Electrophysiological signatures of Entorhinal–Hippocampal Circuit Disruption in the S305N Mouse Model of Early Brain Tauopathy

Clarke-Williams, CJ.[1], Kerekes, P.[1], Krstulovic, M.[1], Ho, H.[1,2], Duff, K.[1], Bauza, M.[3] and Krupic, J.[1]

1. UK Dementia Research Institute, University College London
2. Department of Physiology, University of Cambridge
3. Sainsbury Wellcome Centre for Neural Circuits and Behaviour, University College London.

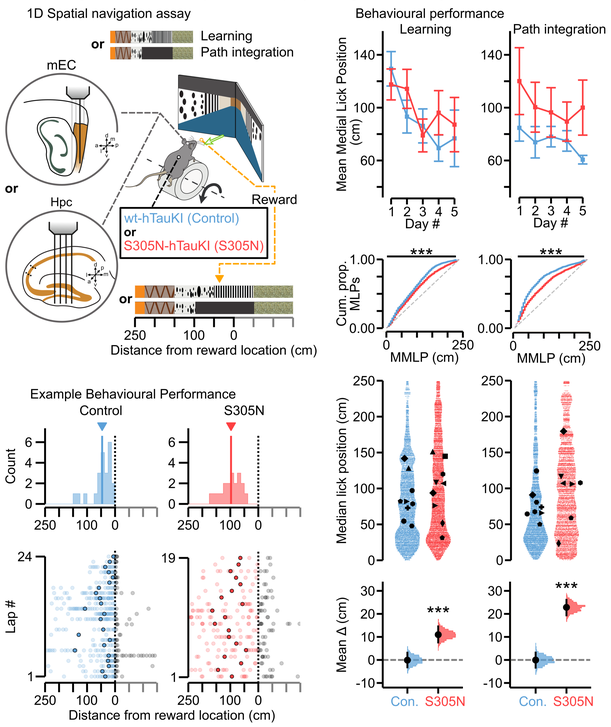
Summary

Tau pathology is a hallmark of Alzheimer's disease (AD); with the medial entorhinal cortex (mEC) and the hippocampus (Hpc) being amongst the earliest affected by the pathology. Interplay between these regions is well-known to support cognitive abilities related to spatial navigation; in-line with data showing that such detriments are often the earliest seen in individuals who become diagnosed with AD. While such cognitive biomarkers might be able to highlight higher-risk individuals of AD diagnoses, it remains to be elucidated what the neurophysiological signatures of these early perturbations are, their mechanistic underpinnings and how they relate to cognitive impairment. We sought to model this behavioural and neurophysiological phenomenology using the S305N hTauKI mouse-model of early tauopathy, revealing:

- S305N mice showed poorer spatial navigation performance
- Increased frequency of theta (4–11 Hz) oscillations
- Reduced theta–mid-gamma (~40–80 Hz) amplitude modulation
- Mid-gamma-associated magnification of theta cycle frequency effect size more predictive of poorer spatial navigation performance
- Inflexible theta cycle frequency transition dynamics with pathology-associated spiking and mid-gamma correlates
- Theta cycle frequency linked to Layer-III/IIb interneurons exhibiting mid-gamma modulation gain

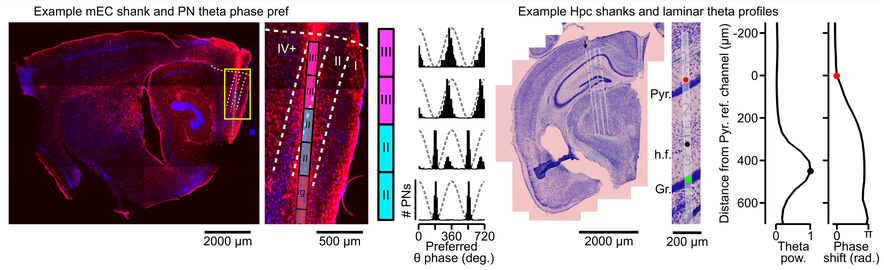
1. Spatial navigation deficits in S305N mice

We assessed spatial behaviour deficits in the S305N-hTau knock-in mouse model of fronto-temporal tauopathy; using a virtual-reality behavioural navigation paradigm, combined with Neuropixels 2.0 recordings of mEC or Hpc electrophysiological activity.



