Polymorphism in *PERIOD3* predicts fMRI-assessed inter-individual differences in the effects of sleep deprivation

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A variable number tandem repeat polymorphism in *PERIOD3* is a genetic marker for inter-individual differences in sleep homeostasis and the effects of sleep loss on cognitive performance, in particular during the circadian alertness nadir. Individuals homozygous for the longer repeat ($PER3^{5/5}$) are more susceptible than individuals homozygous for the shorter allele ($PER3^{4/4}$). However, the brain bases of the effects of the polymorphism on cognitive performance are unknown.

Brain responses to an auditory 3-back working memory task were recorded in 15 $PER3^{4/4}$ and 13 $PER3^{5/5}$ individuals during 4 fMRI sessions separated in 2 visits. These subjects had not previously participated in any of our *PER3* related research projects. In each visit, subjects were recorded in the evening, close to the circadian alertness crest, and the following morning, close to the circadian alertness nadir. In one visit, they slept in the laboratory between both sessions, in the other, they remained awake (25h SD). The order of the sleep and SD condition was counterbalanced.

Performance and fMRI results showed that subjects could perform the task in all sessions and were affected by SD. FMRI data revealed striking differences between genotypes in the changes in brain responses observed after 25h of SD. In $PER3^{4/4}$, activity increased in frontal and temporal cortices, thalamus, cerebellum, and parahippocampus. By contrast, $PER3^{5/5}$ exhibited marked deactivations in frontal, temporal, parietal and occipital cortices.

The ability to recruit higher cognitive prefrontal areas after SD is maintained in $PER3^{4/4}$ but not in $PER3^{5/5}$. These data provide a brain basis for genetically determined interindividual differences in susceptibility to the effects of SD during the circadian alertness nadir.

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