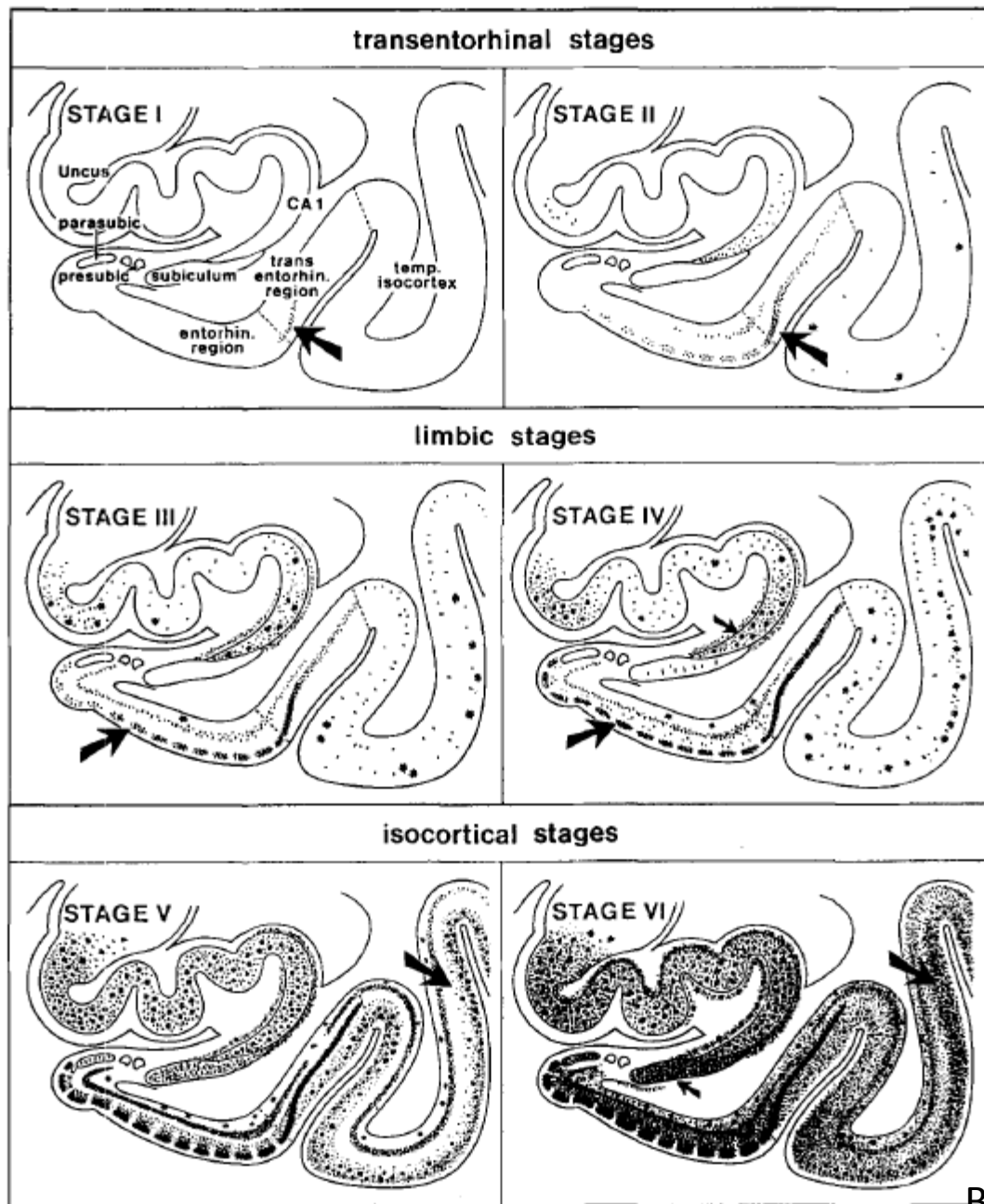
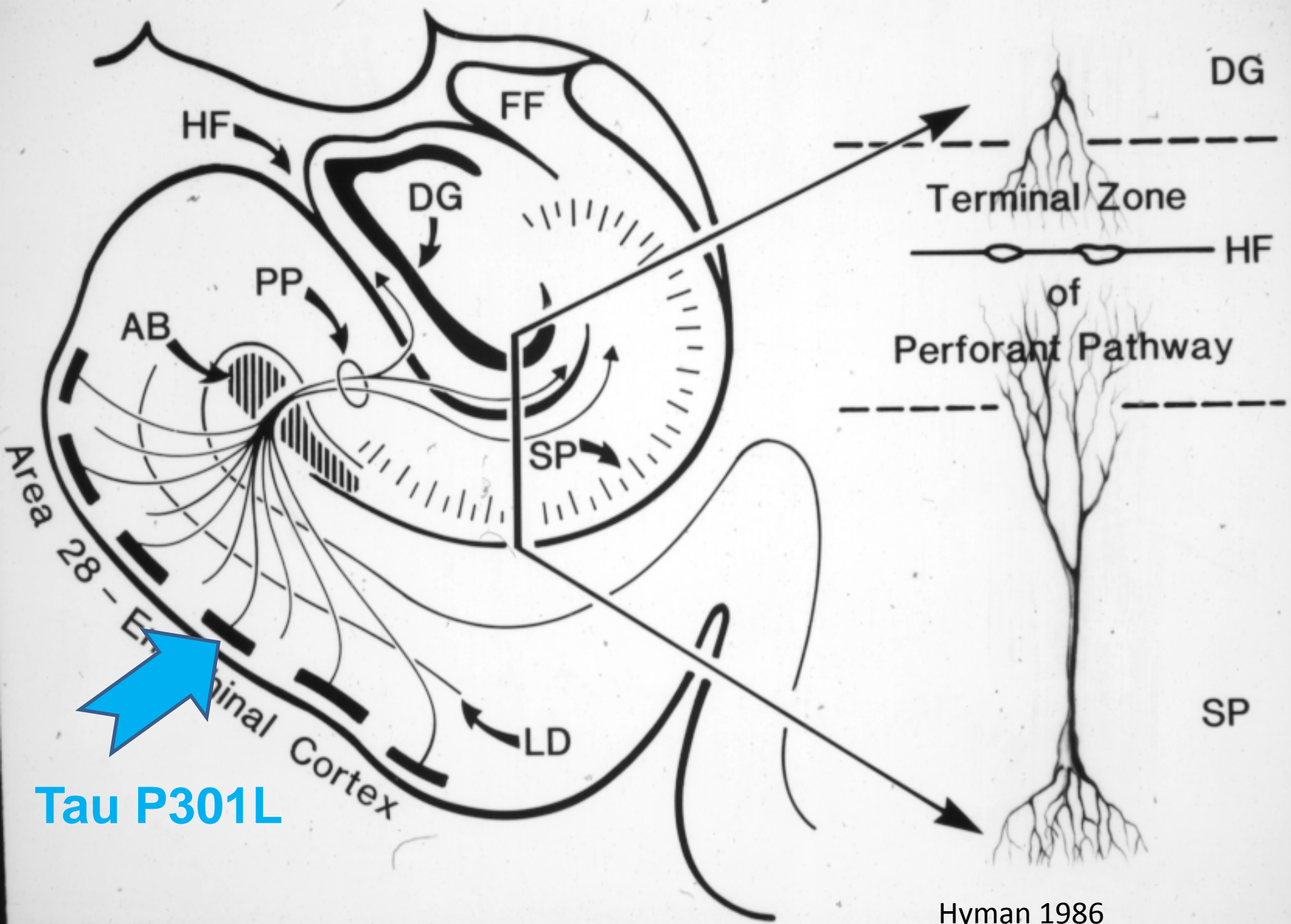


