Tackling the complexity of Parkinson’s disease

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Title of project or programme

Title of PI Tackling the complexity of Parkinson’s disease

Principal Investigators of project/programme grant

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Address of institution of lead PI

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- Netherlands

Source of funding information

Netherlands Organisation for Health Research and Development (ZonMw)

Total sum awarded (Euro)

600000

Start date of award

1-10-2006

Total duration of award in months

68

The project/programme is most relevant to

- Parkinson’s disease

Keywords

Parkinson’s disease (PD), adaptive plasticity, mutations in known PD-genes

Research abstract in English

Parkinson’s disease (PD) is a frequent and disabling disorder. Improved treatment is urgently needed. Here, we propose to develop new therapies that address the complex pathophysiology of PD, where clinical symptoms are the net result of primary disease and secondary neuronal compensation (‘adaptive plasticity’). Our premise is that stimulation of adaptive plasticity offers therapeutic relief, thereby providing an indispensable supplement to conventional therapies that target primary disease

processes. We first identify where adaptive plasticity is located, with emphasis on cortical areas that are accessible to non-invasive therapeutic intervention (Project A). This is examined in asymptomatic carriers of mutations in known PD-genes, where we expect ‘spontaneous’ adaptive plasticity that keeps carriers asymptomatic. Cortical circuits involved in generating adaptive plasticity will be identified using functional MRI and structural brain imaging. We also examine the dynamics of adaptive plasticity across the spectrum of disease severity (Project B). This is addressed in Macaques with experimentally induced parkinsonism. Cortical circuits involved in generating adaptive plasticity are stimulated or inhibited using transcranial magnetic stimulation. We expect inhibition of adaptive plasticity to provoke symptoms in animals with a carefully titrated subclinical dopaminergic lesion that spares overt behaviour. Furthermore, we expect stimulation of adaptive plasticity to improve symptoms in mildly symptomatic animals. Finally, in a randomised clinical trial, we explore the therapeutic potential of facilitating adaptive plasticity in early PD (Project C). For this purpose, we use theta burst stimulation (TBS), a promising new approach for modulating cortical excitability in a robust and clinically feasible fashion. We expect facilitatory TBS over adaptive plasticity areas to offer symptomatic relief, particularly when combined with stimulation of primary disease areas. This proposal provides fundamental pathophysiological insights, and offers a rationale not only for innovative treatment in symptomatic patients, but also for postponing symptoms in patients during presymptomatic stages of the disease.

Lay Summary
In which category does this research fall?

- Basic research