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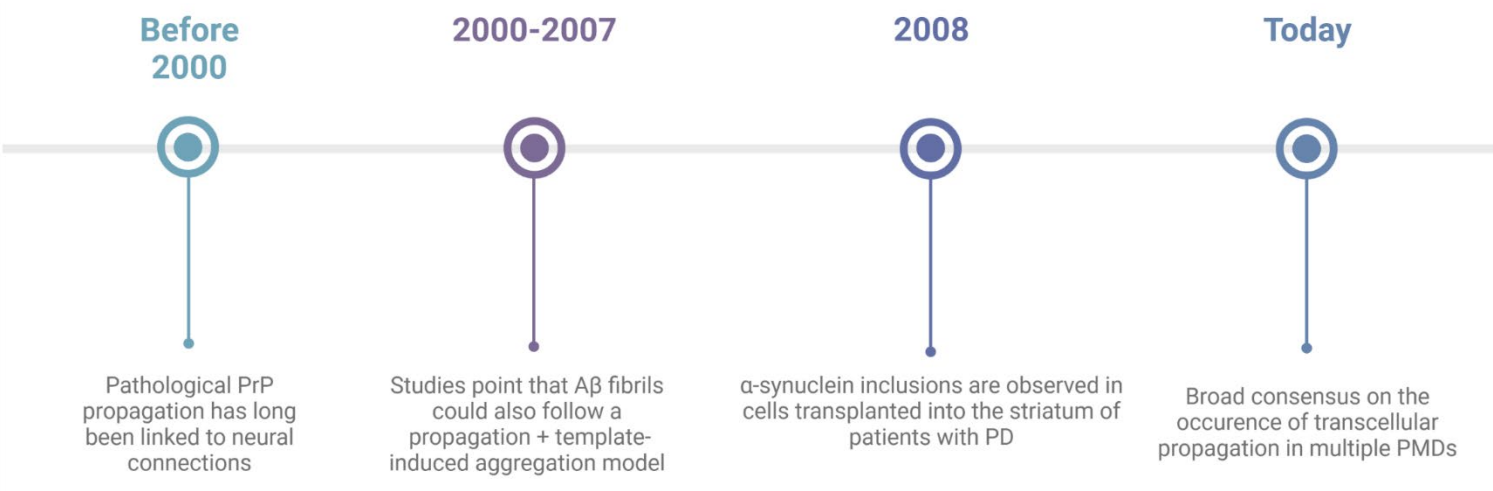
The importance of animal models in understanding cell-to-cell propagation of prions and prionoids

Carlos Morales

Transcellular propagation of prions and prionoids

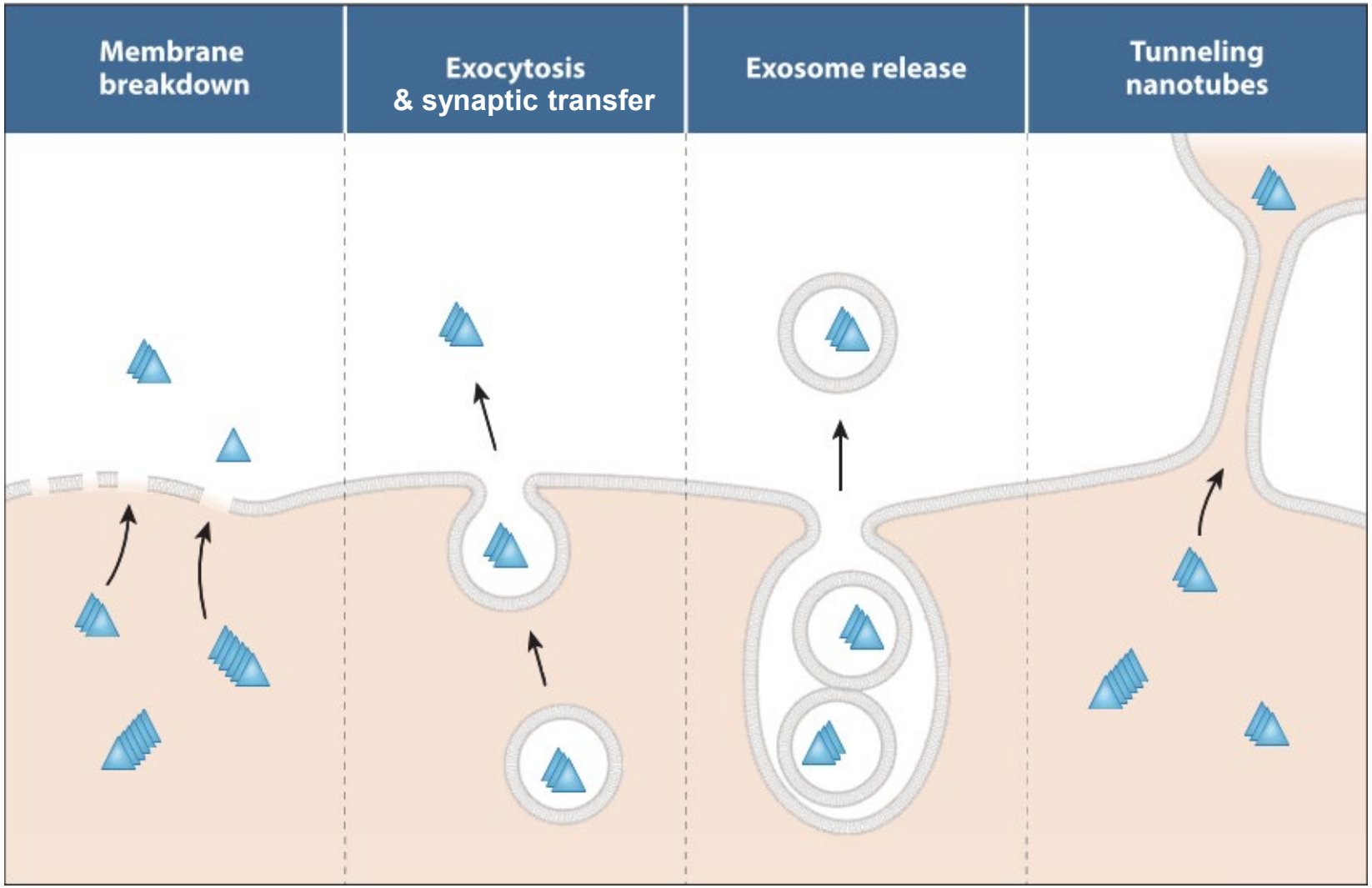
- **Definition**: process by which a specific amyloid structure grows within a cell, followed by its movement to a second cell and its subsequent amplification there based on interactions with the native protein

- **Timeline**:



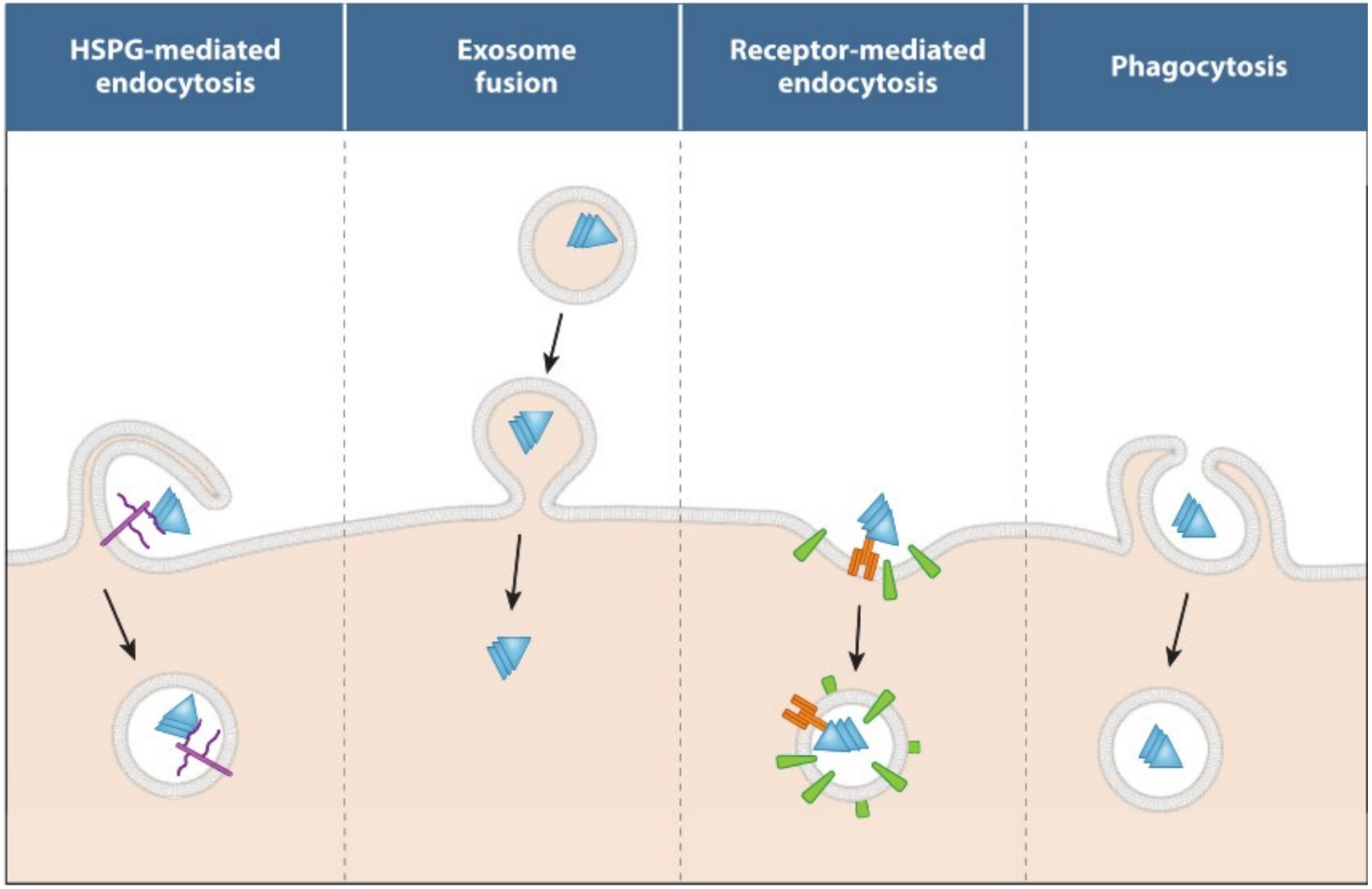
- **Relevance**: multiple lines of evidence have pointed to cell-to-cell propagation of amyloids to play a key role in the progression of multiple neurological diseases

Potential mechanisms driving prion & prionoid transcellular propagation



Modified from Vaquer-Alicea et Diamond, 2019, Annual Review of Biochemistry

Potential mechanisms driving prion & prionoid transcellular propagation



Vaquer-Alicea et Diamond, 2019, Annual Review of Biochemistry

Why do we need to use animal models?

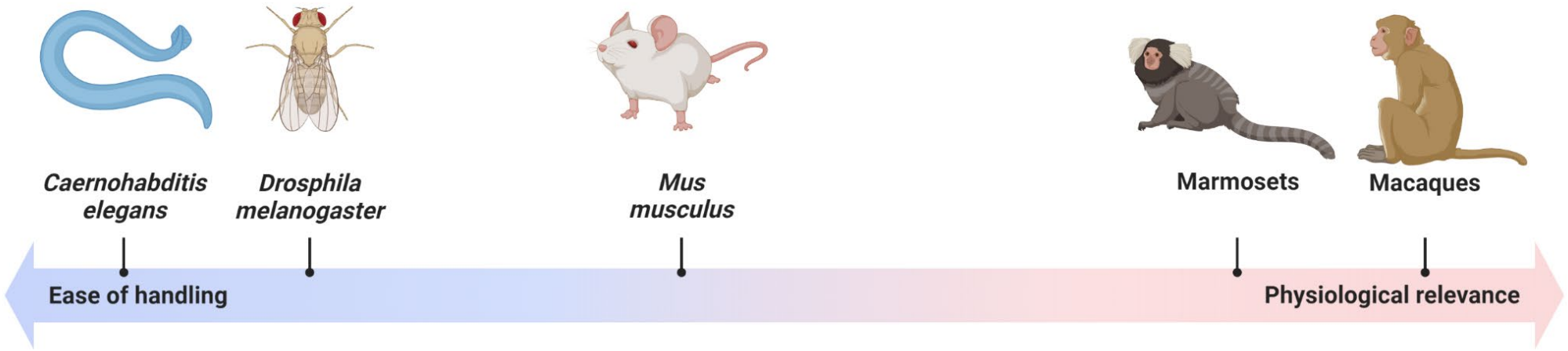
Cellular models

- ✓ Indispensable to achieve a first, basic understanding of the mechanisms of disease
- ✓ Comparatively easy and cheap to work with vs animal models
- ✗ Cannot begin to truly reproduce the pathophysiological processes that takes place in living beings

Animal models

- ✗ Much more laborious to generate, maintain and study
- ✓ They provide a complete physiological system
- ✓ They can (partly) reproduce the hallmarks of disease
- ✓ Necessary to corroborate the findings made in cellular models

