

Spotlight

Timing is everything: myelin and coincidence detection

Kimberly Gagnon^{1,2},
Gustavo Della Flora Nunes³,
Cristin G. Welle^{1,2}, and
Ethan G. Hughes^{1b 3,*}



Myelin is traditionally viewed as a passive determinant of conduction velocity, yet emerging work suggests a critical role in shaping the precision of spike propagation. In a recent study, Jamann *et al.* show that myelination enables burst propagation and coincidence detection, shaping how spikes propagate and establishing myelin as a substrate for neural computation.

Oligodendrocytes ensheath axons with myelin, an insulating membrane that enables saltatory conduction and ensures the rapid, reliable propagation of action potentials to downstream neurons. Myelin is currently understood to shape the timing of action potential propagation by modulating conduction delays and temporal variability and has been implicated in promoting synchrony across neural circuits [1]. Yet, how these biophysical effects translate into specific neuronal and circuit-level computations remains largely unresolved. This challenge is compounded by the heterogeneity of myelin organization across the nervous system, with dense, continuous myelination in long-range white matter tracts contrasting with sparse, discontinuous myelination in the cortex that preferentially targets specific cell types, such as parvalbumin interneurons. As a result, the role of myelin in shaping neural transmission across heterogeneous circuits

operating in distinct computational regimes has come into sharper focus.

A recent study by Jamann *et al.* [2] substantially advances our understanding of how myelin contributes to circuit-level computation by interrogating a well-defined, timing-sensitive neural circuit in mice. The authors focused on the corticothalamic pathway linking layer 5 pyramidal neurons in the somatosensory cortex to posteromedial thalamic neurons, carefully characterizing the circuit architecture and the temporal structure of neuronal firing between putative monosynaptic partners. Consistent with a growing body of work, the authors first demonstrated that demyelination of corticothalamic axons produces only modest changes in average conduction delay while markedly increasing trial-to-trial spike-timing variability, reinforcing the view that myelin stabilizes temporal precision rather than simply accelerating transmission. This finding provides additional mechanistic support for myelin's role in preserving temporal precision, as a prior report shows that the loss of myelin-mediated metabolic support also induces a loss of temporal reliability [3].

The authors then asked how degraded timing precision reshapes the neural codes that transmit information to downstream neurons. Because bursts of neural activity are particularly effective at driving coincidence detection and downstream integration, they examined how demyelination affects burst firing and its propagation. Although demyelination increased the generation of action potential bursts in layer 5 cortical neurons, burst propagation to downstream targets was compromised. This dissociation revealed that spike generation and spike communication can be uncoupled: neurons may fire more vigorously, yet exert less functional influence on downstream circuits. Through careful experimentation and analyses, the authors lend support for a dual mechanism impeding proper burst

transfer: conduction delays and conduction failures. Together, these findings establish a central computational insight of the study: that myelin determines which forms of neural communication survive transmission, rather than simply how fast signals travel.

Importantly, the authors constrained a biophysical model with experimental evidence of region-specific demyelination. They demonstrated that localized myelin loss along layer 5 pyramidal neurons in the cortex and posteromedial thalamic nuclei is sufficient to increase spike-time jitter and selectively disrupt burst transmission without inducing large, global conduction delays. This finding carries broad clinical relevance, as myelin loss in conditions such as multiple sclerosis, stroke, and aging is typically focal and heterogeneous rather than uniform. Although the behavioral consequences of temporal jitter and conduction failure remain an important open question in this study, these results offer insight into selective deficits induced by demyelination in experimental models and demyelinating disorders. From a therapeutic perspective, the distinction between functional outcomes of focal versus uniform demyelination is critical, as the nervous system retains an endogenous capacity for myelin repair through remyelination. While remyelination can restore gross conduction properties, whether it can reinstate the precise pattern of myelin required to rescue neuronal computation and circuit function remains a critical question for understanding behavioral recovery following demyelination. Together, the results by Jamann *et al.* underscore the importance of interrogating region-specific myelin loss and changes in myelin patterning as a framework for linking circuit-level dysfunction to behavioral impairment in demyelinating disorders.

