

MONTEMURRO7492586BIOL30101

by David Adler

WORD COUNT
CHARACTER COUNT

9513
54037

TIME SUBMITTED
PAPER ID

22-NOV-2012 02:05PM
19367830

7492586

BSc Neuroscience

Dr. Marcelo Montemurro

The Computational Role of Astrocytes in Information Processing and Synaptic Plasticity

1 - INTRODUCTION

The central nervous system consists of two main cell types: neurons and glia. Classically, neurons are considered the cell type responsible for mediating computational, learning and cognitive functions of the brain. These long-held ideas originate from the acclaimed “father of modern neuroscience”, Santiago Ramon Y Cajal [1]. 1906 marked the victory of the neuronal doctrine with a Nobel Prize and the neglect of research into glia as functional elements of cognition for the majority of the 20th century [2]. Our current general understanding of the brain can be reduced to a simple definition: the brain is a learning system which stores memories as synaptic weight adjustments (synaptic plasticity; SP). These synapses are used to process novel sensory inputs (information processing; IP) to coordinate mechano-sensory outputs. The current cellular theories of SP, such as spike-time dependent plasticity (for review see [3]), originate from Hebbian concepts of presynaptic and postsynaptic neuronal pairing. However, these neurocentric paradigms are being challenged by the seminal concept of a tripartite synapse, originally introduced by Araque et al. [4].

Glial cells make up approximately 90% of the human brain [5, 6] and consist of three main varieties. Astrocytes make up 85% of glial cells in the mammalian CNS [6] and are classically considered as supportive cells to neurons. Accumulating evidence suggests that astrocytes are involved in IP and SP and therefore challenges the neuronal dogmas of cognitive function. It is worth noting that astrocyte number, morphology and variety distinguish the human brain from other mammals. There is a phylogenetic relationship between neuron-to-glia ratio and “intelligence” of the organism (Fig.1 C) [6-8]. In a comparison between rodent and human brain, neuronal size and morphology show a relatively linear change with brain size whereas protoplasmic astrocytes (the most abundant type of astrocyte) show a supralinear change (Fig.1 A-B) [6, 7, 9]. Interlaminar and polarized astrocytes are found exclusively in the primate brain and are implicated in the advanced structural organization of cortical columns [7, 9]. Moreover, Varicose-projection astrocytes are found exclusively in the human brain [7, 9]. Thus whilst much of the literature discussed originates from rodents, human astrocytes may operate differently.

2 - ASTROCYTIC EXCITABILITY

Seminal discoveries in the early 1990s initiated an interest in astrocyte excitability and signalling. Cornell-Bell et al. [10] observed glutamate induced propagating calcium (Ca^{2+}) waves in cultured hippocampal cells. Shortly afterwards, others demonstrated these waves *in situ* [11] and have since been demonstrated to occur in response to sensory stimulation *in vivo* [12, 13]. Furthermore, astrocytes in the visual cortex were shown to have distinct receptive fields and an even sharper tuning to visual stimuli than neurons [12]. Ca^{2+} responses are the basis of astrocyte excitability.

2.1 - ASTROCYTE ACTIVATION

Abstraction of neuronal activation can be simplified into three steps: (i) receptor activation (ii) changes in cytosolic ion concentrations (iii) if step two surpasses a threshold, a mechanism further potentiates step two resulting in cell activation. A similar such mechanism is present in astrocytes.

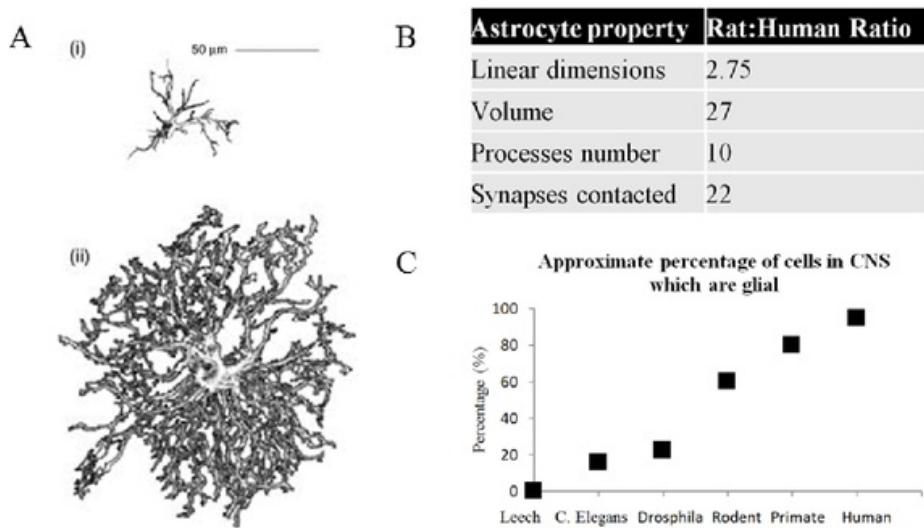


Fig. 1 Evolution of Astrocytes (A) Modified from Fig. 2 of Ref. [7]; Graphical representation of GFAP immunostaining of astrocytes (i) mouse and (ii) human cortical astrocytes. (B) Rat to human astrocyte morphology comparison, data extracted from [6, 14]; (C) Graph of evolution of proportion of glia in CNS, plotted from data in Refs. [5, 6, 15-17]

2.1.1 – MOLECULAR MECHANISM

Ca^{2+} responses can be initiated either spontaneously [18-21] or by synapse mediated receptor activation [12, 18, 19, 21-23]. Astrocytes have been shown to express a myriad of ionotropic and metabotropic receptors capable of detecting virtually every neuroactive substance, see Table 1. Glutamatergic, GABAergic, adrenergic, dopaminergic, purinergic, serotonergic, histaminic, muscarinic and peptidergic have been confirmed *in situ* and *in vivo* (reviewed in [24-26]). Astrocytes are not electrically excitable, as they express a low density of voltage-gated sodium channels and show high potassium permeability [27].

Receptor mediated Ca^{2+} responses are derived from two Ca^{2+} sources: the endoplasmic reticulum (ER) or the extracellular space (ECS) [28]. Ca^{2+} influx from the ECS partially contributes to astrocyte activation. Influx from the ECS is mediated by ligand-gated channels, voltage-gated Ca^{2+} channels and reversal of exchangers [29]. The predominant source of intracellular Ca^{2+} rise in astrocytes is the ER, mediated by perisynaptic metabotropic receptors [28, 29]. Many astrocytic metabotropic receptors are coupled to the $\text{G}_{\alpha q}$ G-protein subunit causing activation of phospholipase C (PLC) [24, 29, 30]. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) [22]. DAG remains bound to the membrane and IP3 is released into the cytosol [18]. IP3 diffuses through the cytosol to the ER and binds to IP3 receptors (IP3Rs), predominantly IP3R2 [22]. It is estimated that IP3Rs require 40msec [31] to be activated and allow mobilization of Ca^{2+} from the stores in the ER. IP3 receptors conduct Ca^{2+} down the steep Ca^{2+} gradient into the cytosol, producing a spatially restricted Ca^{2+} microdomain [32]. Note that astrocytic activation is dependent on metabotropic activation, hydrolysis of signalling molecules, and diffusion of IP3 in the cytoplasm, slow activation of IP3Rs and therefore relatively slow in comparison to ionotropic mediated neuronal influx of ions.

Table 1 Astrocyte input and output molecules

Molecule	Ca ²⁺ response observed by	Astrocyte release observed by
Glutamate	[10, 19, 33-50]	[51-54]
GABA	[43, 55-61]	[59, 62]
D-serine	[63-65]	[66-70]
ATP	[40, 71, 72]	[34, 72-74]
Acetylcholine	[20, 51, 75, 76]	[77, 78]
Dopamine	[79, 80]	
Adrenaline	[81]	
Nitric oxide	[82-84]	[85-88]
TNF-α		[89]
Endocannabinoids	[90-92]	

2.1.2 – FROM MICRODOMAINS TO WHOLE-CELL RESPONSES

Microdomains are functionally independent subcompartments within a process which may develop to intracellular Ca²⁺ waves and cause complex whole-cell responses in the astrocyte [31, 75, 93]. High resolution two photon microscopy has revealed that Ca²⁺ microdomains have complex dynamics and have identified two main varieties [21, 94]. Focal transients of about 4 μm (type 1) and robust regional microdomains of about 12 μm (type 2). Focal transients have a much higher frequency and are generated by spontaneous single vesicle release at single synapses [94]. Type 2 microdomains are induced by action potentials activating many synapses within the astrocyte's domain. [Supplementary video 3](#) [95] provided by Di Castro et al. [94] demonstrates that neuronal blockade with tetrodotoxin (right in video) blocks type 2 responses but not type 1. Only type 2 microdomains appear to have an influence on synaptic transmission [94]. Thus microdomains may represent low-order subcellular threshold units of information processing in astrocytes [30-32].

