

## Impairment of Attentional Networks after 1 Night of Sleep Deprivation

**Here, we assessed the effects of sleep deprivation (SD) on brain activation and performance to a parametric visual attention task. Fourteen healthy subjects underwent functional magnetic resonance imaging of ball-tracking tasks with graded levels of difficulty during rested wakefulness (RW) and after 1 night of SD. Self-reports of sleepiness were significantly higher and cognitive performance significantly lower for all levels of difficulty for SD than for RW. For both the RW and the SD sessions, task difficulty was associated with activation in parietal cortex and with deactivation in visual and insular cortices and cingulate gyrus but this pattern of activation/deactivation was significantly lower for SD than for RW. In addition, thalamic activation was higher for SD than for RW, and task difficulty was associated with increases in thalamic activation for the RW but not the SD condition. This suggests that thalamic resources, which under RW conditions are used to process increasingly complex tasks, are being used to maintain alertness with increasing levels of fatigue during SD. Thalamic activation was also inversely correlated with parietal and prefrontal activation. Thus, the thalamic hyperactivation during SD could underlie the reduced activation in parietal and blunted deactivation in cingulate cortices, impairing the attentional networks that are essential for accurate visuospatial attention performance.**

**Keywords:** brain function, functional connectivity, sleep deprivation, visuospatial attention

Sleep is essential for memory and learning (Gais and Born 2004; Wagner et al. 2004; Gais et al. 2006), and behavioral studies have shown that sleep deprivation (SD) can impair cognitive performance (Pilcher and Huffcutt 1996; Harrison and Horne 2000a, 2000b; Harrison et al. 2000; Jennings et al. 2003; Nilsson et al. 2005; Tsai et al. 2005; Hsieh et al. 2007). Neuroimaging studies that used positron emission tomography (PET) suggested that SD-related decreases in cognitive performance reflect decreased cerebral metabolic rate of glucose in the thalamus, parietal, and prefrontal cortices (PFC) (Thomas et al. 2000). Paralleling the PET findings, functional magnetic resonance imaging (fMRI) studies on working memory tasks have reported activation decreases in the parietal cortex and the thalamus (Chee and Choo 2004; Chee et al. 2006; Chee and Chuah 2007) after SD. Furthermore, these fMRI studies have suggested that working memory tasks with increased levels of difficulty produce larger activation increases (from the easiest to the hardest task, i.e., working memory load activation) in the PFC and the thalamus during SD than during rested wakefulness (RW) (Chee et al. 2006). Only few fMRI studies on SD have been carried out with other cognitive tasks, and these appear to show that the brain response to SD is task specific (Drummond et al. 2000). These studies used verbal learning,

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3-dimensional navigation, attention to visual stimulus, divided attention, arithmetic, or Go/No-Go inhibitory tasks and reported increased (Drummond et al. 2000, 2001; Strangman et al. 2005), unchanged (Portas et al. 1998), or decreased (Drummond et al. 1999, 2000; Chuah et al. 2006) cortical activation as well as increased thalamic activation (Portas et al. 1998) after SD. However, none of these studies used parametric variations of cognitive load.

SD impairs alertness (Thomas et al. 2000), a sustained attention state that is essential for accurate performance on highly demanding cognitive tasks. The thalamus is a key region involved with alertness and arousal, and indeed, decreased levels of arousal have been associated with reductions of thalamic activity (Volkow et al. 1995; Fiset et al. 1999). Alertness directly influences attention processes, which are among the most sensitive to the effects of SD (Fisher 1980; Wimmer et al. 1992; Doran et al. 2001; Drummond et al. 2001; Kendall et al. 2006). Attention engages multiple brain regions, and several models have been proposed on how the brain modulates attention (Posner and Dehaene 1994; Sturm et al. 1999, 2006; Sturm and Willmes 2001; Fan et al. 2005; Hahn et al. 2007). One model, extensively validated by imaging studies, postulates 3 attentional networks, comprised of an alerting component (thalamus), an orienting component (parietal cortex), and an executive component (prefrontal cortex) (Fan et al. 2005). In addition, attention has also been shown to modulate the intensity of activation of cortical regions in response to sensory stimulation (Jack et al. 2006). Inasmuch as arousal modulates attention here, we hypothesize that disrupted performance by SD is driven by neuronal responses to maintain arousal when the drive for sleep increases, which comes at the expense of decreased reserve for cognitive tasks that engage the alerting component of attention. Specifically, we hypothesized that during SD performing an attentional task would result in hyperactivation of thalamus, even for a simple task, and a reduced capacity to further activate as the task difficulty increases. We also hypothesized that this thalamic hyperactivation would be associated with reduced activation of cortical regions that process the task. Thus, we hypothesized that disruption in sustained attention after SD is mediated in part by disruption in the activity of thalamocortical regions (parietal, occipital, and prefrontal).

