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Mild Cognitive Impairment and Astrocytic Influences Affecting Network Communication

Denis Larrivee

[1]*Mind and Brain Institute, University of Navarra Medical School, Spain*
[2]*Loyola University Chicago, USA*

*Correspondence

Denis Larrivee
Mind and Brain Institute, University of Navarra Medical School, Spain

Abstract

Amnestic mild cognitive impairment (MCI) is generally understood to mean an age-related impairment in cognition beyond that normally observed in the elderly, where amnestic refers to a loss of the ability to recall stored information. The significance of this classification has traditionally rested on a presumptive clinical indication of dementia, based on a documented 5% to 10% annual rate of progression to dementia, a rate much higher than the 1% to 2% incidence observed within the general population. Because recollection mechanisms have been shown to center on the hippocampal cortical network (HCN), amnestic MCI is likely to entail an interruption of this network. Accumulating evidence indicates that a crucial cellular element regulating information flow in the HCN is the astrocyte. By extension, astrocytic mechanisms involved in regulating information flow within the HCN are likely to be disrupted in MCI. Consistent with this, astrocyte influence in memory networks is multimodally affected in MCI and AD patients, with impairments seen, for example, in interregional oscillatory coupling. Astrocyte pathologies thus appear to drive clinically relevant phenotypes of MCI and could represent novel and significant therapeutic targets for MCI treatment. Understanding the mechanisms astrocytes employ to enable communication within the HCN may not only advance our understanding of how and which processes are likely to go awry in MCI, but how they may be treated to arrest the loss of this most iconic MCI symptom.

Introduction

Mild cognitive impairment (MCI) is currently understood to refer to an age related impairment in cognition beyond that normally observed in elderly individuals, though not so severe as to substantially impair daily function [1]. Although six main cognitive domains have been identified to associate with MCI (learning and memory, social functioning, language, visuospatial function, complex attention, or executive functioning) [2,3], MCI is also differentiated broadly as either amnestic or nonamnestic, where amnestic MCI refers to impairment purely in one's ability to recall stored information. By contrast, nonamnestic MCI refers to impairment in one or more other cognitive domains, with memory in these instances otherwise remaining relatively intact.

The significance of a classification concerned with the inability to recall stored information has traditionally been linked to a presumed clinical indication of dementia. This conclusion has been buttressed by a documented 5% to 10% annual rate of progression to AD, a rate much higher than the 1% to 2% incidence per year observed within the general population [4,5]. The observation of clinically observed memory loss has thus often led to a common diagnostic inference that a reduction in capacity for recollection beyond that seen in normal age related, memory decline was highly prognostic for dementia. Although this presumed inference is today more nuanced, the high proportion of MCI patients evolving to AD makes the manifestation of amnestic MCI a cause for significant concern, one for which early monitoring and possible treatment of causal aspects is requisite before long lasting and irreversible cognitive loss1[1].

In amnestic MCI, a frequent observation made in neuroimaging studies is atrophy of

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1   *The detection of differentiable predisposing factors, reflected in the dichotomy between the annual reversion rate to normal cognition and the conversion rate to dementia [1], indicates that there are modifiable factors that may be contributing to cognitive decline. When considered together with these predispositional aspects, the differential prognosis of influencing factors from various etiological groups have made a strong case for early diagnosis and therapeutic intervention. Accordingly, major research efforts have sought to identify tools capable of resolving the causal ambiguities inherent in MCI and to develop therapeutic avenues addressing such underlying aspects before long lasting and irreversible cognitive loss.*

the hippocampus, an observation consistent with widely shared hypotheses of memory, based on studies of the loss of memory in patient HM following bilateral medial, temporal lobectomy. These hypotheses now generally acknowledge the central role of the hippocampus in memory formation [6] in which the hippocampus functions as a site of integration of a larger and more distributed hippocampal cortical network (HCN) known to support episodic memory [7]. Interactions of the hippocampus with other HCN regions, for example, are frequently observed during memory encoding and retrieval using fMRI. Moreover, episodic memory is disrupted by lesions affecting the HCN [8] and these lesions alter fMRI measures of connectivity among the HCN network in association with a variety of amnestic states [9].

Traditionally, brain networks have been attributed to the brain's ability, either locally or globally, to assume stable configurations that resist the tendency to destabilize when affected by perturbations [10,11], a result of the brain's tendency to converge to stable fixed point or other dynamical states. Computational processes like those occurring during memory formation must therefore accommodate the properties of these states for functional behaviors [12]. Considerable evidence indicates that network states are instantiated as neural activation patterns, which enable information exchange and facilitate cognitive transitioning [13]. The stability of resting state networks, for example, is typically conceived in the context of the synchronicity of oscillatory phenomena, which has been associated with mechanisms of information exchange [14-16]. Accordingly, a growing body of evidence shows that memory events, including retrieval, storage, and formation, involve brain oscillations (in the gamma and delta and theta frequencies) that couple distributed brain regions during recollection and memory formation.

While oscillations have often been attributed to inhibitory-excitatory neuron pairing [17], that is, involving neurons alone, an increasing number of findings suggest that a crucial cellular element contributing to these dynamical features is the astrocyte [18,19]. Astrocytes, for example, can detect neuronal activity via their sensitivity to glutamate by metabotropic glutamate receptors and receptor activation can in turn mediate transient increases of astrocytic intracellular calcium concentration through inositol 1,4,5-trisphosphate production. By propagating calcium changes either directly to synapses or indirectly to neighboring astrocytes, calcium signaling could affect synaptic information transfer between neurons comprising memory networks. Additionally, astrocytes are known to express a repertoire of receptors, transporters, and other molecules, enabling them to sense numerous synaptic mediators as well as other cell activators, like cytokines, prostaglandins, and signals related to changes in local ionic concentrations and pH.

