

## TOWARDS A COGNITIVE GLIASCIENCE: A BRIEF CONCEPTUAL FRAMEWORK

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**Abstract:** Recent brain studies show the emerging importance of glia functions in relation to our knowledge of the brain. A new, hypothetical area of research is described to enriching the poverty of cognitive studies on glia. The cognitive methodology has been used because of its interdisciplinarity, and in particular for a possible foundation of a computational glia-neuroscience

**Keywords:** Glia cells, Cognitive Gliascience, Philosophy of mind & Cognitive Science, Computational glia-neuroscience.

### Historical Introduction

It is said that the Pythagorean Alcmeon of Croton was one of the first philosophers that considered the brain as the seat of mind and was, probably, the founder of experimental psychology (McCulloch, 1955); this idea was then considered true by Galen, during the Roman Empire, Mondino de Liuzzi, during the Middle Age, and Andreas Vesalius and Leonardo da Vinci in the Modern era. Moreover, Golgi, in the 19<sup>th</sup> century, discovered a method of staining nervous tissue and, more recently, has been discovered a new method for glia: the modified Golgi-Cox one (Ranjan & Mallick,2012). The concept of glia, that represents the majority of brain cells, as an interstitial substance which supplies a structural ground of the cerebrum and spinal cord and ties neurons together was, ab initio, created by Rudolf Virchow (1858), that, in effect, never regarded the cellular being of this substance; in Virchow opinion, neuroglia was not more than a type of extracellular linking structure, and he usually called it the "cement of neurons". Very soon, nevertheless, the cellular pattern of glial cells was detected and many kinds of glial cells were discovered (Golgi,1871; Cajal Ramon,1913), at a time that still came before the formulation of the neuronal doctrine, introduced by Ramon y Cajal. The stream turned in the 2000s and lately the relevance of glia in formation of central nervous system circuits get more precise. The current brief review will consider the actual opinion on central nervous system organization grounded on dynamic neuronal-glial networks, developing some seminal ideas contained in a previous paper (Spadaro,2013:4) for a foundation of a new, interdisciplinary area of research.

### Neuronal and glial signaling

Functioning of excitability and signal propagation of neurons and glial cells are essentially diverse. Basically, neuronal excitability is a type of electrical excitability and is due to a characteristic complement of voltage-gated ion channels (Na<sup>+</sup> channels, K<sup>+</sup> channels, and, to a lower degree, Ca<sup>2+</sup> channels) in the plasmalemma.

Depolarization of the neuronal plasma membrane to a determined sill primes these channels and produces an action potential that propagates primarily along the axon. Glia is electrically unexcitable and incapable to produce plasmalemmal action potentials. Nevertheless, many kinds of glial cells hold several kinds of voltage-gated channels, including Na<sup>+</sup> and Ca<sup>2+</sup> channels (Nedergaard et al., 2010), but the density of these channels is quite lower, and therefore the currents produced upon their activation are incapable to depolarize glial membrane (Seifert et al.,2006). Thus, the glial cells are excitable: they can respond to information from their surrounding, and one of the most important mechanisms used is Ca<sup>2+</sup> signaling.

Often, the initial Ca<sup>2+</sup> release occurs in distant glial processes, for example in the neuronal-glial contacts, and after this release, Ca<sup>2+</sup> propagates into the soma (Ralevic & Burnstock,19). In adjunct to the evoked Ca<sup>2+</sup> signals and intracellular waves, astroglial cells are able of producing spontaneous Ca<sup>2+</sup> oscillations, which

were identified in astroglial cells both in culture and in situ, in hippocampus, cerebellum and neocortex (Parri & Crunelli,2003).

### **The active role of astrocytes in neurotransmission**

Another relevant expansion of the complexity of signal transduction in the cerebrum comes from the ability of glia to start the release of neurotransmitters. The capacity to secrete neurotransmitters in an adjusted fashion was for so many years the unique prerogative of neurons; but latter studies are modifying this dogma. As a matter of fact, some early reports demonstrating that astroglia are able to release neuroactive substances, comprehending neurotransmitters such as glutamate, appeared in early 1990s (Martin,1992); more recent researches prove even clearer this mechanism and unveil that astrocytes can regulate exocytotic secretion of various mediators. Exocytotic release needs both the presence of the secretory vesicles, holding the neurotransmitter, and of peculiar exocytotic proteins. Cytoplasmic vesicles, holding glutamate, were lately discovered in mature hippocampal astrocytes (Marmiroli & Cavaletti,2012). The astroglial vesicles have vesicle glutamate transporters, and therefore can accumulate glutamate (Haydon & Carmignoto,2006). Most significantly the  $[Ca^{2+}]$ -induced exocytosis of astroglial vesicles and successive release of glutamate were immediately visualized by total internal reflection fluorescence imaging (Marmiroli & Cavaletti,2012), and exocytosis fusion succeeding  $Ca^{2+}$  signals was also gauged by membrane capacitance recordings (Montana et al.,2006).

