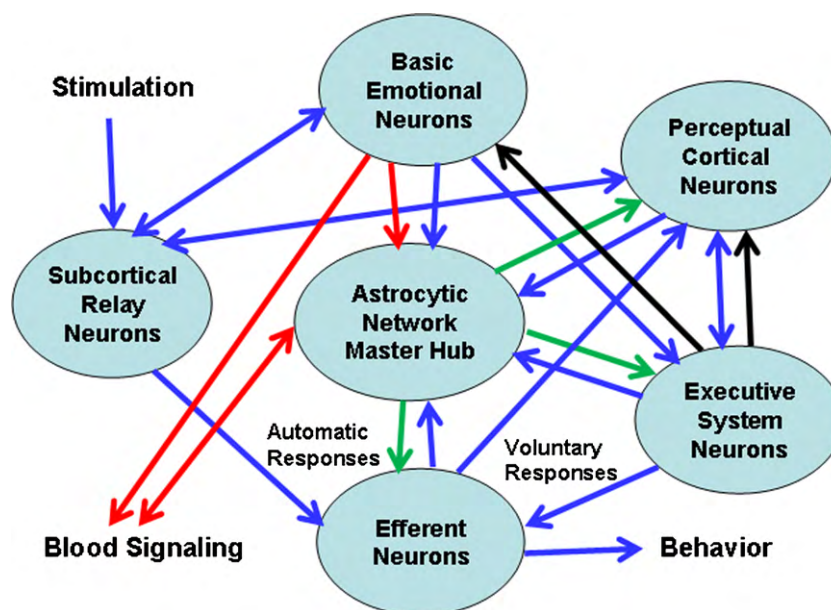
Long-term memory is widely believed to be supported by an increase of concentration of AMPARs in neuronal membranes. Several kinases are critical to signal-transduction pathways that lead to the expression of genes that produce AMPAR. Sacktor (2008) considers that “only a single molecule has been found both necessary and sufficient for maintaining LTP, the brain-specific, atypical protein kinase C isoform, protein kinase Mzeta (PKMzeta)... the first molecule found to be a component of the long-term memory trace”. We can also mention other lines of research about long-term memory formation and maintenance in neurons, as the study of “Stargazer” mutant mice, indicating a role for synaptic PDZ proteins in long-term memory-related fixation of AMPA (Chen et al., 2000) and experiments with chemically induced over-expression of CamKII (Cao et al., 2008).

Although astrocytes may not store long-term memory, as long as they support conscious processing they should be important for short-term/working memory, formation and retrieval of declarative (semantic and episodic) memories, as well as for some kinds of multimodal associative learning (e.g. Pavlovian conditioning). In a systemic overview of astrocytic function, their action towards neurons in the context of tripartite synapses is likely to be reinforcing or weakening consciously processed patterns, facilitating or blocking their fixation as long-term memories. Once patterns are stored (by neurons), astrocytes can also induce their retrieval in the presence of a conscious cue (e.g., remembering the name of an old colleague after seeing a photo taken during school days).

## 11. Astrocytic network mediates voluntary behavior

The diagram (Fig. 10) provides an overview of cognitive functions of astrocytes in brain function. The Master Hub is activated by means of signaling from neurons to astrocytes in tripartite synapses, as well as panglial communication triggered by signaling molecules carried by blood (e.g. hypothalamic function; see Gordon et al., 2009; Panatier, 2009) and cerebrospinal fluid.

The above diagram is a simplified view of interactions of main functional systems in the human brain. Neuronal and astroglial networks are represented separately. The “Executive System” includes, besides association cortices, also the hippocampal-entorhinal neuronal system. “Emotional neurons” are mostly in the limbic system, but the term applies to all neurons that process information related to emotional phenomena. It should be clarified that, according to the presented model, such neurons detect (e.g. amygdala neurons) and process (e.g. orbitofrontal neurons)



**Fig. 10.** An overview of cognitive functions of astrocytes in the brain. Legend: blue arrows: excitatory transmission; black arrow: inhibitory transmission; red arrow: blood flow (and cerebrospinal fluid) signaling; green arrows: modulation of membrane potentiation/depression. Astroglial cells function as an integrated network (“Master Hub”) that modulates the activity of neuronal systems and mediates voluntary responses to stimulation and psychosomatic effects. Conscious processing by astrocytes can influence behavior by means of modulation of neuronal activity. An automatic behavior is produced by the sequential activation of relay, basic emotional and efferent neurons, bypassing the astrocytic network. It is based on previously strengthened connections between neurons that recognize kinds of sensory patterns and neurons that trigger the corresponding kinds of behavior; it does not require conscious processing of the stimulus.

emotional information, but do not convey the feeling (e.g., pain, hunger) elicited by the emotional state (e.g., tissue injury, empty stomach). Feeling is proposed to be a function of the astrocytic network. Each feeling is generated by the response of astrocytes connected to the neurons that detect and process the respective information patterns.

Voluntary responses require the participation of executive neurons that make all logical operations necessary to implement coherent behavior. Astrocytes only “approve” or “veto” executive plans. An important feature of the diagram is that astrocytes cannot directly depress basic emotional neurons (e.g. there is no habituation to pain), but can indirectly contribute to their inhibition by means of executive mediation (e.g., repressing an automatic aggressive response). Psychosomatic effects are mediated by the actions of efferent neurons (e.g., on the endocrine and immune systems) by means of diffuse blood and cerebrospinal fluid signaling. They require conscious processing of the stimulus, but the generation of the effect is unconscious.

