Effects of Chronic Sleep Disruption on Hippocampal Tau and Locus Coeruleus Projections

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Introduction

- **Chronic sleep disruption (CSD)** leads to neural responses consistent with early **Alzheimer's Disease (AD)**, common biomarkers being Aβ plaques and tau tangles.
- Using a mouse model with **humanized amyloid precursor protein knocked-in (HAβ-KI)**, we can explore the effects of sleep loss on human APP and the downstream effects on tau.[1]
- The **locus coeruleus (LC)** is the earliest site in the brain to have tau phosphorylation and is injured by sleep loss. The **CA1** region of the **hippocampus (HC)** is also vulnerable to neurodegeneration and is made up of three layers: Oriens, Pyramidal, and Stratum Radiatum.

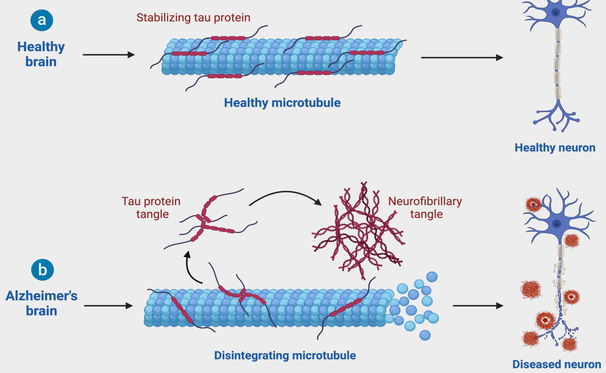


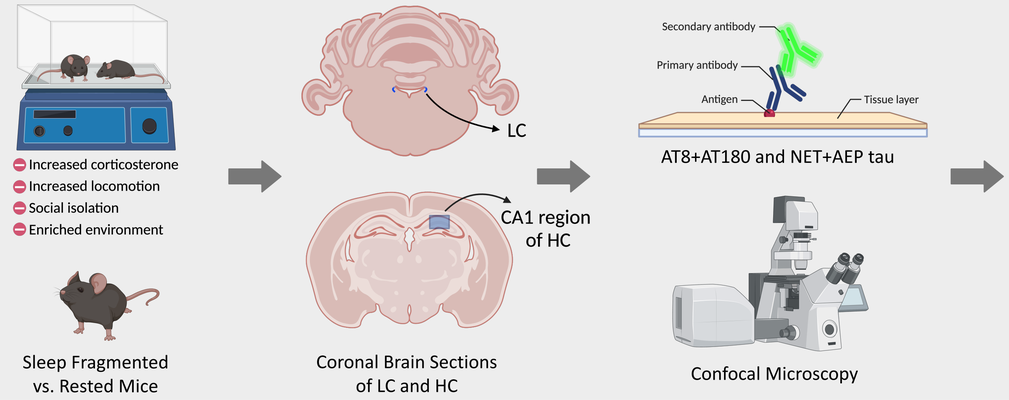
Figure 1. Tau is a protein that helps stabilize the internal skeleton of nerve cells (neurons) in the brain. In AD, an abnormal form of tau clings to other tau proteins inside the neuron and form tau tangles. Neurofibrillary tangles result from hyperphosphorylated tau that accumulates in specific brain regions involved in memory. **Asparagine endopeptidase (AEP)** is an age-dependent cysteine protease highly activated in AD patients and cleaves tau at both N255 and N368 promoting its aggregation.[2] Tau is expressed in neurons and mainly distributed in axons.

Hypotheses

Q: Do **locus coeruleus (LC)** projections into forebrain areas, specifically the **hippocampus (HC)**, show greater dilations with **sleep fragmentation (SF)**?

1. LC neurons will be more susceptible to sleep loss injury in HAβ-KI mice.
2. Tau phosphorylation and cleavage will be more accentuated in HAβ-KI mice.

