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Review

The Syncytial Theory of Consciousness

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Abstract: 1. Complex bidirectional communication exists between astrocytes and neurons at each active tripartite synapse. 2. Individual astrocyte domains monitor and integrate excitatory and inhibitory synaptic information throughout the territory occupied. 3. Individual human astrocyte domains interact with up to 2 million excitatory and inhibitory synapses with multiple origins and neurotransmitter profiles. 4. Astrocytes alter structural and functional properties of presynaptic and postsynaptic elements that affect long term potentiation or depression. 5. Astrocytes, along with microglia, modify neuronal networks through synaptogenesis and synapse elimination throughout the lifespan. 6. Astrocyte domains form a functional astroglial syncytium through gap junction intercellular channels that transmit electrical and chemical signals throughout the neocortex. 7. From an evolutionary perspective, human astrocytes, unlike neurons, have undergone dramatic exaptations including vastly enlarged protoplasmic astrocytes as well as three unique human/primate-specific astrocytes. 8. Human exapted astrocytes significantly enhance learning and memory in mice chimeras. 9. A recent study demonstrates rapid electrical signaling from one group of neurons to another through a bridge of syncytial astrocytes. This strongly supports the astroglial syncytium as a structure for rapid long-range signaling on a timescale required for binding wide-spread regions of the brain into consciousness. Conclusion: Conscious expression occurs in the human astroglial syncytium. The syncytium also provides mechanisms for encoding and storing memories that return into consciousness as needed.

Keywords: theory of consciousness; astrocytes and consciousness; astrocytes and memory; glia in consciousness; glia and behavior

1. Introduction

"It's evident that the classical notion that information processing relies solely on neuron-to-neuron communication is essentially obsolete." Agid and Magistretti 2021 [1]

Tripartite Synapse is currently coined to acknowledge that astrocytes are active partners in synaptic functions in addition to traditional presynaptic and postsynaptic components [2]. Astrocyte peripheral process terminals extend into the synaptic cleft [3] or envelop individual excitatory and inhibitory synapses [4–7]. They also surround or insert into complex specialized groups of synapses [8].

Astrocytes modify excitatory and inhibitory synaptic signaling within each individual domain [9–18]. Subsequently they process and integrate synaptic information [19–28]. They also regulate global neuronal networks through synaptogenesis and elimination of synapses throughout the lifespan [29–44].

The most significant difference between astrocyte information processing and that of neurons is that astrocytes interconnect through innumerable gap junctions, electrically and chemically, to form a contiguous and continuous isoelectric syncytium throughout the neocortex. This massive structure assures astrocyte protoplasmic continuity throughout the brain and is known as the astroglial syncytium (AS) [45–50].

Gap junctions transmit integrated synaptic information throughout the AS, forming a complex network that is continuously processing information originating from individual synapses.

Thereafter, the AS is capable of sensory, associative and motor, integration that is required for detection, binding and directing behavioral responses from and to the external environment through equivalent afferent and efferent synaptic signaling [51–58]. The representation of the external world, and subsequent behavioral responses, is the function of consciousness.

The major criticism of all neuron-based theories of consciousness is that it has repeatedly been demonstrated that perceptual sensory information is continuously subdivided and parcellated as it progresses within the neocortex [59]. Furthermore, the arrival of synaptic signals within subdivisions of brain functional areas do not coincide. This indicates a "disunity of consciousness" [60].

2. Astrocyte Domains, Microdomains, and Synaptic Interactions

Astrocytes express "virtually any type of receptor found in the CNS, which allows astroglia to perceive the neurochemical landscape of the nervous system". Verkhratsky and Nedergaard 2018 [61]

It is widely accepted that rapid and complex bidirectional information occurs between synapses and perisynaptic astrocyte processes (PAP) at each tripartite synapse [62–65]. PAPs constitute approximately 80% of the surface area of individual astrocyte domains, and their terminals are known as microdomains [66–69].

Microdomains contain structural and neurochemical elements essential for information processing (glutamate and GABA neurotransmitters, neurotransmitter metabotropic and ionic receptors, glutamate and ionic transporters), aerobic and glycolytic energy production (mitochondria and glycogen), motility (actin filaments), and intercellular communications (gap junctions). [1,7,25,28,70–78].

PAPs are compartmentalized. For example, there are two compartments related to different calcium responses evoked by synaptic activity as well as the spatial relation of astrocyte NMDA receptors [25,74–78]. Additionally messenger RNAs (mRNA), are confined to subcellular compartments where translation occurs [78].