Consistent with this notion, chemogenetic activation of astrocytes has been shown to affect memory performance [20- 22]. Gq DREAD (designer receptors exclusively activated by designer drugs) activation in astrocytes of the medial central amygdala, for instance, cause extinction of learned fear memories in fear conditioning tasks. Additionally, optogenetic and chemogenetic activation of the astrocyte Gq signaling pathway in the hippocampus enhance memory allocation and cognitive performance [22].

These findings suggest that disruption of astrocytic mechanisms affecting communication impairs memory networks and could contribute to MCI. In line with this notion,

various astrocytic processes such as calcium signaling, glutamate clearance, extracellular potassium buffering, and energetic metabolism are compromised in Alzheimer's [23,24]. Moreover, in mouse models of Alzheimer the dynamic morphological changes normally occurring during memory induction are substantially affected. For example, in these models the total number of astrocyte–neuron tripartite synapses are significantly decreased relative to controls. Moreover, astrocyte selective, inducible tetanus toxin expression inhibits astrocytic exocytosis and impairs gamma frequency oscillations in vivo.

Collectively, astrocytic influences on synaptic transmission are likely to play a critical role in facilitating information exchange in memory networks, potentially influencing oscillatory interactions on which such communication is based. Considerable information is now known about the intracellular and extracellular events of astrocytes that potentially could influence interneuronal exchange and be evoked to affect the generation, coupling, and desynchronization of these rhythmic patterns during memory related events. Because specific aspects of synaptic communication could be targeted by abnormal astrocytic signaling, this review will explore astrocyte signaling features likely to affect inter- oscillatory interaction and to influence memory network generation.

Astrocyte Specializations at Synapses

Recent studies have linked astrocyte signaling at synaptic levels to brain activity and have generated findings demonstrating that cognition requires the coordinated activity of specialized synaptic junctions formed by astrocytes with their neuron partners [22]. Termed microdomains, these points of contact with synapses show pronounced, activity dependent and spontaneous changes in intracellular Ca levels. Much evidence indicates that the transduction of these calcium fluctuations is directly involved in modulating intercellular information flow across synaptic clefts. For instance, despite being distributed throughout the astrocyte, genetically encoded Ca indicators respond to Ca changes only locally, i.e. within the microdomains, and fail to respond to Ca increases that may occur elsewhere in the astrocyte.

This observation indicates that astrocytic calcium signaling is spatially distributed within the astrocyte to affect information flow chiefly within the highly localized zone of the synapse. In support of this, most perisynaptic astrocytic structures appear as nodes. There is also a strict correlation between the nodes, the area of dendritic spines, and the Ca transients occurring there [25], thus implicating the domains structurally and functionally with their synaptic neuronal partners. The spatial spread of the Ca transients as a function of time course, further, is consistent with an area smaller than 1 μm^2, additionally supporting the notion that spontaneous astrocytic Ca events are restricted to individual microdomains.

Serial electron microscopy with 3D reconstruction [26] has revealed the cellular organelles within these zones that potentially could participate in signaling events and that would apparently provide for support of local calcium modulation. Reconstruction of these zones shows five distinct organelles, including phagosomes, mitochondria, empty and full endosomes, and endoplasmic reticulum (ER) cisternae. Endosomes and phagosomes comprise the largest organelle volume, accounting for more than 60% of the space occupied by all organelles. The remaining organelle related volume is composed of cisternae of ER and mitochondria. The known roles of ER and mitochondria

in calcium dynamics are consistent with those carried out by various astrocytic functions at this junction and so appear to represent a "primary source" of astrocytic Ca signaling within the tripartite synapse [18] together with that of extracellular influx. Microdomains thus appear to be endowed with adequate machinery and functionally specialized to modulate calcium signaling and enable bidirectional astrocyte-neuron dynamics.

Besides these local specializations, astrocytes elaborate a highly complex arborization, extending the influence of astrocytes over large neuronal territories. Individual human astrocytes, for example, can cover in excess of 2 million synapses and have a synaptic density of about 1100 million synapses per mm. This dense syncytia of astrocyte networks covers the brain [27] thus permitting regulatory control both at the locus of the tripartite synapse as well as over large-scale populations of neurons. By means of this structure astrocytes have been shown, for example, to induce slow and infra-slow oscillations [28].

Importantly, the synaptic morphology of these astrocyte domains is actively modulated, affecting the degree to which dendritic and axonal components are covered. When responding to strong behavioral stimuli, like that of either arousal or recovery from general anesthesia, for instance, astrocytes remodel the perisynaptic astrocyte processes rapidly and reversibly, modulating the extent of neuropil coverage [27]. The resultant change in intracellular volume within the processes has been shown to be coupled to the activity of the Na-Ca exchanger and is strongly correlated with the appearance of Ca oscillations within these zones [29,30]. Additionally, synaptic plasticity is apparently coupled to the dynamic morphological changes occurring at this site since generation of an LTP is sufficient to cause rapid (within minutes) motility of PAPs and increased astrocytic coverage of spines [31]. The coverage and volume effects thus originate within a dynamic structure that can be actively deployed to locally enhance or constrain communication between neurons.

