Paired Vagus Nerve Stimulation Drives Precise Remyelination & Motor Recovery After Myelin Loss

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BIOElectrics Lab

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Introduction

The Clinical Challenge

Multiple Sclerosis (MS) is characterized by the loss of oligodendrocytes and myelin, causing axonal dysfunction that may lead to permanent motor and cognitive deficits [1, 2].

Current Limitations: While immunotherapies reduce the frequency of demyelinating episodes, they fail to repair lost myelin or reverse the established disability [3].

The Myelin Role: Precise myelination patterns are critical for fine-tuning action potential timing and population synchronization [4].

The Gap in Repair

Anatomical Variation: Spontaneous remyelination is often opportunistic. New sheaths are frequently placed in previously unmyelinated locations rather than restoring the native circuit topology [5--9].

The Unmet Need: There is an unmet need to develop innovative therapeutic approaches that focus on the restoration of function through remyelination [10, 11].

A Promising Solution?

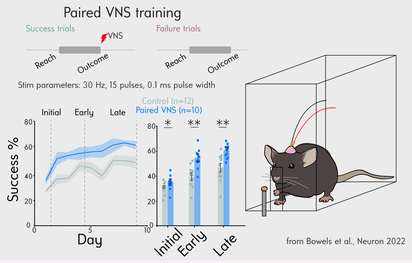
Vagus Nerve Stimulation (VNS)

VNS is is a well-established neuromodulation therapy that enhances neuroplasticity and is FDA-approved for treating motor impairment following stroke [12].

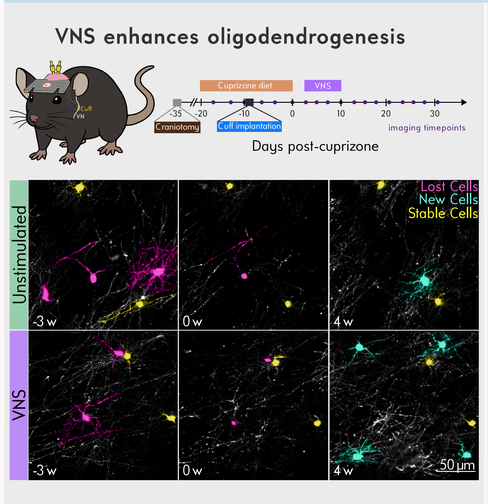
The Mechanism: Critically, neural activity regulates remyelination. This suggests that repair is not passive, but driven by circuit engagement [13].

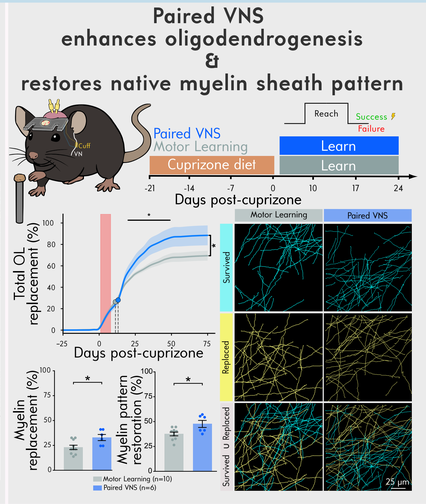
The Hypothesis

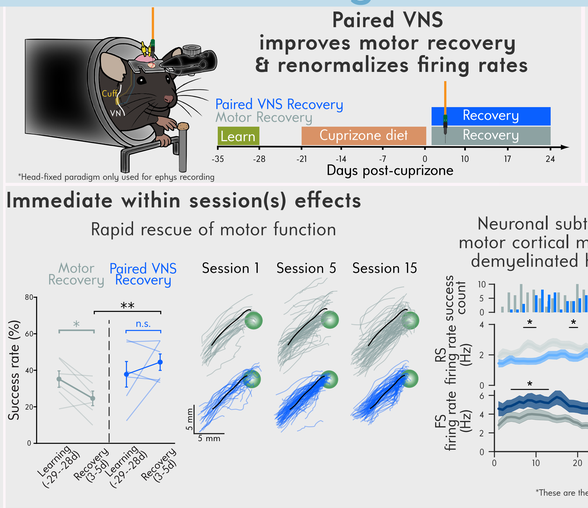
Activity-Dependent Repair: When paired with skilled, motor learning, VNS drives circuit-specific neural plasticity and accelerates motor learning [14]. We *hypothesize* that *Paired VNS* can leverage these activity-dependent mechanisms to guide targeted myelin repair and improve motor function after a demyelinating injury (such as MS).

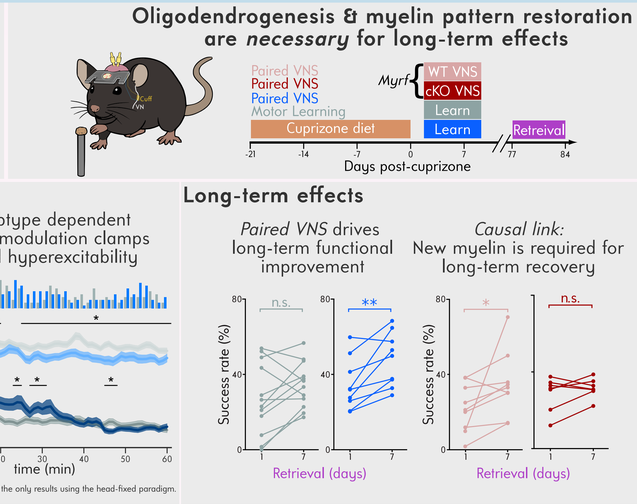


Executive Summary



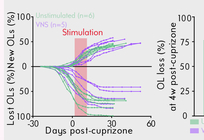






VNS enhances OL replacement

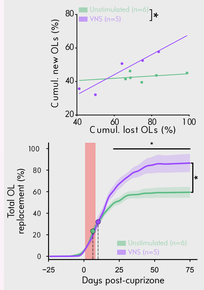
Identical Demyelination Severity



VNS did not alter OL loss .