Methods



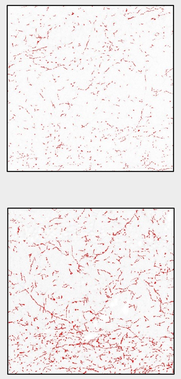
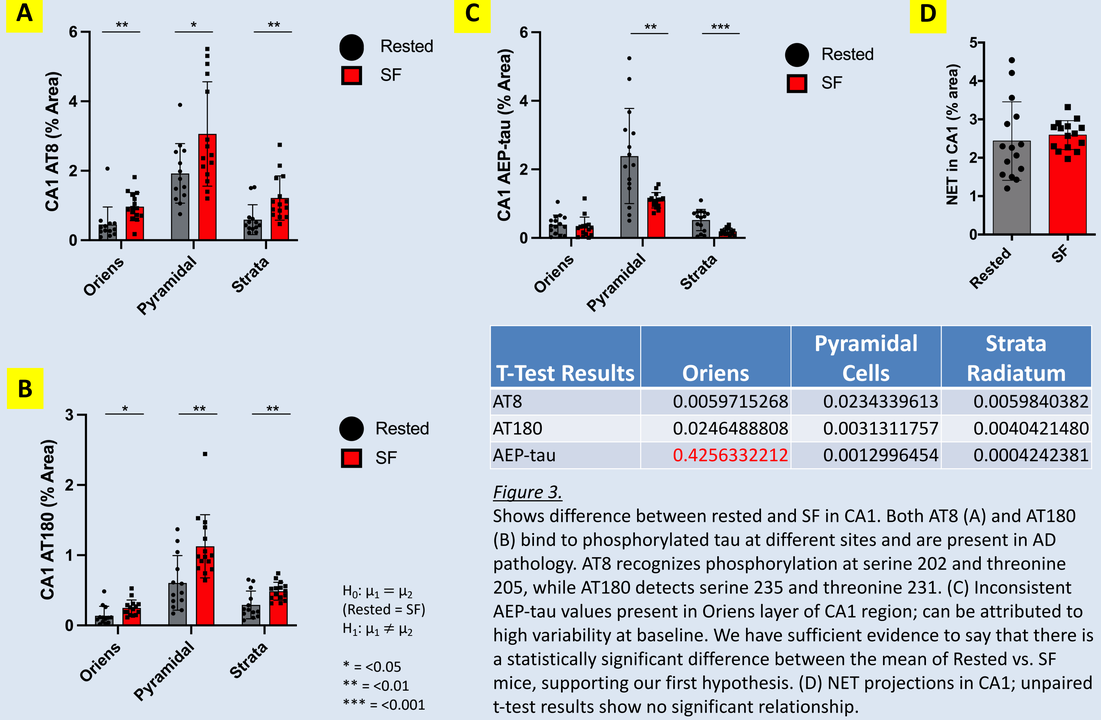


Figure 2.
Final edited images from ImageJ. Initially taken using the confocal microscope. Comparison of NET projections fragmented (top) vs. unfragmented (bottom). Blind to whether the images were of SF or Rested mice.

The percentage area of CA1 regions stained using AT8, AT180, and AEP tau antibodies was calculated using ImageJ, an open-source image processing software. Each of the layers (Oriens, Pyramidal, Stratum Radiatum) were highlighted separately. The NET projections were calculated through a program coded with Python.

Results



T-Test Results	Oriens	Pyramidal Cells	Strata Radiatum
AT8	0.0059715268	0.0234339613	0.0059840382
AT180	0.0246488808	0.0031311757	0.0040421480
AEP-tau	0.4256332212	0.0012996454	0.0004242381

H_0: $\mu_1 = \mu_2$ (Rested = SF)
H_1: $\mu_1 \neq \mu_2$

* = <0.05
** = <0.01
*** = <0.001

Figure 3.
Shows difference between rested and SF in CA1. Both AT8 (A) and AT180 (B) bind to phosphorylated tau at different sites and are present in AD pathology. AT8 recognizes phosphorylation at serine 202 and threonine 205, while AT180 detects serine 235 and threonine 231. (C) Inconsistent AEP-tau values present in Oriens layer of CA1 region; can be attributed to high variability at baseline. We have sufficient evidence to say that there is a statistically significant difference between the mean of Rested vs. SF mice, supporting our first hypothesis. (D) NET projections in CA1; unpaired t-test results show no significant relationship.

**2-tail distribution & two-sample equal variance (homoscedastic) test was performed for graphs (A), (B), and (C).*

Conclusion

- **CSD results in early phosphorylation of tau in CA1 but does not increase AEP cleaved tau suggesting that the phosphorylated tau cannot be attributed to CA1 AEP activation.**
- CSD does not influence NET %Area in CA1.
- Future directions include determining how significant APP is in the LC relating to sleep loss. We can also compare mouse vs. human results in tau as we can expect to see differences in tau phosphorylation and tau processing.

References

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