Low-frequency deep brain stimulation

Drug-resistant epilepsy treatment, with deep brain stimulation (DBS) showing promise for alleviating intractable seizures. This study explores the efficacy of low-frequency stimulation (LFS) on specific neuronal targets within the entorhinal-hippocampal circuit in a mouse model of MTLE.

Objective: /Hypothesis: Our previous research demonstrated that LFS of the medial perforant path (MPP) fibers in the sclerotic hippocampus reduced seizures in epileptic mice. Here, we aimed to identify the critical neuronal population responsible for this antiepileptic effect by optogenetically stimulating presynaptic and postsynaptic compartments of the MPP-dentate granule cell (DGC) synapse at 1 Hz. We hypothesize that specific targets for LFS can differentially influence seizure activity depending on the cellular identity and location within or outside the seizure focus.

Methods: We utilized the intrahippocampal kainate (ihKA) mouse model of MTLE and targeted specific neural populations using Channelrhodopsin2 (ChR2) and stereotactic optic fiber implantation. We recorded intracranial neuronal activity from freely moving chronically epileptic mice with and without optogenetic LFS up to three hours.

Results: We found that LFS of MPP fibers in the sclerotic hippocampus effectively suppressed epileptiform activity while stimulating principal cells in the MEC had no impact. Targeting DGCs in the sclerotic septal or non-sclerotic temporal hippocampus with LFS did not reduce seizure numbers but shortened the epileptiform bursts.

Conclusion: Presynaptic stimulation of the MPP-DGC synapse within the sclerotic hippocampus is critical for seizure suppression via LFS [1)]

Patients with Parkinson's disease can develop axial symptoms, including speech, gait, and balance difficulties. Chronic high-frequency deep brain stimulation (>100 Hz) can contribute to these impairments while low-frequency stimulation (<100 Hz) may improve symptoms but only in some individuals.

DBS at frequencies below 100 Hz is a therapeutic option in select cases of Parkinson's disease with freezing of gait and other axial symptoms, and in select patients with dystonia and other hyperkinetic movements, particularly those requiring an energy-saving strategy [2)].

Comprehensive literature review and meta-analysis

In ten studies with 132 patients, the pooled results showed no significant difference in the total Unified Parkinson's disease Rating Scale part III (UPDRS-III) scores (mean effect, -1.50; $p = 0.19$) or the rigidity subscore between HFS and LFS. Compared to LFS, HFS induced a greater reduction in the tremor subscore within the medication-off condition (mean effect, 1.01; $p = 0.002$), while no significance was shown within the medication-on condition (mean effect, 0.01; $p = 0.92$). LFS induced greater reduction in akinesia subscore (mean effect, -1.68, $p = 0.003$), the time to complete the stand-walk-sit (SWS) test (mean effect, -4.84; $p < 0.00001$), and the number of freezing of gait (FOG) (mean effect, -1.71; $p = 0.03$). These results suggest that two types of frequency settings may have different effects, that is, HFS induces better responses for tremor and LFS induces greater response

for akinesia, gait, and FOG, respectively, which are worthwhile to be confirmed in a future study, and will ultimately inform the clinical practice in the management of PD using STN-DBS [3].

Case series

Vijiaratnam et al. from the Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, Unit of Functional Neurosurgery, the National Hospital for Neurology and Neurosurgery, London, Unit of Neurology of Ospedale “M. Bufalini” of Cesena, Cesena, Italy Department of Neurology, the Walton Centre NHS Foundation Trust, Liverpool recruited patients who developed axial motor symptoms while using high-frequency stimulation and objectively assessed the short-term impact of low-frequency stimulation on axial symptoms, other aspects of motor function and quality of life. A retrospective chart review was then conducted on a larger cohort to identify which patient characteristics were associated with not only the need to trial low-frequency stimulation but also those which predicted its sustained use. Among 20 prospective patients, low-frequency stimulation objectively improved mean motor and axial symptom severity and quality of life in the short term. Among a retrospective cohort of 168 patients, those with less severe tremor and those in whom axial symptoms had emerged sooner after subthalamic nucleus deep brain stimulation were more likely to be switched to and remain on long-term low-frequency stimulation. These data suggest that low-frequency stimulation results in objective mean improvements in overall motor function and axial symptoms among a group of patients, while individual patient characteristics can predict sustained long-term benefits. Longer follow-up in the context of a larger, controlled, double-blinded study would be required to provide definitive evidence of the role of low-frequency deep brain stimulation [4].

To investigate whether LF-SNr-DBS combined with standard HF stimulation of the subthalamic nucleus (STN) is clinically relevant in improving gait disorders that no longer respond to levodopa in PD patients, compared with HF-STN or LF-SNr stimulation alone.

Methods: Patients received LF-SNr or HF-STN stimulation alone or combined (COMB) stimulation of both nuclei (crossover design). The nucleus to be stimulated was randomly assigned and clinical evaluations performed by a blinded examiner after three months follow-up for each. Clinical assessment included the Freezing of Gait questionnaire, Tinetti Balance and Walking Assessing tool, and Unified Parkinson's Disease Rating.

Results: We included six patients (mean age 59.1 years, disease duration 16.1 years). All patients suffered motor fluctuations and dyskinesias. The best results were obtained with COMB in four patients (who preferred and remained with COMB over 3 years of follow-up) and with HF-STN in two patients. SNr stimulation alone did not produce better results than COMB or STN in any patient.

Conclusion: COMB and HF-STN stimulation improved PD-associated gait disorders in this preliminary case series, sustained over time. Further multicenter investigations are required to better explore this therapeutic option [5].

Sidiropoulos et al. studied the effects of low-frequency stimulation (LFS) (≤80 Hz) for improving

speech, gait, and balance dysfunction in the largest patient population to date. PD patients with bilateral STN-DBS and resistant axial symptoms were switched from chronic 130 Hz stimulation to LFS and followed up to 4 years. Primary outcome measures were total motor UPDRS scores, and axial and gait subscores before and after LFS. Bivariate analyses and correlation coefficients were calculated for the different conditions. Potential predictors of therapeutic response were also investigated. Forty-five advanced PD patients who had high-frequency stimulation (HFS) for 39.5 ± 27.8 consecutive months were switched to LFS. LFS was kept on for a median period of 111.5 days before the assessment. There was no significant improvement in any of the primary outcomes between HFS and LFS, although a minority of patients preferred to be maintained on LFS for longer periods of time. No predictive factors of response could be identified. There was overall no improvement from LFS in axial symptoms. This could be partly due to some study limitations. Larger prospective trials are warranted to better clarify the impact of stimulation frequency on axial signs [6].

1)
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