Taken as a group, these findings indicate that microdomains represent independently functioning and targeted compartments that are generated by astrocytes to respond to, initiate, and modulate information flow across synapses.

Intracellular Signaling Mechanisms Affecting Information Flow

Accumulating evidence suggests that the calcium fluctuations occurring within the microdomains are due to calcium influxes that have their genesis from several sources. These include both intracellular and extracellular sources and involve mitochondrial and ER cell organelles as well as cellular membrane channels and transporters. The identification of these sources has traditionally been difficult to determine due to the small size of the microdomains. Recent technical developments of genetically encoded calcium indicators [32], however, have partially overcome size constraints imposed by these domains and/or the disruption of the cell membrane that often occurs during dye loading, revealing how these sources modulate domain specific, calcium levels.

Intracellular sources of calcium: ER and mitochondria

Intracellularly, stimulation of metabotropic excitatory and inhibitory, G-protein-coupled receptors (GPCRs) at the extracellular membrane induces the production of IP3, which activates IP3 receptors (IP3 Rs) on ER membranes and releases of Ca^{2+} from the endoplasmic reticulum (ER) [33]. Consistent with the observation of ER in microdomain nodes, genetic deletion of the IP3 R type 2 (IP3R2), decreases the number and/or amplitude of spontaneous Ca^{2+} events by approximately half [34]. The fact that not all Ca events are eliminated suggests that there are other internal calcium sources that contribute to calcium elevation during stimulation. This inference was confirmed when Ca^{2+} transients were found to originate from mitochondria [35], leading to the hypothesis that mitochondrial IP R1/3 or ryanodine receptors act in concert with IP3R2 ER receptors to release Ca to the node cytosol. Besides these routes, intracellular calcium elevations can arise from mitochondrial efflux in response to the opening of the mitochondrial permeability transition pore (mPTP).

Extracellular sources of calcium

Although Ca microdomain events rely in part on Ca^{2+} release from intracellular stores, increasing evidence reveals a greater dependence of calcium based oscillatory signaling on the influx of extracellular, transmembrane Ca [36]. While GPCR pathways can evoke IP3 signaling and internal release of Ca - the so called calcium initiated calcium release events (CICR) - the relative slowness of CICR changes with respect to fast onset calcium events suggests the presence of other calcium sources capable of providing for fast calcium level changes. These sources of rapid calcium influx are now known to involve extracellular calcium, which can occur through multiple and distinct ionotropic receptors and ion channels.

Among the chief ionotropic receptors are those sensitive to glutamate. These receptors (iGluRs) are ligand-gated ion channels that become permeable to the cations Na, Ca, and K when activated by glutamate. They are generally classed into iGluRs according to their respective sensitivity to either kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropi- acid (AMPA), or N-methyl-D-aspartate (NMDA). Studies employing patch-clamping of astrocytes have shown the induction of both depolarization and Ca changes, an apparent indication of the extracellular origin of Ca in intracellular calcium changes [37]. While the functional significance of astrocyte AMPA receptors has remained uncertain, astrocyte NMDA receptors appear to have functionally significant roles in maintaining astrocyte Ca levels, which has implications for Ca microdomain activity pertinent to gliotransmission and/or the regulation of synaptic strength. Topical superfusion of either AMPA or NMDA receptor antagonists, for instance, when applied directly to the brain, reduces fast Ca events in astrocyte processes, but only the NMDA antagonist CNQX reduces fast Ca events in nodes [38].

Astrocytes also express alpha-7 nicotinic acetylcholine receptors in their membranes and acetylcholine activation of these receptors can induce intracellular Ca^{2+} transients [39] in culture or in hippocampal slices. The nicotinic receptors have high Ca permeability, but are rapidly deactivated, suggesting their involvement is limited to very short-lived astrocytic Ca events. Activation of astrocyte α7nAChRs has been shown to cause D-serine release, leading to nearby neuronal NMDA receptor modulation and the induction of patterned gliotransmission during the circadian cycle. Importantly, nicotinic receptor activation also induces morphological changes in perisynaptic processes, which affects spine and synapse coverage.

Another ligand gated, ionotropic receptor permitting Ca influx into astrocytes is the purinergic (P2X) class of receptors, which are sensitive to ATP. P2X activation has been shown to cause astrocyte Ca transients in cell soma in brain slices and

isolated astrocytes, as measured with Ca dyes [40].

Finally, a Ca transporter, the Na/Ca exchanger (NCX), has been shown to have several notable functions in modulating domain located, calcium events. In astrocytes the Na/Ca exchanger (NCX) extrudes intracellular Ca in exchange for Na influx [41]. Increases in intracellular Na+ levels, however, cause the NCX to reverse direction and to bring extracellular Ca2+ into the cell in exchange for Na+ efflux, leading to Ca2+ increases in astrocytes. Hence, it functions as both a homeostatic and a calcium signaling regulator. Significantly, NCX is primarily confined to fine peri-synaptic astrocyte processes where it is frequently localized with the Na+/K+ ATPase and glutamate transporters that work together to take up glutamate and buffer ion gradients [42]. This creates an insular compartment for Ca2+ and Na+ signaling that is restricted to the astrocyte perisynaptic processes.