Consequences of tau expression in the entorhinal cortex: Synaptic Propagation of tau and synaptic degeneration

Brad Hyman MDPhD

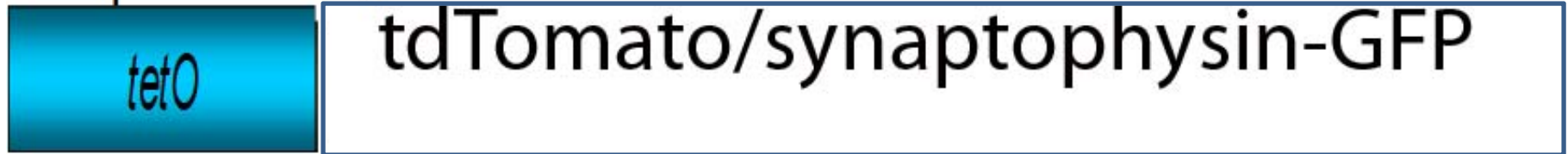
Mass General Hospital, Boston





Generation of EC / perforant pathway transgenic line

Responder transgene

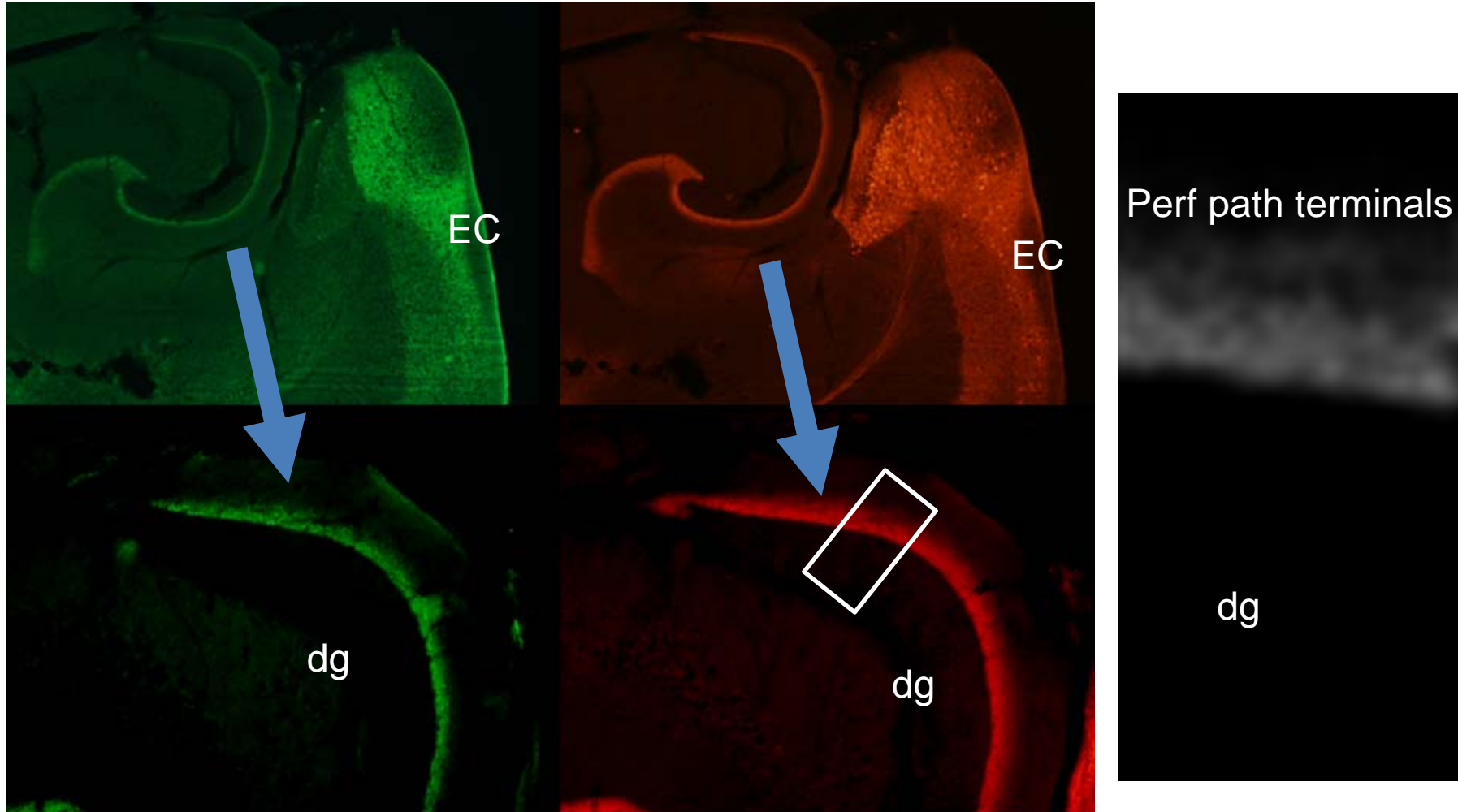


X

Activator transgene



Reporter genes reveal exquisite anatomic specificity of neuropsin promoter mice



Generation of rTauP301L EC line

Responder transgene



Santa Cruz et al 2005

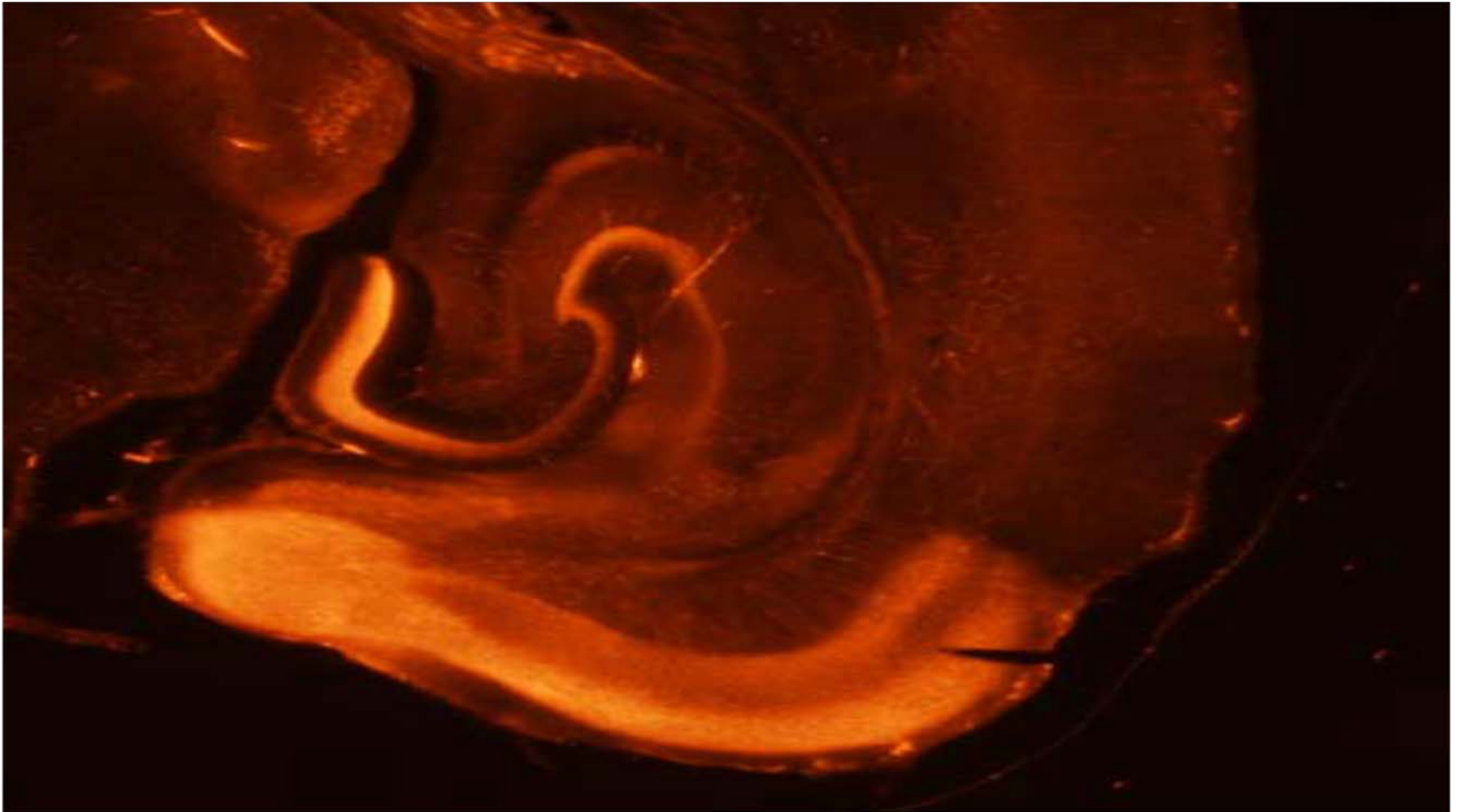
X

Activator transgene