Sufficient microdomain events can induce intracellular Ca²⁺ waves and whole-cell Ca²⁺ responses [18, 32, 75]. Intracellular Ca²⁺ wave propagation is facilitated by two positive feedback mechanisms: (i) Ca²⁺ is a co-agonist at IP3Rs and (ii) Ca²⁺ activates PLC thus producing more IP3 [96]. Intracellular wave propagation is suppressed by the Ca²⁺ buffering of mitochondria and Ca²⁺ binding proteins [96]. Although an attractive mechanism, it is unlikely that ryanodine receptors contribute to Ca²⁺ wave propagation [32, 39]. The above mechanisms for regulation of intracellular wave propagation represent are a feasible additional functional threshold for information processing in astrocytes. Intracellular Ca²⁺ waves travel relatively slowly (~25 μm/s [29, 31, 93]) compared to the speed of dendritic propagation of inputs.

Intracellular Ca²⁺ waves may develop into complex whole-cell Ca²⁺ responses which are known to be biphasic. Following an initial IP3 induced peak, astrocytes may exhibit a plateau phase or an oscillatory phase [29]. The secondary phase is dependent on neurotransmitter type, concentration and receptor expression [29]. For example, astrocytic type 1 metabotropic glutamate receptors (mGluR1s) produce a non-oscillatory response whereas mGluR5s evoke Ca²⁺ oscillations [21, 29, 97]. mGluR5 is the predominant receptor implicated in detection of glutamate by astrocytes and oscillations are a common feature of astrocyte excitability [21]. The frequencies of Ca²⁺ oscillations are dependent on the frequency of synaptic activity [30, 39, 98]. The amplitude and duration of Ca²⁺

oscillations are dependent on the frequency and duration of the synaptic input [24, 99, 100]. Whole-cell responses in astrocytes are several orders of magnitude slower than neuronal depolarization. Exogenous agonist application can take up to 10 seconds to produce whole-cell responses in astrocytes [101]. Astrocyte Ca^{2+} signals generally peak around 1 to 2 seconds [93] after stimulation and return to baseline levels around 7-30s after stimulation [31, 93]. Contrasting the rapid propagation of an action potential down an axon ($\sim 150\text{m/s}$) [102].

An important astrocytic attribute is that astrocytes have non-overlapping anatomical domains. Thus each astrocyte integrates a distinct set of synapses [14]. This morphological property of astrocytes may represent an important mechanism of information processing where astrocytes may act as central integrators of neuronal populations (Fig 2). However, the exact mechanism of how astrocytes integrate their processes and how processes integrate their microdomains remains to be determined.

2.1.3 – NON-LINEAR INTEGRATION OF INPUTS

Some of the literature which provides some clues as to how astrocytes integrate their inputs will now be discussed. The findings of Fiacco and McCarthy [31] suggest that Ca^{2+} responses initiated closer to the soma may be more influential in the synchronization of microdomains and induction of intracellular Ca^{2+} oscillations. Perea and Arque [100] demonstrated that astrocytes sum their inputs selectively. Either glutamatergic or cholinergic Schaffer collateral (Sc) terminals evoked Ca^{2+} responses in astrocytes. Cholinergic inputs originating from the alveus also evoked Ca^{2+} responses in these astrocytes. However, glutamatergic input originating from the alveus did not elicit a Ca^{2+} response [100]. Therefore, astrocytes in CA1 are capable of responding preferentially to different pathways using the same neurotransmitters. Similarly, thalamic astrocytes respond to sensory and corticothalamic inputs but rarely respond upon simultaneous stimulation [103]. Furthermore, astrocytes of the barrel cortex respond to glutamatergic inputs of the same column but not from adjacent barrels [104]. These examples strongly suggest that astrocytes have synaptic weights. Finally, PAR-1 and P2Y1 receptor activation causes whole-cell Ca^{2+} responses in hippocampal astrocytes. However, only PAR-1 activation produces slow inward currents (SICs) through NMDARs in adjacent neurons [105]. Thus, astrocytes may have complex mechanisms of regulating local astrocytic output.

2.2 - ASTROCYTE OUTPUT

In an excited state, astrocytes are able to influence the activity of neurons and other astrocytes. Astrocytes have two major output pathways: diffusion of signalling molecules through gap junctions and release of signalling molecules into the ECS, termed gliotransmission [28, 96]. Like astrocytic activation, astrocytic output acts on a timescale several orders of magnitude slower than neuronal output.

2.2.1 – ASTROCYTE TO ASTROCYTE

A defining characteristic of astrocytes is that they are highly coupled by gap junctions. Gap junctions are high-conductance high-permeability pores located at highly specialized regions of closely opposing membranes [6, 106, 107]. Gap junctions allow for direct inter-cytoplasmic diffusion of ions and small molecules of molecular weight less than approximately 1kDa [6, 106]. (For reviews on gap

junctions see [108, 109]) Gap junctions allow for intracellular Ca^{2+} waves to develop into intercellular Ca^{2+} waves (ICWs). ICWs are thought to be predominantly mediated by the diffusion of IP₃ [110]. ICWs develop when astrocytes are stimulated by sustained high frequency synaptic activity and/or large numbers of incident active synapses [93, 111]. Therefore, astrocytes have an intrinsic threshold which must be surpassed before the induction of an ICW. ICWs may also be generated by astrocytic release of ATP, which may provide a means of long distance communication [73, 107]. Most agree that ICWs travel at approximately 16 $\mu\text{m/sec}$ [29, 72] which, again, is relatively slow when compared to interneuronal signalling. However, the distance of wave propagation and number of cells activated by a single wave can vary enormously. *In vivo* experiments have reported ICWs involving small clusters of 2-5 astrocytes [18, 112] to tens and hundreds of astrocytes [113, 114]. The highly variable connectivity of the astrocytic syncytium suggests that gap junctions have synapse-like weightings. ICWs are likely to be the highest order form of information processing in astrocytes as these waves will incorporate the synaptic activity of the tens of thousands of synapses monitored by each astrocytic domain over several seconds/minutes [107, 115]. More research will be necessary to determine how gap junctions are plastically modified.

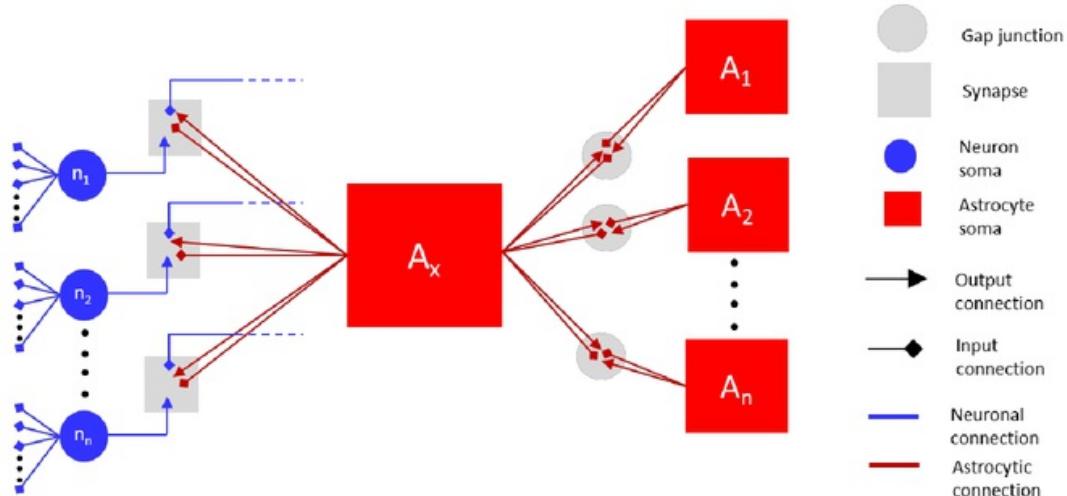


Fig. 2 Astrocyte potential for IP and plasticity. A_x represents a particular astrocyte of interest. Input connections are represented by diamond headed arrows. Output connections are represented by pointed arrow heads. A_{1-n} represent other astrocytes that A_x is connected to via gap junctions. The left half of the schematic illustrates the specific set of synapses the astrocyte is connected to. A likely important feature of astrocytic IP is that synapses innervated by A_x are unlikely to be innervated by any another astrocyte. Thus, astrocytes have the potential to act as slow integrators of a unique set of synapses. Furthermore each synapse offers the opportunity for plasticity at each connection and thus each synapse may have four synaptic parameters: neuron-to-neuron, neuron-to-astrocyte, astrocyte-to-neuron and astrocyte-to-astrocyte. Similarly, connections to other astrocytes at gap junctions (right half of schematic) offer potential for plastic weightings. Finally, it is worth considering the highly convergent capacity of A_x as A_{1-n} also will have a unique set of input synapses and gap junctions.

