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Review

Astrocytes Imagined

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Abstract

The cellular, molecular and physiological basis of cognition has proved elusive until emerging studies on astrocytes. The appearance of a deliberate aggregating element in cellular neurophysiology was difficult to satisfy computationally with excitatory and inhibitory neuron physiology alone. Similarly, the complex behavioral outputs of cognition are challenging to test experimentally. Astrocytic reception and control of synaptic communication has provided the possibility for study of the missing element. The advancement of genetic and neurophysiological techniques have now demonstrated astrocytes respond to neural input and subsequently provide the ability for neural synchronization and assembly at multiple and single synaptic levels. Considering the most recent evidence, it is becoming clear that astrocytes contribute to cognition. Is it possible then that our cognitive experience is essentially the domain of astrocyte physiology, ruminating on neural input, and controlling neural output? Although the molecular and cellular complexities of cognition in the human nervous system cannot be overstated, in order to gain a better understanding of the current evidence, an astrocyte centric basis of cognition will be considered from a philosophical, biological and computational perspective.

Keywords: astrocyte; cognition; synapse; learning and memory; neural synchrony; computational neuroscience; philosophy of mind; neurophilosophy

1. Introduction

The discovery of the astrocytic control of synaptic communication has implications beyond molecular and cellular interactions. Initially, the clear evidence of astrocytic modulation of unconscious behaviors in neuroendocrine systems [1], as well as learning and memory in the hippocampus [2], led to further studies on astrocytic regulation of neuronal communication in the cortex. Gliotransmission from astrocytes has the ability to control and respond to many or single synapses, with interastrocyte communication on a separate time scale than neurons, allowing astrocytes to aggregate neural communication [3,4], which seems to satisfy the spatial and temporal problem of a strictly neurophysiological interpretation of cognition [5–7]. Astrocytes connect 270,000–2 million synapses compared to 20,000–120,000 in rodents, and are 2.6 times larger with 27 times greater volume due to 10 times more processes, and can communicate 4 times faster than astrocytes in rodents [8,9]. Therefore, working in concert with neurons, astrocytes contribute to cognition [10–12]. How much they contribute will become clearer as techniques continue to advance [13], and new ideas on experiments of cognitive outcomes are developed. However, based on the evidence to date, it is worth considering the possibility astrocyte physiology is cognition itself: the cell of perception, imagination, creativity, conception of ideas, and decisions to act. From a historical perspective, astrocyte physiology could be the biological basis of that aspect of human existence that until recently many religious and philosophical interpretations traditionally placed as supernatural, when contrasted with the material body in terms of sense and movement.

2. Early Philosophical and Religious Interpretations

2.1 Divine Attributions

Our perception of the world, and our imagination, which seems to magically cognate from nothing, as well as our conception to action, had throughout human history seemed separate from the material realm. Philosophical and religious interpretations of our conscious experience and cognition generally incorporated a supernatural, otherworldly or divine attribution. In Theravada Buddhist traditions the Pāli Canon considerers the mind in three components, the *citta*, the *manas* and the *viññāṇa*. Perhaps oversimplified here, the *citta* refers to thought, while *manas* is the non-verbal cognition of the sensory input. The *viññāṇa* is our consciousness, with six components, the five consciousness from the senses and the mind consciousness of ideas — it is supernatural within and outside our body across time and lives [14]. In Hinduism, although with some differences among the various schools, the analogous Sanskrit *vijñāna* is considered the way of attaining the knowledge of Brahman, or in the *Bhagavad Gita*, knowledge of Brahma or Supreme Spirit [15]. In western philosophy, this ethereal mind with corporeal body dualism of experience also prevailed, with one aspect our material body, and the other an immaterial supernatural psych or soul, as

developed by Plato. Plato considered the soul and mind immaterial, and while Aristotle disagreed, and considered our body material intertwined with a material soul, he believed the intellect was immaterial and otherworldly [16]. Parts, or all of the workings of our "mind's eye", or cognitive self, have been described as a supernatural 'soul' or some form of divine influence or entity, in many religious interpretations of our experience that have evolved in human history. In the 'Abrahamic religions', many beliefs have the individual's souls existing in some form in the afterlife. Where animism prevails, all living things possess it, along with our human entity.

