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ROLE OF MYELIN PLASTICITY IN OSCILLATIONS AND SYNCHRONY OF NEURONAL ACTIVITY

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Abstract—Conduction time is typically ignored in computational models of neural network function. Here we consider the effects of conduction delays on the synchrony of neuronal activity and neural oscillators, and evaluate the consequences of allowing conduction velocity (CV) to be regulated adaptively. We propose that CV variation, mediated by myelin, could provide an important mechanism of activity-dependent nervous system plasticity. Even small changes in CV, resulting from small changes in myelin thickness or nodal structure, could have profound effects on neuronal network function in terms of spike-time arrival, oscillation frequency, oscillator coupling, and propagation of brain waves. For example, a conduction delay of 5 ms could change interactions of two coupled oscillators at the upper end of the gamma frequency range (~100 Hz) from constructive to destructive interference; delays smaller than 1 ms could change the phase by 30°, significantly affecting signal amplitude. Myelin plasticity, as another form of activity-dependent plasticity, is relevant not only to nervous system development but also to complex information processing tasks that involve coupling and synchrony among different brain rhythms. We use coupled oscillator models with time delays to explore the importance of adaptive time delays and adaptive synaptic strengths. The impairment of activity-dependent myelination and the loss of adaptive time delays may contribute to disorders where hyper- and hypo-synchrony of neuronal firing leads to dysfunction (e.g., dyslexia, schizophrenia, epilepsy).

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INTRODUCTION

The functional and evolutionary significance of myelin is typically interpreted in terms of the increased conduction velocity (CV) it confers through the mechanism of saltatory conduction (Tasaki, 1939). However, faster is not always better, as many aspects of brain function require precise temporal relationships among the signals originating from distant brain areas and, thus, a proper distribution of the CVs. In the vertebrate nervous system, CVs range from a small fraction of a m/s to hundreds of m/s in different axons. The speed of conduction is largely dependent on the thickness of myelin, axon diameter, and the spacing and width of nodes of Ranvier. Glial cells form myelin and influence the spacing of nodes, and in the PNS at least, affect axon diameter as well (de Waegh et al., 1992; Garcia et al., 2003). In order to mediate proper spike-time arrival among axons of different lengths converging onto a common target, these axonal parameters are crucial to establish proper conduction delays. It is commonly assumed that the transmission speeds and delays are genetically specified and fixed at the developmental stage, and the changes in degree of myelination in an adult brain are only considered in cases of pathology (e.g., demyelination and dysmyelination). This view is changing, and there is growing evidence that neurotransmitters mediate communication between axons and myelinating glia (Kukley et al., 2007; Ziskin et al., 2007; Bakiri et al., 2009), and that myelination is a dynamical, activity-dependent process (Fields, 2010).

Two principal mechanisms for changing CV are altering axon diameter and myelination (in vertebrates), the latter being the most effective means of increasing the CV. Enlarging axon diameter only is much less effective because CV increases in proportion to the square root of the axon diameter in unmyelinated fibers (Tasaki, 2004), while it increases linearly with the diameter of myelinated axons (Hursh, 1939). Additionally, the enlargement of axon caliber is metabolically and anatomically less feasible as a means of activity-dependent regulation of conduction delays. There is ample evidence now that the functional activity and action potentials influence proper development of myelin sheaths (Fields, 2013 for review). For example, in the experiments with the development of barrel cortex in mice (Barrera et al., 2013) sensory deprivation (removal of whiskers on one side), while not changing the onset of myelination relative to the controls, does significantly decrease the amount of myelin ensheathing each axon in

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Abbreviations: CV, conduction velocity; CO, coupled oscillators; ITD, interaural time difference; PFC, prefrontal cortex; STDP, spike-time-dependent plasticity; VB, ventrobasal nucleus; WM, white matter.

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the barrel region. Several molecular mechanisms for activity-dependent regulation of myelination have been identified *in vitro* (Stevens et al., 1998, 2002; Ishibashi et al., 2006; Wake et al., 2011) and social isolation in mice alters myelination of prefrontal cortex (PFC) with behavioral consequences (Makinodan et al., 2012; Liu et al., 2012). Human brain imaging shows structural differences in white matter regions of the brain after learning (Zatorre et al., 2012).