2.1. Astrocyte to Neuron Signaling

Microdomains are extremely metabolically active [61]. They alter tripartite synapses by releasing a complex array of so-called gliotransmitters [79–83]. This includes "classical" neurotransmitters glutamate and GABA that are synaptically excitatory and inhibitory respectively. The exocytic release of glutamate "controls synaptic strength" [84].

Importantly, D-serine is released by astrocytes, which is a necessary cofactor for NMDA activation at postsynaptic sites [85,86]. It is proposed that astrocytes control the release of D-serine, resulting in a temporal sliding scale to activate neuronal NMDA activation [87].

Microdomains also release other neuroactive molecules such as cytokines, purines, prostaglandins, and nucleotides, among others [80]. Astrocytes release glutathione, an amino acid, that ameliorates free radical damage to neurons [88].

There is also evidence that the perisynaptic net of extracellular matrix molecules is important for synaptic formation and functions. The perisynaptic net is secreted by astrocytic cell adhesion and matricellular molecules as well as contributions from oligodendrocytes and microglia [89,90].

Specialized astrocytes in the mammalian retina, known as Müller cells, are essential for visual acuity. They function as "light guides" that transmit photons through the entire substance of the retina to activate one cone photoreceptor and, also in humans, ten rod photoreceptors. They act as "single cell optical fibers" that "convey light directly to photoreceptors with minimal distortion or loss of photons." [91].

Lactate released from astrocytes promotes neuronal NMDA signaling [92] and is required for long-term memory formation. [93]. Lactate is also increased during sleep, a time when memories are being consolidated [94]. Lactate is converted from glucose in astrocytes following transport of glucose from cerebral capillaries via the AS [95].

Astrocyte-specific connexin 30 drives PAPs into synaptic clefts beginning at postnatal day ten and continues throughout the lifespan in mice. It functions as an adhesive molecule and sets the basal synaptic scale [3]. Interestingly, 10-14 days is the time of visual (eye opening) and hearing awareness in postnatal mice.

2.2. Neuron to Astrocyte Signaling

A single axon passes through the territory of multiple astrocyte domains as it ramifies within wide-spread areas of cortical grey matter. Furthermore, each domain is influenced by multiple axons with diverse origins that express a variety of neurotransmitters and neuromodulators.

Synaptic glutamate is taken up by astrocyte glutamate transporters that converts it into glutamine. The glutamine is subsequently released to neurons for conversion back to glutamate, which is the essential transmitter for excitatory synapses. Neurotoxicity occurs unless glutamate and potassium are rapidly removed following synaptic discharge. This important function is performed by astrocyte microdomain glutamate and ionic transporters [96]. In addition to glutamate and GABA receptors, astrocytes express norepinephrine, serotonin, dopamine, acetylcholine, endocannabinoid and opioid receptors [1,61,97]. Up to five receptors may be expressed in individual astrocytes [98].

Neuromodulators respond slowly compared to extremely fast-acting neurotransmitters. Among these, norepinephrine is known to ''play an important role in defining what psychologist call the ego, the awareness we each have of being a distinct person separate from all others, confronting the universe on our own'' [99]. Serotonin serves ''an important role in engendering feeling states, such as love and hate, joy and sadness'' [99]. Norepinephrine and serotonin receptors are known to coexist on individual astrocytes [100].

Stimulation of the locus coeruleus activates cortical astrocyte adrenergic receptors in vivo [101]. Astrocyte beta-adrenergic receptors induce cyclic AMP-generated pathways in response to catecholamines [102]. Astrocytes activation by endocannabinoids potentiate synaptic activity and are important in working memory [103].

An ultrastructural study confirms adrenergic synapses on astrocytes in addition to en passant terminals [104]. In fact, astrocyte adrenergic receptors are more abundant than those on neurons [102].

3. Astrocyte Domains Integrate Synaptic Activity

Microdomains integrate synaptic information from up to 2 million excitatory and inhibitory tripartite synapses within each human astrocyte domain [19–28]. Astrocytes incorporate synaptic information by the generation of elevated intracellular calcium transients and the induction of electrical currents.

3.1. Calcium Excitability

Neurons release glutamate and GABA to activate analogous receptors on astrocytes that increase intracellular calcium levels ([Ca2+]i) that occur simultaneously with synaptic activation [105]. A recent in vivo study unequivocally demonstrates that whisker stimulation in live mice simultaneously increases astrocyte [Ca2+]i in barrel cortex astrocyte microdomains and astrocyte endfeet surrounding blood vessels [75].