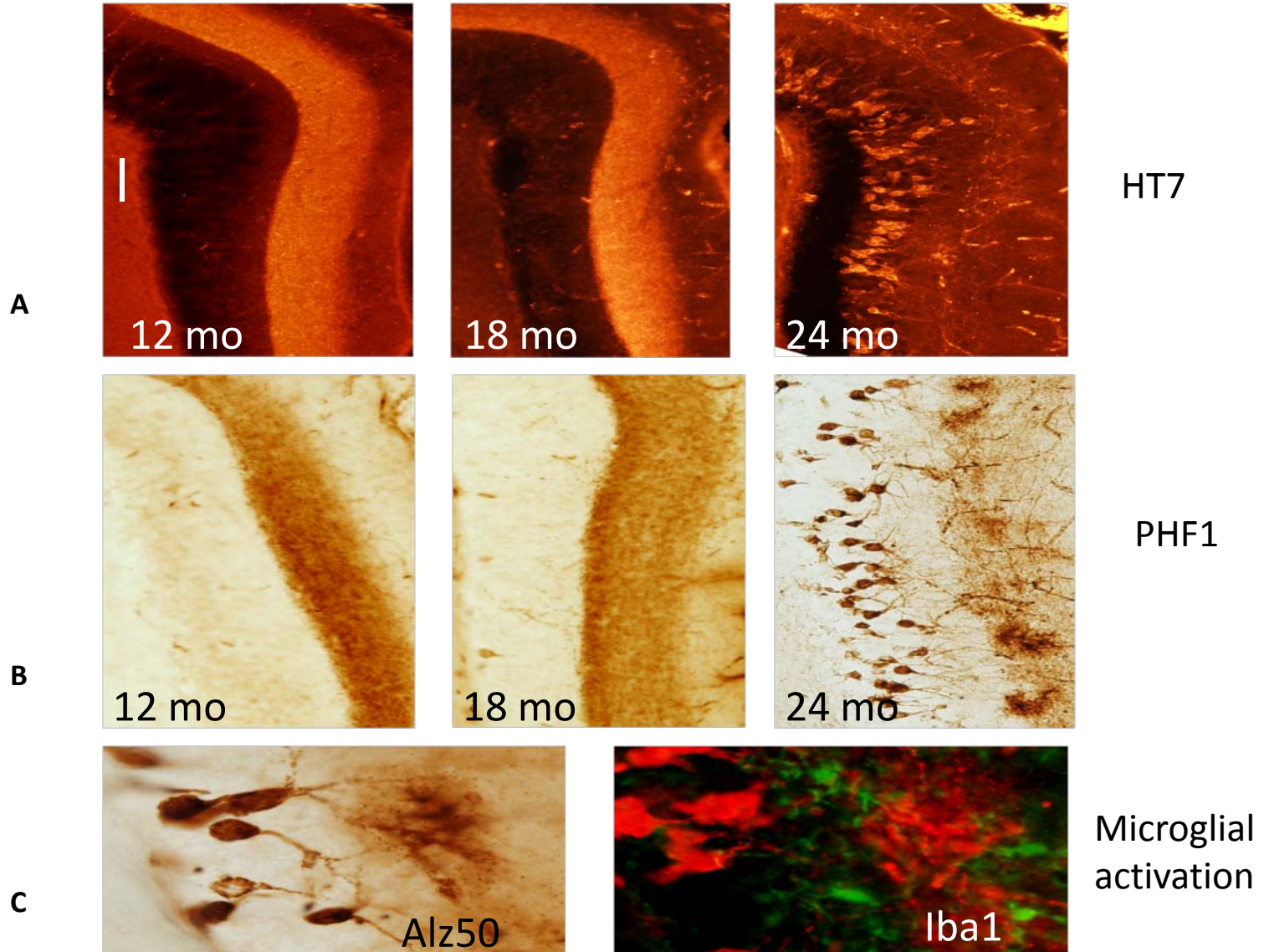


Yasuda and Mayford 2006

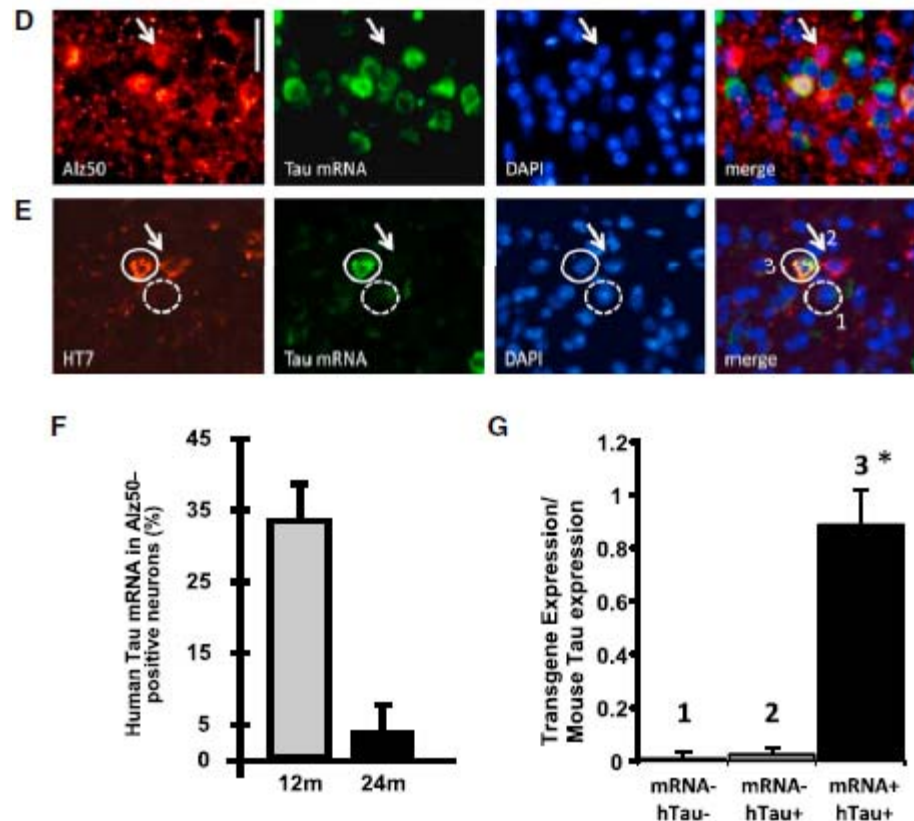
hTau ICC shows transgene in Entorhinal and perforant pathway terminal zone at 3 months of age



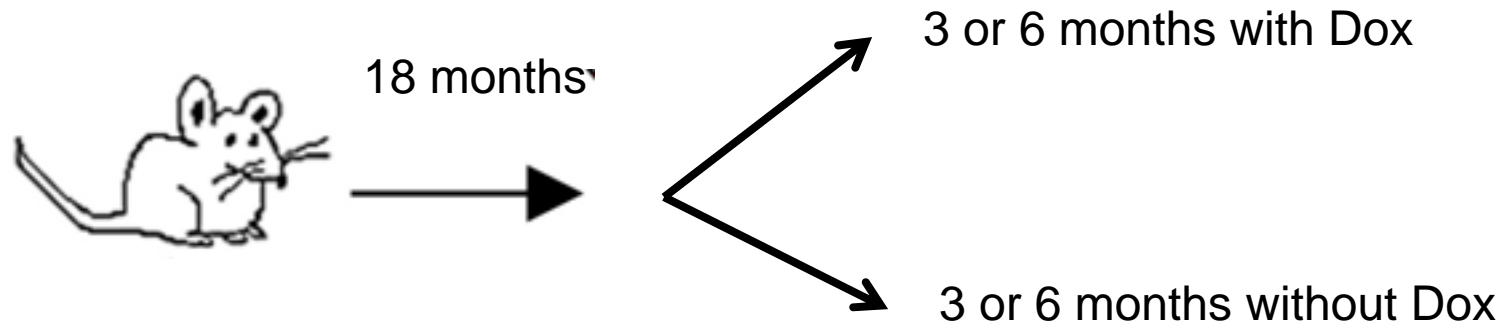
Degeneration of the terminal zone of the perforant pathway