2.2.2 – ASTROCYTE TO NEURON

Although much less common, there have also been several reports of gap junctions directly between neurons and astrocytes in cultured cells. The function of these connections is unknown but may be important for neuronal synchronization [110, 116, 117].

Astrocytes are inherently linked to neuronal activity since they are essential to normal neuronal function. Variations in their more passive roles, such as nutrient support and regulation of microcirculation are potential ways for actively modulating neuronal function. For example, Wang et al. [118] recently demonstrated that Ca^{2+} responses can cause active uptake of extracellular potassium ions and increase neuronal hyperpolarization. It has been proposed that this may be a mechanism to improve the signal-to-noise ratio of synaptic transmission.

The main way astrocytes are able to influence neuronal activity is by the active release of a range of signalling molecules, collectively referred to as gliotransmitters. There are three main categories of gliotransmitters: amino acids, nucleotides and peptides [119]. Reported gliotransmitters include glutamate, GABA, D-serine, ATP, acetylcholine, dopamine, prostaglandins, BDNF, GDNF and TNF α . [6, 120-122], see Table 1. Astrocytes are able to exocytose gliotransmitters [36, 123]. In addition to exocytosis, astrocytes possess several other mechanism of gliotransmitter release, some of which are Ca^{2+} dependent [124, 125]. However this review will focus on astrocytic exocytosis, as these other mechanisms are poorly understood and are thought to occur under pathological conditions. Ca^{2+} dependent exocytosis was previously thought to be the prerogative of neurons. However, several groups have demonstrated astrocytic exocytosis [29, 36, 37, 65, 66]. Astrocytes are equipped with vesicles similar to those found in neurons and with molecular machinery necessary for exocytosis, for reviews see [121, 126]. Astrocytic exocytosis commonly causes slow inward currents (SICs) and synchronization of neuronal populations, which are discussed in more detail in subsequent sections [53, 127]. Astrocytic exocytosis has been shown to modulate synaptic plasticity [128].

3 - SYNAPTIC PLASTICITY

There are two forms of synaptic plasticity: short term and long term. Short term synaptic plasticity (STSP) is a change in synaptic strength lasting up to 10 seconds and is thought to underlie the computational functions of the brain [101]. Long term synaptic plasticity (LTSP) may last several minutes to hours and is thought to underlie learning and memory [101]. Astrocytes have been implicated in both forms of STSP; short term potentiation (STP) [21, 37, 52, 53, 91, 129, 130] and short term depression (STD) [34, 131]. For example, ATP is released from astrocytes and rapidly degraded extracellularly to adenosine. Adenosine has been shown to have transient positive and negative modulatory effects on Schaffer collateral (Sc) synapses. Panatier et al. [21] demonstrated that presynaptic A2A receptor activation causes STP whereas others [34, 131] found that A1 receptor activation causes STD. Thus astrocytes are capable of transient modulation of synaptic activity.

LTSP is the most widely accepted theory for the cellular basis of learning and memory [132]. LTSP has two forms: long term potentiation (LTP) and long term depression (LTD). Astrocytes have been implicated in both LTP and LTD. Space does not permit a review of all gliotransmitters involved in LTSP so this review will focus on D-serine and glutamate. However it is worth noting two particular examples. Firstly, ATP has been implicated in STSP [21, 133, 134], LTP [134] and LTD [133, 135] as well as having a strong role in interastrocytic communication [107, 136], as mentioned above. Secondly, there has also been some evidence that the release of lactate from astrocytes is necessary for the maintenance phase of LTP [137, 138].

3.1 - D-SERINE

NMDAR activation is required for both LTP and LTD [132, 139]. NMDAR activation is considered a coincidence detector of presynaptic and postsynaptic cell activation. The presynaptic cell confers its activation by agonist (glutamate) binding to the NMDAR. The postsynaptic cell confers its activation by depolarization which displaces Mg²⁺ blockade from the NMDAR pore [139]. Both glutamate and postsynaptic depolarization are required for NMDAR activation. However, it is often overlooked that NMDAR activation also requires co-agonist binding of glycine or D-serine at its co-agonist site [132]. In the mammalian brain the co-agonist is predominantly D-serine [140]. Astrocytes are the principal source of D-serine in the brain [101]. Astrocytic exocytosis of D-serine has been shown to gate the induction of LTP in multiple brain regions including the hippocampus [66, 141], hypothalamus [63] and prefrontal cortex [64]. Either clamping internal astrocytic Ca²⁺ or disrupting astrocytic D-serine exocytosis was shown to impair LTP and was restored by exogenous D-serine at hippocampal synapses [66]. These findings have been reinforced by an *in vivo* study in the rat barrel cortex [20]. The study reported that cholinergic input, stimulated astrocytic release of D-serine which allowed for the induction of LTP if coincident with sensory stimulation [20]. Thus it appears that the NMDAR is a coincidence detector of presynaptic, postsynaptic and astrocytic activity. This raises the question of why would astrocytic activity be a useful input factor for the induction of LTP? Perhaps the answer lies in that astrocytes integrate synaptic activity over larger temporal scale than neurons and thus provide information about time-averaged synaptic activity.

Astrocytic release of D-serine has also been implicated in LTD [142, 143]. Impairment of astrocytic functions in the hippocampus with sodium fluoroacetate, reduced the magnitude of LTD and could be restored with exogenous D-serine [142]. Interestingly, it was reported that D-serine was able to regulate LTD in a "concentration-dependent" [142] like manner which suggest a role of astrocytes in metaplasticity. Metaplasticity is defined as a higher-order form of plasticity which alters the ability of a synapse to undergo subsequent plasticity [144]. A potential role of astrocytes could be metaplasticity. During lactation, astrocytes in the hypothalamus undergo a dramatic retraction of their processes, leading to a decreased availability of astrocytic D-serine [63]. This change of D-serine has been found to shift the presynaptic activity threshold required for the induction of long term plasticity [63].

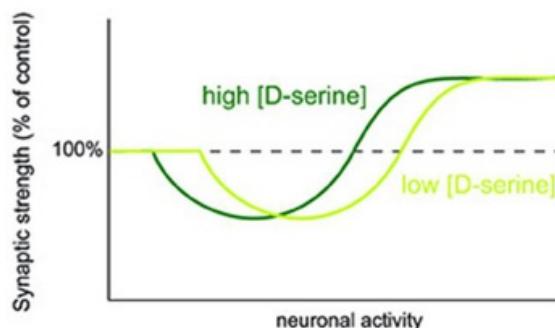


Fig. 3 Taken from Min et al [101]. A hypothetical BCM curve of the neuronal activity required for the induction of LTD and LTP is dependent on D-serine concentration available from astrocytes.

3.2 - GLUTAMATE

Glutamate is one of the best studied gliotransmitters and has been implicated in the slow synchronization of neuronal populations [145]. Glutamate release from a single astrocyte in the hippocampus can activate postsynaptic NMDARs and cause slow inward currents (SICs) lasting several hundred milliseconds in several pyramidal neurons [53, 100]. SICs are a common astrocytic response [44-50] and have been described in the cortex [145], thalamus, [127] spinal cord [54] and nucleus accumbens [146].

Perea and Araque [52] demonstrated that astrocytes mediated transient increases in the release probability of Sc terminals without affecting amplitude of synaptic events. Interestingly, pairing of presynaptic and astrocytic stimulation produced a non-NMDA LTP-like response in postsynaptic neurons mediated by type I mGluR activation [52]. Similar to a study of the rat barrel cortex mentioned earlier [20], cholinergic input stimulates astrocytic release of glutamate and LTP *in vivo* [51].

Astrocytic glutamate has also been implicated in LTD [90, 135]. Han et al. [90] recently demonstrated that exogenous cannabinoid application induces astrocytic release of glutamate, postsynaptic NMDAR activation, postsynaptic AMPAR endocytosis and LTD *in vivo*.

Arguably there is one astrocytic attribute that is most relevant to information processing and synaptic plasticity: timescale. Astrocytic activation and output is several orders of magnitude slower than that of neuronal signalling, as emphasised above. LTP in neurons often requires repeated presentation of fast millisecond stimuli over several minutes [147]. Thus astrocytes may be involved in the processing of synaptic activity patterns over several stimuli presentations. Indeed, Min and Nevian [148] have recently demonstrated that astrocytes gradually increase their Ca^{2+} oscillation frequency during the induction of LTD. This increased frequency was due to an accumulation of endocannabinoid synthesis by the postsynaptic cell during repeated pairings [148]. It was suggested that the astrocyte may release a retrograde glutamate signal when a threshold astrocytic activity had been reached thus inducing LTD [148]. However, the exact characteristics of these thresholds remain to be determined.

