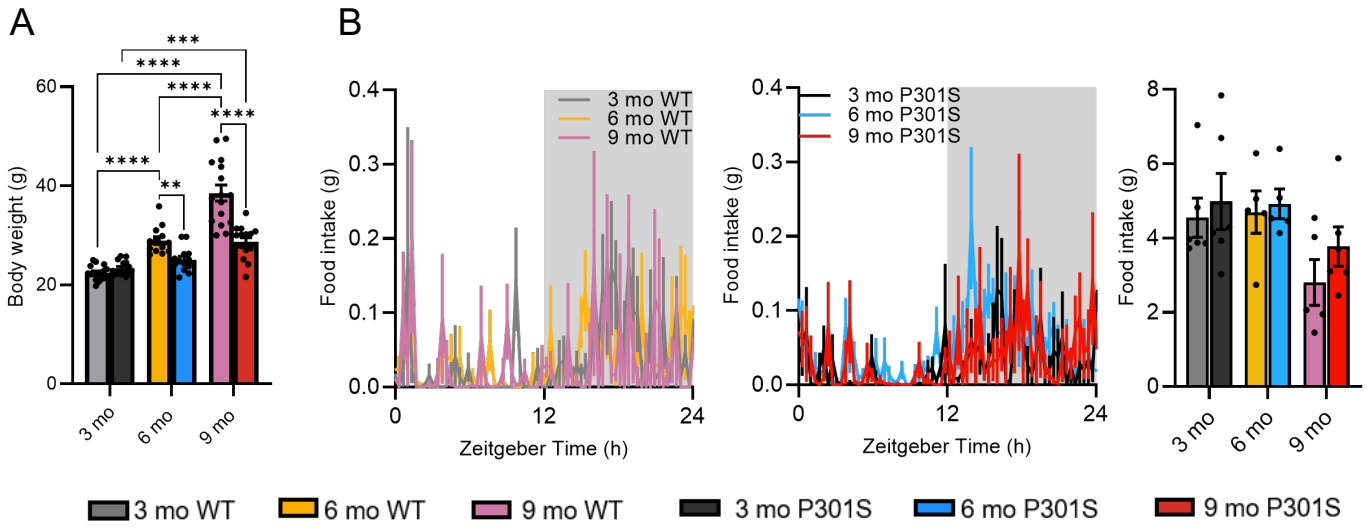
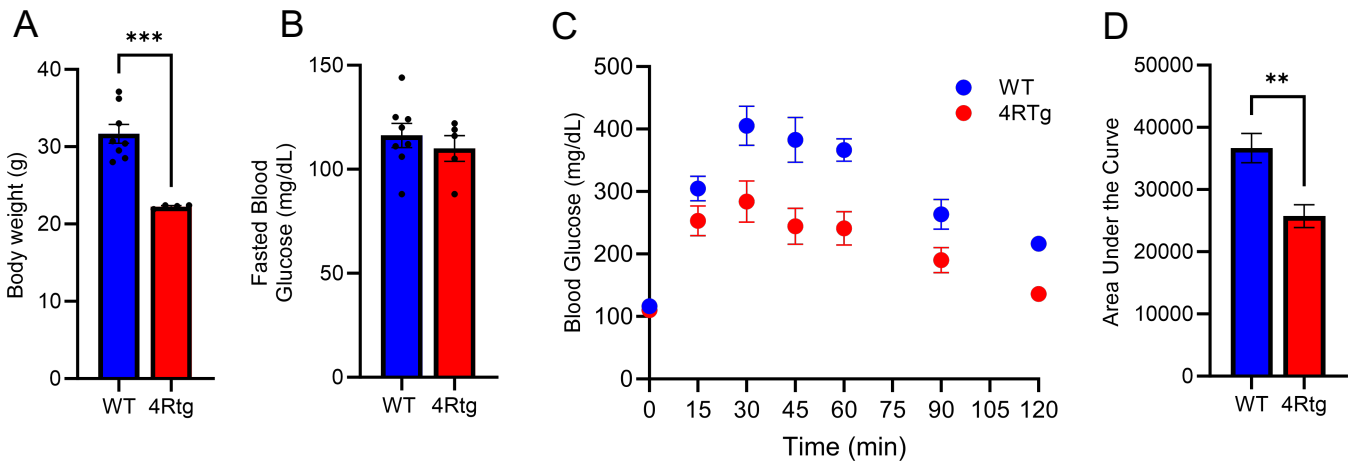
