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Converging metabolic and functional networks for tremor expression and deep brain stimulation-mediated control.

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Deep brain stimulation is an effective treatment for tremor, yet the mechanism behind this benefit remains poorly understood. Normative connectome models point to a distributed network mechanism rather than a local effect, yet direct biological validation is lacking. We combined within-subject [^{18}F]FDG-PET and normative functional connectivity imaging in 14 essential tremor patients treated with thalamic DBS, comparing their clinically optimised Stim-On to their Stim-Off states.

Stimulation reduced tremor by 75% on average and raised glucose metabolism surrounding the stimulation site and in connected motor and cerebellar hubs, including the supplementary motor area, primary motor cortex, and dentate nuclei. Crucially, while local metabolic change scaled with stimulation amplitude, it did not predict clinical outcome once amplitude was accounted for, arguing against a purely local, dose-dependent mechanism of tremor relief.

In contrast, network-level effects told a different story. The stimulation-induced metabolic pattern showed significant spatial similarity to a previously published tremor treatment network derived from normative functional connectivity, and each patient's individual alignment with that network predicted their tremor improvement independently of stimulation amplitude (R^2 = 0.593, p = 0.007). An additional exploratory whole-brain model showed normative functional connectivity from the stimulation site shaped cortical metabolic changes observed, whereas amplitude-related effects remained confined to the vicinity of the lead. Furthermore, the metabolic network expressed during untreated tremor closely resembled the treatment network, indicating that effective DBS engages the same circuit that generates the symptom.

These results favour a network-level mechanism over local inhibition. DBS appears to relieve tremor by disrupting the propagation of pathological activity through the cerebello-thalamo-cortical circuit while preserving physiological signalling. Most intriguingly, several of these network hubs showed increased metabolism during both tremor expression and its suppression. This apparent paradox may in fact reflect a brain-state shift. Rather than simply returning the network to a pre-pathological baseline, high-frequency stimulation could transition it into a distinct, therapeutically relevant functional state that carries its own metabolic demands without it reflecting stronger pathological activity. In a cross-disease comparison the same core hubs, including the motor cortex and dentate nucleus, are also implicated in Parkinson's disease tremor. However, tremor-relieving DBS there has instead been associated with reduced network metabolism, contrasting the increases we observed in essential tremor. This divergence could imply that while these hubs form a shared, symptom-specific network, both its functional state and the changes induced by DBS are disease-specific and underscores the value of multimodal imaging in dissecting how DBS reshapes brain networks.

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