Here, we used fMRI and a sustained parametric visuospatial attention (VA) task to test the hypothesis that abnormal thalamocortical activation underlies the impairment in performance to a visual attention task during SD. The VA task has graded levels of difficulty and engages thalamic and cortical regions (Chang et al. 2004, 2006; Tomasi et al. 2004, 2007, 2008). We chose a parametric task because SD studies have

shown that the duration as well as the level of difficulty of a task affects the degree of impairment during SD (Wilkinson 1968). A parametric task also allowed us to evaluate if the pattern of disruption by SD corresponded to that which covaried with task difficulty.

## Methods

### Participants

The 14 healthy, nonsmoking, right-handed men (age  $32 \pm 8$  years, education  $16 \pm 2$  years) that participated in the study signed a written consent approved by the Institutional Review Board at Brookhaven National Laboratory prior to the study. These participants were screened carefully with a detailed medical history, physical, and neurological examination, electrocardiogram, breath CO, blood tests, and urine toxicology for psychotropic drugs to ensure they fulfilled all study criteria. Inclusion criteria were 1) ability to understand and give informed consent and 2) 18–50 years of age. Exclusion criteria were 1) urine positive for psychotropic drugs (including phencyclidine, cocaine, amphetamine, opiates, barbiturates, benzodiazepine, and tetrahydrocannabinol); 2) present or past history of dependence on alcohol or other drugs of abuse (except for former nicotine smokers whose last use was about 1 year ago and caffeine  $<2$  cups/day); 3) present or past history of neurological or psychiatric disorder (including sleep disorders); 4) use of psychoactive medications in the past month (i.e., opiate analgesics, stimulants, and sedatives); 5) use of prescription (nonpsychiatric) medications, that is, antihistamines; 6) medical conditions that may alter brain function; 7) cardiovascular disease and diabetes; 8) history of head trauma with loss of consciousness of more than 30 min; 9) history of claustrophobia; and 10) contraindications to MRI environment.

### SD and RW

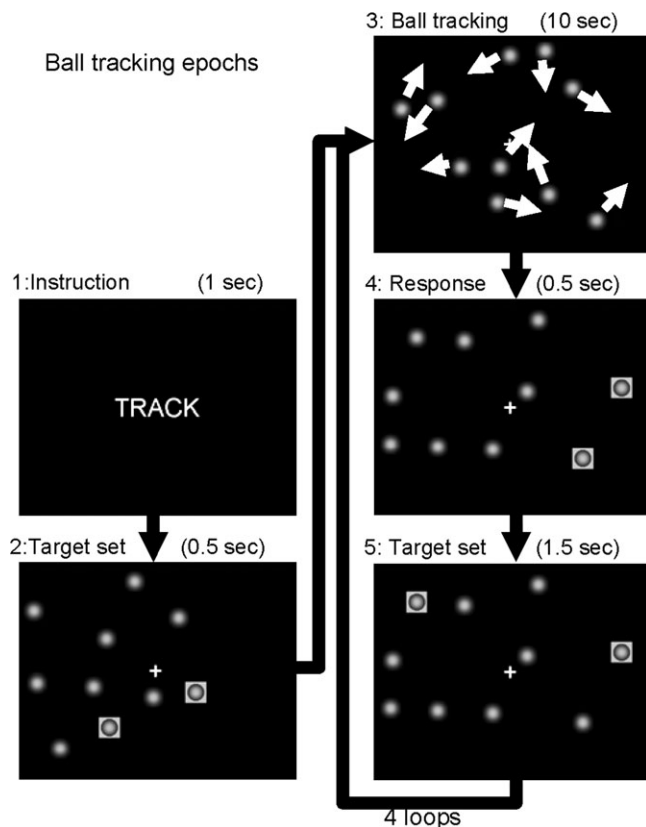
Subjects were asked to self-report diary on their sleep patterns each night for at least a week prior to the study. All subjects were kept overnight at the Brookhaven National Laboratory campus prior to their scheduled sessions to ensure that they did not sleep during the night for the SD session or that they had a good night rest for the RW session. In the morning, subjects were provided with a light breakfast consisting of orange juice or fruit, 2 pieces of toast or bagel or cereal with milk/yogurt and a decaffeinated beverage. A member of the study team remained with them between 9:00 h of the day before the study and 15:00 h of the day of the MRI scan, to ensure that they did not fall asleep prior to the SD session. Subjects did not have food after midnight and no caffeinated beverages were permitted during the 30–35 h that encompassed the SD period. Half the studies started with the RW session; the remaining studies started with the SD session to control for practice effects and effects of novelty to the magnetic resonance (MR) environment (Tomasi et al. 2004). For all subjects, the MRI sessions (RW and SD) took place between 15:00 and 17:00 h.

### Profile of Mood Scales

Subjects were asked to provide self-reports of items related to their current mood such as sleepiness, tiredness, desire to sleep, alertness, and energy (McNair et al. 1992). Self-reports were obtained prior to the fMRI session on each day of the study.