The vesicular glutamate issue from astrocytes is substantially diverse from the neuronal one in respect to the origin of  $Ca^{2+}$  prime: in astrocytes  $Ca^{2+}$  accrues almost only from the intracellular stores, while neuronal exocytosis is ruled mostly by  $Ca^{2+}$  entry via plasmalemmal channels (Hamilton et al., 2008); for the astroglial exocytosis see also a very interesting and wide review by Volterra and Meldolesi (2005).

The gamma of biologically active substances that can be issued by the glia is expanding, creating a new library of glia transmitters (Volterra & Meldolesi, 2005; Kettenmann & Steinhauser,2005). The majority of these substances are released, as argued above, through a functioning of  $Ca^{2+}$ -dependent exocytosis. New researches published in the last years open a totally new area of transmitter release, which is, at least until now, limited to glia. Astroglial cells showed to release transmitters by other ways that imply the opening of plasmalemmal channels permeable for relatively large molecules.

Especially, glutamate and other substances can be issued via hemichannels or via volume-sensitive channels (Jaiswal et a., 2007). This device of transmitters release (via plasmalemmal channels) is not due to  $Ca^{2+}$ .Significantly, glutamate, released from a single astrocyte can work on several close neurons, creating synchronous excitation of the latter (Wang et al.,2006). Astrocytes are capable to release not only glutamate but also ATP (Davalos et al.,2005), which both can work as neurotransmitters or a neuromodulators. When issued by astroglia, these transmitters may affect electrical activity of neurons and/or synaptic transmission (Hanani,2005). In hippocampal and cortical slices, unaffected astrocytes'  $Ca^{2+}$  oscillations were discovered to guide neuronal  $Ca^{2+}$  signals (Rizzuto & Pozzan,2006).

### **Cognitive methods for glia studies**

A cognitive approach, due to its broad and interdisciplinary nature, will be fruitful for the comprehension of glia cells. David Marr considered vision system as an information structure, I think that glial networks and, in particular astrocytes are information structures that could be described with the so-called "Three Level Hypothesis": the computational level that describes what the structure does; this level can be explored designing artificial models able to reproduce some functions of the structure itself; the algorithmic one that describes how the structure makes its processes, using in particular glia-specific markers for brain imaging; and the physical one: it describes the material structure and the physiology of a determined element (Marr,1982; for a revised version of this hypothesis see Pylyshyn, 1984).In my opinion, these levels of analysis can be studied using functional approaches combining patch-clamp electrophysiology and brain

imaging; the most important techniques are functional magnetic resonance imaging (fMRI), positron emission tomography (PET), tractography and two-photon microscopy, used in acute brain slices and in vivo, as well as morphological imaging at the optical and electron microscopic grade, without ignoring the relation between psychobiology and genetics via glial-neural structures working (for a pioneering multi-level study see Oliverio et al.,1983).

PET is probably one of the most powerful techniques for the “algorithmic level” analysis of glia cells and the investigation for the most advantageous glia tracer, usable in brain imaging researches in humans, has been a long time target of a lot of research teams in the field. A very effective glia PET tracer could be useful as a diagnostic marker in a lot of central nervous system disorders matched with regional or global glia accumulation in the brain but also as a tool for the study of cognitive abilities as learning and memory.

The peripheral benzodiazepine binding site (PBBS) is considered one of those binding sites of glia that could be of use as a favored target site of PET radioligands. In these years a certain number of PET ligands with compatibility to the PBBS have been synthesized and tested: these include PK11195 and DAA1106 (Venneti et al.,2007). These glia tracer are usually used during tests of spatial and visual recognition memory, and visual discrimination and reversal learning from the Cambridge Neuropsychological Test Automated Battery (Cagnin et al.,2001); the information of these tests are then analyzed with statistical methods as standard deviations.

