

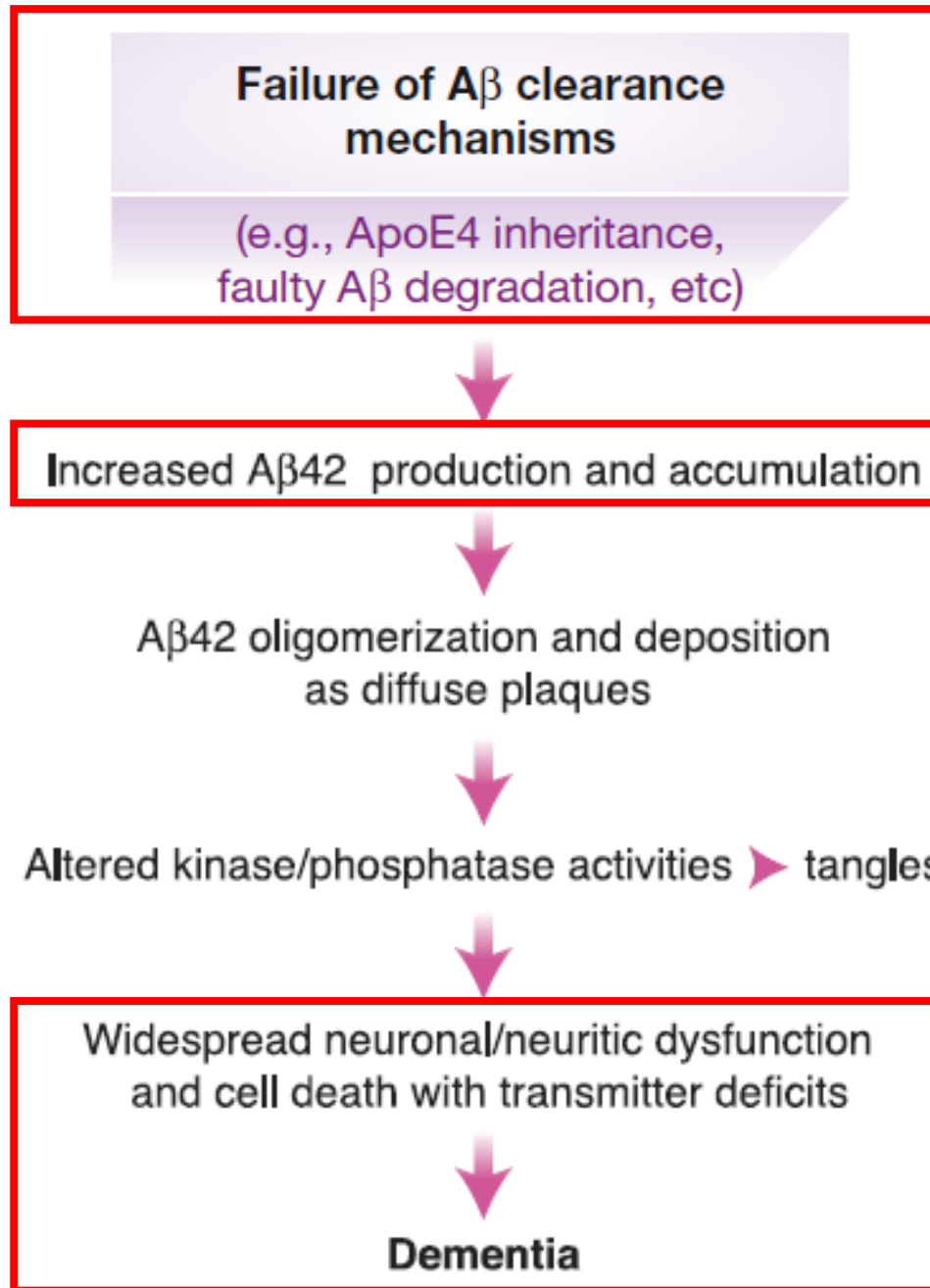
“Neuronal activity regulates the regional vulnerability to amyloid- β deposition”

Bero et al., *Nat Neurosci* (2011)

Alzheimer's Disease

- Most common form of dementia
 - Affects an estimated 40 million people worldwide
- Gradual cognitive decline and memory loss
- Marked by extracellular accumulation of amyloid plaques
 - Potentially causal role (i.e., “the amyloid hypothesis”)