3.3 - CONTROVERSY

The impact of astrocytes on LTSP still remains somewhat controversial, as loading astrocytes with Ca^{2+} chelators has been shown not to impair LTP [149, 150]. This directly contradicts the work of Henneberger and colleagues [66] who showed that clamping of internal astrocyte Ca^{2+} blocks LTP at Sc terminals. It has been argued that Ca^{2+} clamping is a more efficient way of inhibiting Ca^{2+} microdomains [66]. Finally, it is worth noting that the presence of an astrocytic Ca^{2+} response alone is not sufficient for long term plasticity. In a study using transgenic mice to increase and obliterate astrocytic Gq GPCR signalling, no significant change in LTP was observed in either condition [151]. Thus it may be proposed that whilst astrocytic activity is required for long term plasticity it is not sufficient to induce it alone.

3.4 - SYNAPTIC COVERAGE

Synaptic coverage is the amount that the astrocyte processes cover the synapse. Different brain regions show variations in synaptic coverage (e.g. in rodents hippocampus 57% [152, 153], cortex

29% [153]). Synaptic coverage is likely to be important for two reasons. Firstly, approximately 80% of glutamate [6] is removed from the synaptic cleft by astrocytes. Thus variations in the amount of synaptic coverage can affect the neurotransmitter clearance from the synaptic cleft and therefore duration of action of a presynaptic neuron. Secondly, any gliotransmitters released by astrocytes will be less effective. In particular, a reduction in glutamate and D-serine may impair plasticity. Furthermore, astrocyte derived peptides such as BDNF, GDNF and TNF α are thought to be necessary for synaptogenesis and plasticity [122, 154].

A dramatic example of physiologically reduced synaptic coverage occurs in the hypothalamus during lactation, parturition and chronic dehydration. Reduced coverage of hypothalamic synapses is associated with reduced clearance and increased release probability of glutamatergic synapses [155]. Increased release probability is likely to be due to activation of presynaptic receptors from spill-over glutamate [155]. The astrocytic cytoskeleton can undergo rapid remodelling which may be regulated by synaptic activity and spine dynamics [128]. A study involving the induction of LTP *in vivo* in the hippocampus has confirmed the induction of plastic changes in astrocyte ramifications [156]. However, more research is required to determine what triggers astrocytic plasticity. When does astrocytic plasticity occur as opposed to neuronal plasticity? A possible function for astrocytic morphological plasticity is that process retraction is likely to cause higher synaptic activity but lower probability of LTP and LTD due to the lack of D-serine.

4 - COMPUTATIONAL MODELS

There has been a growth in biophysical models of astrocytes over the last decade. Such as the modelling of fault tolerance of astrocytic retrograde signals [157], non-linear intercellular diffusion of IP3 via gap junctions [158, 159] and intercellular ATP signalling [74]. Nadkarni et al. [160] created a model which suggests that astrocytes may optimize the synaptic transmission of information by regulating presynaptic release probability. Another study modelled how astrocytes are able to modulate STSP [161]. Whilst biophysical models help our understanding of the intrinsic properties of astrocytes they do not provide a mathematically viable theory for how astrocytes may form functional elements of a learning network. An additional criticism is that many of these models use generic models, such as the Li-Rinzel model [162], for Ca²⁺ modelling which does not incorporate the complex microdomain dynamics of astrocytes.

Instead, when addressing the learning potential of astrocytes in a neuron-astrocyte network, such biochemically-concerned models are not necessary and more abstract models can be used. One group has used such a model. [163, 164] The Porto-Pazos model (PP) [163, 164] is a multilayer feed forward artificial neuronal network, astrocytes were incorporated to create a biphasic learning algorithm. The learning algorithm consisted of a generic supervised genetic algorithm (for comprehensive explanation see [165]) and an unsupervised "neuroglial" algorithm. The neuroglial algorithm consisted of astrocytes processing neuronal activity over several synaptic events. Persistently active neurons caused threshold in astrocytes and modification of all synaptic weights in the astrocytic domain equally. For full details of the neuroglial algorithm see [section 6.4](#). The results of

PP show that the addition of astrocytes improved the learning ability of the network. Addition of more neuronal elements could not outperform the neuron-astrocyte network. The increased performance depended critically on the timescale of astrocyte properties. Both time for activation of astrocytes and astrocytic output were considerably longer than neuronal properties.[163, 164] This model has promising prospects for the understanding of learning and the computational functions of the brain. Although this model has some limitations: (i) astrocytes do not have synaptic weight attributes (ii) astrocytes do not communicate with each other (iii) the architecture of the model does not allow for a supralinear increase in astrocytes with respect to neuronal number as seen in phylogeny.

5 – CONCLUDING REMARKS

Astrocytes are excitable cells which represent their excitability as a complex Ca^{2+} response. These Ca^{2+} responses can be built from the independent processing of individual synapses. Processing of synaptic inputs in astrocytes is a slow process compared to neurons. Output of astrocytes is similarly slow and can influence both neurons and other astrocytes. Astrocytes have been implicated in synaptic plasticity and are able gate the induction of LTP and LTD. Therefore, the evidence gathered since the early 1990s challenges the widely accepted neuronal paradigm. Current theories for the cellular basis of learning and memory are required to undergo a shift. Indeed, much of neuroscience concerned with humans is ignoring over 50% of the brain and may find that considering astrocytic activity may provide insight into unsolved questions. Unanswered questions about astrocytic functioning include: How independent are microdomains? How independent are processes? What is the function of spontaneous Ca^{2+} events? What thresholds the transition of a local microdomain response to a whole-cell response? How do astrocytes summate the activity of their independent microdomains and processes? What are the functions of intercellular Ca^{2+} waves with respect to information processing? When do astrocytic gap junctions and synaptic weights undergo plasticity? But above all how do astrocytes intercalate with neural networks as functional memory elements in learning? To answer these questions will require a combination of modern experimental techniques and validation of theories using advanced computational modelling. Also it is worth mentioning that there is a need for new technology capable of co-recording neuronal and astrocytic separately and non-invasively on a full brain scale. Such technology will aid in the understanding of how astrocytes and neurons collaborate to perform human cognition.

6 – RESEARCH PROJECT

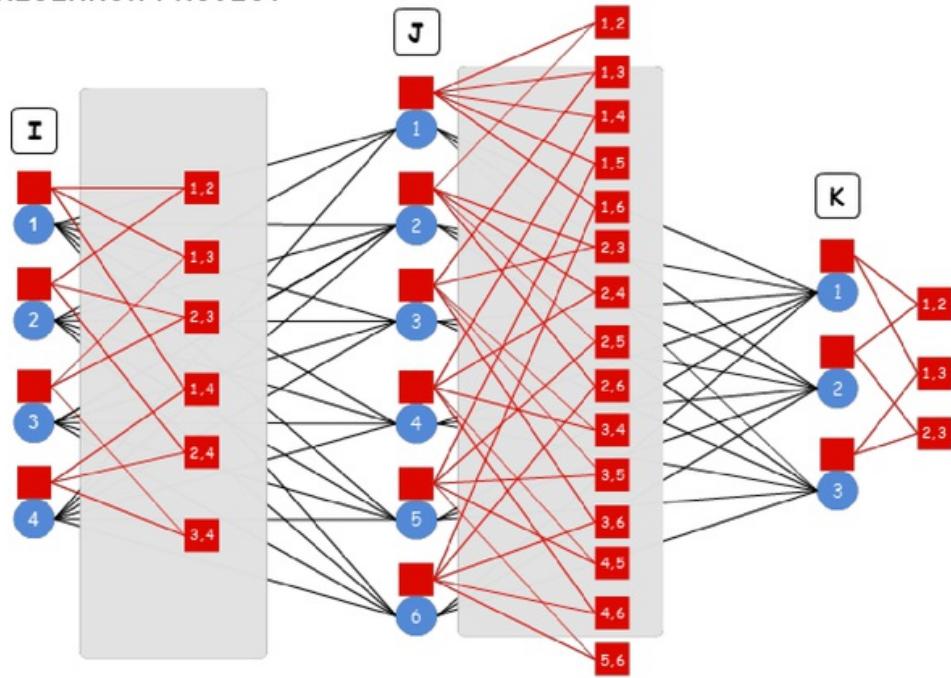


Fig. 4 Schematic representation of proposed model. Blue circles represent neurons. Red squares above neurons represent neuron associated astrocytes (NAAs). Superficial layer of red squares represents astrocyte associated astrocytes, where numbers represent the NAA pair monitored. I represents the input layer, J represents the hidden layer and K represents the output layer.

6.1 – AIM

Invent and implement a novel learning algorithm to provide a mathematically and biologically valid model of learning in an artificial neuron-astrocyte network. Hopefully, this work will encourage research into the computational and learning potential of astrocytes and ultimately a deeper understanding of human cognition.

