Multimodal MRI markers of nigrostriatal pathology in Parkinsons disease

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Principal Investigators

HUANG, XUEMEI

Institution

PENNSYLVANIA STATE UNIV HERSHEY MED CTR

Contact information of lead PI
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USA

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Multimodal MRI markers of nigrostriatal pathology in Parkinsons disease

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1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

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Research Abstract
DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is marked pathologically by

dopamine neuronal loss in the substantia nigra (SN) of the basal ganglia (BG) and the presence of Lewy bodies. The lack of in vivo biomarker(s) reflecting PD-related cell loss and associated pathoetiological/physiological processes has hindered discovery research and limited the ability to evaluate potentially disease-modifying therapies. The best available technology, radioimaging using 18FDOPA-PET and [123I]b-CIT SPECT, can assess the activity or density of striatal dopamine terminals. These techniques, however, do not reflect directly the pathological process in the SN, may not distinguish PD from other parkinsonian syndromes, and can be affected by symptomatic therapy. In addition, both techniques require exposure to radioactivity and PET requires facilities not widely available. Magnetic resonance imaging (MRI) is noninvasive, easily accessible, and widely available, yet its measures have been difficult to relate to a specific pathophysiological mechanism. Diffusion tensor (DTI) and R2* imaging have been reported to detect changes in the SN in PD, and offer the promise of being MRI biomarkers. There is, however, a lack of understanding of their clinical implications and biological/pathological underpinnings. Our pilot data support the hypothesis that fractional anisotropy (FA) and R2* measures reflect different aspects of nigrostriatal pathology that can be used as biomarkers for diagnosing PD and following its progression. We propose to leverage the longitudinal clinical population and existing infrastructure of the PI's R01 (2009-2014) to test the above hypothesis. In addition, we have considerable expertise in developing disease biomarkers, particularly related to iron (Fe) metabolism. By melding in vivo high-resolution DTI and R2* MRI data with assessment of Fe-related protein profiles in body fluids, we expect to gain marked insight into predicting PD progression. Moreover, our strengths in postmortem brain histopathology and analysis of Fe-related proteins will permit the correlation of the in vivo clinical and brain MRI measures with biochemical changes in the brain. This will provide a mechanistic understanding of the role of Fe in PD that may lead to the discovery of new biomarkers or therapeutic targets. Based on power analysis pilot data, four aims will be performed: 1) Establish the differential roles of DTI and R2* in PD detection and progression; 2) Demonstrate that nigrostriatal DTI and R2* differentiate PD from parkinsonian syndromes; 3) Interrogate Fe-related proteins in body fluids as biomarkers; 4) Obtain MRI biomarker and postmortem pathological correlation data. The success of the study shall yield valid markers for both detection of PD and its progression that can be integrated into and hopefully impact disease-modifying clinical trials within the foreseeable future. The clinical and MRI data and the biosamples collected and deposited to the DMR of the PDBP shall provide investigators in the biomarker community the opportunity to explore and understand changes outside of nigrostriatal pathways and non Fe-related proteins and their relationship with our proposed markers.

Lay Summary

The lack of in vivo biomarker(s) reflecting Parkinson’s disease (PD)-related cell loss and associated pathoetiological/physiological processes in nigrostriatal structures has hindered discovery research and limited the ability to evaluate disease-modifying therapies. Recent research has generated excitement for using DTI and R2* MRI measures as biomarker(s) for PD-related pathology in nigrostriatal pathways, but they fall short by the lack of understanding of their clinical implications and biological/pathological underpinnings. Working closely with the NINDS Parkinson’s Disease Biomarkers Program (PDBP), the proposed work will investigate multimodal MRI techniques in combination with fluid-based iron (Fe) protein profiles to serve as in vivo markers for PD-related nigrostriatal pathology that can be used as biomarkers for diagnosing PD, following its progression, and gaining mechanistic understanding of PD pathoetiology and pathophysiology.

Further information available at:

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