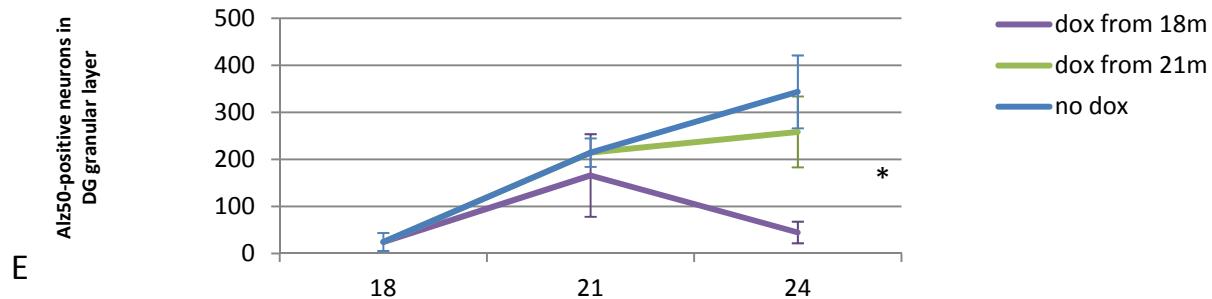
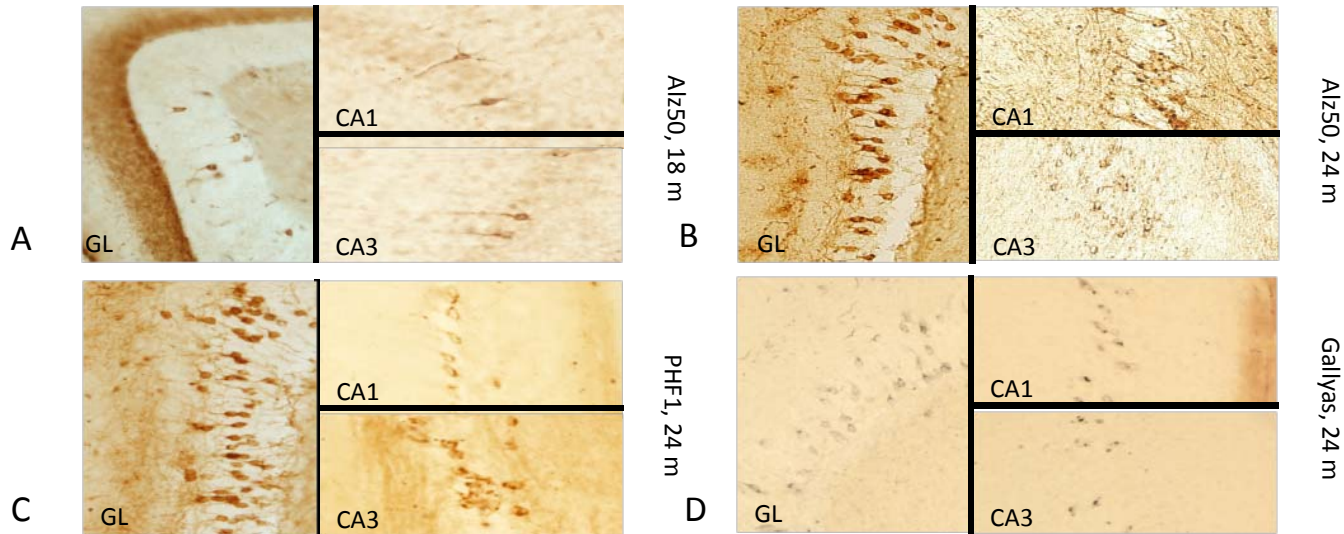
Human tau protein is present in cells with little or no human tau mRNA
As determined by double immunohistochemistry/in situ
followed by laser capture microdissection and qPCR for human tau



