Functional dissection of therapeutic deep brain stimulation circuitry

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Principal Investigators

SHIH, YEN-YU IAN

Institution

UNIV OF NORTH CAROLINA CHAPEL HILL

Contact information of lead PI
Country

USA

Title of project or programme

Functional dissection of therapeutic deep brain stimulation circuitry

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NIH (NINDS)

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15/05/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Deep Brain Stimulation, Structure of subthalamic nucleus, Dissection, STN stimulation, optogenetics

Research Abstract

? DESCRIPTION (provided by applicant): Deep brain stimulation (DBS) is a well-established neurosurgical therapy for multiple neurological and psychiatric disorders. In DBS, an electrode

is stereotactically guided to a target cerebral nucleus and high frequency (~130 Hz) electrical stimulation is delivered through a pacemaker-like subcutaneous stimulating device. It is most commonly employed in the treatment of Parkinson’s disease (PD), generally in cases where other medical therapies have become inadequate or dyskinesias have become intolerable. When applied for the symptomatic treatment of PD, the subthalamic nucleus (STN) is frequently targeted, often resulting in a marked reduction in several hallmark PD symptoms, including resting tremor and rigidity. However, despite these benefits, many parkinsonian symptoms are frequently refractory to, or may worsen during STN-DBS. The STN is both anatomically heterogeneous and fiber-dense, and thus there is a high likelihood of recruitment of off-target circuits during STN-DBS, even with accurate electrode placements. A better understanding of how DBS exerts its therapeutic effects will allow optimization of this procedure to enhance therapeutic outcomes and reduce unwanted side-effects. The proposed project aims to address three critical, yet elusive questions of: 1) which neural circuits represent on- and off-target STN DBS effects, 2) whether selective optogenetic stimulation of STN neurons ameliorate parkinsonian motor deficits, and 3) which neural circuits are necessary for therapeutic STN-DBS. To these ends, we will use state-of-the-art functional magnetic resonance imaging (fMRI), functional connectivity MRI (fcMRI), electrophysiology, optogenetics, and behavioral assessment to dissect therapeutic DBS circuitry in an animal model of PD, in which the amelioration of motor deficits are strongly DBS-dependent. Our central hypotheses are that: 1) on- and off-target DBS exhibit behavior- correlated, distinct brain activity and connectivity patterns, 2) high frequency optogenetic stimulation of the STN cell bodies mimics STN-DBS therapy and suppresses pathological oscillatory activity, and 3) suppressing pivotal circuit elements using optogenetics during therapeutic DBS attenuates motor deficit rescue, and thus allowing effective therapeutic DBS circuits to be separated from DBS side effects. Our group has extensive experience in DBS-fMRI studies in rodents. Our co-investigators are also leaders in understanding and continuing development of DBS, optogenetics, and brain network analysis approaches. Together, we are in the unique position to undertake this much-needed line of research. This project will provide novel insights into DBS mechanisms, and lay a foundation to establish new DBS treatment targets and stimulus paradigms for a wide variety of neurological and psychiatric disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: Deep brain stimulation (DBS) is a powerful therapeutic tool for the alleviation of multiple neurological and psychiatric symptoms. However, the mechanisms by which DBS works are poorly understood, greatly limiting the ability of clinicians to improve this therapy. This project will take novel imaging, electrophysiological and behavioral approaches towards identifying the brain neural circuits responsible for DBS efficacy, with the ultimate goal of enhancing DBS therapeutic outcomes and reducing unwanted side-effects.

Further information available at:

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Investments > €500k

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United States of America

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