

Introduction

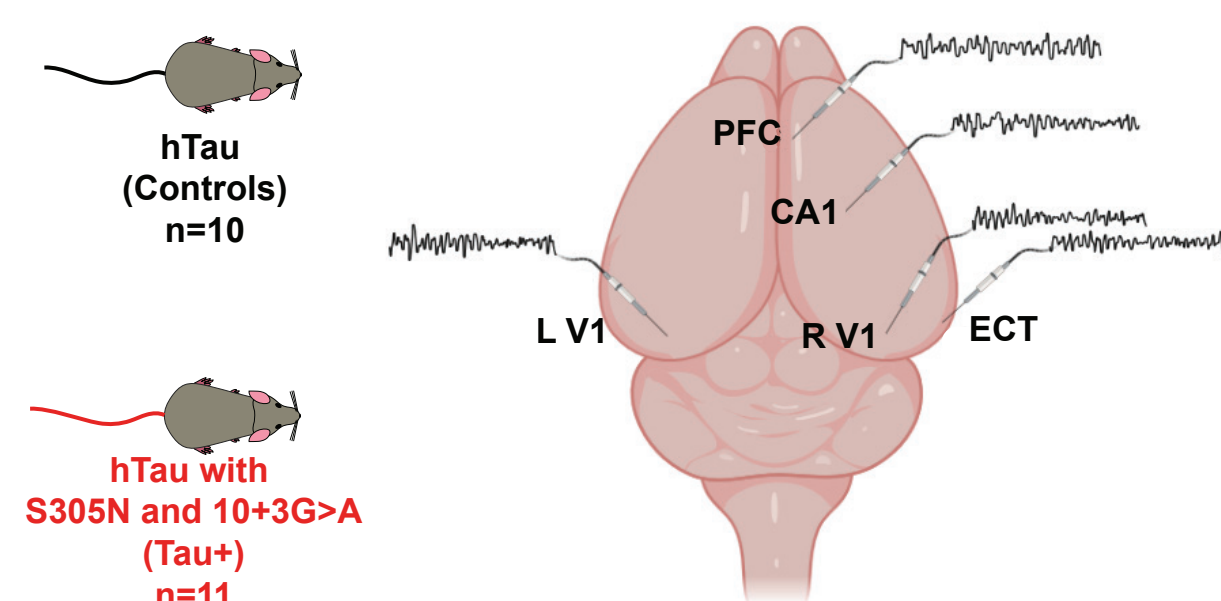
Dementia is commonly associated with malfunction of Tau protein, resulting in hyperphosphorylated aggregates in neurons. This causes synaptic dysfunction, neuronal hypoactivity, and neurodegeneration. In multiple mouse models, tauopathy results in increases in delta range activity, and reductions in theta and gamma power during resting state.

Newer mouse models of tauopathy have been generated by humanising the mouse MAPT gene, with or without familial mutations of frontotemporal dementia. Unlike previous overexpression models, humanised Tau (hTau) animals with mutations develop pathology at more advanced ages, providing a unique opportunity to evaluate the early impact of pathology on brain activity and behaviour.