6.2 – HYPOTHESES

Expected to reject null hypotheses 1-3:

1. Compared to PP and a generic artificial neural network, the prospective model:
 - a) Will not have a significantly faster learning rate.
 - b) Will not be significantly more accurate at classifying training data at end of training.
 - c) Will not be significantly more accurate at classifying test data at end of training.
 - d) Will not be significantly more accurate at classifying more complex data (i.e. more input features).
2. Increasing the number of hidden layers will not significantly improve the learning capacity of the model.
3. Increasing the number of neurons in each hidden layer will not significantly improve the learning capacity of the model.

6.3 – PROJECT MOTIVATION

As discussed above, our fundamental understanding of brain function at a cellular level is changing and we require a new theory of learning, memory and cognition to describe the involvement of astrocytes. Computational models offer mathematical validation to new theories. The prospective model (Fig. 4) improves upon PP [163] by introducing parallel interastrocytic communication and allows for supralinear increase of astrocyte number as neuron number increases.

6.4 – ALGORITHM AND IMPLEMENTATION DETAILS

For clarity I will define grand and minor iterations. A single grand iteration is the execution of phase 1 and phase 2 once, which involves processing of all input patterns. A single minor iteration is the forward pass of a single input pattern once through the neuron-astrocyte algorithm.

Before describing how PP [163] will be progressed by the prospective model, I will briefly describe the PP algorithm. Each neuron has a neuron associated astrocyte (NAA), red squares adjacent to blue neurons in Fig 4, which monitors the neuron's activation over several minor iterations. If the neuron is persistently activated for n out of m minor iterations, the NAA is activated, called positive activation. Over the next α iterations the neuron's weights are increased at a rate of 25% per iteration. Equally, persistent neuronal inactivation results in negative activation and weight reduction of 50% per minor iteration. For the inquisitive reader, a supplementary pseudocode-schematic of PP can be found in [166]. Like PP [163], the prospective algorithm will be biphasic. However, phase 1 will consist of a more biologically plausible supervised Hebbian algorithm [167] and phase 2 will be an unsupervised neuron-astrocyte algorithm, which will now be described in more detail.

The prospective model includes the addition of a superficial layer of astrocyte associated astrocytes (AAAs) (Fig 3) which monitor and influence the activity of NAAs. Each AAA monitors a pair of NAAs. If the pair of NAAs match for positive activation or negative activation the AAA's activity counter is incremented. If the pair of NAAs do not match the AAA's activity is decremented. If the AAA's activation reaches positive-threshold an association is formed between the pair of NAAs. Over the subsequent β minor-iterations, activation of either NAA leads to higher probability of activation of the other NAA. In the case of reaching negative-threshold, a negative association is formed between the pair. Over the subsequent β iterations, activation of either NAA leads to a reduced probability of activation of the other NAA.

6.5 – SEMESTER 6 MILESTONES

Week 2 – PP is recreated and working at efficiency of published model.

Week 4 – Prospective model is implemented.

Week 6 – Prospective model is debugged and producing graphed results.

Week 8 – Project written.

7 - REFERENCES

1. Gold, I. and D. Stoljar, *A neuron doctrine in the philosophy of neuroscience*. Behav Brain Sci, 1999. **22**(5): p. 809-30; discussion 831-69.
2. Lopez-Munoz, F., J. Boya, and C. Alamo, *Neuron theory, the cornerstone of neuroscience, on the centenary of the Nobel Prize award to Santiago Ramon y Cajal*. Brain Res Bull, 2006. **70**(4-6): p. 391-405.
3. Feldman, D.E., *The spike-timing dependence of plasticity*. Neuron, 2012. **75**(4): p. 556-71.
4. Araque, A., et al., *Tripartite synapses: glia, the unacknowledged partner*. Trends Neurosci, 1999. **22**(5): p. 208-15.
5. Sherwood, C.C., et al., *Evolution of increased glia-neuron ratios in the human frontal cortex*. Proc Natl Acad Sci U S A, 2006. **103**(37): p. 13606-11.
6. Verkhratsky A, B.A., *Glial neurobiology*. 2007. John Wiley & Sons, Ltd. Chichester, West Sussex. p. 93-121
7. Oberheim, N.A., et al., *Astrocytic complexity distinguishes the human brain*. Trends Neurosci, 2006. **29**(10): p. 547-53.
8. Leuba, G. and L.J. Garey, *Comparison of neuronal and glial numerical density in primary and secondary visual cortex of man*. Exp Brain Res, 1989. **77**(1): p. 31-8.
9. Oberheim, N.A., et al., *Uniquely hominid features of adult human astrocytes*. J Neurosci, 2009. **29**(10): p. 3276-87.
10. Cornell-Bell, A.H., et al., *Glutamate induces Ca^{2+} waves in cultured astrocytes: long-range glial signaling*. Science, 1990. **247**(4941): p. 470-3.
11. Dani, J.W., A. Chernjavsky, and S.J. Smith, *Neuronal activity triggers Ca^{2+} waves in hippocampal astrocyte networks*. Neuron, 1992. **8**(3): p. 429-40.
12. Schummers, J., H. Yu, and M. Sur, *Tuned responses of astrocytes and their influence on hemodynamic signals in the visual cortex*. Science, 2008. **320**(5883): p. 1638-43.
13. Wang, X., et al., *Astrocytic Ca^{2+} signaling evoked by sensory stimulation in vivo*. Nat Neurosci, 2006. **9**(6): p. 816-23.
14. Bushong, E.A., et al., *Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains*. J Neurosci, 2002. **22**(1): p. 183-92.
15. Sulston, J.E., et al., *The embryonic cell lineage of the nematode *Caenorhabditis elegans**. Dev Biol, 1983. **100**(1): p. 64-119.
16. Bass, N.H., et al., *Quantitative cytoarchitectonic distribution of neurons, glia, and DNA in rat cerebral cortex*. J Comp Neurol, 1971. **143**(4): p. 481-90.
17. Nedergaard, M., B. Ransom, and S.A. Goldman, *New roles for astrocytes: redefining the functional architecture of the brain*. Trends Neurosci, 2003. **26**(10): p. 523-30.
18. Hirase, H., et al., *Ca^{2+} dynamics of cortical astrocytic networks in vivo*. PLoS Biol, 2004. **2**(4): p. E96.
19. Wang, X., et al., *Astrocytic Ca^{2+} signaling evoked by sensory stimulation in vivo*. Nat Neurosci, 2006. **9**(6): p. 816-23.
20. Takata, N., et al., *Astrocyte Ca^{2+} signaling transforms cholinergic modulation to cortical plasticity in vivo*. J Neurosci, 2011. **31**(49): p. 18155-65.
21. Panatier, A., et al., *Astrocytes are endogenous regulators of basal transmission at central synapses*. Cell, 2011. **146**(5): p. 785-98.
22. Ben Achour, S., et al., *Is astrocyte Ca^{2+} signaling relevant for synaptic plasticity?* Neuron Glia Biol, 2010: p. 1-9.
23. Bekar, L.K., W. He, and M. Nedergaard, *Locus coeruleus alpha-adrenergic-mediated activation of cortical astrocytes in vivo*. Cereb Cortex, 2008. **18**(12): p. 2789-95.
24. Porter, J.T. and K.D. McCarthy, *Astrocytic neurotransmitter receptors in situ and in vivo*. Prog Neurobiol, 1997. **51**(4): p. 439-55.
25. Kimelberg, H.K., *Receptors on astrocytes--what possible functions?* Neurochem Int, 1995. **26**(1): p. 27-40.