Employed animal models



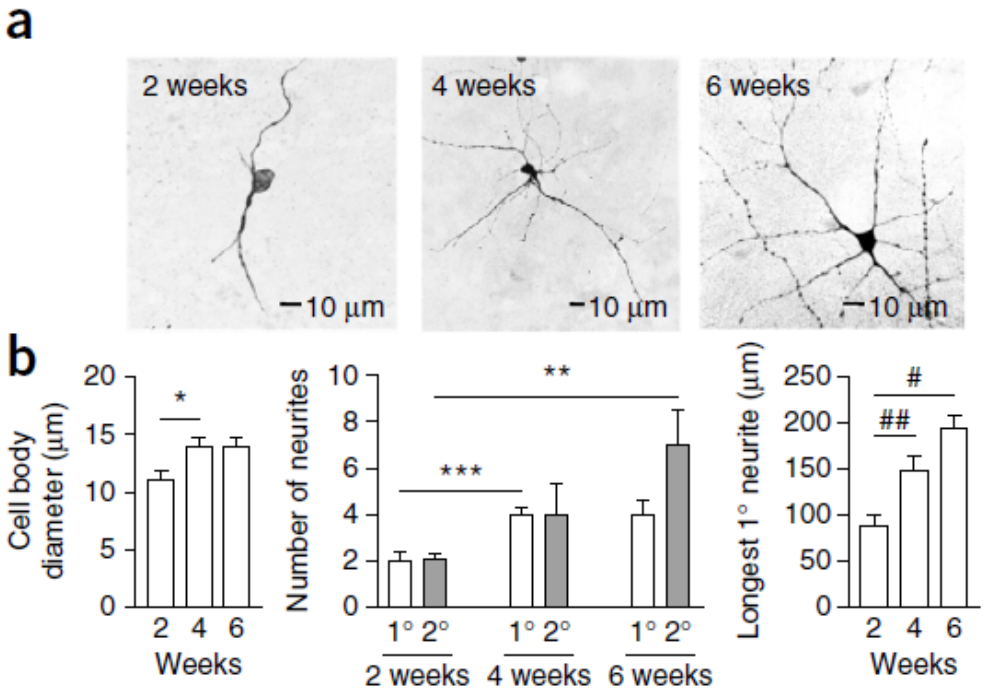
ARTICLES

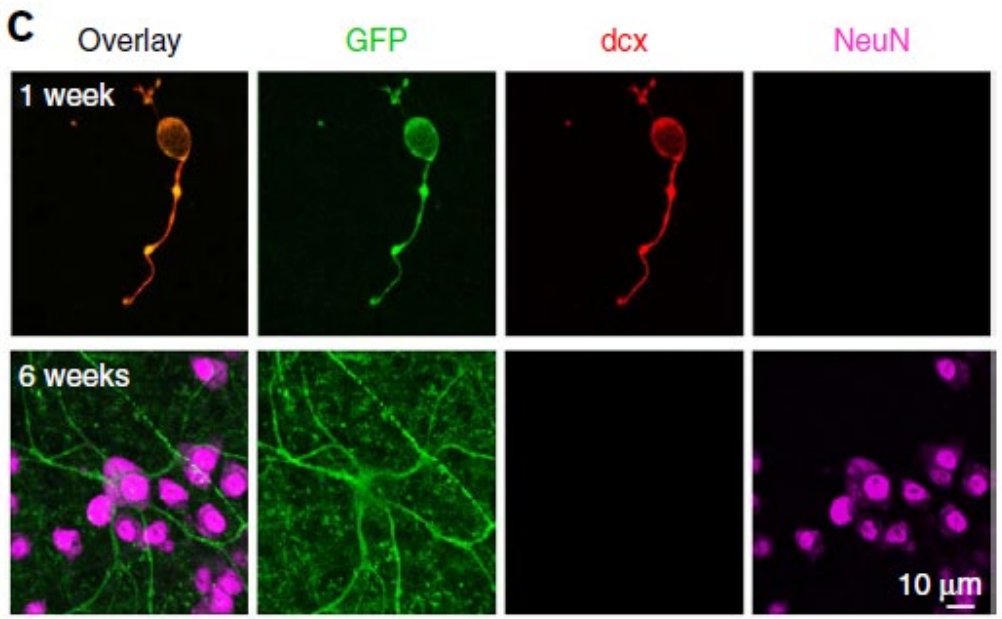
nature neuroscience

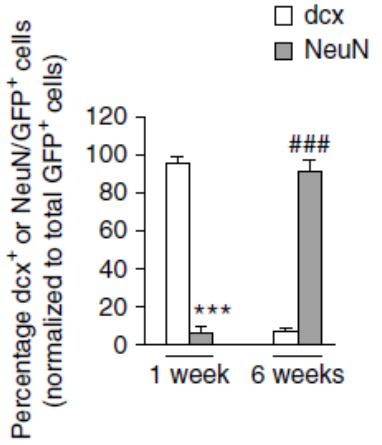
Transneuronal propagation of mutant huntingtin contributes to non–cell autonomous pathology in neurons

Eline Pecho-Vrieseling[1,5], Claus Rieker[1,5], Sascha Fuchs[1], Dorothee Bleckmann[1], Maria Soledad Esposito[2,3], Paolo Botta[2], Chris Goldstein[1], Mario Bernhard[1], Ivan Galimberti[1], Matthias Müller[1], Andreas Lüthi[2], Silvia Arber[2,3], Tewis Bouwmeester[1], Herman van der Putten[1,4] & Francesco Paolo Di Giorgio[1]

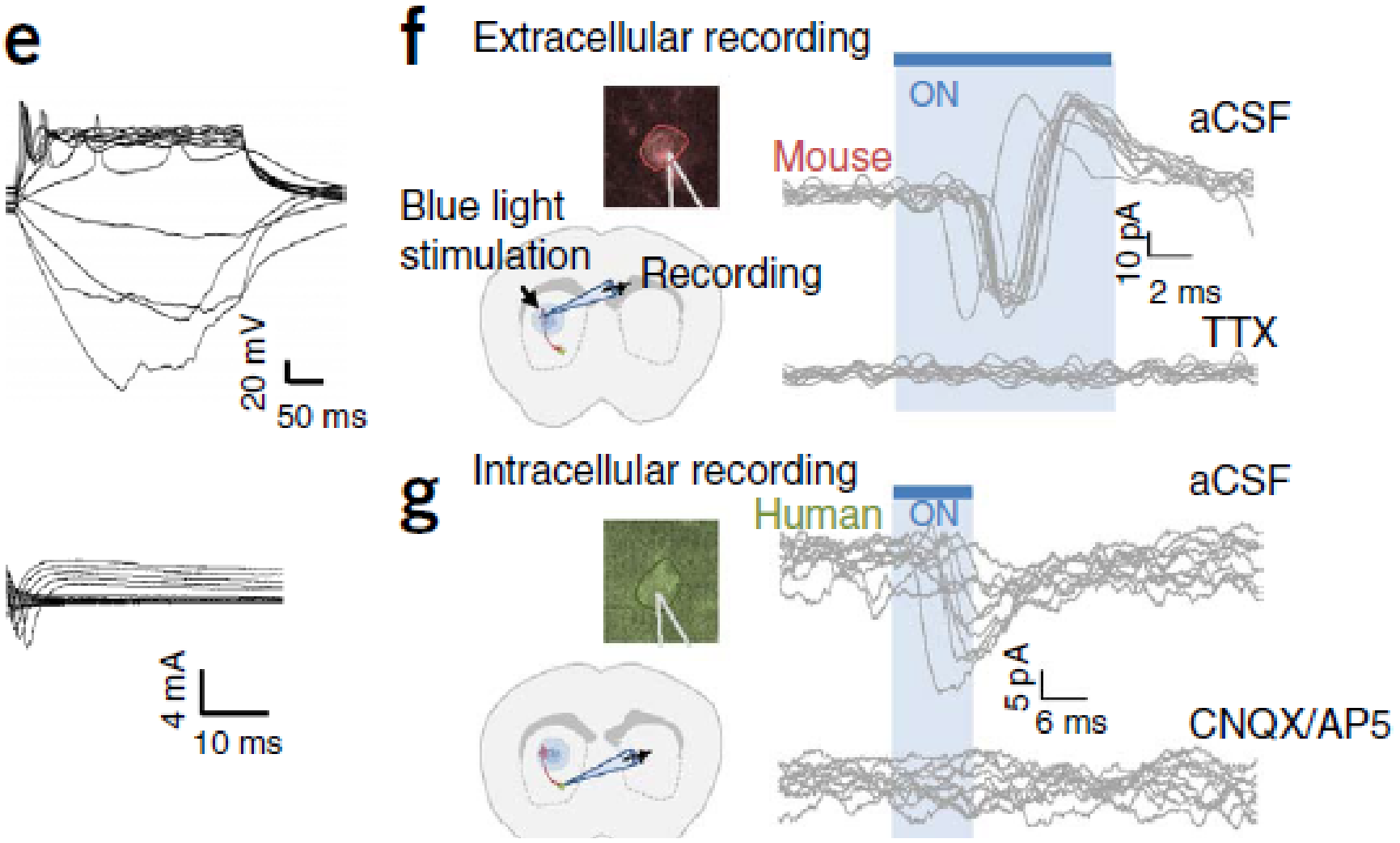
Functional integration of hESC-derived neurons in mouse OTBSs