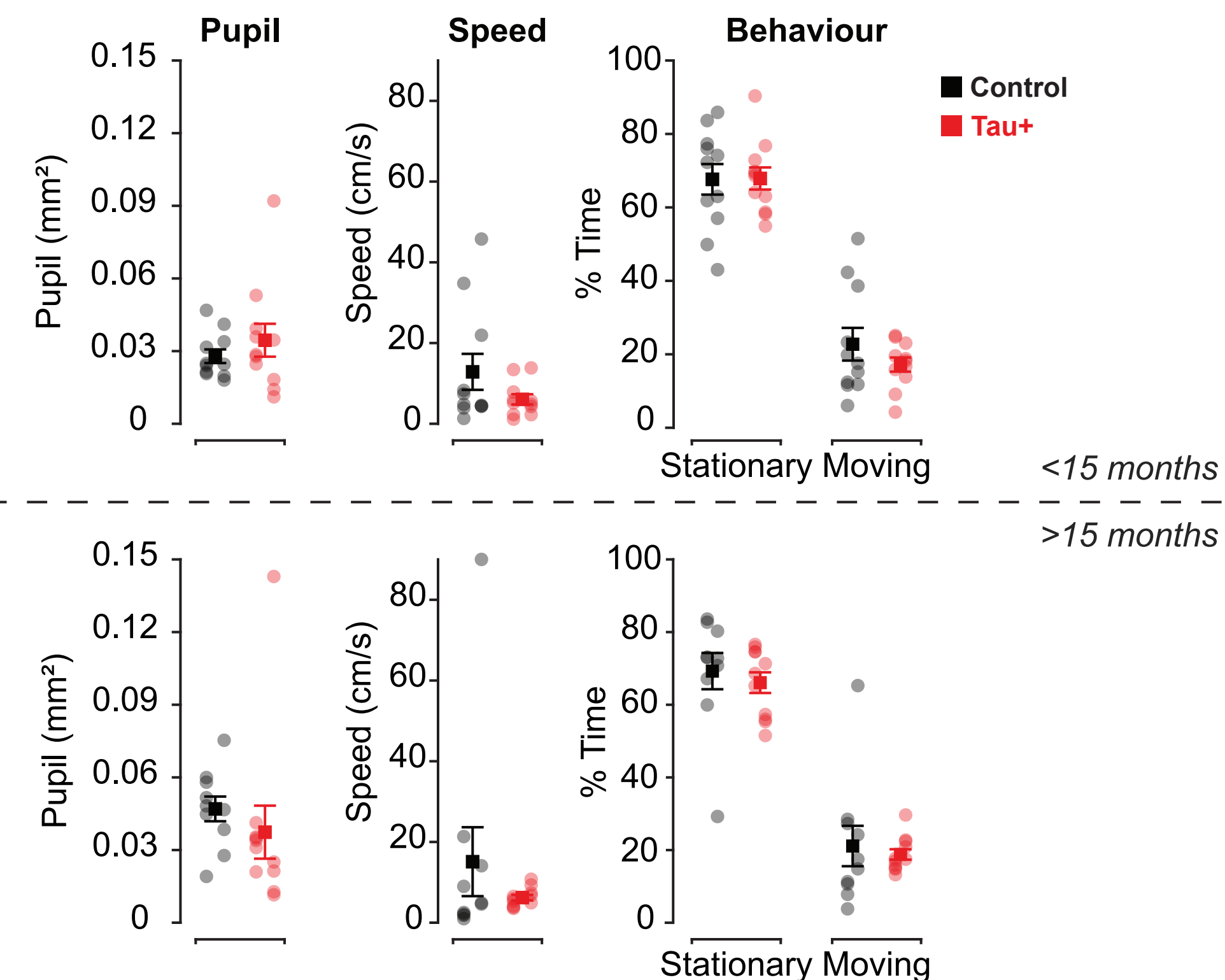
Here we evaluate how pathology progressively affects brain function in a humanised mouse model of fronto-temporal dementia, at multiple ages

Methods

We used humanised Tau (hTau) animals as Controls, and hTau animals carrying mutations associated with familial forms of frontotemporal dementia (Tau+). These animals have increased levels of phosphorylated Tau from about 15 months of age. Animals were implanted with local field potential (LFP) electrodes in pre-frontal cortex (PFC), CA1, left and right visual cortex (V1) and ectorhinal cortex (ECT), at 8-11 months, and recorded until 21 months of age. Speed of locomotion and pupil size were monitored throughout recording sessions. Data is presented as mean±sem, and individual animal values are represented by circles. All comparisons were made using a repeated measured mixed ANOVA, and post-hoc tests were Bonferroni corrected (*, p<0.05; **, p<0.01; ***, p<0.001).