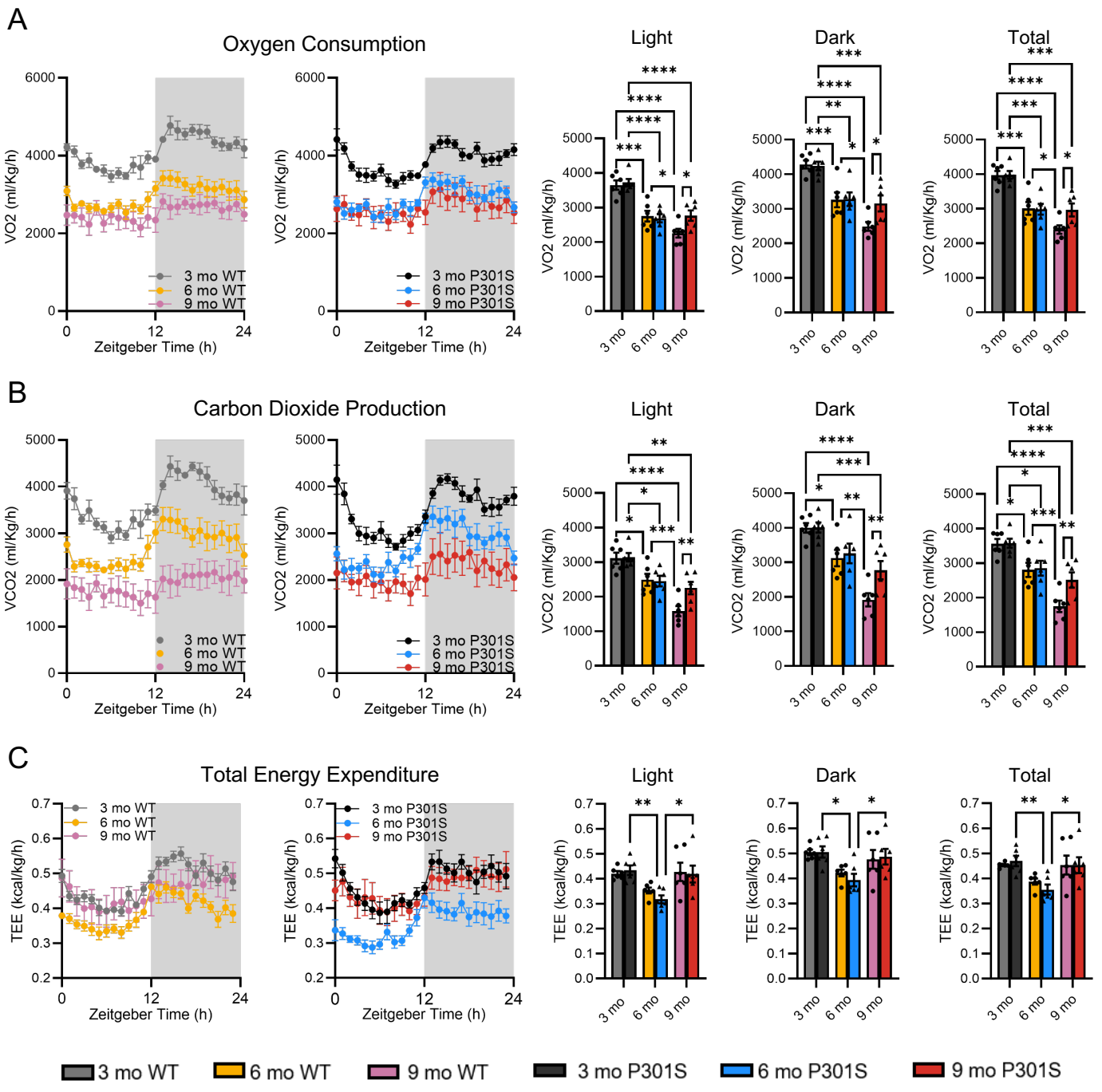
Supplementary Figures



