Restoring brain function: from cortical microcircuits to complex behaviours in neurodegenerative disease.

https://www.neurodegenerationresearch.eu/survey/restoring-brain-function-from-cortical-microcircuits-to-complex-behaviours-in-neurodegenerative-disease/

Name of Fellow

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Institution
Funder

Wellcome Trust

Contact information of fellow
Country

United Kingdom

Title of project/programme

Restoring brain function: from cortical microcircuits to complex behaviours in neurodegenerative disease.

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Wellcome Trust

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5.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Alzheimer | Cognitive impairment | Huntington | Neurodegen

Research Abstract
This program introduces a novel approach to dementia that is both scientifically important and clinically relevant. Frontotemporal dementia (FTD) and Progressive Supranuclear Palsy (PSP) are used as demonstrator conditions. Their importance lies partly in their young onset, high burden and devastating prognosis, but also because they epitomise degenerative network disorders. The first aim is to show how microscopic cellular changes lead to the neuropsychological changes we observe. Understa nding this connection through robust mesoscopic neural models will significantly advance translation to therapies. My hypothesis is that changes in cortical microcircuits, and their gamma oscillations, arise from cell loss in superficial cortical layers and imbalance between GABA, AMPA and NMDA. This is tested using multimodal imaging, biophysical models and pharmacology. Specifically, the impact of disease on brain networks for perception and behaviour will be analysed using hierarchical models , optimised at the level of cortical microcircuits by fitting to the spectral properties of magnetoencephalography. The second aim is to provide a platform to study candidate therapies, using magnetoencephalography to measure the generative networks and gamma-synchronisation that support cognition. The platform will be assessed initially with two test compounds, Tiagabine and Memantine, acting on GABA and NMDA respectively. The resulting theoretically enriched and principled mechanistic models will enable better selection of endpoints, compounds and stratification of novel therapies for complex neurodegenerative disorders such as FTD and PSP. This forward translation to clinical trials is matched by back-translation to improve pre-clinical models of disease and treatment.

Types:
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