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Journal of Brain and Neurological Disorders

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Research Article

Astrocytes and Resting State Network Dynamics

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Received Date: 03 September 2022 | **Accepted Date:** 06 September 2022 | **Published Date:** 14 September 2022

Citation: Denis Larrivee. (2020). Astrocytes and Resting State Network Dynamics, *J. Brain and Neurological Disorders*. 5(3): DOI:10.31579/2692-9422/037

Abstract

Various studies, including computational brain network modelling, indicate that highly structured, dynamical brain organization can be explained in terms of large-scale neural structures that support diverse brain functions. Consistent with this hypothesis, such studies have demonstrated the occurrence of synchronous activity in multiple brain areas, which reflect functionally distributed domains known as resting state networks (RSNs). While mechanisms that underwrite RSN function remain to date obscure, a dominant conception posits that brain activity is constituted in oscillatory phenomena and governed by dynamical principles that exhibit a tendency to converge to stable states or stable trajectories between stability zones. Brain computational processes using these states must accommodate their dynamical properties when engaged in information processing. Increasing evidence suggests that a crucial cellular element modulating dynamical features is the astrocyte. Astrocytes, for example, have been shown to regulate the UP state of the slow oscillation during NREM sleep via their effects on calcium dynamics. Clarification of the astrocyte role in modulating RSN dynamics can be expected to reveal key factors undergirding the brain's organizational stability and function and, conversely, how affecting this role can lead to brain pathologies, themes discussed in this review.

Keywords: resting state networks; astrocytes; slow oscillation wave; brain dynamics; attractors

Introduction

Computational brain network modelling based on neuroimaging data as well as many other studies reveal that the brain's dynamic organization can be explained in terms of resting-state-networks (RSNs), large-scale neural structures that undergird diverse brain functions. Supporting this hypothesis, various studies have demonstrated multiple patterns of synchronous activity occurring throughout the brain, which reflect functionally distributed domains, variously termed functional systems, intrinsic connectivity networks, or resting state networks (RSNs) [1,2]. The topography of RSNs, for example, closely corresponds to responses elicited by a wide variety of sensory, motor, and cognitive tasks.

RSNs are posited to engage in the processing of information that is received within, computed by, and responded to by the brain. Such processing is thought to underwrite mental activity and to involve not only the use of external information but also the generation of new information, i.e., information not present in a received stimulus [3]. On a coarse-grain level of description, brain activity, and RSNs particularly, can be represented by the dynamics of a complex self-organized system [4,5] that remains robust against perturbation. Indeed, despite the fact that the brain is a noisy place, with individual neuronal responses of high variability, the cooperative activity of neurons is robust against noise and reproducible [6]. Although this stability is partly due to underlying neuroanatomical structures, the generation of RSNs is not primarily structural, but results from an interplay between dynamics and structure [7], which together elicit the functional connectivity that stabilizes the network.

Traditionally, network dynamics 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. A dominant conception hypothesizes that dynamical phenomena are the result of the brain's tendency to converge to stable fixed point or other dynamical states such as limit cycles or strange attractors. Accordingly, computational processes using these stable states must accommodate their properties when engaged in information processing, such as those governing transitions between state levels or movements between attractor loci. Alternatively, stability has been conceived in the context of pathway selection, where the trajectory rather than the destination of information flow retains robustness, a state that has been designated as metastable [4].

Several current hypotheses have linked the underlying activation patterns of resting networks to the presence of such stable switching attractors, which enable information maintenance and facilitate cognitive transitions [8,9]. The relationship between these dynamical features and their

instantiation in RSNs at cellular and systems levels has remained obscure, however. Physiologically, there is much support indicating that large scale electrical patterns, associated with resting networks and distributed throughout cortical regions, underpin their highly ordered structure, thereby enabling and regulating information exchange. These repetitive patterns, frequently identified with brain oscillations, can adopt dynamical features that exhibit meta or multistable states that shape and determine information flow. The stability of resting state networks, for example, is typically conceived in the context of the synchronicity of oscillatory phenomena, which has been implicated in mechanisms of information exchange [10].

