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Active presynaptic regulation, besides passive depletion, underlies DBS efficacy

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Li et al. recently proposed a compelling mechanism for subthalamic nucleus (STN) deep brain stimulation (DBS): that high-frequency stimulation (HFS) persistently activates afferent axons while paradoxically suppressing STN neurons via differential synaptic depression—specifically, a more rapid depletion of glutamatergic versus GABAergic vesicle pools.[1] While their use of spectrally resolved fiber photometry provides elegant *in vivo* insights, we suggest that interpreting the observed reduction in sensor fluorescence strictly as "passive vesicle depletion" may overlook crucial adaptive mechanisms. Converging evidence supports a framework in which active presynaptic adaptation, encompassing release mode switching, presynaptic inhibition, and glia-mediated clearance, complements the well-established role of synaptic depletion in DBS mechanisms and more comprehensively explains the observed phenomena and the therapeutic efficacy of DBS.

To investigate the local therapeutic mechanism of DBS, the authors employed advanced spectrally resolved fiber photometry paired with genetically encoded fluorescent sensors *in vivo* under DBS: postsynaptic Ca^{2+} showed a "transient increase followed by sustained suppression", while afferent terminal Ca^{2+} remained "persistently activated". Simultaneously, both glutamate and GABA levels in the STN decreased, with a more pronounced decrease in glutamate. From this, they concluded that this DBS-induced differential synaptic chemical inhibition is responsible for the suppression of STN neurons under high-frequency DBS stimulation. Subsequently, to explain why afferent terminals are activated while local neurotransmitter levels in the STN decrease, the authors made a logical inference. Under high-frequency DBS, the presynaptic vesicle dynamics may undergo collapse, as the turnover rate of the vesicle pool cannot keep up with the depletion rate. They inferred that the cause was likely the depletion of synaptic vesicle pools, which led to a decrease in the release of neurotransmitters, and further speculated that the faster depletion rate of glutamatergic vesicles led to differential inhibition.

The "depletion hypothesis" hinges on the inference that reduced extracellular signals despite high presynaptic Ca^{2+} seemingly indicate the vesicle pool depletion. Indeed, synaptic suppression driven by vesicle pool depletion under HFS is well recognized. In Li et al.'s study, however, signals from genetically encoded sensors (iGluSnFR and iGABASnFR) report net extracellular neurotransmitter concentration near STN somata/dendrites—a dynamic equilibrium of release, diffusion, and reuptake—rather than vesicular fusion events *per se*.[1] While vesicle depletion is undoubtedly a key component of DBS mechanisms, the reduction in sensor fluorescence observed by Li et al. does not uniquely confirm depletion as the primary explanation in this specific context. In fact, the sensor signal only provides the net outcome of neurotransmitter arrival at the postsynaptic sensor location and does not serve as a direct readout of presynaptic vesicle fusion. Therefore, the reduction in sensor fluorescence is equally compatible with enhanced clearance and presynaptic inhibition, which might operate alongside synaptic depletion. STN-DBS does not selectively target afferent terminals; it also activates surrounding neurons and adjacent glial cells. Indeed, HFS has been shown to upregulate the surface expression of the transporter EAAT2 on astrocytes, significantly accelerating glutamate reuptake.[2] This indicates that astrocytes can rapidly clear neurotransmitters from the synaptic cleft to prevent sustained exposure and potential damage to the postsynaptic neurons. Even if direct electrical excitation of glia may be minimal, the evoked surge in neurotransmitter release may engage glial clearance mechanisms, establishing an inhibitory feedback loop. Moreover, neurotransmitters themselves can act on presynaptic auto-receptors, exerting negative feedback to inhibit further release. In Parkinson's disease models, presynaptic $GABA_B$ receptors in the pallido-subthalamic pathway exhibit widespread "tonic inhibition", and their antagonism increases basal GABA release frequency. And it has been reported that metabotropic $GABA_B$ receptors expressed on glutamatergic and GABAergic presynaptic membranes can mediate the inhibition of spontaneous glutamate and GABA release independently of presynaptic Ca^{2+}.[3] In response to a robust perturbation like sustained 130 Hz stimulation, the engagement of multiple negative feedback processes by the intrinsic homeostatic mechanisms of the nervous system is an inevitable consequence to maintain equilibrium. These examples emphasize that active neuroregulatory mechanisms are not mere epiphenomena but are integral to maintaining network stability. Thus, the "depression" reported may reflect an active upregulation of clearance and presynaptic inhibition machinery rather than merely a passive failure of presynaptic supply. In the context of DBS, a therapeutic intervention for Parkinson's disease, the potential contribution of active neuroregulation to the observed neurotransmitter decrease is not only plausible but likely fundamental to achieving the desired therapeutic reset of pathological circuits.