### VA Paradigm

The participants performed a visual attention task with blocked design that was described previously (Culham et al. 1998; Jovicich et al. 2001; Chang et al. 2004; Tomasi et al. 2004, 2007). Briefly, the “TRACK” epochs are composed of 5 “ball-tracking” and respond periods, as outlined in Figure 1. In these periods, 2, 3, or 4 out of 10 target balls are briefly highlighted (Fig. 1, frame 2) and then all balls start to move (Fig. 1, frame 3); the subjects’ task is to fixate on the center cross and track the target balls as they move randomly across the display ( $12^\circ$  of the central visual field) with instantaneous angular speed of  $3^\circ/s$ . The 10 balls move in a simulated Brownian motion and collide with, but do



**Figure 1.** Outline of TRACK epochs of the 2-ball-tracking task. Subjects track the target ball set, which is briefly highlighted (frame 2) after the instruction (frame 1), while all 10 balls move with a random motion for 10 s (frame 3). Then, they respond with a button press if the highlighted balls are those they were tracking (frame 4). The target set is rehighlighted to refocus the subjects’ attention on the balls (frame 5).

not penetrate each other. At the end of ball-tracking periods, the balls stop moving and a new set of balls is highlighted (Fig. 1, frame 4); the subjects are instructed to press a button if the highlighted balls are the target set. Button press events are used to record performance accuracy and reaction times (RTs) during the fMRI tasks. After a 0.5-s delay, the original target balls are rehighlighted to refocus the subjects’ attention on those balls (the target set; Fig. 1, frame 5). The “DO NOT TRACK” baseline epochs are composed of 5 consecutive “resting” periods. In these periods, all 10 balls move and stop in the same manner as during TRACK epochs; however, no balls are highlighted, and subjects are instructed to not track the balls and view them passively. The use of this “resting baseline” condition allows us to control for the confounding effect of visual input activation. This task activates attention-related brain regions comprising prefrontal, parietal, and occipital cortices, thalamus, and cerebellum.

The stimuli (movies in “Audio Video Interleave” format) were created using Matlab and presented to the subjects on MRI-compatible goggles connected to a personal computer. The display software is synchronized precisely with the MR acquisition using an MRI trigger pulse. All response button events during stimulation were recorded using the Visual Basic and Visual C languages, to determine RT and performance accuracy. Subjects performed a brief training session (~10 min) of a shortened version of the paradigm outside the scanner to ensure that they understood and were able to perform the tasks. The entire set of VA tasks was repeated in each session (SD and RW).

### Data Acquisition

Subjects underwent blood oxygen level-dependent (BOLD) fMRI in a 4 T whole-body Varian/Siemens MRI scanner using a  $T_2^*$ -weighted single-shot gradient-echo planar imaging sequence with ramp sampling (time echo [TE]/time repetition [TR] = 20/1600 ms, 4-mm slice thickness,

1-mm gap, 35 coronal slices, 64 × 64 matrix size, 3.1 × 3.1-mm in-plane resolution, 90° flip angle, 231 time points, bandwidth: 200.00 kHz) covering the whole brain. Padding was used to minimize motion. Task performance and subject motion were determined immediately after each fMRI trial, to assure performance accuracy better than 80%, and motion <1-mm translations and <1° rotations (Caparelli et al. 2003). Anatomical images were collected using a  $T_1$ -weighted 3D-MDEFT sequence (Lee et al. 1995) (TE/TR = 7/15 ms, 0.94 × 0.94 × 1-mm spatial resolution, axial orientation, 256 readout and 192 × 96 phase-encoding steps, 16 min scan time) and a modified  $T_2$ -weighted hyperecho sequence (Hennig and Scheffler 2001) (TE/TR = 42/10,000 ms, echo train length = 16, 256 × 256 matrix size, 30 coronal slices, 0.86 × 0.86-mm in-plane resolution, 5 mm thickness, 1-mm gap, 2-min scan time), which were reviewed to rule out gross morphological abnormalities in the brain.

### Data Processing

The first 4 volumes in the time series were discarded to avoid nonequilibrium effects in the fMRI signal. Subsequent analyses were performed with the statistical parametric mapping (SPM) package SPM2 (Wellcome Department of Cognitive Neurology, London, United Kingdom). A 6-parameter rigid body transformation was used for image realignment and to correct for head motion. Head motion was less than 1-mm translations and 1° rotations for all scans. The realigned datasets were normalized to the standard brain (Talairach) using a 12-parameter affine transformation (Ashburner et al. 1997) and a voxel size of 3 × 3 × 3 mm<sup>3</sup>. An 8-mm full-width-half-maximum Gaussian kernel was used for spatial smoothing. A general linear model (Friston et al. 1995) was used to calculate the activation maps for each condition (2, 3, and 4 balls), session, and subject. The blocked analysis was based on a boxcar design convolved with the canonical hemodynamic response function (HRF), and low-pass (HRF) and high-pass (cut-off frequency: 1/256 Hz) filters.