Amyloid hypothesis

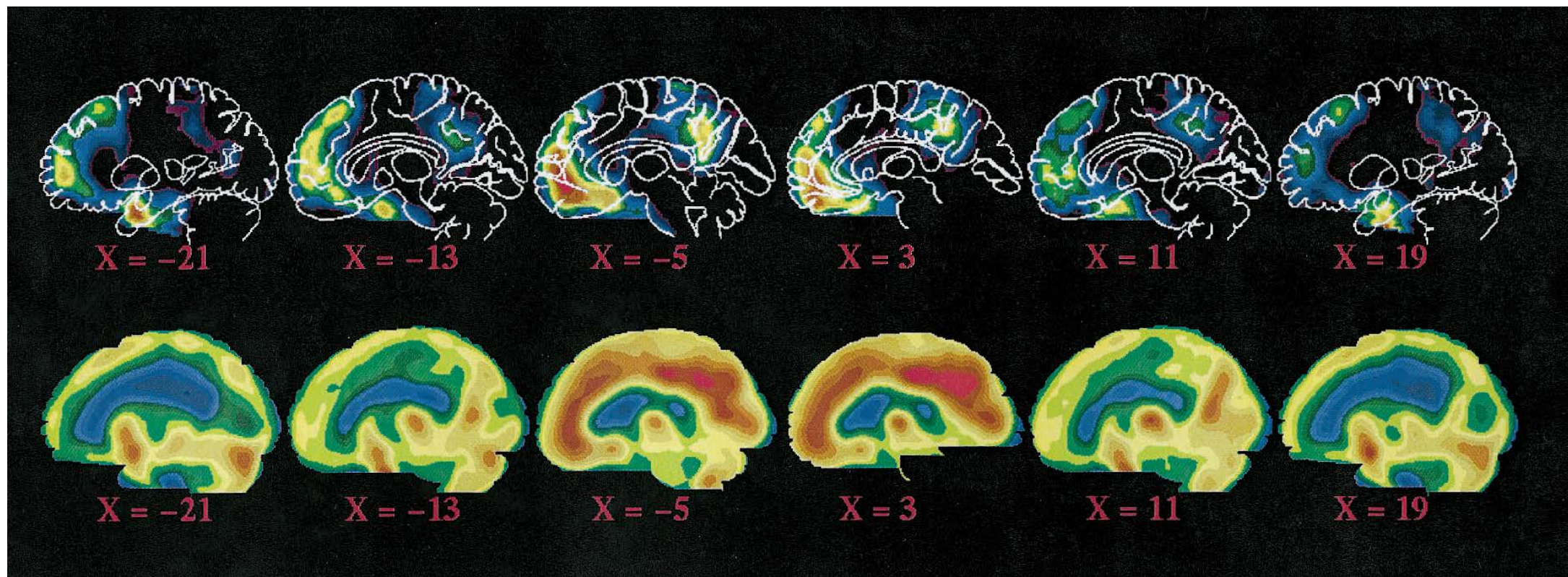


Modified from Hardy & Selkoe,
Science (2002)

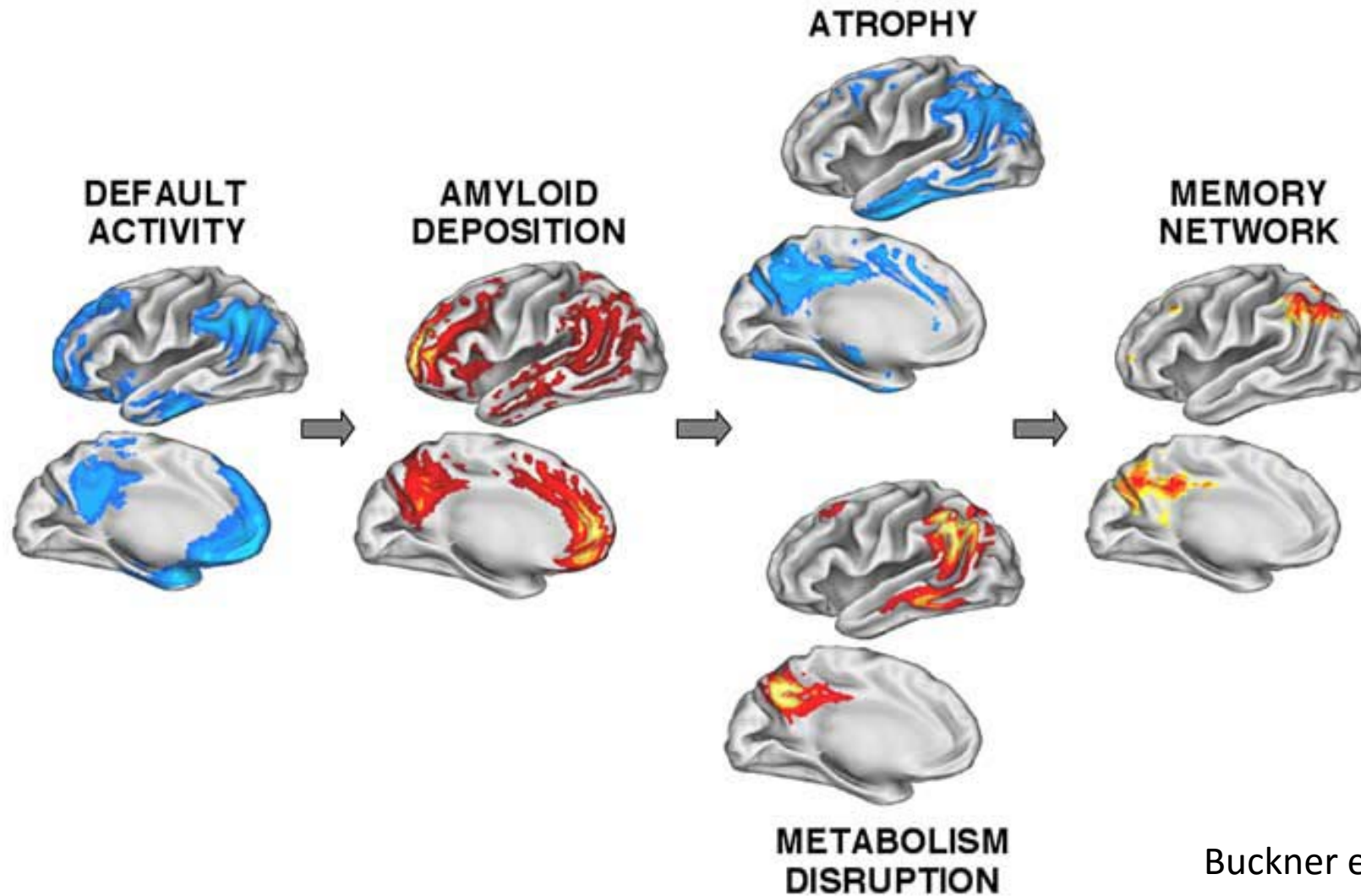
Amyloid deposition

- In humans, vulnerability to amyloid accumulation is highest in the “default mode network”
 - Set of regions that are more metabolically active during the “resting-state”