hGFP neurons exhibit non–cell autonomous pathology in R6/2 OTBSs



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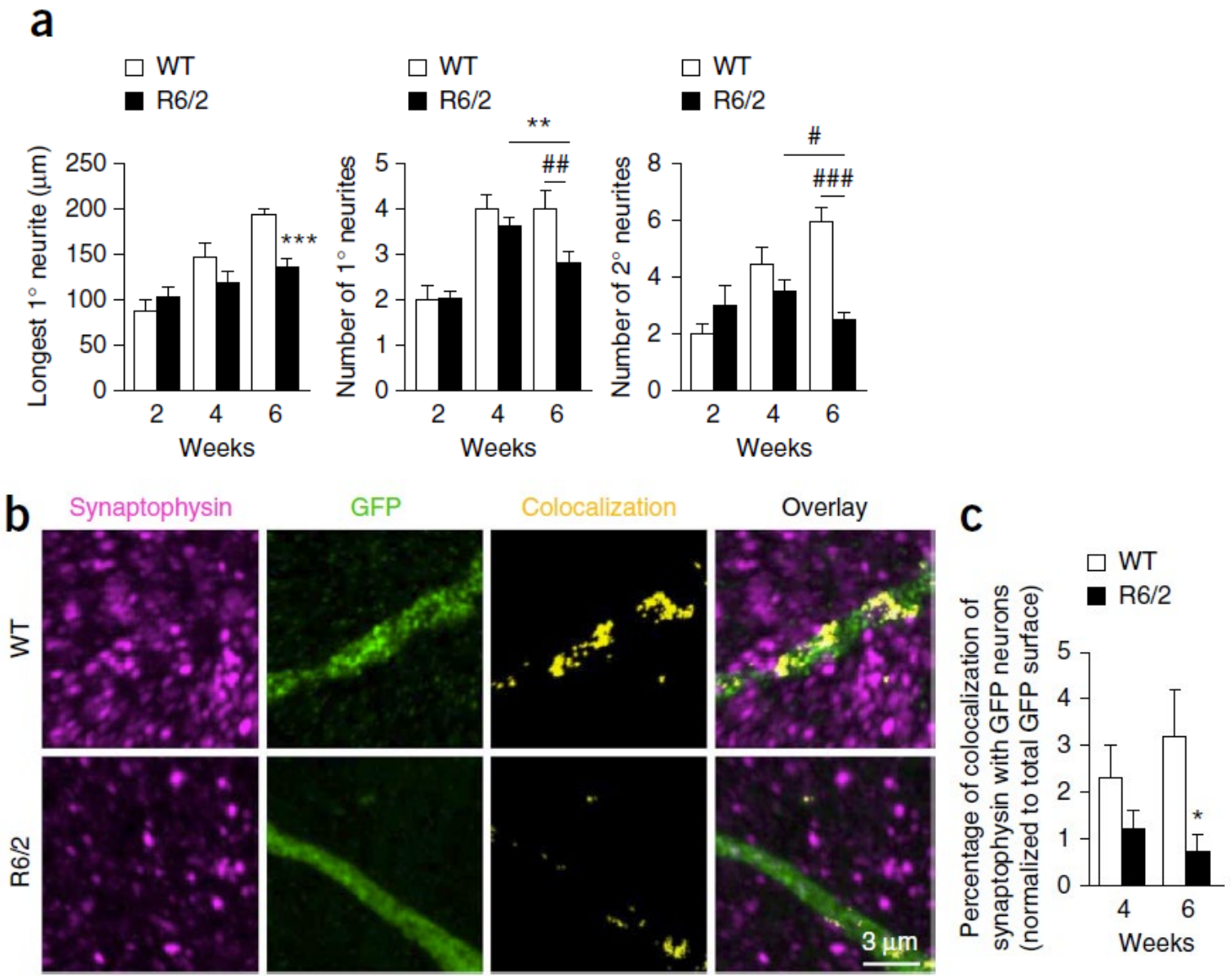
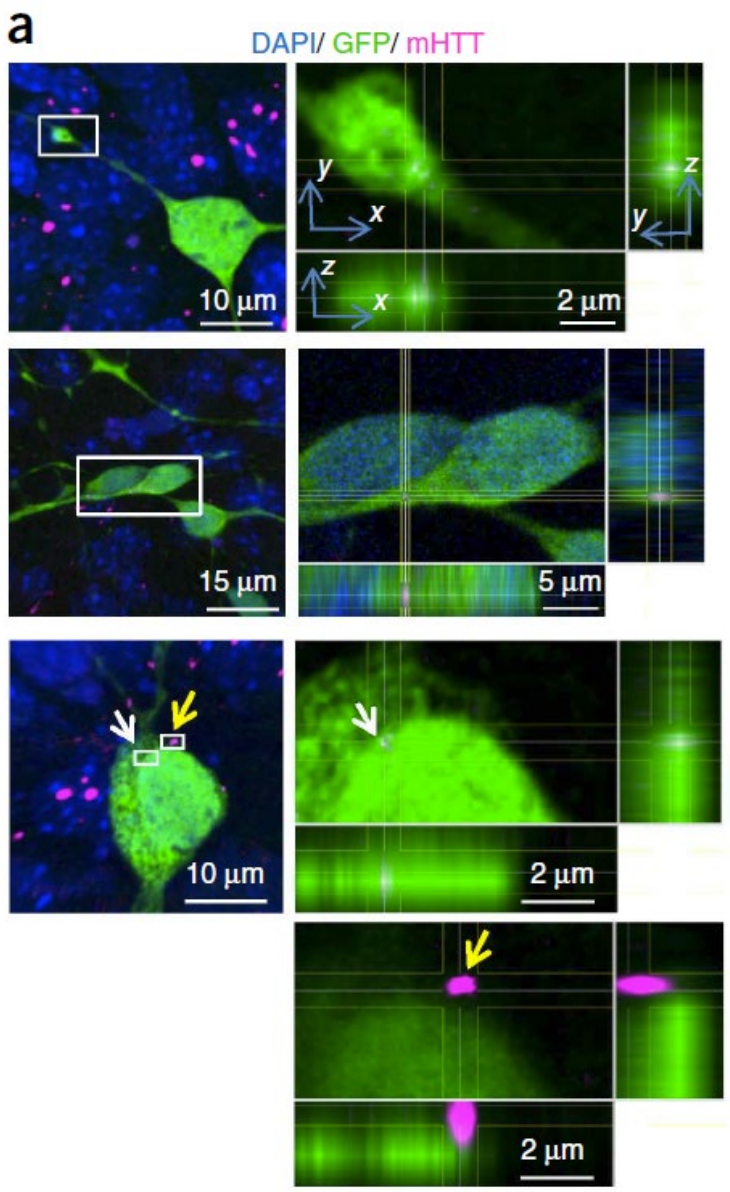
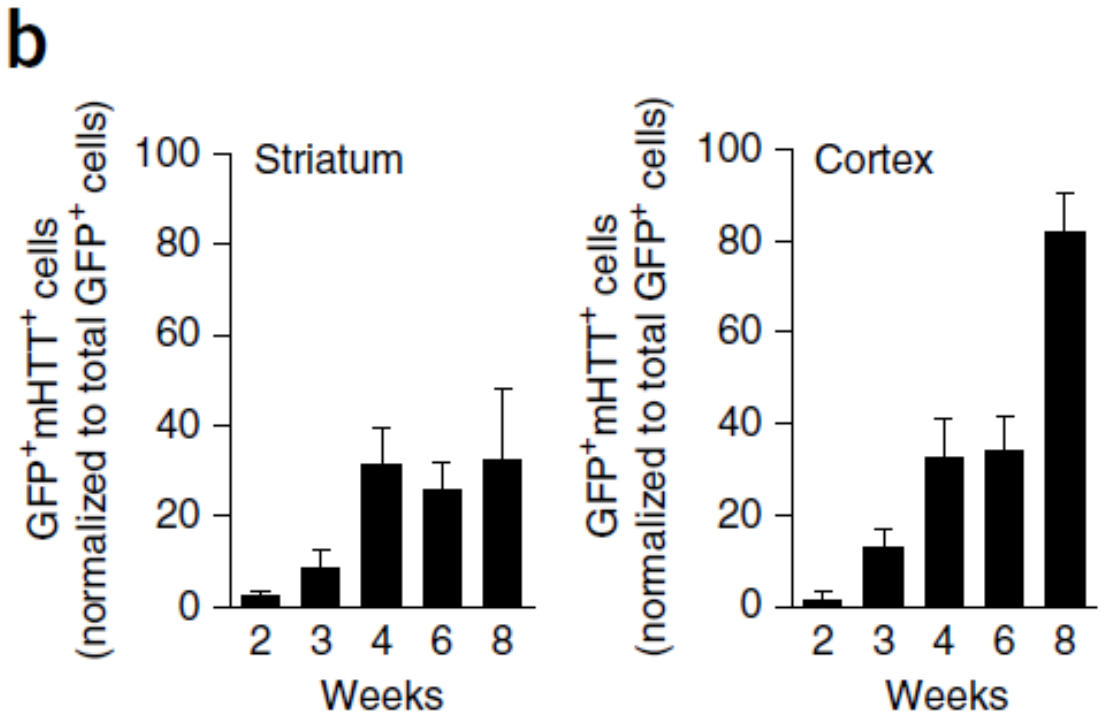


mHTT aggregate pathology spreads from R6/2 OTBSs to hGFP neurons





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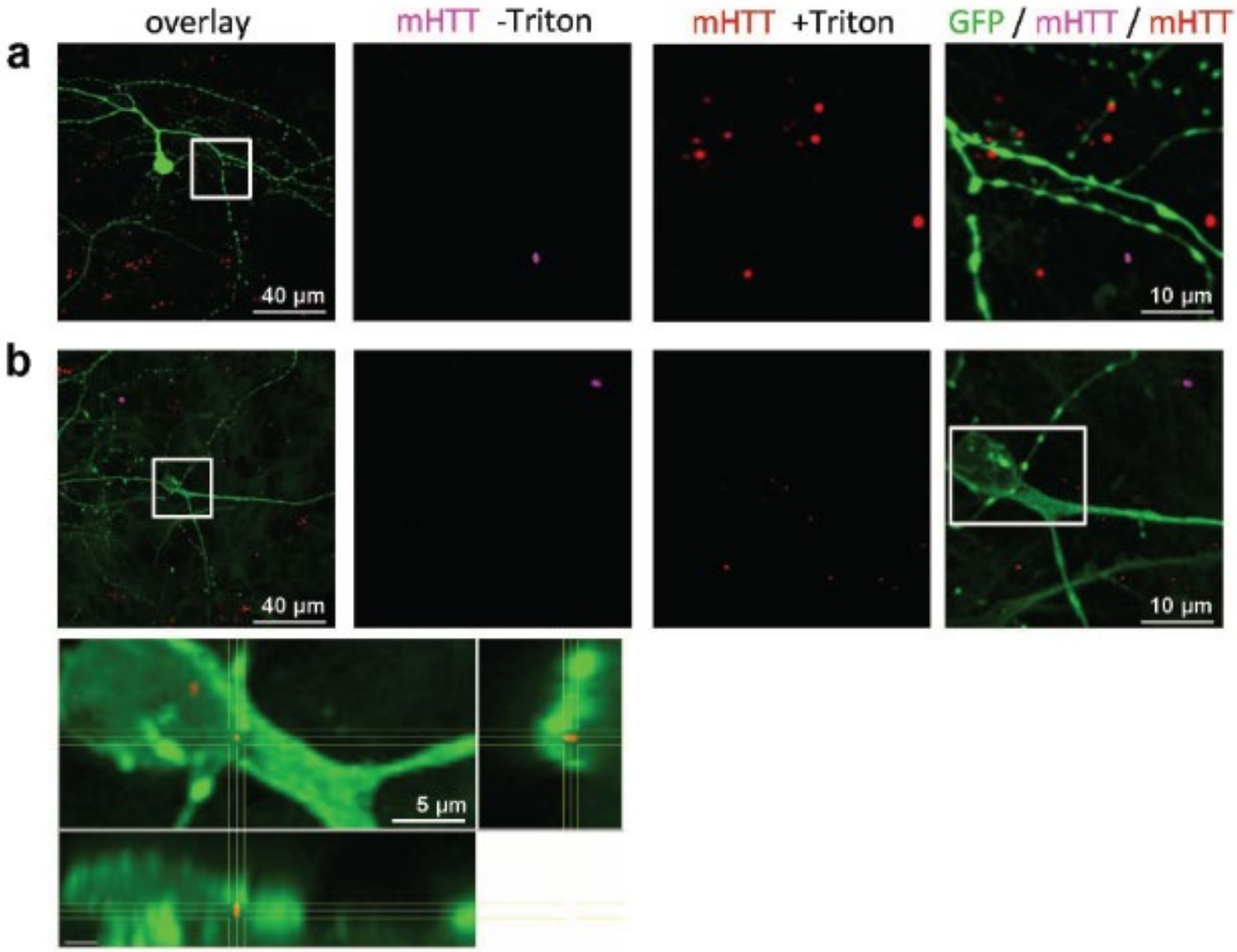

