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Self-Structuring of Motile Astrocytic Processes within the Network of a Single Astrocyte

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Abstract

Dynamic structuring and functions of perisynaptic astrocytic processes and of the gap junction network within a single astrocyte are outlined. Motile perisynaptic astrocytic processes are generating microdomains. By contacting and retracting of their endfeet an appropriate receptor pattern is selected that modulates the astrocytic receptor sheath for its activation by neurotransmitter substances, ions, transporters, etc. This synaptic information processing occurs in three distinct time scales of milliseconds to seconds, seconds to minutes, hours or longer. Simultaneously, the interconnecting gap junctions are activated by building a network within the astrocyte. Frequently activated gap junction cycles become embodied in gap junction plaques. The gap junction network formation and gap junction plaques are governed and controlled in the same time scales as synaptic information processing. Biomimetic computer systems may represent an alternative to limitations of brainphysiological research. The model proposed allows the interpretation of affective psychoses and schizophrenia as time disorders basically determined by a shortened, prolonged or lacking time scale of synaptic information processing.

Keywords

Perisynaptic Astrocytic Processes, Glial Network, Self-Structuring, Time Scales, Autonomous Function

1. Introduction and Hypothesis

Glial-neuronal synaptic units are composed of the pre- and post-synapse as the neuronal components and the astrocyte as the glial component, termed tripartite synapse [1]. This concept is very fruitful in research on synaptic

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plasticity and it enables significant improvements in understanding how the brain basically works. Araque and coworkers [2] propose unifying hypotheses that may be essential for the interpretation of abundant experimental data and new experimental and theoretical approaches. There is broad agreement that the detailed cartography of astroglial synaptic profiles throughout the CNS is very much longed for [3].

The arrangement of astrocytic domains interacting via gap junctions with other astrocytic domains is in principle similar to that within a single astrocyte [4] [5]. The majority of synapses in the CNS are embraced with perisynaptic astrocytic sheaths that spread out from peripheral astrocytic processes [6]. The perisynaptic astroglial structures that cover synapses are exceedingly thin: the profiles are on average less than 200 nm in diameter [3] [6]. Big stem processes of the protoplasmic astrocyte ramify progressively, elaborating terminal processes that are in close contact with neuropil, synapses and other neuronal elements [7].

Perisynaptic astrocytic processes (PSAPs) not only have a complex morphological plasticity but may also exert a fundamental effect on synaptic information processing, since they are able to dynamically regulate the degree of synaptic coverage by contacting and retracting their membranes [8] [9]. Most importantly, gap junctions could operate between PSAPs originating from a single astrocyte [10] in the sense of reflexive gap junctions [11] constituting an autonomous network within a single astrocyte.

Searching for principles that may govern neuro-glial interactions in the tripartite synapse and its gap junction network and that enable the autonomous operation within a single astrocyte, my hypothesis is as follows: Motile perisynaptic astrocytic processes (PSAPs) are generating microdomains interconnected by gap junctions that embody an autonomous network. PSAPs contact and retract their processes dependent on synaptic activation in different time scales. Gap junctions interconnecting PSAPs are able to build cyclic pathways which, when frequently activated, become embodied in gap junction plaques. This feedback structure within a time period of synaptic activation feeds forward to the PSAP movement pattern that selects astrocytic receptors modifying the glia-neuronal interaction period based on the frequently working astrocytic receptor pattern.

The model outlined in the present paper is supported by pertinent experimental evidence. Finally, some implications for interdisciplinary research and neuropsychiatric diseases are suggested.

2. Dynamic Microdomain Generation by Perisynaptic Astrocytic Processes

Basically all mammal protoplasmic astrocytes are organized into spatially non-overlapping domains that encompass both neurons and vasculature. An astrocyte domain defines a contiguous cohort of synapses interacting exclusively with a single astrocyte. Synapses within a particular territory are thereby linked via a shared astrocyte partner, independent of neuronal networking [12]. Importantly, such an astrocytic domain organization consists of various separate anatomical domains.