Default Mode Network



Default Mode Network and Amyloid

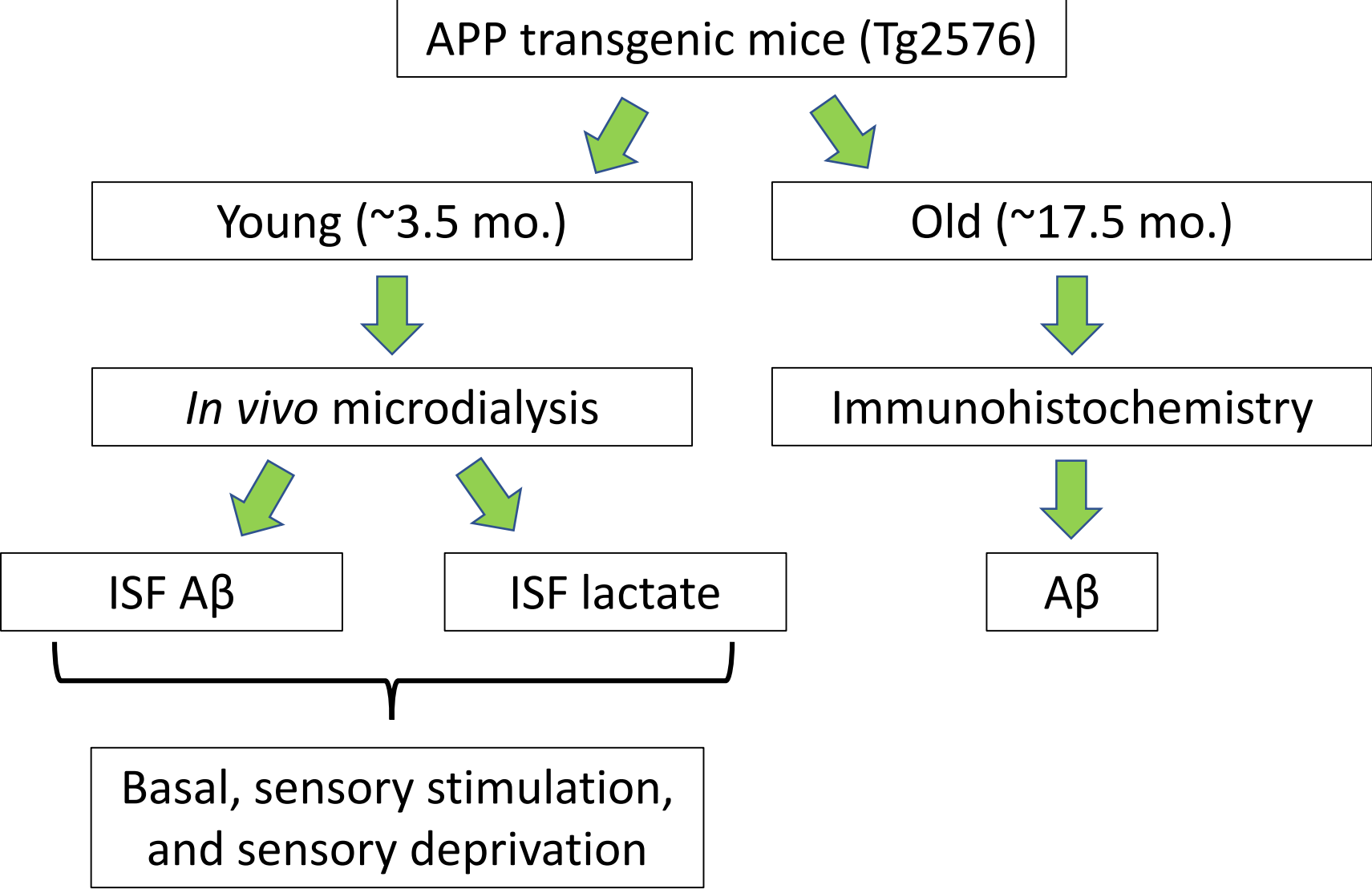


Buckner et al., *J Neurosci* (2005)

Hypothesis

Regional differences in endogenous neural activity determine the spatial pattern of amyloid accumulation

