*Journal of Scientific Research & Reports*
*8(6): 1-11, 2015; Article no.JSRR.20247*
*ISSN: 2320-0227*

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# Towards a Cognitive Gliascience: A Brief Conceptual Framework

**Salvatore Spadaro[1*]**

*[1]Department of Philosophy, Sapienza University of Rome, via Carlo Fea n.2, 00161, Rome, Italy.*

***Author's contribution***

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

***Article Information***

DOI: 10.9734/JSRR/2015/20247
Editor(s):
(1) Leszek Labedzki, Institute of Technology and Life Sciences, Kujawsko-Pomorski Research Centre, Poland.
Reviewers:
(1) Arturo Solís Herrera, Human Photosynthesis Study Center, Mexico.
(2) Pietro Scicchitano, Bari University, Bari, Italy.
Complete Peer review History: http://sciencedomain.org/review-history/11213

***Review Article***

***Received 18th July 2015***
***Accepted 18th August 2015***
***Published 1st September 2015***

## ABSTRACT

Recent brain studies show the emerging importance of glia (and, in particular, of astroglia) in cognitive abilities like learning and memory. A new, hypothetical area of research is described to enriching the poverty of cognitive studies on glia. This methodology has been used because of its intedisciplinarity, and in particular for a possible foundation of a computational glia-neuroscience. The point of the paper is to raise awareness about a new perspective on these brain cells.

*Keywords: Glia cells; astroglia; cognitive gliascience; philosophy of mind & cognitive science; computational glia-neuroscience.*

## 1. 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 [1]; 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 19th century, discovered a method of staining nervous tissue and, more recently, has been discovered a new method for glia: The modified Golgi-Cox one [2]. The concept of glia, that represents the majority of brain cells, as an interstitial substance which supplies a structural

**Corresponding author: Email: spadaro.1308624@studenti.uniroma1.it, savvo90@live.it;*

ground of the cerebrum and spinal cord and ties neurons together was, ab initio, created by Rudolf Virchow [3], that, in effect, never regarded the cellular being of this substance; in Virchow's 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 [4,5], 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 has become more precise. The current brief review will consider the actual opinion on central nervous system organization grounded on dynamic neuronal-glial networks for a foundation of a new, interdisciplinary area of research.

## 2. NEURONAL AND GLIAL SIGNALING

Excitability and signal propagation in neurons and glial cells are very different. Basically, neuronal excitability is a type of electrical excitability and is due to a characteristic complement of voltage-gated ion channels ($Na^+$ channels, $K^+$ channels, and, to a lower degree, $Ca^{2+}$ channels) in the plasmalemma. Depolarization of the neuronal plasma membrane to a determined level primes these channels and produces an action potential that propagates primarily along the axon. On the other hand, glia is electrically unexcitable and incapable of producing plasmalemmal action potentials. Nevertheless, many kinds of glial cells hold several kinds of voltage-gated channels, including $Na^+$ and $Ca^{2+}$ channels [6], but the density of these channels is much lower, and therefore the currents produced upon their activation are incapable of depolarizing glial membrane [7]. However, the glial cells are nevertheless excitable: They can respond to information from their surrounding, and one of the most important mechanisms used is $Ca^{2+}$ signaling.

Often, the initial $Ca^{2+}$ release occurs in distant glial processes, for example in the neuronal-glial contacts, and after this release, $Ca^{2+}$ propagates into the soma [8]. In adjunct to the evoked $Ca^{2+}$ signals and intracellular waves, astroglial cells are able of producing spontaneous $Ca^{2+}$ oscillations, which were identified in astroglial cells both in culture and in situ, in hippocampus, cerebellum and neocortex [9].

## 3. MORPHOGENESIS AND COMPARED DEVELOPMENT OF GLIA

Current researches [10-12] on evolution and morphogenetic development of a specific type of glia cells: The radial ones, in the murine and human brain, shows both analogies and, at the same time, peculiar characteristics in the order of development and biochemical structure that clarify the morphogenesis and evolution of our brain; these mechanisms are also inportant in the study pathogenetic conditions of cortical structures.