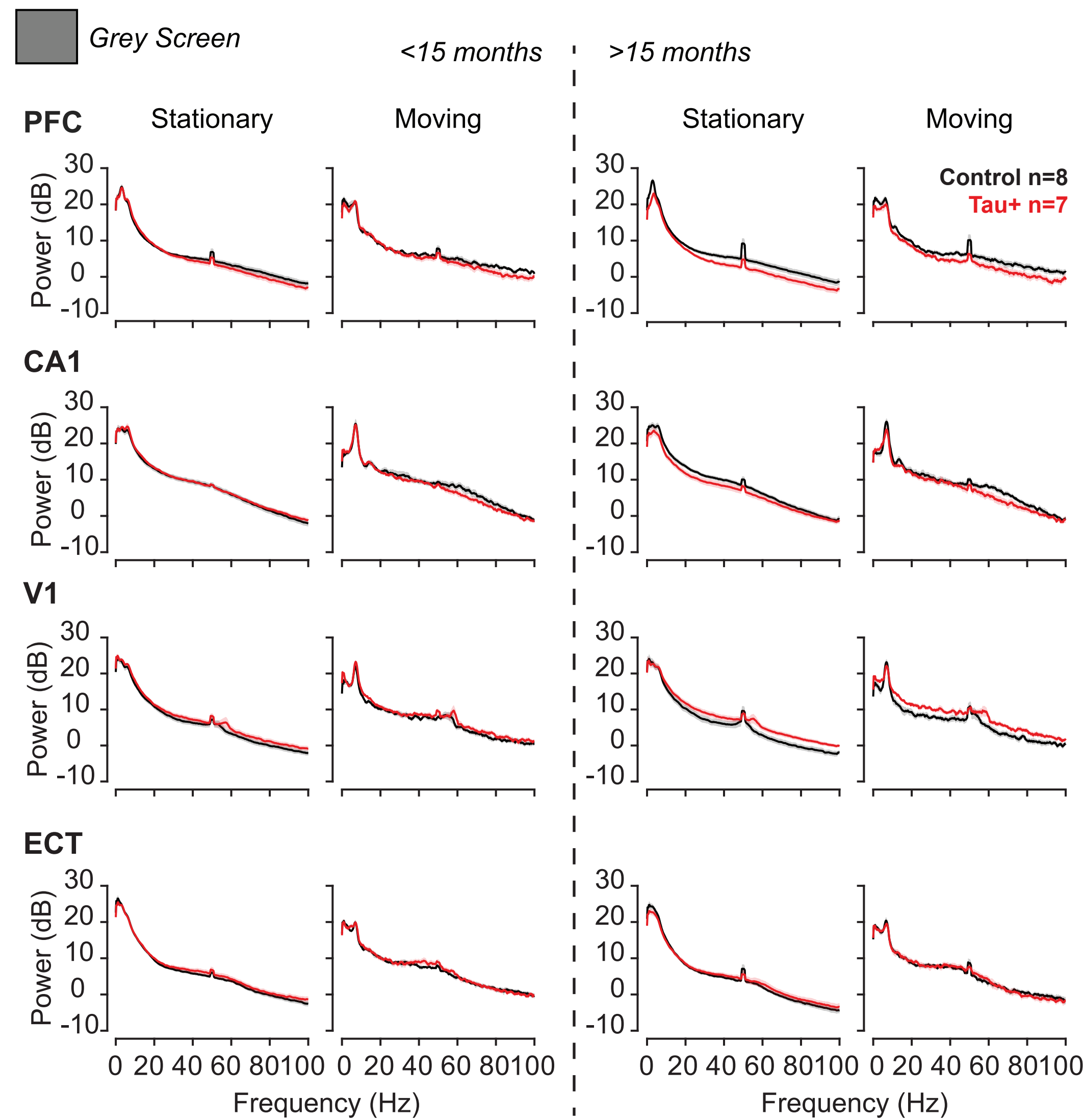


Behaviour dynamics of Control and Tau+ animals did not differ. Overall pupil area, speed of locomotion, and time spent in either moving or stationary states was similar between groups and across ages.



