Sleep loss changes executive brain responses in the wake maintenance zone

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Objectives: Brain mechanisms underlying executive processes are regulated by circadian and sleep homeostatic processes. Furthermore, during sleep deprivation (SD), cognitive performance and neural responses are differentially modulated by a clock gene *PERIOD3* polymorphism. Here, we investigated inter-individual differences on executive brain responses under SD. Critically, we focused on the circadian evening wake maintenance zone (WMZ), a key time-point for sleep-wake regulation.

Methods: Thirty healthy young volunteers, genotyped for the *PER3* polymorphism (10 $PER3^{5/5}$;20 $PER3^{4/4}$ homozygotes), underwent42-h SD under constant routine conditions. They performed a 3-back working memory task in 13successivefMRI sessions. To compare neural activity in the WMZ before and during SD, sessions were realigned according to individual dim light melatonin onset.

Results: We tested for a group ($PER3^{5/5}$>$PER3^{4/4}$) by session effect (WMZ before vs. during SD). From the first evening WMZ(i.e. during a normal waking day) to the second (i.e. following 40h of continuous waking), $PER3^{5/5}$individuals relative to$PER3^{4/4}$showed significantly larger increase in responses in the left mid-cingulate, bilateral precuneus and thalamus. Interestingly, these regions are involved in executive processes and arousal regulation (thalamus).

Conclusions: These results show that the strong circadian wake-maintenance signal depends on sleep pressure, in a *PER3*-genotype dependent manner. Interestingly, pronounced genotype differences were observed in the thalamus, an area that compensates potential lower cortical activity under SD.

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