During the scientific revolution, Descartes attempted to reconcile Christian interpretations of our existence in Europe at the time with technological advances in hydraulics, and provide an explanation for dualism in the form of the 'mind-body problem'. His theory speculated that the mind is one with God's unseen ether, which then manipulates the pineal gland like a pump, to contract fluid through our nerves to coordinate movement in the body [17–19]. Ingenious in its time, Descartes 'balloonist' theory of fluid filled nerves intricately considered hydraulics as well as his contemporary's research on the pineal gland, even if it continued to ascribe a supernatural basis of our consciousness and cognition. Analogies on nervous system operation have traditionally drawn upon major technological advances, from hydraulics in Descartes time, to electricity of Galvani persisting into the 19th and early 20th centuries, to the late 20th and early 21st analogy of brain activity a computational code and our perception the manifestation of these like on a screen or 3D projection. By the 20th century, mind-body dualism was philosophically refuted by Gilbert Ryle in *The Concept of Mind*, where he states that despite appearances and feeling of the mind as a separate entity that lives outside and without the body, that it is just "the ghost in the machine", or a philosopher's myth [20]. However, our experience of this pervasive duality that inspired the mind-body problem may have at its biological foundation in the difference between neural and astrocyte communication and physiology, and could be revisited in relation to the philosophy of the mind with the new evidence from a completely biological perspective.

2.2 Schopenhauer's Vorstellung

In Western philosophy, by the 18th century, the supernatural notion had begun to wane in some philosophical circles, and instead the immaterial world outside space and time was perceived by our inborn material. Kant had developed influential concepts of the mind as part of the individual, from perception to conception that he categorized into various schema to demonstrate how we perceive the immaterial world [21,22]. However, perhaps a better analogy for our cognitive experience, and the difference between astrocyte/neuron physiology, as seen in the current experimental evidence, comes from Schopenhauer in the early 19th century. Schopenhauer's ideas had a broad impact on the early formation of the psychological sciences. He placed the importance of the mind as the central entity within ourselves with the word *Vorstellung* [23]. The *Vorstellung* was inborn in our self, our interpretation of that information from our senses, the illusion of our existence, as our perception, our imagination, and conception of ideas to volition. Like Kant's schema, it was our interpretation of that true reality we cannot know due to the limitations of our senses, the immaterial world which is outside space and time. For Schopenhauer, it was an individual's limited material's illusion of the immaterial world. Therefore, this situatedness of our consciousness in space and time is just a property of our inherent ability to make sense of the immaterial world from the input we receive from the senses. As Schopenhauer mentions: "if occasioned by the accession of certain sensations in my sense-organs, there comes about in my mind a perception of things which are extended in space, permanent in time, and casually active, that by no means justifies my assumption that such things exist in themselves... [24]".

What biomatter is responsible for this illusory perception, this imagination, this conception to action? Until the advent of modern cognitive sciences, this had not been biologically addressed. In biopsychology, the dominance of behaviorism in the mid-20th century placed all study on behavioral outcomes in response to sensory stimulus, because they were concrete and measurable. What happened between, the *Vorstellung*, was the unstudied, indeterminate 'black box' of BF Skinner. Radical behaviorism proposed by Skinner thought that since only defined behaviors were measurable, higher thought processes within were not able to be adequately studied, and though the approach of cognitive science to be futile [25]. With advanced tools and understanding of molecular biology, these mysteries are under active pursuit by neuroscientists and neurophysiologists in the 21st century: mainly, from a cellular biology perspective, what is the basis of the *Vorstellung*?

3. Initial Experimental Considerations of Astrocytes in Cognition

3.1 Synaptic Position

The current belief is that cellular learning and memory at the base of cognition likely results from 'neuroplasticity', or experiential changes in the synaptic connections between neurons over time, which had been theoretically proposed by Donald O. Hebb in *Organization of Behavior* in 1949 [26]. Robert Galambos, who conducted pioneering work on the physiology of echolocation in the bat nervous system, considered astrocytes intimate position at the synapse in a published a review in 1961 [27]. This seminal work was prescient, with his concepts now realized experimentally. In the review, he uses the word glia, as all other non-neuronal cell types in the nervous system were blanketed with the term 'glia', even though now it is understood the different main types are in some cases as dif-