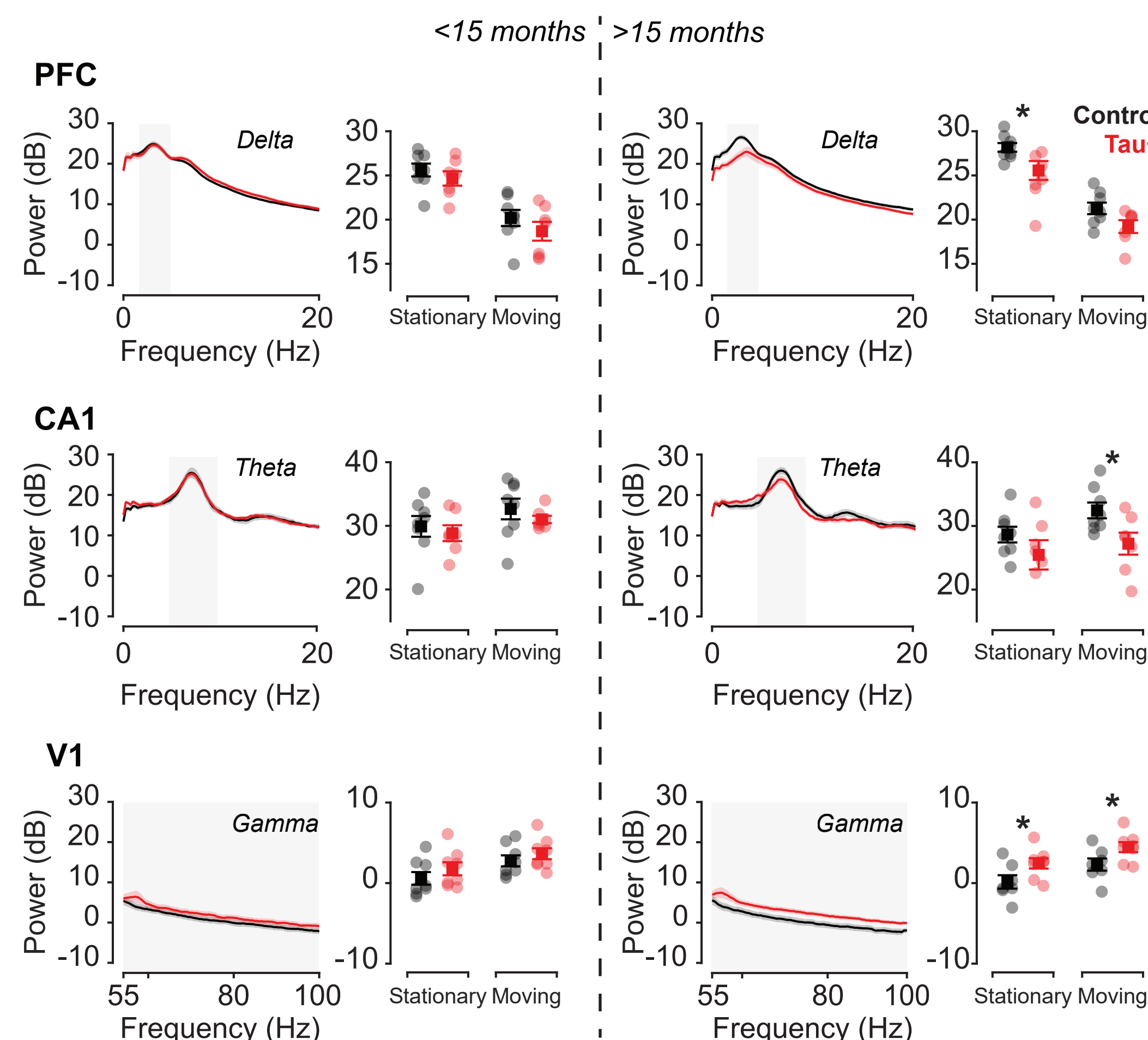
Power of brain rhythms in Tau+ animals progressively changes with ageing

Plots show mean±sem of power spectral densities before and after 15 months.