26. Ben Achour, S. and O. Pascual, *Glia: the many ways to modulate synaptic plasticity*. Neurochem Int, 2010. **57**(4): p. 440-5.
27. Verkhratsky, A. and C. Steinhauser, *Ion channels in glial cells*. Brain Res Brain Res Rev, 2000. **32**(2-3): p. 380-412.
28. Zorec, R., et al., *Astroglial excitability and gliotransmission: an appraisal of Ca²⁺ as a signalling route*. ASN Neuro, 2012. **4**(2).
29. Carmignoto, G., *Reciprocal communication systems between astrocytes and neurones*. Prog Neurobiol, 2000. **62**(6): p. 561-81.
30. Perea, G. and A. Araque, *Synaptic information processing by astrocytes*. J Physiol Paris, 2006. **99**(2-3): p. 92-7.
31. Fiacco, T.A. and K.D. McCarthy, *Intracellular astrocyte Ca²⁺ waves in situ increase the frequency of spontaneous AMPA receptor currents in CA1 pyramidal neurons*. J Neurosci, 2004. **24**(3): p. 722-32.
32. Kostyuk, P. and A. Verkhratsky, *Ca²⁺ stores in neurons and glia*. Neuroscience, 1994. **63**(2): p. 381-404.
33. Bezzi, P., et al., *Prostaglandins stimulate Ca²⁺-dependent glutamate release in astrocytes*. Nature, 1998. **391**(6664): p. 281-5.
34. Zhang, J.M., et al., *ATP released by astrocytes mediates glutamatergic activity-dependent heterosynaptic suppression*. Neuron, 2003. **40**(5): p. 971-82.
35. Ye, Z.C., et al., *Functional hemichannels in astrocytes: a novel mechanism of glutamate release*. J Neurosci, 2003. **23**(9): p. 3588-96.
36. Zhang, Q., et al., *Fusion-related release of glutamate from astrocytes*. J Biol Chem, 2004. **279**(13): p. 12724-33.
37. Jourdain, P., et al., *Glutamate exocytosis from astrocytes controls synaptic strength*. Nat Neurosci, 2007. **10**(3): p. 331-9.
38. Parpura, V., et al., *Glutamate-mediated astrocyte-neuron signalling*. Nature, 1994. **369**(6483): p. 744-7.
39. Pasti, L., T. Pozzan, and G. Carmignoto, *Long-lasting changes of Ca²⁺ oscillations in astrocytes. A new form of glutamate-mediated plasticity*. J Biol Chem, 1995. **270**(25): p. 15203-10.
40. Sershen, H., *Astrocyte origin of activity-dependent release of ATP and glutamate in hippocampal slices: real-time measurement utilizing microelectrode biosensors*. Br J Pharmacol, 2012. **167**(5): p. 1000-2.
41. Parfenova, H., et al., *Functional role of astrocyte glutamate receptors and carbon monoxide in cerebral vasodilation response to glutamate*. Am J Physiol Heart Circ Physiol, 2012. **302**(11): p. H2257-66.
42. Padmashri, R. and S.K. Sikdar, *Glutamate pretreatment affects Ca²⁺ signaling in processes of astrocyte pairs*. J Neurochem, 2007. **100**(1): p. 105-17.
43. Schummers, J., H. Yu, and M. Sur, *Tuned responses of astrocytes and their influence on hemodynamic signals in the visual cortex*. Science, 2008. **320**(5883): p. 1638-43.
44. Perea, G. and A. Araque, *Properties of synaptically evoked astrocyte Ca²⁺ signal reveal synaptic information processing by astrocytes*. J Neurosci, 2005. **25**(9): p. 2192-203.
45. Araque, A., et al., *Glutamate-dependent astrocyte modulation of synaptic transmission between cultured hippocampal neurons*. Eur J Neurosci, 1998. **10**(6): p. 2129-42.
46. Angulo, M.C., et al., *Glutamate released from glial cells synchronizes neuronal activity in the hippocampus*. J Neurosci, 2004. **24**(31): p. 6920-7.
47. Fellin, T., et al., *Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors*. Neuron, 2004. **43**(5): p. 729-43.
48. Navarrete, M. and A. Araque, *Endocannabinoids mediate neuron-astrocyte communication*. Neuron, 2008. **57**(6): p. 883-93.

49. Shigetomi, E., et al., *Two forms of astrocyte Ca^{2+} excitability have distinct effects on NMDA receptor-mediated slow inward currents in pyramidal neurons*. J Neurosci, 2008. **28**(26): p. 6659-63.
50. Liu, Q.S., et al., *Astrocyte-mediated activation of neuronal kainate receptors*. Proc Natl Acad Sci U S A, 2004. **101**(9): p. 3172-7.
51. Navarrete, M., et al., *Astrocytes mediate in vivo cholinergic-induced synaptic plasticity*. PLoS Biol, 2012. **10**(2): p. e1001259.
52. Perea, G. and A. Araque, *Astrocytes potentiate transmitter release at single hippocampal synapses*. Science, 2007. **317**(5841): p. 1083-6.
53. Angulo, M.C., et al., *Glutamate released from glial cells synchronizes neuronal activity in the hippocampus*. J Neurosci, 2004. **24**(31): p. 6920-7.
54. Bardoni, R., et al., *Glutamate-mediated astrocyte-to-neuron signalling in the rat dorsal horn*. J Physiol, 2010. **588**(Pt 5): p. 831-46.
55. Le Meur, K., et al., *GABA release by hippocampal astrocytes*. Front Comput Neurosci, 2012. **6**: p. 59.
56. Yoon, B.E., J. Woo, and C. Justin Lee, *Astrocytes as GABA-ergic and GABA-ceptive Cells*. Neurochem Res, 2012. **37**(11): p. 2474-9.
57. Molnar, T., et al., *gamma-Hydroxybutyrate (GHB) induces GABA(B) receptor independent intracellular Ca^{2+} transients in astrocytes, but has no effect on GHB or GABA(B) receptors of medium spiny neurons in the nucleus accumbens*. Neuroscience, 2009. **162**(2): p. 268-81.
58. Desrues, L., et al., *Effect of GABA A receptor activation on UT-coupled signaling pathways in rat cortical astrocytes*. Peptides, 2008. **29**(5): p. 727-34.
59. MacVicar, B.A., et al., *GABA-activated Cl^- channels in astrocytes of hippocampal slices*. J Neurosci, 1989. **9**(10): p. 3577-83.
60. Kang, J., et al., *Astrocyte-mediated potentiation of inhibitory synaptic transmission*. Nat Neurosci, 1998. **1**(8): p. 683-92.
61. Serrano, A., et al., *GABAergic network activation of glial cells underlies hippocampal heterosynaptic depression*. J Neurosci, 2006. **26**(20): p. 5370-82.
62. Gallo, V., M. Patrizio, and G. Levi, *GABA release triggered by the activation of neuron-like non-NMDA receptors in cultured type 2 astrocytes is carrier-mediated*. Glia, 1991. **4**(3): p. 245-55.
63. Panatier, A., et al., *Glia-derived D-serine controls NMDA receptor activity and synaptic memory*. Cell, 2006. **125**(4): p. 775-84.
64. Fossat, P., et al., *Glial D-serine gates NMDA receptors at excitatory synapses in prefrontal cortex*. Cereb Cortex, 2012. **22**(3): p. 595-606.
65. Mothet, J.P., et al., *Glutamate receptor activation triggers a Ca^{2+} -dependent and SNARE protein-dependent release of the gliotransmitter D-serine*. Proc Natl Acad Sci U S A, 2005. **102**(15): p. 5606-11.
66. Henneberger, C., et al., *Long-term potentiation depends on release of D-serine from astrocytes*. Nature, 2010. **463**(7278): p. 232-6.
67. Schell, M.J., M.E. Molliver, and S.H. Snyder, *D-serine, an endogenous synaptic modulator: localization to astrocytes and glutamate-stimulated release*. Proc Natl Acad Sci U S A, 1995. **92**(9): p. 3948-52.
68. Panatier, A., et al., *Glia-derived D-serine controls NMDA receptor activity and synaptic memory*. Cell, 2006. **125**(4): p. 775-84.
69. Wolosker, H., S. Blackshaw, and S.H. Snyder, *Serine racemase: a glial enzyme synthesizing D-serine to regulate glutamate-N-methyl-D-aspartate neurotransmission*. Proc Natl Acad Sci U S A, 1999. **96**(23): p. 13409-14.
70. Wolosker, H., S. Blackshaw, and S.H. Snyder, *Serine racemase: a glial enzyme synthesizing D-serine to regulate glutamate-N-methyl-D-aspartate neurotransmission*. Proc Natl Acad Sci U S A, 1999. **96**(23): p. 13409-14.