While oscillations have often been attributed to inhibitory-excitatory neuron pairing [11], that is, involving neurons alone, an increasing number of findings suggest that a crucial cellular element contributing to these dynamical features is the astrocyte [12,13]. 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 to adjacent astrocytes, calcium signaling could affect synaptic information transfer between neurons. Additionally, astrocytes are known to express a repertoire of receptors, transporters, and other molecules, enabling them to sense numerous synaptic mediators as well as cytokines, prostaglandins, and signals related to changes in local ionic concentrations and pH.

This array of mechanisms suggests that astrocytes could significantly modulate brain states through their influence on the stabilizing and destabilizing of rhythmic activity associated with resting networks and the regulating of transitions between these states. Indeed, Ca waves within astrocytes have been shown to regulate slow and infraslow oscillatory activity that characterize NREM sleep as well as modulate other global physiological functions [14]. The currently understood properties of astrocyte signaling thus implicate their intimate participation in brain communication at various spatiotemporal scales of interaction, from the synaptosome to the mesoscale.

These findings support the notion that astrocytes are key elements in resting state network dynamics, maintaining their structure and guiding the trajectory of their transitions; that is, in the generation of new brain states with their state dependent capacities for processing and disseminating information. The thesis that information flow in the brain is guided by ordered sequences of metastable states [1,15], for example, has been related to events having their origin in astrocytic function.

This introductory chapter will discuss the role of astrocytes in shaping the dynamical features of RSNs using a representative resting state network, the slow wave. The discussion will highlight the role of astrocytes in mediating neuroplastic events and in structuring calcium movement within astrocytes and between members of their networks, which are tightly coupled to the slow wave [14]. It will also highlight neuromodulatory influences on astrocytes that result in shifts between stability levels, chiefly through oscillatory desynchronization, thereby yielding mesoscale shifts affecting global brain states. Importantly, while clarification of the astrocyte role in modulating dynamical states can be expected to reveal the biological basis of the brain's organizational stability and function, this understanding is also likely to advance understanding of how these processes go awry in pathological brain events.

(1) Long Range Networks: Stability And Transition

Resting-state networks possess multiple intrinsic properties that identify them as brain networks. Besides neuroanatomical structure, documented findings also include local neuronal dynamics, signal transmission delays, physical features of the neuropil, glial elements, and genuine noise. Increasingly, astrocyte contributions to network stability and dynamics are being reported [16].

The slow wave

Illustrative of these networks is the slow wave, a global activity state that incorporates cortical and, to a limited extent, subcortical activity occurring during NREM sleep. This slowly oscillating wave originates from both the thalamus and cortex with oscillations that take place roughly every second between an Up period of depolarization with spiking and a Down/Off period of hyperpolarization in which neurons are silent [17]. Occurring roughly in synchrony across all neurons, these features allow the pooled activity to be detected at the cortical surface as slow waves. Studies of select, slow oscillation phases reveal that the negative peak is continuously shifted across the cortex [18]. On average, the maximum delay across the cortex is about 120 msec. Additionally, slow oscillations are found more frequently in anterior regions and propagate posteriorly. Streamline maps that condense the spatio- temporal dynamics of these slow oscillations reveal that the origin of the waves coincides with the position of the anterior electrodes, with the average delay map oriented predominantly in a fronto-occipital direction. Together these data show that the slow wave is a global, synchronized network phenomenon, involving neurons throughout the cortex and, to a lesser degree, neurons in subcortical areas, including the thalamus, striatum, and cerebellum.

The oscillation period of the slow wave depends upon the intersection between initiation mechanisms of the Up state and the refractory mechanisms occurring during the Down state [19]. After an Up state terminates, sufficient synaptic activity, must gather in the network to generate the next Up state. The potential for synaptic activity to yield another Up state depends on when this activity occurs during the network refractory period, which appears to be determined by the level of activation and inactivation of activity-dependent K^+ conductances opened during the Up state. Like the absolute and relative refractory periods associated with single action potentials, there occurs an interval of time following an Up state during which another Up state cannot be elicited [20]. This ''absolute'' network refractory period sets a lower bound on the oscillation period of the slow oscillation

Gating of sensory stimuli in slow wave generation

Neural activity contributing to the slow wave is distinctive for its independence from sensory sources, a defining behavioral feature of sleep that distinguishes it from other behavioral states, all of which otherwise retain the ability to respond promptly to stimuli. Although the mechanisms for gating remain to be identified, various studies suggest that there is significant influence from thalamic nuclei that suppresses afferent input. Contributions from sensory thalamic nuclei via the relay cells, including the ventral posterior medial nucleus and the lateral geniculate nucleus, are strongly inhibited, thus preventing spiking at nearly all times except at the onset of the Up state. By contrast, excitation is dominant in neurons within non-sensory thalamic nuclei, including the posterior nucleus and the intralaminar nuclei. Their continuous activity persists throughout the duration of the Up state [21].