ferent from each other as they are from neurons, and like neurons, have innumerable subtypes within each classification. Galambos lamented that the conventional consideration from Santiago Ramón y Cajal's Neuron Doctrine that glia are passive insulators in the nervous system prevented researchers from seeing the brain as an independent observer would, unpolluted by the doctrine, as "a huge collection of glia cells through which a nerve process occasionally wanders". Furthermore, Galambos stated that "perhaps glia…'tell' the neuronal masses what they are supposed to do — in the same sense, I suppose, that the computer program 'tells' its digital units what order and sequence of processes they must execute." He then concludes the essay stating: "Neurophysiology, dominated by the neuron theory of Cajal, has generated over the past 50 years a mountain of data without being able to formulate a convincing explanation for even such a commonplace behavioral event as remembering a name. It's data, furthermore, repeatedly imply that something else besides mere neuronal activity is at work. Could the 'something else' …..be the physiological properties of that other cell population of the brain, the glia?" Galambos was referring to astrocytes based on the synaptic position and type of glia cell he considered. Even Cajal himself, perpetually acute *ad infinitum*, seemed to foretell the death knell of a strictly Neuron Doctrine of cognition in 1899, and realized how the focus on neurons with his theory might sideline glia. He said that to consider them passive was "the main obstacle that the research needs to remove to get a rational concept about the activity of neuroglia [28]".

3.2 Emerging Physiological Evidence and Challenges

3.2.1 Calcium Physiology

As techniques advanced, emerging physiological evidence on neurons did indicate there was something else. Rapid fire neuronal signaling did not satisfy the slower assembly of neuronal units that occurred along with cognitive behaviors, and the persistent perception in cognition that another element needed to receive neural input, and coordinate and assemble the output—a cell type in the brain that was the matter of the *Vorstellung*.

It wasn't until the 1990s, when experimental breakthroughs began to shed light on a possible regulatory element in the brain that could function on a different time course and coordinate neural assembles. Like all cells, astrocyte were discovered to regulate internal calcium levels, but in a manner that allowed them to signal to other astrocytes and respond to neurotransmitters [29]. This was subsequently observed in organotypically cultured slices of rat hippocampus, where 'calcium waves' were initiated from astrocyte to astrocyte via gap junctions in response to neuronal activity [30], which prompted the question 'do astrocytes process neural information [31]?' Afterwards, experiments further illuminated that this could occur in vivo, when glutamatergic Schaffer collaterals in the hippocampus were stimulated and caused increased intracellular calcium levels in astrocytes, suggesting it was occurring via metabotropic and ionotropic glutamate receptors [32]. Astrocytes are known to express glutamate receptors, and the phenomena was originally believed to occur via mGLUR5, a G_q pathway receptor capable of upregulating IP_3, which can release calcium from internal organelles [33]. Soon afterwards, the discovery of 'gliotransmitters' such as glutamate, GABA, D-Serine and ATP that could be released from astrocytes in response to calcium increases in astrocytes, indicated that they could respond to and affect neuronal communication [34–38]. This exciting early evidence of astrocyte calcium physiology, and the astrocytic expression of receptors, transporters and transmitters, provided initial support of Galambos' theory that astrocytes were an intimate player in neurocommunication. Because of their unique position, astrocytes were modulating the synapse, which was now 'tripartite', and consisting of pre- and postsynaptic elements, as well as the astrocyte [39]. After the initial evidence, many reviews and texts, with some publishing companies in this nascent field even hastily constructing grammatically incorrect subtitles [40], actively considered an astrocytic role in cognition.

3.2.2 Crux of Synaptic Communication

However, could astrocytes experimentally cogitate rapid fire neuronal input? Subsequent experiments have importantly shown astrocytes control synaptogenesis in learning through the release of thrombospondins [41] neuroligins [42], the glypicans [43] and release of TNFα [44]. Glutamate, GABA and glycine homeostasis is known now to be a function of astrocytes, and dysregulation through astrocyte dysfunction can be neurotoxic [45]. It appears that long term potentiation (LTP), can be achieved via the astrocyte [37]. Astrocytes communicate with microglia at the synapse to control synaptic pruning and synaptic communication in what has been coined the quadripartite or tetrapartite synapse [46,47]. Also, neurovascular coupling is controlled by the astrocyte to provide nourishment to the parenchyma, due to their ability to monitor neurons simultaneous to their endfeet sensing of the microvasculature [48].