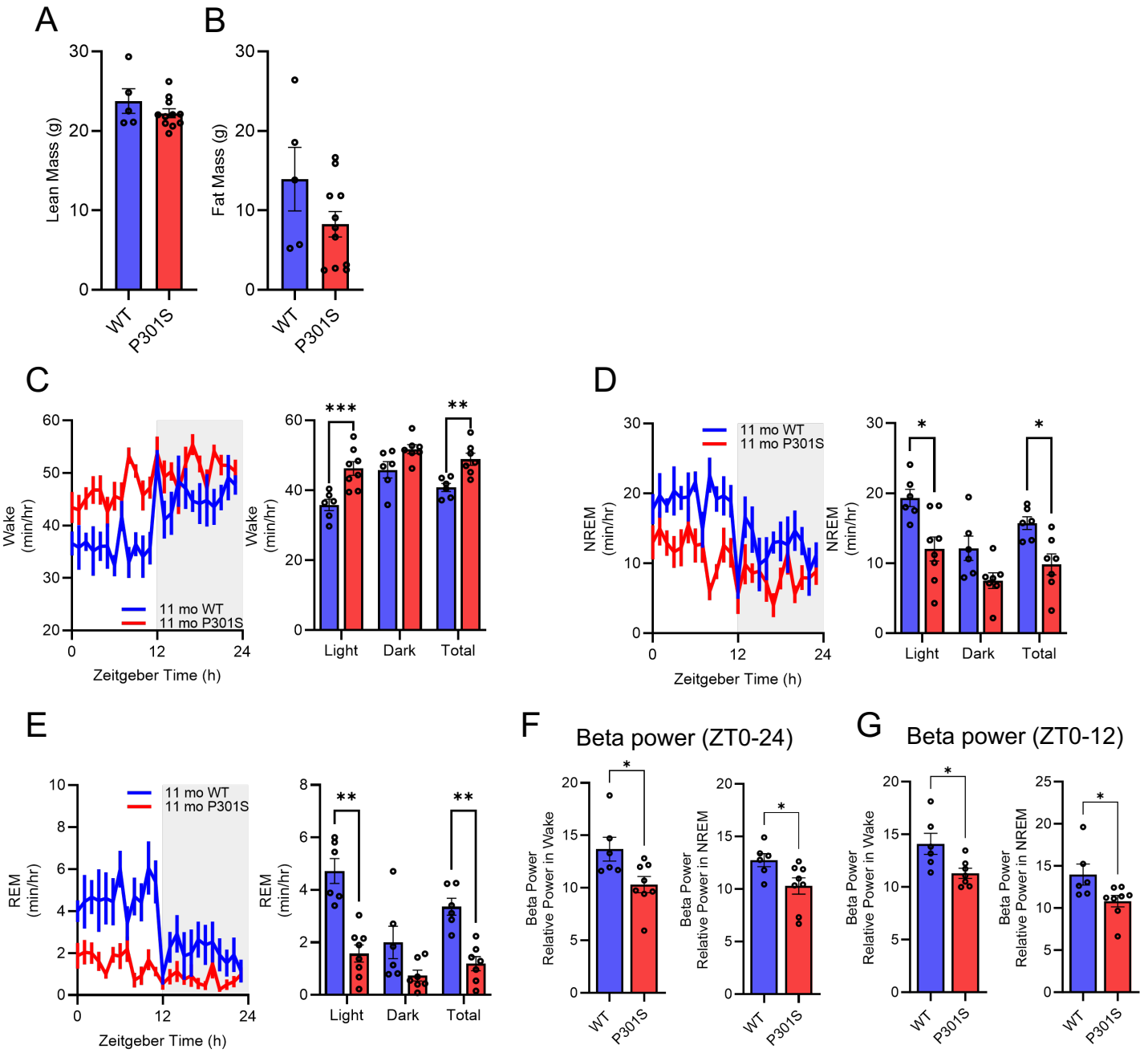
Suppl. Fig 1. Tau pathology decreases body weight despite no change in food intake. (A) WT mice gain weight in a step wise fashion from 3 to 9 months. There is no difference in body weight between 3- and 6 month in P301S mice. By 9 months, P301S mice weigh less than age matched WT mice. (B) P301S and WT mice exhibit no change in food intake with age, despite differences in body weight. Statistical significance was determined using a two-way ANOVA with Tukey's post-hoc tests. Data is represented by means ± SEM. *n* = 9-12 mice/group *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001