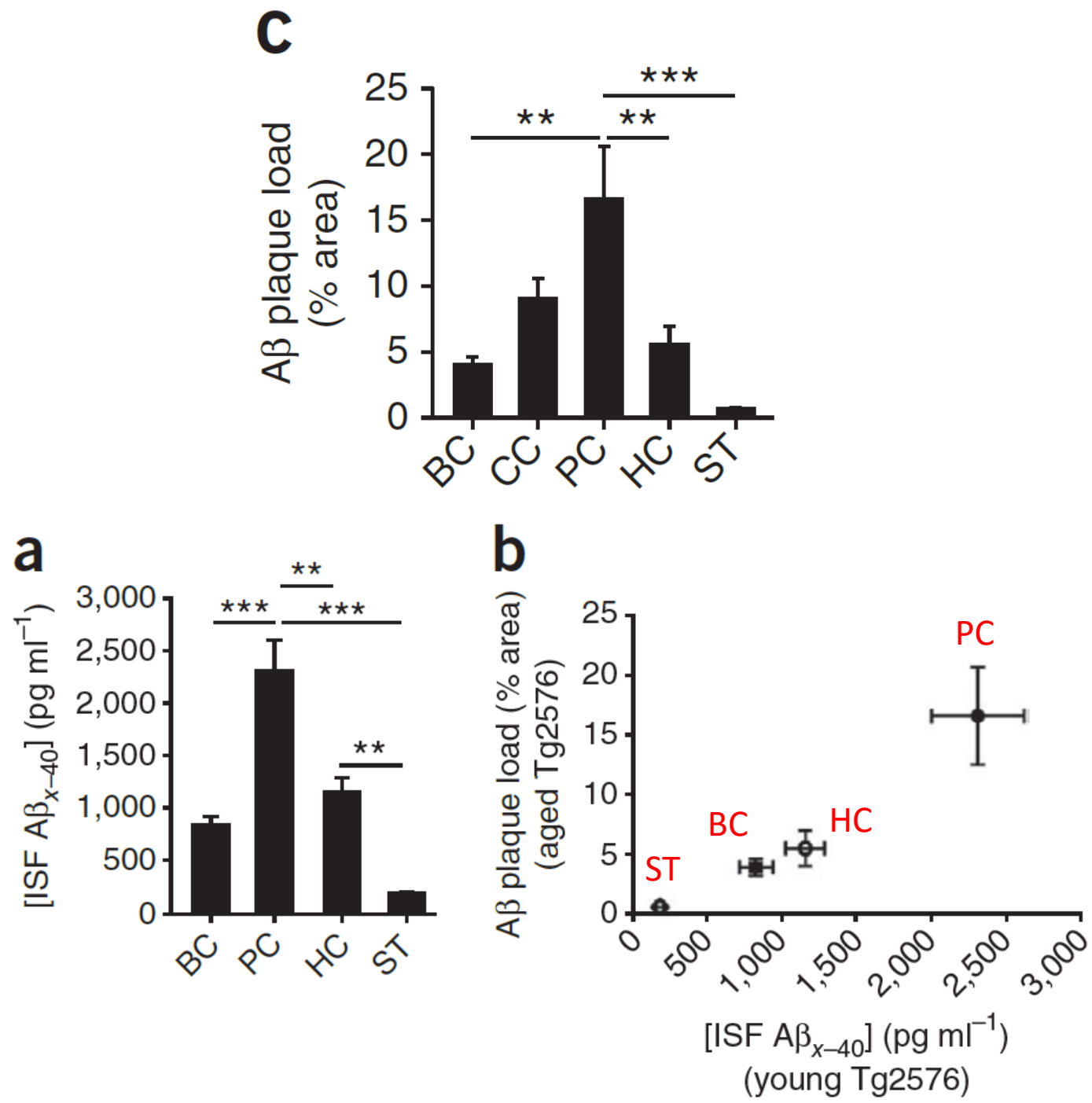
Experimental design



Results & Interpretations

Is there a regional pattern to A β deposition?

- Immunostaining for A β in old APP mice
- *In vivo* microdialysis measurements of ISF A β in young APP mice

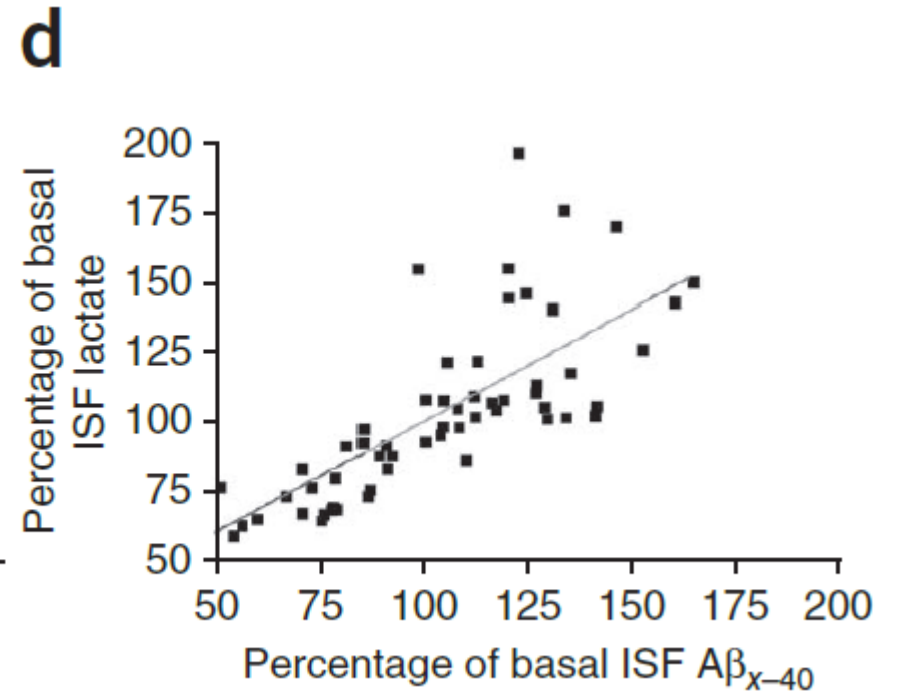
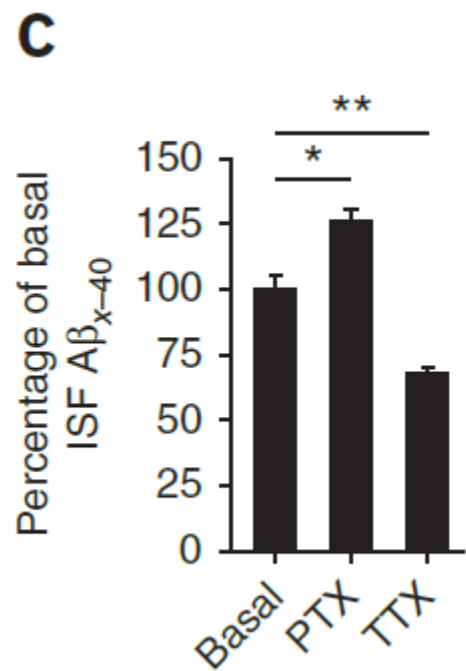
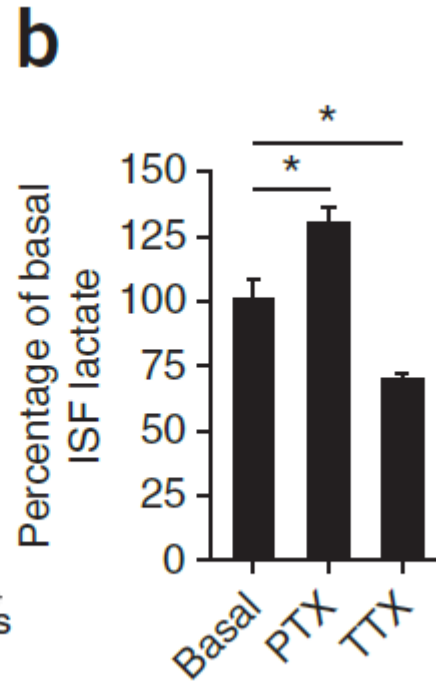
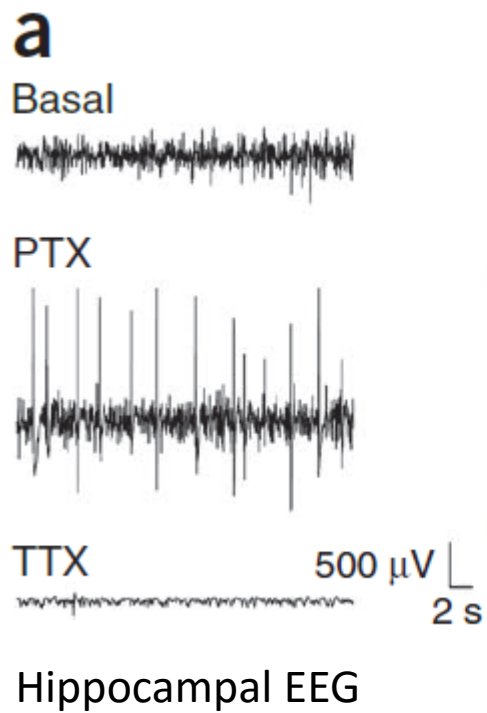