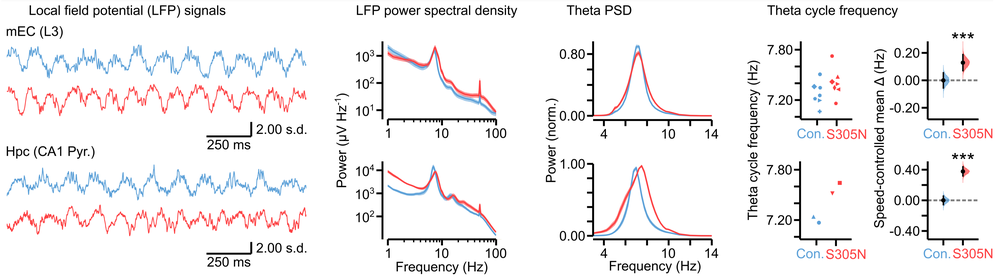
2. Assignment of LFP reference channels

We identified reference channels in mEC (layer 3) and Hpc (dCA1 pyramidal layer) using established electrophsiological features and cross-validating with histological section overlays.



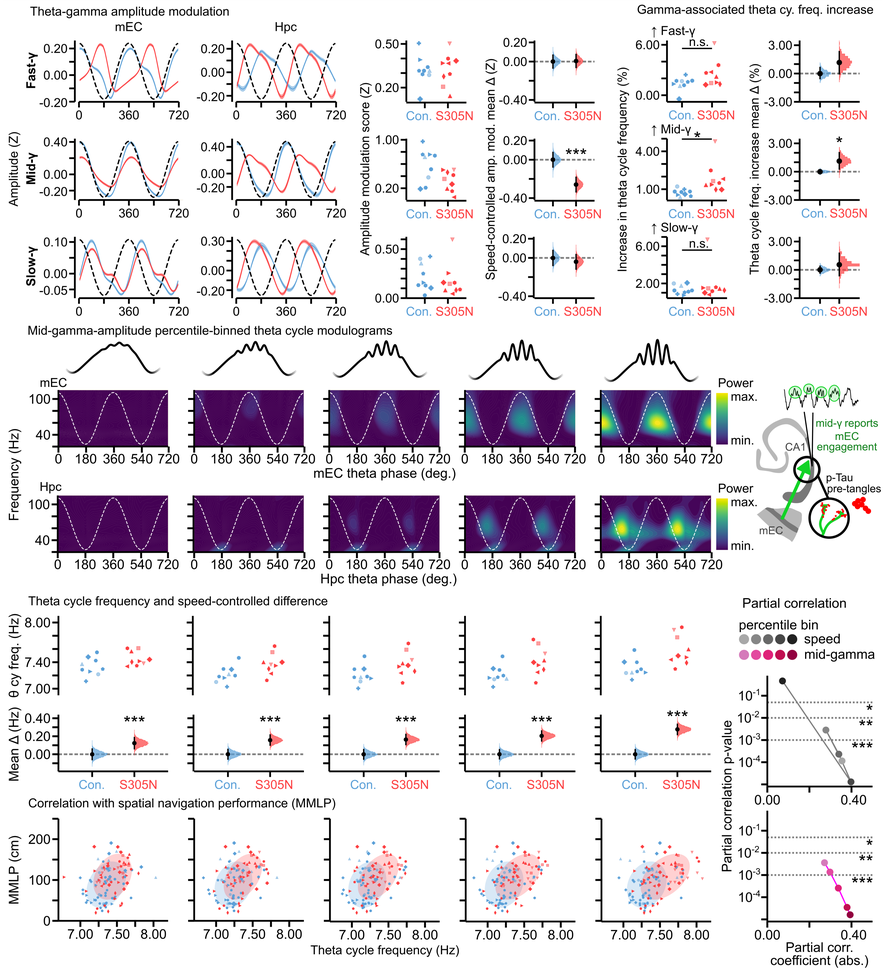
3. Theta cycle frequency is faster in S305N animals

We observed that the dominant theta (4–11 Hz) oscillation is faster in S305N animals compared to controls; this effect remaining significant after controlling for the influence of locomotion speed.