These firing patterns appear to be due to the inhibition of sensory thalamic nuclei by the thalamic reticular nucleus (TRN) and the corresponding lack of inhibition of non-sensory thalamic nuclei, which receive the majority of their inhibitory input from the zona incerta [22]. TRN neurons that

project to sensory thalamic nuclei, particularly, display high activity during the slow oscillation, while those with projections to limbic thalamic nuclei show relatively low activity [23]. This means that excitation from non-sensory thalamic nuclei is likely to have the greatest influence on Up state initiation, as well as its persistence. Indeed, the prolonged excitation of thalamocortical neurons by non-sensory thalamic nuclei during Up states suggests that these neurons are likely to suppress most afferent influence into the cortex besides assisting in synchronizing the slow oscillation.

Slow wave network influences on synaptic strength

After prolonged periods of wakefulness, global EEG slow-wave activity and the incidence of slow oscillations (SO) during subsequent SWS is enhanced, whereas these measures decrease over the course of sleep [24,25].

Electrophysiologically, experimental evidence supports distinct physical changes during wake or sleep periods that are reflected in spontaneous miniature excitatory postsynaptic currents (mEPSCs) in the rodent cortex. In line with the EEG recordings, by the end of the wakeful period the mEPSCs increase in amplitude and frequency in the superficial layers of the rat and mouse frontal cortices whereas following recovery from sleep they decrease. These electrophysiological measures are not the only indication of an overall increase in synaptic strength, reflected in stronger responses by neurons at their synapses that occurs during wakeful periods. This potentiation can also be observed in the slope used to measure cortical evoked responses, where a steeper slope indicates a greater response. During NREM recovery periods the slope becomes shallower, indicating a lesser response. The reduction in potentiation that is coincident with slow wave activity suggests that it functions to restore neuroplastic capacity, which is progressively reduced by sensorial input during vigilant periods (24).

Ultrastructurally, the increase in the former has been correlated with the insertion of calcium permeable AMPA receptors into synapses [25]. During sleep, this GluA1 synaptic expression decreases in parallel with a shrinkage of the axon-spine. Whereas wake related neuroplastic changes are most clearly observed in synaptic potentiation there are often also additional structural and morphological changes that change in relation to the sleep state [26]. In vivo two-photon microscopy has revealed a net loss of synapses during sleep in the developing mouse cortex and in the mushroom bodies of fruit flies. At the molecular level changes in the strength of excitatory synapses involve modification of the surface expression and subunit composition of the glutamatergic AMPA receptors, as well as their phosphorylation, post-translational changes that alter the open probability of these receptors, and affecting their ability to remain anchored to the membrane. Surface insertion of GluA1-containing receptors, as well as the phosphorylation of GluA1 at Ser831 and Ser845by CaMKII and PKA, have also all been correlated with synaptic potentiation.

Slow wave transition to wakefulness

The arousal events leading to the vigilant state and the transitional processes leading to sleep together constitute a bidirectional set of global movements in which the brain's neural activity undergoes a state shift in its governing regime. The hallmarks of these two states include the brain's highly synchronized, patterned electrical events and insensitivity to sensorial input during sleep and the reversal of these features with the return of vigilance. When cortical circuits are in a waking, desynchronized state, individual cortical neurons are persistently depolarized close to threshold for action potentials, the local field potentials (LFP) and EEG show low-amplitude, high-frequency components, and multiunit activity is maintained at a sustained level [27]. However, some rhythmic delta presence during wakefulness, at roughly 10% of all recording sites, has been detected in various cortical lobes.