Interpretation

- A β deposition has regionally-specific pattern in old APP mice
 - Shares common features with humans (kind of)
- ISF A β in young mice predicts eventual patterns of regional plaque deposition in old mice

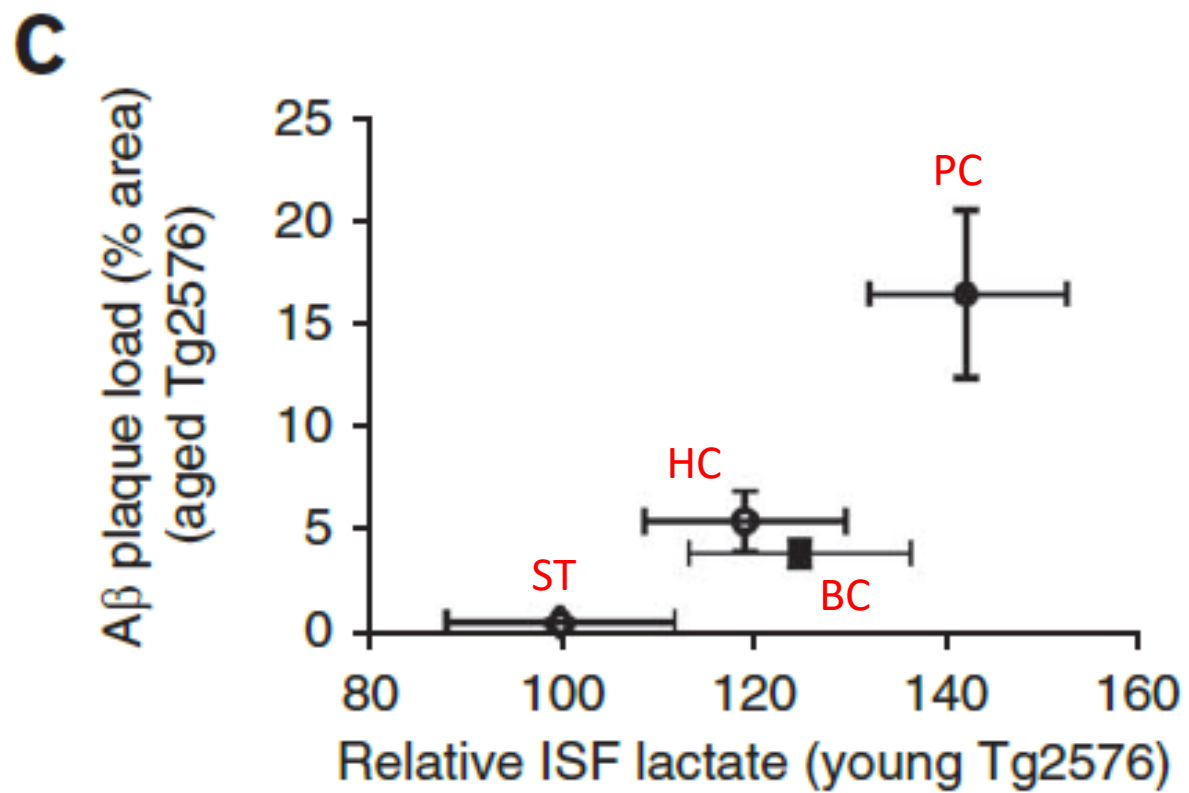
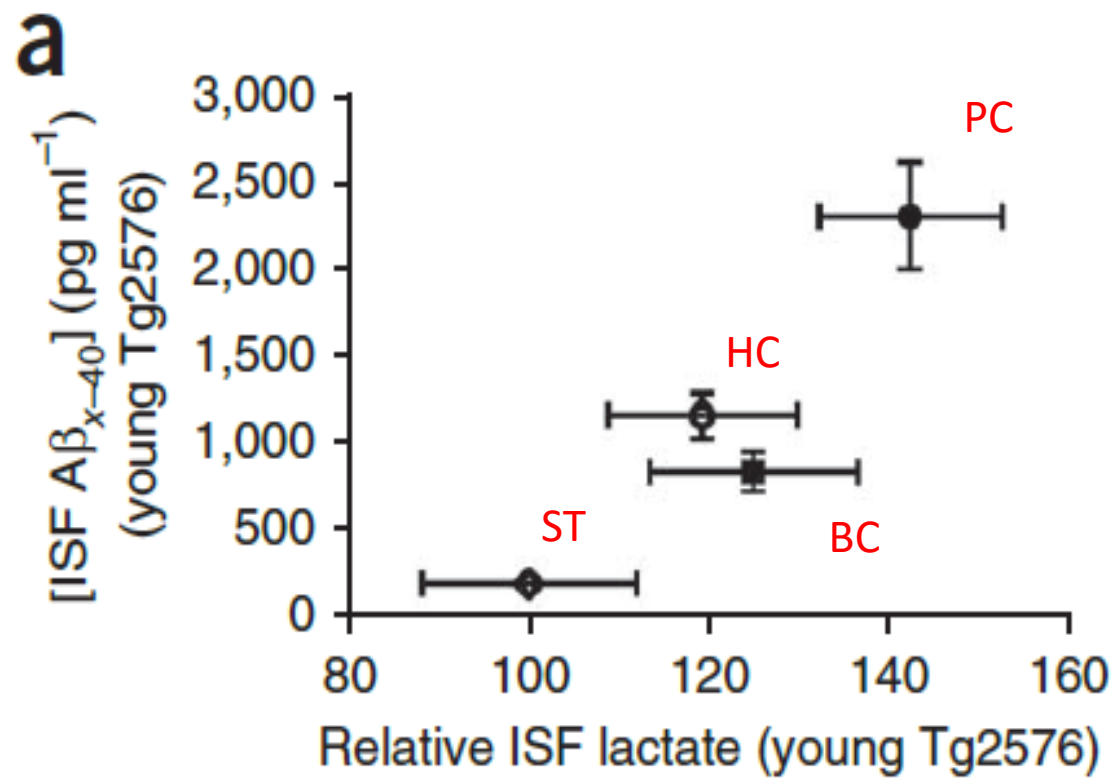
Does the regional pattern of A β match that of basal neural activity?