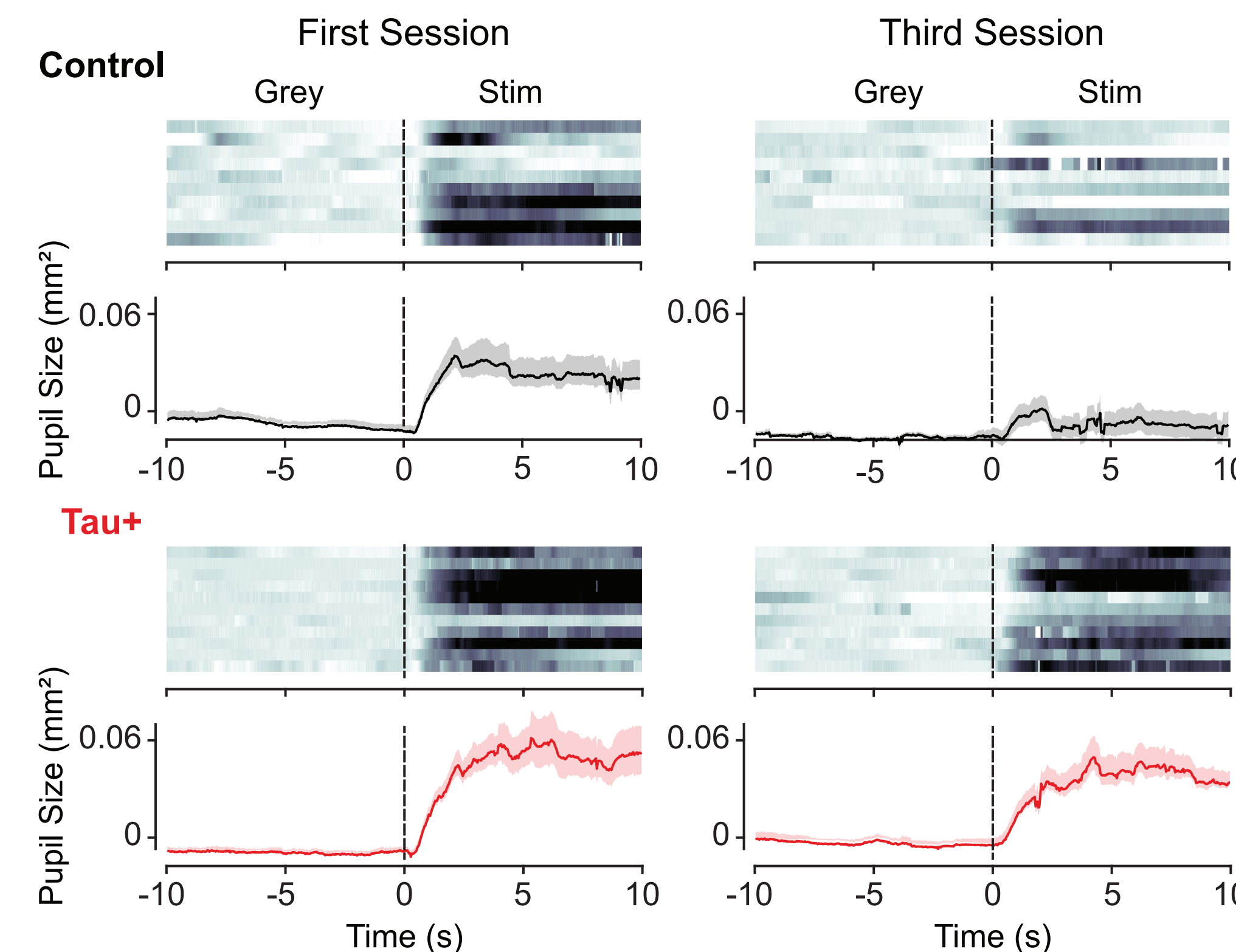


Changes in oscillations in Tau+ animals are specific to brain areas and behaviour states

