Progressive functional disruption of inhibitory neurons in tauopathy

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Name of Fellow

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Institution
Funder

Alzheimer's Society

Contact information of fellow
Country

United Kingdom

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Progressive functional disruption of inhibitory neurons in tauopathy

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Alzheimer's Society

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3.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Tauopathy is a canonical pathological feature of multiple forms of dementia including Alzheimer’s disease (AD). Tauopathy is thought to disturb the function of CNS circuits and lead to neurodegenerative processes. To date, practically all experimental work examining circuit function in laboratory models of tauoapthy has focussed on the excitatory glutamatergic

synapse. My own recent work in models of AD-related amyloidopathy, however, has uncovered neurophysiological deficits in inhibitory neurons. In this fellowship I propose to use a well-established murine model to address how hippocampal inhibitory synaptic function is modified by progressive tauopathy. A key motivation for these studies is observations recently made in my host groups that are suggestive of dysregulated synaptic inhibition in these same mice. I propose to combine neurophysiology, neuroanatomy and in vivo imaging to address inhibitory neuron properties. Neurophysiologically, I will study the properties of inhibitory cells using brain slices obtained from mice at 4 different pathological stages. I will look at excitatory drive to hippocampal interneurons, their intrinsic excitability properties and their GABAergic output to pyramidal cells. By filling the cells during these recording and then reconstructing their architecture I will also examine how the neuroanatomy of GABAergic cells is impacted by tauopathy. Finally, I will look at GABAergic cell activity within intact networks in vivo using 2-photon imaging of stratum oriens cells virally expressing the genetically-encoded Ca2+ indicator GCaMP6. Together these data will provide the first wide-reaching assessment of inhibitory synaptic function in tauopathy, and may point to new potential for therapeutic avenues for AD.

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