- Electrophysiological and pharmacological validation of lactate as biomarker for neural activity in hippocampus
- *In vivo* microdialysis measurements of ISF lactate and ISF A β



PTX = picrotoxin ($GABA_A$ receptor antagonist)

TTX = tetrodotoxin (voltage-gated sodium channel blocker)

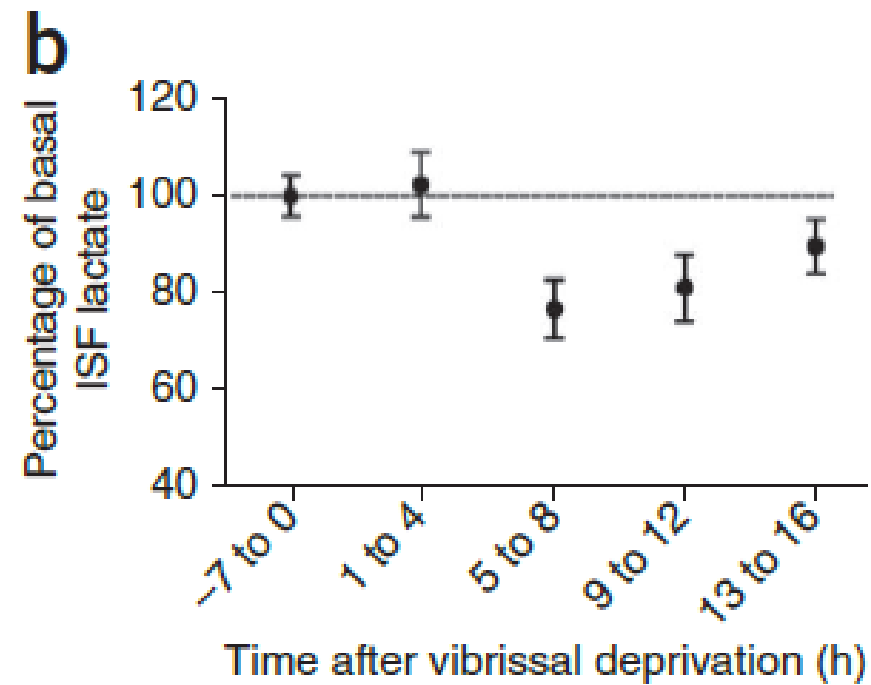
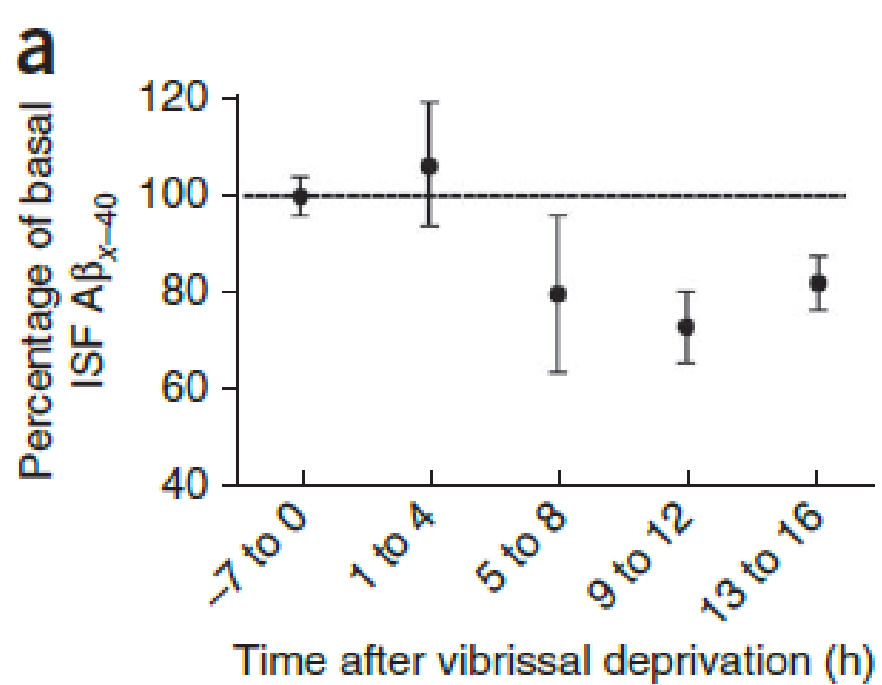