Combined intracellular and extracellular sourcing for fine tuning of Ca changes

While calcium fluctuations in microdomains may have an exclusively intracellular or extracellular calcium source, cooperativity among multiple sources is known to exist in cases, contributing to the amplitude and spatiotemporal dimensions that shape the overall features of transient calcium events [32]. Under typical conditions, for example, ER calcium release triggers activation of calcium influx via store operated calcium entry (SOCE). The depletion of ER calcium in such cases induces the migration of sensor stromal, interaction molecules (STIMs) to the plasma membrane and activates Ca - release-activated Ca2+ channels (CRAC channels) formed by Orai proteins. This movement enables calcium influx from the extracellular space. In line with this observation, Ca transients evoked by thrombin in PAPs from Orai1- /- mice are substantially attenuated, an indication that Ca events in microdomains rely on the coordinated release of calcium from the ER and the extracellular space.

Although a complete picture of Ca microdomain processes contributing to calcium signaling is not fully resolved, it is significant that microdomain calcium events can be differentiated according to fast and slow events and implicates at least two classes of functional mechanisms by which astrocytes could govern communication between neurons. The dominant contribution to fast calcium influx due to NCX [43] indicates that this transporter is likely to be critical to the ability of astrocytes to initiate or respond quickly to neuronal events; hence, this also likely implicates its participation in interneuronal events on time scales comparable to those of neuronal transmission. More slowly occurring calcium events, on the other hand, can be expected to affect information flow over longer time scales, possibly related to plastic changes associated with synaptic events like long term potentiation (LTP) or long term depression (LTD) [31] that shape the spatiotemporal aspects of interneuronal information flow.

Regulating calcium fluctuations in micro domains

Cytosolic calcium increases are among the earliest events that follow stimulation of many different types of cells by extracellular signaling molecules such as neurotransmitters or hormones and frequently transition to periodic patterning like that of oscillations or waves. The adoption of such patterning across a wide variety of cell types has been shown to have functional relevance [44] suggesting that deviations in such patterning could result in cellular pathologies. In astrocytes,

both neuronally driven and spontaneous Ca oscillations are implicated in modulating interneuronal communication [32,45]; hence, impaired astrocytic influences on Ca oscillations have the potential for eliciting pathological cellular functioning.

Neuron driven and spontaneous oscillations

In the visual cortex and hippocampus, neuronal afferents can trigger Ca oscillations within astrocytes, with oscillation frequency varying as a function of afferent firing rates [46]. Increases in either intensity or frequency of a neuronal stimulus induces an increase in the frequency of calcium oscillations. Repetitive episodes of neuronal stimulation or the application of glutamate receptor agonists amplifies these effects, resulting in long-lasting increases in Ca oscillation frequency. The dynamic control exercised by neuronal activity over oscillation frequency suggests, as in other cell types, that the pattern of stimulation could encode neuronal specific information.

In addition to neuronally driven oscillations , astrocytes also display calcium oscillations that are not driven by neuronal activity [45]. These spontaneous oscillations can trigger NMDA receptor-mediated inward currents in neuron partners thereby directly initiating neuronal activity. Significantly, spontaneous calcium oscillations appear to be subject to non-linear dynamical properties, exhibiting bifurcations and synchronization, suggesting that calcium encoding within astrocytes may also entail computational processing. Such observations reveal not only bidirectional influences between astrocytes and neurons that involve Ca oscillations but also that astrocytes can act as primary sources for modulating neuronal activity.

Regulating NCX oscillations in astrocytes

Increasing evidence indicates that the coupling between synaptic neuronal activity and microdomain calcium oscillations is subject to tight control and that a primary candidate for this coupling is the Na+/ Ca2+ exchanger (NCX) [42] located on the astrocyte microdomain membrane. [29,30]. Supporting a primary role for the transporter, Ca fluctuations in thin astrocytic processes are preserved in IP3 type 2 receptor (IP3R2) knock-out animals, indicating that local Ca oscillations are not primarily driven by ER store-operated mechanisms. Instead, regulation of NCX activity may involve processes capable of changing intracellular Na concentrations, since slight changes in Na from 15 mM to 20 mM reverses the transporter, revealing a high degree of sensitivity to intracellular Na, which ordinarily lies within the 15 - 20 mM range.

The use of the NCX as a mechanism for driving intracellular calcium oscillations appears to occur in magnocellular neurons also, where many of the putative influx sources that could affect calcium oscillations have been explored pharmacologically [47]. Using this system, studies have been specifically conducted on transport and channel mechanisms including voltage gated calcium channels, Na channels, signaling species, and neurotransmitters. These studies have found that inhibitors of voltage gated calcium channels (VGCC) such as nicardipine, conotoxin GVIA, conotoxin MVIIC, agatoxin IVA (for L-, N-, P and P/Q-type channels, respectively) do not affect Ca oscillations, although a specific R type VGCC blocker, SNX-482, was observed to diminish their magnitude. Inhibition of the Na channel with TTX also did not affect the occurrence of oscillations, whereas the elimination of extracellular Na or inhibition of NCX reverse mode operation with KB-R7943 blocked them. Intracellularly, the inhibitor of mitochondrial coupling, CCCP, irreversibly blocked spontaneous Ca

fluctuations. On the other hand, the attenuation of intracellular signaling by inhibitors of phospholipase C and adenyl cyclase had little effect. The neurotransmitter GABA, but not glutamate, also blocked oscillations. Pharmacological investigations thus indicate that spontaneous oscillations in a class of neurons are mediated by mechanisms affecting intracellular Na concentration that may drive the NCX exchanger and by mitochondrial inhibition. These findings reveal the presence of a general intracellular signaling mechanism linking NCX influx mechanisms with calcium oscillations, a mechanism likely to be widely distributed among both glial and neuron cells of the brain that may undergird fast bidirectional communication between the two cell classes [48].

