**A *PERIOD3* polymorphism predicts fMRI assessed brain responses following sleep loss**

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A variable number tandem repeat polymorphism in the clock gene *PERIOD3 (PER3)* is a genetic marker for inter-individual differences in effects of sleep loss. Individuals homozygous for the longer repeat ($PER3^{5/5}$), previously associated with morningness, are more susceptible than individuals homozygous for the shorter allele ($PER3^{4/4}$). It was hypothesized that the effects on cognitive decline during sleep loss are mediated through the polymorphism's effects on sleep homeostasis, rather than on circadian phase. However, the brain bases of the effects of this polymorphism on cognitive performance are unknown.

Fifteen $PER3^{44}$ and 13 $PER3^{55}$ healthy individuals were recruited solely on the basis of their *PER3* genotype. Brain responses to an auditory 3-back working memory task were recorded in 4 fMRI sessions during 2 separate visits. In each visit, they were recorded in the evening and the following morning. In one visit they slept in the laboratory between both sessions, while in the other, they remained awake (24h sleep deprivation). Sleep deprivation and sleep visits were counterbalanced within and between genotypes.

Performance and fMRI results showed that subjects could perform the task in all 4 sessions and were affected by sleep deprivation. FMRI data revealed striking differences between $PER3^{4/4}$ and $PER3^{5/5}$ in the changes in brain responses observed after 24h of sleep deprivation, even though performance did not yet differ significantly between the genotypes. In $PER3^{4/4}$ activity increased in frontal and temporal cortices and in the thalamus, cerebellum, and parahippocampus. In contrast, $PER3^{5/5}$ exhibited marked deactivations in frontal, temporal, parietal and occipital cortices and no activations.

The ability to recruit higher cognitive prefrontal areas after extended wakefulness is maintained in $PER3^{44}$ but not in $PER3^{5/5}$ individuals. These data provide a brain basis for genetically determined inter-individual differences in susceptibility to sleep loss.

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