Posteromedial thalamic neurons in rodents act as coincidence detectors, integrating top-down cortical bursts and

bottom-up whisker-evoked sensory signals only when they arrive within a narrow millisecond-scale time window [4]. This architecture makes the circuit exquisitely sensitive to spike-timing precision and, therefore, well suited for probing how myelin integrity shapes timing-dependent circuit computation. Jamann *et al.* used experimentally controlled optogenetic stimulation of L5 neurons paired with whisker stimulation to reveal that demyelination broadens the temporal window of integration in thalamic neurons. Rather than uniformly shifting input timing, demyelination increases variability while preserving mean arrival times between L5 projections and whisker-evoked inputs to the thalamus. As a result, coincidence-based integration becomes less reliable rather than misaligned, revealing that myelin supports computation by stabilizing timing precision, not by simply enforcing a fixed temporal delay.

From this framework emerges an exciting implication for adaptive myelination: the capacity for myelin to change in response to neuronal activity. Diversity in myelination patterns across the brain may therefore contribute to computational specialization, rather than serving solely to optimize the speed of signal propagation [5,6]. If myelination governs which temporal patterns of activity propagate reliably, then dynamic variation in myelin organization may reflect

tuning for specific computational demands. Consistent with this view, recent work in mice has shown that oligodendrocyte maturation constrains experience-dependent plasticity in the visual cortex [7] and that activity-dependent myelination in adult circuits is required for reward learning [8]. Rather than simply facilitating signal transmission, myelin plasticity may thus act over longer timescales to stabilize particular patterns of circuit activity during development or learning in adulthood.

Finally, circuit architecture is likely to dictate how myelin supports computation. Whereas spinal cord projection pathways may depend primarily on canonical roles for myelin to maximize conduction velocity over long distances, recurrent cortical networks, feedforward cerebellar circuits, and widespread inhibitory systems place distinct demands on reliability, precision, and high-frequency propagation. Together, these observations suggest that myelin's functional role is not uniform but may be tuned to the computational requirements of the circuits it supports. To investigate these diverse functions of myelin, it will be critical to develop new tools that target myelin in specific circuits and neuronal cell types. Understanding how myelin formation and plasticity interact with diverse neuronal regimes represents an essential frontier for linking cellular mechanisms to system-level brain function.

Acknowledgments

This work was supported by National Institutes of Health grants NS137560 (C.G.W.), NS115975 (C.G.W. and E.G.H.), NS125230, NS132859, and NS134829 (E.G.H.); National Multiple Sclerosis Society Postdoctoral Fellowship FG-2107-38324 (G.D.F.N.); and National Science Foundation Graduate Research Fellowship Program DGE-1938058 (K.G.).

Declaration of interests

The authors declare no competing interests in relation to this work.

¹Department of Physiology and Biophysics, University of Colorado School of Medicine, Aurora, CO, USA

²Department of Neurosurgery, University of Colorado School of Medicine, Aurora, CO, USA

³Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora, CO, USA

*Correspondence:

ethan.hughes@cuanschutz.edu (E.G. Hughes).

<https://doi.org/10.1016/j.tins.2026.02.001>

© 2026 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

References

- Osso, L.A. and Hughes, E.G. (2024) Dynamics of mature myelin. *Nat. Neurosci.* 27, 1449–1461
- Jamann, N. *et al.* (2025) Layer 5 myelination gates corticothalamic coincidence detection. *Nat. Commun.* 16, 10922
- Moore, S. *et al.* (2020) A role of oligodendrocytes in information processing. *Nat. Commun.* 11, 5497
- Qi, J. *et al.* (2022) Posteromedial thalamic nucleus activity significantly contributes to perceptual discrimination. *PLoS Biol.* 20, e3001896
- Lefebvre, J. *et al.* (2025) Myelin-induced gain control in nonlinear neural networks. *Commun. Phys.* 8, 145
- Pajevic, S. *et al.* (2023) Oligodendrocyte-mediated myelin plasticity and its role in neural synchronization. *Elife* 12, e81982
- Xin, W. *et al.* (2024) Oligodendrocytes and myelin limit neuronal plasticity in visual cortex. *Nature* 633, 856–863
- Yalcın, B. *et al.* (2024) Myelin plasticity in the ventral tegmental area is required for opioid reward. *Nature* 630, 677–685