Remodeling of cognitive circuits in Parkinson’s disease

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Institution
Funder

SNSF

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Switzerland

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Remodeling of cognitive circuits in Parkinson’s disease

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SNSF

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5.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Parkinson's disease | cholinergic modulation | substantia nigra pars reticulata | cognitive actions | inhibitory circuitry

Research Abstract
Parkinson’s disease (PD) is a neurodegenerative disease characterized by motor symptoms;

however, these patients also suffer from cognitive decline and in some cases dementia. Attention, working memory, executive function and information processing are the main affected cognitive domains in PD. These changes may be present as early as the time of diagnosis, and strongly affect the patients' quality of life. An imbalance between acetylcholine (ACh) and dopamine (DA) in the striatum has been shown to mediate some cognitive deficits. And in line with these observations, anticholinergic drugs have proved effective. A brain area of relevance in PD is the substantia nigra pars reticulata (SNr). Our preliminary work provides evidence for its heterogeneity, which dictates a specific ACh receptor expression pattern. In addition, ACh is released locally and by brainstem cholinergic afferences. Based on this new finding, we hypothesize that ACh finely coordinates the activity of the SNr circuitry through the modulation of specific subpopulations of SNr cells. In addition we propose that DA depletion induces a remodeling of SNr circuitry such that ACh modulation is altered, leading to the pathological cognitive symptoms observed in PD.
We will use multiple techniques such as confocal imaging to visualize cholinergic receptor expression by SNr cell subtypes, in vitro and in vivo electrophysiology to characterize these cells and their modulation by ACh. Finally a set of behavioral tasks will be performed to measure the impact of such modulation on cognitive processes. Both pharmacological and optogenetic tools will supplement these techniques to selectively manipulate one circuital component at a time.
These four aims will be pursued:
1- Identify the cholinergic modulation of SNr neuron subtypes.
2- Dissect the underlying sub-circuits.
3- Assess the role of ACh in cognitive behaviors.
4- Identify the morphological, functional and behavioral alterations of the cognitive loops in a mouse model mimicking PD's symptoms (DA depletion through DA toxin infusion).
The ultimate goal is to develop strategies compensating for circuit dysfunction caused by DA-ACh deficits and would thereby alleviate the PD cognitive symptoms.

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