Special Issue

Tripartite Synapses and the Glial Network

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Abstract

A brain model of glial-neuronal interactions is proposed. It focuses on tripartite synapses and the glial network. A tripartite synapse not only consists of the presynapse and the postsynapse as neuronal components, but also of the astrocyte as the glial component. This synaptic structure processes information between the neuronal and glial network. My model of the astrocyte network focuses on the structures and functions of gap junctions and gap junction plaques. It is hypothesized that gap junctions and gap junction plaques embody cyclic memory structures generated by sequential synaptic information processing. Synaptic information processing occurs in different time scales, which may also work on gap junction plaque formation. In parallel, the dynamic memory structures may function as intentional phase programs activated by appropriate neurotransmitter substances balancing intended glial-neuronal interactions. There is experimental evidence for feedforward and feedback loops between the main locations of glial-neuronal interaction, comparable to the cognitive Action Cycle Theory by Baer.

Key Words: tripartite synapse, glial network, gap junction plaque formation, time scales, feeding loops

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Introduction

My previously proposed model (Mitterauer, 2013) focuses on "consciousness-generating glial-neuronal units" termed as "the proemial synapse". The glial component of a synapse is interpreted as the embodiment of the subjective subject ("I"), and the neuronal component embodies the objective subject ("You") with its inner and outer environment. On these locations reflection cycles are generated, which form glial-neuronal synaptic units (tripartite synapses) activated by the glial and neuronal network.

A tripartite synapse is composed of the presynapse and the postsynapse as neuronal components and the astrocyte with its network as the glial component.The present article attempts to describe local processing structures of the glial component interconnected with the neuronal component in the tripartite synapse acting as "feeding loops" between the physical material phases. I hypothesize that gap junctions and gap junction plaques of the astrocytic network embody cyclic memory structures generated by sequential synaptic information processing. Synaptic information processing occurs in different time scales, which may also work on gap junction formation. In parallel, the dynamic memory structures may function as intentional phase programs activated by appropriate neurotransmitter substances balancing intended glial-neuronal interactions. There is experimental evidence for feedforward and feedback loops between the main locations of glial-neuronal interactions, which may correspond to the Cognitive Action Cycle

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Theory by Wolfgang Baer (2013). The underlying formalism of transclassic ontology (Guenther, 1962) is not described in the present paper.

According to the main topic of the present study, it does not explicitly deal with the problem of consciousness. In this context I refer to the work by Pereira and Furlan (2010) conceiving the active astroglial network as a "Master Hub" that integrates results of distributed processing from the neuronal network. Theoretical results of this model are contributing to the development of new experimental research programs to test cognitive functions of astrocytes and their networks in conscious states based on a conceptual framework for the science of human consciousness (Pereira, 2013).

First, the relevant biological structures of the tripartite synapse and the astroglial network must be described.

1 - Biological interaction structures

1.1 - Tripartite synapses

The basic anatomical components of a tripartite synapse are composed of the presynaptic neuron, the postsynaptic neuron, and the astrocyte embodying the glial cell with a synaptic cleft in between. The glial-neuronal interactions in chemical tripartite synapses occur via neurotransmitters, gliotransmitters and other substances (neuromodulators, neurotransporters, ions, etc.). Experimental neurophysiological research has demonstrated that the glial system exerts a modulatory function in its interactions with the neuronal system (Haydon and Carmignoto, 2006). Since the topic of the present study is focused on tripartite synapses and the astrocytic network, other main glial structures and functions (oligodendroglia, myelin, microglia, etc.) are not considered. Figure 1 depicts a schematic diagram of glial-neuronal interactions in the tripartite synapse. Sensory-motor networks compute environmental information activating the presynapse (1). The activated presynapse releases neurotransmitter substances (NT) from vesicles (v) occupying both presynaptic receptors (poR) and receptors on the astrocyte (acR) (2). NT also activate gap junctions (g.j.) in the astrocytic network (syncytium) enhancing the spreading of calcium waves (Ca $^{2+}$) (3). In parallel, the oocupancy of acR by NT also activates Ca^{2+} ions within the astrocyte (4). This mechanism exerts the production of gliotransmitters (GT) (5, 6) within the astrocyte. The occupancy of extrasynaptic pre- and postsynaptic receptors (prR, poR) by GT is excitatory (7) and on extrasynaptic poR inhibitory (8). Neurotransmission is also inactivated by the reuptake of NT in the presynaptic membrane mediated by transporter molecules (t) (9). Moreover, GT inhibit the presynaptic terminal via occupancy of prR temporarily turning off synaptic transmission in the sense of a negative feedback (10). Synaptic information processing can be transmitted to the neuronal network activating the synapse again (11).

