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Studying the Cognitive Involvement of Glia Using Stochastic Functional Microscopy

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

The latest brain researches are showing the relevance of glia in cognitive processes like learning and memory. One of the main problems related to this type of investigations is about complexity: there are between 10 and 40 times more glia than neurons in the central nervous system of mammalians; the other main problem is about synaptic communication: glia cells (like astrocytes and microglia) use basically a chemical information system, therefore electrophysiological tecniques are not very efficient. The recent development of PALM and STORM microscopy can be a very powerful solution to these two main problems. This strategy can be included in a broader, hypothetical discipline called cognitive gliascience.

Keywords: Glia; astroglia; microglia; glial chemical synapses; methods in cognitive gliascience; PALM; STORM; philosophy of mind; cognitive science.

1. INTRODUCTION

During the last years, new empirical results have arised involving electrically passive glia cells in processes like learning and memory [1], showing the dominant role of glia (in particular of astroglia and microglia) in human cognition. Nevertheless, this paradigm shift is far to be widely accepted,

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principally for the reason that the data on glial cells, that represent the majority of brain cells [2] are largely limited compared with the neural ones. Empirical proofs are starting to show that the synaptic information system of astroglia and microglia is active and it is connected to the neural structure, producing synaptic plasticity in the entire brain and deeply influencing cognitive abilities.

It is known that synaptic dynamic behaviour is considered to be the ground for learning and memory in the brain; glial chemical synapses have probably also a relevant role in influencing electrical neural synapses [3]. Notwithstanding, the molecular mechanisms of glia that produce cognitive phenomena are not totally clear. New empirical data in this way are only starting to arise. This technical report will examine the most recent researches focusing on microscopic level of glial structures, particularly in the proximity of chemical synapses. We will analyze some molecular signaling processes that could demonstrate that glial chemical synapses (in particular, astroglial and microglial ones) have a dominant role in the information processing system of the brain and that neural electrical synapses are deeply influenced by them. Finally, we will consider new technological tools like PALM and STORM imaging. These tools can analyze single molecules within the synaptic region: their functioning is grounded on the integration of a great number of particles positions data (via the use of points) into high resolution pictures (see [4,5]). These methodologies are compatible with the study of glial processes connected with cognitive abilities because their performance is particularly suitable for imaging finer or capilliform elements (like the molecules connected with the biochemical transmissions around the synaptic regions). Therefore, they can allow to go beyond standard techniques and analyze formerly inaccesible processes into the nanoscopic level of glial communication.

2. GLIAL CHEMICAL SYNAPSES AND COGNITIVE PROCESSES

Growing evidences are showing the relevant role of glia cells within the chemical synaptic system of the cerebrum; in particular astroglia and microglia could have a significant role in the cognitive processes (e.g. learning and memory) emerging from these synaptic mechanisms.

One of the early suggestions that the contiguity betwixt the dynamical functioning of astroglia and the synapse could have a central part in the activity of neural excitation has been demonstrated by the empirical analysis that this type of glia possesses receptors for neurotransmission. Because astroglial cells possess receptors for a the majority of neurotransmitters [6,7], that are connected to the Ca^{2+} discharge from stores within cells, the astroglial mechanism can recognize neurotransmitter discharged at the synaptic bouton, conducting to astroglial stimulation via the release of their internal Ca^{2+}.

When astroglial cells are operating, they are able to release a relevant number of molecules cabable to modulate neural synaptical activity like ATP, glutamate, and D-serine [8-10] and are able to guide neural synapse development [11]. This type of signaling between astroglia and neurons could be interpreted as new way of information processing within the brain where astroglia serve as a third dynamic part of the synapse together with the pre- and postsynaptic terminals [12].

Subsequently the findings that astroglial cells possess receptors for neurotransmission, it has been proved that astroglial glutamate has a central role in the modulation of actions on neural structures. In particular , glial glutamate has been proved to have a function on neural metabotropic glutamate receptors [13]. However, astroglia is largely implicated in glutamatergic processes because of their role in the glutamate production and for the glutamate-glutamine shuttle; these mechanisms have a causal role in the synaptic dynamics connected with learning and memory [14,15]. Glutamate delivery is carried via Na+-dependent specific transporters [16,17] and then glutamate is converted to glutamine via glutamine synthetase (GS) by astrocytes themselves [18]; after that, glutamine produced by astroglia is carried back to neurons and transformed again into glutamate [19]. Therefore, the glutamate-glutamine shuttle shows that astroglial processes have a central role in neurotransmission. Moreover, astroglia have a relevant role in determing the features of conductance modifications produced by GABA in neurons by the elimination of extracellular GABA around the synaptic field [20]. In conclusion, it seems clear that astroglia have high-affinity uptake sites for GABA [21,22].

Despite it is evident that astroglia are able to regulate synaptical activity, a comprehension of these mechanisms is still incomplete.