Some technical issues have persisted, however, as many of the initial studies to drive protein expression to observe effects in astrocytes were via the GFAP promoter, which is typically expressed in reactive states, and expressed by few cells in the normal healthy brain [13]. Likewise, the effects of gliotransmission needed to be revisited, because experiments studying astrocytic transmitter release by overexpressing a dominant-negative domain of vesicular SNARE (dnSNARE), was subsequently shown to also have low neuronal expression that could confound some early results [49]. Additionally, mGLUR5, the G_q pathway through IP_3 signaling to release endoplasmic reticulum internal calcium in glutamatergic synapses, is essential for tripartite synapse formation in development, but

the astrocytic expression may diminish in the adult, except in certain conditions [50,51]. Astrocytes express many other metabotropic transmitter receptors, including adrenergic, purinergic, serotonergic, muscarinic and peptidergic receptors, in additional to glutamatergic and GABAergic, depending on the temporal expression and astrocytic subtype [52]. One explanation for the effects in the adult brain in response to glutamate would be through the mGLUR2/3 receptors which are $G_{i/o}$ metabotropic receptors that do not directly activate IP_3 but could indirectly effect calcium levels [53]. And lastly, some initial studies with IP_3R2 –/– mice, which would abolish astrocytic IP_3 signaling, did not display neuronal or neurovascular deficits [54]. However, further analysis in response to startle responses that considered different astrocytic compartments and cell anatomy, observed astrocytic calcium transmission at endfeet and fine processes via extracellular calcium, which contribute to 30–40% of the internal calcium elevations, enough to effect rapid neuronal and neurovascular communication [55]. Calcium can enter extracellularly through ionotropic receptors, as well as TRPA1 channels, which was demonstrated to cause inhibition of GAT-3 GABA uptake to increase extracellular GABA and inhibit adjacent neurons [56]. In order to better understand the relation of this discovery of calcium microdomain transients in endfeet and fine processes compared to IP_3 induced somatic calcium release from endoplasmic reticulum stores, astrocytes and neurons in barrel cortices were observed after whisker deflection in mice. Calcium responses rapidly followed neuronal events and were independent of neuromodulatory activity from IP_3R2 mediated signaling via acetylcholine, serotonin or norepinephrine receptors, which indicated astrocytes were quick enough to play a role in synaptic modulation and neurovascular coupling, while also capable of slower responses via IP_3 [57].

3.3 Regulation of Unconscious Behaviors

The processing and subsequent control of neuronal communication at the synapse by astrocytes is responsible for many unconscious processes. In these experiments, defined measurable behavioral outputs are able to be tested in conjunction with cell physiology. Initial studies of the astrocytic effect of unconscious behaviors can provide a window into how the astrocyte might influence cellular communication in cognition. For example, astrocytes are the initial cell in the brain stem detecting pH increases due to elevated CO_2 in the blood, the astrocyte signal neuronal firing, which stimulates the lungs to take a breath [58]. Astrocytes have also been shown to control oxytocin neurons in response to sensory stimuli that drives lactation and other behaviors in the hypothalamus [59]. Likewise, in the suprachiasmatic nucleus, astrocyte signaling controls neuronal communication to drive our circadian rhythms [60–62]. In feeding behaviors, it was initially observed that leptin receptors on astrocytes were essential for leptin-regulated feeding [63]. Astrocytes are also required for osmoregulation in the supraoptic nucleus [64,65]. In the amygdala, fear processing to stressful stimuli is determined through an astrocyte intermediary before the neuronal communicatory stress response, and astrocyte activation decreases the firing rate of central amygdala neurons, which reduces fear expression [66]. Most recently, it has been discovered that astrocytes also play a role in modulating reward through dopaminergic pathways and expression of opioid receptors in the nucleus accumbens [67,68]. This list is by no means exhaustive, but astrocyte regulation of neuronal processes on measureable behaviors, indicates that their control of neuronal activity in cognition in seems likely.