1.2 - Astroglial network (syncytium)

The biological structure proposed focuses on gap junctions between astrocytes, the main glial cell type beside oligodendrocytes and microglia. Gap junctions provide a structural link by which single cells are coupled to build a functional network, called syncytium, with communication dynamics that cannot be exerted by individual cells. Gap junctions of an astrocyte syncytium consist of connexins forming gap junction channels by hemichannels of different kinds (Ransom and Giaume, 2013). Whereas astrocytes are interconnected with their neighbors via gap junctions, the interactions of astrocytes with neurons (Araque, 1999) occur mainly in tripartite synapses.

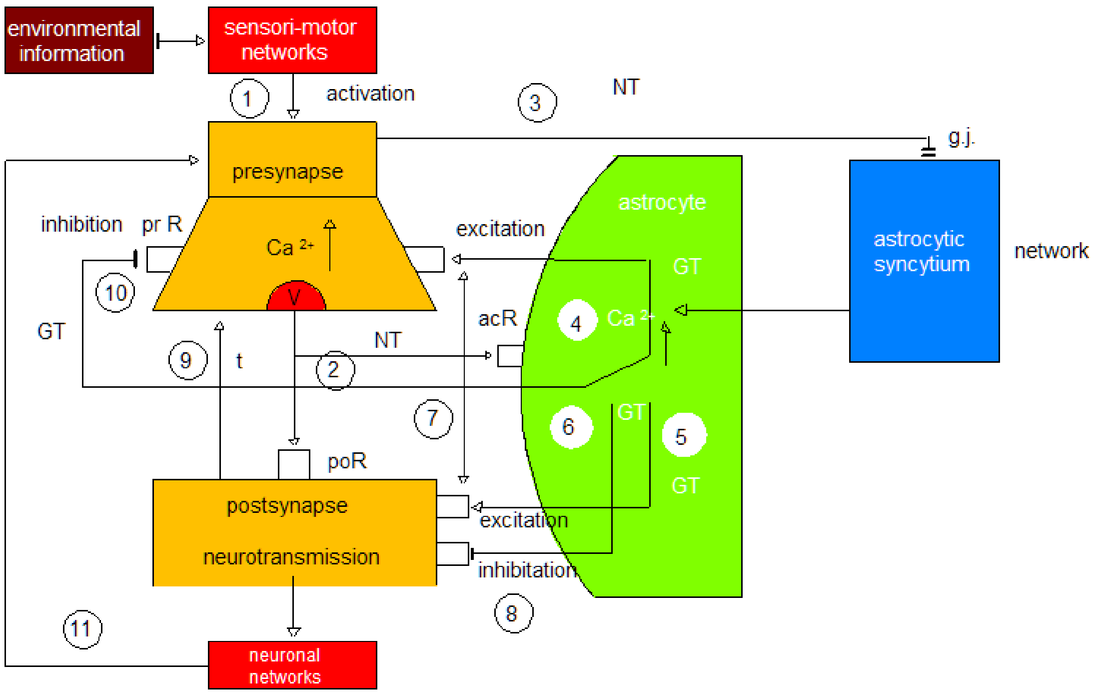

Figure 1. Schematic diagram of glial-neuronal interactions in a tripartite synapse

The number and composition of gap junctions can be dynamically regulated by upregulating connexin biosynthesis or decreasing the rate of connexin degradation in the endoplasmic reticulum, and by enhancing gap junction assembly. If gap junctions are frequently coupled within time scales of seconds or hours, they form plaques (Ransom and Giaume 2013).