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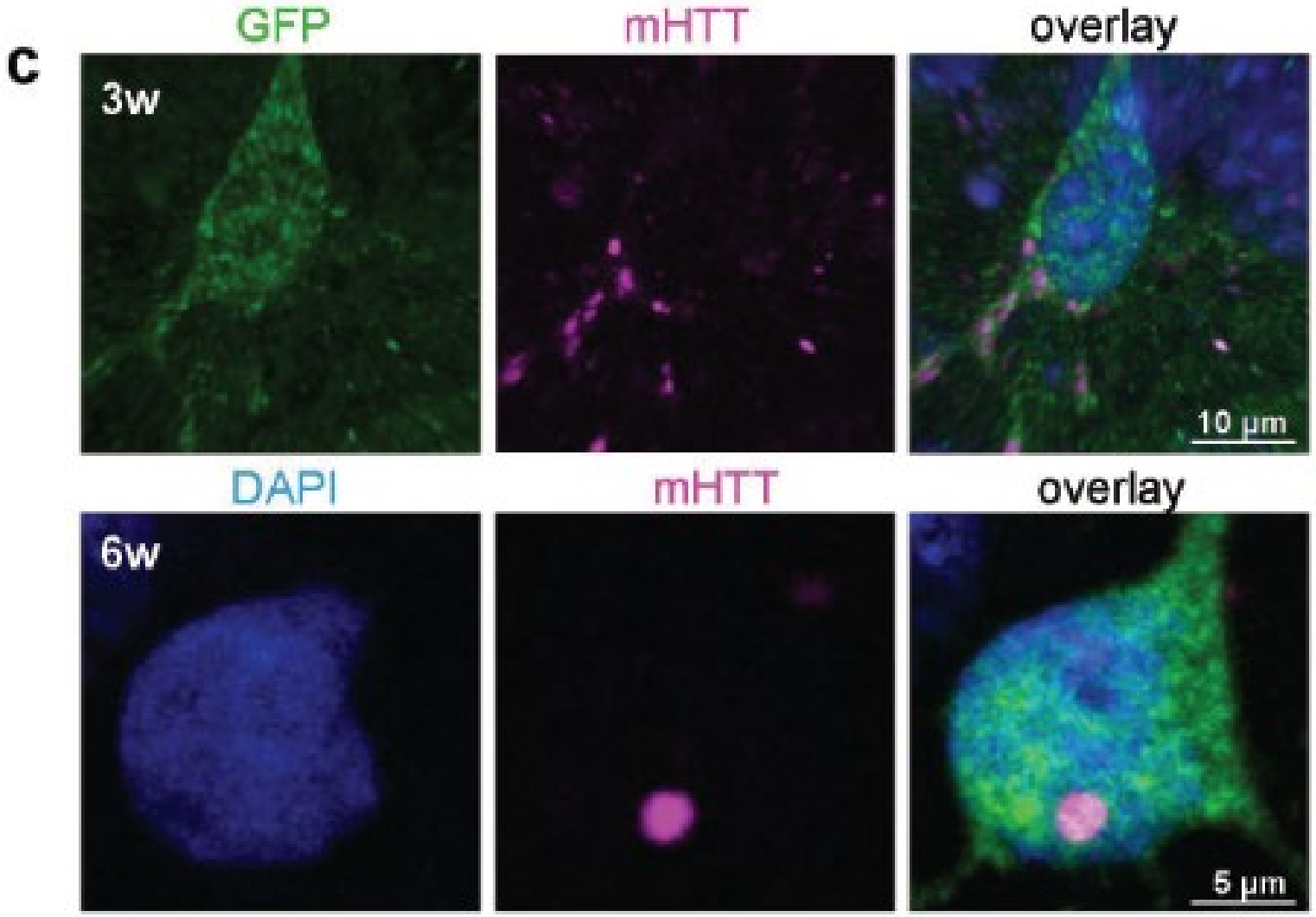
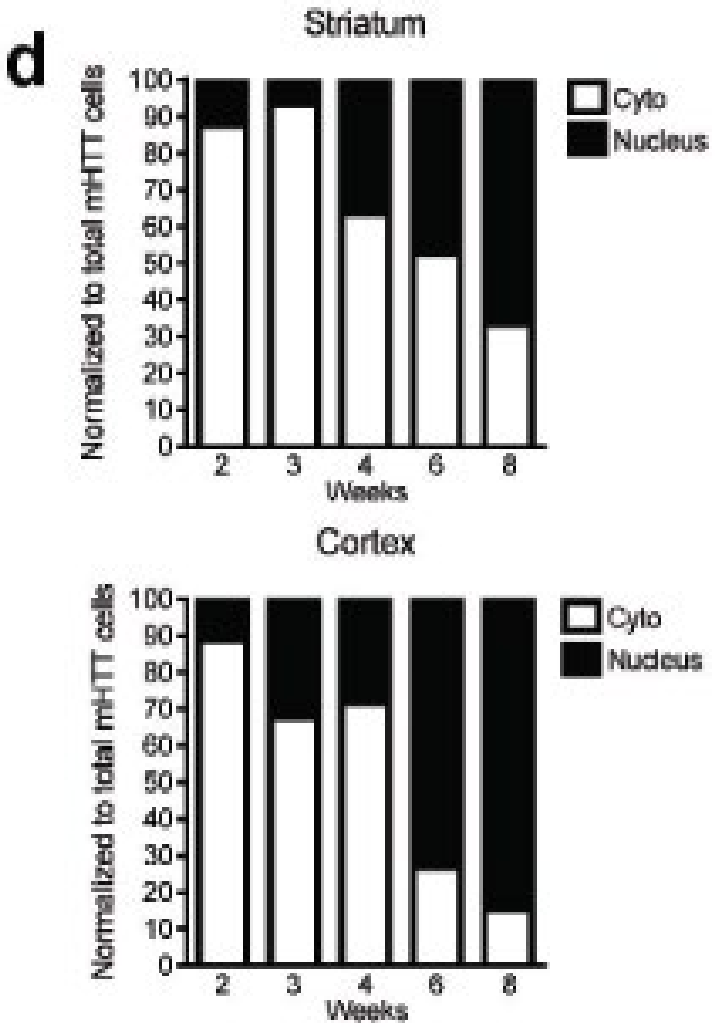
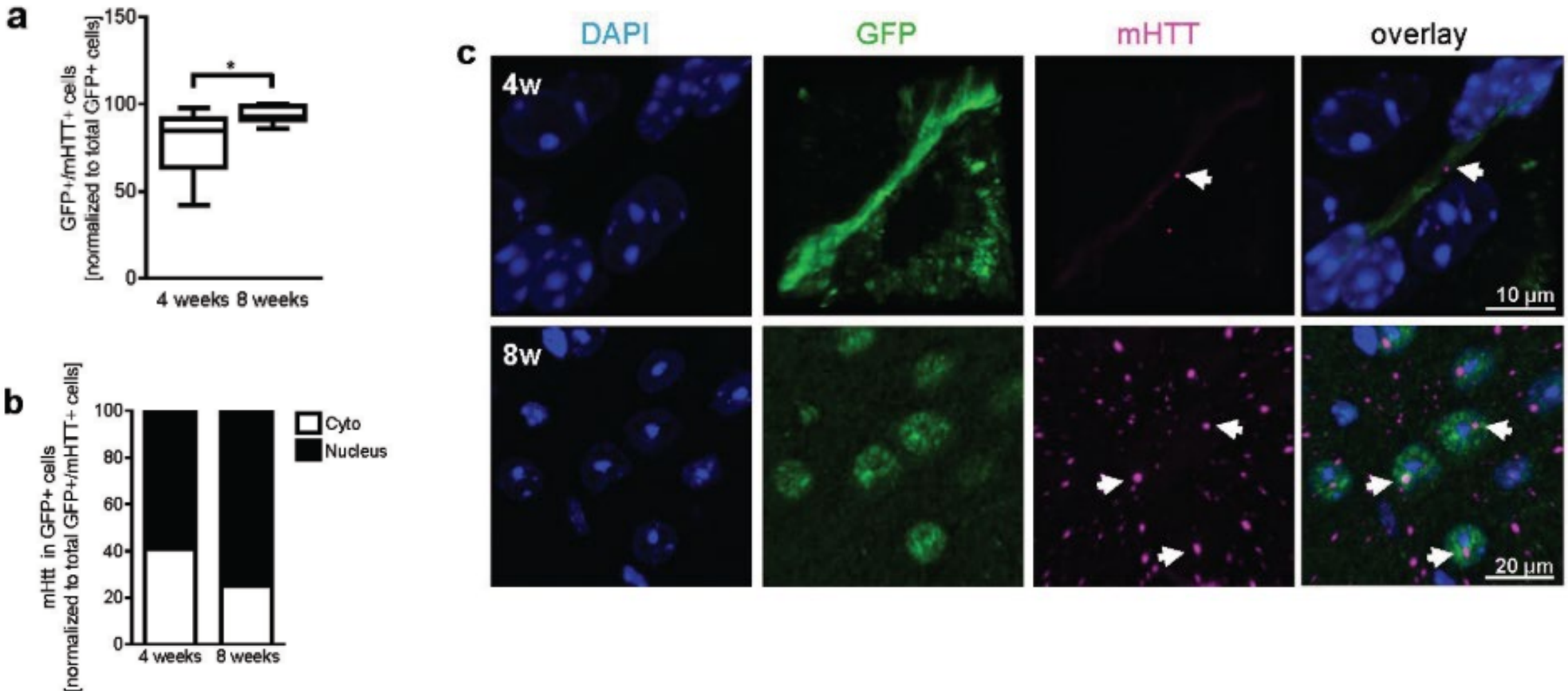
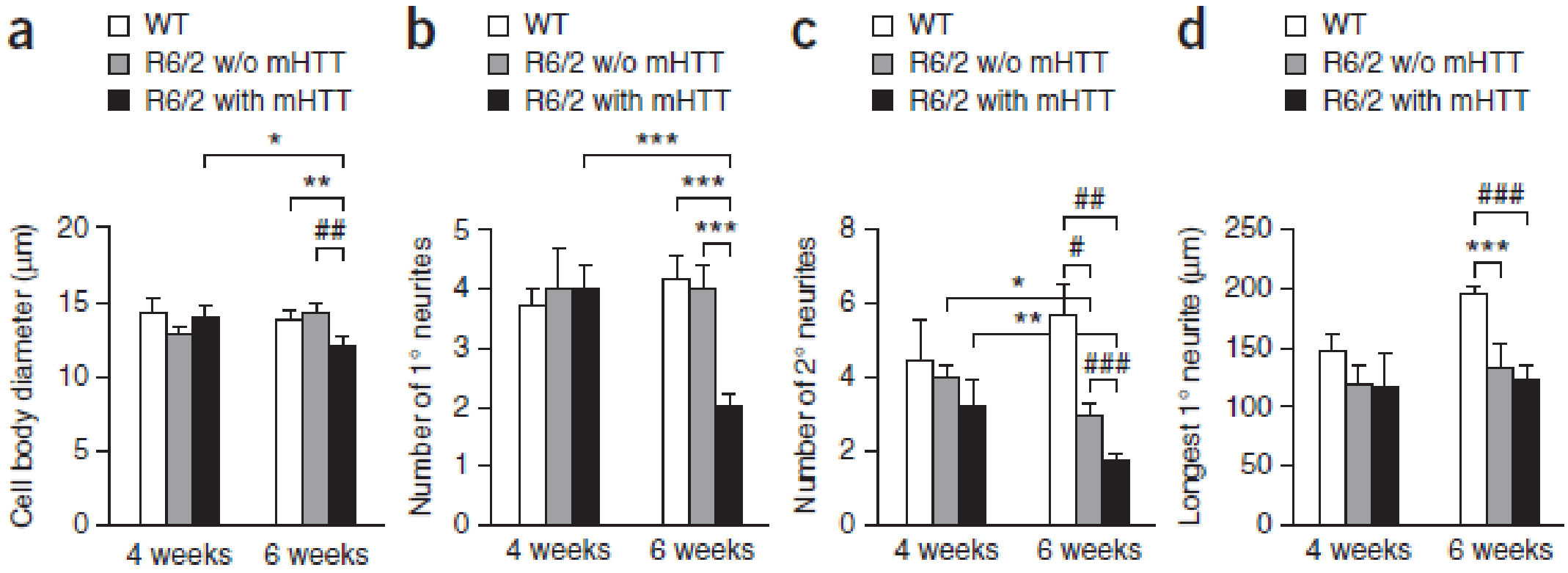




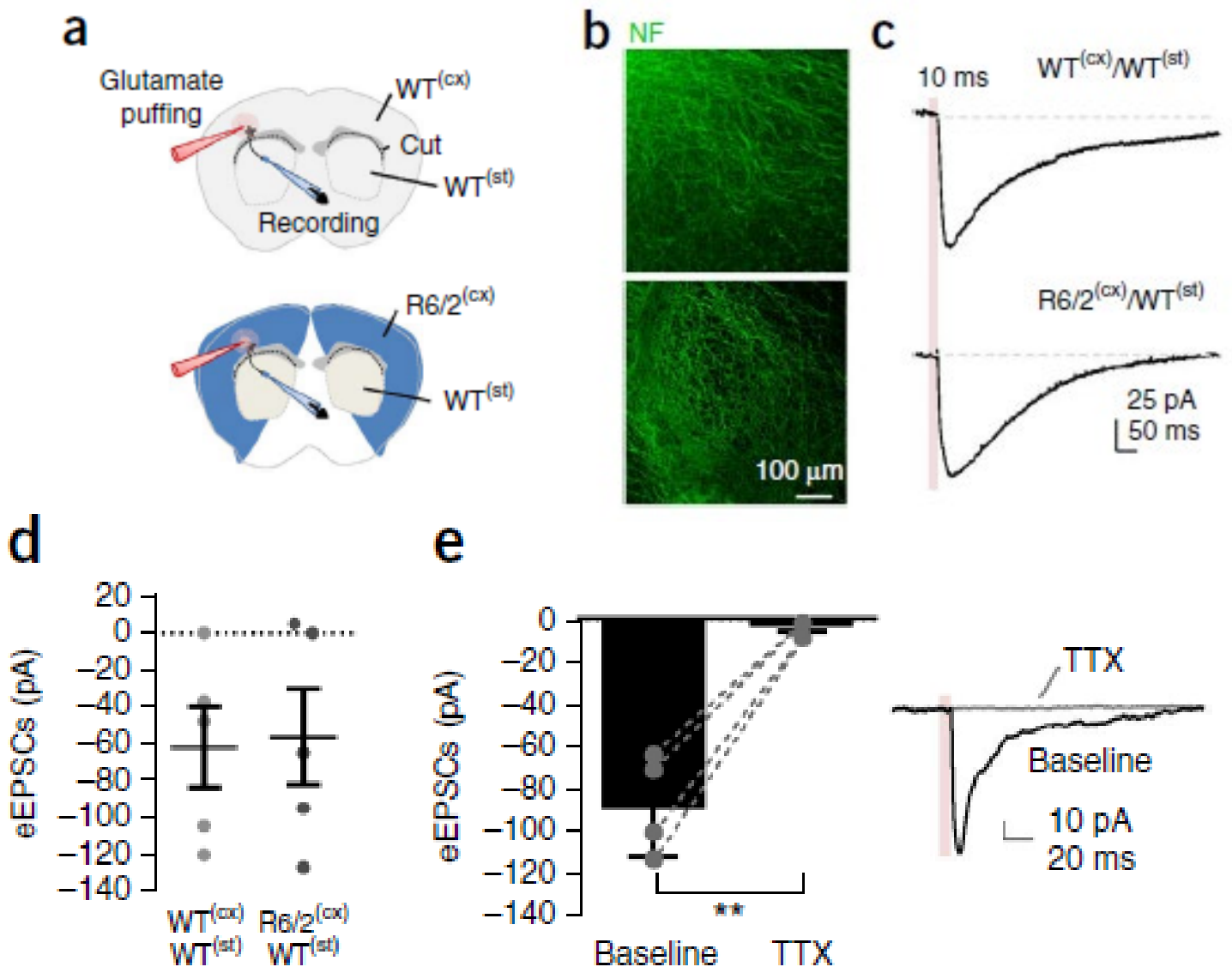
mHTT aggregate pathology spreads to hGFP neurons *in vivo*



