Intact Circuit Assessment of Aging Dopamine Neurons vis Optogenetics and CLARITY

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Contact information of lead PI
Country

USA

Title of project or programme

Intact Circuit Assessment of Aging Dopamine Neurons vis Optogenetics and CLARITY

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,765,066.97

Start date of award

01/06/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

pars compacta, Substantia nigra structure, optogenetics, dopaminergic neuron, Aging

Research Abstract
DESCRIPTION (provided by applicant): During aging, motor function declines, with deficits in fine and fast movement and coordination. Experimental studies associate age-dependent motor

deficits with the malfunction of dopaminergic (DA) pathway, which originates in the substantia nigra pars compacta (SNc). However we do not understand how the activity of DA neurons varies throughout aging in the different tiers of nigral neurons in vivo, what type of activity changes precede neurodegeneration, how these activity changes affect behavior, and whether restoring perturbed activity can delay neurodegeneration and/or behavioral deficits. To characterize, for the first time in the intact circuit, the function and anatomy of aging nigral dopaminergic circuits, we propose to use two powerful technological advances in neuroscience: one for cell-type specific bidirectional control of neuronal activity in vivo with high temporal precision (optogenetics); and one for intact brain circuit mapping and phenotyping, slicing-free (CLARITY). Optogenetics uses microbial opsins, light-sensitive proteins that can be expressed in specified cells via targeting promoters and turned on/off with millisecond speed, thus providing control of cell function with high spatial, temporal, and genetic specificity. Their abilty to control the electrical activity of neural circuits and confer reversible gain and loss of functin of specific neuronal phenotypes allows us to study neural systems and diseases in unprecedented manner. To target subsets of SNc DA neurons we will take advantage of the TH- Cre transgenic lines as well as localized stereotaxic opsin delivery and targeted light application We hypothesize that throughout aging, DA neurons in different SNc tiers have distinct behavioral contributions (Aim 1), which is due to differences in their intrinsic excitability (Aim 2) and changes in synaptic inputs (Aim 3). This proposal combines powerful complementary techniques (optogenetics, electrophysiology, and neuroanatomy by CLARITY) to advance our understanding of dopaminergic function and contribution to behavior throughout aging by performing studies in the intact circuit. The PI has been involved in the development of both techniques and our laboratory is ideally positioned to apply these techniques to the aging brain with a focus on the DA system. A better understanding of the properties of DA neurons in the aging SNc can aid in identifying circuit targets and/or behavioral/nutritional methods to delay/reverse age-related alterations in these neurons and in motor functions.

Lay Summary
PUBLIC HEALTH RELEVANCE: Brain disorders and especially age-related brain disorders take a great toll in the US and worldwide. Progress to understand the impact of aging on activity of defined brain areas and behavior has been limited by the availability of tools to investigate neuronal circuits with temporal and special specificity. We will use the optogenetics and CLARITY to advance our understanding of the neural circuit mechanisms underlying the malfunction of aging dopaminergic neurons and motor deficits in the aged.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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