VNS does not act as "protection" from OL loss.

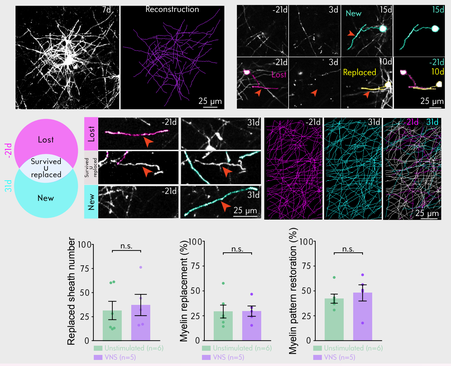
VNS amplifies the capacity for "repair"



VNS ↑ cumul. gen. of new OLs relative to loss indicating more robust regenerative response.

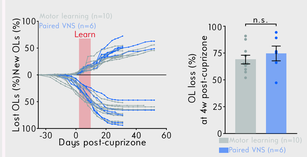
VNS animals reached higher OL replacement plateau (86% vs 57%) & sustained replacement after recovery stalled (Days 21--75).

VNS alone *does not* restore mylein pattern



Paired VNS drives robust OL regen.

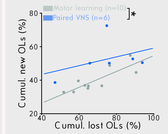
Identical Demyelination Severity



OL loss is not altered.

Paired VNS also enhances OL gain

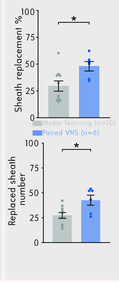
Higher OL replacement plateau (92% vs 72%) with sustained growth (Days 20--49).



↑ cumul. gen of new OLs relative to loss extent.

Paired VNS restores native myelin pattern

Success-triggered VNS guides myelin to original locations, restoring circuit topology. Results in myelin pattern restoration ↑ & sheath replacement ↑.



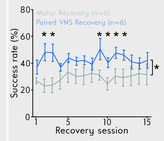
Paired VNS guides individual OLs to place nearly half (47%) of their new sheaths on previously myelinated locations.

Active rebuilding of the lost circuit structure rather than adding myelin in new locations.

Short-term Paired VNS Effects & Mechanism

Immediate Rescue of Motor Function

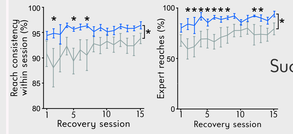
Paired VNS fully rescues performance to pre-demyelination injury levels within 3 days!



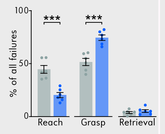
Significant increase in overall success rates both early & later during recovery.

'Performance floor' raised, stabilizing success even on the animals' worst days.

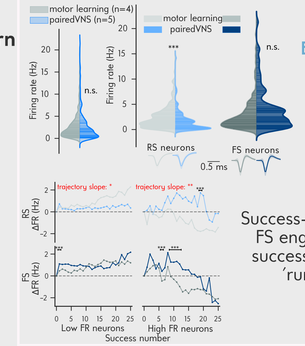
Rapid 'Expert Reach' attainment and stabilization before remyelination begins.



Success is driven by precision & accuracy.

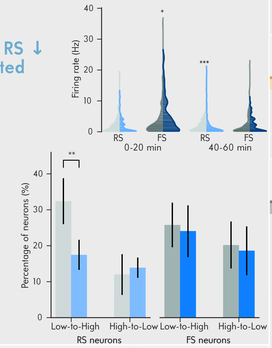


Inhibitory Recruitment Prevents Cortical Hyperexcitability



Early FS ↑ leads to late RS ↓ preventing demyelinated hyperexcitability.

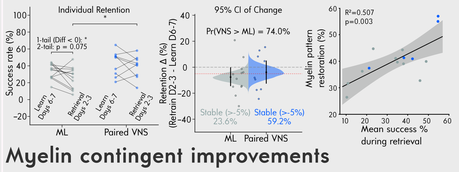
Success-locked modulation. Rapid FS engagement from very first success across animals. Clamps 'runaway' RS excitation.



Long-term Paired-VNS Effects & Mech.

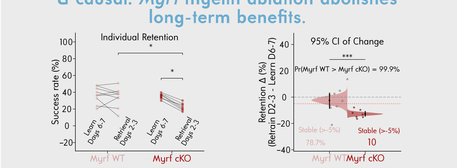
Long-term functional benefits

Improvement across retrieval & increased motor memory consolidation.



Myelin contingent improvements

Critically, improvement is both correlated (above) & causal: *Myrf* myelin ablation abolishes long-term benefits.



Future works

- Elucidate mechanisms of Paired VNS targeted remyelination.
- Translational work: closed-loop taVNS for MS motor rehabilitation in humans.

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Detailed methods

Funding

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