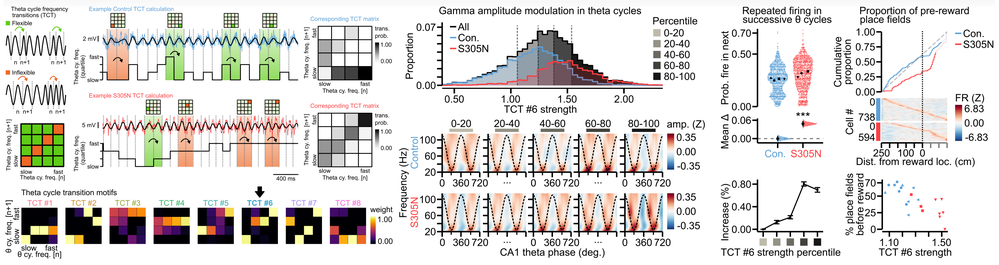
4. Pathological theta-nested mid-gamma activity

We noted weaker modulation of mid-gamma (~40–80 Hz) activity by theta oscillations; and that this oscillatory proxy for mEC–Hpc interactivity was linked to tau-pathology-related theta cycle frequency increase; these cycle subsets being more correlated with poorer spatial navigation performance.



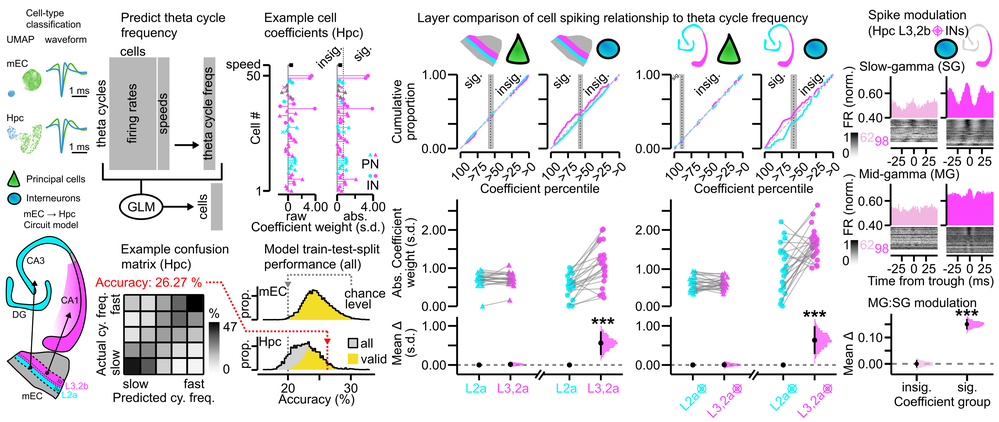
5. Inflexibility of theta cycle frequency transitions

We observed more inflexible theta cycle frequency transition properties with spiking and memory representation correlates that were reminiscent of abhorrent network dynamics linked to mid-gamma-reported mEC–Hpc interactivity.



6. Layer-III/IIb-pathway interneuron activity linked to theta cycle frequency

We observed that the firing patterns of L3/2b-related interneurons were more predictive of theta cycle frequency than their L2a counterparts; and that such theta-cycle-frequency-linked cells in CA1 showed stronger mid-gamma [~mEC input] modulation gain versus slow-gamma [~CA3 input].



Acknowledgements

This work was supported by the UK Dementia Research Institute, through UK DRI Ltd, principally funded by the Medical Research Council, by funding from the Cure Alzheimer's Fund (J.K.). J.K. is a Wellcome Trust/Royal Society Sir Henry Dale Fellow (206682/Z/17/Z). M.B. is supported by the Wellcome Trust, grant 100154/Z/12/A.