In the majority of mammalians radial glia is morphogenetically comparable, but there are also some species-specific relevant changes. Considering, in particolar, the volume of migratory neurons (that we could consider as morphogenetic products of radial glia) in the murine and human fetus is more or less similar, the mediation of the labyrinthine, microscopic passage in the complex human brain causes a significant guiding question for developing cells [13]. As a matter of fact, the majority of human neurons develops during the third, fourth month of gravidity, contemporary with the fast growth in the diameter of the brain structure and rise of its convolutions [14]. Dissimilarly to the right and brief development in mice, in the complex human brain, this process of growth evolved into a more extended and progressively circumvoluted way.

We should suppose that this morphogenetic process about radial glia cells, able to create a population of cells that continue to generate neurons in the adult human brain, is the consequence of evolutive mechanisms concerning the structure of the brain neocortex; it develops more in amplitude than in depth and, therefore, human brain structures become increasingly more convoluted than in other species; this process, where radial glia have a central role, is dramatically important for the development of cognitive abililities like learning, memory, goal- oriented behaviour.

On the other hand, another kind of human glia: astrocytes have evolved. They are bigger and more complex than the murine ones; these cells can have different shapes and can be polarized.

Considering the development in volume of astroglia that is connected to the development of the number of synepses, it has been calculated [15] that each astroglial cell sustains and regulates the behaviour of two million synapses.

Despite their importance in coordinating processes between these synapses, their complete functioning remains unclear.

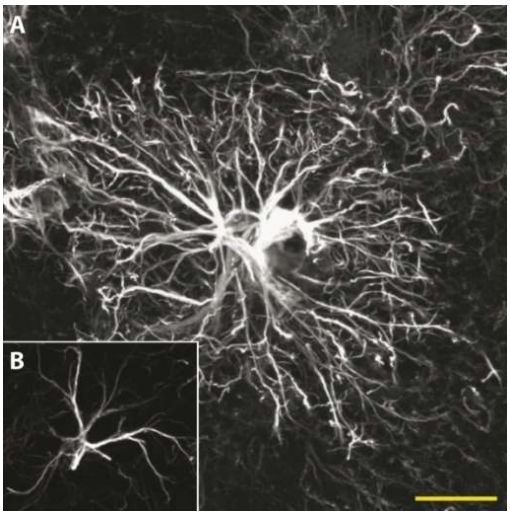


**Fig. 1. A comparison between a human astroglial cell (A) and a murine one. The human one is not only bigger but also more complex [16]. Open Access Licence.**

Murine astroglia are arrangeded into a specific way [17] where every astroglial cell maintains tiny overlap among contiguous elements. Therefore, every neuron within an astroglial area of influence will be connected with functional mechanisms from only one astroglial cell; while it has been proved [18] that in contrast with mice, human astroglia from neocortex shows ten times more functional mechanisms. It has been hypothesized that astroglia is an hub for information analysis and binding of brain functioning that is autonomous from neural mechanisms.

From an othodox viewpoint, differences in cognitive abilities between species have been correlated to neurons; notwithstanding, compared analyses betwixt the cerebral structures of various kinds of animals show that the increasing number and complexity of glia rises cognitive skills. Also for this reason, I think that a cognitive approach can be useful for a clearer comprehension of glial structure and functioning.

## 4. 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, such as glutamate, appeared in early 1990s [19]; 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 [20]. The astroglial vesicles have vesicle glutamate transporters, and therefore can accumulate glutamate [21]. Most significantly the $[Ca^{2+}]$-induced exocytosis of astroglial vesicles and successive release of glutamate were immediately visualized by total internal reflection fluorescence imaging [20], and exocytosis fusion succeeding $Ca^{2+}$ signals was also gauged by membrane capacitance recordings [22].

The vesicular glutamate issue from astrocytes is substantially more 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 [23]; for the astroglial exocytosis see also a very interesting and wide review by Volterra and Meldolesi [24].

The gamma of biologically active substances that can be issued by the glia is expanding, creating a new library of glia transmitters [24,25]. 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 have been shown to release transmitters by other ways that imply the opening of plasmalemmal channels permeable for relatively large molecules.