Regulation of the astrocyte sodium calcium exchanger

The dominant role played by the NCX in mediating rapid internal changes in calcium implicates, by extension, regulatory mechanisms of the transporter in synaptic activity. Besides the role played by intracellular Na concentration changes on the orientation of NCX calcium mediated transport, several other factors contributing to the magnitude of NCX mediated calcium influx are likely to affect synaptic communication. These factors include phosphorylation of the exchanger and the dynamic morphological changes occurring in the microdomain region that stimulate exchanger dynamics.

Phosphorylation

Studies of NCX phosphorylation show that ATP hydrolysis is unlikely to be needed by the exchanger to power net calcium extrusion. On the other hand, cytosolic ATP appears to have a significant effect on exchanger kinetics [42]. This is likely to be due to the phosphorylating of critical sites on the exchanger [49], since removal of the nucleotide in the presence of Mg is known to deactivate the exchanger. When thiophosphorylated, moreover, it is only partially deactivated following substrate removal [42], consistent with the greater stability of the thiophosphorylated residue and reduced access to phosphatase action. In dialyzed squid axons thiophosphorylation stimulates all exchange modalities, so long as Mg is present. As a group, these data implicate the involvement of kinase action in exchanger transport. The ineffectiveness of inhibitors of various kinases such as the PKA, PKC, TyrK, and CAMK kinases, however, suggests that the kinase phosphorylating the exchanger is not a member of these kinase classes. Nonetheless, some involvement of PKA phosphorylation of exchanger may occur since cAMP signaling modulates a slow pattern of ex- changer related calcium fluctuations.

Volume changes and actin mobilization effects on calcium fluctuations

Astrocytic perisynaptic processes are highly dynamic and these dynamic features have been linked to effects on interneuronal transmission. Oscillatory Ca fluctuations also appear to be coupled to these morphological changes, which can involve greater or lesser synaptic coverage of microdomains over pre- or postsynaptic contacts and which have been correlated with NCX transporter activity [33]. Additionally, the occurrence of Ca fluctuations strongly depends on the astrocytic surface to volume ratio (SVR). High astrocytic SVR values, for example, are correlated with large amplitude astrocytic Ca fluctuations, whereas medium SVR values - in conjunction with high coverage of both presynaptic axon terminal and postsynaptic dendritic spines - are correlated with medium Ca fluctuations.

Significantly, power spectral density changes over a range of 100 to 500 Hz are also directly correlated with increasing SVR. Together with the finding that NCX induced calcium oscillations are dependent on the surface to volume ratio, these rapid changes in perisynaptic regions highlight a prominent role for a dynamic cytoskeleton during structural remodeling of astrocytes that is likely to influence neuronal communication via NCX activity.

Since microdomains lack microtubules and intermediate filaments [26], microdomain shape changes are likely to involve cytoskeletal reorganization of actin filaments. Accordingly, mechanisms for regulating the microdomain actin cytoskeleton can be expected to also influence the generation of calcium oscillations within these zones.

In analogy with the lamellipodia of migrating non-neuronal cells that have F-actin-rich subcellular compartments, dynamic movements of astrocytic microdomains are largely inactivated upon inhibition of the GTPase Rac1 protein [50], an ubiquitous GTPase that drives lamellipodia formation. Inhibition of Rac1 inactivates downstream target proteins Arp2/3 that enable actin branching, which results in extensive changes in normal astrocyte morphology. For example, Arp2/3 inactivation in situ has been associated with the loss of fine extensions [51] and knockdown of Arp associated proteins like profilin reduce the astrocytic volume [52]. Besides these proteins, dynamic changes at the synapse are also modulated by the actin linker proteins ezrin and connexin30 that enhance synaptic potentiation. Synaptic proteomics, in line with this, show that new translation is required for changes in perisynaptic astrocyte protein composition that occur after fear conditioning [53].

Cumulatively, the occurrence of rapid cytoskeletal remodeling in astrocytes in response to synaptic activity and LTP suggests the presence of a transducing, excitable actin network. Since actin dynamics are known to be altered by chemophysical stimuli and topography these latter may be among the predisposing factors that modulate NCX induced, calcium fluctuations.

Astrocyte Contribution to Information Coding and Decoding

In principle, calcium oscillations can encode diverse and specific signals via various modes that are subject to modulation. Modulation may occur by altering oscillation frequency or magnitude, or by shifting coupling regimes, which are known to occur in a wide variety of cell types and cellular functions including oocyte fertilization, cell secretion, muscle contraction, neuronal migration, and neurite growth, development, and apoptosis [44,54,55]. Similarly, encoding of information in astrocytes could be linked to rapidly occurring calcium oscillations that are generated by the NCX exchanger. As noted, the spatial geometry of microdomain regions has significant influence on spontaneous Ca oscillations generated by the NCX exchanger, with increases in the surface area to volume ratio yielding large amplitude calcium fluctuations, synaptic coverage changes, and frequency dependence. Effects on calcium signaling related to the intracellular spatial distribution of various microdomain constituents may be mediated by other influx mechanisms also, albeit to lesser degrees and occurring more slowly. In one model the frequency of calcium signals is critically dependent on the spatial organization of the IP3R ER channels, based on the dynamics of calcium induced calcium release (CICR) into small spatial volumes that correspond to microdomains [46]. Depending on the spatial distribution of

the calcium channels, different types of calcium signals can be elicited. Simulations of channel kinetics, for example, show that spontaneous calcium signals are due to the interplay between system excitability and its stochasticity and that this interplay is highly dependent on where the channels are located. In still other cases, mechanical stimulation-evoked Ca2+ responses in astrocytes of the rat brainstem can be blocked by antagonists of connexin channels, connexin 43 (Cx43) blocking peptide Gap26 or Cx43 gene knock-down or antagonists of TRPV4 channels.