The global impact of sleep on cortical activity and the necessity to cyclically regulate afferent input implicate precise mechanisms that oversee the transition between the highly synchronized state of sleep and the desynchronized, wakeful periods of interactive learning. Extant studies have linked these mechanisms to the arousal system, which regulates the transition from sleep to wakefulness. Insight into the mechanisms associated with this shift has emerged from investigations of trauma lesions in humans, pharmacological experiments, and in situ preparations. As a group, these studies have revealed a crucial dependence of sleep like states on the modulation of arousal systems, with the inhibition of GABA release resulting in sleep and its release leading to wakefulness. To date these have been the primary mechanisms identified for transitioning between sleep and wakefulness, although other work has also revealed a few physiological mechanisms that can directly induce REM sleep.

Many studies have demonstrated that GABAergic transmission in the pontine nucleus (PnO) promotes wakefulness [28]. For example, inhibition of GABAergic transmission in the PnO by microinjection of the GABA synthesis inhibitor (3-MPA) decreases anesthesia induction time with isoflurane and/or propofol. Elevating GABA levels with the uptake inhibitor (NPA) into the PnO reverses this effect. Besides GABA, the peptides hypocretin-1 and -2, termedorexin A and B, also act via the arousal system to modulate sleep stage transitioning. As in the case of GABA receptors, hypocretin receptor are widely dispersed and site specific, including sites in the brainstem, midbrain, hypothalamus, thalamus, and cortex. Cell bodies of hypocretin-producing neurons have been localized to the dorsolateral hypothalamus but distribute projections to all the major brain regions involved in regulating arousal. A few studies have revealed a direct induction of sleep via neurotransmitter up regulation. Of these, REM sleep was induced in rats with the vasoactive intestinal polypeptide (VIP). A closely related peptide, the pituitary adenylyl cyclase-activating polypeptide (PACAP), was shown to be even more effective [30]. The IC50 for the latter was 2.4 and 3.2 nM, as compared with VIP IC50 > 1 mM, implicating the peptide in a highly specific and effective role in the induction of REM sleep.

(1) Bistable Brain States: Astrocyte Influences on the Slow Wave

Sleep and wakefulness and the transitions between these states constitute global events in which the brain adopts a bistable operation, fluctuating between two positions of relative stability. Similar fluctuations have been shown to characterize other RSNs, which occupy states poised for maximum network switching [9]. An increasing number of findings implicate the direct participation of astrocytes in these transitional movements.

Astrocyte morphology and resting network function

The contribution of astrocytes to resting state network function is multimodal. Among the factors directly influencing RSN function is the complex morphology of these cells. Astrocytes are characterized by an intricate arborization nearly rivaling that of neurons and by anatomical specializations that control local interactions with other CNS elements, including synapses, blood vessels, and other glial cells. Each astrocyte occupies a distinct brain territory from that of other astrocytes, but together they form large, dynamic networks via gap junctions that establish connectivity among groups of astrocytes. An individual human astrocyte can cover ~2 million synapses, with a synaptic density of ~1100

million synapses mm. Regionally, astrocytes form dense syncytia, creating functional networks that span across brain domains [31]. These networks tile the brain in a grid pattern forming a synaptic, biophysically constrained association within which astrocytes have been shown to induce slow and infra- slow-oscillations. Importantly, because astrocytes are fundamental elements of most synapses, for which brain synaptic structure has been characterized as tri-partite [32], their morphological structure can play a significant role in brain communication and information processing; hence, such structural arrangements provide the physical substrate for large scale, tight interactions between astrocytes and neurons.

Astrocyte morphology, moreover, is not static but undergoes a wide morphological range, which can dynamically modulate the physiological properties of local synapses. Astrocytes show rapid - within a few hours - and reversible structural remodeling occurring in perisynaptic astrocyte processes (PAPs) that changes the extent of the coverage of the neuropil in response to strong behavioral stimuli, like that experienced during arousal and recovery from general anesthesia. During natural sleep and general anesthesia, increased extracellular synaptic volume (ESV) is observed while the opposite changes are detected during arousal and recovery from anesthesia, state dependent changes modulated by PAP plasticity. Additionally, synaptic activation that generates an LTP is sufficient to induce rapid - within dozens of minutes - motility of PAPs accompanied with increased astrocytic coverage of spines. These effects are thus of particular significance for their influence on brain communication. By shielding the synapse from external sources of neurotransmitter, for example, astrocytes carry out the critical function of tuning neurotransmitter responsivity and sharpening the temporal window within which postsynaptic stimulation is effective.