Cellular atrophy is associated with the presence of mHTT



mHTT transneuronal propagation in the corticostriatal pathway



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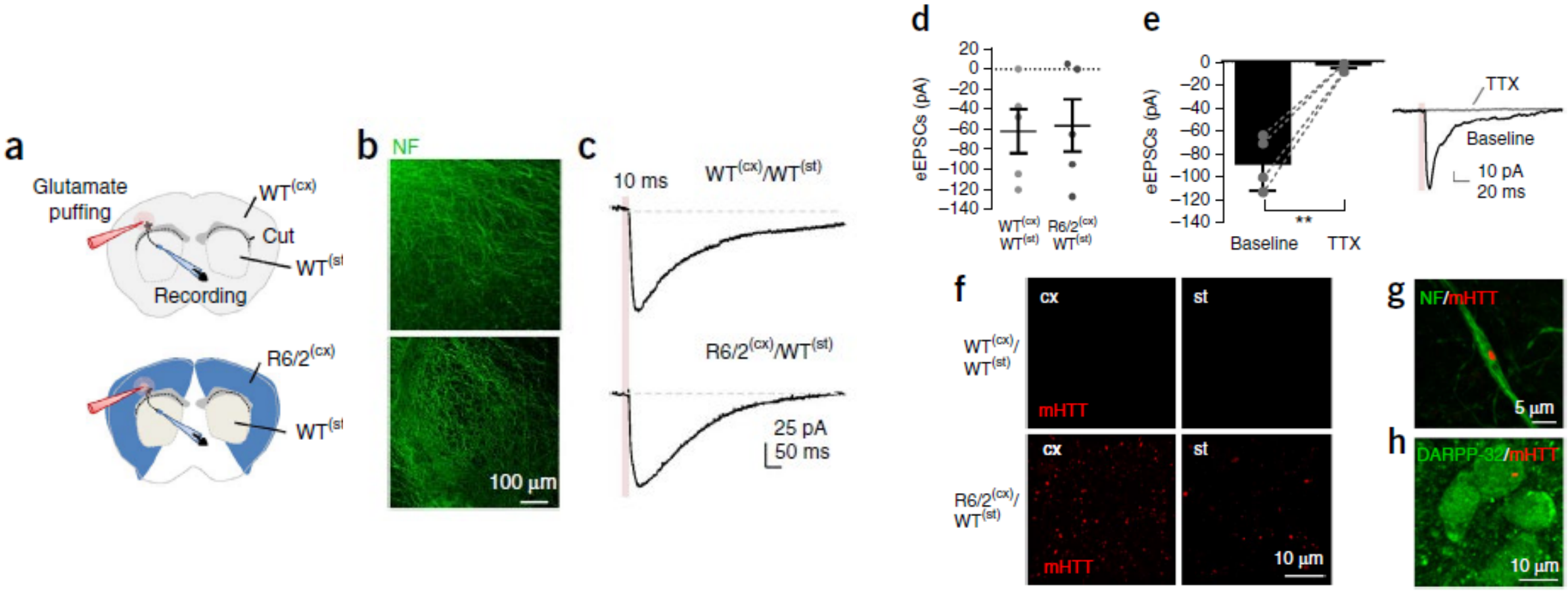
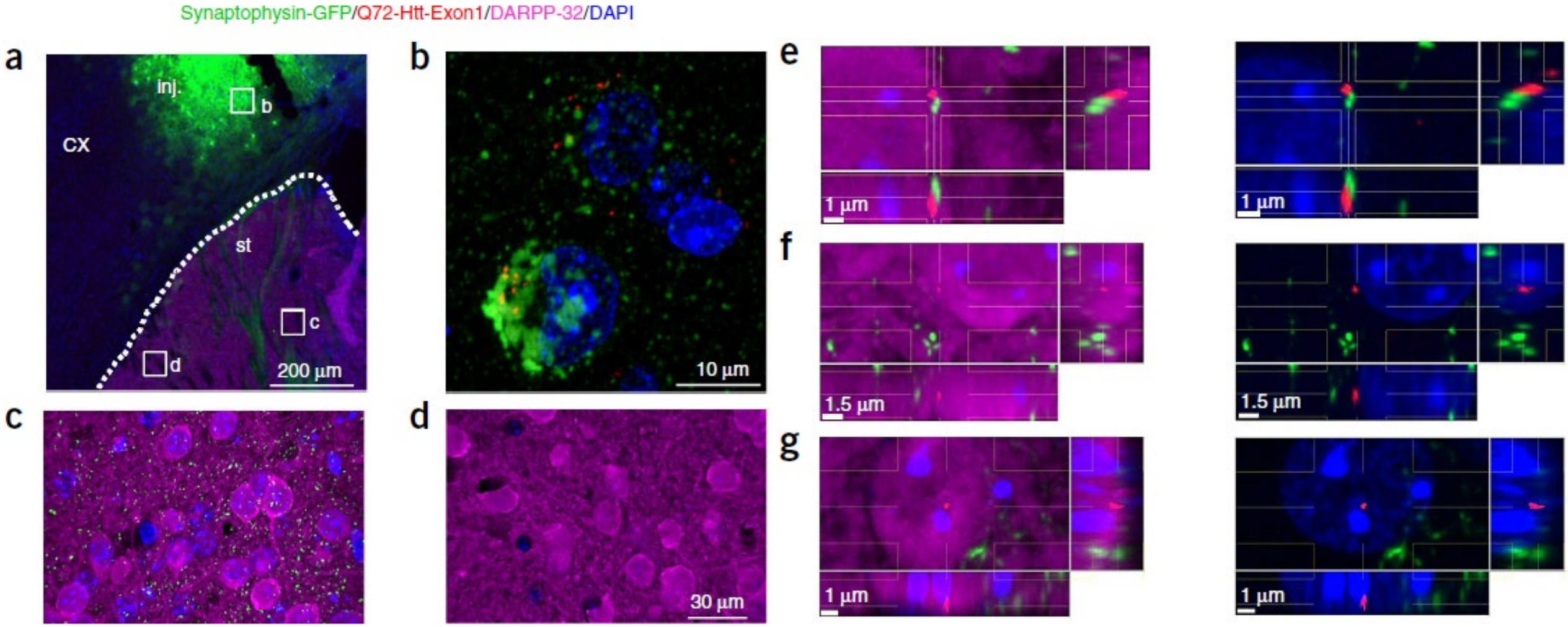
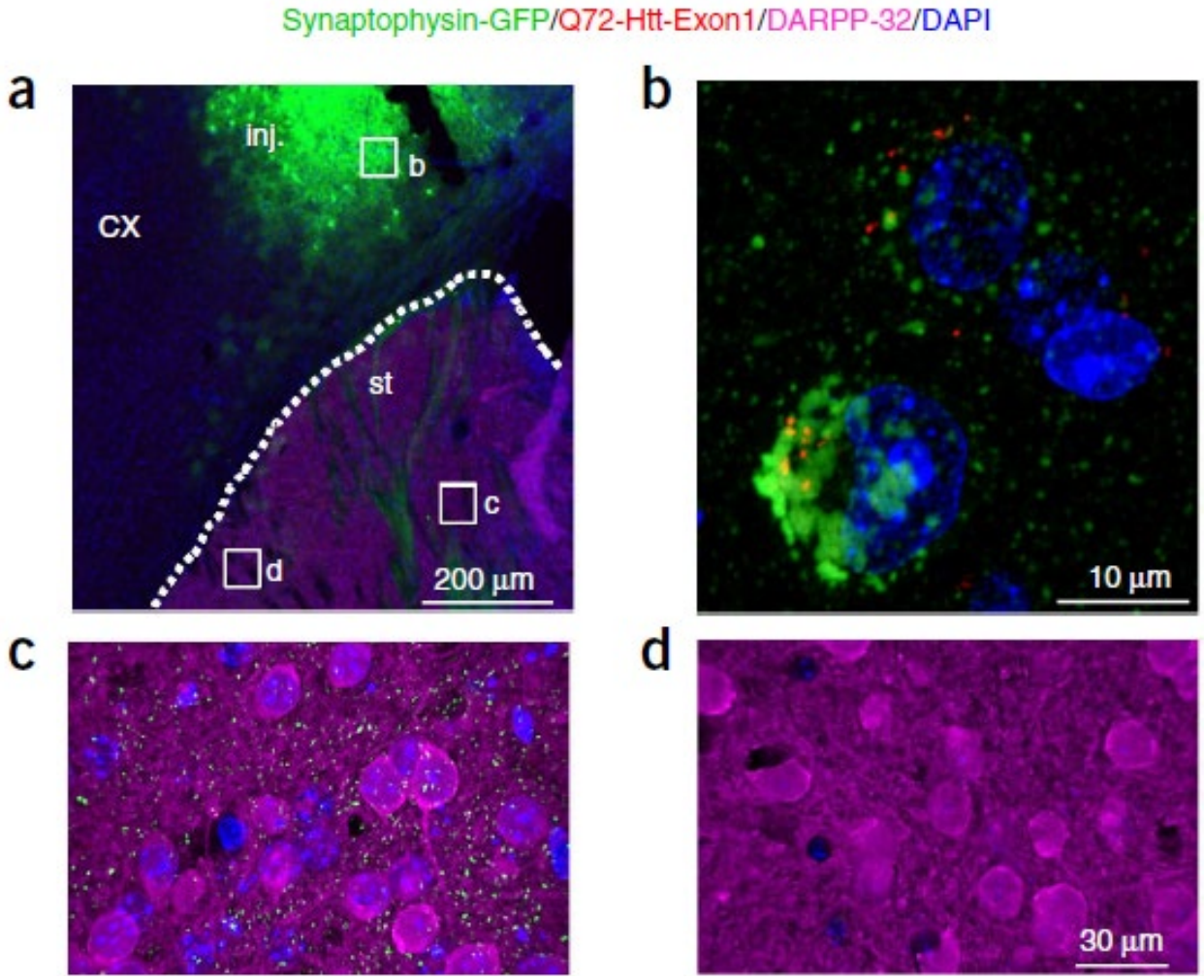
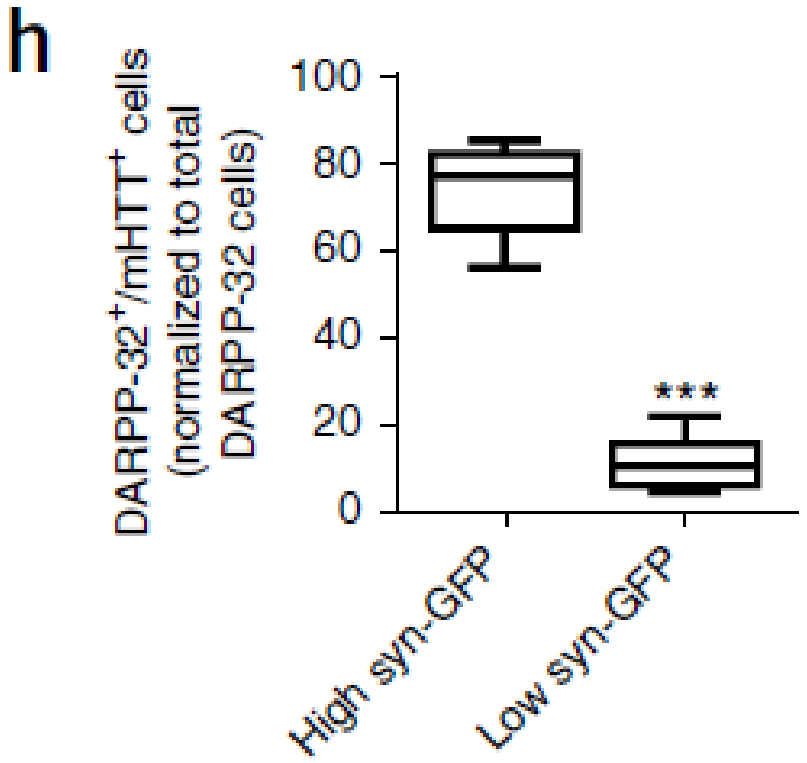