Figure 2 shows a diagrammatic schema depicting an astrocytic syncytium (a). Six astrocytes (A_{c1} ... A_{c6}) are completely interconnected via fifteen gap junctions (g.j.). Each astrocyte contacts a neuronal synapse building a tripartite synapse (tSy, only one is shown). This simple diagram refers to the elementary components and their connections in the astrocytic syncytium. In this network organization frequently activated gap junctions generate a plaque. An example of plaque formation (b) is given between an A_{c3}, A_{c4}, A_{c5}, A_{c3} –loop (fat connection lines) generated by repeated activation (arrows). This loop becomes embodied in a gap junction plaque composed of a hierarchical loop structure (cycles).

1.3- Glial-neuronal interactions in different time scales

An astrocyte responds to prolonged synaptic activity in comparison to pure neuronal synapses (Winship, 2007). It is acting in a continuously prolonged time frame from seconds, minutes or longer (Santello, 2011). These local phenomena are capable of triggering gliotransmission and modulating basal transmission at individual tripartite synapses (Volterra, 2013).

Gap junction channels formed by the connexin family of proteins have different sensitivities and time courses. They act on a millisecond time scale termed fast-gating or substrate-gating, and on a slower time course (seconds or longer), termed slow-gating (Bargiello and Brink, 2009). Importantly, gap junctions are dynamic structures with channels being continually added and removed forming the structure of gap junction plaques (Sosinsky, 2009). We hypothesize that in tripartite synapses and the astrocytic syncytium comparable time periods are at work and may be interconnected in feeding loops.

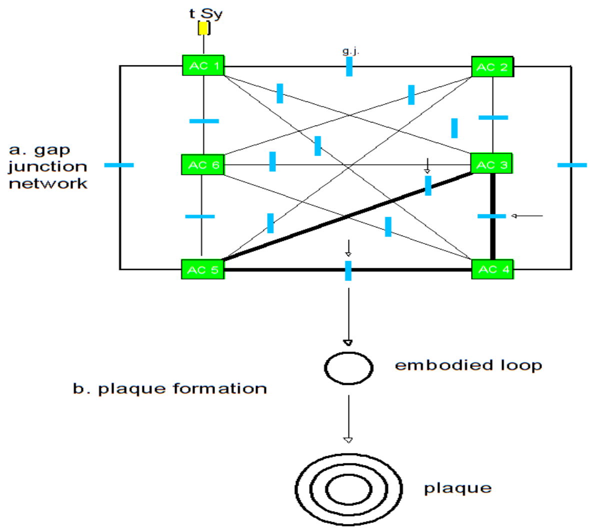

Fig. 2. Outline of an astroglial network
a. gap junction network
b. plaque formation

Figure 3 shows diagrams of glial-neuronal interactions in different time scales.

a. Action cycles within milliseconds in a tripartite synapse (tSy) and in the corresponding astrocytic network (aN) (syncytium). Production of neurotransmitters (N) activates (arrow) expression of astrocytic receptor pattern (acR) that in turn activates the production of gliotransmitters (GT), closing the loop. In the aN activation of tSy occurs by gap junctional loop generation (indicated as a cycle).

b. Within the second to minute scale the repeated activations (double headed arrows) between N, acR, GT and N and the repetition of the interconnection with aN generate a loop embodiment (fat cycle).