We exemplify the explanatory power of the diagram with the example of Conditioned Taste Aversion (CTA). This is a kind of learning process present in several mammalian species, consisting of an acquired aversion for previously ingested food that caused digestive pain and/or damage. Although the learning process is mostly unconscious (leading to the formation of non-declarative memory), there are three phases in the whole process that imply conscious processing:

- Initial tasting of the food. Although the aversion is not generated by the food having a bad taste, this tasting is necessary to create a register of what it tastes like;
- Unpleasant (conscious) sensation of nausea and/or digestive pain caused by the food;
- Tasting and recognition of the food after conditioning, both necessary to trigger the aversion behavior.

The CTA process begins with the sensing of food properties. Perception of properties of the stimulus (e.g., how it tastes) is

mediated by thalamic relay neurons that transmit the signal to somatosensory cortex neurons (Perceptual Cortical Neurons in the diagram). These neurons interact with higher level neurons and neighboring astrocytes, generating a taste and other sensations elicited by the stimulus. When the taste (itself not relevant for CTA) and digesting experience (relevant for CTA) are satisfactory, astrocytes reinforce neuronal synapses involved in the processing of the stimulus by means of membrane potentiation (green arrows). The signal is also transmitted to subcortical neurons belonging to circuits that control feelings of hunger and satiation (Basic Emotional Neurons). Interaction with the basic emotional system can trigger an automatic behavior (activation of Motor Neurons) of swallowing or rejecting the food.

When, after ingestion, a nausea or digestive pain occurs, astrocytes induce the inhibition of basic emotional neurons that mediate the response, by means of potentiating the respective inhibitory neurons of the Executive System, thus conditioning the response to new presentations of the same kind of stimulation. In this case, there will be both automatic and voluntary responses to the stimulus. The automatic response, mediated by an interaction of subcortical relay neurons with the basic emotional system, consists of avoidance. The voluntary response, following the sensing of the taste, can be e.g. a throw off.

## 12. Concluding remarks

In this review of recent astrocyte research and related psychophysiological modeling we made a set of theoretical claims which – if true – would correspond to a scientific revolution in brain sciences, moving from a neurocentric to an astrocentric perspective on cognitive and emotional processing. In spite of the boldness of the claims, they are all experimentally tangible and lead to exciting new perspectives in the interdisciplinary field of Physiological Psychology. Our model favors the development of new experimental research programs to test the cognitive function of astrocytes, by means of the development of new methods and

techniques, or by reinterpreting results obtained with classical tools as the several modalities of EEG.

Among the future experimental possibilities opened by this approach, we would like to highlight the following. An exciting prospect would be testing the proposed association of different kinds of human astrocytes identified by Oberheim et al. (2006, 2009) with the cognitive functions we attribute to them (operating as Local or Master Hubs). Another important line of investigation is paying (more) attention to behavioral effects of genetic and pharmacological knockout of astroglial proteins to evaluate cognitive functions, e.g. by means of the usage of paradigms for voluntary and automatic responses. Also the observation of behavior of pannexin knockout mice may lead to important discoveries, since this protein is involved in ATP mechanisms relevant for the propagation of calcium waves. In contrast, analysis of behavioral effects of drugs – like fluorocitrate – that have effects on single astrocytes cannot confirm or disconfirm the astrocentric hypothesis, since the crucial cognitive effect may be on the neurons that interact with the astrocytes.

If the hypothesis happens to be true, then the final target of action of all general anesthetics has to be the astrocytic network. From this reasoning, several testable hypothesis can be raised and experimentally proven, e.g. that the anesthetic effect of halothane is on astroglial – not neuronal – gap junctions, or that the anesthetic action of ketamine and other NMDAR blockers impair the operation of the Master Hub. Other important predictions are that the Master Hub is functionally deactivated during dreamless SWS and severely disturbed during generalized epileptic seizures with loss of consciousness.

The development of new ‘in vivo’ imaging technologies, which has already begun with two-photon microscopy combined with fluorescent markers, may bring new and important evidence about the cognitive role of astrocytes. We have suggested (Pereira, 2007) the development of ultraviolet laser technology for imaging of large-scale calcium ion population movements in the brain. More conventional techniques may also be reinterpreted in this new perspective. Astrocyte activity may contribute to scalp and intercellular EEG registers, as well as to conscious modulation of brain rhythms in neurofeedback therapy (for an overview of the sources of EEG signals, see Buszák, 2006).

Astrocytes may also become the main target of electric and magnetic therapeutic methods. According to Banachlocha, “it has been well established that astrocytes produce steady state (DC) magnetic field while neurons produce time-varying (AC) magnetic fields” (2007). In this case, astrocytes are not directly involved in the effects of electroshock (using AC), but there is a possibility of therapeutic use of astrocyte stimulation by means of DC. It has also been suggested that deep-brain stimulation, which in many cases relieves the symptoms of Parkinson’s disease, may act on astrocytic calcium waves that coordinate the activity of large populations of neurons controlling movement (Douglas Fields, 2009).

Last but not the least, we would like to stress the importance of having a theoretical model of astrocyte cognitive functions, even if it is still sketchy and incomplete, to inspire new research programs. In the spirit of modern science, we will feel content if any (or all) of our assumptions and claims are corrected by future experimental results, leading to progress of knowledge about how animals execute cognitive operations.

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