Crucially, high-temporal-resolution electrophysiological data challenge the depletion hypothesis. Xu et al. recently demonstrated that under identical 130 Hz stimulation, presynaptic terminals actively switch from a synchronous release mode (phase-locked to pulses) to an asynchronous mode (delayed and stochastic).[4] It has been shown that asynchronous GABA release remains robust throughout prolonged 130 Hz stimulation, with its ratio and baseline current significantly elevated, indicating that vesicular release is reconfigured; the temporal progression from synchronous to asynchronous release reflects a specific active reconfiguration of Ca^{2+} sensor engagement (e.g., from synaptotagmin-1 to -7). Notably, when asynchronous release is enhanced by genetically reduced synchronous release, "ineffective" low-frequency (20 Hz) stimulation, which is less likely to lead to vesicle depletion, becomes therapeutically effective. Accordingly, the efficacy of DBS correlates with the robustness of this asynchronous release mode, probably not the depletion of vesicles. This implies that Li et al.'s photometry signals likely reflect the loss of synchronous fidelity (which sensors track well) while missing the sustained asynchronous background activity that drives therapeutic benefits. Furthermore, the "differential depletion" hypothesis, which posits that therapeutic efficacy arises from faster glutamate depletion than GABA shifting the excitation/inhibition (E/I) balance toward inhibition, can be tested through pathway-specific experiments. If this hypothesis were correct, then selective HFS of GABAergic afferents alone would be predicted to deplete GABAergic vesicles, thereby shifting the local E/I balance toward excitation and rendering stimulation ineffective or even deleterious. However, Xu et al. demonstrated that selective GABAergic stimulation alone is sufficient to alleviate motor deficits.[4] This finding is difficult to reconcile with the differential depletion hypothesis and instead suggests that the macroscopic differential decrease in glutamate and GABA reported by Li et al. probably is an epiphenomenon of presynaptic adaptation rather than primary therapeutic mechanism.