Among the key astrocytic processes affecting resting state network dynamics are those of neuroplasticity modulation and calcium concentration fluxes. Both processes have the capacity to alter the dynamic state of brain oscillations that underpin resting networks.

Neuroplastic mechanisms affecting oscillations vary as a function of the time course of their induction, which can range from milliseconds in the case of spike timing dependent plasticity (STDP) to many days for cortical memory storage, with astrocyte effects generally mediated at longer time scales than those of neurons. STDP is one form

of neuroplasticity in which a millisecond-scale change in the relative timing of presynaptic and postsynaptic spikes will cause differences in postsynaptic Ca^{2+} signals by either potentiating (long term potentiation (LTP)) or depressing (long term depression (LTD)) subsequent synaptic signaling [33]. While spike induction entails

a transient activation of calmodulin kinase II and protein kinase C, maintenance of the early LTP involves

their ongoing activation. Active CaMKII and PKC carry out two major mechanisms underlying the expression of the initial LTP phase, the phosphorylation of existing AMPA receptors, which increases their activity, and the insertion of additional AMPA receptors into the postsynaptic membrane. Unlike the LTP, which is due in part to the activation of protein kinases, the LTD arises from the activation of calcium-dependent phosphatases that dephosphorylate the receptor proteins. The activation of postsynaptic phosphatases leads to the internalization of synaptic AMPA receptors into the postsynaptic cell by endocytosis, which diminishes the sensitivity to glutamate release. STDP thus selectively promotes and consolidates specific synaptic modifications, while suppressing extraneous global ones, resulting in a sharpened signal to noise ratio in human cortical networks.

While activation of presynaptic receptors by astrocytic gliotransmitters can initiate different receptor-specific downstream signaling pathways that differentially modulate the probability of synaptic release, astrocyte-mediated modulation has been demonstrated to last between tens of seconds to several minutes. Thus, astrocyte influences occur over much longer time scales than those of typical processes affecting synaptic release like those involved in spike generation or the onset of LTP and LTD, which take place on the orders of hundreds of microseconds to milliseconds. These timing differences therefore implicate the presence of intermediary neuromodulatory events.

Neuromodulators, notably, typically bind to metabotropic G-protein coupled receptors (GPCRs) to initiate a second messenger, signaling cascade that induces a long-lasting signal affecting multiple synapses. This modulation can last for hundreds of milliseconds to several minutes and can alter, for example, intrinsic firing activity, increase or decrease voltage-dependent currents, alter synaptic weighting, stimulate bursting, and reconfigure synaptic connectivity. Multiple neuromodulatory mechanisms influence STDP. At the network level, neuromodulation alters the excitability and spiking features of neural circuits, and so can determine whether STDP in fact occurs.

Depending on receptor type, additionally, the modulation of synaptic release probability by gliotransmitter-activated presynaptic receptors may effect either an increase or a decrease in the frequency of spontaneous [34] and evoked neurotransmitter release, both in excitatory and inhibitory synapses. As a result, synapses whose release probability is increased by astrocytic gliotransmitters display a reduction in the paired-pulse ratio [35], a parameter measuring the ratio of the first to second postsynaptic currents induced by a pair of timed presynaptic pulses. By contrast, synapses whose release probability is decreased by gliotransmission display an increase in this ratio, effects related to the rate of depletion of stored neurotransmitter in the presynaptic terminal. The result of these neuromodulatory events is the effect on the circuit's ability to filter and transmit action potentials [36] as band-pass filters. Due to the interplay of frequency-dependent facilitation and depression, synapses are most effective in transmitting action potentials at intermediate rates of presynaptic activity. In the presence of synaptic potentiation by astrocyte transmitters, by contrast, an increase of release probability mediated by these gliotransmitters could result in long term depression that generates a low-pass filter effect.

At global levels, neuromodulators affecting brain states have been linked to the activation of astrocytic networks. Arousal, which involves the locus coeruleus and widespread noradrenaline release, activates astrocytes in projection areas. This increases the gain of astrocyte networks to local cortical activity and so modulates neuronal function. For example, acetylcholine, which is released during vigilance states by long- range cholinergic fibers, activates astrocyte networks, thus effecting astrocyte-mediated neuronal modulation. Acetylcholine-activated astrocytes that release d-serine at excitatory synapses and cholinergic input to astrocytes have been shown to induce LTP, causing glutamatergic transmission when cholinergic fibers and CA3–CA1 synapses are active within the time window of LTP generation. Significantly, both noradrenaline and acetylcholine regulate brain-wide oscillations. Acetylcholine, for example, is important for shifting network dynamics from sharp wave-ripples to theta-gamma oscillations in the hippocampus and from slow oscillations to desynchronized states in the neocortex.