### Statistical Analyses

Estimated BOLD maps (% signal change) for each trial and subject were included in a 1-way (within-subjects) analysis of variance (ANOVA)

model with 6 conditions (2, 3, and 4 balls; “RW” and “SD”) and the session order as a covariate, in SPM2. Brain activation and deactivation clusters with at least 15 voxels (400 mm<sup>3</sup>) and  $P < 0.05$  (corrected for multiple comparisons) were considered significant in the group analysis (Friston et al. 1994).

### Region-of-Interest Analysis

Functional regions of interest (ROIs) with an isotropic volume of 0.73 ml and containing 27 imaging voxels were defined at the centers of activation clusters to extract the average statistical significance ( $t$ -scores) from group activation maps (spmT\_\*.img files resulting from the SPM2 ANOVA model; Table 1). Specifically, 9-mm cubic masks were created and centered at the precise coordinates listed in Table 1, and the average and standard deviation (SD) of  $t$ -score values within these regions were computed using a custom program written in IDL (ITT Visual Information Solutions, Boulder, CO). Similarly, the average and SD values of BOLD responses in these regions were computed from the individual SPM2 contrast images (con\_\*.img files resulting from the boxcar model) for each subject and condition using the IDL script. Specifically, the coordinates of the ROI masks were kept fix across subjects, conditions, and sessions. Statistical analyses of individual average BOLD signals were carried out in StatView (SAS institute, Cary, NC). Additional regression analyses of behavioral measures (RT, performance accuracy, and sleepiness) and BOLD responses in the brain were conducted to determine the significance of brain activation in relation to subject’s performance and behavior. Statistical significance for ROI analyses was defined as  $P = 0.05$  (uncorrected).

### Functional Connectivity of the Thalamus

To study the thalamocortical connectivity, we adopted a method recently proposed by Fair et al. (2007), which allows for functional connectivity studies based on standard blocked fMRI datasets. Specifically, the SPM2 HRF was used to identify time points of the resting baseline epochs. These imaging time points were sequentially grouped to form resting time series with 105 time points, which were low-pass filtered (0.1-Hz frequency cut-off) to enhance the spontaneous low-frequency fluctuations of the

**Table 1**

Location of major areas of brain activation in the Talairach frame of reference and average statistical significance of BOLD responses in 27 voxels (0.73 cc; cubic) ROI centered at these cluster locations

ROI	Brain region	BA	x	y	z	RW		SD		SD > RW
						Main	Load	Main	Load	Δmain
1	Superior frontal gyrus	6	0	12	51	9.6	—	10.4	3.0	-1.7
2	Anterior CG	32	-3	33	12	-6.5	-3.1	-6.9	—	—
3	Middle frontal gyrus	6	-27	-3	60	8.2	—	8.2	1.7	-2.3
4			21	0	57	14.4	—	12.7	2.2	-4.4
5	Middle frontal gyrus	9	-51	6	39	4.4	—	3.3	2.1	—
6			36	6	33	9.7	3.2	9.6	3.9	—
7	Thalamus (ventral lateral nucleus)		-15	-15	12	3.6	2.1	6.7	—	3.9
8			15	-18	15	4.9	2.3	7.6	—	3.3
9	Anterior insula	13	-36	15	9	6.2	—	5.9	—	—
10			27	18	9	7.6	—	6.8	—	-1.6
11	Locus ceruleus		0	-21	-9	6.4	3.4	5.0	2.1	—
12	Posterior insula	13	-36	-21	18	-9.2	-2.3	-8.3	-2.2	—
13			30	-12	15	-8.6	-2.8	-7.8	-2.0	1.6
14	Parahippocampus	30	-12	-45	-3	-5.9	—	-7.7	—	—
15			18	-45	-3	-6.4	—	-5.6	—	—
16	Precuneus	31	3	-63	21	-13.4	-2.0	-11.8	—	1.6
17	Cuneus	18	-6	-81	18	-11.2	-2.4	-5.5	-2.5	5.0
18	CG	24	-6	-9	39	-6.7	-3.3	-6.4	—	—
19	Paracentral lobule	6	-9	-36	60	-6.1	-1.7	-3.0	—	1.7
20	Inferior parietal	40	-30	-51	54	6.9	2.3	6.3	2.5	-2.3
21			33	-54	60	5.9	—	5.1	—	-1.8
22	Superior parietal	7	-12	-69	57	9.6	2.3	8.0	—	-2.9
23			21	-69	54	11.6	—	9.4	2.8	-2.1
24	Lingual gyrus	18	-3	-81	-9	5.7	—	4.8	—	-1.8
25			12	-72	-15	6.4	—	4.8	—	—
26	Fusiform gyrus	19	-33	-72	-12	4.4	—	3.3	—	-1.8
27			33	-72	-12	4.2	—	3.7	—	-1.7
28	Cerebellum vermis		3	-45	-9	4.0	2.7	—	—	-2.9
29	Cerebellum nodule		12	-57	-30	6.8	3.1	7.1	2.6	—

Note: Sample size—14 healthy nonsmoking men.



