Correlation of changes in brain activation and cognitive impairment during 30 hours of continuous sleep deprivation using latent growth curve analysis

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Purpose Cognitive impairment due to sleep deprivation-induced fatigue has a significant impact on human performance and safety in a variety of work settings [1]. However, the neural correlates of cognitive impairment due to sleep deprivation remain poorly understood. An active area of research is in the use of functional MRI (fMRI) to study changes in the brain during sleep deprivation and the possible effects of these changes on cognitive impairment [2]. Generally these studies have assumed a linear increase in cognitive impairment over a period of sleep deprivation [3], but this approach fails to model the nonlinear effects of circadian rhythm on cognition. In this work, we seek to use a latent growth curve analysis which models each individual subject's fatigue vulnerability profile using a 3rd order polynomial to correlate changes in brain activation and deactivation between rested wakefulness (RW) and 30 hours of sleep deprivation (SD) with cognitive impairment.

Materials and Methods *Subjects* Eight healthy male subjects participated in this study. All subjects wore wrist monitors for 3 days leading up to the study to ensure they kept normal sleeping hours. *Experimental Procedure* On the day of the study, subjects were required to wake at 6AM and arrive at the study site by 9:30AM. At 12PM a brain imaging session was performed consisting of standard 3D T1-weighted anatomical imaging (TR/TE=1900/3.37ms, 256x256 matrix elements, 160 slices, voxel dimensions = 1.0x1.0x1.0mm^3, 1Nex) and two fMRI acquisitions (single-shot EPI, TR/TE=2000/40ms, 64x64 matrix elements, 24 slices, voxel dimensions = 4.0x4.0x6.0mm^3). The first fMRI acquisition used a Sternberg Working Memory Task (SWMT) as a stimulus while the second used a conjunctive visual search (CVS) task. The CVS task required subjects to search images of blue squares and red circles to determine if a blue circle was present, and we have previously shown this stimulus is a good indicator of attention and vigilance. Subjects were then kept awake in a laboratory setting where they completed a battery of tests which included a spatial working memory task every 2 hours for 24 hours, leading to a total of 13 evaluations of cognitive function over 30 hours of total sleep deprivation. The spatial working memory task used a 2-choice forced discrimination paradigm with outcome measured as the time required to complete each correct discrimination, averaged over the entire paradigm (mean search time). The subjects then underwent a second brain imaging session identical to the first imaging session. *Data Analysis* Mean number of globally activated and deactivated voxels across all subjects was calculated for both tasks at RW and SD. A latent growth curve model was then used to investigate the correlation between changes in brain activation and cognitive performance. Using difference from baseline values, the two-step model first fit a 3rd order polynomial to the results of the 13 spatial working memory tests over the period of sleep deprivation for each subject, and then correlated the resulting parameter estimates with the change in number of activated and deactivated voxels from RW to SD, as well as the total number of activated and deactivated voxels at SD.

Results Mean global activation decreased and mean global deactivation increased from RW to SD for both activation tasks (Fig. 1). The results of fitting a 3rd order polynomial to each subject's cognitive performance, measured by the change in mean search time from baseline, over the period of sleep deprivation, are shown in Fig. 2. An increase in mean search time indicates increased cognitive impairment. When considering all imaging quantities, the latent growth curve analysis found that fMRI activation and deactivation associated with core working memory, attention, and vigilance, is significantly related to fatigue vulnerability ($p<0.003$). When investigating the imaging findings independently, change in deactivation and deactivation at SD using the CVS were found to be significantly related to fatigue vulnerability ($p<0.003$ and $p<0.01$, respectively). The most fatigue vulnerable and fatigue resistant subjects were determined based on the difference in maximum and minimum mean search time. A qualitative comparison of their images indicated that the increase in global deactivation may be more greatly influenced by resistant subjects than vulnerable subjects (Fig. 3).

Conclusion Global activation decreased from RW to SD for both tasks, which is in agreement with previous findings. The effects of circadian rhythm caused an increase in cognitive impairment in all subjects near hour 16, followed by a recovery period near hour 24, and support the use of the latent growth curve analysis when correlating imaging findings with longitudinal measures of cognitive impairment. An increase in global deactivation when using the conjunctive visual search was found to be significantly correlated with resistance to fatigue. To our knowledge, this increase in global deactivation has not been observed before, and these findings could be indicative of an effort to focus resources while fatigued. Future work will seek to apply the latent growth curve analysis to specific areas of the brain known to be related to sleep deprivation-induced cognitive impairment including the thalamus, precuneus, and cortical areas.

Figures and References

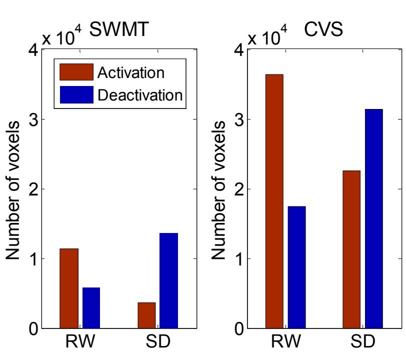

Fig. 1. Global activation and deactivation at RW and SD for the two fMRI tasks.

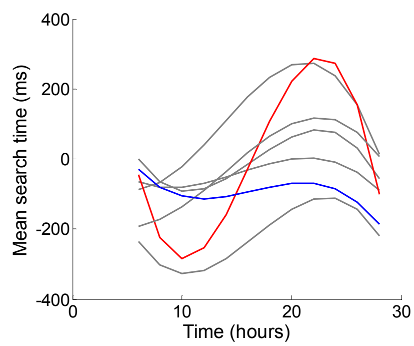

Fig. 2. Third-order polynomial fits to the change in mean search time over the period of sleep deprivation. Red line = most vulnerable subject, blue line = most resistant subject.

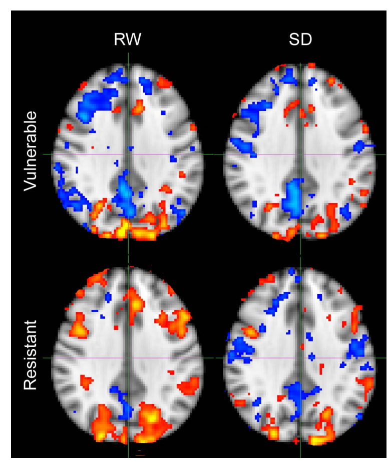

Fig. 3. Transaxial slices for the most vulnerable subject (top row) and most resistant subject (bottom row). Both subjects appear to have decreased activation at SD, but the resistant subject appears to also have increased deactivation.

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