rTauEC mice: Preliminary results of transgene suppression

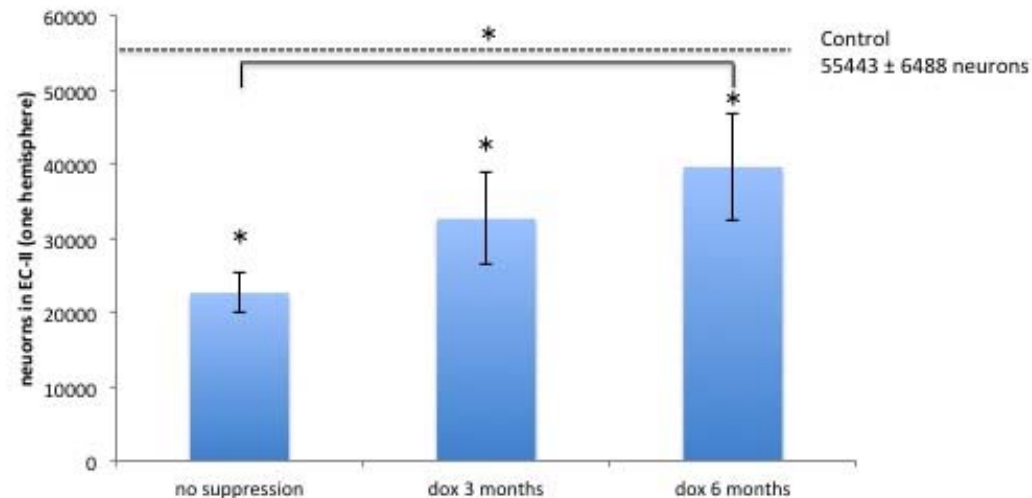
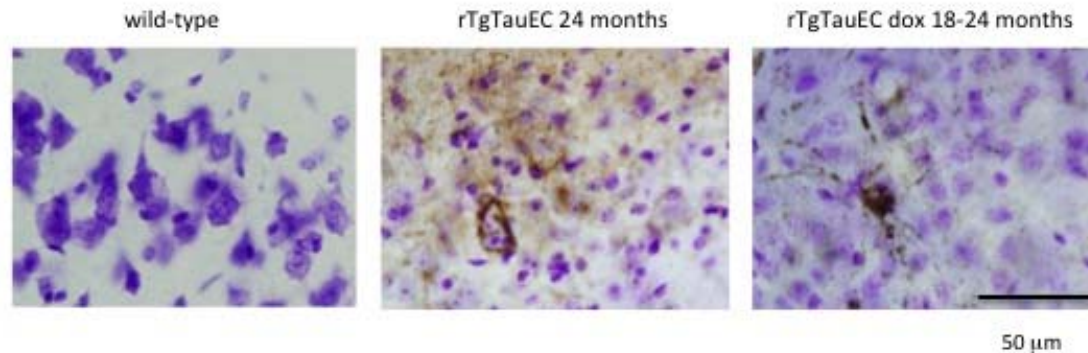