BOLD fMRI signals and used to compute correlation maps reflecting the functional connectivity between a seed voxel in an area where the ventral lateral nucleus of the thalamus is located (see Table 1) and all other voxels in the brain. The Fisher transform was used to convert the step distributed Pearson linear correlation factors into normally distributed functional connectivity coefficients. These functional connectivity maps were computed and saved in Analyze format using IDL for all conditions (2-, 3-, or 4-ball tracking), sessions (RW or SD), and subjects and loaded into SPM2 for group analyses of functional connectivity. A 1-way (within-subjects) ANOVA (random-effects) model with 1 covariate (session order) was used for group analyses of functional connectivity. Clusters with at least 15 voxels ( $400 \text{ mm}^3$ ) and  $P < 0.05$  (corrected for multiple comparisons) were considered significant in group analysis of functional connectivity.

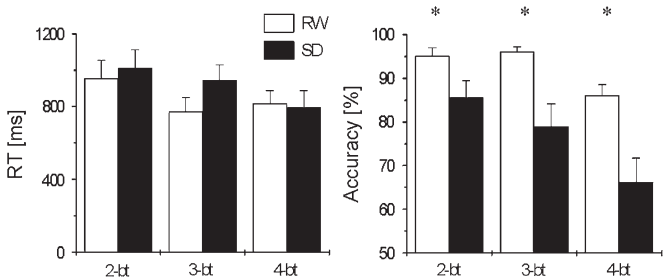
## Results

### Behavior

Subjects reported higher sleepiness prior to the SD session than prior to the RW session (RW:  $3.8 \pm 0.5$ ; SD:  $8.8 \pm 0.4$ ;  $P < 0.0001$ , paired  $t$ -test). Other Profile of Mood Scales measures did not differ significantly between sessions (data not shown). Performance accuracy decreased with increased task difficulty (from 2 balls to 4 balls;  $P < 0.0001$ , repeated-measures ANOVA), reflecting the increased cognitive load of the tasks as reported previously (Tomasi et al. 2004) and was lower during the SD fMRI session than during the RW fMRI session ( $P = 0.02$ , repeated-measures ANOVA; Fig. 2). The RT did not differ significantly across tasks or sessions. There were no statistically significant load  $\times$  session interaction effects on subject's performance (accuracy or RT). Increased sleepiness correlated linearly with performance accuracy during the fMRI tasks ( $R = 0.59$ ;  $P = 0.025$ ); the sleepier the subjects the lower their accuracy.

### Brain Activation

The VA tasks activated a bilateral network (main effect of VA; 1-way within-subject ANOVA; Table 1 and Fig. 3) that includes the prefrontal, parietal, and occipital cortices, thalamus, and cerebellum and deactivated the insula and the default network (Raichle et al. 2001), including the cingulate gyrus (CG). The bilateral activation in the ventral lateral, dorsal medial, lateral posterior, and ventral posterior lateral nuclei of the thalamus was higher and that in the superior parietal cortex was lower for the SD session than for the RW session ( $P_{\text{corr}} < 0.001$ , corrected for multiple comparisons; Table 1 and Fig. 3); the lower activation after SD in the cerebellar vermis was not statistically significant after correction for multiple comparisons.



**Figure 2.** Performance accuracy and RTs for the RW (white) and SD (black) sessions, as a function of the number of tracked balls (VA load). Sample size: 14 healthy men.

Deactivation in the cuneus (Brodmann area [BA] 18) and precuneus was lower for the SD session than for the RW session ( $P_{\text{corr}} = 0.001$ ). For the less demanding conditions (2- and 3-ball-tracking tasks), deactivation in the CG (BAs 32 and 24) was larger for SD than for RW ( $P_{\text{corr}} = 0.03$ ). The differential brain activation of the pons (superior peduncle) across sessions (negative during RW, positive during SD;  $t$ -score = 4.5, cluster size = 52 voxels) did not survive corrections for multiple comparisons in the whole brain, probably reflecting the small size of this brain region.

Increased cognitive load, from 2-ball tracking to 4-ball tracking, produced larger activation in the VA network and larger deactivation of the default network (Table 1 and Fig. 3). The VA-load effect on deactivation in the CG (BA 24) was higher for RW than for SD ( $P_{\text{corr}} = 0.048$ ). Increased cognitive load increased deactivation in the anterior CG (BA 32) during the RW but not during SD.