Astrocytes and Ca dynamics

Neuromodulatory events initiate astrocyte responses through calcium dynamics, although fast astrocytic calcium responses approaching the

pace of neuronal events may be independent of these influences. Much evidence shows that glia respond to neuronal activity with an elevation of their internal Ca^{2+} concentration, which stimulates the release of chemical transmitters from glia and results in feedback regulation of neuronal activity and enhanced synaptic strength.

Several mechanisms can trigger the elevation of astrocyte intracellular Ca^{2+} levels. The activation of Gq-protein- coupled receptors (GPCR) initiates the IP3 signaling cascade and results in robust intracellular Ca^{2+} elevations, mainly via IP3 receptor type 2 activation (IP3R2) [37]. Moreover, astrocytes express several types of transient receptor potential (TRP) channels [38] that contribute to basal calcium levels and modulate calcium - dependent vesicular glutamate release from cortical astrocytes. Mitochondria, which are abundant in astrocytic processes, have also been shown to be active sources of Ca^{2+} for localized events in distant microdomains of astrocyte processes.

Calcium dynamics are also strongly influenced by astrocyte morphology, which can influence global events via largescale astrocyte networks or local sites at individual synapses via calcium microdomains. In astrocytic networks, calcium waves can propagate laterally up to 100s of microns in distance, thereby facilitating synchronization of brain oscillations. Microscopic analysis of the spatial relationship with excitatory synapses shows that most PAPs are compartmentalized structures (0.07–0.7 μm^2), where localized Ca levels are restricted from propagating to nearby synapses. Calcium transients have been correlated with these compartments, which are identified with spines, implicating PAPs functionally and not only morphologically with their synaptic partners; hence, they are intimately associated with synaptic communication. Importantly, by modulating their morphology astrocytes can trigger calcium fluctuations that result in calcium oscillations. Altering their surface to volume ratio changes Na concentrations in the vicinity of the shafts thereby shifting the equilibrium position of the Na/Ca membrane exchanger [39]. The resulting increase in the levels of intracellular astrocytic Na+ concentration can in turn generate the appearance of Ca^{2+} fluctuations. Besides the Na/Ca exchanger, astrocyte calcium channels have also been implicated in oscillatory phenomena. In a computational, in silico analysis, voltage gated Ca channels reproduced typical oscillatory calcium phenomena under a wide range of experimental conditions where the oscillation frequency changed several hundred percent (~400%), while the amplitude and duration of the Ca oscillations remained unaltered.

Astrocyte calcium and slow wave oscillation

Consistent with these results, calcium fluxes in astrocytes are required for generating the Up state of the slow wave. Supporting this are the following salient findings [14]: electrical stimulation of astrocytes activates other astrocytes in the local circuits and triggers UP state synchronization of neighboring neurons; intracellular injections of a calcium chelator into individual astrocytes inhibit spontaneous and induced UP states; and finally, both astrocytic activity and neuronal UP states can be regulated by purinergic signaling in the circuit. Together these results indicate that calcium fluxes in astrocytes are likely to be causally involved in regulating the synchronized activation of neuronal ensembles. Regional studies have further shown that activation of local ensembles via calcium can lead to slow wave dominated states. Optogenetic activation of astrocytes, for instance, can convert irregular activity in local neuronal circuits to patterned, slowly-oscillating activity.

At global scales, these changes in synchronization function to drive the network toward a state of global functional connectivity. Blood oxygenation level-dependent (BOLD) responses that reveal a cortex-wide and spatially organized correlate of local neuronal activity, for example, are directly related to slow calcium waves [40].

Moreover, during slow wave activity, the slow wave events are correlated with the strength of functional connectivity between different cortical areas. These findings suggest that the transition from neuronal excitability to the synchronized slow wave state drives a cortex- wide increase in functional connectivity, which links the changes in functional connectivity directly to the generation of slow waves. In line with this, filtering of the BOLD signal at different frequency intervals prior to conducting a cross-correlation analysis has revealed a significant correlation decrease in the frequency interval associated with the UP Down phases, chiefly between 0.01 and 0.4 Hz. This latter finding shows that slow wave UP Down phases are likely to be main factors involved in the increase in cortical functional connectivity across the cortex.

