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Molecular glucose imaging reveals functional brain re-configuration by subthalamic DBS in Parkinsonian rats.

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Animal models of Parkinson's disease (PD) serve as a fundamental tool for elucidating the molecular mechanisms underlying therapeutic subthalamic deep brain stimulation (STN-DBS). However, a major translational challenge persists: the lack of methodologies to parameterize DBS-induced electric field effects and integrate them with molecular readouts in PD model studies. This gap hinders cross-center comparability and data integration, thereby limiting our understanding of the neural mechanisms underlying DBS. The current study introduces a pipeline designed to address this gap by enabling the simulation of focal electric field effects and the subsequent characterization of both local and brain-wide network responses by STN-DBS.

We implemented a human-mimicking A53T alpha-synuclein PD rat model and used an integrative framework that combines CT-based electrode localization with electric field (E-field) and volume of tissue activated (VTA) modeling, molecular imaging using 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), and histological validation. We employed a fully wearable microstimulator and conducted a behavioral test (pellet reaching task) and PET scan during acute STN-DBS (DBS ON) and after a washout period (DBS OFF), with a CT scan acquired. To capture a comprehensive picture of circuit-level modulations induced by unilateral, therapeutic STN-DBS, we first characterized brain functional changes in A53T rats compared to empty vector (EV) control rats in the OFF-stimulation state, and second, elucidated the DBS response by comparing ON-stimulated with OFF-stimulated A53T rats. Our results demonstrate that hypometabolism within the subthalamic nucleus (STN)—substantia nigra (SN)/entopeduncular nucleus—thalamus pathway was predominantly exhibited in A53T rats compared to EV controls. By integrating E-field and VTA simulation methods with FDG-PET imaging analysis, we uncovered that therapeutic STN-DBS activates the targeted region, a finding corroborated by both FDG-PET imaging results and histological validation via hexokinase 1 (HK1) immunofluorescence staining. Furthermore, acute STN-DBS ameliorated aberrant metabolic activity within the ipsilateral STN–SN loop by reversing Parkinsonian-state hypometabolism in these regions, while simultaneously deactivating bilateral cortico-striatal circuitry.

Our study provides mechanistic insights into therapeutic STN-DBS and presents a reverse-translational pipeline that bridges DBS profiling with molecular-level analysis, thereby advancing basic DBS research and enabling forward translation from animal models to patients.

Jiazhi Chen, PhD

Jiazhi Chen is a Postdoc at Universitätsklinikum Würzburg with the Ip lab. His research focuses on the translational neuromodulation field, including neural network and cellular mechanisms of acute and chronic deep brain stimulation, as well as the disease-modifying effects of neurostimulation.

Prof. Chi Wang Ip

Chi Wang Ip is the Vice Chairman of Neurology department in Würzburg. His research focuses on understanding the molecular, cellular and network mechanisms underlying movement disorders and utilizing this understanding to develop novel treatment strategies to improve patient outcomes.

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