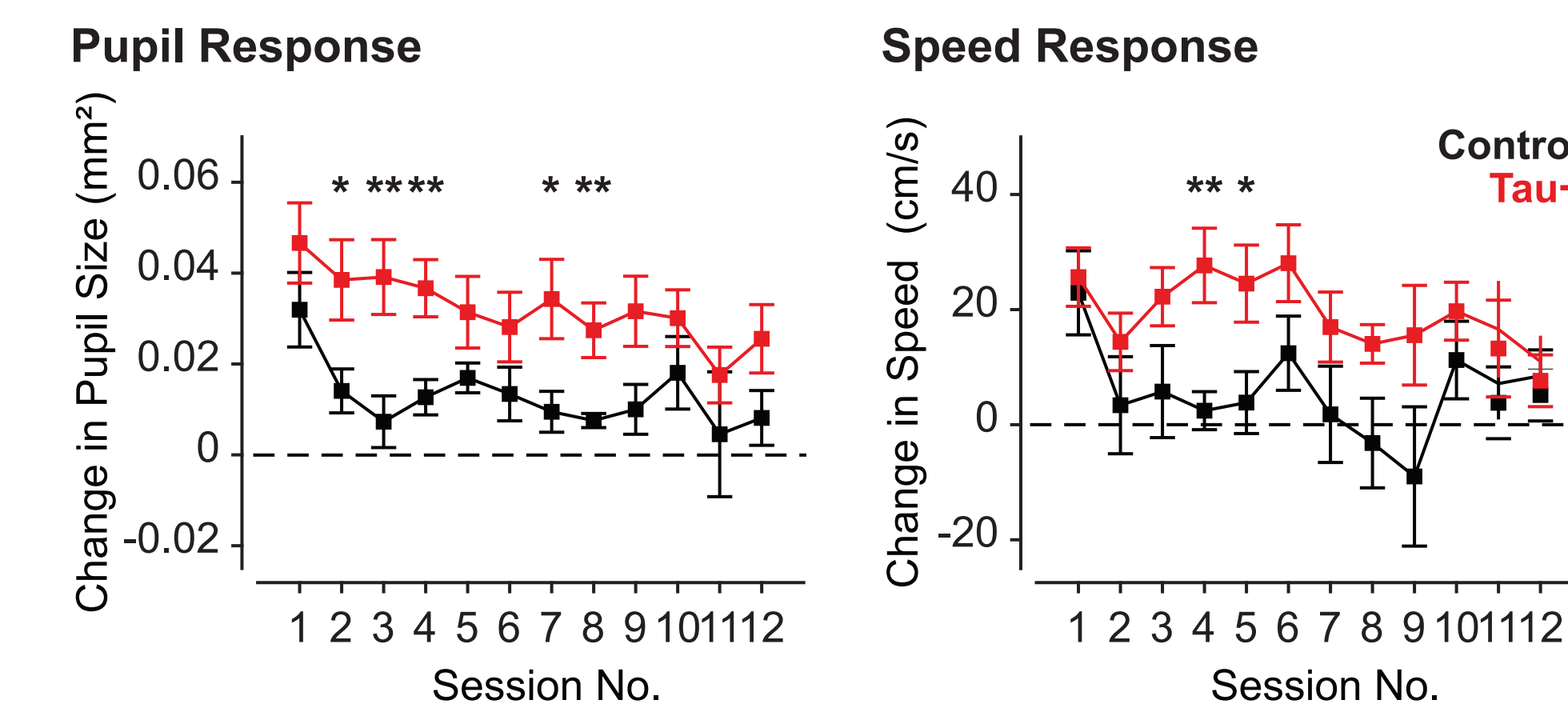
We quantified changes in rhythms across both groups and ages. Below are ranges and areas where we observed significant differences between Tau+ and Control animals.