Figure 1 gives an overview of my model [2]. The neuronal synapse activates the production of transmitter substances. Transmitter substances occupy the astrocytic receptor sheath which is dynamically contacted by motile perisynaptic astrocytic processes (PSAPs). This structure of a single astrocyte is interconnected by gap junctions constituting a gap junction network. Frequently activated pathways are selected composing a gap junction plaque feeding forward to PSAPs and modifying their movement pattern. PSAPs represent the final structures of a stem process emanating from the astrocytic body. PSAP movement patterns may be integrated within the astrocytic body that feeds back to PSAP in a pulsating manner (see Section 5).

Big stem processes of an astrocyte contact typical bundles of intermediate filaments 8 - 9 nm in diameter representing around 15% of the total volume of an astrocyte [13]. These processes ramify progressively to finally generate a dense matrix of thinly elaborated terminal processes which infiltrate brain tissue and closely associate with neuropil elements and particularly with synapses (reviewed by [14]).

Panatier and coworkers [15] showed that astrocytes detect synaptic activity induced by single-synaptic stimulation in functional compartments along their processes. Astrocytes exhibit intricate spongioform morphology with dense process ramification of irregular shape with frequent broadings. These enlargements measured along the main axis of the astrocytic process create astrocytic compartments, also termed microdomains. The regulation of basal synaptic transmission allows astrocytes to integrate and adapt synaptic strength according to the history of the synapse. Such structuring function suggests that astrocytes themselves undergo synaptic plasticity changes as was recently shown for perisynaptic glial cells [15] [16]. In addition, gap junctions and gap junction plaques are primarily located within perisynaptic domains that are activated as rapidly as postsynaptic domains

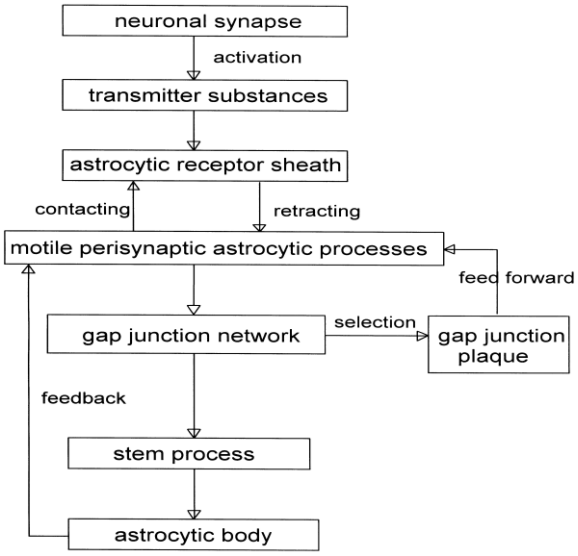

Figure 1. Block diagram of elementary components and relations of perisynaptic astrocytic processes (see text).

[15] [17]. Intraastrocytic gap junctions are currently somewhat neglected in research on synaptic plasticity, and the organization of glial-neuronal synaptic units or tripartite synapses is presently faced with technical limitations.

Figure 2 outlines the elementary structure of astrocytic processes focusing on the generation of microdomains by the endfeet of perisynaptic astrocytic processes (PSAPs) [18]. In addition, a perivascular astrocytic process [16] is shown. From the body of the astrocyte stem processes emanate (about 5 - 6). Endfeet of a PSAP are capable of generating dynamic microdomains. The interconnecting structure of gap junctions is also depicted. PSAPs demonstrate morphological plasticity, since by retracting and extending astroglial membranes the degree of synaptic coverage (**Figure 5**) can be dynamically regulated [9]. This structural function of PSAPs generates a micro-architecture of glial-neuronal interactions within a single astrocyte. According to Verkhratsky and Nedergaard [3], the PSAPs act as an astroglial cradle representing the fundamental mechanism contributing to synaptic connectivity, synaptic plasticity, and information processing in the nervous system. Since the structuring function of motile PSAPs within the network of a single astrocyte operates in different time scales, these mechanisms must be described more closely.

