Dissecting molecular mechanisms involved in resilience of Alzheimers pathology

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Country

USA

Title of project or programme

Dissecting molecular mechanisms involved in resilience of Alzheimers pathology

Source of funding information

NIH (NIA)

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€ 1,941,533.03

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01/09/2013

Total duration of award in years

4

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... Dementia... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): It is clear from recent clinical-neuropathological correlation studies and PET amyloid imaging studies that there can be a dissociation between the occurrence of Alzheimer's (AD) pathology and cognitive impairment. In the Nun Study, 12% of cognitively intact participants at the time of death had abundant amyloid plaques and neurofibrillary tangles at postmortem exam and met pathological criteria for AD (Riley et al., 2005). Recent data from the Religious Orders Study and the Memory and Aging Project also showed that about one third of brains from older people without symptoms of cognitive impairment demonstrated enough AD pathology to meet NIA-Reagan Institute criteria for intermediate or high likelihood of AD (Schneider et al., 2009). Consistent with these observations, elevated PET Pittsburgh Compound B (PIB) retention (fibrillar Aß deposits) has been reported in more than 20% of clinically unimpaired elderly volunteers (Lopresti et al., 2005; Mintun et al., 2006; Rowe et al., 2007; Aizenstein 2008). All together the above data suggest that some individuals can remain asymptomatic for dementia while alive despite having substantial amounts of both amyloid and tau pathology at autopsy. The goal of this application is to evaluate two competing hypotheses: are some human brains resistant to the insult of Alzheimer's pathology (amyloid plaques and neurofibrillary tangles), and in this case, what are the neuroprotective mechanisms involved? or is the type of Abeta/tau species (soluble oligomeric Abeta/tau vs. fibrilar amyloid plaques/neurofibrillary tangles) what determines structural damage and impaired cognition in AD? We believe that these cases of AD by neuropathological criteria that were found to be non- demented during life (we refer to them as ""mismatches""), although uncommon, are of importance to understand why some individuals are resilient to AD pathology. We have pooled resources from 5 Centers, Massachusetts ADRC, Pittsburgh ADRC, Mayo ADRC, Washington University ADRC and Columbia ADRC, that are each actively studying this problem, to take advantage of a large sample size and accelerate answers to these important questions. We plan to use a combination of detailed quantitative histopathology and biochemical assessments focused on examining the role of soluble Abeta and tau assemblies and glial activation/inflammation in neuronal and synaptic damage to extend our understanding of these cases towards their biochemical and molecular characterization. We believe the expected outcomes of this research have the potential to significantly impact the field of therapeutics in AD as they may contribute to provide a rational approach to neuroprotective and cognitive sparing therapies in the elderly.

Lay Summary

PUBLIC HEALTH RELEVANCE: This study is designed to understand why some individuals with substantial Alzheimer's pathology at autopsy do not get demented while alive. We plan to use a combination of detailed quantitative histopathology and biochemical assessments on these unique brains. We believe these uncommon cases may hold key clues for a rational design of neuroprotective and cognitive sparing therapies in the elderly.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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