Suppl. Fig 2. (A) 13 month 4RTg2652 mice weigh significantly less than age matched controls. (B) Fasting blood glucose levels were unchanged between 4Rtg and control mice. (C) 4RTg mice exhibited increased glucose tolerance compared to age matched controls as shown within the GTT curve by decreased peak and shorter tail. (D) Area Under the Curve indicated increased blood glucose levels in control mice compared to 4RTg mice. Significance determined by unpaired t-tests and two-way ANOVA with Sidak's post-hoc corrections. *n* = 5-8 mice/group. Data is represented by means ± SEM. *p<0.05, **p<0.01, ***p<0.001



Suppl. Fig 3. Tau pathology slows age dependent decreases in whole body metabolic characteristics. (A) As WT and P301S mice age, they exhibit decreased oxygen consumption (VO2) over the entire 24-hour period. However, 9-month-old P301S mice exhibit increased VO2 compared to WT mice. (B) As WT and P301S mice age, they exhibit decreased carbon dioxide production (CO2) over the entire 24-hour period. However, 9-month-old P301S mice exhibit increased VCO2 compared to WT mice. (C) At 6-months-old, P301S mice exhibit decreased total energy expenditure (TEE) compared to 3- and 9-month-old P301S mice at all times of day. Data reported as means ± SEM. *n* = 9-12 mice/group. Significance determined using two-way ANOVA with Tukey's post-hoc correction. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001



Suppl. Fig 4. Time spent in NREM and REM and beta power are reduced in 11 month old P301S mice despite no changes in body composition. (A,B) Body composition of lean and fat mass are unchanged in 11 month old P301S mice compared to age matched controls. At late stages of tau pathology and neurodegeneration, sleep/wake and power spectral impairments mirror the effects seen at 9 months in P301S mice. (C-E) 11 month old P301S mice exhibit increased time spent in wake and decreased time spent in NREM and REM driven by changes in the light period. (F,G) Beta EEG power is reduced in 11 month old P301S mice compared to age matched controls across the 24 hour period and during the light period during wake and NREM. Statistical significance was determined using two-way ANOVA with Sidak's post-hoc tests and unpaired t-tests. *n* = 5-11 mice/group. Data is represented by means ± SEM. *p<0.05, **p<0.01, ***p<0.001