Propagation of tau pathology blocked by tau suppression



Propagation blocked to some extent by tau suppression

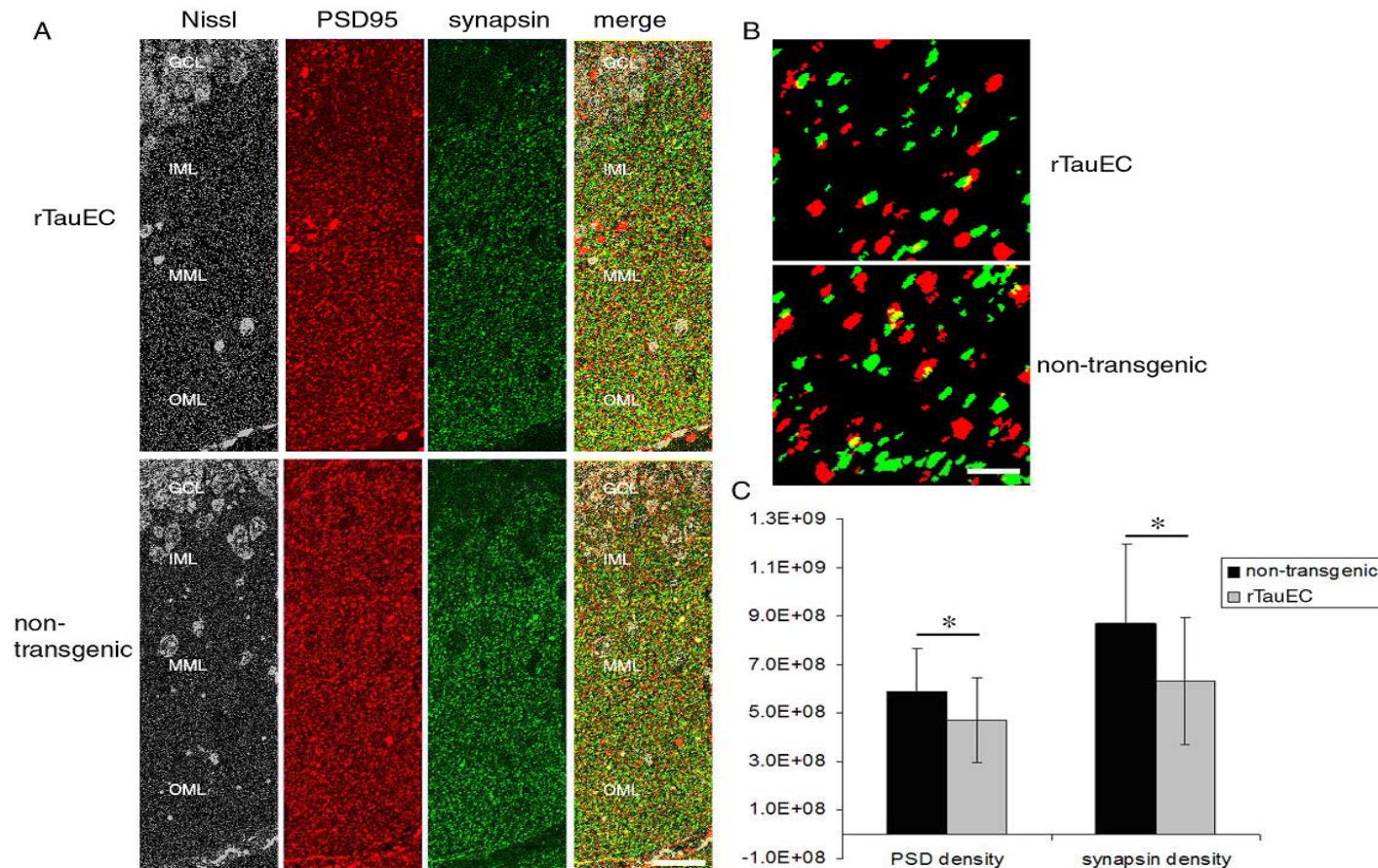
Transgene suppression ameliorates neuronal loss as well



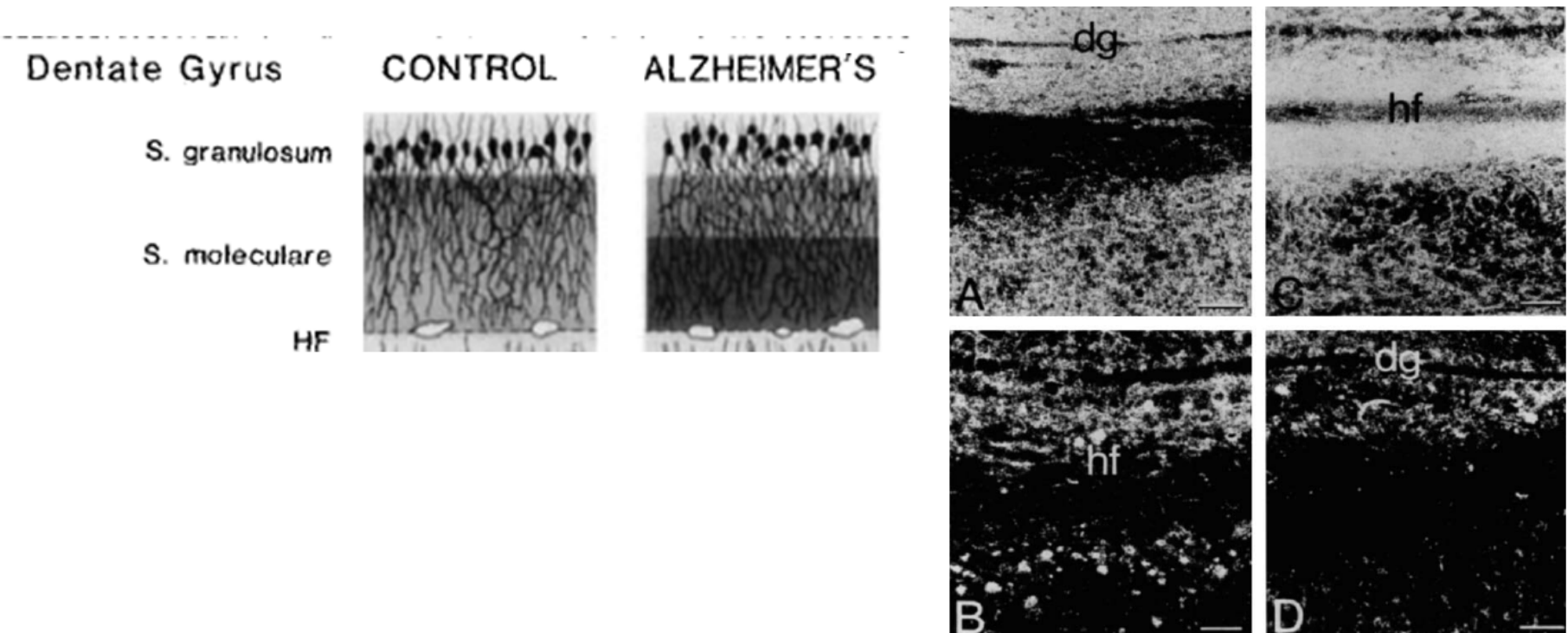
Loss of perforant path terminals leads
to synaptic dysfunction and plasticity
response