These findings raise significant questions on the nature of the information that may be encoded, how this information may be affected by the type and spatial distribution of various effectors, and how and where this information may be decoded so as to modulate synaptic transmission.

Decoding calcium oscillations: Calmodulin, calcineurin, and S100b proteins

Although the nature of the information encoded by the spatial dynamics of microdomains is uncertain, there is increasing understanding of the mechanisms likely to be employed to decode this information. This understanding may yield insight into the sources and nature of the encoding processes as well as the transmission of this information by interneuronal exchange. The involvement of the NCX in Ca-dependent, exocytotic glutamate release, for example, could be linked to the activation of plasmalemmal ionotropic glutamate receptors and glutamate transporters at the synapse to mediate messaging via fast and spatially localized gliotransmission [48].

Among the potential decoding processes, there is accumulating evidence that coupling to gliotransmission utilizes transducing molecules that include the calcium binding protein calmodulin and the protein phosphatase, calcineurin. Both calmodulin and calcineurin are known ubiquitous players in intracellular calcium signaling. Calmodulin (CaM) is a small, but highly conserved protein that is activated when bound to calcium. In the Ca-free state, its structure is collapsed but when bound to calcium its conformation opens, such that it can interact with a wide range of target proteins. For example, the predominantly hydrophobic nature of this binding permits some 300 known target proteins to be recognized via a wide variety of CaM-binding sequences. Among the most important targets are calmodulin kinase II and the phosphatase calcineurin.

Calcium binding of calmodulin is required to yield the activated CaM unit that binds to calcineurin, one of the most abundant proteins in the CNS [57], which yields the active phosphatase form. This process thus links calcium signaling to dephosphorylation in a manner resembling the coupling of calcium signaling to phosphorylation that occurs via CaM-activated kinases. Significantly, the affinity of CaM for calcineurin is in the low picomolar range. This extraordinarily tight binding suggests an important role for calcineurin as a CaM substrate, as well as its downstream targets, in transducing Ca fluctuations.

In nervous tissue, calcineurin has been shown to be needed both for normal information processing and in pathological astrocytic gliosis [58]. Calcineurin deficient mice, for example, exhibit abnormal spatial memory behaviors, adopting a broad variety of learning strategies, which suggests that memory acquisition requires CaN. Astrocytic CaN can also be strongly activated in response to LTP induction, revealing a potential role for astrocytic CaN in transducing high frequency, neuronal activity.

Nonetheless, how calcineurin may decode calcium signals remains to be determined. In pancreatic islet cells calcineurin activation follows the oscillatory dynamics of the intracellular calcium fluctuations [59], indicating rapid rephosphorylation of the target protein after calcineurin phosphatase activity and suggesting that embedded codes are found in the oscillatory dynamic per se. Significantly, calculations of the kinetics of Ca2+ binding and dissociation from CaM indicate that the calcium bound form of calmodulin can diffuse only a short distance, about 0.1 μm, before calcium dissociation, which indicates that Ca2+/CaM is likely to act primarily as a highly localized signal [57]. Consistent with this, the subcellular spatial distribution of calcineurin activation is tightly coupled to CaM locations in cells [59]; revealing that the localization of CaM actively shapes both the spatial and temporal aspects of coded messages that may be transduced by calcineurin.

Another calcium transducing candidate that has been shown to have a role in modulating synaptic, information flow is the S100b protein. Like calmodulin, S100B is a small acidic, calcium-binding protein. Originally isolated in the nervous system, it is concentrated in astrocytes, though also present in other glial cells, as well as in certain neuron subpopulations. The protein shares common structural domains with calmodulin and is a member of the S100 family of proteins that contain the 2 EF-hand calcium-binding motifs. Both calcium binding proteins bind to the microtubule associated protein tau and prevent PKC phosphorylation of tau via interaction with the substrate protein rather than the kinase. In line with a role in cytoskeletal modulation, S100b is known to promote neuronal proliferation, oligodendrocyte differentiation, and the assembly of cytoskeletal components employed to maintain astrocyte morphology [60].

Calcium activation of protein S100β has been also shown to modulate neuronal oscillations [61], with increases in activation being correlated with increases in phase amplitude coupling between theta and gamma oscillations. While changes in neuronal oscillations and alterations in the coupling across frequency ranges have been correlated with memory, the demonstration that S100b is likely to modulate their interaction provides the novel finding that astrocyte cytoskeletal dynamics may affect synaptic communication.

Significantly, the S100b protein appears to also function in a calcium dependent manner as a suppressor of Aβ42 aggregation and toxicity [62], which characterize Alzheimer's dementia. Nuclear magnetic resonance experiments reveal that the suppression of aggregation is due to a dynamic interaction between Aβ42 and S100B at a peptide- binding region within the S100B homodimer. This physical interaction prevents the aggregation of Aβ42 by interacting with Aβ42 monomers to inhibit the initial nucleation. The calcium-bound state also significantly affects secondary clustering by preventing fibril catalyzed reactions through S100B binding to the growing Aβ42 oligomers.