There is no difference between the latency of astrocyte microdomains and neurons. Domain activity occurs 125 ms following synaptic activation. It was concluded that "astrocyte signal dynamics are sufficiently fast to influence cortical information processing and/or neurovascular coupling" [75]

Low synaptic activity induces small increases in [Ca2+]i, whereas stronger synaptic activity results in synchronous [Ca2+]i transients that, at higher levels of activity, form long range calcium waves throughout the AS via gap junctions [1,19,45,50,61,106–108]. Intercellular calcium waves "generate signals that establish bridges between different neuronal networks, which then become

functionally interconnected" … "because of their ability to conduct broad spatial interactions over long periods of time" [1].

Neural networks, however, are incapable of such long-term activation because of the very short lifespan of synaptic molecular components that excludes them from persisting for the time required to encode and retain memories [51,109].

3.2. Electrical Activation

Electrical currents were first observed in astrocytes surrounding the optic nerve upon visual stimulation [110]. Subsequently, several groups demonstrate that individual astrocytes respond with electrical membrane transients as rapidly as neurons [55,105,111–114]. Such rapid astrocyte responses are "compatible with a physiological role in fast activity-dependent synaptic modulation" [79]

Although decades of accumulating evidence demonstrate the importance of astrocyte calcium signaling, electrical signaling in astrocyte networks lagged because of difficulties in eliminating interference from neuronal electrical currents. However, recent groundbreaking techniques have solved the problem of separating astrocyte electrical activity free of neural entanglement.

An ingenious technique demonstrates that electrical currents rapidly traverse a bridge of syncytial astrocytes from one isolated group of neurons to another. They note that such rapid electrical signaling globally could "bind" perceptive elements between associated areas of the neocortex. Such electrical activity occurs in a timeframe required for consciousness [115]. Additionally, enhanced electric activity may be "a prerequisite for memory formation or behavioral response". [55]

The entire AS is isoelectric with low impedance [116,117]. This allows the "entire syncytium to electrophysiologically behave as a singular unit" [118]. Interestingly, this is not limited to protoplasmic astrocytes but also extends to fibrous astrocytes that are interspersed in myelinated white matter tracts, including the corpus callosum that interconnect the hemispheres. The cerebellar syncytium and the spinal cord syncytium, components of the AS, are also isoelectric [119]. Therefore, isoelectric connectivity with low impedance is a "general feature of astrocyte networks" [118].

Gap junctions also elicit electrical activity by intercellular transport of ions [96]. Potassium is the most critical, since it must be removed immediately after action potential discharges to avoid neurotoxicity and cell death that occurs with prolonged retention within the synapse. Gap junction communication increases with higher potassium levels. [120] The rapid removal of potassium by astrocytes, and its discharge into the cortical vasculature, occurs simultaneously in all active tripartite synapses in the brain concurrently [50]. This is a major factor contributing to the isoelectric characteristic of the AS.

4. The Astroglial Syncytium Integrates Multiple Neural Networks Throughout the Brain

"Without the presence of the astrocytic syncytium and its capacity for integration, how else could the specificity of a signal be preserved amid this neuronal clutter." Agid and Magistretti 2021 [1]

The AS is currently viewed as a complex multifunctional system of astrocytes connected by gap junctions composed of Connexin 43 (Cx43) or Connexin 30 (Cx30) hexamers (known as connexons or hemigap junctions). Connexons interlock with adjoining astrocytes to form a completed gap junction [45–50,121–123]. Gap junction heterogeneity correlates with underlying neuronal functional areas [124]. For instance, astroglial networks integrate within functional regions in the neocortex, such as the somatosensory cortex [125] and the glomerular layer of the olfactory bulb [126].

Gap junctions coalesce at the outer membranes of adjoining astrocytes to form tightly packed quasicrystalline clusters known as plaques (GJP). These are extremely dynamic and pleomorphic, assuming ever-changing shapes and numbers of gap junctions that can be visualized as they travel across the membrane surface.

Interestingly, astrocyte only form homotypic gap junctions (Cx43-Cx43 or Cx30-Cx30) . Heterotypic (Cx43-Cx30) gap junctions do not form because of unique biophysical characteristics that inhibit heterotypic formation. Surprisingly, Cx43 and Cx30 GJs colocalize within the same GJP. However, they are segregated and do not perform overlapping functions. Adult rat brain astrocytes contain 64% such mixed plaques [127].