3. Time Scales of Neuronal Perisynaptic Astrocyte Interactions and the Gap Junction Network

Astrocytes act as time and space integrators, decoding neuronal information occuring in a larger array of neuronal activity. This time and space integration encompasses faster and more local changes based on the rapid activation of small compartments along the astrocyte process [15] [17] [19] [20] up to complex multi-astrocytic and neuronal interactions that are induced by sustained, intense, and extended activity resulting in long-term changes in the synaptic network properties [2]. An astrocyte responds to synaptic activity in time frames of seconds, minutes or longer. Basically, astrocytes possess Ca^{2+} excitability and display intracellular CA^{2+} elevations in response to synaptic activity from physiological sensory and motor stimuli [21] [22]. Astrocytes exhibit circadian rhythms in clock gene expression, are entrained by neurotransmission and are capable of calcium-dependent release of neurotransmitters. Most calcium signals in astrocytes are brief, lasting from milliseconds to minutes [23].

Most of our knowledge comes from monitoring CA^{2+} signals in astrocyte soma as an indicator of astrocytic responsiveness. These are slow Ca^{2+} events occuring at a slower time scale with respect to fast responsiveness at synaptic sites. Importantly, recent experiments detected that small, rapid and localized Ca^{2+} responses can be elicited in microdomains of astrocytic processes by minimal synaptic activity. These data suggest that astrocytes may integrate the activity of several individual synapses to generate larger Ca^{2+} responses observed upon sus-

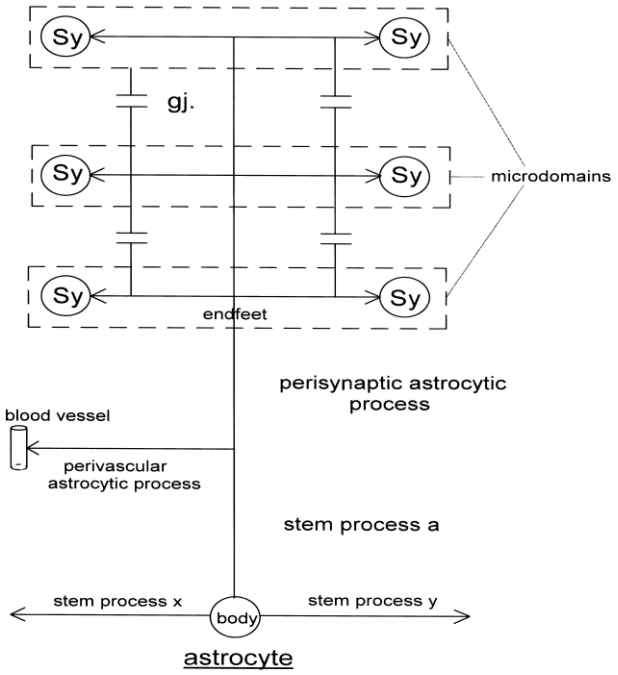

Figure 2. Schematic diagram of microdomain generation by the endfeet of a perisynaptic astrocytic process (PSAP).

tained and intense stimulation [2]. Stimulation-evoked Ca^{2+} signals in astrocytic processes differ from those in astrocyte somata and are modulated by glutamate and ATP as has been shown in CA3-CA1 synapses in the hippocampus of adult mice [24].

Figure 3 outlines interactions between neuronal-perisynaptic astrocytic processes and the gap junction network formation in 3 different time scales (modified after [25]). In the milliseconds to seconds time scale (t1) the neuronal synapse (NS) produces transmitter substances (neurotransmitters, ions, transporters etc.) activating (arrow) perisynaptic astrocytic processes (PSAP). An increase of Ca^{2+} ions activates the production of gliotransmitters (GT) that occupy (arrow) cognate receptors on the neuronal synapse (NS). In parallel, Ca^{2+} waves determine the activation of a gap junction pattern in the network (GN). In the seconds to minutes time scale (t2) bidirectional interactions (double headed arrow) between NS, PSAP, GT and NS occur repeatedly. The pattern of repetition may generate a cyclic pathway in the gap junction network (circles) [26]. During the time scale of hours to days (or longer) (t3), repeated interactions between PSAPs are stepwise forming (fat double headed arrow) a gap junction plaque (concentric circles).