In particular, glutamate and other substances can be issued via hemichannels or via volume-sensitive channels [26]. 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 [27]. Astrocytes are capable to release not only glutamate but also ATP [28], 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 [29]. In hippocampal and cortical slices, unaffected astrocytes' $Ca^{2+}$ oscillations were discovered to guide neuronal $Ca^{2+}$ signals [30]. Moreover, astroglia create a material connection with cerebral arterioles, because increasing quantities of intracellular $Ca^{2+}$ in astroglia endfeet is capable to cause very quick modifications in vascular tone. Therefore, it has been speculated that neuron-astroglia mechanisms can have a relevant role in this hyperemia [31], and glutamate flux on astroglial cells has been correlated in the hemodynamic reaction to neuronal functions. Furthermore, some brain analyses [32] demonstrated that stimulation of cortical astroglia causes a calcium surge in these astroglial cells and a following expansion or contraction of adjacent arterioles. However, vasodilation is caused by activation by the glutamate receptors of astroglia. As a mediator between neurons and blood vessels, astroglia could have also a relevant role in brain diseases like in multiple scerosis [33,34] because infiammation can happen as a circumscribed mechanism that can be caused by activated glial cells (like astrocytes), without the response of immune cells recalled from the outer edge.

## 5. 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 also glial networks and, in particular astrocytes are information structures[1] 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 [37]; (for a revised version of this hypothesis see [38]). 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 (as an example of multi-level study see [39]).

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 the target for a long time 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 [40](Venneti et al.,2007). These glia tracers are usually used during tests of spatial and visual recognition memory, and visual discrimination and reversal learning from the Cambridge Neuropsychological Test Automated Battery [41]; 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 distributions over network states and their connections: we can observe that the brain works with a certain level of unpredictability connected to the stochastic oscillations created by the undeterministic spiking periods of neurons and glia cells [42,43]. The intrinsic stochastic dynamics of common cortical microcircuits allows them to rapidly create approximate solutions to

[1] *I used the concept of information also in connection to the definition given by Tononi: ''a difference that makes a difference from the intrinsic perspective of a system'' [35]; in my opinion, these informational processes are active in particolar in glutamatergic synapses that are usually made of two neurons and an astroglial cell; the glial cells being part of the synapse share information with the presynaptic neuron, creating an informational loop [36].*

complex problems, where stored information and present inputs mutually bind possible solutions. Moreover, these cerebral networks show that the spiking periods of each brain cell can be interpreted with Poisson statistics, in other words, noise in the brain seems an intrinsic feature [44,45]. The stochastic firing times of neurons introduces noise into neuronal-glial networks, and it significantly increases the complexity of brain processes. This phenomenon shows that the noise not only allows the comprehension of some relevant features of decision making mechanisms in the cerebrum, but it is also useful to understand decision-making optimizations more in general (see [46]). This provides an effective new computing approach for networks of glia cells that also contribute to clarify 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. This randomness in the brain produced by the complex interactions between neurons and glia is relevant , because it allows the system of connections to pass from a fixed level of firing to a more dynamic and rapid firing level and, as showed by computational models (see the next section for a explanation and implementation of this mechanism), there are more stochastic communications betwixt neurons and glia of one attractor than another one. The requisite for a stochastic oscillation to cause a dynamic output derives in broad trial-and-error mechanisms, with a certain period of constant behavior in an attractor state.

A common application of this cognitive and statistical methodology to these structures is in the utilization of Bayesian networks (related to Markov chains) 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 easily 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 nanoscale brain imaging (see [47]). These data have, basically, a biochemical nature and include: Glutamate (and the related flux of calcium ions), glycine, serine and glutathione. They have been recently analyzed using in particular the ''General Linear Model'': It is an equation that describes an examined response Y as a linear combination 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, β stands for a vector of regression coefficients, and e is a T x 1 error vector.

Dynamic features of glia are described like a matrix X. Every column of this matrix represents some biochemical characteristics one has implemented. Parameters are usually unknown for the simulation of noise. 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 [48]).

This type of linear models are usually boosted using sampling techniques that include also statistical information from biochemical substances in the Brain-Blood Barrier. Glia cells like astrocytes or radial glia [49] have complex biochemical interactions with neurons. This complexity is probably the main problem for the comprehension of their implications in brain cognitive processes. As suggested by Occhipinti and colleagues [42]: ''The stochastic reformulation of the problem is not only in better agreement with the stochastic nature of biological processes but also important from the mathematical and computational perspective.''