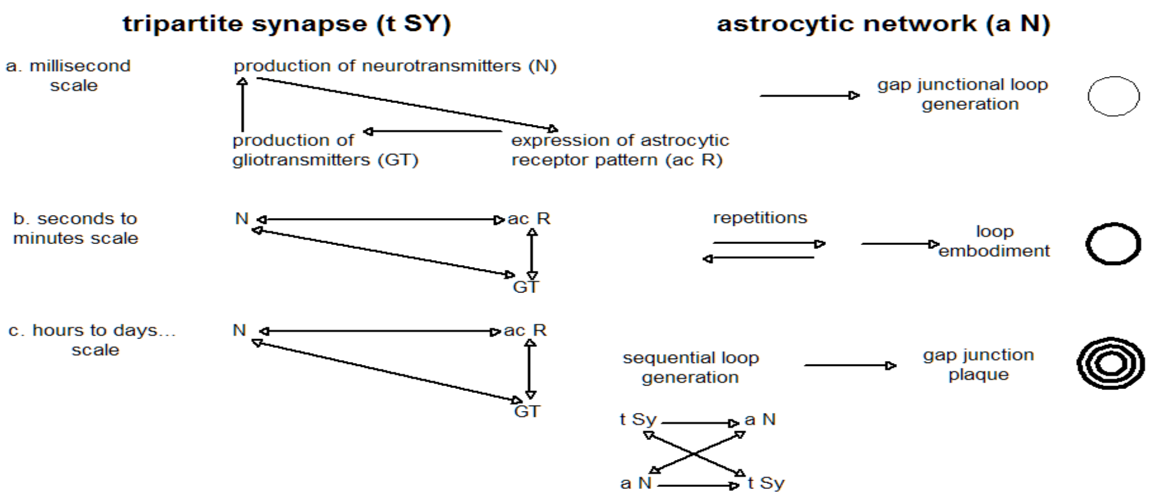

Fig. 3. Glial-neuronal interactions in different time scales a. action cycles in milliseconds
b. action cycles in seconds to minutes c. action cycles in hours, days or longer

c. In the hours and longer duration of tSy-aN-interactions a repeated generation of action loops occurs, and in sequential modifications a hierarchical loop embodiment is built as a gap junction plaque. The sequential modification is based on an interplay between tSy → aN ↔ aN → tSy ↔ tSy. Formally interpreted, the tripartite synapse (tSy) operates as a relator and the astrocytic network (aN) as a relatum and vice versa (Mitterauer 2013). As embodiments of sequential modifications in action loops it generates a gap junction plaque.

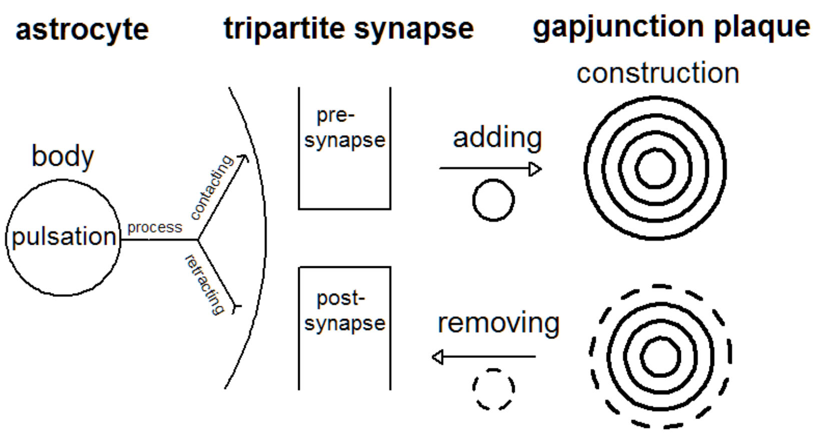

Fig. 4. Motile astrocytic process and network structuring

1.4 - Motile astrocytic processes and glial network structuring

As experimentally verified, the processes of an astrocyte body exert a motile behavior contacting synapses and retracting from synapses (Hirrlinger, 2004; Winkler, 2013). Figure 4 depicts an astrocyte contacting (arrow) the pre-postsynaptic components of a synapse and its endfoot or retracting (reversed arrow) from the synapse. The body of the astrocyte exerts a pacemaking via the motile astrocytic process as observed in experiments (Parri and Crunelli, 2007). This rhythmic pulsation of the astrocyte occurs in a time scale of minutes, whereas the synaptic activation of its processes may occur in shorter time scales. This mechanism may be responsible for a dynamic gap junction construction by adding (fat cycle) and removing an embodied cycle (dashed cycle) (Sosinsky, 2009).

2 - Memory and realization of intentions in glial-neuronal interactions

The quasi-crystalline gap junction plaques activated during consciousness may be converted into memories by crystallization into a long-lived highly resistant state. An ultrastructural study confirms that interastrocytic gap junctions are packed in a crystalline array (Robertson, 2013).