Tau+ animals show less habituation to visual stimuli

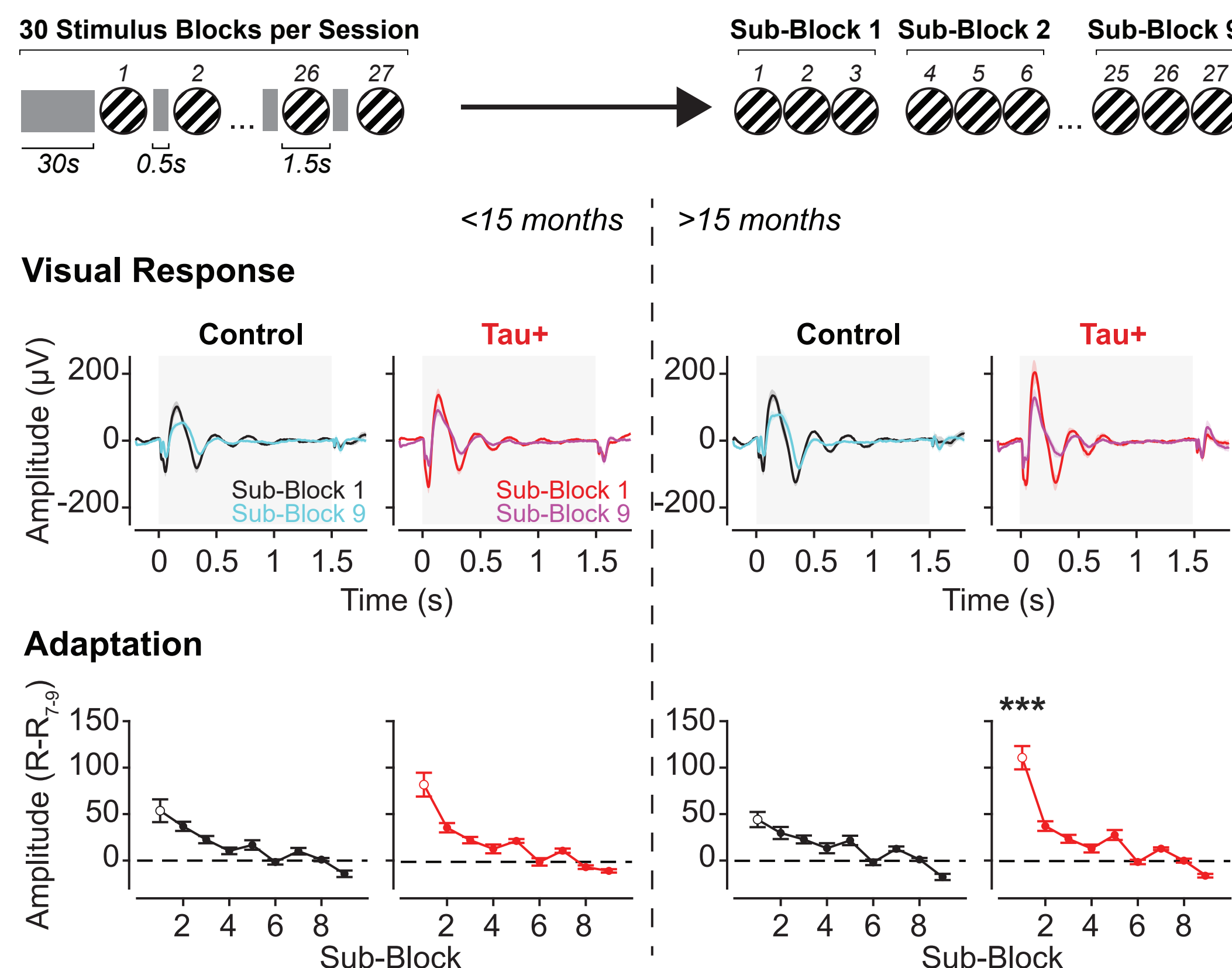


Pupil responses habituate in Control but not Tau+ animals. The same pattern was seen for locomotion responses (not shown).