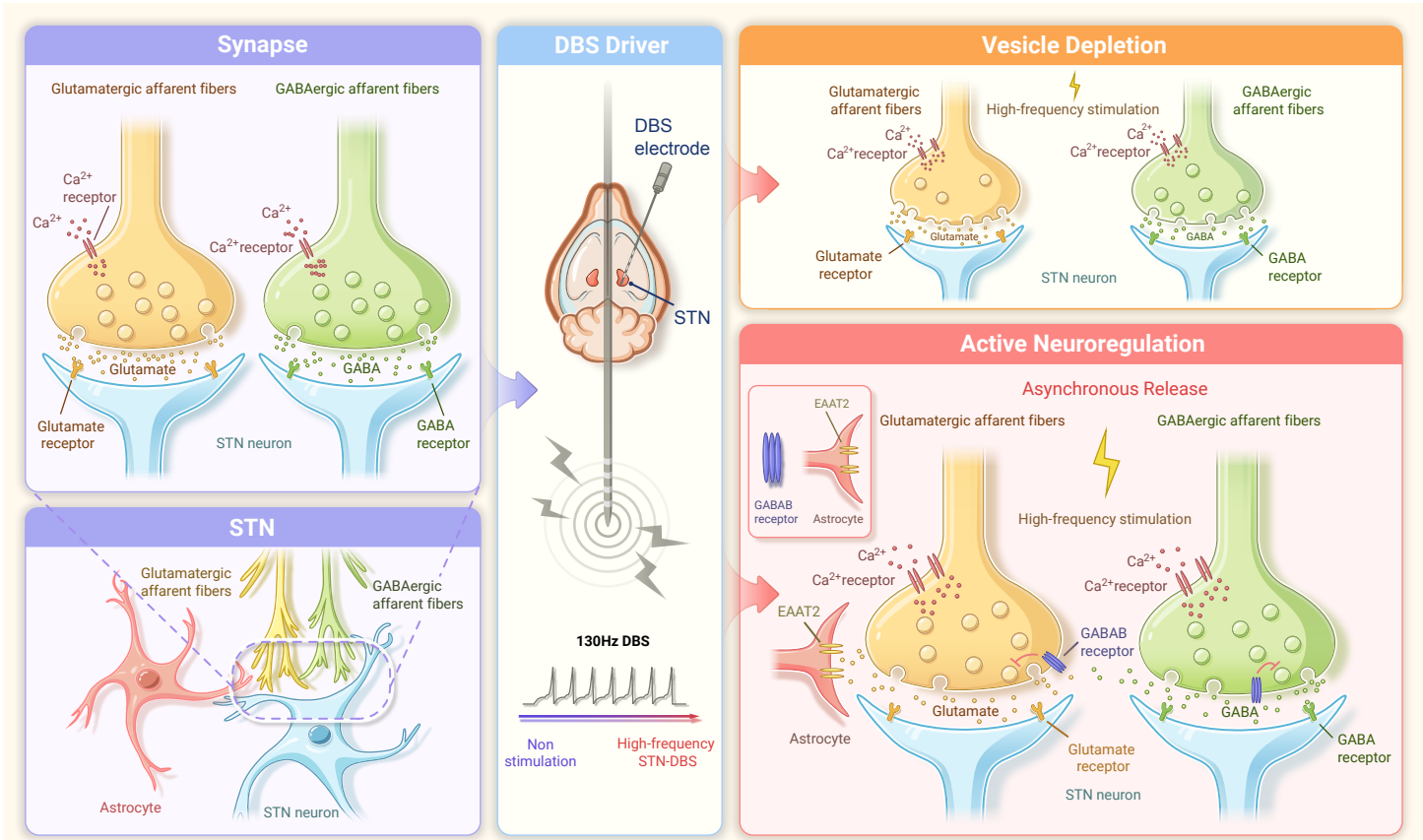

Figure 1. Schematic diagram of two neural mechanism hypotheses for high-frequency STN-DBS in treating Parkinson's disease The left panels illustrate the local STN microenvironment and synapses within the STN under the non-stimulation condition. The right panels show 130 Hz high-frequency STN-DBS: the upper panel demonstrates the passive vesicle depletion hypothesis—high-frequency DBS continuously activates the glutamatergic and GABAergic afferent fiber terminals of the STN, leading to passive depletion of synaptic vesicles with more significant depletion of glutamate vesicles, which shifts the local excitation/inhibition (E/I) balance toward inhibition and further inhibits the activity of STN neurons to produce therapeutic effects; the lower panel offers the active neuromodulatory framework—after high-frequency DBS activates afferent fibers, the inhibition of STN neurons is mediated through three major active mechanisms, including the conversion of synaptic release mode from synchronous release to asynchronous release, $GABA_B$ receptor-mediated presynaptic inhibition, and enhanced glutamate clearance by astrocytic $EAAT_2$.

In summary, while Li et al. demonstrate that high-frequency DBS alters the local neurochemical landscape, the data are seemingly better explained by a model of active neuroregulation. We propose that HFS drives a transition to asynchronous release and recruits presynaptic inhibition, and homeostatic clearance mechanisms (Figure 1). Testing this model, for instance, by combining DBS with local pharmacological blockade of presynaptic receptors or astrocytic transporters, may represent a crucial next step. In response to strong perturbations, multilayered presynaptic regulatory mechanisms act as key effectors that maintain homeostasis and may provide therapeutic benefits for Parkinson's disease. Reconceptualizing DBS as an active driver of neuroplasticity, rather than solely a cause of passive depletion, may open new directions for optimizing stimulation protocols—for example, by targeting protocols that enhance asynchronous release or modulate glial clearance or presynaptic inhibition. We sincerely appreciate the authors' contribution to the mechanistic study of STN-DBS and hope this perspective encourages further investigation into the active regulatory mechanisms that underlie its therapeutic efficacy and other therapies for PD.[5]

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.