Experimental data from brain science suggest that a relevant amount of information is stored in the brain in the form of Bayesian (or statistical) distributions over network states and their connections (Clark, 2013; Tenenbaum et al., 2011).The intrinsic stochastic dynamics of common cortical microcircuits allows them to rapidly create approximate solutions to complex constraint satisfaction problems, where stored information and present inputs mutually bind possible solutions. This provides an effective new computing approach for networks of glia cells, that also throws new light on how networks of neurons and glia (in particular, astroglia) in the brain may carry out difficult cognitive tasks such as memory recall and problem solving.

A common application of the methodology to these structures is in the utilization of Bayesian networks (related to graph theory) to define the statistical features of the structure’s connectivity, which can supply relevant insights into underlying organizational processes. The graphical features of structures can be straight associated to properties of the structure’s function and to outer constraints that could have modelled the system’s development and functioning. As we have seen glia represents the majority of brain cells and, due of their number, a Bayesian (or statistical) approach will be also useful for the interpretation of glia data derived from brain imaging, in particular using the “General Linear Model”: it is an equation that describes an examined response Y as a linear combine of explanatory variables X:

$$Y = X \beta + e,$$

Y stands for a T x 1 vector including outputs at determined T time points, X is a T x K design matrix,  $\beta$  stands for a vector of regression coefficient, and e is a T x 1 error vector.

This model, as suggested by its theorists, could be applied to different methodologies as fMRI and PET (using, in particular, glia tracers) and the obtained data can be combined in a multimodal integration to find out the areas where glial activations occur in connection to metabolic activities (for a deeper analysis of this methodology see Penny & Friston,2006).

### **Computational models of glia functioning**

This cognitive approach will consider also the *multiple realizability* (for a clear description of this concept see Putnam,1988) of the glial structures; therefore these new discoveries on glial physiology will be important for Artificial Intelligence and, in particular, for the connectionist approach (Rumelhart &

McClelland,1986). This perspective has a quite long tradition (for an historical introduction to AI methodologies see Cordeschi,2002) and its goal is to achieve good performance via thick interconnection of mere computational components. One of the most used Artificial Neural Network (ANN) algorithm is Back-propagation. The back propagation methodology of Rumelhart et al. (1986) is a gradient descent approach that will assign the weights in a multi-layer, feed-forward adaptive "neural" network. Small arbitrary weights are selected to initialize the network; learning is obtained by subsequently regulating the weights based on a group of input patterns and the corresponding group of wished output patterns, unfortunately this algorithm often falls into local minima; recently, has been developed a method, inspired by glial physiology and in particular astrocytes, to avoiding this problem. Ikuta, Uwate and Nishio (2010) designed a Chaos Glial Network, connected to a Multi-Layer Perceptron (MLP); this network gave chaotic oscillations to the second hidden layer's neuron and this chaotic oscillation propagates to other neurons, increasing the performance than the conventional MLP. Moreover, Chaotic oscillations in Glial Network are distance-dependent; for instance, when the glial cell is positioned two units far from a determined neuron, reaction of chaotic oscillation reaches the neuron after two learning steps. And chaotic oscillation decreases while chaos is propagating in the network.

Another computational model (unfortunately, they are actually very few), developed by Pereira (2012), could be useful, in my opinion, to solve the question of polarized astrocytes in the brain (Oberheim et al.,2006). This model seems to agree with the conjecture (Oberheim et al.,2006:551) that the polarization of this type of glia cells allows faster communications than non-polarized cells.

This artificial astrocyte is influenced by ion-trap computing and quantum information theory (Wineland et al.,2003); it uses piezoelectric transducers to control the ions in the system. The structure is made of a star-shaped box with walls of metal, encasing one cubic centimeter of free space. The structure also has a gate, by way of which a calcium solution is injected. The case is replenished with the solution in a certain concentration (not stated). The six branches of the main space, three at each of two fronting parts, are utilized as inputs and outputs. The remaining four parts are positively magnetized, constraining the ions to interact faster and to reach the input and output parts speedy.

At the micro level, the intercommunications generate correspondences of electronic states of the ions. Spatial and temporal changes of kinetic energy modify their vibrational states, briefly changing the electronic distribution to higher or lower configurations of energy. This hypothetical and theoretical model could be integrate, in my opinion, with the previous model by Ikuta et al., trying to implement chaotic oscillations also in a material structure.