4. Astrocytes in Aging and Dementia

Synapse loss and cognitive decline is a byproduct of aging, and synapse loss is observed early in dementias such as Alzheimer's disease [69,70]. Astrocytes and microglia work in concert to react to injury, disease and aging by changing their morphology and genetic expression profile in the hopes of rescuing apoptotic neurons, phagocytosing necrotic neurons and degrading protein accumulation [71–73]. Astrocytes in this state of neuroinflammation are 'reactive', and devote their activities to the disrupted parenchyma [74]. Increased astrocyte reactivity correlates with cognitive decline [75,76]. Because astrocytes are responsible for maintaining synaptic integrity, and synapse loss is the prevalent hallmark of dementia and aging, recent studies have begun to consider neurodegeneration and cognitive decline from the perspective of early astrocyte dysfunction or atrophy [71]. Astrocyte atrophy has been observed early in the entorhinal cortex in mouse models of Alzheimer's disease [77,78]. In mice, it has also been recently shown that astrocyte gene expression changes as a function of age, increasing synaptic pruning biomarkers that may accelerate disease [79]. Astrocyte senescence can cause vascular dysfunction, glutamate excitotoxicity and neural stem cell loss [80]. In a study on 766 individuals from publicly available whole-brain transcriptomes in human Alzheimer's disease compared with control or mild cognitive impairment, the main difference found was in endolysosomal organelle loss early in disease in astrocytes followed by mitochondrial dysfunction, which suggests astrocyte dysfunction is the driver of the onset of dementia [81]. Likewise, monoclonal antibody treatments to target amyloid-β from the brain have been effective at removing plaques thought to be responsible for neuronal cell death, but cognitive decline persists [82–84]. Using a reactive astrocyte PET tracer 11C-BU99008, it was discovered that in late Alzheimer's decreased astrocyte ability for tracer uptake corresponded to increased amyloid-β load in the region, indicating a loss of astrocyte function may correlate or precede amyloid-β deposition [85]. The astrocyte endolysosomal system is also responsible for the removal and

degradation of proteins such as amyloid precursor protein, α-synuclein, tau, and huntingtin which accumulate in aging and dementia [86]. The proteins now appear to be ancillary byproducts of disease instead of the cause of cognitive decline, providing further evidence astrocyte dysfunction precedes their accumulation. Lastly, blood flow through neurovascular coupling, which is dependent on astrocytes, is also reduced in aging and dementia [87]. Therefore studies on dementia and aging demonstrate that cognition is inversely proportional to the fitness of the astrocyte: is this because of the quondam notion that neurons are dependent on them for support, or because astrocytes are the reason for cognition themselves?

5. The *Vorstellung* Cell

5.1 Astrocyte Anatomy in the Hippocampus and Cortex

Brainbow techniques confirmed the previous research that protoplasmic astrocytes in the cortex and hippocampus occupy distinct non-overlapping territories called tiling domains [88–90]. In these positions, in areas of the brain responsible for cognition, astrocytes can influence and respond to a single synapse, or hundreds/thousands of synapses, and are responsible for synchronous neuronal activity thought the be the basis of our unitary consciousness [91,92]. In addition to the influence on synaptic plasticity [93], there is emerging evidence of the complexities of astrocyte heterogeneity throughout and within brain regions, which could provide further nuance to their physiological role [94]. Additionally, two astrocyte subtypes are unique to the primate cortex, the interlaminar astrocyte in the molecular layer, and the varicose projection astrocyte, which is only found in the human cortex in layers V and VI, and can extend a long process into other cortical layers [9]. Therefore, astrocytes are uniquely positioned to contribute the spatial integration and temporal regulation that is unsatisfactorily explained from a neural centric view alone [10]. Likewise, in all transmitter systems, astrocytes are positioned to provide intimate involvement in assembly and circuitry [95].

5.2 Astrocyte Learning and Memory

5.2.1 Excitatory Modulation

In the hippocampus, in order to facilitate cellular learning in the form of LTP and long term depression (LTD), or synaptic changes as defined by "Hebb's rule", it was discovered that spike timing is required, and that another element to provide this is required besides pre-synaptic and post-synaptic elements [96]. In initial experiments that included the astrocyte, it was thought they could only respond to intense synaptic activity, but it was soon realized that astrocytes can modulate and control basal activity in a regulated way, and were involved in all synaptic activity in the hippocampus [97]. During retained memory by place cells in the hippocampus and grid cells in the entorhinal cortex, astrocytes could respond to input and facilitation of synaptic strength to control cellular memory in adjacent neurons [98]. Likewise, LTP, long held to be the gold standard of learning and memory at the cellular level, can be caused by increase calcium levels in astrocytes causing the release of NMDA receptor binding D-serine [99]. When CA1 astrocytes were specifically activated, it was demonstrated that astrocytes alone can cause memory enhancement and potentiation in neurons [100]. Reduction of gamma frequency was also observed by impaired performance on the novel object recognition test when hippocampal astrocytes were manipulated. However, fear conditioning as responsible for the amygdala and working memory for the prefrontal cortex remained unchanged [101].

