

Review Article

TOWARDS A COGNITIVE GLIASCIENCE: A BRIEF CONCEPTUAL FRAMEWORK

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.

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 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 (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'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 (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 has become 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

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 (Nedergaard et al., 2010), but the density of these channels is much lower, and therefore the currents produced upon their activation are incapable of depolarizing glial membrane (Seifert et al.,2006). 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 (Ralevic & Burnstock,1998). In adjunct to the evoked

Ca²⁺ signals and intracellular waves, astroglial cells are able of producing spontaneous Ca²⁺ 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, 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 [Ca²⁺]-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 Ca²⁺ signals was also gauged by membrane capacitance recordings (Montana et al.,2006).

The vesicular glutamate issue from astrocytes is substantially more diverse from the neuronal one in respect to the origin of Ca²⁺ prime: in astrocytes Ca²⁺ accrues almost only from the intracellular stores, while neuronal exocytosis is ruled mostly by Ca²⁺ 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 Ca²⁺-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 (Jaiswal et al., 2007). This device of transmitters release (via plasmalemmal channels) is not due to Ca²⁺. 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' Ca²⁺ oscillations were discovered to guide neuronal Ca²⁺ 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 also glial networks

and, in particular astrocytes are information structures¹ 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 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 (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 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 (Occhipinti et al.,2009; Tenenbaum et al., 2011). The intrinsic stochastic dynamics of common cortical microcircuits allows them to rapidly create approximate solutions to 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 (Pijn,1991; Friston,2011). 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

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”(Tononi,2012:298); in my opinion, these informational processes are active in particular 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 (Pereira,2012:55). I think these informational loops can be interpreted as Markov chains Monte Carlo (MCMC) where a set of distinct matrices are utilized on account of each is skillful for a specific type of mixing, but every matrix adheres to the same equilibrium distribution. This methodology is motivated by biochemical differences in information processing between neurons and glia cells.

Lozovanu et al., 2015). 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 Nagerl et al., 2014). 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 Penny & Friston, 2006).

Moreover, 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 (Fields et al., 2002) 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 (2009): "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."

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 very 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) algorithms 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, inspired by glial physiology has been developed to avoid this problem, a method has been developed.

Ikuta, Uwate and Nishio (2010) 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 oscillations (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 glia's 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 has 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 glia 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 colleagues (2009). Despite there are other theoretical models (see Pereira, 2012; Sajedinia, 2014), this one seems to respect the biological features of glia cells, in particular radial glia and astroglia.

Glial 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 (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 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 colleagues (1994), 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.

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 (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 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.

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 20th 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 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.

References

- Anderson, B. J., Li, X., Alcantara, A. A., Isaacs, K. R., Black, J. E., & Greenough, W. T. (1994). Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. *Glia*,11(1), 73-80.
- Angulo, M. C., Kozlov, A. S., Charpak, S., & Audinat, E. (2004). Glutamate released from glial cells synchronizes neuronal activity in the hippocampus. *The Journal of neuroscience*, 24(31), 6920-6927.
- Ben Menachem-Zidon, O., Avital, A., Ben-Menahem, Y., Goshen, I., Kreisel, T., Shmueli, E. M., ... & Yirmiya, R. (2011). Astrocytes support hippocampal-dependent memory and long-term potentiation via interleukin-1 signaling. *Brain, behavior, and immunity*, 25(5), 1008-1016.
- Bolton, M. M., & Eroglu, C. (2009). Look who is weaving the neural web: glial control of synapse formation. *Current opinion in neurobiology*, 19(5), 491-497.
- Cagnin, A., Myers, R., Gunn, R. N., Lawrence, A. D., Stevens, T., Kreutzberg, G. W., ... & Banati, R. B. (2001). In vivo visualization of activated glia by [11C](R)-PK11195-PET following herpes encephalitis reveals projected neuronal damage beyond the primary focal lesion. *Brain*, 124(10), 2014-2027.
- Cajal SR (1913) Contribucion al conocimiento de la neuroglia del cerebro humano. *Trab Lab Investig Biol* 11:255–315
- Cordeschi, R. (2002). *The discovery of the artificial: Behavior, mind and machines before and beyond cybernetics* (Vol. 28). Kluwer Academic Pub.
- Davalos, D., Grutzendler, J., Yang, G., Kim, J. V., Zuo, Y., Jung, S., ... & Gan, W. B. (2005). ATP mediates rapid microglial response to local brain injury in vivo. *Nature neuroscience*, 8(6), 752-758.
- Fields, R. D., & Stevens-Graham, B. (2002). New insights into neuron-glia communication. *Science*, 298(5593), 556-562.