### **Astroglia: boosting learning**

In the past few years, astroglia has been shown to be crucial for neuronal proliferation and synapse development. Now, in a fundamental research from Goldman and Nedergaard's teams (Han et al., 2013), human glia progenitor cells have been transplanted into mouse forebrains. These cells survived, migrated largely, and gave rise to astroglia that showed the features of this human cells in the mouse host brains. Exceptionally, the mouse with transplanted human cells showed boosted long term potentiation (LTP) and learning, indicating the potential relevance of human astroglia in some peculiar cognitive skills of human brains. This foundational article is a significant first step towards deeper analyses of how human astroglia has a role in distinguishing the cognitive features of mankind from those of different animals. Han et al. achieved human glial progenitor cells from human fetal brains and transplanted them into the murine brain, where they gave rise to astroglia with features of humane astroglia. To evaluate the selective working of human astroglia on neural transmission within the mouse's neural networks, they correlated the synaptic activations in hippocampal slices assembled from humane glial chimeric mouse to that of both their non-engrafted and allografted littermate controls. They focused their analyses on the hippocampal dentate granule layer because of the many cognitive and behavioral tests by which hippocampal function,

learning, and LTP may be determined (Morgado-Bernal, 2011). Therefore, slices with human glia showed a relevant improvement of their basal level of excitatory synaptic transmission over an extensive field of intensities of stimulation. Thus, mice with human astroglia performed better in learning but also memory exercises, raising the eventuality that human astroglia allow to make us more intelligent.

### **The necessary function of glia in memory**

There is an emerging interest on potential support of astroglia to memory formation and consolidation. Its participation in memory forming is grounded by a relevant number of studies. As an operative partner in the synaptic communication, astroglia regulates excitatory and inhibitory transmission between neurons (Bolton & Eroglu, 2009); moreover, glia cells release glutamate (Angulo et al., 2004) when conjoined to post-synaptic depolarization. Panatier et al. (2006) proposed, using different experimental approaches, that memory formation could be based on the astroglial release of d-serine. They have demonstrated that there are high levels of d-serine in the rat hypothalamic supraoptic nucleus and that it is the only endogenous ligand of NMDARs in this area of the hypothalamus. Therefore, their discoveries are a good example of synaptic plasticity managed by astroglia via d-serine release. Another secondary function of astroglia could be sustaining memory consolidation, as demonstrated by Ben Menachem-Zidon et al. (2011).

The study of memory capabilities of astroglia should be considered, in my opinion, as a relevant research field, since there are, as we saw, good evidences that glia cells participate to mnemonic processes. Moreover, astroglia probably sustains conscious actions: it should be relevant for working memory, formation of declarative (for example semantic) memories, and for some types of associative memory; when some semantic inputs have been consolidated by neurons, astroglia could stimulate their recovery if these is some conscious stimulus.

### **Philosophical conclusion**

These years have been crucial for glia studies, because of a wider amount of information on the glial nature and functions (despite, there is only one or two journals devoted *specifically* to glia). These studies on glia don't seem always agree with neuronal doctrine, which predominated Psychobiology since the first years of the 20<sup>th</sup> century, and produced the dogma that the cognitive abilities of the cerebrum are grounded, only, on neurons; researches on glia rapidly are modifying their status from a simple assistant of neurons to a core role: their number is very high in cerebral areas dedicated to cognitive processes (e.g. language) as the frontal cortex (Sherwood et al., 2006), finally, as showed above, a new brain study shows that human glia allows both activity-dependent plasticity and acquiring information in mice (Han et al., 2013). The new information about the functional organization of the brain obliges us to rethink the dogma of neuronal doctrine that the substratum for the integration of information (binding problem) in the central nervous system is obtained by the neurons and their synapses. Our current knowledge show that it is the astroglia are capable to bind neurons and synapses into single and separate elements. Moreover, the astroglial network allows a complex intercellular communication pathways, which allows direct transfer of ions and metabolic factors. The arising potential for parallel processing and integration is important and could be wider (for this reason, statistical analyses will have an important role) than the binary coded electrical information of neurons. Synthesizing, astroglia could have a relevant role in information processing, integration and retention.

Salvatore Luria, Stephen J. Gould and Sam Singer described the brain as "the most complex organ known" (Luria et al., 1981:506) and glia cells play a significant role in this complexity. I think that the concept of "neuroscience" negatively influenced glia research (in particular, cognitive approaches) and as a consequence: "current knowledge about astrocytes, oligodendrocytes, and microglia and their dynamic changes is rudimentary in comparison to neurons, and little effort has been made to include glia into realistic computational modeling" (Fields et al., 2013:5). Moreover, following David Hull's theory on the conceptual evolution in science (Hull, 2010), I think that the introduction of the concept of "cognitive

glioscience" (that is the main goal of this short review) could be useful for the expansion of our knowledge on this peculiar type of cells of our brains.

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