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Mini Review

Imbalances in Astrocyte Signaling Affecting the Hippocampal Cortical Network in MCI

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Abstract

Amnestic mild cognitive impairment (MCI) is generally understood to mean an age-related impairment in recollection mechanisms beyond that normally observed in the elderly. Various studies show that these mechanisms involve the hippocampal cortical network (HCN), a distributed cluster of mediotemporal brain regions that communicate with the hippocampus, which acts as a network hub. Accumulating evidence indicates that a crucial cellular element regulating information flow within the HCN is the astrocyte. Accordingly, 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 affected in MCI and AD patients, with impairments seen, for example, in reductions in functional connectivity, a measure of interregional coupling. Astrocyte pathologies thus appear to drive network imbalances leading to clinically relevant phenotypes of MCI and could represent novel and significant therapeutic targets for MCI treatment, the subject of this short review.

Keywords: *Mild Cognitive Impairment; Dementia; Astrocytes; Microdomains; Theta-Gamma Coupling*

Introduction

Mild cognitive impairment (MCI) is currently understood to be an age related impairment in cognition exceeding 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 that potentially could be affected [2,3], MCI is also classified broadly as either amnestic or nonamnestic, where amnestic MCI refers to impairment purely in one's ability to recall stored information.

The significance of this classification has traditionally been linked to a presumed clinical indication of dementia, an indication supported by a documented 5% to 10% annual rate of amnestic MCI 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 the capacity for recollection beyond that seen in normal age related, memory decline was highly prognostic for dementia. Although this presumed inference is currently more nuanced, the high proportion of MCI patients evolving to AD nonetheless 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 loss.

In amnestic MCI, a frequent observation made in neuroimaging studies is atrophy of the hippocampus, an observation consistent with widely shared hypotheses of memory. These hypotheses 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].

A growing body of evidence shows that the functional connectivity underlying memory events entails brain oscillations that couple distributed brain regions during recollection and memory formation. While oscillations have often been attributed to inhibitory-excitatory neuron pairing [10], that is, involving neurons alone, an increasing number of findings suggest that a crucial cellular element contributing to these dynamical features is the astrocyte [11,12]. 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 the propagation of calcium changes either directly to synapses or indirectly to neighboring astrocytes, calcium signaling could affect synaptic information transfer between neurons comprising memory networks.

Supporting this, chemogenetic activation of astrocytes has been shown to affect memory performance [13,14]. Gq DREAD (designer receptors exclusively activated by designer drugs) activation in astrocytes of the medial central amygdala, for instance, causes extinction of learned fear memories in fear conditioning tasks. Additionally, optogenetic and chemogenetic activation of the astrocyte Gq signaling pathway in the hippocampus enhances memory allocation and cognitive performance [15].

These findings suggest that disruption of astrocytic mechanisms affecting communication between regions of the HCN 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 energy metabolism are compromised in Alzheimer's [16,17]. Moreover, in mouse models of Alzheimer the dynamic morphological changes normally occurring during memory induction are substantially altered. 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. This opinion piece will argue that the diminished capacity for recollection in MCI is due to a disruption of inter-oscillatory interactions in memory networks, which is likely to be causally associated with astrocytic imbalances affecting network dynamics.

Network level mechanisms of memory

Structural models of the hippocampal cortical network hypothesize that the hippocampus functions to integrate memory representations from (minimally) the perirhinal cortex (PRC), entorhinal cortex, and parahippocampal cortex, the latter collectively known as the medial temporal lobe (MTL) [18]. More regionally 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 [6].

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 [9,19]. Implicating gamma oscillations in regional

loci, analysis of local field potential (LFP) and spiking from the prefrontal cortex (PFC) has shown that during the performance of a working memory task narrow-band gamma oscillations (45 - 100 Hz) occur during encoding and re-activation of sensory information. How local gamma oscillatory interactions are regulated by interregional communication has remained obscure, however.

Several findings indicate that coupling is not likely to rely on fast gamma oscillations alone [20]. Above 50 Hz, for instance, interregional phase-synchronization of principal cell spikes has been shown to occur mostly in the hippocampal CA1 region, 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. These findings thus suggest that for interregional communication gamma coupling is unlikely to be used and may be a relatively ineffective mechanism.