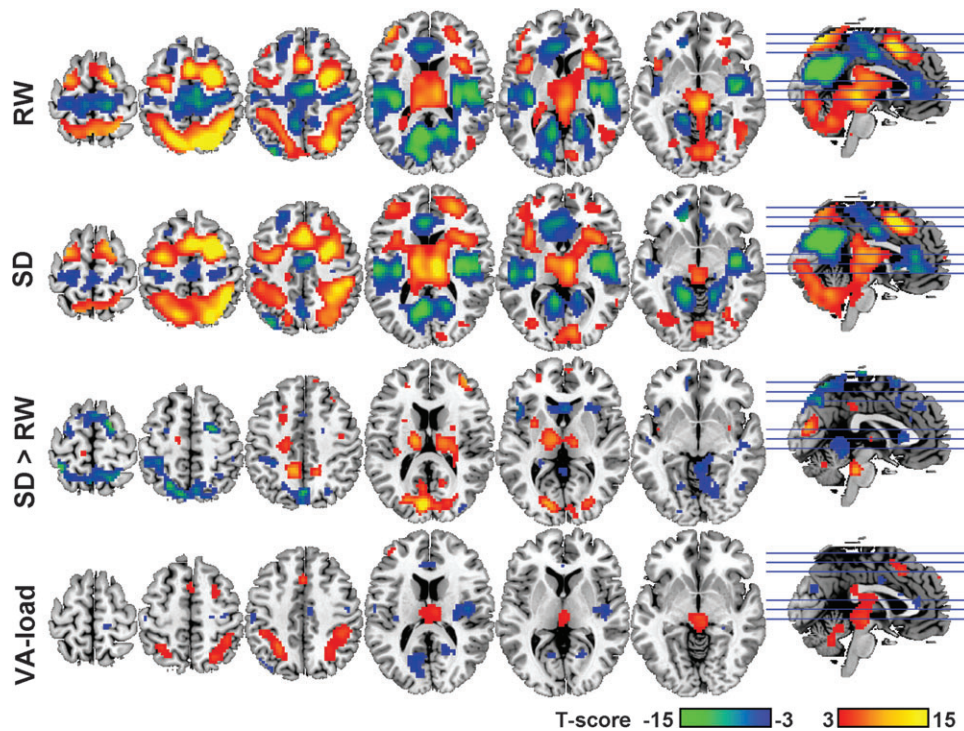
Averaged across all 3-ball-tracking conditions, the BOLD fMRI signal decreases in the CG (BA 32) from RW to SD, correlated with changes in sleepiness from RW to SD ( $R = +0.68$ ; cluster volume = 406 voxels;  $P_{\text{corr}} < 0.0005$ ). Behavioral changes did not correlate with fMRI activation/deactivation in any other brain region.

### ROI Results

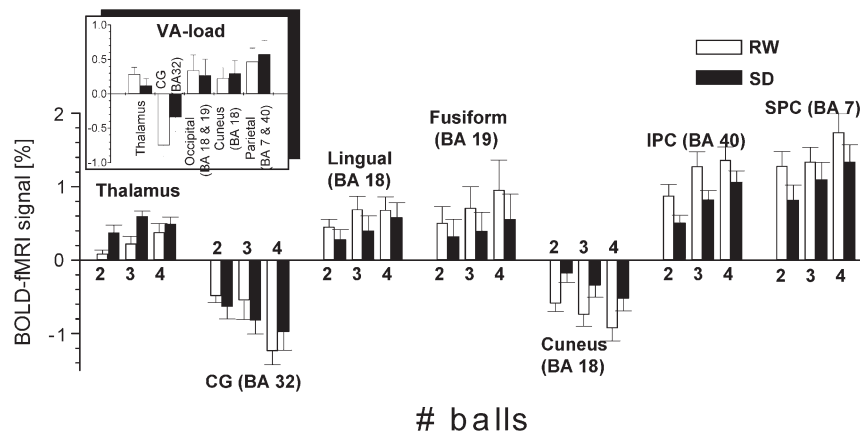
The ROI analyses showed that when compared with RW, the SD condition produced activation increases in the thalamus, activation decreases in the prefrontal, parietal, and occipital cortices (fusiform and lingual gyri), and deactivation decreases in the occipital cortex (cuneus; Table 1). Figure 4 exemplifies the observed thalamic and cortical activation changes. Thalamic activation was higher during SD than during RW, particularly for the less demanding conditions (2 and 3 balls). Conversely, parietal and occipital (left fusiform and lingual gyri) activation and deactivation in the cuneus were lower for SD than for RW. Increased difficulty (VA load) produced lower signal increases in the thalamus (Fig. 4, top-left insert) during the SD session than during the RW session. VA accuracy (2, 3, and 4 balls, averaged) correlated positively with BOLD fMRI signals (2-, 3-, and 4-balls, averaged) in the left lingual (BA 18) and right fusiform (BA 19) gyri during SD ( $P < 0.05$ ;  $R > 0.55$ ) but not during RW ( $P > 0.87$ ;  $-0.05 > R < 0.03$ ; linear correlation analyses). VA accuracy did not correlate significantly with BOLD fMRI signals in other ROIs. The correlation analyses between BOLD fMRI signal changes in the thalamus and those in parietal (BA 40) and cingulate (BA 24 and 32) cortices demonstrated an association between increased thalamic activation and decreased cortical activation ( $R = -0.36$ ;  $P = 0.019$ ; all tasks levels included) during RW but not during SD. However, failure to see a correlation during SD could reflect the lower dynamic range of BOLD fMRI responses in the parietal cortex during SD.