Based on my model of glial-neuronal interactions the role of gap junction in memory formation can be interpreted as follows: gap junctions may register already generated cyclic pathways in the syncytium. Depending on a feedback from the neuronal network to the glial syncytium based on feasible intentions with regard to environmental information, gap junctions could strengthen their structure embodying a memory mechanism. In this case we have a double memory function of gap junction: a local embodiment of memories and a pathway memory determined by gap junctions (Mitterauer, 2015). This double memory function of gap junction plaques may work as intentions expressed in tripartite synapses as an expectation pattern experienced in synaptic neuroglial interactions and realized in the neuronal network via sensori-motor activation in the environment (Mitterauer, 2001; 2004).

A “feeding” loop between the local structures of gap junction plaques, tripartite synapses and the neuronal network is outlined in Figure 5.

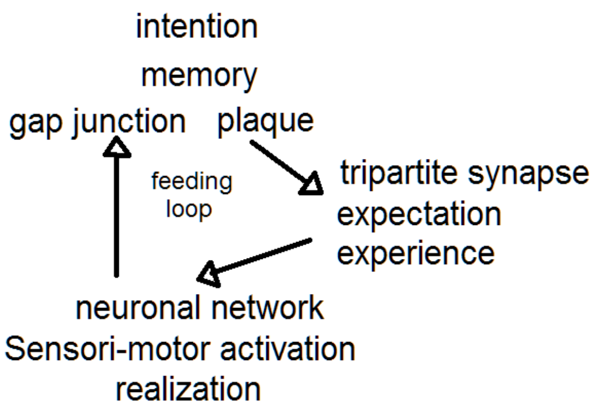

Fig. 5. Memory and realization of intention in glial-neuronal interactions

As proposed in my model of glial-neuronal interactions, the formation of gap junction plaques occurs in cycles composed in different time scales embodying memories that act as intentional phase programs in glial-neuronal interactions (Mitterauer, 2001). Most importantly, the memory architecture does not operate immediately on actual informations for neuronal activation, but it is generated by sequential phases of formation. According to the Event oriented World View (Baer, 2015) regarding memory we are not only talking about the conventional physical symbol in an objective worldview, but of the action in the entire refresh cycle.

Dependent on a given intentional phase program, a corresponding set of astrocytic receptors is expressed in the tripartite synapse ready for occupancy with cognate neurotransmitter substances. Thus, the expression of an astrocytic receptor pattern may determine which neurotransmitter substance must work on neurotransmission in the sense of a qualitative synaptic information processing (Mitterauer, 2012). This elementary mechanism in tripartite synapses is based on a glial expectation program experienced by neuronal information within the brain.

If the amount of neurotransmitters exactly corresponds to the amount of expressed astrocytic receptors, a balance between the glial and neuronal network is produced and gliotransmitters released occupy presynaptic receptors, which exert a feedback mechanism. The comparison between expected internal and measured external signals provides an update feedback to the glial network that modifies the information flow through the neuronal network. Extremely important, cognitive processes such as thinking and planning occur on a time scale of minutes, hours, days or longer, since they need a relatively long time span for generating feeding loops for the realization of intentions with appropriate information from the inner and outer environment (Mitterauer, 2012). In the sensory-motor network the phase program may also code the motor program that controls the effectors. Feedback loops to an associative memory can change the intended phase program according to a successful realization in an appropriate environment (Mitterauer, 2001).

3 - Basic loops in glial-neuronal interactions

The Event View of reality maps the cycling event architecture to cognitive systems by identifying interactions between the internal and external action flow as the present Now-experience. In the human brain a similar architecture may be implemented by identifying the glial network as the internal "I" process cycle that interacts with the external "You" process cycle implemented by the neuronal network. The specific interactions between the glial network and the neuronal network may take place in tripartite synapses (Baer, 2015). There is experimental evidence for feedforward and feedback loops acting in the glial network and in tripartite synapses (Kimelberg, 2012; Scemes and Giaume, 2006).

