Cortico-basal ganglia connectivity in a non-human primate model of Huntingtons disease

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Country

USA

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Cortico-basal ganglia connectivity in a non-human primate model of Huntingtons disease

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NIH (NINDS)

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15/09/2016

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5

The project/programme is most relevant to:

Huntington's disease

Keywords
Research Abstract

PROJECT SUMMARY The goal of the proposed research in this application is to characterize alterations in cortico-basal ganglia connectivity in a novel non-human primate model of Huntington’s disease (HD) recently developed in my laboratory. Previous K99/R00 funding (2010-2015) from the NINDS supported the development of this new model, wherein we found that AAV-mediated expression of mutant HTT in the caudate and putamen of rhesus macaques

lead to a wide array of behavioral manifestations of disease including the progressive development of both motor and cognitive phenotypes also seen in human HD patients. Brains from HD NHPs showed DARPP-32 loss, inclusion formation and gliosis, along with reduced levels of key striatal transcripts, including reduced glutamate and dopamine receptor levels (manuscript in preparation). In addition to striatal pathology, we found mHTT expression, inclusion bodies and gliosis in numerous cortical areas (frontal and motor) and regions throughout the basal ganglia (globus pallidus, substantia nigra), likely owing to transport of the AAV vector. These findings strongly suggest that basal ganglia connectivity may be disrupted in our NHP HD model. The objective of this current proposal is to characterize cortico-basal ganglia connectivity in the brains of our HD NHPs using resting state fMRI and diffusion tensor imaging to assess functional connectivity and white matter integrity, respectively (Aim 1). Additionally, we will evaluate glutamate and dopamine neurotransmission in the caudate and putamen using electrophysiological analyses (Aim 2). We will test our central hypothesis that there is a progressive decline in basal ganglia connectivity in our HD NHP brains that correlates with 1) the longitudinal development of cognitive and motor phenotypes, 2) reduced glutamate and dopamine transmission in cortico-striatal and nigro-striatal connections with medium spiny neurons in the caudate and putamen and 3) neuropathology including inclusion formation, gliosis and neuronal dysfunction. I have assembled an excellent team of scientists to accomplish these goals with cumulative expertise in resting state fMRI analysis of cortico-striatal functional connectivity (Dr. Christopher Kroenke), electrophysiological recordings of medium spiny neurons in the rhesus macaque striatum (Dr. Verginia Cuzon Carlson), statistical analysis of complex datasets (Dr. Byung Park), as well as my background and expertise in HD neurobiology, AAV-mediated gene transfer, NHP MRI-guided neurosurgery, complex NHP motor and cognitive behavioral assessment and the use of molecular and histological techniques to assess HD neuropathology. By the end of the studies proposed here, we will have characterized alterations in basal ganglia connectivity in a novel AAV- mHTT mediated monkey model of HD, elucidating potential pathophysiological mechanisms that underlie motor and cognitive decline. Additionally, the data obtained from these studies will provide the unique opportunity to identify imaging, behavioral, electrophysiological and neuropathological endpoints that will be used for future therapeutic studies using this model.

Lay Summary
PROJECT NARRATIVE Huntington’s disease (HD) is a fatal neurodegenerative disorder caused by a CAG repeat mutation in the HTT gene that leads to robust, debilitating behavioral and neuropathological decline. Large animal models that recapitulate the complex motor and cognitive disease phenotypes, and associated neuropathology, observed in human HD patients are severely lacking. The proposed research in the current application will use state-of- the-art neuroscience technologies (resting state functional magnetic resonance imaging, touchscreen behavioral analyses and electrophysiological techniques) in a novel non-human primate model of HD recently created in our laboratory to 1) study alterations in functional brain connectivity in these animals and 2) correlate changes in brain connectivity to the progressive development of behavioral phenotypes and related neuropathology germane to this monkey model of HD.

Further information available at:

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Investments > €500k

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United States of America

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Huntington's disease

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