## 6. COMPUTATIONAL MODELS OF GLIA FUNCTIONING

This cognitive approach will consider also the *multiple realizability* (for a clear description of this concept see [50]) of the glial structures; therefore these new discoveries on glial physiology will be important for Artificial Intelligence and, in particular, for the connectionist approach [51]. This perspective has a very long tradition (for an historical introduction to AI methodologies see [52]) and its goal is to achieve good performance via thick interconnection of mere computational components. One of the most used Artificial Neural Network (ANN) algorithms is Back-propagation. The back propagation methodology of Rumelhart et al. [51] 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, inspired by glial physiology has been developed to avoid this problem, a method has been developed.

Ikuta, Uwate and Nishio [53] attempted to reproduce glia network's mechanisms, closely placed to the neural network; they significantly improve the performance of it. These researchers projected a Multi-Layer Perceptron (MLP) with a glial network whose elements produced autonomous osclillations (or fluctuations) and these ones spread to artificial neurons and glia cells. They implemented them by computational models showing that glial network boosted the learning ability of the MLP by combining the neurons in a more powerful way than the traditional one. They hypothesized that all glia cells produce impulses at casual periods each other, the glias' stochastic mechanisms positively influence the MLP.

They 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. 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 oscillations diminish when random behaviors propagate in the network.

In particular, they analyzed the learning mechanisms of the MLPs by estimating the time development of the errors. They decided to make 100 trials; the MLPs have the ability to learn 25000 times during a single trial. They computed the average of error , the minimum error, the maximum error and the standard deviation. In the average of error, they observed that the traditional procedure is the most wanting. The MLP with the impulse glial network decreases more the maximum error than the traditional MLP and the MLP with simple noise. Moreover, they acknowledged that the MLP with the glial chaos networks could avoid the largest local minimum and recognized that this MLP has a time of inactivity. In the glial network, all artificial glia cells produce chance value output, therefore,it is possible that the MLP can learn false results during long extents of time. The MLP with this improved glial network is able to recognize true values during the time of inactivity. Because if the artificial glias spike wide impulse, the output is fallen off and is not produced impulse during this time.

This computational model of glia functioning is, in my opinion, particularly interesting because integrates the ''stochastic reformulation'' of glia-neuron complex interactions discussed by Occhipinti and collegues [42]. Despite there are other theoretical models (see [36,54]), this one seems to respect the biological features of glia cells, in particular radial glia and astroglia.

Moreover, the incorporation of glia in an artificial neural network can be useful because a new type of information processing element would improve the performance of the entire system. This is possible because artificial astrocytes have been conceived to mirror the signaling capabilities of natural astroglial cells, that react to neurotransmitters and organize neurotransmission in a wider temporal range (some seconds) than neuronal transmission (milliseconds) . Therefore, artificial astroglia are, at the same time, excited by working synapses and able to react with neurons at a lower temporal lapse; consequently, taking in account the time unit as one iteration, the neural network weights constantly have been intensify or not if the related astroglia was functioning or not, correspondingly. However, the Chaos Glia Network discussed here can, with variations, be utilized for mapping, categorization or associative memory. The most relevant benefit of this network is that training is more effective. It can be utilized instantly because when a pattern representing each class has been analyzed, the system can rapidly start to create wider patterns; These ones will allow a more dynamic decision surface. Some properties of this system are: a) The parameters of the decision surfaces can be modified as desired. b) The decision surfaces can be interpretated as Bayes-optimal. c) It can work for a great number of cases. d) For time-varying statistics , patterns can, quite easily, be modified. In my opinion, a pragmatic feature of the Chaos Glial Network is that, unlike many networks, it totally works in parallel without a necessity for feedback from the specific artificial cells.

## 7. GLIA IN LEARNING PROCESSES

In the past few years, glia cells and in particular astroglia has been shown to be crucial for

neuronal proliferation and synapse development. Now, in fundamental research from Goldman and Nedergaard's teams [55], 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 [56]. 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, mouses with humane astroglia performed better in learning but also memory exercises, raising the eventuality that human astroglia allow us to be more intelligent.

Also Bergmann glia seems to have an important role in learning; as showed by Anderson and collegues [57], mice that acquired new motor abilities had a higher quantity of synapses per neuron without a growth in the density of capillaries. The research showed that glial volume correlates with synaptic amount and not with capillary quantity.