Figure 6 shows a diagram of basic glial-neuronal interaction loops. A sole neuronal loop is acting between the environment (env), the presynapse (pre) and the postsynapse (post) back to the environment (env) (green interconnecting lines). A loop between an astrocyte (Ac), gap junctions (g.j.) and gap junction plaque back to the astrocyte (Ac) acts between the main localizations of the glial network as a glial loop (blue interconnecting lines). The basic loop between the neuronal and glial network as a neuro-glial loop is acting between the presynapse (pre), the astroglial network (acN), the astrocyte (Ac) and back to the presynapse (pre).

The implementation of the action cycle theory must be based on the ontological architecture of our brain constituted of the realms of I-subjectivity and You-subjectivity, as mediated in specific localizations of interactions. Note that the diagram of basic loops in Figure 6 shows a feedforward loop mediating between the inner glial network and the outer neuronal network. Such a loop operates between subjective subjectivity and objective subjectivity and it may in accordance with our brain model embody the architecture of an action cycle of interactions in tripartite synapses.

Conclusion

The brain model proposed here represents a model of glial-neuronal interactions focusing on the role of tripartite synapses and the glial network. As already hypothesized, memory and intentional phase programs may be generated and embodied in the glial network. The present study elaborates on the dynamically in different time scales generated structure. Feedforward and feedback loops may constitute intentional phase programs expressed in the astroglial component of a tripartite synapse ready for the activation of occupancy by appropriate neurotransmitters released from the presynapse. This mechanism is able to balance synaptic information processing.

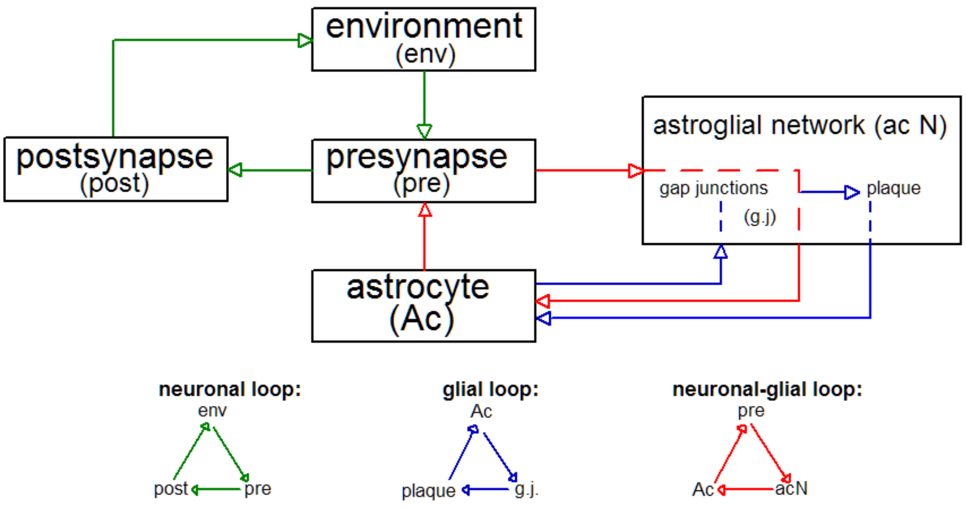

Fig. 6. Diagram of basic glial-neuronal interaction loops

Brain biological findings support this interpretation of glial-neuronal interactions: the interaction between the neuronal system that embodies objective subjectivity of the inner and outer environment, and the glial system embodying subjective information processing are generated by action loops. This structure could implement the cognitive action cycle architecture in the Event oriented World View (Baer, 2015).

Despite rapid improvements of techniques for brain biological experiments, testing methods of our brain model are faced with limitations with regard to the explanation how our brain operates as a self-conscious unit. Here, I see a real progress in the implementation of the cognitive action cycle theory in computer systems or robots "with a touch of subjectivity".

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References

Araque A, Parpura V, Sanzgiri RP, Haydon PG. (1999) *Tripartite synapses: glia, the unacknowledged partner.* Trends Neurosci; 22: 208-215.

Baer W. (2015) *Unity through an Event Oriented World View* (Special Issue of Quantum Biosystems).