Similarly, astrocytes isolated from human brain, and implanted into mice were preferentially taken up into synaptic circuits. Mice performed better on a battery of learning tasks to assess whether improved LTP by human astrocyte in the hippocampus resulted in improved learning. The mice with human astrocyte implants performed better on auditory fear conditioning, contextual fear conditioning, the Barnes maze and an object recognition test. Human astrocytes were much larger, more complex with more rapid calcium communication and connectivity [102].

Although some conflicting evidence on the neuronal influence and astrocyte control through somatic calcium [54,103] or transient calcium at fine processes [104], the general evidence supports an astrocyte as the bridge of neuronal input and output in learning and memory in the hippocampus [105]. Recently, the use of designer receptors exclusively activated by designer drugs (DREADDs) to effect G_q and G_i pathways showed that astrocytes drive synaptic potentiation through G-protein coupled receptors (GPCRs) [106].

5.2.2 Inhibitory Modulation

Additionally, astrocytes respond to inhibitory neurons through expression of $GABA_B$ receptors and uptake of GABA through GAT-3, which can cause transmitter release from astrocytes that can regulate excitatory transmission in the hippocampus [36,107]. $GABA_B$ receptor activation on astrocytes [108] by somatostatin expressing inhibitory neurons also demonstrated the facilitated repression of excitatory glutamatergic pyramidal neurons in the hippocampus [36,109]. Astrocytes have also been shown to decode inhibitory signals in the CA3-CA1 glutamatergic synapse to affect hippocampal theta and gamma oscillations [110], two phenomena historically thought to be strictly neural correlates of consciousness regulating hippocampal-cortical communication during episodic memory [111]. Further studies demonstrated that inhibitory neuron activation of barge activity was completely mediated by astrocytes [112].

5.3 Keystone Cell in the Cortex

5.3.1 Excitatory Modulation

Although not as simply measured as unconscious and learning and memory behavioral outcomes, astrocytes unique keystone position in the cortex also provides them with the ability to respond to, assemble and manipulate cortical neuronal communication. For example, it was shown that in the ventrobasal thalamus, CA1 hippocampus and somatosensory cortex, astrocyte gliotransmission can synchronize neurons up to 200 microns away, and that an individual astrocyte determines a neuron's synchronized network [113]. In the whisker barrel cortex of mice, stimulation of the whisker and subsequent neuronal input will cause increases in astrocytic cytosolic communication [114]. One measureable output, vigilance, demonstrated that cortical astrocytes receiving projections from the locus coeruleus of noradrenergic synapses caused increased vigilance through astrocytic second messenger pathways [115]. Astrocytes have been shown to be responsible for memory consolidation and performance through vigilance and arousal in other experiments on learning and memory as well as cortical communication [116]. Injection of astrocyte toxin L-AA in the prefrontal cortex caused attentional set-shifting, working memory and reversal learning deficits. In surviving neurons in the area of the application of the toxin, dendritic atrophy was widespread [117]. Inhibition of gliotransmission with the controversial dnSNARE technique, which may inhibit some neurotransmission, also disrupted the synchronization of theta oscillations, thought to be essential for cognition, between the dorsal hippocampus and prefrontal cortex [118]. Cortical UP states and synchronization of cortical circuits has shown to be governed by astrocytes, demonstrating astrocytic control of neuronal ensembles in the cortex [119,120].

5.3.2 Inhibitory Modulation

Recently, the idea that inhibitory interneurons are the regulatory element in cortical cognition was challenged when it was observed that astrocytes act as an intermediary through GABAergic interneurons to control gamma oscillation, and that effecting astrocytes themselves could also change gamma oscillations in the cortex [121]. In the visual cortex, photostimulation of astrocytes could enhance both inhibitory and excitatory neuronal firing through type 1a mGLURs, indicating independent astrocytic control of neuronal firing [122]. The observed effect of astrocyte $GABA_B$ receptors responding to inhibitory interneurons and in turn effecting other interneurons has also been demonstrated in the cortex [123].

