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Multiplexed simultaneous long-term imagine of glial and neuronal circadian activities in the suprachiasmatic nucleus.

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Circadian rhythms depend on well characterised intra-cellular transcription-translation negative feedback loops (TTFLs) of clock gene expression. In multicellular animals, these self-sustained cellular clocks need to achieve multi-cellular integration to drive daily rhythms of physiology and behaviour. In mammals, the suprachiasmatic nucleus (SCN) is essential for achieving such multicellular integration, both for the wider internal synchronization of body clocks and for their alignment to the external light dark-cycle, via retina input.

A general assumption is that neurons are exclusively responsible for integrating such multicellular information, whereas glia mostly play a supportive and/or modulatory role. However, we have recently challenged such assumption, by showing that astrocytes of the SCN can autonomously initiate and drive *de novo* circadian behaviour in mouse models of genetic clock ablation (Brancaccio et al. *Neuron* 2017, Brancaccio et al. *Science* 2019). By performing long-term integrated imaging in organotypic SCN explants transduced with genetically encoded bioluminescent/ fluorescent reporters of neuronal and glial function and gene expression, we were able to follow their reciprocal coordination simultaneously, for several weeks.

This approach has revealed a striking day/ night separation of neuronal and astrocytic activities in the SCN, which is essential to mediate robust circadian timekeeping in mammals. In particular, night-time release of extracellular glutamate from astrocytes is sufficient to restore rhythmic calcium activity and gene expression of associated neuronal populations. Recent evidence demonstrates that both amyloid β and secreted tau levels show strong daily oscillations in the brain interstitial space and that circadian dysfunction is associated with preclinical Alzheimer's disease. Interestingly, here we show strong circadian patterns of tau gene expression in the SCN, thus suggesting a putative direct link between early circadian and sleep disturbances and pathogenic landmarks of Alzheimer's disease progression.