mHTT transneuronal propagation in the corticostriatal pathway *in vivo*

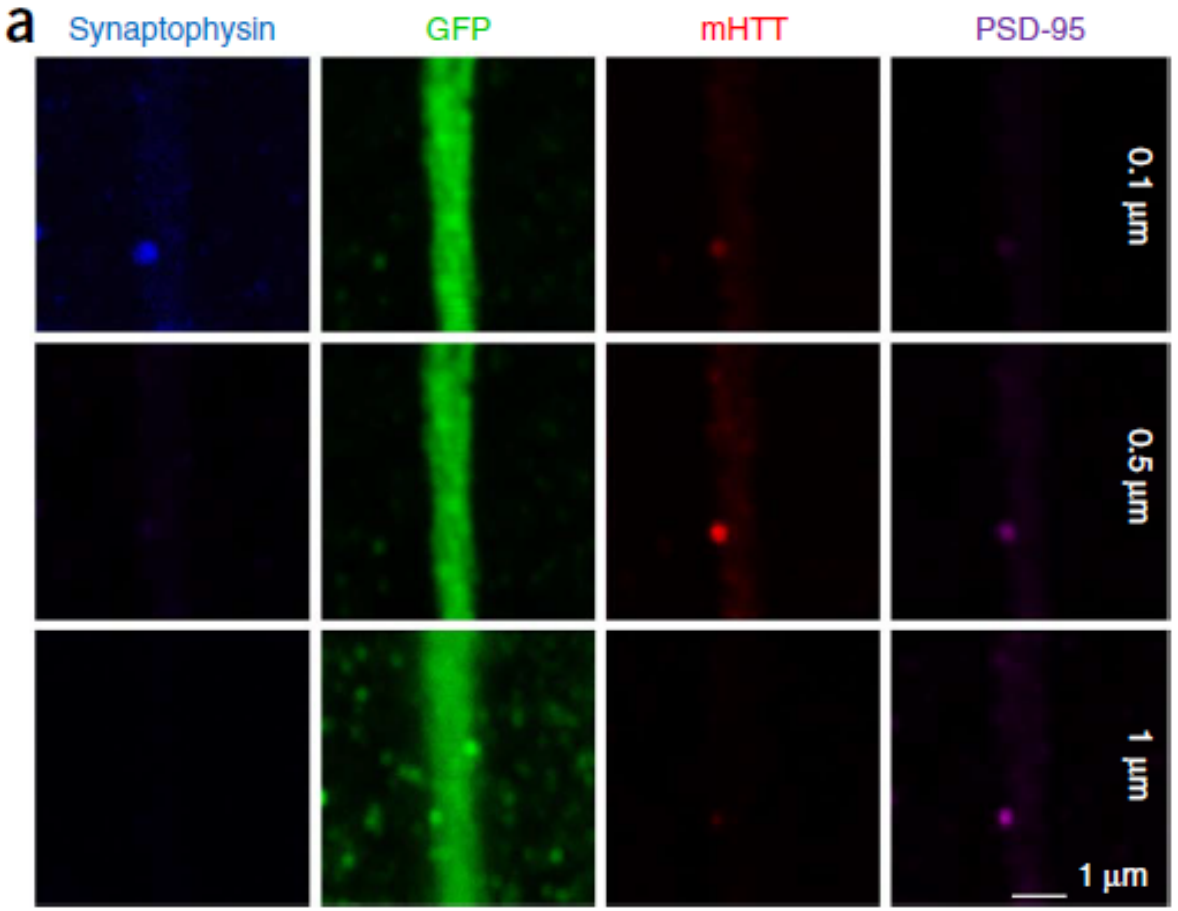


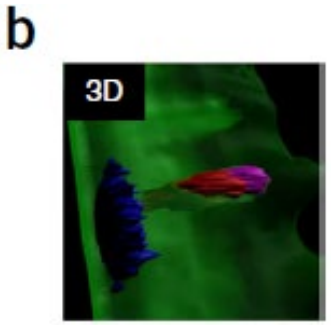
mHTT transneuronal propagation in the corticostriatal pathway *in vivo*

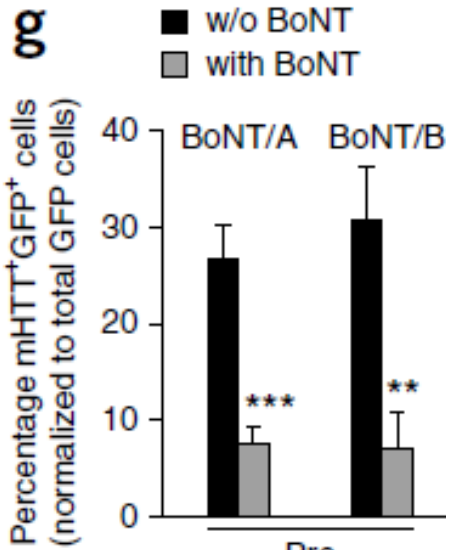




Inhibitors of synaptic vesicle fusion block propagation of mHTT







Main conclusions

- Transneuronal propagation of mHTT protein pathology occurs in neuronal networks, both *ex vivo* and *in vivo*
- Spreading was found to affect neural integrity
- Spreading was largely blocked by treatment with BoNTs, known to interfere with synaptic vesicle fusion
- **This leads to believe that transneuronal propagation of mHTT likely acts as a contributor to neuronal pathology in HD**

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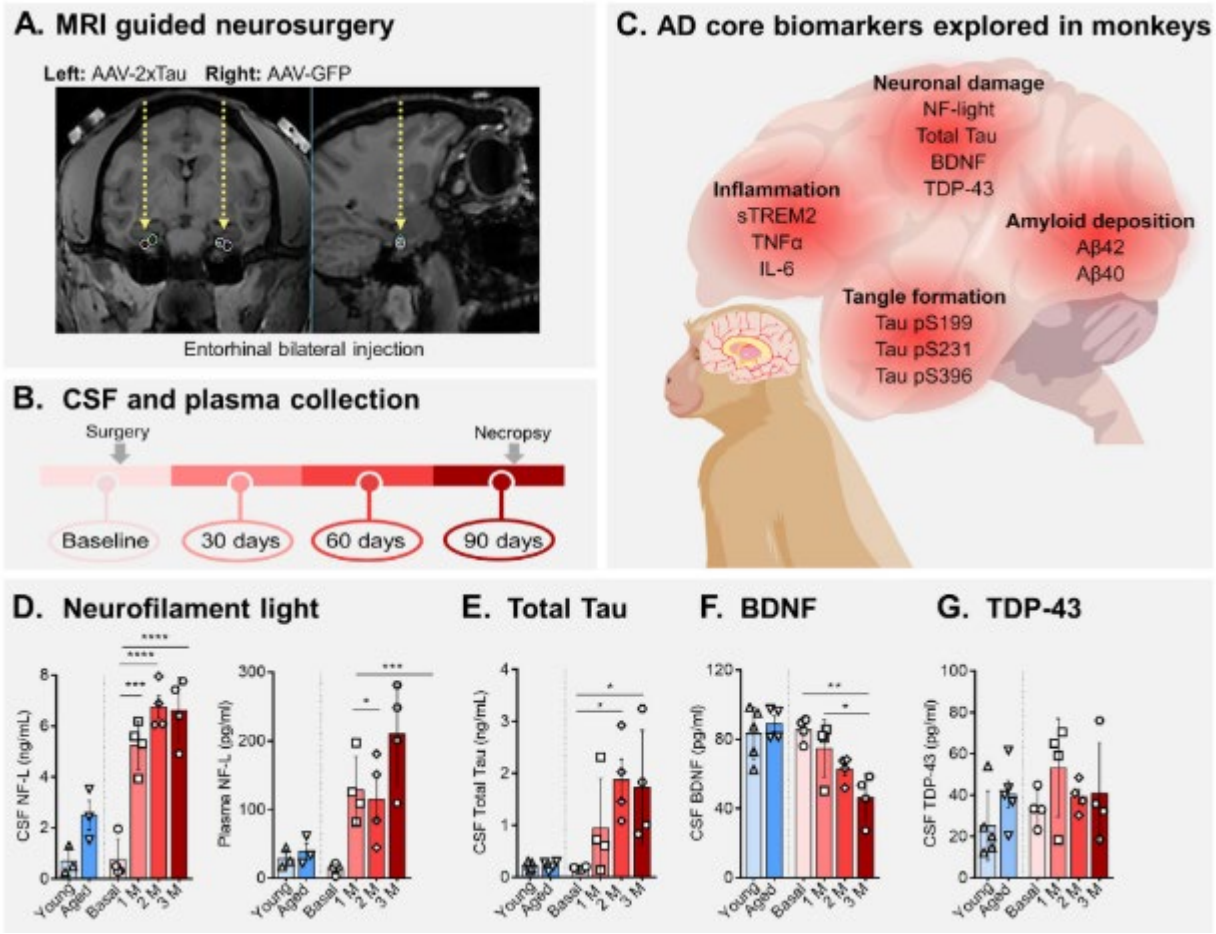
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

A novel tau-based rhesus monkey model of Alzheimer's pathogenesis

Danielle Beckman[1] | Paramita Chakrabarty[2] | Sean Ott[1] | Amanda Dao[1] | Eric Zhou[1] | William G. Janssen[3] | Kristine Donis-Cox[1] | Scott Muller[4] | Jeffrey H. Kordower[4,6] | John H. Morrison[1,5]

Injected monkeys develop AD core biomarkers in CSF and plasma



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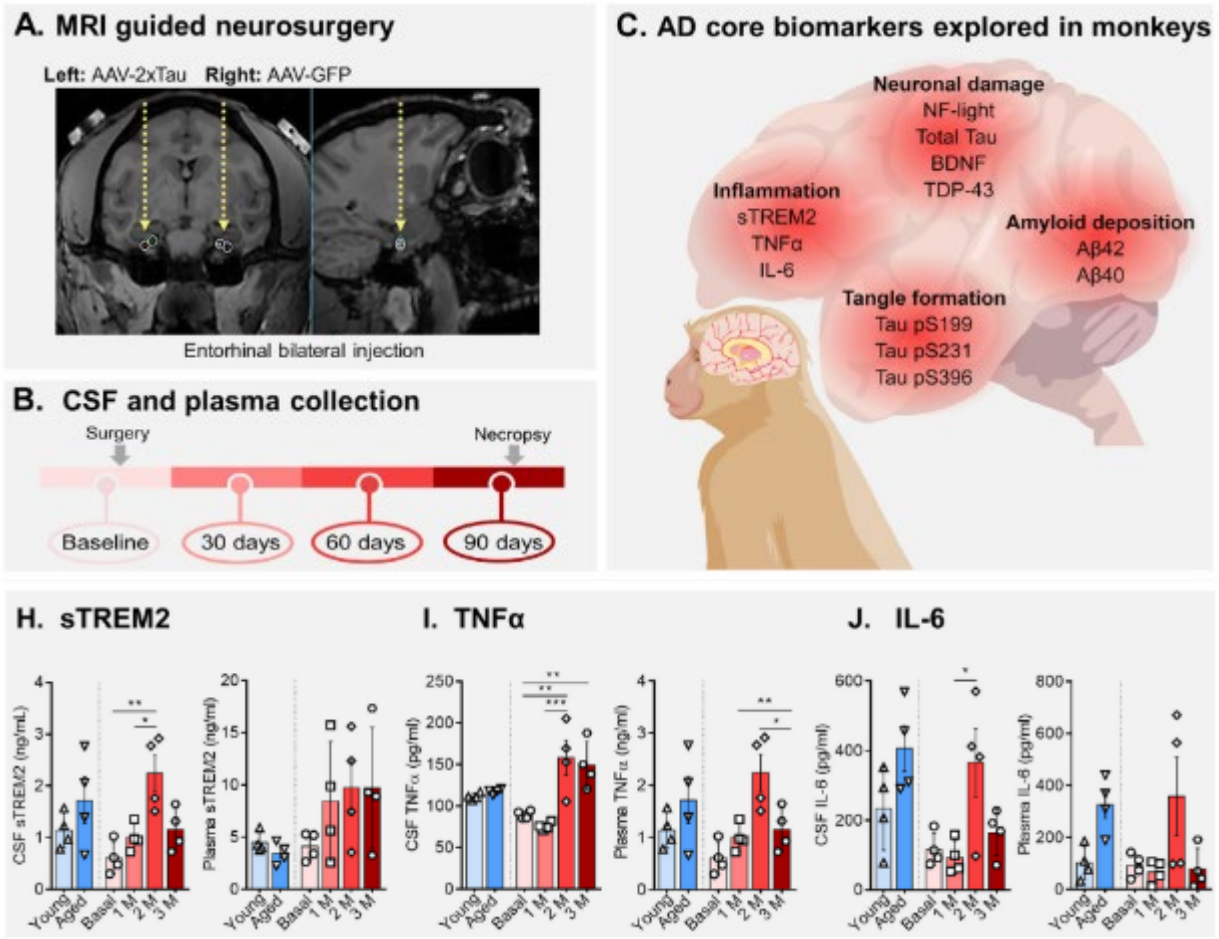