Approximately 30,000 gap junctions connect rodent astrocytes [6]. However, there are vastly more gap junctions in human protoplasmic astrocytes that are 2.5 times larger with 27 times the volume. PAPs are 10-fold more numerous with microdomains that are 2.6 times longer than rodents [66–68].

Each gap junction has a tightly sealed quasicrystalline intercellular channel that enables transmission of molecules from 1-1.5 kDa in size. This includes molecules critical for information processing (e.g. glutamate, GABA, ATP, cyclic AMP, cytokines, messenger RNA (mRNA), short interfering RNA (siRNA) and microRNA (miRNA) to transmit from one astrocyte to another, providing "a wealth of information to flow throughout the neocortex". [1] "In principle, a small group of cells or possibly a single cell within a syncytium has the potential to affect gene expression in a larger group of cells or possibly an entire organ" [128].

Both siRNAs and miRNA s are particularly interesting because of their lifespan of several days and influence on translational activities associated with innumerable targets, including those critical for cognition [128–130], Both are gap junction-specific. They only travel through gap junction networks comprised of astrocytic Cx43.

Translation occurs primarily in microdomains [129]. siRNAs and miRNAs have "key roles in learning and memory" [131]. In fact, "siRNA can be delivered from the interior of one cell to that of another independent of the extracellular space and influence gene expression in the recipient cell" [128].

Syncytial astrocyte, by regulating synaptic connectivity, "establish bridges between different neuronal networks, which then become functionally interconnected because of their ability to conduct broad spatial interactions over long periods of time" [1].

Spatial Distribution of Astrocyte Domains

Uniquely, the AS exists in a three-dimensional and seamless confluence of regular polygon-shaped astrocyte domains [67,132]. The three-dimensional and seamless structure of the syncytium is perplexing. The functional significance of this peculiar structural organization is unknown.

Similarly, consciousness is also three-dimensional and seamless that is evident *a priori*. This morphological equivalency led to the proposal that this complex geometric matrix created by global tiling of astrocyte domains provides a template for the expression of consciousness and explicit memories" [24].

Over a century ago, William James noted a paradox related to consciousness. He stated that ''there is no cell or group of cells in the brain of such anatomical or functional pre-eminence as to appear to be the keystone or center of gravity of the whole system" [133]. It is proposed that the AS is the "keystone" of "the whole system". Furthermore, there is no empirical evidence that consciousness occurs in the laminae and minicolumns of cortical grey matter.

Mountcastle notes the major problem in extending minicolumns to general cognitive constructs: "How the patterns of neural activity involved in a sensory discrimination or categorization, distributed as they are in wide areas of the brain, are unified into perceptual wholes, and how they flow through to conscious experience, remain among the great enigmas in brain science" [134].

5. The Panglial Syncytium Integrates the Entirety of Brain Information

''Glial cells are engaged in a global communication network that literally coordinates all types of information in the brain. Fields 2014 [51]

Although Cx43 and Cx30 gap junctions are distributed in the cortex, coupling of these gap junctions with other glia and vascular components expressing different gap junction connexins are

important in the maintenance of the blood brain barrier, neurovascular coupling and action potential-dependent myelin plasticity.

The formation of AS gap junctions with heterotypic connections to oligodendrocytes and vascular elements form the panglial syncytium (PS) that allows the transfer of metabolic molecules to and from brain capillaries to maintain neuronal homeostasis. Less appreciated is its ability to control dynamic myelin plasticity based on action potential activity within white matter fiber tracts.

Astrocytes are the linchpins and integrator of this structure, since it is the only cell that forms universal gap junctional connections to all macroglia throughout the brain. This complex integrative system of multiple glial networks leads Fields to conclude that ''glial cells are engaged in a global communication network that literally coordinates all types of information in the brain'' and that ''such oversight and regulation must be critical to brain function, and neurons are incapable of it'' [51].

5.1. Myelin Plasticity

Astrocyte Cx30 and Cx43 couple to oligodendrocytes-specific connexins to form heterotypic gap junctions (Cx43-Cx47 and Cx30-Cx32)   [127,135] The most abundant Cxs in these two cell types, Cx43 and Cx32, do not pair with each other [136,137].

Gap junction communication between astrocytes and axons in the nodes of Ranvier alter axonal signaling even before the action potential arrives at the synapse by spreading of the electrical current [138].

