NEURAL ENGINEERING SEMINAR SERIES

Developing therapeutic strategies for neurological disorders, particularly those of the cerebellum

April 26

3:00 p.m.-4:00 p.m. (E.T.)

Dr. Collin Anderson

Postdoctoral Research Associate
Department of Neurology
University of Utah

ABSTRACT: Several forms of movement disorders arise through neurodegeneration affecting the basal ganglia and cerebellum. Parkinsonism arises through the loss of dopaminergic substantia nigra neurons and affects more than 1% of the population above 60 years of age. High frequency, 100+ Hz, deep brain stimulation (DBS) of the subthalamic nucleus has become a common late-stage therapy for parkinsonism, but its mechanisms are unclear. To better elucidate the mechanisms of DBS, we evaluated the effects of deep brain stimulation in a rodent 6-hydroxydopamine lesion model of hemiparkinsonism. We made simultaneous electrophysiological recordings within the basal ganglia and downstream thalamic neurons prior to lesion and in a hemiparkinsonian state, both on and off DBS. Applying information theoretic metrics to simultaneously recorded neuronal spike trains, we demonstrated that the parkinsonian network is characterized by an over-coupling of neuronal signals across regions compared to the healthy state, and this is reversed by successful DBS. Thus, high frequency DBS may function as an informational lesion. Progressive cerebellar ataxias can arise through the degeneration of Purkinje cells, affecting 1 in every 5000 individuals, with few receiving any treatment beyond palliative care. While dozens of genetic causes have been identified, most cases are sporadic. Unlike in parkinsonism, we hypothesized that ataxic symptoms arise through a loss of motor coordination-relevant information caused by Purkinje cell degeneration. Further we hypothesized that low, rather than high-frequency, deep brain stimulation targeting the deep cerebellar nuclei may reduce ataxic symptoms by enhancing the throughput of remaining signals. We tested this hypothesis in the shaker rat, a spontaneous model of Purkinje cell degeneration and ataxia. We found that while standard 100+ Hz DBS worsened ataxia, low frequency (~30 Hz) stimulation improved both ataxia and cerebellar tremor. Thus, low frequency cerebellar DBS may function as a catch-all therapy for sporadic ataxias. However, in a small subset of genetic cases, gene therapy may provide a more attractive treatment option. We recently found evidence suggesting that the shaker phenotype may be caused by a loss of function mutation in the Slc9a6 gene. Slc9a6 mutations cause Christianson syndrome in humans, characterized by cerebellar degeneration, progressive ataxia, and several other severe symptoms. Therefore, we generated an adeno-associated virus targeting expression of the Slc9a6 gene to Purkinje cells as a form of gene replacement therapy. Administration of this virus prior to Purkinje cell death generated substantial motor protection, with a subset of rats developing virtually no tremor or gait ataxia. Current and future work in these lines of work will focus on further optimization of neuromodulatory strategies and the full preclinical testing of a human treatment-specific viral construct for Christianson syndrome.

BIOGRAPHY: Dr. Collin Anderson completed his undergraduate in Biomedical Engineering at Johns Hopkins University. He then earned his PhD in the Neural Interfaces track of Bioengineering at the University of Utah under Dr. Chuck Dorval, performing in vivo studies to characterize the mechanisms of deep brain stimulation. Dr. Anderson is currently a postdoc with Dr. Stefan Pulst in the University of Utah department of Neurology, where he works on therapeutic optimization and several novel therapeutics for movement disorders. Dr. Anderson's primary research goals in recent years have revolved around degenerative cerebellar ataxic disorders, and his work in this area spans both neuromodulatory and gene therapeutic strategies. Dr. Anderson's work has been funded by numerous granting organizations, with most recent awards from the National Ataxia Foundation and the RTW Charitable Foundation.