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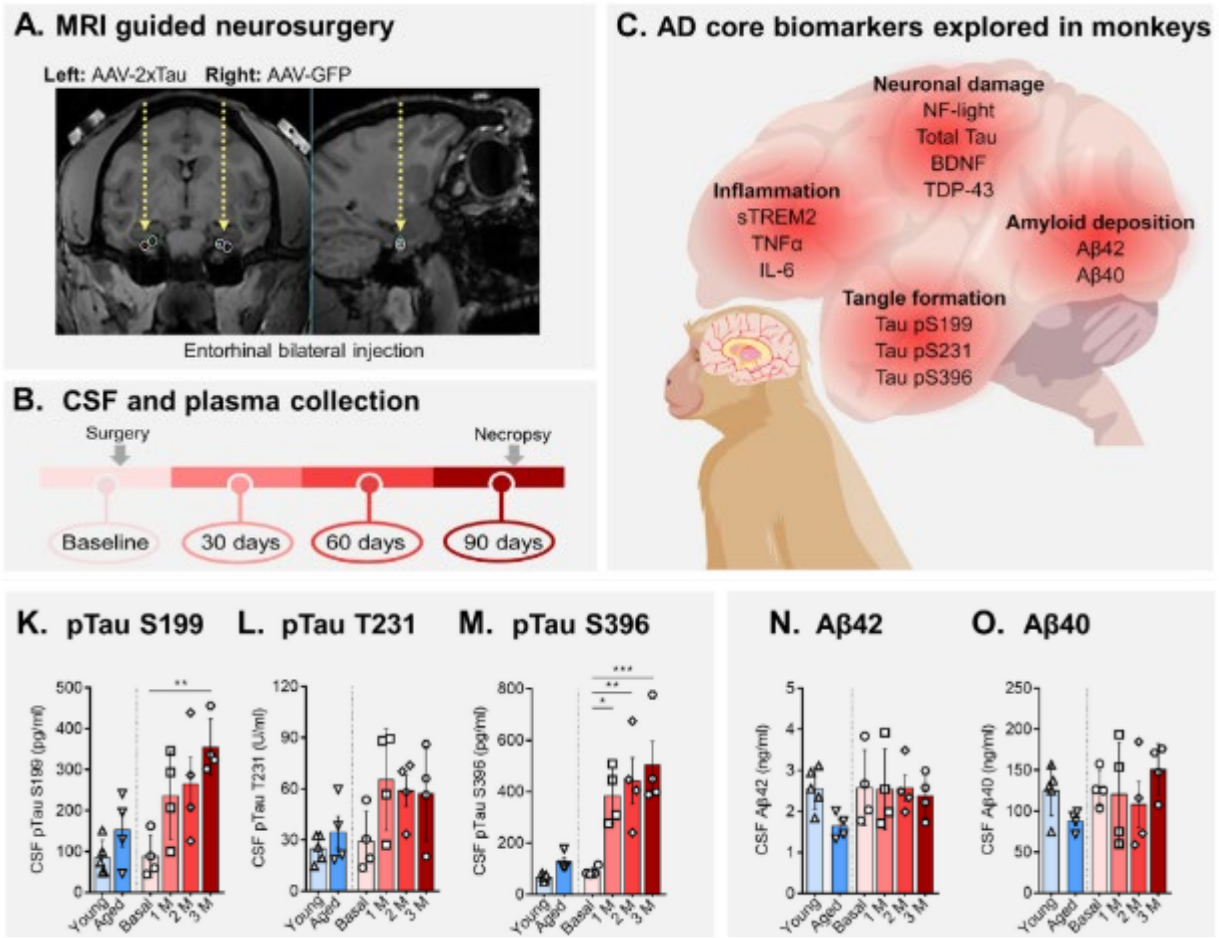
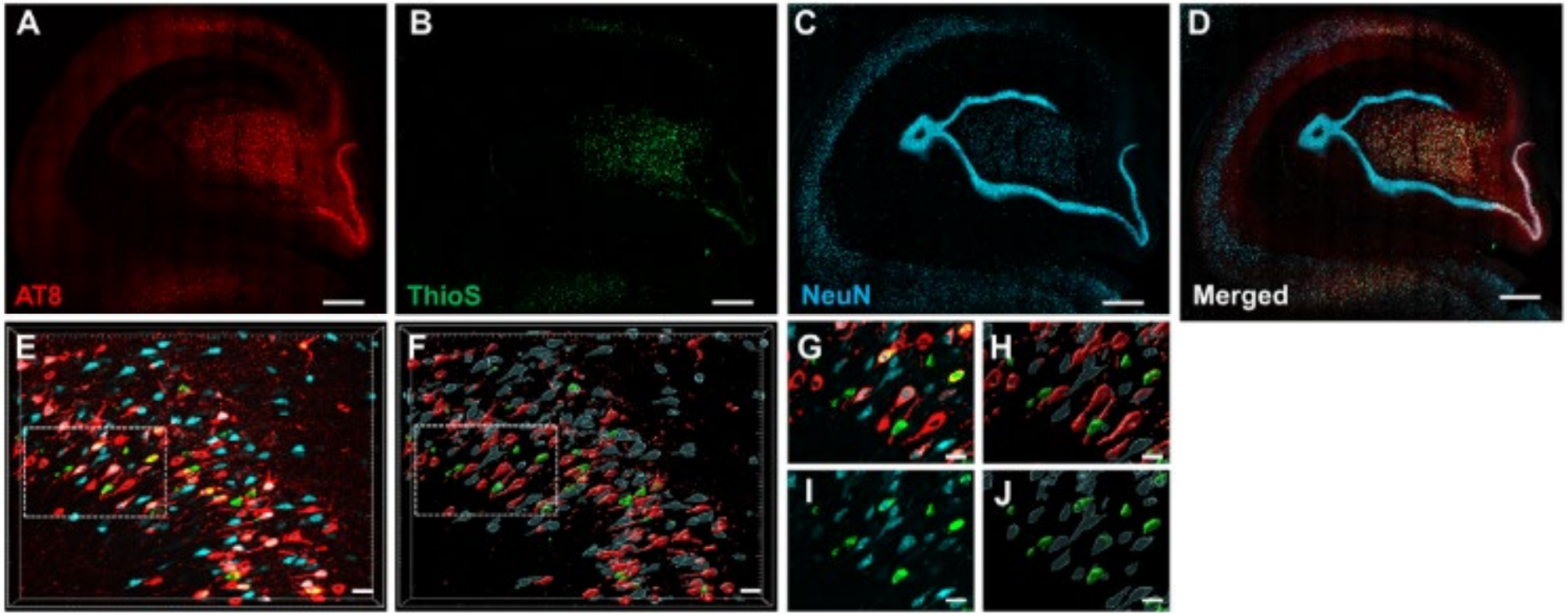


AAV-2xTau injection in the ERC induces extensive tau pathology in the hippocampus



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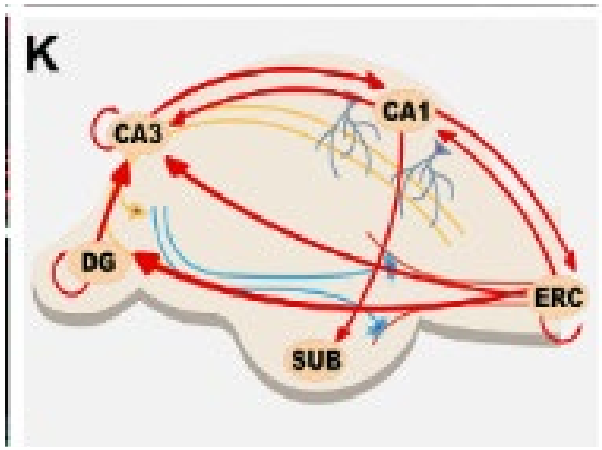
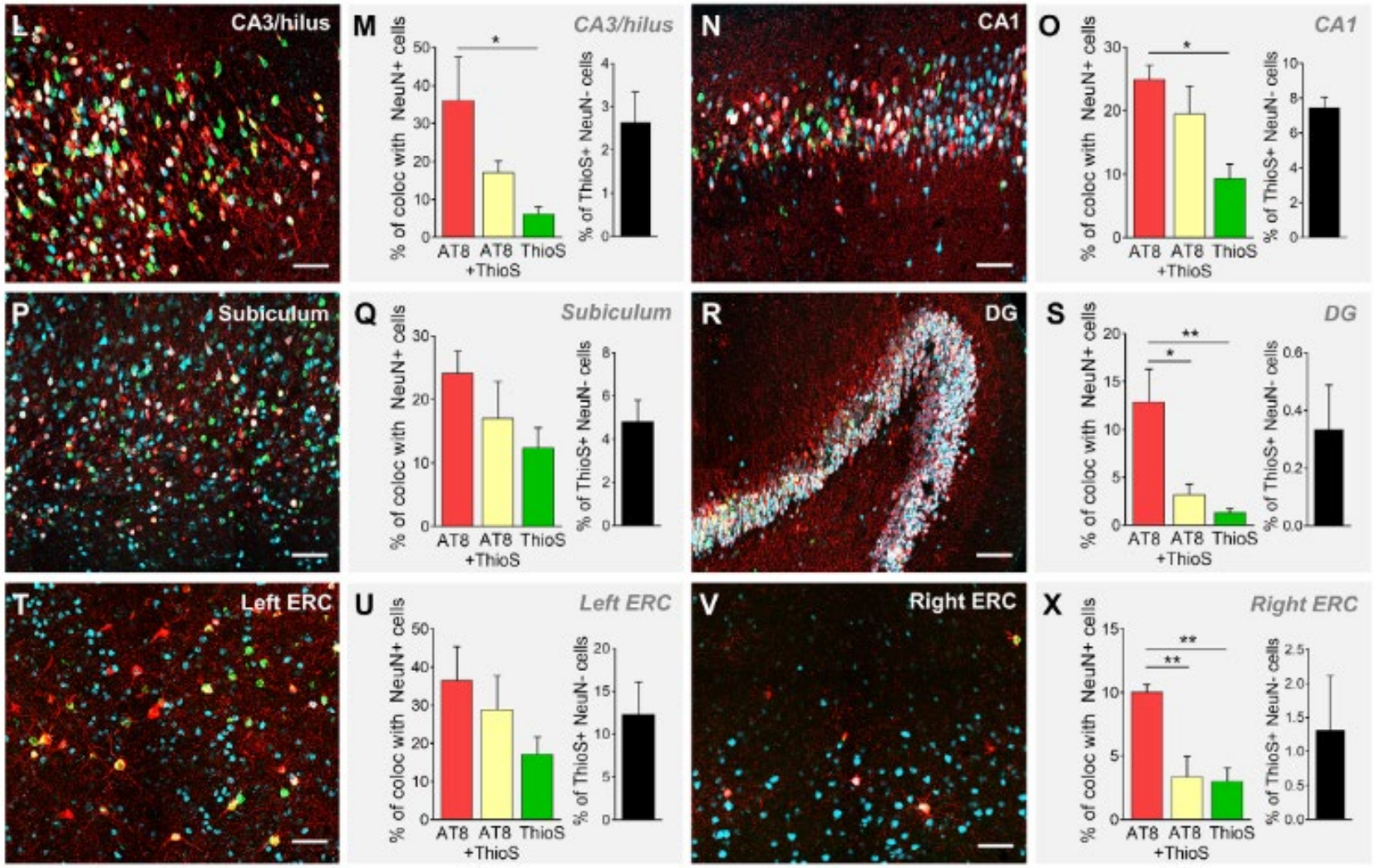
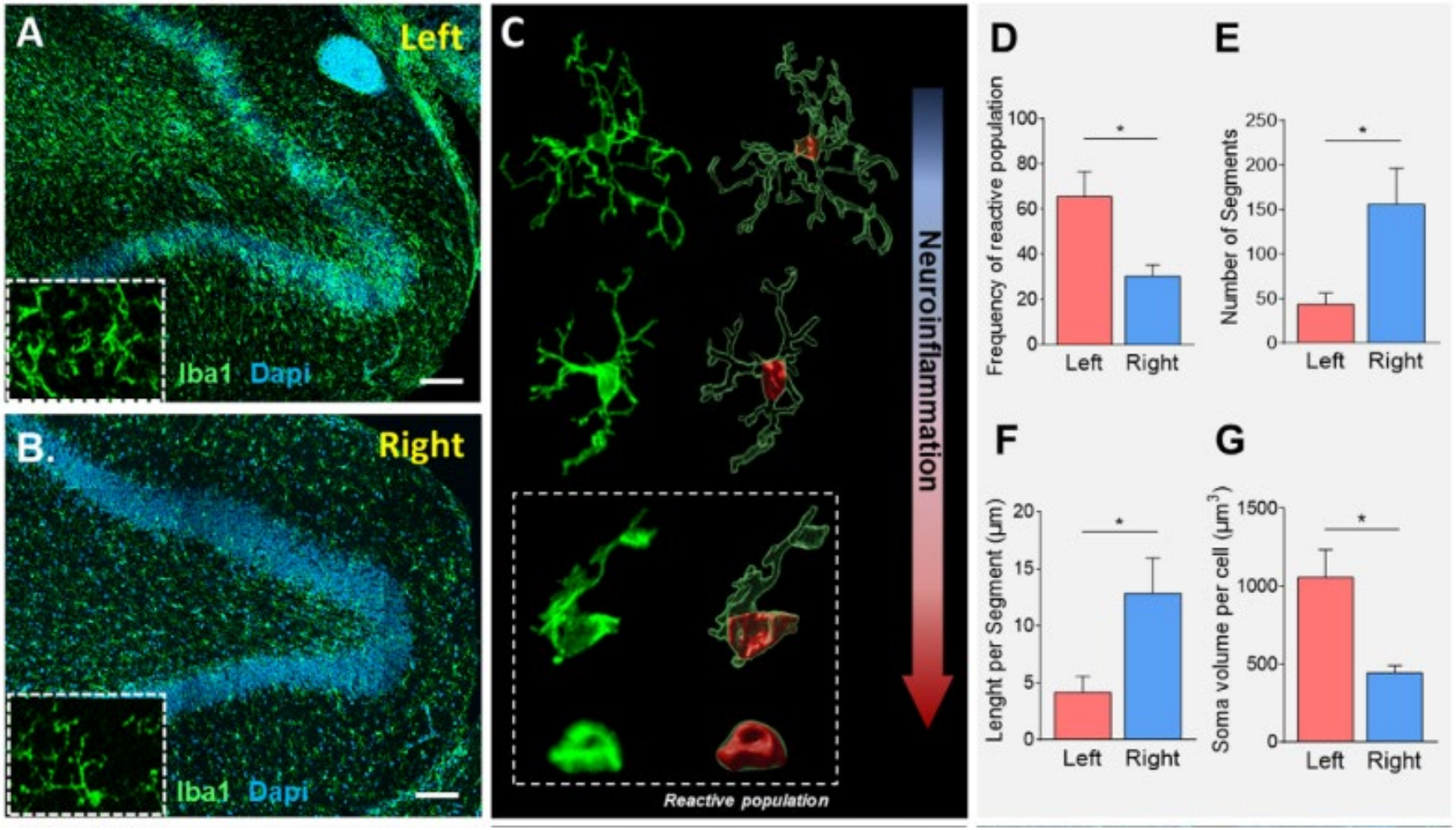