However, the self-structuring function of this model must be further elaborated [25] [27].

4. Synaptic Modulation by Motile Perisynaptic Astrocytic Processes

Astrocytes can specifically decode the pattern of synaptic activity and, in turn, differentially modulate the output of synaptic transmission [2]. This is supported by experimental findings showing that specific patterns of Ca^{2+} activities induce distinct forms of synaptic plasticity at the neuromuscular junction [28]. Here I focus on the motility of perisynaptic astrocytic processes that are able to rapidly remodel synaptic coverage by extending and retracting from dendritic spines in a time scale of minutes or even seconds [9] [29] [30]-[32]. Moreover, the refinement of synaptic circuitry leads to a restriction in the expression of the receptors to perisynaptic processes where it is needed for tripartite synapse modulation [33].

In my model the contacting and retracting mechanism of PSAPs exerts a selection of an astrocytic receptor pattern that already had been working in a time scale according to its realization in the environmental state and repeatedly activated by PSAPs. This mechanism of selection enables the astrocyte to filter synaptic activity. During this structuring function the astrocyte selects information from the outside synaptic world in fine tuning with the synaptic circuitry according to the environmental state. Synaptic information selection may represent a

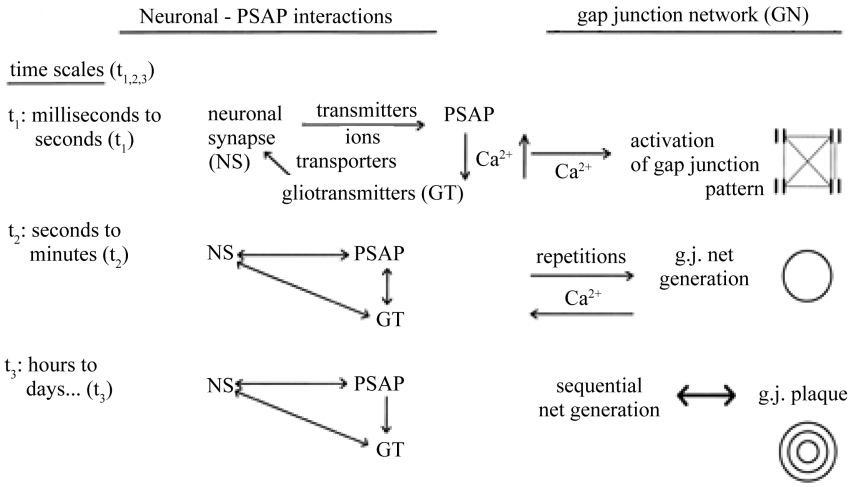

Figure 3. Neuronal - PSAP interactions in 3 different time scales ($t_{1.2.3}$). Gap junction network formation in these time scales.

basic function of self-structuring within a single astrocyte. Significantly, the large diversity of astrocytic receptors, their spatial location, and the spatiotemporal properties or qualities provide the necessary properties that allow a single astrocyte to detect, process, and decode the activity of a variety of synapses upon which it can provide distinct feedback and feedforward modulations [2]. PSAPs can exert qualitatively different effects dependent on the frequency of synaptic activity or time.

Figure 4 shows a schematic diagram of synaptic modulation by motile PSAPs [33]. A stem process of the astrocyte body arborizes in PSAPs. The endfeet contact and retract astrocytic receptors (1⋯6) on the synaptic sheath. As an example, endfeet interchange between contacting (direct arrows) and retracting (inverse arrows). The activation of the receptor pattern at a time scale in milliseconds to seconds (t_1) by contacting and retracting motility of PSAP selects a new action program at the time scale of seconds to minutes (t_2). This selecting operation exerts a feed forward function modifying the action program as receptor pattern 1, 3, 5 feeding back to the endfeet of PSAP generating a new astrocytic pattern.

