Human cortical excitability depends on time awake and circadian phase

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Objectives: The dynamics of neuronal excitability is considered to be mainly driven by sleep homeostasis directly depending on time spent awake. However, no study has been properly designed to investigate a putative circadian timing system influence on human cortical excitability. Here we assessed this circadian modulation using transcranial magnetic stimulation coupled with electroencephalography (TMS/EEG).

Methods: Twenty-two healthy young men (18-30 years) underwent 8 TMS/EEG sessions during a 28h sustained wakefulness under stringent constant routine conditions. Participants were stratified in two groups according to a polymorphism in *PERIOD3* (*PER3*), known to affect sleep-wake regulation (15 *PER3*$^{4/4}$; 7 *PER3*$^{5/5}$). Cortical excitability was inferred from the normalized amplitude of the first component of TMS-evoked EEG potentials over the prefrontal cortex, a brain region highly sensitive to sleep deprivation.

Results: Cortical excitability significantly increased with time spent awake. However, the dynamics of this change was not linear and presented a pronounced local decrease around the so-called evening wake-maintenance zone. Conversely, a marked local amplification was found at the end of biological night when the circadian system maximally promotes sleep. This time-course was best predicted by the interaction of linear (sleep homeostasis) and sine-wave (circadian) functions. Interestingly, analyses by genotypes showed that the overnight difference in cortical excitability between sleep and wake maintenance zones was more pronounced in *PER3*$^{5/5}$.

Conclusions: These results demonstrate that temporal changes in cortical excitability depend on the interplay between sleep homeostasis and circadian timing system.

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