Astrocytes sense ATP released by axons while action potentials travel along the axonal nodes of Ranvier [138]. Subsequently, they signal to oligodendrocytes by releasing leukemia inhibitory factor, which stimulates oligodendrocytes to increase myelin production [139–141].

Interestingly, the degree of myelination, determined by diffuse tensor studies, positively correlate with intelligence of children and teens. Increased myelination is evident with learning [142,143]. For example, expert pianist exhibit increased myelination in areas related to this specialized ability [144].

5.2. The Corpus Callosum and Consciousness

"The appearance of the corpus callosum in the placental mammals is the greatest and most sudden modification exhibited by the brain in the whole series of vertebrated animals." Thomas Huxley 1863 [145]

The human corpus callosum is the largest myelinated white matter fiber tract in the human brain with over 200 million axons connecting the two hemispheres. Subsequently, it was shown that surgical ablation of the human corpus callosum resulted in the discovery of bihemispheric specializations of specific brain functions.

For instance, the left hemisphere is verbal, analytical, arithmetical, and aware of details related to time and conceptual similarities. The right hemisphere is nonverbal, musical, aware of spatial relations, and pattern recognition. [146].

Sperry postulated that there are two forms of consciousness, one in each hemisphere. However, this is obscured in the right hemisphere because of its lack of verbal expression [147]. The existence of full consciousness is only possible with the extremely rapid bidirectional synergy between the two hemispheres via the corpus callosum. Therefore, the corpus callosum is viewed as a binding structure that rapidly incorporates the diverse mental functions of each hemisphere into consciousness [148].

On the molecular level, transcription factor SATB homeobox 2 (SATB2) specifies axon guidance via the corpus callosum, whereas transcription factor BCL11B/CTIP specifies axons to project within each hemisphere [149]. Both are directed to their appropriate placement by astrocyte attractant and repellent molecules through "glial slings" prior to the onset of perinatal synaptogenesis [150]

5.3. Neurovascular Coupling

Astrocytic endfeet directly contact the blood–brain barrier (BBB) through capillary endothelial cells and pericytes [1,95]. Astrocytic endfeet express the GLUT1 transporter that facilitates the transfer of blood-borne glucose into the AS. Glucose is subsequently converted into nutrients, such as lactate and pyruvate, that are essential for neuronal survival [151].

Nutrients are distributed on an "as needed" basis, with the most active neurons receiving most essential metabolites (i.e. neurovascular coupling). Such "metabolic networks" sustain synaptic transmission [152]. Interestingly, these networks coincide with "metabolic" sodium waves within the AS [153,154].

Conversely, metabolic and ionic elements that are neurotoxic are transported through the AS and released into the general circulation. The most important electrolyte is potassium, which is neurotoxic if not immediately removed from the synapse following synaptic discharge. Since the greatest brain metabolic requirement is dedicated to maintaining synaptic activity, it is essential to rapidly remove potassium efficiently from the brain into the general circulation. In fact, removal is so efficient that it is the basis for the isoelectric with low impedance characteristic of the AS. [1,120].

5.4. Metabolic Pathways and Human Brain Evolution

RNA Retrotransposons have incorporated novel genes into the human genome. The most important related to human metabolism is the Human Specific Endogenous Retrovirus K (HTML variant) (HERV-K (HTML) [155,156].   It was incorporated into the human genome approximately 1 million years ago following the separation of humans from Chimpanzees (approximately 9 million years ago).

HERV-K (HTML) resulted in a massive increase in mTOR (Mammalian Target of Rapamycin), a major metabolic pathway involved in protein synthesis and increased cell proliferation [155,156]. This was a major factor in increased human brain size and energy demands compared to other primates (e.g. Chimpanzees).

Increased mTOR activation in the human subventricular radial glia differentiate human embryonic brain corticogenesis from other primates. It is also important in human adult neurogensis [155,156]. Significantly, mTOR also regulates the translation of extensive novel mRNA targets with multiple intracellular functions in human brains [157,158].

6. Discussion

"Nonetheless, the presence of astrocytes is likely a necessary, if not sufficient, condition for explaining the existence of consciousness." Agid and Magistretti 2021 [1]

The Syncytial Theory of Consciousness is a non-neuronal theory of consciousness. Stated simply, consciousness is expressed electrically throughout the global AS within hundreds of milliseconds, a time scale required for consciousness [115].

