Title: Modelling age-related changes in human sleep across the 24h-cycle: impact of circadian amplitude and wake-promoting inputs to the monoaminergic system

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Ageing goes along with advanced sleep timing and reduced sleep consolidation. The objective of this study was to probe the mechanisms of age-related changes in sleep-wake regulation, such as altered circadian sleep-wake-propensity and build-up of homeostatic sleep pressure. To achieve this, we use an interdisciplinary approach combining experimental data and biophysical modelling. Ninety four healthy older adults (69 ± 5.4 years, 34% female) underwent a 40h multiple nap protocol (10 short sleep-wake cycles of 160 min of wake and 80 min of nap opportunity), preceded and followed by an 8h night-time sleep opportunity. In-lab polysomnography was used to derive sleep efficiencies and onsets. Data were confronted to a model of arousal dynamics (Postnova et al., 2018), which was previously used to account for circadian and sleep-dependent homeostatic modulations in healthy young individuals. We assessed whether adapting physiologically-relevant model parameters could accommodate for observed changes in the aged. Agreement between model predictions and group averaged experimental measurements were quantified by root mean-squared error (RMSE). As expected, predictions made with the model tuned on data from young adults did not agree with the measurements for the older adults (RMSE = 1.31). The model predicted higher sleep efficiencies during the biological night (baseline night and naps) and lower sleep efficiencies during nap opportunities in the wake maintenance zone. Our data were best predicted by reducing simultaneously the parameters reflecting circadian amplitude and the wake-promoting input to the monoaminergic system (RMSE=0.52). Our results suggest that ageing goes along with decreased amplitude of the circadian drive, together with an altered cholinergic/orexinergic input to the monoaminergic system. The latter might reflect decreased wake-state

stabilization, a mechanism by which higher prevalence of daytime napping at older age can potentially be explained.

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