## 8. THE COMPLEMENTARY 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 [58]; moreover, glia cells release glutamate [59] when conjoined to post-synaptic depolarization. Panatier et al. [60] 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. [61].

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 despite the classical Hebbian theory is not questioned here. 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.

## 9. PHILOSOPHICAL CONCLUSION

These years have been crucial for glia studies, because of a wider amount of information on the glial nature and functions (even though there are 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$^{th}$ 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 [62], finally, as showed above, a new brain study shows that human glia allows both activity-dependent plasticity and acquiring information in mice [55]. 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'' ([63]:p. 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'' [64]. Moreover, following David Hull's theory on the conceptual evolution in science [65] (Hull, 2010), I think that the introduction of the concept of ''cognitive gliascience'' (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.

In conclusion, could we hypothesize a Copernican Revolution or a (Kuhnian) paradigm shift where glia cells are not considered passive and inert but active and having a dominant role in determining human cognition?

## ACKNOWLEDGEMENTS

I would like to thank my former thesis co-advisor: Prof. Alberto Oliverio (Dipartimento di Biologia e Biotecnologie ''Charles Darwin'',Sapienza Università di Roma) for his very useful explanations on various neuroimaging techniques and on Einstein's brain studies.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

## REFERENCES

1. McCulloch WS. Information in the head. Synthese. 1955;9(1):233-247.
2. Ranjan A, Mallick BN. Differential staining of glia and neurons by modified Golgi-Cox method. Journal of neuroscience methods; 2012.
3. Virchow R. Die Cellularpathologie in ihrer Begründung auf physiologische and pathologische Gewebelehre. Verlag Von August Hirschfeld, Berlin; 1858.
4. Golgi C. Contribuzione alla fina anatomia degli organi centrali del sistema nervoso. Rivista clinica di Bologna,Bologna; 1871.
5. Cajal SR. Contribucion al conocimiento de la neuroglia del cerebro humano. Trab Lab Investig Biol. 1913;11:255–315.
6. Nedergaard M, Rodríguez J, Verkhratsky A. Glial calcium and diseases of the nervous system. Cell Calcium. 2010;47(2): 140-9.
7. Seifer G, Schilling K, Steinhäuser C. Astrocyte dysfunction in neurological disorders: A molecular perspective. Nature Reviews Neuroscience. 2006;7(3):194-206.
8. Ralevic V, Burnstock G. Receptors for purines and pyrimidines. Pharmacological reviews. 1998;50(3):413-492.
9. Parri HR, Crunelli V. The role of Ca2+ in the generation of spontaneous astrocytic Ca2+ oscillations. Neuroscience. 2003; 120:979–92.
10. Bystron I, Blakemore C, Rakic P. Development of the human cerebral cortex: Boulder Committee revisited. Nature Reviews Neuroscience. 2008;9(2):110-122.
11. Malatesta P, Appolloni I, Calzolari F. Radial glia and neural stem cells. Cell and tissue research. 2008;331(1):165-178.
12. Reillo I, De Juan Romero C, García-Cabezas MÁ, Borrell V. A role for intermediate radial glia in the tangential expansion of the mammalian cerebral cortex. Cerebral Cortex. 2011;21(7):1674-1694.
13. Cameron RS, Rakic P. Glial cell lineage in the cerebral cortex: A review and synthesis. Glia. 1991;4(2):124-137.
14. Hansen DV, Lui JH, Parker PR, Kriegstein AR. Neurogenic radial glia in the outer subventricular zone of human

neocortex. Nature. 2010;464(7288):554-561.