The possibility that activity-dependent regulation of myelination could adaptively influence temporal relations, oscillations and synchrony in the interactions of distant brain regions, provides a novel and previously unexplored form of activity-dependent nervous system plasticity. Plasticity of conduction time delays in neural circuits might complement the well-studied plasticity of synaptic function. Plasticity of conduction delays would be most relevant for complex cognitive functions and consciousness, since the timing of signals is of great importance in neural processing of information across different time and length scales. At the small scale of neuronal cells, precise arrival of action potentials at the postsynaptic neuron is perhaps the most important factor in triggering a new action potential, since different spikes arriving only a few milliseconds apart will fail to integrate to cause sufficient depolarization. At the scale of the whole body, signals sent from brain to the peripheral nervous system need to preserve precise timing and phase relationships in order to ensure coordinated motion. For example, in the case of limb coordination (Haken et al., 1990; Schöner et al., 1990) the same phase relationship in the movement of different limbs is preserved for a particular type of gait, but can differ among different animal species or among different types of gaits within the same species. The importance of timing in perception is also evident at the system level. For example, auditory neurons preserve the temporal structure of tones by phase-locking their responses with the stimulus. Using information-theoretic measures it was found that the temporal precision of the auditory information coding is coarser than 1 ms, but finer than 5 ms (Kayser et al., 2010). Similar findings hold for visual (Victor and Purpura, 1996; Butts et al., 2007) and other temporal tasks (Nemenman et al., 2008), with the consensus that the required precision for spike arrival timing was on the order of few or several milliseconds. In some specialized circuits, at the system level, the timing constraints can be at the sub-millisecond range. A well-known example of such fine temporal detection is that of spatial localization of sound based on interaural time difference (ITD), where across many vertebrate species ITDs as small as 10 μs can be resolved. The precision that is required at cellular and axonal level to achieve such precision at the system level is largely dependent on the details of the detection mechanism. In one of the earliest explanations of how such spatial localization might occur, the Jeffress model (Jeffress, 1948), the existence of precisely arranged "delay lines" is posited, which through coincidence detection positionally code (place code) the ITDs. Evidence for the existence of such delay lines has been found in birds (Carr and Konishi, 1990; Cheng and Carr, 2007; Seidl et al., 2010; see Seidl, 2014 for review) but their existence in mammals is more controversial (Grothe et al., 2010). Presence of such coincidence detection circuitry suggests that the sub-millisecond precision needs to be maintained at the axonal level.

Considering such stringent requirements for precision, as well as general importance of timing in the interaction between different signals, it would appear that the plasticity mediated through glia and myelination, which can adaptively modulate the CV along the axons and thus the timing, would be highly beneficial for the vertebrate brains. In the majority of computational models of neural network function, temporal conduction delays are typically ignored or are held constant. In a simple network shown in Fig. 1a, traditional neuronal networks would only keep the information about the connectivity and the weights between the source neuron and the target neurons. A more elaborate approach would account for temporal delays, τ_i, however, these are usually treated as fixed. This is an incorrect assumption if the CV is allowed to change. Since the intrinsic activity in the mammalian brain is often oscillatory (Bullock, 1997), one would similarly have to account for changes in the phase difference, ϕ_i. While the importance of spike timing in excitable systems has already been recognized, the emphasis on the importance of temporal and phase delays in the context of brain oscillations is lacking. Brain rhythms of various frequencies have been associated with selective attention, arousal, sleep, information processing, sensory gating of information, memory formation, emotion, perception, and consciousness (Buzsáki, 2006; Ainsworth et al., 2012). Furthermore, entrainment and interactions between the oscillation generators in different brain regions are essential, e.g., the entrainment of neocortical neurons through phase locking to the hippocampal theta rhythm (Buzsáki, 2006; Burgess et al., 2007; Sirota et al., 2008).

The outline of this review is as follows. We first reiterate some basic notions behind the role of myelin plasticity in spike timing, since the oscillations in the brain are certainly a reflection of the underlying spike timing. We then focus on the role of myelin plasticity in synchrony and oscillations, first reviewing basic literature on their generative mechanisms and coupling between them. While the details of precise mechanisms that underlie the maintenance and interactions can be elucidated in some cases (Destexhe and Sejnowski, 2003), in most cases the details of such interactions are not known. Instead, we take a more general approach and review some basic models of coupled oscillators (CO) with delay encountered in physics literature. Through them we elaborate on the consequences that activity-dependent myelin plasticity, i.e., the adaptive propagation speed and time delays, can have on improved neural system function.

SPIKE TIMING AND CONDUCTION DELAYS IN EXCITABLE SYSTEMS

For spiking activity to propagate in a feed-forward neuronal network, usually several spikes are needed to