- 287 Fields, R. D., Araque, A., Johansen-Berg, H., Lim, S. S., Lynch, G., Nave, K. A., ... & Wake, H. (2013). Glial
288 biology in learning and cognition. *The Neuroscientist*, 1073858413504465.
- 289 Friston, K. J. (2011). Functional and effective connectivity: a review. *Brain connectivity*, 1(1), 13-36.
- 290 Golgi C. (1871). Contribuzione alla fina Anatomia degli organi centrali del sistema nervoso; Rivista clinica di
291 Bologna,Bologna.
- 292 Hamilton N, Vayro S, Kirchhoff F, Verkhatsky A, Robbins J, Gorecki DC, Butt AM. (2008). Mechanisms of
293 ATP- and glutamate-mediated calcium signaling in white matter astrocytes. *Glia*, 56(7), 734-49.
- 294 Han, X., Chen, M., Wang, F., Windrem, M., Wang, S., Shanz, S., ... & Nedergaard, M. (2013). Forebrain
295 engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. *Cell*
296 *Stem Cell*, 12(3), 342-353.
- 297 Hanani, M. (2005). Satellite glial cells in sensory ganglia: from form to function. *Brain Research Reviews*,
298 48(3), 457-476.
- 299 Haydon, P. G., & Carmignoto, G. (2006). Astrocyte control of synaptic transmission and neurovascular
300 coupling. *Physiological reviews*, 86(3), 1009-1031.
- 301 Hull, D. L. (2010). *Science as a process: an evolutionary account of the social and conceptual development*
302 *of science*. University of Chicago Press.
- 303 Ikuta, C., Uwate, Y., & Nishio, Y. (2010, May). Chaos glial network connected to multi-layer perceptron for
304 solving two-spiral problem. In *Circuits and Systems (ISCAS), Proceedings of 2010 IEEE International*
305 *Symposium on* (pp. 1360-1363). IEEE.
- 306 Jaiswal, J. K., Fix, M., Takano, T., Nedergaard, M., & Simon, S. M. (2007). Resolving vesicle fusion from lysis
307 to monitor calcium-triggered lysosomal exocytosis in astrocytes. *Proceedings of the National Academy of*
308 *Sciences*, 104(35), 14151-14156.
- 309 Kettenmann, H., & Steinhauser, C. (2005). 10 Receptors for neurotransmitters and hormones. *Neuroglia*,
310 131.
- 311 Lozovanu, D., & Pickl, S. (2015). *Optimization of Stochastic Discrete Systems and Control on Complex*
312 *Networks*. Springer verlag.
- 313 Luria, S. E., Gould, S. J., & Singer, S. (1981). *A view of life*. Benjamin/Cummings Publishing Company.
- 314 Marmioli, P., & Cavaletti, G. (2012). The glutamatergic neurotransmission in the central nervous system.
315 *Current medicinal chemistry*, 19(9), 1269-1276.
- 316 Marr, D. (1982). *Vision*. San Francisco: Freeman.
- 317 Martin, D. L. (1992). Synthesis and release of neuroactive substances by glial cells. *Glia*, 5(2), 81-94.
- 318 McCulloch, W. S. (1955). Information in the head. *Synthese*, 9(1), 233-247.
- 319 Montana, V., Malarkey, E. B., Verderio, C., Matteoli, M., & Parpura, V. (2006). Vesicular transmitter release
320 from astrocytes. *Glia*, 54(7), 700-715.
- 321 Morgado-Bernal, I. (2011). Learning and memory consolidation: linking molecular and behavioral data.
322 *Neuroscience*, 176, 12-19.