71. Ding, S., *In vivo imaging of Ca(2)(+)* signaling in astrocytes using two-photon laser scanning fluorescent microscopy. *Methods Mol Biol*, 2012. **814**: p. 545-54.
72. Bowser, D.N. and B.S. Khakh, *Vesicular ATP is the predominant cause of intercellular Ca²⁺ waves in astrocytes*. *J Gen Physiol*, 2007. **129**(6): p. 485-91.
73. Guthrie, P.B., et al., *ATP released from astrocytes mediates glial Ca²⁺ waves*. *J Neurosci*, 1999. **19**(2): p. 520-8.
74. Macdonald, C.L., et al., *Diffusion modeling of ATP signaling suggests a partially regenerative mechanism underlies astrocyte intercellular Ca²⁺ waves*. *Front Neuroeng*, 2008. **1**: p. 1.
75. Araque, A., et al., *Synaptically released acetylcholine evokes Ca²⁺ elevations in astrocytes in hippocampal slices*. *J Neurosci*, 2002. **22**(7): p. 2443-50.
76. Shelton, M.K. and K.D. McCarthy, *Hippocampal astrocytes exhibit Ca²⁺-elevating muscarinic cholinergic and histaminergic receptors in situ*. *J Neurochem*, 2000. **74**(2): p. 555-63.
77. Sharma, G. and S. Vijayaraghavan, *Nicotinic cholinergic signaling in hippocampal astrocytes involves Ca²⁺-induced Ca²⁺ release from intracellular stores*. *Proc Natl Acad Sci U S A*, 2001. **98**(7): p. 4148-53.
78. Wessler, I., et al., *Mammalian glial cells in culture synthesize acetylcholine*. *Naunyn Schmiedebergs Arch Pharmacol*, 1997. **356**(5): p. 694-7.
79. Vaarmann, A., S. Gandhi, and A.Y. Abramov, *Dopamine induces Ca²⁺ signaling in astrocytes through reactive oxygen species generated by monoamine oxidase*. *J Biol Chem*, 2010. **285**(32): p. 25018-23.
80. Liu, J., et al., *Activation of phosphatidylinositol-linked novel D1 dopamine receptor contributes to the Ca²⁺ mobilization in cultured rat prefrontal cortical astrocytes*. *Cell Mol Neurobiol*, 2009. **29**(3): p. 317-28.
81. Bekar, L.K., W. He, and M. Nedergaard, *Locus coeruleus alpha-adrenergic-mediated activation of cortical astrocytes in vivo*. *Cereb Cortex*, 2008. **18**(12): p. 2789-95.
82. Bal-Price, A., Z. Moneer, and G.C. Brown, *Nitric oxide induces rapid, Ca²⁺-dependent release of vesicular glutamate and ATP from cultured rat astrocytes*. *Glia*, 2002. **40**(3): p. 312-23.
83. Yamagata, K., M. Tagami, and Y. Yamori, *Nitric oxide reduces astrocytic lactate production and induces neuronal vulnerability in stroke-prone spontaneously hypertensive rats*. *Glia*, 2008. **56**(4): p. 387-93.
84. Schipke, C.G., et al., *Temperature and nitric oxide control spontaneous Ca²⁺ transients in astrocytes*. *Cell Ca²⁺*, 2008. **43**(3): p. 285-95.
85. Murphy, S., *Production of nitric oxide by glial cells: regulation and potential roles in the CNS*. *Glia*, 2000. **29**(1): p. 1-13.
86. Ikeda, H. and K. Murase, *Glial nitric oxide-mediated long-term presynaptic facilitation revealed by optical imaging in rat spinal dorsal horn*. *J Neurosci*, 2004. **24**(44): p. 9888-96.
87. Mehta, B., et al., *Nitric oxide-mediated modulation of synaptic activity by astrocytic P2Y receptors*. *J Gen Physiol*, 2008. **132**(3): p. 339-49.
88. Zhuo, M., et al., *Nitric oxide and carbon monoxide produce activity-dependent long-term synaptic enhancement in hippocampus*. *Science*, 1993. **260**(5116): p. 1946-50.
89. Beattie, E.C., et al., *Control of synaptic strength by glial TNFalpha*. *Science*, 2002. **295**(5563): p. 2282-5.
90. Han, J., et al., *Acute cannabinoids impair working memory through astroglial CB1 receptor modulation of hippocampal LTD*. *Cell*, 2012. **148**(5): p. 1039-50.
91. Navarrete, M. and A. Araque, *Endocannabinoids potentiate synaptic transmission through stimulation of astrocytes*. *Neuron*, 2010. **68**(1): p. 113-26.
92. Navarrete, M. and A. Araque, *Endocannabinoids mediate neuron-astrocyte communication*. *Neuron*, 2008. **57**(6): p. 883-93.
93. Grosche, J., et al., *Microdomains for neuron-glia interaction: parallel fiber signaling to Bergmann glial cells*. *Nat Neurosci*, 1999. **2**(2): p. 139-43.

94. Di Castro, M.A., et al., *Local Ca²⁺ detection and modulation of synaptic release by astrocytes*. Nat Neurosci, 2011. **14**(10): p. 1276-84.
95. Di Castro, M.A., et al., *Local Ca²⁺ detection and modulation of synaptic release by astrocytes*, in *Nat Neurosci*. 2011. p. 1276-84.
96. Scemes, E. and C. Giaume, *Astrocyte Ca²⁺ waves: what they are and what they do*. Glia, 2006. **54**(7): p. 716-25.
97. D'Ascenzo, M., et al., *mGluR5 stimulates gliotransmission in the nucleus accumbens*. Proc Natl Acad Sci U S A, 2007. **104**(6): p. 1995-2000.
98. Pasti, L., et al., *Intracellular Ca²⁺ oscillations in astrocytes: a highly plastic, bidirectional form of communication between neurons and astrocytes in situ*. J Neurosci, 1997. **17**(20): p. 7817-30.
99. Araque, A., et al., *Synaptically released acetylcholine evokes Ca²⁺ elevations in astrocytes in hippocampal slices*. J Neurosci, 2002. **22**(7): p. 2443-50.
100. Perea, G. and A. Araque, *Properties of synaptically evoked astrocyte Ca²⁺ signal reveal synaptic information processing by astrocytes*. J Neurosci, 2005. **25**(9): p. 2192-203.
101. Min, R., M. Santello, and T. Nevanian, *The computational power of astrocyte mediated synaptic plasticity*. Front Comput Neurosci, 2012. **6**: p. 93.
102. Purves D, A.G., Fitzpatrick D, et al., *Neuroscience. 2nd edition: Increased Conduction Velocity as a Result of Myelination*, ed. S.M.S. Associates. 2001.
103. Parri, H.R. and V. Crunelli, *Astrocytes, spontaneity, and the developing thalamus*. J Physiol Paris, 2002. **96**(3-4): p. 221-30.
104. Schipke, C.G., B. Haas, and H. Kettenmann, *Astrocytes discriminate and selectively respond to the activity of a subpopulation of neurons within the barrel cortex*. Cereb Cortex, 2008. **18**(10): p. 2450-9.
105. Shigetomi, E., et al., *Two forms of astrocyte Ca²⁺ excitability have distinct effects on NMDA receptor-mediated slow inward currents in pyramidal neurons*. J Neurosci, 2008. **28**(26): p. 6659-63.
106. Giaume, C. and L. Venance, *Intercellular Ca²⁺ signaling and gap junctional communication in astrocytes*. Glia, 1998. **24**(1): p. 50-64.
107. Bennett, M.V., et al., *New roles for astrocytes: gap junction hemichannels have something to communicate*. Trends Neurosci, 2003. **26**(11): p. 610-7.
108. Saez, J.C., et al., *Connexin-based gap junction hemichannels: gating mechanisms*. Biochim Biophys Acta, 2005. **1711**(2): p. 215-24.
109. Sosinsky, G.E. and B.J. Nicholson, *Structural organization of gap junction channels*. Biochim Biophys Acta, 2005. **1711**(2): p. 99-125.
110. Allbritton, N.L., T. Meyer, and L. Stryer, *Range of messenger action of Ca²⁺ ion and inositol 1,4,5-trisphosphate*. Science, 1992. **258**(5089): p. 1812-5.
111. Matyash, V., et al., *Nitric oxide signals parallel fiber activity to Bergmann glial cells in the mouse cerebellar slice*. Mol Cell Neurosci, 2001. **18**(6): p. 664-70.
112. Sasaki, T., et al., *Locally synchronized astrocytes*. Cereb Cortex, 2011. **21**(8): p. 1889-900.
113. Hoogland, T.M., et al., *Radially expanding transglial Ca²⁺ waves in the intact cerebellum*. Proc Natl Acad Sci U S A, 2009. **106**(9): p. 3496-501.
114. Kuga, N., et al., *Large-scale Ca²⁺ waves traveling through astrocytic networks in vivo*. J Neurosci, 2011. **31**(7): p. 2607-14.
115. Dermietzel, R., *Gap junction wiring: a 'new' principle in cell-to-cell communication in the nervous system?* Brain Res Brain Res Rev, 1998. **26**(2-3): p. 176-83.
116. Nedergaard, M., *Direct signaling from astrocytes to neurons in cultures of mammalian brain cells*. Science, 1994. **263**(5154): p. 1768-71.
117. Alvarez-Maubecin, V., et al., *Functional coupling between neurons and glia*. J Neurosci, 2000. **20**(11): p. 4091-8.