On the other hand, recent studies are demonstrating that also microglia are able to modulate the dynamical structure of synapses and respond to its changes. Moreover, they are revealing the central role of these glia cells in synaptic plasticity. For example, "synaptic pruning" (the selection and elimination of synapses) has been always considered as dependent only on neuronal activity [23], but in the last years, new findings are showing that microglia have a fundamental role for this mechanism; for example, in the cortex, the maximum amount of microglia corresponds with the top of synaptogenesis [24]. The activity of microglia is not limited to synaptic pruning but they have a dominant role for the adequate development of excitatory synaptic transmission. Constant transformation and adaptation of synaptic connections are considered to be one of the most important biological dynamics connected with cognitive abilities like learning and memory. Synaptic plasticity can be the result of either an increment or a reduction in synaptic activity,called respectively long-term potentiation (LTP) and long-term depression (LTD); interestingly, novel studies are showing that microglia have a central role as regulators of synaptic dynamics [25], learning [26] and memory [27,28].

3. STORM-PALM FOR COGNITIVE GLIASCIENCE

The great majority of contemporary studies on cognitive processes are still concentrated on electrical activity of neural synapses. As we have seen, the information system of glial synapses is mostly biochemical therefore current electrophysiological methodologies like EEG are not able to detect these fundamental phenomena.

The main problem connected with the investigation of these very fine processes is old: we need an adequate view of them. However, the recent development of a couple of super-resolution methodologies able to recognize single molecule such as photo-activated localization microscopy (PALM) and stochastic optical reconstruction microscopy (STORM) can be a novel and suitable solution for the study of glial biochemical synapses and the cognitive processes connected to them (see [29]). These types of microscopy need statistical excitation of a very tiny number of fluorescent molecules per imaging session; therefore, rerunning these sessions, it is possible to detect the dynamics of fluorescent molecules in the field of enquiry. Moreover, this methodology presents a very high spatial resolution that is grounded on the reproduction of the object, like a molecule, from its detected image. Emerging studies on the general structure of brain functions (there aren't, to my knowledge, specific studies on glial synapses and their cognitive correlates) are showing new phenomena connected to the dissemination of pre- and postsynaptic receptors (see [30]). Therefore, general researches on glia-neuron interactions using STORM demonstrated the validity of this methodology.

A stochastic functional microscopy methodology connected to PALM allows recording of single molecules in vivo [31]; in particular, this methodology enacts point-source fluorescence registration and therefore identification of particles within chemical synaptic field of glia. PALM analysis does not need powerful switching and it has been already used, in some studies, for the investigation of neural synapses [32]. In the next years, a new interest on these methodologies and their application to glial chemical synapses can improve our knowledge on basic mechanisms of them and their connections to cognitive processes like learning and memory. Nonetheless, use of these techniques to glia are very few and limitated to neural synapses or glia-neuron interactions. For example, PALM has been used to analyze the variety of proteins at the plasmalemma [33]. However, only new studies, specifically orientented to glial synapses and their cognitive correlates can allow a wider comprehension of the entire brain functioning.

4. EPISTEMOLOGICAL CONCLUSION

New data on glia cells (in particular astroglia and microglia) are spreading doubts on neuronal doctrine, which predominated the entire last century studies on the brain, and created the dogmatic belief that brain cognitive abilities are grounded, only, on neural electrical synapses; as we have seen, new studies on glial chemical synapses are showing that they may have a central role in learning and memory.

As I reported in a previous paper [34], I think that the concept of ''neuroscience'' negatively influenced researches on glial mechanisms and

precluded the possibility to consider these processes as the core of human cognition; for this reason, I think that the foundation of a new discipline called cognitive gliascience could be useful.

Otto Loewi [35] and Henry Dale [36], in their outstanding studies on neural chemical transmission, demonstrated that electrical activity of the brain is modulated by the neural chemical one but they didn't investigate glial synapses. In my opinion, the reason is that they were influenced by a ''neurocentric'' conception that it is still dominating.

This ''neurocentric'' conception is connected with an ''electrocentric'' conception where cognitive processes are mainly considered as the result of electrical spikes. However, if we consider that, in the human brain the number of glia cells are 10-40 times higher than neurons, that glial synapses have, de facto, a chemical nature, and that neural activity is not only electrical but also chemical, we could infer that cognitive processes in human brains are based on chemical (and not electrical) synapses.

However, the great majority of ''neuroscientific'' studies still deeply overlooks or, in a relevant number of cases, ignores the chemical nature of glial synapses and their fundamental role in human cognition.

In conclusion, could we hypothesize that (astro, micro-, etc.) glial *chemical* synapses, instead of neural electrical ones, dominate and determinate higher cognitive processes like learning, memory, and integration of information because of their prevailing number and complexity in the human brain?

In my opinion, investigations using new methodologies like PALM and STORM can help us for the resolution of this question and the definition, as Kuhn [37] would say, of a paradigm shift.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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