15. Perea G, Navarrete M, Araque A. Tripartite synapses: Astrocytes process and control synaptic information. Trends in neurosciences. 2009;32(8):421-431.
16. Bélanger M, Magistretti PJ. The role of astroglia in neuroprotection. Dialogues in Clinical Neuroscience. 2009;11(3):281. Available:http://openi.nlm.nih.gov/detailedresult.php?img=3181926_DialoguesClinNeurosci-11-281-g001&req=4
17. Sofroniew MV, Vinters HV. Astrocytes: Biology and pathology. Acta Neuropathologica. 2010;119(1):7-35.
18. Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: Redefining the functional architecture of the brain. Trends in Neurosciences. 2003;26(10):523-530.
19. Martin DL. Synthesis and release of neuroactive substances by glial cells. Glia. 1992;5(2):81-94.
20. Marmiroli P, Cavaletti G. The glutamatergic neurotransmission in the central nervous system. Current Medicinal chemistry. 2012;19(9):1269-1276.
21. Haydon PG, Carmignoto G. Astrocyte control of synaptic transmission and neurovascular coupling. Physiological Reviews. 2006;86(3):1009-1031.
22. Montana V, Malarkey EB, Verderio C, Matteoli M, Parpura V. Vesicular transmitter release from astrocytes. Glia. 2006;54(7):700-715.
23. Hamilton N, Vayro S, Kirchhoff F, Verkhratsky A, Robbins J, Gorecki DC, Butt AM. Mechanisms of ATP- and glutamate-mediated calcium signaling in white matter astrocytes. Glia. 2008;56(7): 734-49.
24. Volterra A, Meldolesi J. Astrocytes, from brain glue to communication elements: The revolution continues. Nature Reviews Neuroscience. 2005;6(8):626-640.
25. Kettenmann H, Steinhauser C. 10 Receptors for neurotransmitters and hormones. Neuroglia. 2005;131.
26. Jaiswal JK, Fix M, Takano T, Nedergaard, M, Simon SM. Resolving vesicle fusion from lysis to monitor calcium-triggered lysosomal exocytosis in astrocytes. Proceedings of the National Academy of Sciences. 2007;104(35):14151-14156.
27. Wang X, Lou N, Xu Q, Tian GF, Peng WG, Han X, Nedergaard M. Astrocytic Ca2+ signaling evoked by sensory stimulation in vivo. Nature Neuroscience. 2006;9(6):816-823.
28. Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Gan WB. ATP mediates rapid microglial response to local brain injury in vivo. Nature Neuroscience. 2005; 8(6):752-758.
29. Hanani M. Satellite glial cells in sensory ganglia: from form to function. Brain Research Reviews. 2005;48(3):457-476.
30. Rizzuto R, Pozzan T. Microdomains of intracellular Ca2+: Molecular determinants and functional consequences. Physiological Reviews. 2006;86(1):369-408.
31. Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. Nature Neuroscience. 2007;10(11):1369-1376.
32. Howarth C. The contribution of astrocytes to the regulation of cerebral blood flow. Frontiers in Neuroscience. 2014;8.
33. Ciccone MM, Innocente Galeandro A, Scicchitano P, Zito A, Gesualdo M, Sassara M, Trojano M. Multigate quality Doppler profiles and morphological/hemodynamic alterations in multiple sclerosis patients. Current Neurovascular Research. 2012;9(2):120-127.
34. Ciciarello F, Mandolesi S, Innocente Galeandro A, Marceca A, Rossi M, Fedele, F, Matteo Ciccone M. Age-related vascular differences among patients suffering from multiple sclerosis. Current Neurovascular Research. 2014;11(1):23-30.
35. Tononi G. Integrated information theory of consciousness: An updated account. Arch Ital Biol. 2012;150(2-3):56-90.
36. Pereira Jr. A. Perceptual information integration: Hypothetical role of astrocytes. Cognitive Computation. 2012;4(1):51-62.
37. Marr D. Vision. San Francisco: Freeman; 1982.
38. Pylyshyn ZW. Computation and cognition. Cambridge, MA: MIT Press; 1984.
39. Oliverio A, Castellano C, Puglisi-Allegra S. Psychopharmacogenetics of opioids. Trends in Pharmacological Sciences. 1983;4:350-352.
40. Venneti S, Lopresti BJ, Wang G, Slagel SL, Mason NS, Mathis CA, Wiley CA. A comparison of the high-affinity peripheral benzodiazepine receptor ligands DAA1106 and (R)-PK11195 in rat models of

neuroinflammation: Implications for PET imaging of microglial activation. Journal of Neurochemistry. 2007;102(6):2118-2131.