Interpretation

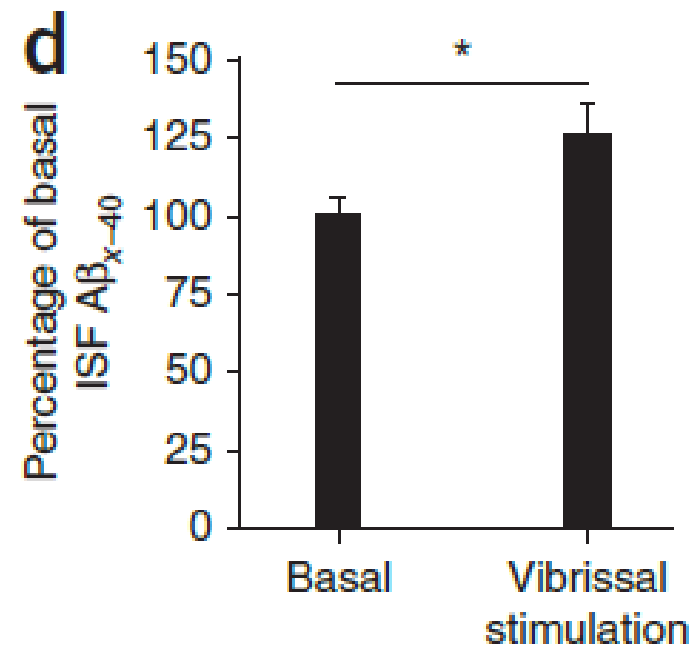
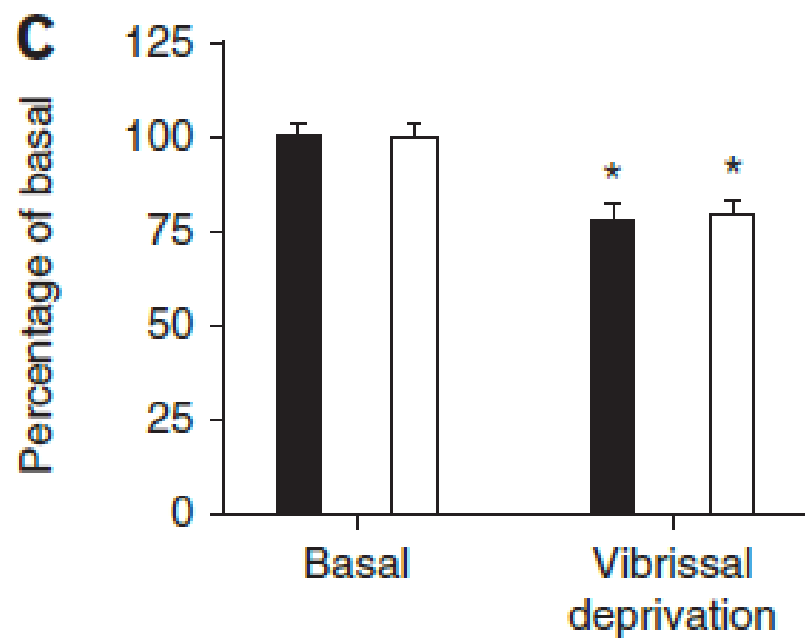
- ISF lactate is a valid biomarker of neuronal activity
- Regional lactate concentration predicts ISF A β and A β plaque deposition
 - Piriform outlier? Should look at more regions

Can neural activity be manipulated to affect lactate and A β ?

- Vibrissal stimulation/deprivation in young mice during *in vivo* microdialysis in contralateral barrel cortex
- Prolonged (28d) vibrissal deprivation in old mice & multi-photon *in vivo* microscopy to view plaque growth and formation