A

ISF Glucose

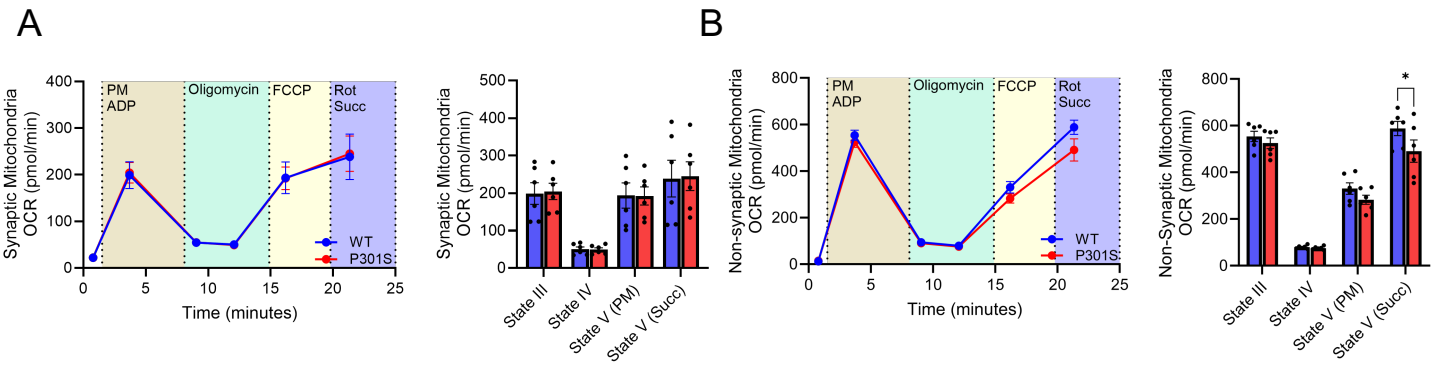
Genotype	Age (mo)	ADJ.P	Period	Lag	Amp
WT	3	3.17E-04	24	17	2.096
WT	6	1.09E-06	24	16	1.416
WT	9	5.5E-03	21	6	0.160
P301S	3	9.11E-06	24	15.5	1.237
P301S	6	5.79E-08	23	18	1.622
P301S	9	4.27E-03	24	19	0.918