Network Level Astrocytic Influences on Memory

Increasing evidence indicates that through Ca protein transducers microdomain calcium signals regulate memory network communication, modulating the oscillations that bind networks together. Existing models of the memory network hypothesize that the hippocampus functions to integrate memory representations from the perirhinal cortex (PRC), entorhinal cortex, and parahippocampal cortex (minimally), the latter collectively known as the medial temporal lobe (MTL) [63]. More extended models posit a two part system functioning

together with the hippocampus, one that includes the closely related retrosplenial cortex (RSC), posterior cingulate, precuneus, angular gyrus, anterior thalamus, presubiculum, mammillary bodies, and medial prefrontal cortex. Included in the second part are the ventral anterior temporal cortex, lateral orbitofrontal cortex, and amygdala. In this latter model, the first part of the memory system is hypothesized to aid in processing context information while the second processes item concepts [64].

There is a growing consensus that the memory circuits and network pathways distributed within these regions communicate between and within regional nuclei by engaging various modes of rhythmic, oscillatory coupling [65,66]. Astrocyte influences are manifested in their effects on these interactions, affecting the presence of rhythmic patterns within the network, their inter and intra-regional coupling, and the direction of information flow [19,20,32]. Implicating gamma oscillations in regional loci, analysis of local field potential (LFP) and spiking from the prefrontal cortex (PFC) has shown that during a working memory task narrow-band gamma oscillations (45–100 Hz) are correlated with the encoding and re-activation of sensory information. How local gamma oscillatory interactions are regulated by interregional communication has remained obscure, however.

Several findings, notably, indicate that coupling is not likely to rely significantly on fast gamma oscillations [67]. For example, above 50 Hz interregional phase-synchronization of principal cell spikes has been shown to occur mostly in the hippocampal CA1 region, which is the perforant target domain. CA1 pyramidal cells here become synchronized mainly to fast gamma LFP patterns (above 100 Hz) that remain confined to CA1. Additionally, LFP gamma patterns below this frequency range are layer specific. Together these findings suggest that gamma coupling is a relatively ineffective mechanism for interregional communication.

By contrast, an increasing number of studies indicate that interregional coupling involves an active association with theta-frequency signals [68]. Human intracranial recordings, for example, exhibit neuronal synchrony and phase locking at theta band frequencies (4–8-Hz) during memory formation [69, 70]. These results have suggested that interregional theta oscillations couple to local gamma oscillatory events both when memories are formed and when retrieved. Supporting this, high spatial resolution electrophysiology has shown that the theta band of afferent CA3 and entorhinal inputs regulates distinct CA1 interneuron populations in a variety of tasks and behavioral states [66]. Feedback potentiation of inhibition at distal dendrites by CA1 place cells suppresses the excitatory entorhinal input at the place field site of input, establishing the timing needed for CA3 input to regain control over the interneuron population following the initial excitatory phase. Collectively, these studies indicate that inputs from outside the hippocampus interact with local mechanisms to generate the theta- phase timing of hippocampal neurons, which then couple with gamma oscillations used for memory and spatial navigation.

The significance of theta control over local hippocampal gamma oscillations lies in its potential for encoding multiple information states, a property due to the weak nature of the coupling event. While the tendency of oscillators to mutually adapt their rhythms [71] is a known and ubiquitous, natural phenomenon, occurring also in neuronal populations [72], weak coupling results in a continual adjustment of phase,

where the rate of phase adjustment varies as a function of the phase separation between oscillators; that is, phase precession between the two oscillating partners is enabled, a phenomenon characterized in phase response curves and mathematically described by the Adler equation [73,74], which also predicts the forces the oscillators exert on each other as a function of their instantaneous phase difference. Under strong coupling, and for widely separated frequencies such as those of theta and gamma rhythms, the faster gamma rhythm ordinarily becomes 'nested' within the slower theta oscillation at fixed periodic intervals. During weak coupling, the variance in phase separation generates multiple theta-gamma phase combinations. The significance of phase precession for memory has been demonstrated in the correlation of oscillatory properties with memory states, with memory performance, and with effects on memory resulting from disrupting the oscillations [66]. Recent work suggests that theta gamma precession generates the coding scheme that coordinates communication between brain regions and that is involved in sensory as well as memory processes [75-77].

Current evidence suggests that astrocytes actively participate in this oscillatory communication and that this participation is multi-level and multi-modal. Astrocytic influences, firstly, appear crucial to the genesis of the oscillatory events. In basic paradigmatic neuronal structures capable of generating oscillations, comprised of a GABAergic interneuron, pyramidal neuron, and a single CA3-CA1 glutamatergic synapse, interneuron-astrocyte signaling dynamically affects excitatory neurotransmission in an activity dependent manner and can also determine the direction (inhibition vs potentiation) of the GABA-mediated effects [78].

Gamma oscillations are known to typically emerge from the coordinated interaction of excitation and inhibition, which can be detected as local field potentials [79]. Astrocytes modulate oscillation formation by contributing to inhibitory potentiation through astrocyte GABAB receptors, astrocytic glutamate release, and presynaptic metabotropic glutamate receptors. In line with this, the use of conditional astrocyte-specific GABAB receptor (Gabbr1) knockout mice show that astrocytes are the origin of the interneuron-induced potentiation and demonstrate the involvement of astrocytes in hippocampal theta and gamma oscillations.