5.4 Computational Considerations of the Astrocyte

Systems and computational neuroscience has now begun to appreciate the burgeoning experimental evidence of the astrocyte regulatory element and the implications for cognition. Although until recently, this field has been conventionally the study of neurons, neuronal circuits and units, the incorporation of astrocytes in computational models and systems has proven to be particularly fruitful [124, 125]. The unsatisfactory explanation of computational self-tuning synapses [126] and self-regulating synaptic model attempt to design learning [127], with the model creator inserting a nuance that could now be achieved by a third element, the astrocyte [128]. The astrocyte is now the element that can synchronize, organize and bind neural input and output [129]. Initially, the computational power of astrocyte mediated synaptic plasticity was explored [130], especially in excitatory synapses, and how glutamate uptake by astrocytes can influence transmission and neural spiking [131]. The astrocyte has been shown to be the element to satisfy the computational quest to understand regulation of neuroplasticity [132]. Astrocytes in silico cell models have also now emerged as a player in neural networks [133]. Likewise, in a computational system, the tripartite synapse adds another dimension to the development and understanding of aggregation of neuronal units into synchronization observed in consciousness [134–137]. These models provide a window into how astrocytes contribute to the neuron in a single unit level, and consider the implication it might have in complex circuits, networks and re-entrant signaling [138,139].

The initial models have proven to be a spring board to further development to show how astrocytes improve such things as pattern recognition performance [140]. Similarly, models have been built and extended to incorporate astrocytes in the whole network level [141]. Including a model that considers the essential role of astrocytes in neural synchrony [142]. Researchers have also created a neural-neuroglia network builder interface, where novice computational biologists can now create models taking into account the two elements [143]. And more recently, artificial intelligence hardware containing a controlling astrocyte-like element have been constructed [5]. All of these studies are concluding something known in the experimental evidence: in order to replicate human intelligence, imagination, perception, the astrocyte is the keystone regulatory cell responsible for orchestrating neuronal communication.

6. Discussion

Astrocytes clearly respond to and effect all processes previously linked to cognition and perception. How involved are they? Experimentation has just touched the surface of astrocyte physiology and cognition—for example, observations indicate astrocytes change in early post-natal development—could this be the basis for childhood amnesia [144]? What about the difference in the perception of time in infants and children compared to adults: could this have an astrocytic basis? Consider the recent ground breaking discovery of the glymphatic pathway, where astrocytes provide waste clearance through the CSF during sleep. Is this why we cognitively shut down during sleep,

for astrocytes to clean up and repair [145,146]? Are astrocytes the cells that dream? And what of the various astrocyte subtypes currently being discovered, how do they each contribute to cognition [147]? On an artificial intelligence level, it appears this dichotomy of signaling, neuronal and astrocytic, and not neuronal alone, will be the only way to understand or replicate human perception and intellect.

Taking it further, is it possible astrocytes are the cells that give us the feeling of a separate mind and body so pervasive in human historical religious and philosophical texts—that they are our perception, imagination, moments of inspiration, decision to move, the *vijñāna*, Kant's schema and Ryle's 'ghost' in the machine? Are our astrocytes the biological basis for Schopenhauer's *Vorstellung,* providing the illusion of reality in our consciousness? This may seem to place astrocytes on a pedestal above neurons. However, consider neurons in this paradigm: they can manipulate and trick astrocytes with false input, or be fine-tuned to send more accurate information to astrocytes about the world around us. They are the messenger, like someone describing the complexities of the infinite with finite tools, as astrocytes contemplate what it means and what to do about it. The objective reality outside space and time that we attempt to perceive, is an illusion cogitating from limited neuronal input. And although this creates a subjective experience, how we handle it is real to us, and as Schopenhauer believed, to be valued beyond our basic wants, and the only way to avoid the objective will and suffering. "The subjective and objective do not form a continuum. That of which we are made immediately conscious is limited by our skin, or rather by the very tips of the nerves which emanate from the cerebral system. Beyond this lies a world of which we have no knowledge except through the pictures in our head", said Schopenhauer [24].

It may be that astrocytes are the *Vorstellung*, the subjective pictures in our head, our illusion of objective reality. To use an analogy that draws upon Schopenhauer's belief that music was the highest form of art that could tap into the objective will—our *Vorstellung* is the bushy astrocyte guitarist listening, creating and strumming a multitude of neuronal strings.

Unless of course, an astrocytic basis to our imagination, is only in our imagination.

Abbreviations

DREADs, designer receptors exclusively activated by designer drugs; GAT-3, GABA Transporter-3; GPCR, G-protein coupled receptor; IP_3, inositol triphosphate; IP_3R2, inositol triphosphate receptor 2; mGLUR, metabotropic glutamate receptor; L-AA, L-α-aminoadipate; LTP, long term potentiation; LTD, long term depression; TNFα, tumor necrosis factor alpha.

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Ethics Approval and Consent to Participate

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