**Dynamics of human cortical ensembles are set by circadian system and sleep homeostasis**

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**Objectives:** Animal and human studies indicate linear alterations in inhibitory/excitatory neurotransmission during sleep and wakefulness, suggesting an exclusive sleep homeostatic influence. However, recent data posit a circadian, non-linear influence on neuronal function. We investigated whether this circadian drive impacts on human brain function in vivo.

**Methods:** We applied neural mass models using dynamic causal modeling (DCM), a Bayesian technique for neuronal identification, to transcranial magnetic stimulation (TMS)-evoked EEG signals from the prefrontal cortex (PFC, highly sensitive to sleep pressure). Twenty-two healthy young participants (18-30y) underwent 8 TMS-EEG recordings, during 28-h of sustained wakefulness, under stringent constant routine conditions. All significant effects are *P*corr< 0.05.

**Results:** Using DCM, we estimated GABAergic/glutamatergic functions, inhibitory/excitatory drives, and inhibitory/excitatory action potentials across PFC neuronal subpopulations. Overall control (self-inhibitory gain) within superficial pyramidal cells and inhibitory interneurons decreased with time awake, with nadir and peak in the circadian evening wake-maintenance zone and early morning sleep-maintenance zone, respectively. Conversely, GABAergic function and inhibitory action potentials across neuronal subpopulations increased with time awake, with local decrease and increase during wake- and sleep-maintenance zones, respectively. Excitatory action potentials slightly increased with time, with local decrease in the wake-maintenance zone. All time-courses were best predicted by the interaction of sine-wave (circadian) and linear (sleep homeostasis) functions.

**Conclusions:** Our results provide a proof-of-principle that inhibitory/excitatory changes in neuronal subpopulations reflect the interaction of circadian system and sleep homeostasis. Ultimately, the data provide a unique window on the hidden neuronal milieu setting the temporal organization of human brain function.

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