### Functional Thalamocortical Connectivity

A conjunctive analysis across sessions (RW and SD), conditions (2-, 3-, and 4-balls), and subjects demonstrated that the functional connectivity of the left thalamus was positive with the right thalamus, cuneus (BA 17 and 18), and with an area in the brain stem where the locus ceruleus is located and negative with brain regions belonging to the "default network" (CG [BA 32], paracentral lobule [BAs 4-6], the postcentral [BAs 2, 3,



**Figure 3.** BOLD fMRI activation patterns for the main (RW, SD) and differential (SD > RW and VA load: 4 balls > 2 balls) effects of visual attention, rendered to a structural MRI image. Random-effects analyses (1-way within-subjects ANOVA).



**Figure 4.** Average BOLD fMRI signals in specific ROIs (Table 1). Volume = 1.46 cc (left and right ROIs averaged). Sample size: 14 healthy nonsmoking men.

and 5], medial frontal [BA 6] gyri), the inferior frontal (BA 44) gyrus, and the insula (BAs 13 and 22) ( $P < 0.0005$  corrected for multiple comparisons for all clusters; random-effects 1-way within-subjects ANOVA SPM2 model; Fig. 5). The functional connectivity of the ventral lateral nucleus of the thalamus with the left precentral and middle frontal gyri (BA 6) was lower for SD (negative functional connectivity) than for RW (positive functional connectivity;  $P_{corr}$  (SD - RW) < 0.015). During SD, the thalamus did not show higher connectivity with any brain region than during RW.

## Discussion

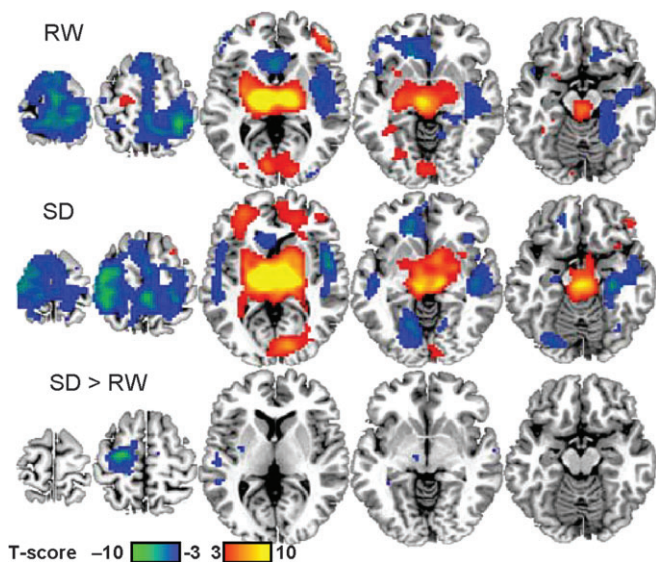
The present study demonstrates that during visual attention tasks, SD alters cognitive performance (decreases accuracy)

and brain activation in healthy men. Specifically, thalamic activation was higher, whereas parietal activation and occipital activation were lower for the SD than for the RW condition, and these cortical regions were functionally connected to the thalamus.

## Behavior

As previously reported in behavioral studies, subjects were sleepier and had lower accuracy in the VA tasks during SD than during RW (Pilcher and Huffcutt 1996; Harrison and Horne 2000a, 2000b; Harrison et al. 2000; Jennings et al. 2003; Nilsson et al. 2005; Tsai et al. 2005; Hsieh et al. 2007). In our study, the decline in performance with increased task difficulty was also more pronounced for SD than for RW (Fig. 2). Moreover, the self-reports of sleepiness correlated negatively with the





**Figure 5.** Statistical maps of functional thalamocortical connectivity during resting epochs, across all 14 healthy subjects and ball-tracking conditions (2, 3, and 4 balls), superimposed to axial slices of a reference brain. Top row: conjunctive analysis of the RW and SD sessions; middle and bottom rows analyses of individual sessions. SPM2 random-effects model: within-subjects ANOVA.

subject's accuracy in the VA tasks, which suggests that increased sleepiness reduced performance accuracy during SD.