It is likely that depending on the coincidence pattern and level of synaptic activity the local modulation may be extended to the whole astrocyte by the propagation of Ca^{2+} signals along astrocytic processes [15]. Since the astrocyte body is pulsating in a time period of about 6 - 7 minutes, it may be capable of integrating the activation pattern of PSAPs generated in shorter time scales by the stem processes of the astrocyte (t_3).

Together, astrocytes can provide a balanced and easily tunable feedback and feedforward response that regulates neuronal communication in a different time domain. Moreover, astrocytes are in contact with thousands of synaptic inputs targeting many dendrites of several neurons [2]. In my view, an information selecting function must be at work filtering the flood of synaptic information.

5. Outline of a Gap Junction Network and Plaque Formation within a Single Astrocyte

Gap junctions operate between processes originating from a single astrocyte, *i.e.* within its own domain. Such reflexive gap junctions have already been described at the ultrastructural level by Wolff and coworkers [10]. Reflexive gap junctions are elements that constitute subcellular interactions taking place in astroglial microdomains [17]. The arrangement of astrocytic domains interacting via gap junctions with other astrocytic domains is in principle similar to that within a single astrocyte [4] [5]. The distribution of reflexive gap junctions is compatible with the hypothesis that autocellular coupling serves the organization of cytoskeleton during formation of cell processes and branches [8]. If gap junctions are repeatedly coupled within time scales of seconds to hours, they form plaques [34].

Figure 5 outlines a gap junction network consisting of PSAPs (1⋯6) on synapses (Sy, only one is shown) [34]. PSAPs are completely interconnected via gap junctions (g.j.). Gap junctions between PSAP3, PSAP4, PSAP5, and PSAP3 are frequently activated (arrow in fat interconnecting lines). This closed structure is selected

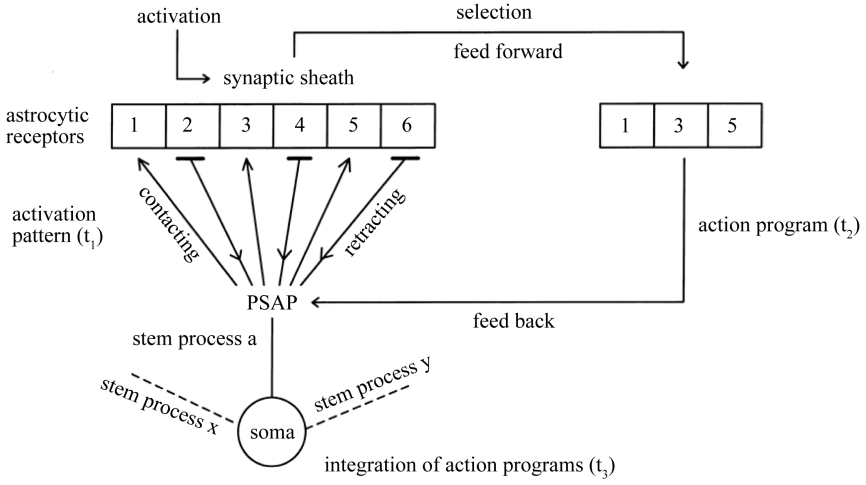

Figure 4. Synaptic receptor modulation by motile PSAPs.