B

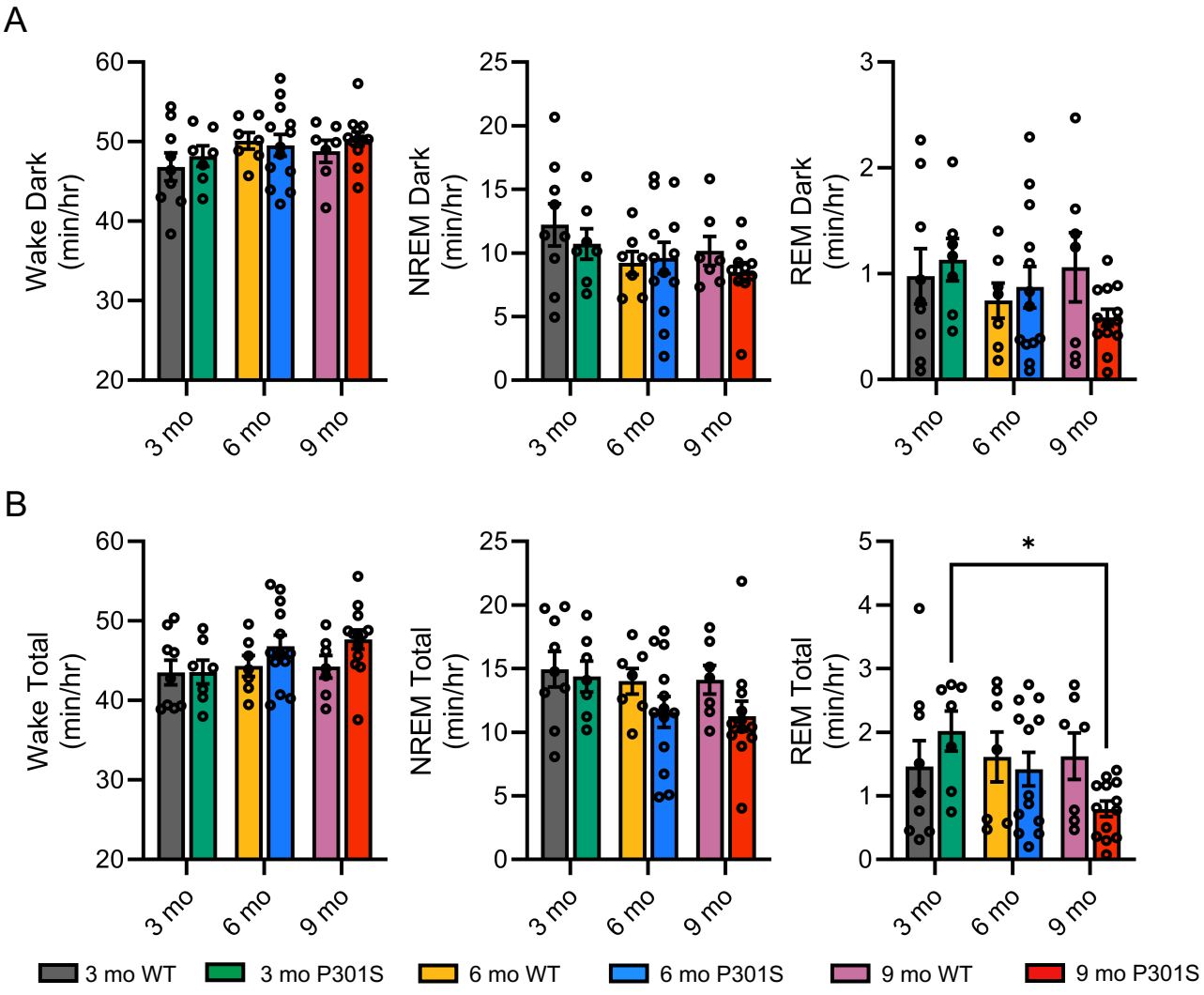
ISF Lactate

Genotype	Age (mo)	ADJ.P	Period	Lag	Amp
WT	3	7.98E-04	24	16.5	2.186
WT	6	1.09E-06	24	15.5	1.435
WT	9	5.7E-02	24	17	0.321
P301S	3	8.98E-10	24	16	1.481
P301S	6	4.03E-06	23	17.5	0.920
P301S	9	9.79E-08	24	17	0.918

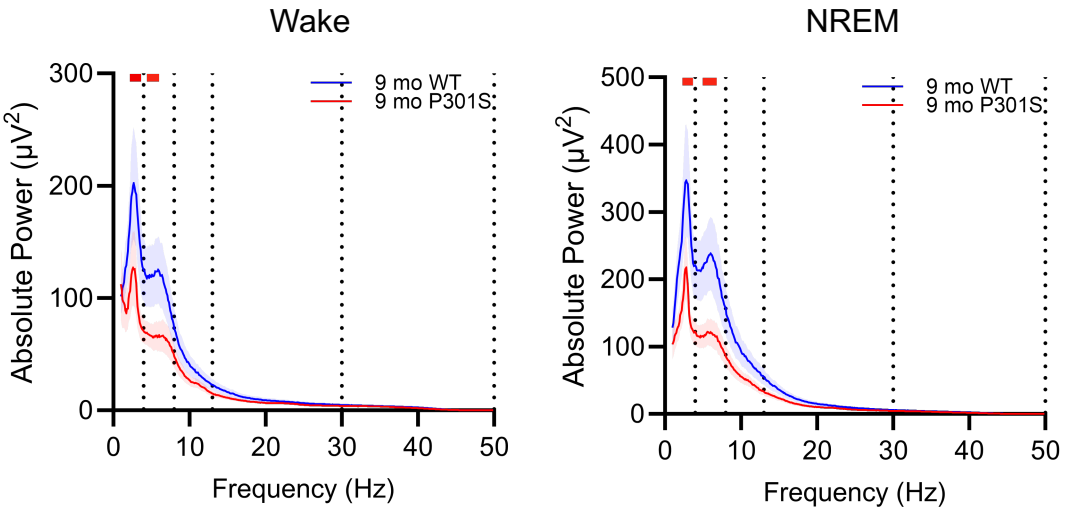
Supp. Table 1. JTK Analysis for ISF glucose and lactate rhythmicity. (A) JTK Analysis confirmed the presence of diurnal ISF glucose rhythms in 3-, 6-, and 9-month-old P301S and WT mice. While ISF glucose rhythmicity is maintained in 9 mo WT mice, lag analysis suggesting the rhythm peaks during the light period. (B) JTK analysis confirmed diurnal ISF lactate rhythms are lost in 9 month WT mice but not P301S mice at any age. *n* = 6-10 mice/group. ADJ.P = adjusted p-value, Period = length of cycle, Lag = ZT time of peak, Amplitude = peak expression.