### **Hyperactivation of Thalamus and Pons**

Activation of the thalamus was higher during the SD session than during the RW session (Table 1, Figs 3 and 4). Previous studies have shown a higher level of attention-related activity in the thalamus during SD than during RW, and suggested that the thalamus mediates the interaction of attention and arousal in humans (Portas et al. 1998). Though it is difficult to determine the precise location in the thalamus of the SD-related hyperactivation because of spatial resolution limitations, the Talairach coordinates identified by the SPM analysis include the dorsal medial, lateral posterior, and ventral posterior lateral nuclei in addition to the ventral lateral nucleus that exhibited the maximal BOLD fMRI activation differences between RW and SD. This location is consistent with the involvement of the ventral lateral nucleus of the thalamus in the alerting component of attention (Fan et al. 2005; Christian et al. 2006; Vandewalle et al. 2006). Thus, it is possible that the increased activation of the thalamus in the SD condition reflects an adaptation to sustain alertness during task performance and that this may help compensate for the decreased parietal activation during SD. This hypothesis is further supported by the negative correlation between BOLD fMRI signals in the parietal cortex (BA 40) and those in the thalamus during RW, which suggest a compensatory attention processing in the thalamus to sustain alertness. Thus, hyperactivation of the thalamus might reflect increased alertness effort to compensate for the parietal activation deficits during SD.

The pons deactivated during RW but activated during SD. Previous sleep studies have shown that the pons is involved in the sleep-wake cycle. Specifically, serotonin increases in the pons were associated to decreases in paradoxical sleep (Paz and Huitron-Resendiz 1996; Shouse et al. 2000), and differential

spike activity of neurons in the parabrachialis medialis and oral nuclei of the pons was recorded during each sleep-waking state in anesthetized (Dergacheva et al. 2004) and unanesthetized unrestrained cats (Sieck and Harper 1980). Furthermore, wakefulness-promoting medications (modafinil) may enhance arousal in humans by activation of the noradrenergic locus coeruleus of the pons (Hou et al. 2005). Thus, the SD-related activation increases in the pons may reflect increased effort to sustain arousal during SD.

### **Parietal Hypoactivation**

Activation of the superior parietal cortex was lower during the SD session than during the RW session (Table 1, Figs 3 and 4). These results are in agreement with previous fMRI studies on working memory (Chee and Choo 2004; Chee et al. 2006; Chee and Chuah 2007), verbal learning (Drummond et al. 2000), arithmetic (Drummond et al. 1999), and inhibitory (Chuah et al. 2006) tasks that reported cortical activation decreases after SD. The parietal cortex, which is hypoactivated in the SD session, has been shown to be essential for sustained attention (Buchel et al. 1998; Le et al. 1998; Arrington et al. 2000; Leonards et al. 2000; Adler et al. 2001; de Fockert et al. 2001; Lawrence et al. 2003; Fassbender et al. 2004; Tomasi et al. 2007). Thus, it is possible that under SD, the subjects were unable to activate sufficiently cortical attention resources that are essential to cope with more demanding tasks (VA load; Fig. 3).

### **Occipital Hypodeactivation**

In the present study, deactivation of the cuneus was lower for SD than for RW. The cuneus is involved in secondary visual processing and commonly deactivate during VA tasks, presumably reflecting active neural inhibition to minimize interference of irrelevant visual processing and enhance attention to the target balls (Tomasi et al. 2006). Deactivation of the cuneus, precuneus, and the cingulate cortex has been associated with enhancement of alertness during VA (Hahn et al. 2007). Thus, the lower deactivation of the cuneus could reflect lower neural inhibition of interfering secondary visual processing in the cuneus and impaired alertness during SD.

### **Thalamic Connectivity**

The left and right sides of the ventral lateral nucleus of the thalamus were positively interconnected and have positive functional connections to the cuneus and the brain stem area where the locus ceruleus is located. The latter is consistent with the known role of the noradrenergic system in arousal (Berridge 2007) and provides evidence in the human brain that this modulation is brought about in part by modulating thalamic activity (Devilbiss et al. 2006). In contrast, the left ventral lateral nuclei of the thalamus had a negative functional connectivity with the precentral motor cortex of the default network. Previous studies in macaques have shown that the medial dorsal, ventrolateral, and the ventral posterior lateral nuclei of the thalamus have afferent projections to the precentral motor cortex (Akert et al. 1979; Darian-Smith et al. 1990), supporting our findings on SD-related connectivity. Thus, when the thalamus is activated, this would result in deactivation of the default network, enabling the recruitment of neuronal resources to process the task. Therefore, the enhanced thalamic activation with failure to further activate/deactivate as a function of task difficulty could explain why the

parietal and occipital activation is lower during SD than during RW and why as the task difficulty increases the cortical areas fail to accommodate. Thus, it is possible that enhanced thalamic activation required to maintain arousal during SD as fatigue increased may have resulted in lower inhibition of secondary visual processing in the cuneus and other interfering processing in the parietal and CG default network (Raichle et al. 2001).

## Conclusions

Increased activation of the thalamus, decreased activation of the parietal, and decreased deactivation of the occipital cortex and CG suggest that under SD, accurate performance during VA tasks requires larger recruitment of resources in brain regions involved with alertness (thalamus), possibly to compensate for impaired orienting (parietal cortex) and executive processes (CG).

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## Notes

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