- 323 Nägerl, U. V., & Triller, A. (Eds.). (2014). *Nanoscale imaging of synapses: new concepts and opportunities*.
324 Humana Press.
- 325 Nedergaard, M., Rodríguez, J. & Verkhratsky, A (2010). Glial calcium and diseases of the nervous system.
326 *Cell Calcium*, 47(2), 140-9.
- 327 Oberheim, N. A., Wang, X., Goldman, S., & Nedergaard, M. (2006). Astrocytic complexity distinguishes the
328 human brain. *Trends in neurosciences*, 29(10), 547-553.
- 329 Occhipinti, R., Somersalo, E., & Calvetti, D. (2009). Astrocytes as the glucose shunt for glutamatergic
330 neurons at high activity: an in silico study. *Journal of neurophysiology*, 101(5), 2528-2538.
- 331 Oliverio, A., Castellano, C., & Puglisi-Allegra, S. (1983). Psychopharmacogenetics of opioids. *Trends in*
332 *Pharmacological Sciences*, 4, 350-352.
- 333 Panatier, A., Theodosis, D. T., Mothet, J. P., Touquet, B., Pollegioni, L., Poulain, D. A., & Oliet, S. H. (2006).
334 Glia-derived D-serine controls NMDA receptor activity and synaptic memory. *Cell*, 125(4), 775-784.
- 335 Parri HR, Crunelli V.(2003). The role of Ca²⁺ in the generation of spontaneous astrocytic Ca²⁺ oscillations.
336 *Neuroscience*; 120: 979–92.
- 337 Penny W. & Friston K. (2007). Bayesian Treatments of Neuroimaging Data. In Doya, K. (Ed.). *Bayesian brain:*
338 *Probabilistic approaches to neural coding*. MIT Press.
- 339 Pereira Jr, A. (2012). Perceptual information integration: hypothetical role of astrocytes. *Cognitive*
340 *Computation*, 4(1), 51-62.
- 341 Pijn, J. P., Van Neerven, J., Noest, A., & da Silva, F. H. L. (1991). Chaos or noise in EEG signals; dependence
342 on state and brain site. *Electroencephalography and clinical Neurophysiology*, 79(5), 371-381.
- 343 Pylyshyn, Z. W. (1984). *Computation and cognition*. Cambridge, MA: MIT press.
- 344 Putnam, H. (1988). *Representation and reality* . Cambridge, MA: MIT press.
- 345 Ralevic, V., & Burnstock, G. (1998). Receptors for purines and pyrimidines. *Pharmacological reviews*, 50(3),
346 413-492.
- 347 Ranjan, A., & Mallick, B. N. (2012). Differential staining of glia and neurons by modified Golgi-Cox method.
348 *Journal of neuroscience methods*.
- 349 Rizzuto, R., & Pozzan, T. (2006). Microdomains of intracellular Ca²⁺: molecular determinants and functional
350 consequences. *Physiological reviews*, 86(1), 369-408.
- 351 Rumelhart, D. E., & McClelland, J. L. (1986). *Parallel distributed processing: explorations in the*
352 *microstructure of cognition*. Volume 1. Foundations.
- 353 Seifert, G., Schilling, K., & Steinhäuser, C. (2006). Astrocyte dysfunction in neurological disorders: a
354 molecular perspective. *Nature Reviews Neuroscience*, 7(3), 194-206.
- 355 Sajedinia, Z. (2014). Artificial Astrocyte Networks, as Components in Artificial Neural Networks.
356 In *Unconventional Computation and Natural Computation* (pp. 316-326). Springer International Publishing.
- 357 Sherwood, C. C., Stimpson, C. D., Raghanti, M. A., Wildman, D. E., Uddin, M., Grossman, L. I., ... & Hof, P. R.
358 (2006). Evolution of increased glia–neuron ratios in the human frontal cortex. *Proceedings of the National*
359 *Academy of Sciences*, 103(37), 13606-13611.

360 Spadaro, S. (2013). The dilemma of the symbols: analogies between philosophy, biology and artificial life.
 361 SpringerPlus, 2(1), 1-10.
 362
 363 Tenenbaum, J. B., Kemp, C., Griffiths, T. L., & Goodman, N. D. (2011). How to grow a mind: Statistics,
 364 structure, and abstraction. *science*, 331(6022), 1279-1285.

365 Tononi, G. (2012). Integrated information theory of consciousness: an updated account. *Arch Ital*
 366 *Biol*, 150(2-3), 56-90.

367 Wang, X., Lou, N., Xu, Q., Tian, G. F., Peng, W. G., Han, X., ... & Nedergaard, M. (2006). Astrocytic Ca²⁺
 368 signaling evoked by sensory stimulation in vivo. *Nature neuroscience*, 9(6), 816-823.

369 Venneti, S., Lopresti, B. J., Wang, G., Slagel, S. L., Mason, N. S., Mathis, C. A., ... & Wiley, C. A. (2007). A
 370 comparison of the high-affinity peripheral benzodiazepine receptor ligands DAA1106 and (R)-PK11195 in rat
 371 models of neuroinflammation: implications for PET imaging of microglial activation. *Journal of*
 372 *neurochemistry*, 102(6), 2118-2131.

373 Virchow R. (1858). *Die Cellularpathologie in ihrer Begründung auf physiologische and pathologische*
 374 *Gewebelehre*; Verlag von August Hirschfeld, Berlin.

375 Volterra, A., & Meldolesi, J. (2005). Astrocytes, from brain glue to communication elements: the revolution
 376 continues. *Nature Reviews Neuroscience*, 6(8), 626-640.

377
 378