Besides affecting the genesis of oscillations, astrocytes have the important task of distinguishing between specific memory events. Competition between overlapping memories constitutes a major cause of forgetting. Although it is still unknown how the human brain resolves such mnemonic conflict, it is known that astrocytic regulation assists in increasing firing synchronicity and extending the region of coherent oscillations. In particular, astrocyte-mediated potentiation of inhibitory synaptic transmission markedly enhances the coherence of network oscillations over a broad range of model parameters and leads to emergence of synchronization in the interneuron network. Gliotransmitter-induced depression of synaptic transmission between pyramidal cells and interneurons improves the robustness of the interneuron network gamma oscillations induced by physiologically relevant low and heterogeneous excitatory drive [80].

Supporting a role for astrocyte resolution of mnemonic conflict via gamma synchronization, target and competitor reactivations lock to different phases of the hippocampal theta rhythm after repeated recalls. Participants who behaviourally experience lower levels of interference also show larger phase

separation between two overlapping memories. Such findings provide evidence that the temporal segregation of memories, orchestrated by slow fast oscillatory coupling, plays a functional role in resolving mnemonic competition, differentiating and prioritizing relevant memories under conditions of high interference [81]

The ability of astrocytes to modulate oscillatory events depends upon their innate capacity to influence synaptic events directly. Coding embedded in Ca signaling, for example, can be transmitted via transducer molecules during gliotransmission thereby affecting oscillatory activity. In transgenic mice, for example, tetanus toxin expression in astrocytes inhibits astrocytic exocytosis, leading to impaired gamma frequency oscillations in vivo. Behaviorally, the treated mice are unable to recall objects in recognition tasks but can do so when toxin expression is halted [82].

Other studies have shown that astrocytic intracellular signaling mechanisms specifically involve G proteins. DREAD experiments, for instance, show that the formation of remote memories can be disrupted by activation of G proteins involved in CA3 to CA1 communication. Downstream communication to the anterior cingulate cortex (ACC) [83], particularly, is affected when the G protein receptor is activated by Gi , which suppresses CA1 to ACC communication.

MCI and Pathologies Affecting Astrocytic Regulation of Information Flow

Pathological conditions that manifest as amnestic MCI could arise through perturbation of the cellular and connectivity pathways described above that are normally used by astrocytes to modulate information flow. Shifting the sign of potentiation from normal, astrocyte induced, long-term potentiation (LTP) to long term depression via tetra- hydrocannabinol use, for example, has been shown to lead to impaired working memory [19]. Under normal conditions of high frequency stimulation at CA3 to CA1 synapses, induction of LTP causes endocannabinoid release from post synaptic neurons. These activate receptors located on astrocytes, which then induce d-serine release and binding to NMDA receptors (as a co-agonist) to generate the LTP. By contrast, under pathological conditions tetra- hydrocannabinol activates astrocytic cannabinoid receptors, thereby inducing the LTD, which impairs working memory.

Impaired astrocytic influences have been shown to also disrupt interregional coupling, an effect that could account for working memory deficits observed in AD and MCI. In a cohort of ninety-eight participants theta gamma coupling was the most significant predictor of memory assay results. AD participants in the study demonstrated the lowest level of coupling and poorest performance, followed by MCI patients and finally by controls [84].

Dysfunctions of network activity and functional connectivity (FC) represent early events in Alzheimer's disease and are likely to be present in some forms of MCI as well [85]. While the astrocytic events that may participate in these disruptions remain to be clarified there is good evidence that memory related changes in connectivity entail astrocytic signaling events, as suggested in the G-protein studies. This notion has received confirmation in studies of AD mice models. In this system, early cingulate functional connectivity disruption and neuronal hyperactivity seen in AppNL- F mice are accompanied by decreased astrocyte calcium signaling. Recovery of astrocytic calcium activity reverses these effects, normalizing neuronal

hyperactivity and FC, as well as seizure susceptibility and day/night behavioral disruptions [85].

Conclusion

Although MCI is currently recognized to embrace a spectrum of cognitive impairments, its traditional association with abnormal memory loss leading to dementia has nonetheless retained diagnostic significance. With some 10 to 15% of MCI patients evolving to AD each year, there is a substantial need for addressing the causes of MCI before significant and irreparable cognitive loss.

Here, we review the current understanding of a crucial cellular element involved in regulating and modulating memory networks, the astrocyte. The review presents evidence that astrocytes are critically involved in normal memory functions and that their abnormal functioning leads to pathological influences on memory processes, which may be similarly affected in MCI. While the manner in which abnormal astrocyte functioning may affect memory is unknown, much evidence supports the notion of the central role of the astrocyte in modulating information flow within these networks and identifies many of the mechanisms employed by astrocytes to carry out this role. These findings reveal a highly specialized organization elaborated by astrocytes for achieving multispatial and multitemporal influence over memory formation and retrieval. Perturbation of these astrocytic processes can be expected to lead to disruption of memory networks, and to impair memory formation and retrieval, as shown in the several examples presented here.

Knowledge of how astrocytic signaling enables network formation and cognitive processing thus has implications for understanding the basis of cognitive alterations in MCI pathology, where altered astrocytic signaling could affect synapses, networks, and ultimately memory performance. These findings suggest that targeting astrocyte pathways may represent an important new therapeutic opportunity for treatment of MCI.

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