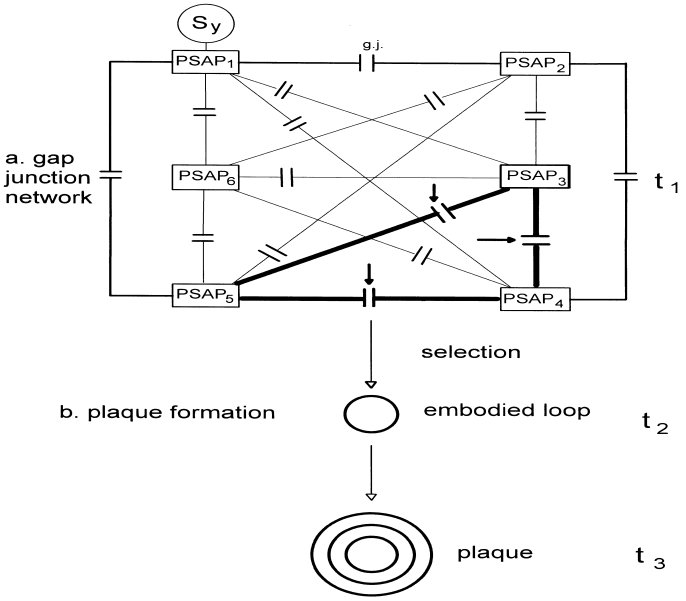

Figure 5. Outline of a gap junction network (a) and plaque formation (b) in a single astrocyte.

and embodies a loop (fat circle) contributing to plaque formation (concentric loop structure). The operations of the gap junction network (a) between PSAP and the synaptic sheath occur in the milliseconds to second range (t_1), the formation of a loop structure in seconds to minutes (t_2), and its incorporation in a plaque requires a time duration of minutes to hours (t_3). Such plaque formation may primarily be localized within synaptic microdomains of a single astrocyte [5] [15].

6. Composition and Decomposition of Plaque Formation by Adding and Removing of Gap Junction Loops

The brain connexin-based communication is subject to long- and short-term regulation [35]. This may be associated with changes in the number of junctions and plaques. Moreover, changes in the rate of gap junction internalization and connexin degradation may also occur [34]. Gap junction plaques are clusters of cell-cell channels which can be packed at densities of up to 10.000 nm^2. Note that astrocytes are not universally coupled hinting at the possibility that coupling operations are purposeful and not dictated solely by proximity [36] [37]. Basically,

plaque formation is a cooperative self-assembly process [38]. Experimental observations reveal that in connexin 43 gap junctions new channels have been added outside of the plaque, whereas older ones are found in the center of the plaque. Gap junctions represent dynamic structures with channels being continually added and removed at the plasma level. Whereas these structures are thought to possess great rigidity, large gap junctions can ebb and flow. It is supposed that individual hemichannels have great mobility in the plasma membrane, since they can move to plaque edges [39]. The transition from the fully open state to substates for junctional channels occurs on a faster time scale (milliseconds). This mechanism was termed fast-gating or substate-gating.

In addition, a slow-gating is reflecting the shorter time course (discussed above) of the set of transitions [40]. The mechanism of reflexive gap junctions contributes actively to structuring of functions within a single astrocyte representing a self-structuring autonomous network. **Figure 6** shows gap junction plaque formation by adding and removing of a gap junction loop structure [40]. A loop structure generated in the gap junction network is added to the gap junction plaque (outer fat loop) contributing to plaque composition (a). The mechanism of removing a loop structure from the gap junction plaque (dashed loop) exerts a decomposition of the plaque (b). Both mechanisms work basically on gap junction plaque formation.

7. Discussion and Prospects

Admittedly, the present paper deals with an investigation of synaptic glial-neuronal interaction that is still in its infancy. Moreover, experimental data and observations are contradicting such that the discussion especially on the role of perisynaptic astrocytic processes in information processing seems to be controversial. In addition, in outlining my model I did not elaborate on physiological details.

Currently, new concepts on synaptic glial-neuronal interaction are created that offer progress in our understanding of synaptic information processing. Generally, a tripartite synapse describes a glial-neuronal synaptic unit. In elaborating my brain model over the years the Astrocentric Hypothesis by Robertson [5] [41] has played a significant role. Focusing on the perisynaptic astrocytic processes Verkhratsky and Nedergaard [3] demonstrated that these processes acted as an astroglial cradle essential for synaptogenesis, maturation, isolation and maintenance of synapses, representing the fundamental mechanism contributing to synaptic connectivity, synaptic plasticity and information processing in the nervous system. Such a fundamental organization may ensure communication between neurons of the same circuit [26]. Very constructive for our conception of tripartite synapses is the synaptic modulation hypothesis by Kimelberg [18].

