VALIDATION OF NEUROIMAGING BIOMARKERS FOR NIGROSTRAITAL NEURONS

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Title of project or programme

VALIDATION OF NEUROIMAGING BIOMARKERS FOR NIGROSTRAITAL NEURONS

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1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

neuroimaging, Corpus striatum structure, Intracarotid, vesicular monoamine transporter, Dopamine

Research Abstract

DESCRIPTION (provided by applicant): Parkinson disease (PD) affects more than one million people in North America, and no treatment has been proven to slow progression. To develop and test new interventions to slow disease progression, we must have validated biomarkers that reflect reversible or modifiable pathologic processes. Increasing evidence suggests selective vulnerability to different parts of nigrostriatal dopaminergic neurons; thus biomarkers that reflec different aspects of pathologic processes may be critical to develop these new therapies. Our initial studies in the first 3 years of this proposal have clarified how neuroimaging biomarkers reflect underlying pathologic processes of nigrostriatal neurons. We have data comparing neuroimaging measures with in vitro measures in nonhuman primates two months after giving different doses of unilateral intracarotid MPTP indicating that striatal uptake of [18F]FD (primarily reflecting decarboxylase activity), [11C]CFT (a dopamine transport marker, DAT) and [11C]DTBZ (a vesicular monoamine transporter type 2) reflect striatal dopamine content but only reflect nigral DA cell bodies if the loss of nigral neurons does not exceed 50%. We also demonstrated with in vitro quantitative autoradiography that DAT and VMAT2 presynaptic sites do not differentially regulate as the number nigrostriatal neurons decreases. PET measures of striatal uptake of FD, DTBZ and CFT also change nearly identifically as the number of nigrostriatal neurons decreases. Our results reveal that terminal fields (striatal DA and the PET measures) have greater loss than nigral cell bodies at 2 months post MPTP. We also have preliminary data that MR-based measures of midbrain mean diffusivity correlate with stereologic counts of nigrostriatal dopaminergic neurons. Some initial studies suggest that probablistic tract tracing may be able to quantify nigrostriatal axons. Together these findings set the stage for the studies proposed in this renewal. We will test the hypothesis that these newly validated neuroimaging biomarkers can detect time-dependent changes in different components of nigrostriatal dopaminergic neurons and validate these measures against in vitro measures including stereologic counts of tyrosine hydroxylase (TH) immunostained cell bodies in nigral, TH-stained striatal fibers, DAT immunostained striatal fibers, striatal dopamine content, quantitative autoradiography of DAT and VMAT2 sites in striatum and clinical ratings of motor behaviors using validated rating scales. In addition, we will test the hypothesis that acute or chronic administration of levodopa or the dopamine agonist pramipexole may alter selected neuroimaging biomarkers. This study will provide the critical tools for targeting the relevant pathologic sites for testing new therapies for PD.

Lay Summary

Parkinson disease (PD) affects more than one million people in North America, and no treatment has been proven to slow progression. To develop such a treatment, it is necessary to have an objective measure of the various time-dependent components of disease progression. This application proposes to develop and validate such neuroimaging biomarkers and determine whether commonly used medications either acutely or chronically administered affects these biomarker measures. Development and validation of such biomarkers are critical steps for targeting and testing new therapies for Parkinson disease.

Further information available at:

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Investments > €500k

Member States:

United States of America

Diseases:

Parkinson's disease & PD-related disorders

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