41. Cagnin A, Myers R, Gunn RN, Lawrence AD, Stevens T, Kreutzberg GW, Banati RB. *In vivo* visualization of activated glia by [11C](R)-PK11195-PET following herpes encephalitis reveals projected neuronal damage beyond the primary focal lesion. Brain. 2001;124(10):2014-2027.
42. Occhipinti R, Somersalo E, Calvetti D. Astrocytes as the glucose shunt for glutamatergic neurons at high activity: An in silico study. Journal of neurophysiology. 2009;101(5):2528-2538.
43. Tenenbaum JB, Kemp C, Griffiths TL, Goodman ND. How to grow a mind: Statistics, structure, and abstraction. Science. 2011;331(6022):1279-1285.
44. Pijn JP, Van Neerven J, Noest A, Da Silva FHL. Chaos or noise in EEG signals; dependence on state and brain site. Electroencephalography and clinical Neurophysiology. 1991;79(5):371-381.
45. Friston KJ. Functional and effective connectivity: A review. Brain Connectivity. 2011;1(1):13-36.
46. Lozovanu D, Pickl S. Optimization of stochastic discrete systems and control on complex networks. Springer Verlag; 2015.
47. Nägerl UV, Triller A, (Eds.). Nanoscale imaging of synapses: New concepts and opportunities. Humana Press; 2014.
48. Penny W, Friston K. Bayesian Treatments of Neuroimaging Data. In Doya K, (Ed.). Bayesian brain: Probabilistic approaches to neural coding. MIT Press; 2007.
49. Fields RD, Stevens-Graham B. New insights into neuron-glia communication. Science. 2002;298(5593):556-562.
50. Putnam H. Representation and reality. Cambridge, MA: MIT Press; 1988.
51. Rumelhart DE, McClelland JL. Parallel distributed processing: Explorations in the microstructure of cognition. Foundations. 1986;1.
52. Cordeschi R. The discovery of the artificial: Behavior, mind and machines before and beyond cybernetics. Kluwer Academic Pub. 2002;28.
53. Ikuta C, Uwate Y, Nishio Y. Chaos glial network connected to multi-layer perceptron for solving two-spiral problem. In Circuits and Systems (ISCAS), Proceedings of 2010 IEEE International Symposium on. IEEE. 2010;1360-1363.
54. Sajedinia Z. Artificial astrocyte networks, as components in artificial neural networks. In Unconventional Computation and Natural Computation. Springer International Publishing. 2014;316-326.
55. Han X, Chen M, Wang F, Windrem M, Wang S, Shanz S, Nedergaard M. Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell. 2013;12(3):342-353.
56. Morgado-Bernal I. Learning and memory consolidation: Linking molecular and behavioral data. Neuroscience. 2011;176: 12-19.
57. Anderson BJ, Li X, Alcantara AA, Isaacs KR, Black JE, Greenough WT. Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. Glia. 1994;11(1):73-80.
58. Bolton MM, Eroglu C. Look who is weaving the neural web: Glial control of synapse formation. Current Opinion in Neurobiology. 2009;19(5):491-497.
59. Angulo MC, Kozlov AS, Charpak S, Audinat E. Glutamate released from glial cells synchronizes neuronal activity in the hippocampus. The Journal of neuroscience. 2004;24(31):6920-6927.
60. Panatier A, Theodosis DT, Mothet JP., Touquet B, Pollegioni L, Poulain DA, Oliet SH. Glia-derived D-serine controls NMDA receptor activity and synaptic memory. Cell. 2006;125(4):775-784.
61. Ben Menachem-Zidon O, Avital A, Ben-Menahem Y, Goshen I, Kreisel T, Shmueli, EM, Yirmiya R. Astrocytes support hippocampal-dependent memory and long-term potentiation via interleukin-1 signaling. Brain, Behavior, and Immunity. 2011;25(5):1008-1016.
62. Sherwood CC, Stimpson CD, Raghanti M. A, Wildman DE, Uddin M, Grossman LI, Hof PR. Evolution of increased glia–neuron ratios in the human frontal cortex. Proceedings of the National Academy of Sciences. 2006;103(37:13606-13611.
63. Luria SE, Gould SJ, Singer S. A view of life. Benjamin/Cummings Publishing Company; 1981.

64. Fields RD, Araque A, Johansen-Berg H, Lim SS, Lynch G, Nave KA, Wake H. Glial biology in learning and cognition. The Neuroscientist. 1073858413504465; 2013.

65. Hull DL. Science as a process: An evolutionary account of the social and conceptual development of science. University of Chicago Press; 2010.

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