Connectomic imaging in familial and sporadic frontotemporal degeneration

https://neurodegenerationresearch.eu/survey/connectomic-imaging-in-familial-and-sporadic-frontotemporal-degeneration/

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USA

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Connectomic imaging in familial and sporadic frontotemporal degeneration

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NIH (NIA)

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01/06/2016

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Frontotemporal Dementia (FTD)... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Neurodegenerative disease is a major public health problem. Frontotemporal degeneration (FTD) is a clinical neurodegenerative condition that affects both gray matter (GM) and white matter (WM) and causes a network disorder. FTD is an excellent model for directly imaging the neurobiology of neurodegeneration because the associated pathology involves a monoproteinopathy in each patient – either frontotemporal lobar degeneration (FTLD) due to tau (FTLD-tau) or to TAR DNA binding protein of 43kD (FTLD-TDP). We propose a connectomic approach to identify FTLD-tau and FTLD-TDP in vivo. This is timely because of the discovery of disease-modifying agents, and pressing needs for accurate antemortem diagnosis, biomarkers to gauge response during treatment trials, and elucidation of mechanisms of disease progression even at the preclinical stage. About 25% of cases have familial FTD (fFTD) due to a small set of mutations causing one of these pathologies. The remaining 75% of cases have sporadic FTD (sFTD) with no definitive biomarkers for FTLD- tau or FTLD-TDP pathology. Preliminary data suggest that multimodal structural MRI (sMRI) of GM disease and diffusion MRI (dMRI) of WM disease can identify vulnerable networks in FTLD-tau and FTLD-TDP. We propose a five-site consortium, including Mayo Clinic, MGH/Harvard, Northwestern University, University of California in San Francisco, and University of Pennsylvania, to acquire HCP imaging in FTD. This will be linked to two NIH-funded biomarker registries, and this linkage will result in substantial cost savings. We propose three Specific Aims. In Year 01, Aim 1 will implement and validate the Human Connectome Project (HCP) Lifespan protocol for sMRI, dMRI, resting BOLD MRI (rs-fMRI), task-based functional MRI (tfMRI) and arterial spin labeling (ASL). We will acquire initial data, harmonize data between sites and with HCP, implement quality control procedures, optimize analyses using HCP and locally-developed pipelines, and implement data sharing procedures. In Year 02, Aim 2 will study presymptomatic and symptomatic fFTD associated with FTLD-tau or FTLD-TDP, and assess sFTD in specific phenotypes highly associated with FTLD-tau or FTLD-TDP. Connectomic imaging will be integrated with NIH-funded registries that acquire clinical, genetic and biofluid data. Based on histopathology showing greater WM disease in FTLD-tau than FTLD-TDP, we expect advanced HCP imaging to show partially distinct patterns in multimodal imaging of symptomatic as well as presymptomatic individuals with familial and sporadic FTLD-tau compared to FTLD-TDP. In Years 03-04, Aim 3 will acquire longitudinal data to assess competing hypotheses about mechanisms of disease spread in presymptomatic and symptomatic FTD. Consistent with animal studies, we expect that graph theoretic and multimodal network analyses will show disease spreading locally to adjacent brain regions, affecting different networks in FTLD-tau or FTLD-TDP.

Lay Summary
PUBLIC HEALTH RELEVANCE: Neurodegenerative disease is a major public health problem, and frontotemporal degeneration (FTD) is an excellent model for directly imaging neurodegeneration because the associated pathology involves a monoproteinopathy in each patient – either frontotemporal lobar degeneration (FTLD) due to tau (FTLD-tau) or to TAR DNA binding protein of ~43kD (FTLD-TDP). About 25% of cases have familial FTD (fFTD) due to a small set of pathogenic, autosomal-dominant mutations causing one of these pathologies, while the remaining 75% of cases have sporadic FTD (sFTD) with no definitive biomarkers for FTLD-tau or FTLD-TDP pathology and preliminary data suggest that multimodal structural MRI (sMRI) for gray matter (GM) disease and diffusion MRI (dMRI) for white matter (WM) disease can identify partially distinct networks in FTLD-tau and FTLD-TDP. In this multicenter consortium

linked to two NIH-funded biomarker registries, we propose three Specific Aims for collecting advanced HCP imaging to distinguish between FTLD-tau and FTLD-TDP: In Year 01, Aim 1 will implement and validate the Human Connectome Project (HCP) Lifespan protocol; in Year 02, Aim 2 will study presymptomatic and symptomatic fFTD associated with FTLD-tau or FTLD-TDP, and assess sFTD in specific phenotypes highly likely to be due to FTLD-tau or FTLD-TDP, to test the histopathologically-based hypothesis that advanced HCP imaging will show greater WM disease in FTLD-tau compared to FTLD-TDP, and we also expect partially distinct patterns of GM disease; in Years 03-04, Aim 3 will acquire longitudinal data to assess competing hypotheses about mechanisms of disease spread in presymptomatic and symptomatic FTD due to FTLD-tau or FTLD-TDP, and we expect that graph theoretic and multimodal network analyses will show that disease spreads locally to adjacent brain regions in partially distinct GM-WM networks.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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