118. Wang, F., et al., *Astrocytes modulate neural network activity by Ca(2+)-dependent uptake of extracellular K⁺*. Sci Signal, 2012. **5**(218): p. ra26.
119. Hassanpoor, H., A. Fallah, and M. Raza, *New role for astroglia in learning: Formation of muscle memory*. Med Hypotheses, 2012.
120. Perea, G., M. Navarrete, and A. Araque, *Tripartite synapses: astrocytes process and control synaptic information*. Trends Neurosci, 2009. **32**(8): p. 421-31.
121. Hamilton, N.B. and D. Attwell, *Do astrocytes really exocytose neurotransmitters?* Nat Rev Neurosci, 2010. **11**(4): p. 227-38.
122. Diniz, L.P., et al., *Astrocyte-induced synaptogenesis is mediated by transforming growth factor beta signaling through modulation of D-serine levels in cerebral cortex neurons*. J Biol Chem, 2012.
123. Parpura, V. and P.G. Haydon, *Physiological astrocytic Ca²⁺ levels stimulate glutamate release to modulate adjacent neurons*. Proc Natl Acad Sci U S A, 2000. **97**(15): p. 8629-34.
124. Kimelberg, H.K., et al., *Swelling-induced release of glutamate, aspartate, and taurine from astrocyte cultures*. J Neurosci, 1990. **10**(5): p. 1583-91.
125. O'Connor, E.R. and H.K. Kimelberg, *Role of Ca²⁺ in astrocyte volume regulation and in the release of ions and amino acids*. J Neurosci, 1993. **13**(6): p. 2638-50.
126. Malarkey, E.B. and V. Parpura, *Mechanisms of glutamate release from astrocytes*. Neurochem Int, 2008. **52**(1-2): p. 142-54.
127. Parri, H.R., T.M. Gould, and V. Crunelli, *Spontaneous astrocytic Ca²⁺ oscillations in situ drive NMDAR-mediated neuronal excitation*. Nat Neurosci, 2001. **4**(8): p. 803-12.
128. Ben Achour, S. and O. Pascual, *Glia: the many ways to modulate synaptic plasticity*. Neurochem Int, 2010. **57**(4): p. 440-5.
129. Fellin, T., et al., *Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors*. Neuron, 2004. **43**(5): p. 729-43.
130. Sasaki, T., N. Matsuki, and Y. Ikegaya, *Action-potential modulation during axonal conduction*. Science, 2011. **331**(6017): p. 599-601.
131. Pascual, O., et al., *Astrocytic purinergic signaling coordinates synaptic networks*. Science, 2005. **310**(5745): p. 113-6.
132. Molnar, E., *Long-term potentiation in cultured hippocampal neurons*. Semin Cell Dev Biol, 2011. **22**(5): p. 506-13.
133. Zhang, J.M., et al., *ATP released by astrocytes mediates glutamatergic activity-dependent heterosynaptic suppression*. Neuron, 2003. **40**(5): p. 971-82.
134. Pascual, O., et al., *Astrocytic purinergic signaling coordinates synaptic networks*. Science, 2005. **310**(5745): p. 113-6.
135. Liu, Q.S., et al., *Astrocyte activation of presynaptic metabotropic glutamate receptors modulates hippocampal inhibitory synaptic transmission*. Neuron Glia Biol, 2004. **1**(4): p. 307-16.
136. Evans, W.H., E. De Vuyst, and L. Leybaert, *The gap junction cellular internet: connexin hemichannels enter the signalling limelight*. Biochem J, 2006. **397**(1): p. 1-14.
137. Newman, L.A., D.L. Korol, and P.E. Gold, *Lactate produced by glycogenolysis in astrocytes regulates memory processing*. PLoS One, 2011. **6**(12): p. e28427.
138. Suzuki, A., et al., *Astrocyte-neuron lactate transport is required for long-term memory formation*. Cell, 2011. **144**(5): p. 810-23.
139. Rison, R.A. and P.K. Stanton, *Long-term potentiation and N-methyl-D-aspartate receptors: foundations of memory and neurologic disease?* Neurosci Biobehav Rev, 1995. **19**(4): p. 533-52.
140. Mothet, J.P., et al., *D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor*. Proc Natl Acad Sci U S A, 2000. **97**(9): p. 4926-31.
141. Yang, Y., et al., *Contribution of astrocytes to hippocampal long-term potentiation through release of D-serine*. Proc Natl Acad Sci U S A, 2003. **100**(25): p. 15194-9.

142. Zhang, Z., et al., *Bell-shaped D-serine actions on hippocampal long-term depression and spatial memory retrieval*. Cereb Cortex, 2008. **18**(10): p. 2391-401.
143. Kakegawa, W., et al., *D-serine regulates cerebellar LTD and motor coordination through the delta2 glutamate receptor*. Nat Neurosci, 2011. **14**(5): p. 603-11.
144. Abraham, W.C. and M.F. Bear, *Metaplasticity: the plasticity of synaptic plasticity*. Trends Neurosci, 1996. **19**(4): p. 126-30.
145. Sasaki, T., et al., *Locally synchronized astrocytes*. Cereb Cortex, 2011. **21**(8): p. 1889-900.
146. D'Ascenzo, M., et al., *mGluR5 stimulates gliotransmission in the nucleus accumbens*. Proc Natl Acad Sci U S A, 2007. **104**(6): p. 1995-2000.
147. O'Connor, D.H., G.M. Wittenberg, and S.S. Wang, *Graded bidirectional synaptic plasticity is composed of switch-like unitary events*. Proc Natl Acad Sci U S A, 2005. **102**(27): p. 9679-84.
148. Min, R. and T. Nevan, *Astrocyte signaling controls spike timing-dependent depression at neocortical synapses*. Nat Neurosci, 2012. **15**(5): p. 746-53.
149. Diamond, J.S., D.E. Bergles, and C.E. Jahr, *Glutamate release monitored with astrocyte transporter currents during LTP*. Neuron, 1998. **21**(2): p. 425-33.
150. Ge, W.P. and S. Duan, *Persistent enhancement of neuron-glia signaling mediated by increased extracellular K⁺ accompanying long-term synaptic potentiation*. J Neurophysiol, 2007. **97**(3): p. 2564-9.
151. Agulhon, C., T.A. Fiacco, and K.D. McCarthy, *Hippocampal short- and long-term plasticity are not modulated by astrocyte Ca²⁺ signaling*. Science, 2010. **327**(5970): p. 1250-4.
152. Witcher, M.R., S.A. Kirov, and K.M. Harris, *Plasticity of perisynaptic astroglia during synaptogenesis in the mature rat hippocampus*. Glia, 2007. **55**(1): p. 13-23.
153. Ventura, R. and K.M. Harris, *Three-dimensional relationships between hippocampal synapses and astrocytes*. J Neurosci, 1999. **19**(16): p. 6897-906.
154. Theodosius, D.T., D.A. Poulain, and S.H. Oliet, *Activity-dependent structural and functional plasticity of astrocyte-neuron interactions*. Physiol Rev, 2008. **88**(3): p. 983-1008.
155. Oliet, S.H., R. Piet, and D.A. Poulain, *Control of glutamate clearance and synaptic efficacy by glial coverage of neurons*. Science, 2001. **292**(5518): p. 923-6.
156. Wenzel, J., et al., *The influence of long-term potentiation on the spatial relationship between astrocyte processes and potentiated synapses in the dentate gyrus neuropil of rat brain*. Brain Res, 1991. **560**(1-2): p. 122-31.
157. Wade, J., et al., *Self-repair in a bidirectionally coupled astrocyte-neuron (AN) system based on retrograde signaling*. Front Comput Neurosci, 2012. **6**: p. 76.
158. Matrosov, V.V. and V.B. Kazantsev, *Bifurcation mechanisms of regular and chaotic network signaling in brain astrocytes*. Chaos, 2011. **21**(2): p. 023103.
159. De Pitta, M., et al., *Glutamate regulation of Ca²⁺ and IP₃ oscillating and pulsating dynamics in astrocytes*. J Biol Phys, 2009. **35**(4): p. 383-411.
160. Nadkarni, S., P. Jung, and H. Levine, *Astrocytes optimize the synaptic transmission of information*. PLoS Comput Biol, 2008. **4**(5): p. e1000088.
161. De Pitta, M., et al., *A tale of two stories: astrocyte regulation of synaptic depression and facilitation*. PLoS Comput Biol, 2011. **7**(12): p. e1002293.
162. Li, Y.X. and J. Rinzel, *Equations for InsP₃ receptor-mediated [Ca²⁺]i oscillations derived from a detailed kinetic model: a Hodgkin-Huxley like formalism*. J Theor Biol, 1994. **166**(4): p. 461-73.
163. Porto-Pazos, A.B., et al., *Artificial astrocytes improve neural network performance*. PLoS One, 2011. **6**(4): p. e19109.
164. Alvarellos-Gonzalez, A., A. Pazos, and A.B. Porto-Pazos, *Computational models of neuron-astrocyte interactions lead to improved efficacy in the performance of neural networks*. Comput Math Methods Med, 2012. **2012**: p. 476324.

165. Buckland, M. *Genetic algorithm tutorial in plain english*. Artificial intelligence genetic algorithm neural network tutorial 2000 22/11/2012]; Available from: <http://www.ai-junkie.com/ga/intro/gat1.html>.
166. Author_unnamed-this_literature_review_author. *ANGN schematic-pseudocode*. 2012 22/11/2012]; Available from: http://upload.wikimedia.org/wikipedia/commons/1/12/ANGN_schematic.png.
167. Oja, E., *A simplified neuron model as a principal component analyzer*. J Math Biol, 1982. **15**(3): p. 267-73.