Memories, however, form over significantly longer timeframes. This is particularly true for longterm explicit memories that must be encoded, retained and reintroduced into consciousness over days, months or years. Extremely complex calcium signals traveling through astrocytic networks are ideal for this function. The likely mechanism is epigenetic modification of astrocyte DNA within astroglial networks. It is the extent of the astroglial syncytium, theoretically encompassing all cortical gray matter, that gives it massive computational power compared to current neurocentric models [65].

Galambos over half a century ago proposed that glia are essential components in human cognitive functions, including memory storage and innate and learned behavior. Initial ultrastructural studies of the brain, he notes, show ''huge collection of glia through which a nerve process occasionally wanders''. Similarly, initial intracellular neuronal electrical activity does not support ''behavioral patterns operating on a time base of hours, years, and generations ''[159]. However, his hypothesis was ignored by neuroscientists.

Another ultrastructural study was the first indication that astrocytes are involved in cognition. It demonstrated increased synaptic contact by astrocytes in mice raised in an "enriched environment" compared to those raised in routine laboratory conditions [160].

Over the past three decades Gliobiologist have demonstrated that astrocytes are, either directly or indirectly, associated with cognitive functions long believed to be strictly neuronal [27]. Technical advances that distinguish glial activity from neuronal activity on a millisecond time frame at the level of individual synapse, and determination of the lifetime of synaptic molecules, have further eroded the concept of synaptic primacy in brain information processing.

The most conclusive empirical evidence to date is the transfer of human/primate-specific astrocyte exaptations into chimeric mice. Importantly, the transplanted human cells maintained their extremely large size and substantially increased calcium signaling observed in prior studies. Most remarkable was the marked increase in learning and memory exhibited in the chimeras compared to controls. Since consciousness is the basis of declarative memory and learning, it is reasonable to conclude that the chimeric mice were more conscious, with improved memory, than the normal control population [161]

To support a non-neuronal site for consciousness and memories, it is necessary to explain why the synapse alone, or distributed throughout the brain, cannot support these functions. The major obstacle undermining a neurological basis of consciousness is that perceptual research has increasingly demonstrated that the brain does not process sensory information in a unified manner, but that such information is continuously subdivided or parcellated [59,60].

LeDoux states the overwhelming contemporary view of virtually all neuroscientists regarding the critical nature of synapses in cognition: "Most of what the brain does is accomplished by synaptic transmission between neurons, and by calling upon the information ended by past transmissions across synapses. Given the importance of synaptic transmission in brain function, it should practically be a truism to say that the self is synaptic. What else could it be?" [162]. Synaptologists are skeptical that the synapse alone would explain such a sweeping interpretation.

LeDoux's conclusion ignores historical criticism regarding his synapse-only hypothesis. Sherrington, the discoverer of the synapse, was dubious that synapses were important in higher cognitive functions. He noted a paradox when extending his findings to the cognitive realm, because it would imply that each synapse "both transmit and integrate information simultaneously". He noted that: "To pursue mind into the unicellular would be like looking for a firefly across astronomical distances" [163].

In evaluating the future of synaptology, it was noted that "It will also become increasingly apparent that synapses account for only a subset of the entire range of interactions that exist between neurons and glia and that contribute to their functional properties in mediating behaviour. Neuroglia contribute to the processing of information by neurons through a wide range of mechanisms traditionally viewed as nonneural and nonsynaptic" [164].

More refined methods to determine the lifetime of synaptic molecules have further eroded the concept of synaptic primacy. The post-synaptic density is replaced each hour [165]. Every forty seconds actin molecules, required for dendritic morphological changes during synaptic plasticity, have a half-life of ten minutes [166]. McCrone posits "how the heck do these synapses retain a stable identity when the chemistry of the cell is almost on the boil, with large molecules falling apart nearly as soon as they are made?" [109]

It is now evident that "the classical notion that information processing relies on neuron-to-neuron communication is essentially obsolete" [1]. Furthermore, it is virtually impossible to assign any form of memory, particularly long-term memory, as a function of the collective simultaneous actions of all synapses at any specific moment. Additionally, most synaptic functions are dedicated to a multitude of other functions, rather than nemonic encoding.

The synapse can only be considered the penultimate stage of information processing in the brain. Sherrington was correct when he cited the paradox of the synapse. That it could not possibly be both a signaling and integrating entity simultaneously. Prior to the Neuron Doctrine, the brain was

considered to be a functional syncytium of neurons. Ironically, it is a syncytium, but of glia and not neurons.

Conflicts of Interest: The author declares no conflict of interest.

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