The structural and functional connectome across Alzheimers disease subtypes

https://neurodegenerationresearch.eu/survey/the-structural-and-functional-connectome-across-alzheimers-disease-subtypes/

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Country

USA

Title of project or programme

The structural and functional connectome across Alzheimers disease subtypes

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,297,795.41

Start date of award

30/09/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Diagnostic Radiology... Genetics... Minority Health for IC Use... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): It is now clear that Alzheimer’s disease is not a unitary phenomenon and that it can be divided into subtypes by their genetic origins, each of which may have distinct pathogenetic cascades and therefore may respond differentially to treatments. The Human Connectome Project (HCP) protocol provides the unique opportunity to comprehensively characterize imaging and clinical phenotypes of these AD subtypes. By applying the HCP protocol to persons at-risk for fully-penetrant autosomal dominant AD (ADAD due to either the A431E PSEN1 or V717I APP mutations) in conjunction with positron emission tomography (PET) imaging of tau using the novel ligand 18F-T807, we will be able to test the hypothesis that tau pathology spreads in a trans-synaptic manner along definable neural pathways. Applying the HCP protocol to this unique population will provide the opportunity to test the hypothesis of transynaptic spread of tau in the etiology of AD and provide the opportunity to differentiate pathological processes in subtypes of AD and therefore inform approaches to treatment. As PSEN1-related AD can present with spastic paraparesis, an easily assessed phenotype, we will be able to relate the neurophysiological parameters of central nervous system conduction time to connectivity measures in the HCP, helping to understand this characteristic and also validating HCP measures. We propose the following specific aims: 1) Perform network analyses relating the sequence of cortical deposition of neurofibrillary tangles measured using tau PET to white matter pathways and clinical status. 2) Identify connectomic (structural, functional, and connectional) and cerebral perfusion (ASL) MRI differences during neurodegeneration due to autosomal dominant AD mutations (ADAD due to specific mutations in the PSEN1 and APP genes) potentially revealing diverse pathological phenotypes. 3) Identify connectomic and cerebral perfusion MRI differences between AD of early (due to PSEN1 and APP mutations) and late onset (LOAD, associated or not with the APOE e4 allele). 4) Identify the connectomic bases for changes in central conduction times in motor pathways in ADAD and LOAD using TMS. This study will leverage the relatedness among persons with the A431E PSEN1 and V717I APP mutations to estimate mutation-associated variability in the connectome MRI. It will also provide the opportunity to explore variability of te connectome associated with Mexican Mestizo origin, a population typically under-represented in Alzheimer’s and other neuroscientific research. Finally, by adopting the HCP phenotyping protocol into Spanish and applying it in this population, we will create a database to enable additional future studies in Latinos, a growing segment of the U.S. population.

Lay Summary

PUBLIC HEALTH RELEVANCE: In light of the failure of multiple new interventions to affect the course of Alzheimer’s disease (AD), it is clear that new perspectives on the disease are needed. There is growing evidence that AD consists of subtypes that might respond differentially to interventions and therefore it is critical to understand these. In the current study we propose to leverage the Human Connectome Project protocol towards differentiating genetic subtypes of AD, leading to new insights into the diversity of the illness and clues towards future treatment avenues.

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

Database Tags:
N/A