Striatal dopamine correlates working memory activation during sleep deprivation but not during rested wakefulness: a PET-fMRI study

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INTRODUCTION: Sleep deprivation (SD) increases extracellular dopamine[1] (DA), and reduces performance accuracy and activation responses during working memory (WM) tasks[2]. Here we studied the effect of SD on brain activation with fMRI using a standard n-back verbal WM task[3], and on DA D2 receptors (D2R) with PET and ^{11}C-raclopride. We hypothesized that DA activation occurs during SD to maintain cognitive performance and thus brain activation would correlate D2R availability in the striatum during SD but less so during rested wakefulness (RW).

METHODS: Sixteen healthy non-smoking and right-handed men (age: 36±5 years, education: 14±2 years) participated in the study. All subjects had two fMRI sessions (two different days more than one week apart): (RW) after a good night sleep (8 hours, supervised sleep); (SD) after 1 night of no sleep (supervised by a team member). Session order was randomized across subjects. PET scans were done with [^{11}C]raclopride (4-10 mCi; 20 min half-life) to measure D2R availability in the brain. PET images with 4.5 mm isotropic spatial resolution were acquired in 3D mode and ROIs analyses were used to calculate the availability of D2R in striatum. In each session (RW and SD) and after the PET scan, the subjects performed a set of WM tasks involving recognition of 0-, 1-, and 2-back targets in a sequential-letter paradigm[3] while the corresponding blood oxygenation level dependent (BOLD) signals were measured in a 4-Tesla MRI scanner using a single-shot gradient-echo EPI sequence (TE/TR = 20/1600 ms, 4 mm slice thickness, 1-mm gap, 35 coronal slices, 64x64 matrix size, 156 time points). After motion correction, spatial normalization to the Talairach frame (3×3×3 mm^3 voxel size), and spatial smoothing (8-mm Gaussian), activation maps were calculated for each subject and task using the general lineal model in SPM2. These BOLD maps were used in multiple regression (SPM2, random-effects) statistical analyses and ROI analyses (custom IDL code) to evaluate linear correlations between D2R availability in striatum and BOLD-fMRI signals in the whole brain.

RESULTS: Subjects had slightly lower WM accuracy ($p = 0.05$; one-way ANOVA; Fig 1 left) and lower D2R availability in caudate and putamen ($p < 0.0001$, paired t-test; Fig 1 right) for SD than for RW (previously reported)[1]. The WM task produced a load-dependent bilateral activation in parietal, occipital, and prefrontal cortices, the cerebellum and the thalamus, and deactivation of sensory cortices (A1 and V1) (previously reported)[4] (Fig 2 top panel). During the SD session subjects had lower BOLD-fMRI activation in the cerebellum (vermis; $p_{corr} < 0.001$, cluster corrected for multiple comparisons; Fig 2 middle panel) than during RW. During SD (Figs 2 and 3), D2R availability in putamen correlated positively BOLD-fMRI responses in occipital (**OC**: BA 18/19, $p_{corr} < 0.001$), posterior parietal (**PPC**: BA 7; $p_{corr} < 0.001$), and superior prefrontal (**PFC**: BA 6; $p_{corr} = 0.05$) cortices and negatively those in insula (**INS**, BA 13, $p_{corr} < 0.001$) and precuneus (BA 31, $p_{corr} = 0.02$). During RW, on the other hand, D2R availability in putamen was negatively correlated with brain activation only in the cerebellar vermis ($p_{corr} = 0.035$) and there were no positive correlations between D2R availability in putamen and BOLD signals in the brain. Similarly during SD, D2R availability in caudate correlated positively BOLD-fMRI responses in PFC (BA 6/9, $p_{corr} = 0.05$) and PPC (BA 7; $p < 0.002$, cluster uncorrected), and correlated negatively with those in INS ($p_{corr} = 0.009$) and precuneus (BA 31, $p_{corr} = 0.02$); there were no significant correlations during RW.

CONCLUSIONS: The SD-related decreases in D2R availability might reflect extracellular DA increases to maintain arousal as the drive for sleep increases[1]. The lower performance accuracy and cerebellar activation for SD than for RW are consistent with previous studies on sleep deprivation[2]. Here we show that D2R availability in the striatum and BOLD responses in the WM network (prefrontal, parietal, and occipital cortices) and insula are correlated during SD (but not during RW). This finding suggests that during SD, DA modulated brain activation in these cortical regions, which is consistent with previous evidence of direct dopaminergic innervation in these brain regions[5]. Consequently, BOLD responses in these regions were not different for RW and SD. However, BOLD responses in the cerebellum, a region where brain activation did not exhibit significant correlation with D2R availability in striatum and does not have direct dopaminergic innervation, were lower for SD than for RW. Together with the minimal effects of SD on performance accuracy, these findings highlight the involvement of dopamine in the adaptation responses to maintain cognitive performance under conditions of SD.

REFERENCES: 1-Volkow (2008) J. Neurosci **28**: 8454-8461; 2-Chee (2006) Neuroimage **31**: 419-428; 3-Speck (2000) Neuroreport **11**: 2581-2585; 4-Tomasi (2007) Brain Res 1132: 158-165; 5-Lewis (2001) J Comp Neurol 432:119-136.

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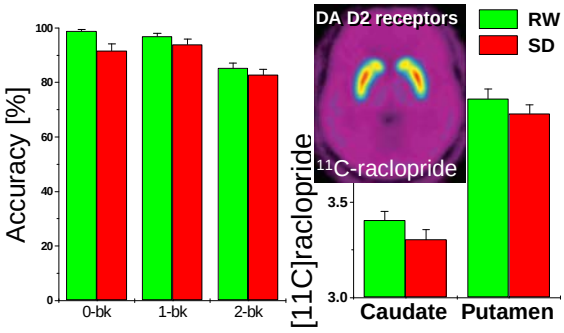
Fig 1: (Left) lower performance during SD; (Right) axial PET image showing radiotracer uptake in the striatum and bar plot showing the lower uptake for SD than for RW.



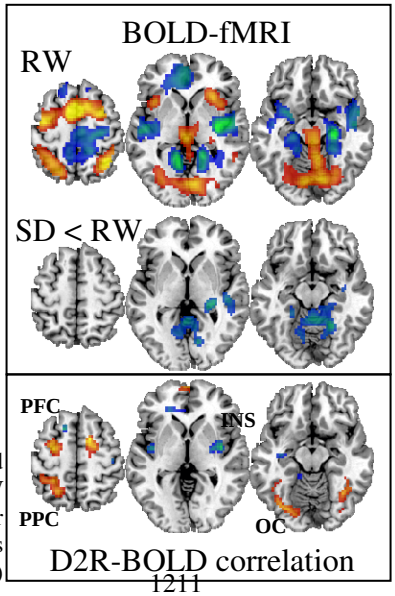


Fig 2: Brain activation (red-yellow) and deactivation (blue-green) during WM for RW (top); lower WM activation for SD than for RW (middle); and correlation of BOLD responses and D2R availability in striatum (bottom)

Fig 3: Scatter plots showing the linear correlation of striatal DA markers and brain activation responses across subjects.