(3) Astrocytes: Dynamical Elements in RSN Stability and Transition

Given the substantial evidence that neuromodulators can shift global brain states by altering astrocyte calcium levels, it follows that vast neuronal networks could be rapidly modulated in response to neuromodulator action on astrocytes. Indeed, the demonstration that optogenetic stimulation can promote global functional connectivity via high-frequency to low-frequency, oscillatory transitions is strong indication that astrocytes are causally associated with cortical circuit switches in resting state network dynamics.

Astrocytes could mediate synchronization of neuronal ensembles in multiple ways. For instance, they can release glutamate simultaneously onto neighboring neurons and coordinately increase their excitability via activation of extrasynaptic NMDAR and other glutamate receptors. Direct dendritic recordings from hippocampal CA1 pyramidal neurons show, for instance, that glutamate targeting of neuronal dendrites by astrocytes can induce LTP, thereby contributing to localized plasticity. Astrocytes can also release glutamate onto axons and their endings, affecting axonal conduction, broadening action potentials [41], or increasing presynaptic transmitter release [42]. By acting simultaneously on multiple afferent fibers or synapses, astrocytes could also promote network coordination involving the synchronized bursting of neuronal networks. Overall, by sustaining the action of neuromodulators astrocytic signaling pathways emerge as relevant contributors to the generation and regulation of various network oscillatory rhythms and to establishing new brain state regimes [40,43,44].

Resting State Networks and Attractors

Resting state networks that maintain their configuration over time possess a regional stability essential to highly ordered brain states. In the case of the slow wave, this stability is sustained across a broad spatial and functional connectivity zone that comprises both cortical and, to a limited extent, subcortical domains. Such stability and the interplay with flexible transitioning to other stable regimes, e.g., between synchronized slow wave behavior and desynchronized conscious states, is necessary for the communication and information processing functions of these networks. Consistent with the presence of global brain dynamics, fMRI detected brain activity can be decomposed as a superposition of multiple activation patterns [45]. Indeed, different RSNs have been associated with specific cognitive networks, as for example, memory, (default mode) networks, fronto-parietal control networks, and others. The demonstration of these patterns as multiple stable networks has led to the hypothesis that underlying these activation patterns is the existence of stable switching attractors that enhance information transfer by facilitating cognitive transitions [46].

Taken together, oscillatory properties appear to constitute the dominant form through which attractor dynamics are instantiated. Unlike fixed point attractors, however, oscillators do not have a single solution, but one that periodically returns to a given state condition. Oscillators also display attractor characteristics when pairing with (phase synchronization) or decoupling from (desynchronization) other oscillators, features essential for information transfer [1,47,48]. As mentioned, astrocytes have been shown to contribute to the stability of the slow wave, generating Up state patterning via calcium fluctuations. Astrocytes also are implicated in the desynchronization events of the slow wave via calcium dynamics. For example, calcium fluctuations within astrocytes adopt stable oscillatory profiles that undergo dissolution as they approach instability zones [49]. Computational modeling studies have shown that the appearance and disappearance of these spontaneous Ca oscillations are due to their embodiment of subcritical Hopf and supercritical Hopf bifurcation points, points of instability (phase separation) where oscillations can no longer be maintained, suggesting that they are the origin of slow wave destabilization.

Conclusion

The notion that astrocytes integrate neuronal functions at synaptic and network levels to influence behavior is relatively new, particularly because these cells have long been thought unable to directly participate in brain communication and computing. Only recently have findings from state-of-the-art approaches and ad hoc design capable of studying astrocytes begun to paint a different picture. The significance of astrocyte influence lies in their capacity to provide organizational order to brain function, enabling both the stability of resting state networks as well as their transitional capacity. Because of their key role in controlling dynamical events, the participation of astrocyte signaling in cognitive processing has implications for understanding the etiology of cognitive pathologies. These findings suggest that targeting astrocyte pathways may represent an important new therapeutic opportunity for neurological dysfunction and cognitive disease.

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DOI: 10.31579/2692-9422/037