By contrast, an increasing number of findings indicate that interregional coupling involves an active association of local gamma oscillatory activity with theta-frequency signals [21]. Human intracranial recordings, for example, exhibit neuronal synchrony and phase locking at theta band frequencies (4 - 8-Hz) during memory formation [22]. On the basis of such findings it has been theorized that interregional theta oscillations couple to local gamma oscillatory events both when memories are formed and when retrieved. Supporting this, high spatial resolution electrophysiology shows that the theta band of afferent CA3 and entorhinal inputs regulates distinct CA1 interneuron populations in multiple tasks and behavioral states [9]. Additionally, feedback potentiation of inhibition at distal dendrites by CA1 place cells suppresses the excitatory entorhinal input at the place field site of input, dictating the theta frequency 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, via coupling 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 feature essential for memory and a property apparently resulting from the weak nature of the coupling event. While the tendency of oscillators to mutually adapt their rhythms [23] is a known and ubiquitous, natural phenomenon, occurring also in neuronal populations [24], weak coupling - in contrast to strong coupling - results in a continual adjustment of phase, where the rate of phase adjustment varies as a function of the phase separation between oscillators. 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, however, such intervals vary with phase separation and such 'nesting' precesses throughout the theta cycle, thus generating multiple theta-gamma phase combinations. (Precession, as well as when two coupled oscillators are synchronized is characterized in phase response curves and mathematically described by the Adler equation [25,26], which also predicts the forces the oscillators exert on each other as a function of their instantaneous phase difference.) 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 [9]. 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 [27].

Astrocyte contributions to memory network dynamics

Astrocyte influences are manifested in their effects on these interactions, modulating the presence of rhythmic patterns within the network, their inter and intra regional coupling, and the directionality of information flow [12]. Current evidence suggests that astrocytes actively participate in this oscillatory communication and that this participation is both multi-level and multi-modal, affecting intra and interregional activity.

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 inhibitory interneuron, pyramidal neuron, and single CA3-CA1 glutamatergic synapse, interneuron-astrocyte signaling dynamically affects excitatory neurotransmission in an activity dependent manner. Gamma oscil-

lations, for instance, typically emerge from the coordinated interaction of excitation and inhibition, where they are detected as local field potentials [28]. Astrocytes modulate oscillation formation by contributing to inhibitory potentiation through astrocyte GABAB receptors, astrocytic glutamate release, and presynaptic metabotropic glutamate receptors. The use of conditional astrocyte-specific GABAB receptor (Gabbr1) knockout mice, for instance, 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, accumulating evidence indicates that astrocytes improve the precision of memory encoding, assisting in the important task of distinguishing between specific memory events. Because different memory events need to be segregated so that they can be individually recalled, the capacity for recollecting distinct memories requires mechanisms individually coding for separate events. Overlap in memory coding due to heterogeneous and noisy inputs, however, blurs the distinction between memories reducing the ability to select individual memories and constituting a major cause of forgetting. Although it is still unknown how the human brain resolves such mnemonic conflict, it is known that astrocytic regulation contributes to enhanced firing synchronicity and to spatial expansion of the zone of coherent oscillations [29]. In particular, astrocyte-mediated potentiation of inhibitory synaptic transmission markedly improves the coherence of network oscillations over a broad range of model parameters leading to enhanced synchronization in the memory network. Additionally, gliotransmitter-induced depression of synaptic transmission between pyramidal cells and interneurons also improves the robustness of network gamma oscillations induced by physiologically relevant low and heterogeneous excitatory drive. Cumulatively, these findings suggest that astrocytes sharpen the distinction between memory events and enable the mechanisms for resolving individual memories to operate under conditions of relatively high noise perturbations [30].

Astrocytes and theta gamma oscillatory coupling

Astrocytes are also likely to directly facilitate interregional communication by promoting theta gamma coupling in response to acetylcholine modulation [31]. In support of this, in networks characterized by local excitation and global inhibition connectivity, like that of the hippocampus, simulated, spatially heterogenous Ach activation leads to the emergence of localized theta and gamma band activity rhythms. Gamma-band activity here is promoted in high-ACh activation regions via the pyramidal-interneuron gamma mechanism [31], where inhibitory interneurons strongly modulate and synchronize the activity of pyramidal cells [32,33]. Theta band modulation of gamma activity within or between high-ACh regions, on the other hand, is associated with spike frequency adaptation [25-27]. The combination of these mechanisms leads to intrinsically tight coupling between gamma and theta band activity where the degree of theta-gamma coupling is linked through its proximity to high ACh regions. Mechanisms underlying this coupling are apparently associated with the differential modulation of potassium M- currents, a well known process carried out by astrocytes. Accordingly, theta-gamma coupling is likely to be due to the spatially segregation of ACh loci that mediate neural response properties via astrocyte mediated changes in M type potassium conductance [33].