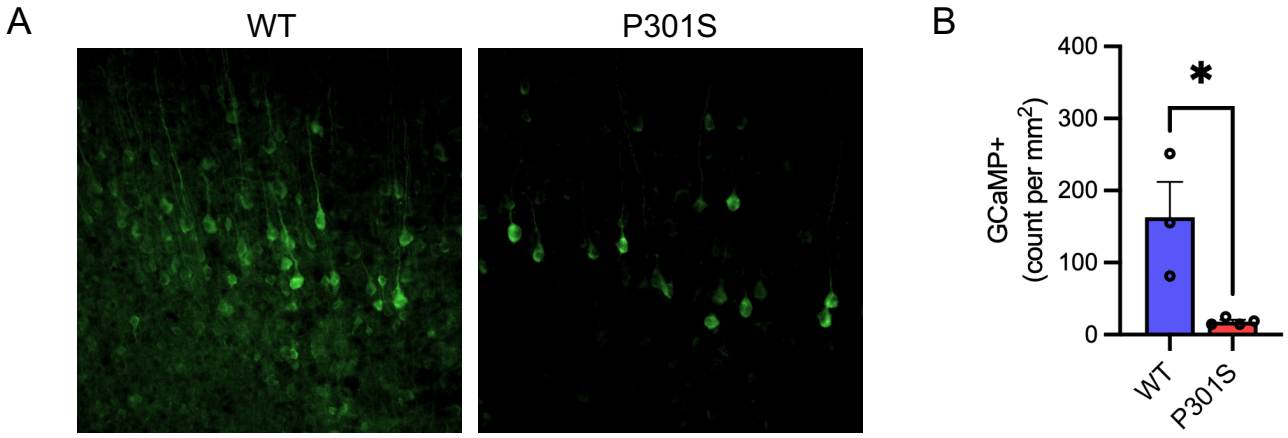
Suppl. Fig 5. Oxygen consumption rate is maintained in synaptic mitochondria, but is reduced at State V in non-synaptic mitochondria. (A) P301S mice show no alterations in mitochondrial oxygen consumption (OCR) in isolated synaptic mitochondria compared to WT controls. (B) Oxygen consumption rate (OCR) is decreased in 9-month P301S mice in non-synaptic mitochondria, including mitochondria found in the neuronal soma and glia, during State V respiration. State V typically is associated with oxygen-limited respiration. Statistical significance was determined using a two-way ANOVA with Tukey's post-hoc tests. *n* = 6 mice/group. Data is represented by means ± SEM. *p<0.05.



Suppl. Fig 6. Time spent in wake, NREM, and REM is unchanged during the dark period and across the 24 hour period. (A) Time spent in wake, NREM, and REM during the dark period (ZT12-24) is unchanged between P301S and WT mice. (B) Time spent in wake and NREM is unchanged across the 24 hour period between P301S and WT mice. Across the 24 hour period, 9 month P301S mice exhibit a reduction in time spent in REM compared to 3 month P301S mice. Statistical significance was determined using a two-way ANOVA with Tukey's post-hoc tests. *n* = 6-12 mice/group. Data is represented by means ± SEM. *p<0.05.



Suppl. Fig 7. Tau pathology reduces absolute power during wake and NREM. (A) Absolute power is reduced in 9 month P301S mice compared to age-matched controls during wake, most notably in delta and theta bands. (B) Absolute power is reduced in 9 month P301S mice compared to age-matched controls during NREM, most notably in delta and theta bands. Statistical significance was determined using a two-way ANOVA with Sidak's post-hoc tests. *n = 9* mice/group. Data is represented by means ± SEM. *p<0.05.



Suppl. Fig 8. (A) Representative images of GCaMP fluorescence from the cortex of 9 month Thy1-GCaMP; WT mice and Thy1-GCaMP; P301S mice. (B) When quantified, this results in a 92.5% reduction in GCaMP+ (counts per mm^2). Statistical significance was determined using an unpaired t test. Data is represented by means ± SEM. *$p<0.05$.