Synaptic Change, Sleep, and Pathological Analyses in Alzheimer's Disease

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INTRODUCTION

- Alzheimer's disease (AD) is a progressive neurodegenerative disease impacting millions.
- Aside from cognitive changes, patients often report changes in sleep patterns.
- Sleep is an essential function and is connected to the clearance of debris in the brain and allows for memory consolidation.
- Amyloid-Beta and Tau protein, the main AD pathology, have been found to fluctuate in response to the sleep-wake cycle.
- Neuroinflammation increases in response to accumulation of proteins in the brain.
- We looked at a human tau model mouse (PS19) and an amyloid model mouse (5xFAD) to understand if AD pathology influences sleep changes or vice versa.

RESULTS

1 PS19 MICE SHOW LOWER AMOUNTS OF DARK SLEEP

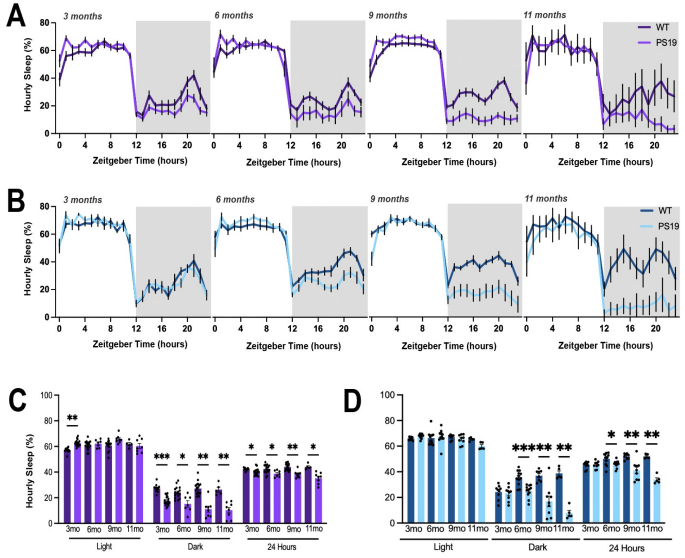

Figure 1. Hourly sleep differs between wildtype and PS19 mice with age. (A-B) Sleep trace of average hourly sleep across 24hours of 3-11 months old females and males. (C-D) quantification of total hourly sleep per day for females and males *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001, ****p-value < 0.0001.

2 PS19 FEMALE SYNAPSES SHOW UPREGULATION AFTER CHRONIC SLEEP DISRUPTION

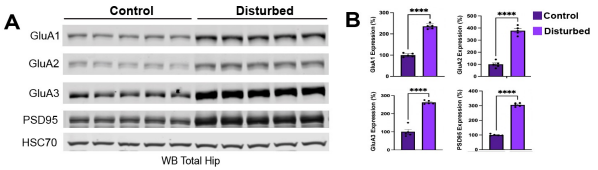

Figure 2. Chronic sleep disruption in PS19 Female Hippocampus. (A) WB analysis of total hippocampal synapses after chronic sleep disruption (CSD) of WT and PS19 female mice. (B) Quantification of synaptic expression. ****p-value < 0.0001.

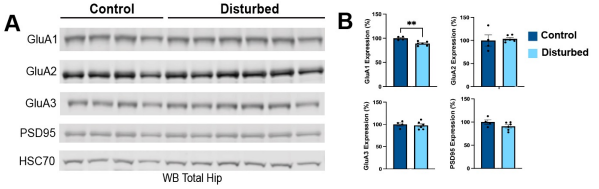

Figure 3. Chronic sleep disruption in PS19 Male Hippocampus. (A) WB analysis of total hippocampal synapses after chronic sleep disruption (CSD) of WT and PS19 male mice. (B) Quantification of synaptic expression. **p-value < 0.01, ****p-value < 0.0001.

3 MALE 5xFAD ANIMALS HAVE LATE STAGE DARK SLEEP BREAKDOWN COMPARED TO WILDTYPE

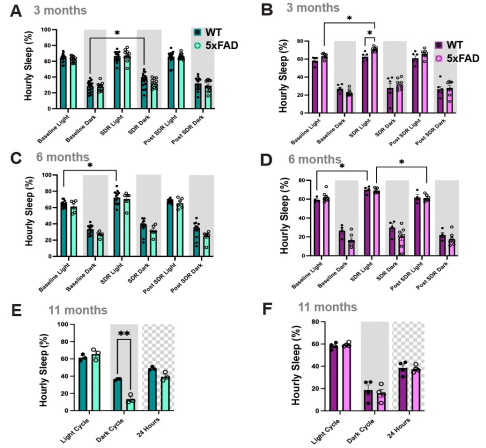

Figure 4. Sleep Behavior Quantification of 5xFAD mice. (A-B) Hourly sleep percentage of 3-month WT and 5xFAD males and females from baseline, sleep deprivation recovery (SDR) and Post-SDR. (C-D) Hourly sleep percentage of 6-month animals from baseline, SDR and Post-SDR. (E-F) Hourly sleep percentage of 11-month animals from baseline. *p-value < 0.05, **p-value < 0.01.

4 5xFAD ANIMALS SHOW TRENDS OF INCREASED INFLAMMATION

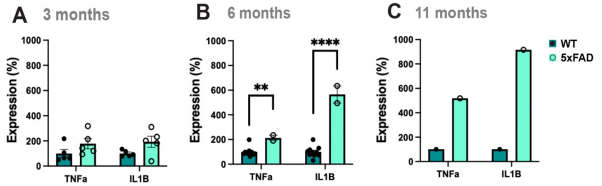

Figure 5. Increased Inflammation in Male 5xFAD Mice. Total hippocampal samples show trends of increased TNFα and IL1B at 3-, 6-, and 11-month old male 5xFAD mice with significance at 6-months. **p-value < 0.01, ****p-value < 0.0001.

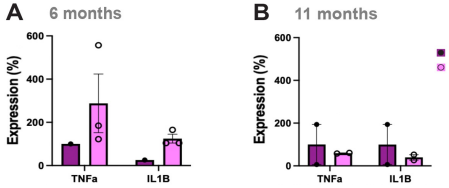

Figure 6. Inflammation Occurs in Young-Aged Female 5xFAD Mice. Total hippocampal samples show trends of increased TNFα and IL1β at 6-months-of age, but are decreased in 11-month old female 5xFAD mice.

CONCLUSIONS

- PS19 male and female mice sleep less that their WT littermate controls with onset of sleep disruption at 3 months in females but at 6 months in males.
- PS19 females show upregulation in synaptic properties after chronic sleep disruption while males do not.
- Young 5xFAD animals do not show a differing homeostatic sleep drive compared to WT animals.
- Older 5xFAD males show a breakdown in dark sleep while females do not.
- 5xFAD males show increased inflammation at all ages.
- 5xFAD females show increased inflammation at 6-months but not 11-months of age.
- Overall we believe that PS19 animals may experience sleep changes that influence AD pathology while AD pathology influences sleep changes in 5xFAD animals.