Misfolded tau propagation in the hippocampus induces an extensive microglial response



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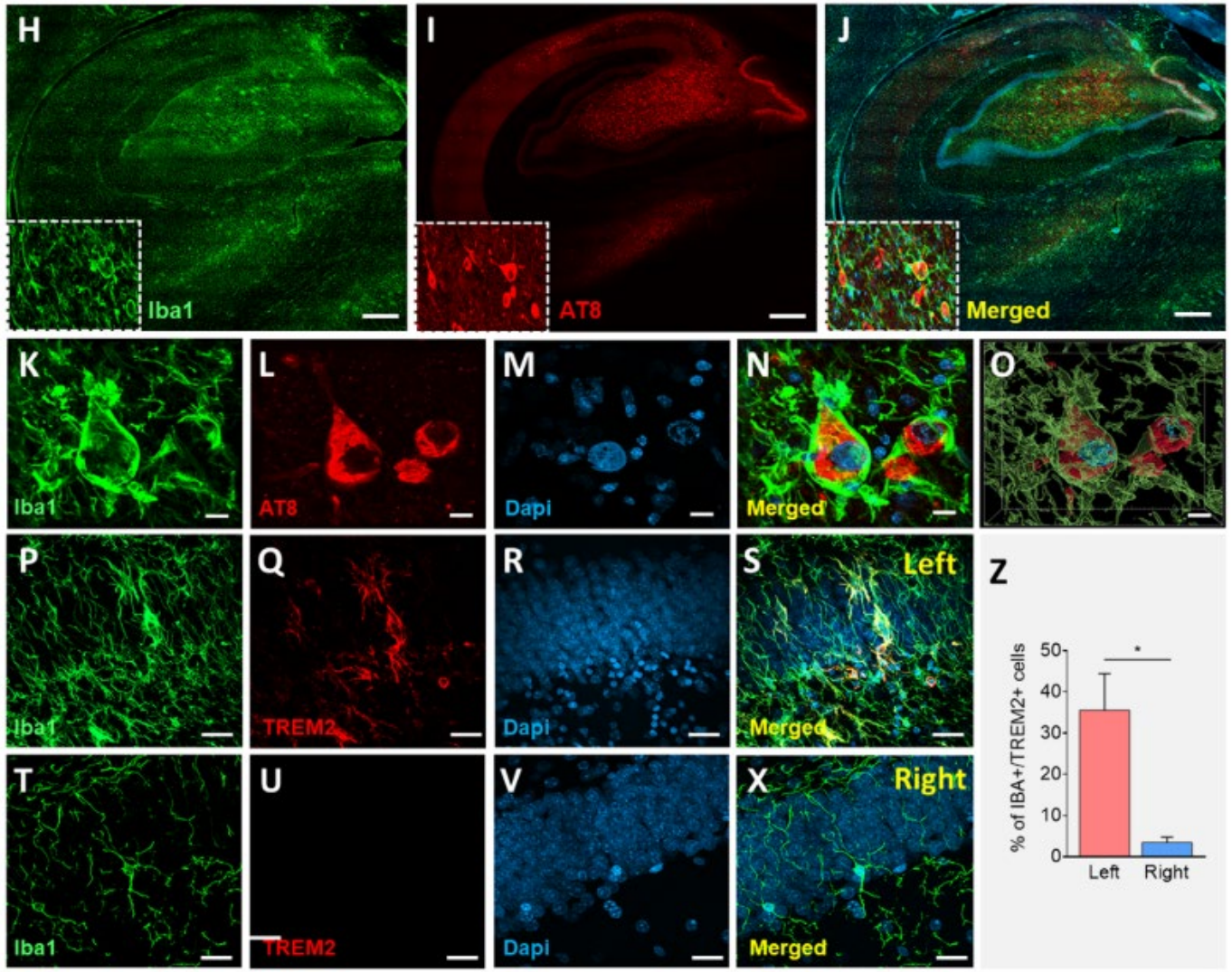
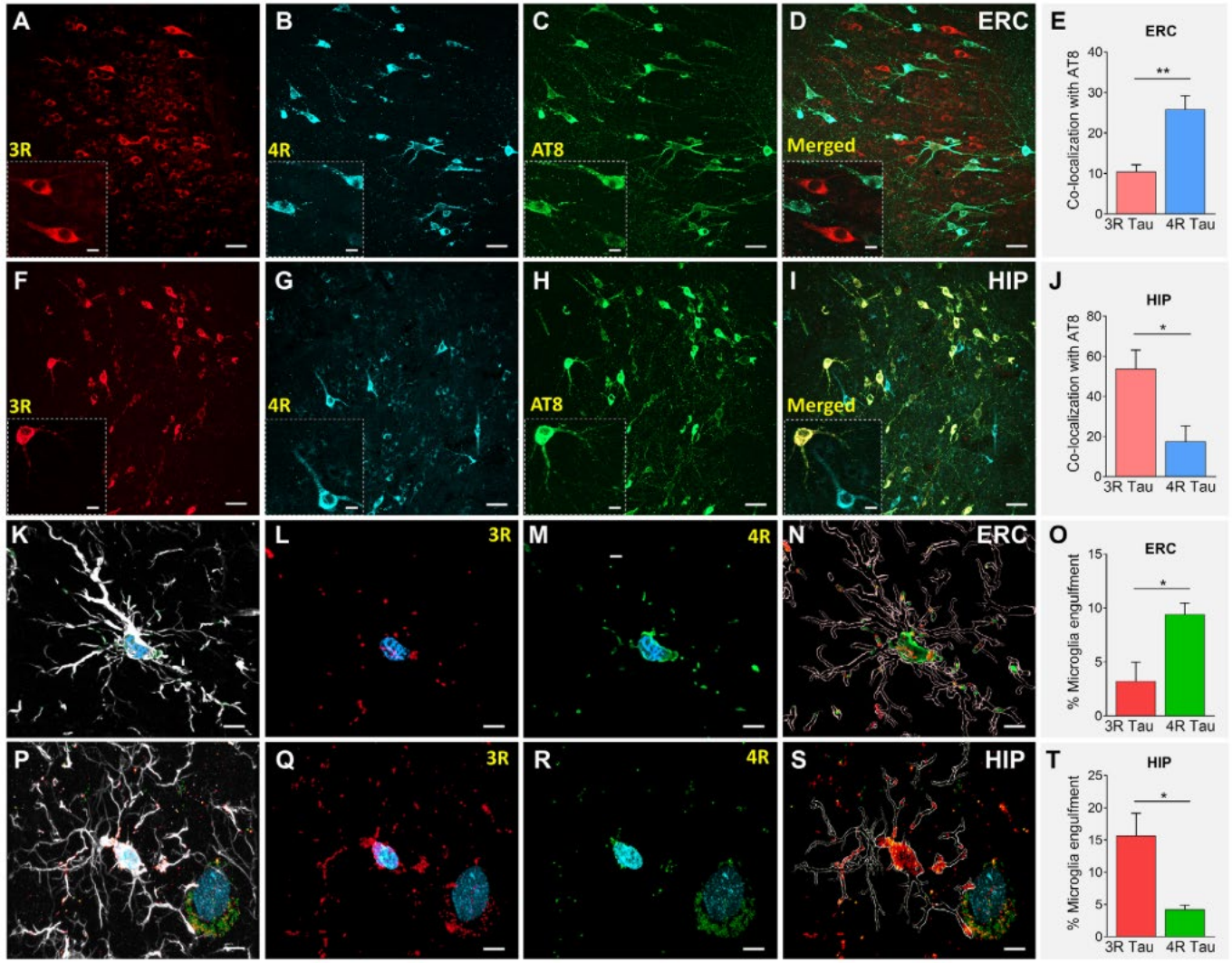
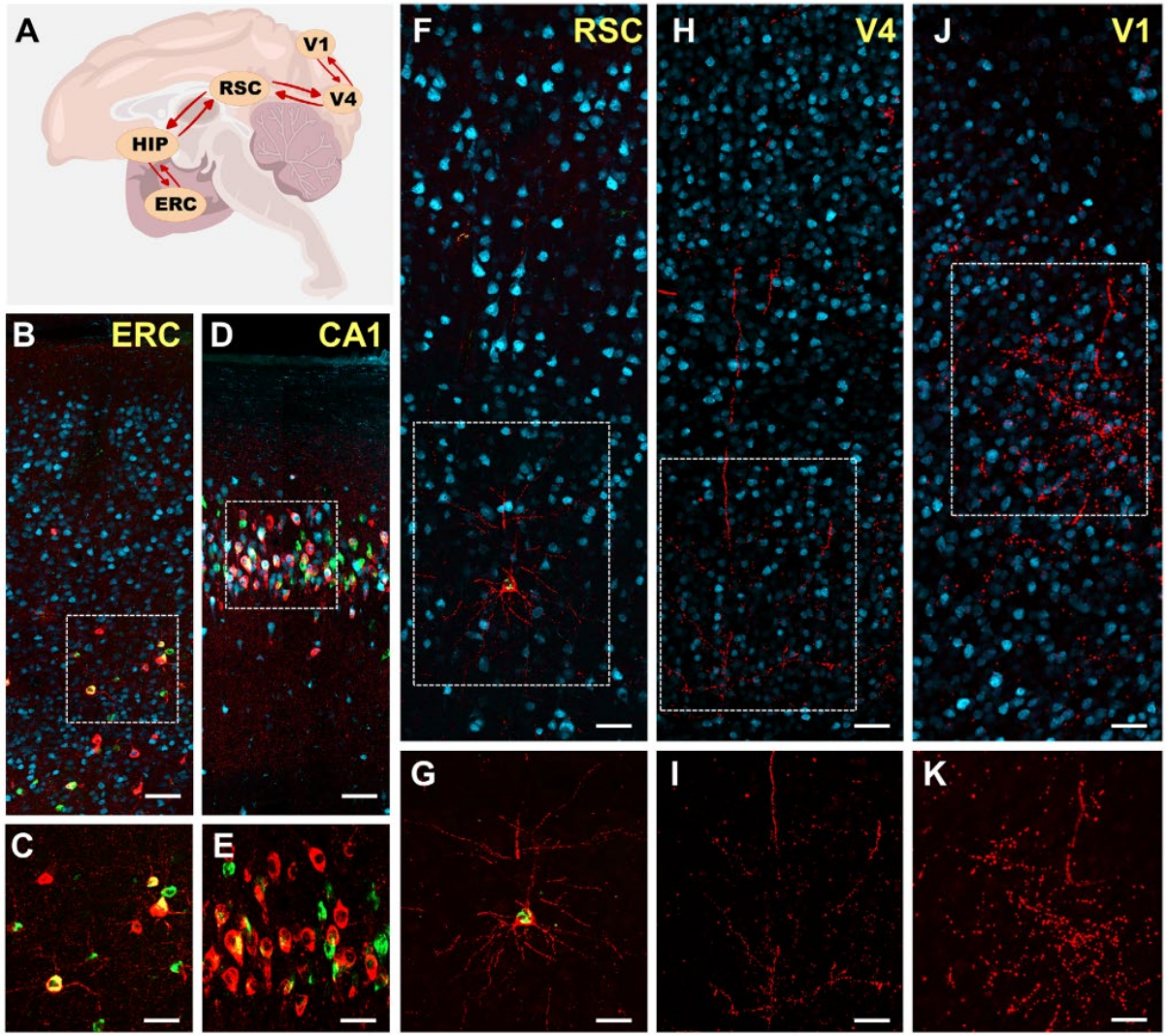


Presence of 4R human tau templates 3R monkey tau to induce propagation



Tau seeds propagate outside ERC-hippocampus in a prion-like manner



Main conclusions

- The development of an AD monkey model with accelerated tau pathology and neuroinflammation allows the study of end-stage NFT tangle development in AD vulnerable areas such as the ERC and hippocampus, as well as tau phosphorylation in regions several synaptic connections away from the site of injection only 3 months after injection

- They confirm the ability of human 4R tau to self-propagate inside the monkey brain via permissive templating of endogenous 3R tau

- **The development of NHP models of AD (and neurodegeneration broadly) can help us close the translational gap between mouse models and human clinical trials**

Thank you very much for your attention!

USZ Universitäts Spital Zürich

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