The appearance of the individual rhythms and theta-modulation of gamma oscillations strongly depends on the specific characteristics of the spatial distribution of the M-current conductances, including the number of conductance (g_{Ks}) hotspots and their radius [31]. This is shown in two ways. In the first, spatially homogeneous models with low g_{Ks} values display no spike frequency adaptation in the network, while homogeneous high g_{Ks} distribution show random neuronal spike-frequency adaptation patterns, without consistent formation of theta band oscillations. In the second, by contrast, spatially heterogeneous regions consisting of low g_{Ks} within confined high g_{Ks} zones allow for theta band modulation of the activity within these regions with the emergence of gamma oscillations during phases of firing activity. Cumulatively, and consistent with an astrocytic role in interregional oscillatory coupling, this means that the location of cortical astrocytes within tripartite synapses would allow bidirectional interaction between neurons and astrocytes to be efficiently controlled by $[K^+]o$ regulation.

Such positioning would also enable rapid modulation of neuronal synchronization and network activity [34]. Of significance, local electrical fields generated by synaptic currents flowing through AMPA receptors are voltage dependent, and can tune the excitatory synaptic

response by altering the dwell time of charged neurotransmitters such as glutamate. Thus, changes of $[K^+]o$ due to alterations in astrocytic K^+ clearance mechanisms could influence local electrical fields, shaping synaptic current waveforms and ultimately impacting the integration and synchronization of the whole network [35].

Additionally, the ability of astrocytes to encode information by modulating intracellular calcium oscillatory events can be expected to affect information content flowing through memory networks. Coding embedded in Ca signaling, for example, can be transmitted via transducer molecules and gliotransmission or by K conductance changes that affect network oscillations. 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 [36].

Still other studies have shown the specific involvement of G proteins in astrocytic intracellular signaling mechanisms. DREAD experiments, for instance, reveal 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) [37], 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 in these networks. Shifting the sign of potentiation from astrocyte induced normal long term potentiation (LTP) to long term depression via tetra-hydrocannabinol use, for example, is known to lead to impaired working memory [12]. 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. Under pathological conditions tetra-hydrocannabinol activates astrocytic cannabinoid receptors, thereby inducing the LTD, which in this latter instance impairs working memory.

Such impaired astrocytic mechanisms have also been shown to disrupt interregional coupling, an effect that could account for working memory deficits observed in AD and MCI. In a cohort of ninety-eight participants, for example, theta gamma coupling was the most significant predictor of memory assay results. AD participants in this study demonstrated the lowest level of coupling and poorest performance, followed by MCI patients and finally by controls [38].

Dysfunctions of network activity and functional connectivity (FC) represent early events in Alzheimer's disease and are likely to be present in MCI as well [39]. While the astrocytic events that may participate in these disruptions remain to be fully clarified there is good evidence that memory related changes in connectivity in MCI 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 App^{NL-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 [39].

Conclusion

Although MCI is currently recognized as embracing a spectrum of cognitive impairments, its traditional association with abnormal memory loss leading to dementia nonetheless retains 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.

This article reviews the current understanding of a crucial cellular element involved in regulating and modulating memory networks, the astrocyte. Considerable evidence now shows that astrocytes are critically involved in the genesis and operation of memory networks and that their abnormal functioning is disruptive to these networks, an effect that may also occur in MCI. While the manner in which ab-

normal astrocyte functioning may affect memory in MCI is unknown, the known role of astrocytes in oscillatory genesis, robustness, and interregional coupling suggests that the impairment of mechanisms underlying these events is a likely causal factor for loss of memory in older patients.

Knowledge of how astrocytic signaling enables network formation and cognitive processing thus has implications for understanding the basis of cognitive alterations in pathological conditions, in which altered astrocytic signaling affects synapses, networks, and ultimately memory performance. These findings suggest that targeting astrocyte pathways may represent an important and novel therapeutic opportunity for care of MCI pathologies.

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