Baer W. (2013) *A conceptual framework embedding conscious experience in physical processes.* In Pereira A Jr, Lehmann D (eds). The Unity of Mind, Brain and World, Cambridge: Cambridge University Press: 113-148.

Bargiello T, Brink P. (2009) *Voltage-gating mechanism of connexin channels.* In Harris LH, Locke D (eds). Connexins, New York: Human Press: 103-128.

Guenther G. (1962) *Cybernetic ontology and transjunctional operations.* In Yovits MC, Jacobi GT, Goldstein GD (eds). Selforganizing Systems, Washington DC: Spartan Books: 313-392.

Haydon PG, Carmignoto G. (2006) *Astrocyte control of synaptic transmission and neurovascular coupling.* Phys Rev; 86: 1009-1031.

Hirrlinger J, Hülsmann S, Kirchhoff F. (2004) *Astroglial processes show spontaneous motility of active synaptic terminals in situ.* Eur J Neurosci; 20: 2235-2239.

Kimelberg HK. (2012) *Mature protoplasmic mammalian astrocytes. Morphology, interrelationships and implications for function.* In Scemes E, Spray C (eds). Astrocytes wiring the brain, Boca Raton: CRC Press: 3-24.

Mitterauer BJ. (2015) *Model of the reticular formation of the brainstem based on glial-neuronal interactions*. Cogn Comput; 7: 64-73.

Mitterauer BJ. (2013) *The proemial synapse: consciousness-generating glial-neuronal units.* In Pereira A Jr and Lehmann D (eds). The Unity of Mind, Brain and World, Cambridge: Cambridge University Press: 233-246.

Mitterauer BJ. (2012) *Qualitative information processing in tripartite synapses: a hypothetical model.* Cogn Comput; 4: 181-194.

Mitterauer B. (2004) *Computer system, particularly for simulation of human perception via sense organs.* US-Patent: 6,697,789B2.

Mitterauer B. (2001) *Clocked perception system.* JIS; 4: 269-297.

Parri R, Crunelli V. (2007) *Astrocytes target presynaptic NMDA receptors to give synapses a boast.* Nat Neurosci; 10: 271-273.

Pereira A Jr. (2013) *Triple-aspect monism: a conceptual framework for the science of human consciousness.* In Pereira A Jr and Lehmann D (eds). The Unity of Mind, Brain and World, Cambridge: Cambridge University Press: 299-337.

Pereira A, Furlan FA. (2010) *Astrocytes and human cognition: modeling information integration and modulation of neuronal activity*. Progr Neurobiol; 92: 405-420.

Ransom BR, Giaume C. (2013) *Gap junctions and hemichannels.* In Kettenmann H, Ransom BR (eds). Neuroglia, Oxford: Oxford University Press: 292-305.

Robertson JM. (2013) *Astrocyte domains and the three-dimensional and seamless expression of consciousness and explicit memories.* MeHy; 81: 1017-1024.

Santello M, Bezzi P. Volterra A. (2011) *TNFα controls glutamatergic gliotransmission in the hippocampal dentate gyrus.* Neuron; 69: 988-1001.

Scemes E, Giaume C. (2006) *Astrocyte calcium waves: what they are and what they do.* Glia; 54: 716-725.

Sosinsky GE, Gaietta GM, Giepmans BNG. (2009) *Gap junction morphology and dynamics in situ.* In Harris LH, Locke D (eds). Connexins, New York: Human Press: 241-261.

Volterra A. (2013) *Astrocytes: modulation of synaptic function and network activity.* In Kettenmann H, Ransom BR (eds). Neuroglia, Oxford: Oxford University Press: 481-493.

Winkler U, Hirrlinger PG, Sestu M, Besser S et al. (2013) *Deletion of the cell adhesion adaptor protein vinculin disturbs the localization of GFAP in Bergmann glial cells.* Glia; 61: 1067-1083.

Winship IR, Plaa N, Murphy TH. (2007) *Rapid astrocyte calcium signals correlate with neuronal activity and onset of the hemodynamic response in vivo*. Neurosci; 27: 6268-72.