Based on the current knowledge Araque and coworkers not only established the early state of research but they also provided a conceptual framework for future studies. These authors propose unifying hypotheses for the research on principal mechanisms in balanced synaptic information processing and suggest that the understanding of glial regulation of neuronal function is both a conceptional and technical challenge [2].

My model proposed here is based on the hypothesis that motile perisynaptic astrocytic processes exert a self-structuring function within the network of a single astrocyte in different time scales. This means that the astro-

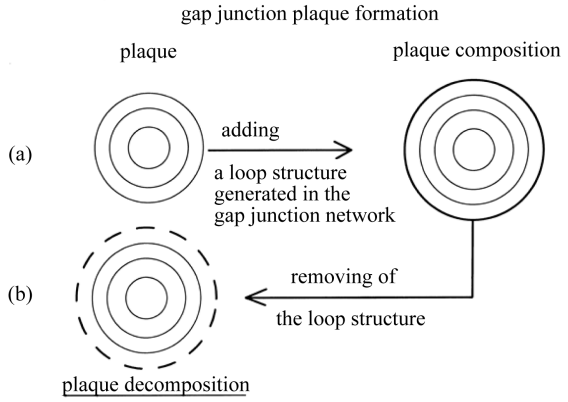

Figure 6. Gap junction plaque composition (a) and decomposition (b) by adding and removing of a gap junction loop structure.

cyte is capable of self-organizing glial-neuronal interactions, fundamentally guiding and controlling organization and reorganization of synaptic plasticity. Hence, this model may contribute towards a unifying hypothesis.

Despite rapid progress in experimental research on synaptic information proessing, we may be faced with limitations, especially what the explanation of intraastrocytic elements and their interactions concerns. Here, I see a real alternative in implementations of biomimetic models of glial-neuronal interactions in computer systems [42] [43]. With regard to consciousness research on the function of glial-neuronal interactions quantum mechanical approaches seem very promising [44] [45]. In the context of the present paper Pereira and coworkers have provided experimental evidence for the modulation of brain microstates by astroglial calcium waves in recurrent cycles during a time interval of 2 seconds [45]. This finding points to an interplay of brain microstates and quantum-like astroglial calcium waves.

My clinical experience and research on psychopathology focusing on glial-neuronal interactions is currently supported by significant pathophysiological findings and hypotheses [46]. If we suppose a fundamental operation principle of balancing information processing in the time scales of glial-neuronal interactions [47] [48], it follows that the etiopathophysiology of neuropsychiatric diseases may be caused by dysregulations of clocked time scales [49] [50]. For instance, patients with a major depressive disorder suffer from severe disturbances of diurnal biorhythms. This time disorder may be generated in glial-neuronal synaptic units of brain locations that cannot operate in short time scales but that are only capable of processing information in larger time periods.

Contrarily, in manic states rapid information processing dominates [48]. Most intriguingly, patients with schizophrenia may be unable to generate distinct time scales. I have characterized this subjective time experience as the “Eternal Now” [51] [52].

In conclusion, the brain model proposed could be of interest for interdisciplinary research. The dynamic microdomain organization within an astrocyte functions not only as a reflexive system in the brain, but may also embody a location of self-observation. Since technical testing devices are limited, the implementation in a robot brain capable of self-observing and structuring environmental information could provide a biomimetic machine that teaches us where we are right and wrong in brain research. The concept of biorhythms must be modified in order to improve the present understanding and treatment of neuropsychiatric disorders. Disturbances of time periods generated in glial-neuronal units and their networks outlined in the present paper may be responsible for the etiopathophysiology of neuropsychiatric disorders and enable a new understanding and treatment of these diseases.

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Abbreviations

ATP: adenosine triphosphate
Ca^{2+}: calcium ions
CA3-CA1: regions 3, 1 in the cornu ammonis (hippocampus)
CNS: central nervous system
g.j.: gap junction
GT: gliotransmitter
NS: neuronal synapse
PSAP: perisynaptic astrocytic process
Sy: synapse
$t_{1\cdots3}$: time scale