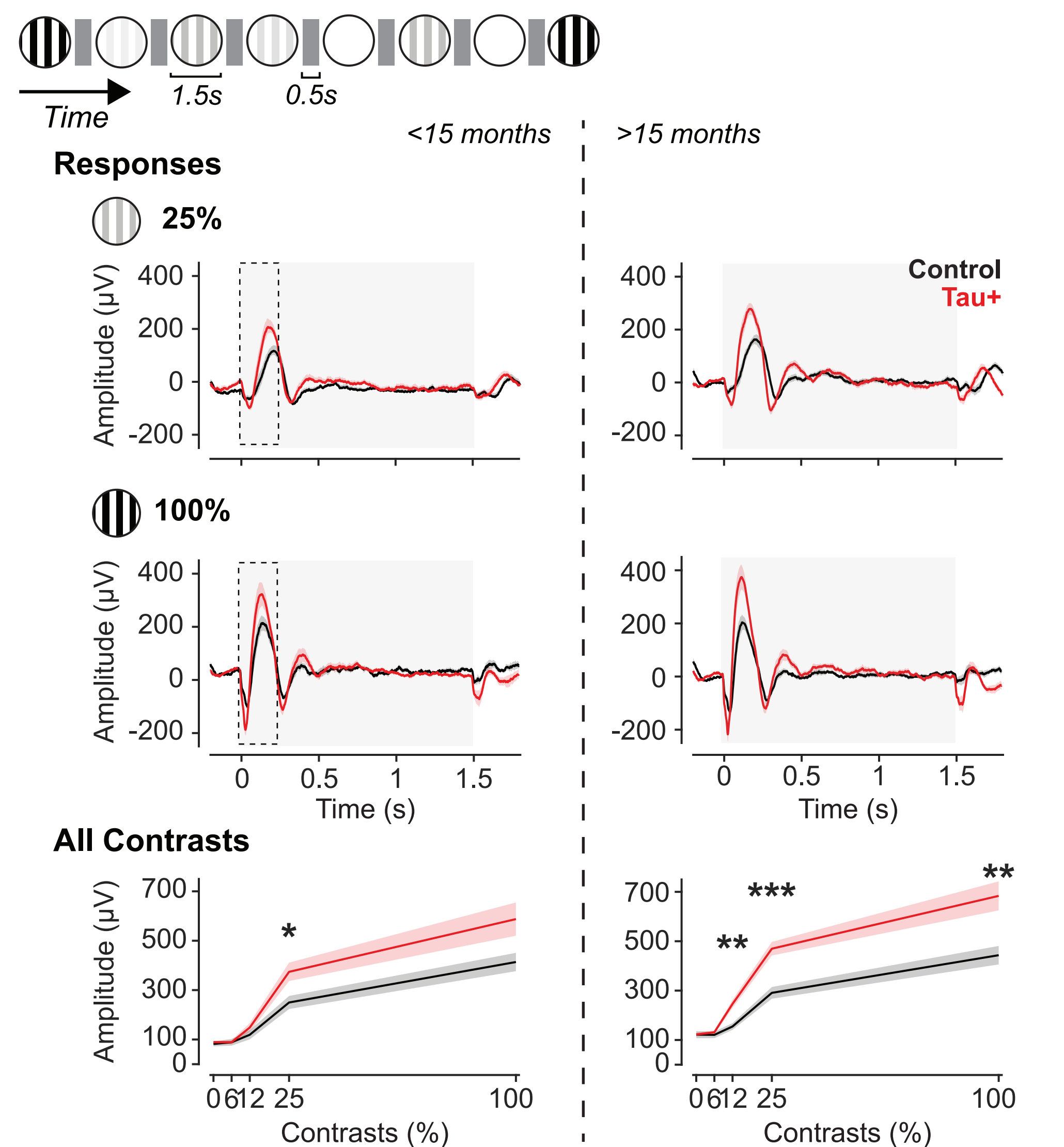
We found a main effect of phenotype on stimulus induced changes in both Pupil Size ($F_{(1,18)}=10.47$, $p=0.005$) and Speed ($F_{(1,17)}=7.65$, $p=0.013$).

Stronger visual cortical responses for sudden stimuli in Tau+ animals



Initial visual responses to the stimulus are larger in Tau+ animals, particularly at older ages, but quick adapt to Control levels.

Stronger visual cortical responses in Tau+ animals are found at low and high contrast



Larger responses to visual stimuli of varying contrasts were larger in Tau+ animals, increasing in amplitude at older ages ($F_{(1,4)}=5.1$, $p=0.005$).

Conclusions

- Small changes in cortical rhythms in Tau+ mice. These changes are different from those observed in previous models of tauopathy
- Humanised Tau+ animals show sustained behavioural reactivity to stimulus presentation
- Visual cortical responses are larger in Tau+ mice, and they are more dependent on recent stimulus history
- Changes in brain rhythms emerge at older ages, while changes in visual and behavioural responses are present early on, and become more prominent with ageing.

- hTau models offer promising avenues to study the early impacts of tauopathy on circuit level function and behaviour
- Arousal control mechanisms may be affected at early stages of pathology in humanised Tau+ animals
- Pathology impacts brain areas differently
 - frontal and hippocampal areas may be more hypoactive
 - visual areas may be more hyperactive
- hTau models may uncover more subtle network level alterations in brain activity present in the earlier phases of these disorders

Supported by



References



Contact