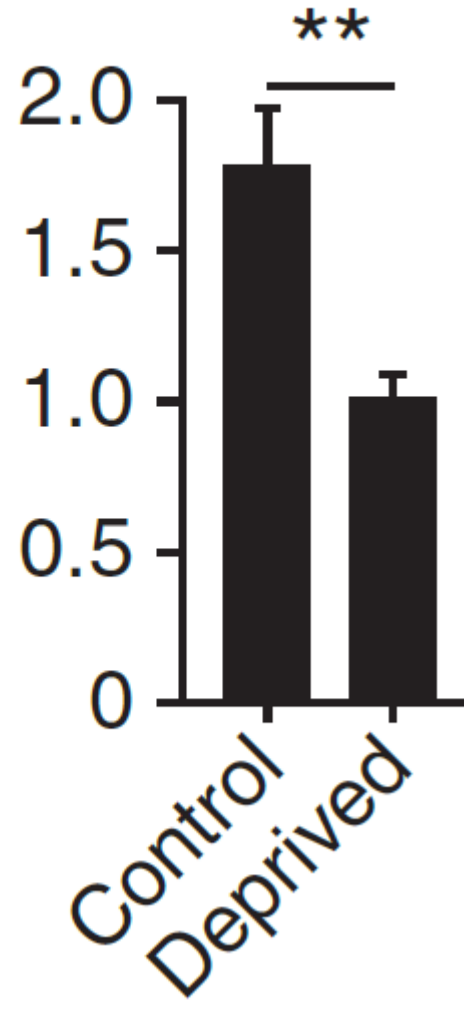


ISF A β
 ISF lactate

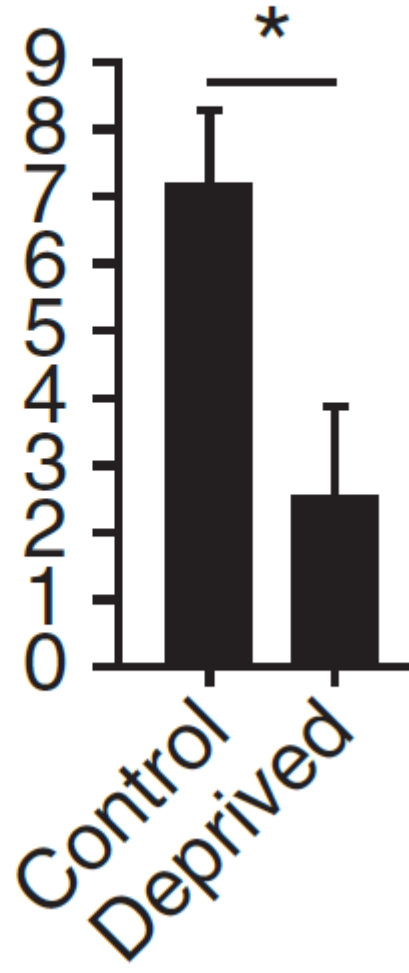


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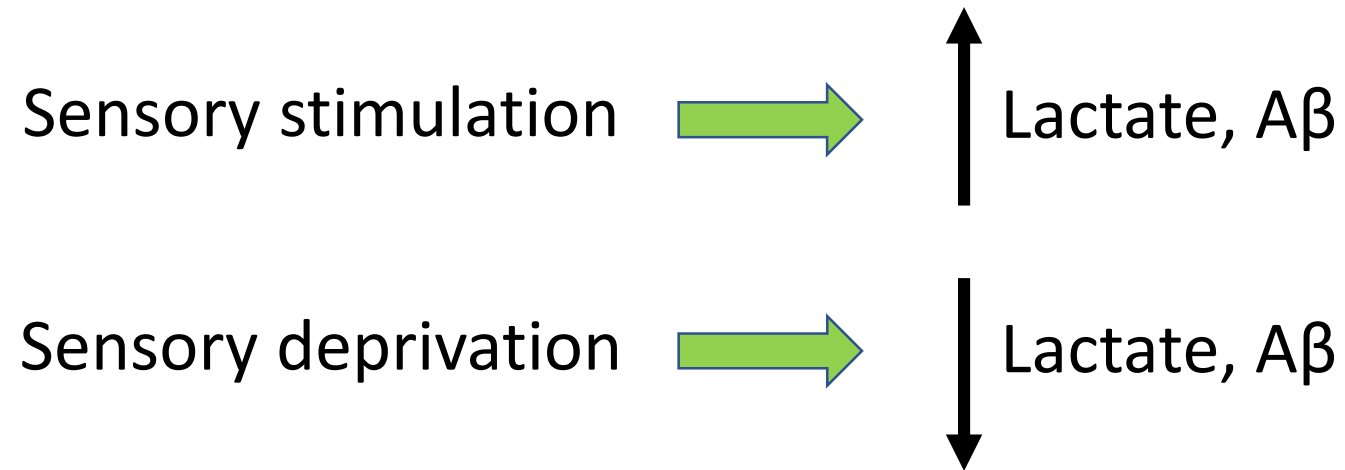
Mean plaque
growth (fold increase)

**f**
New plaque formation

(no. per mm³)

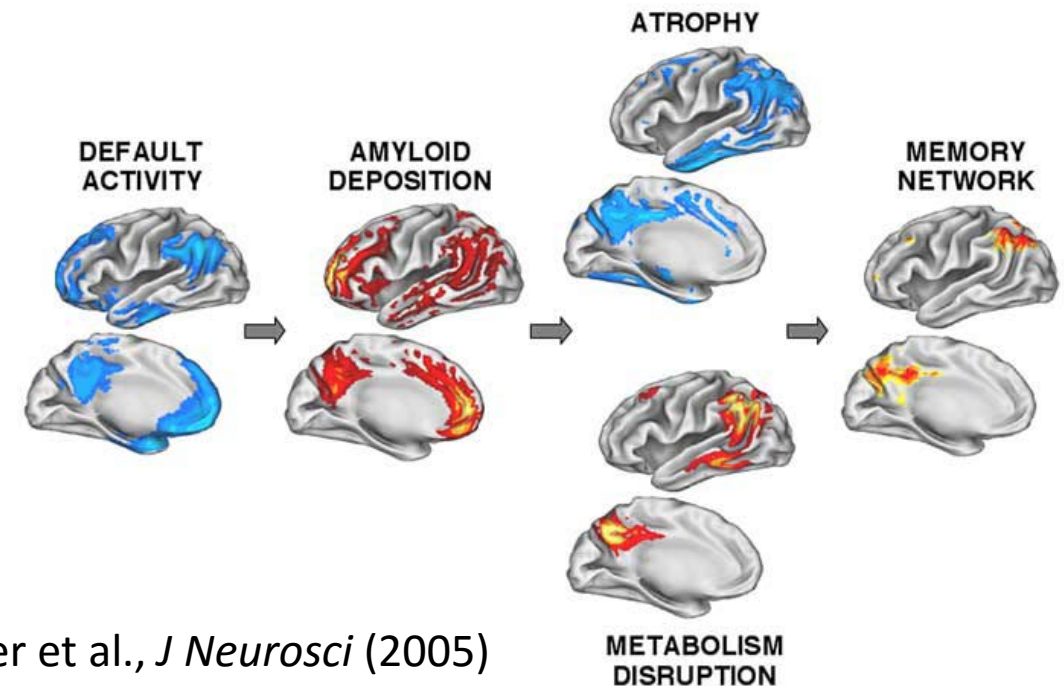


Interpretation



Conclusions

- ISF lactate (neural activity), ISF $A\beta$ and eventual $A\beta$ deposition are closely associated
- Regional differences in baseline neural activity may determine region-specific vulnerability to $A\beta$ deposition



Buckner et al., *J Neurosci* (2005)

Future directions

- Role of brain aerobic glycolysis?
 - (i.e., continued glycolysis despite sufficient oxygen to undergo oxidative phosphorylation)
 - Produces lactate
 - Regional topography matches that of default mode network
- Inhibiting basal metabolic activity
 - Determine whether cognitive tasks can alleviate amyloid burden *in vivo*