Suppression of transgene leads
to partial blockade of tau
propagation and recovery of
plasticity phenotype

Deafferentation: Synaptic loss specifically in the perforant pathway terminal zone at 24 months



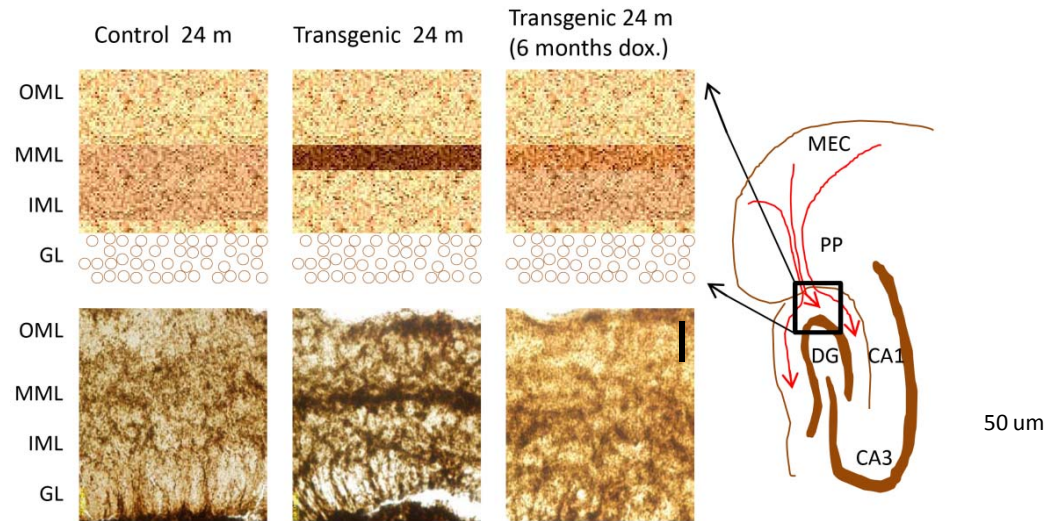
Reinnervation of the perforant pathway terminal zone in Alzheimer disease



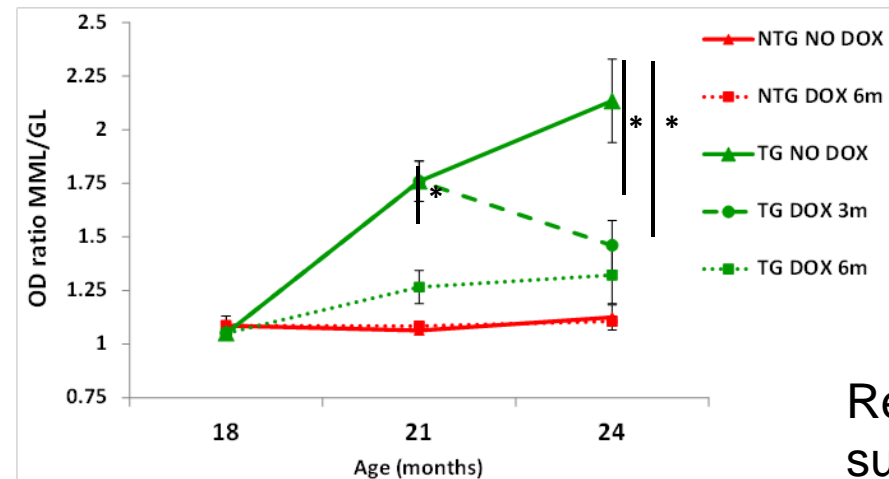
Hyman 1987

AChE staining reveals sprouting into the middle molecular layer

A



B



Recovery by transgene suppression

Mechanisms of neurodegeneration: implications of the rTauEC line

1. Propagation of misfolded tau across neural systems, leading to propagation of inclusions across neural systems
 - Human and mouse tau co-aggregate in these inclusions
 - Mechanism of propagation still uncertain – toxic species unknown
2. Suppression of tau transgene leads to a delay (or reversal?) in propagation phenotype
3. Neuronal loss appears to be a late phenomenon
4. Synaptic loss, though modest, is sufficient to initiate a classic plasticity sprouting response
5. We speculate that the propagation of tau, deafferentation, and altered plasticity lead to progressive neural system failure that in some ways is analogous to the progressive neuropathological changes in AD

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