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Lapsing when sleep deprived: Neural activation characteristics of resistant and vulnerable individuals

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ABSTRACT

Lapses of attention, in the form of delayed responses to salient stimuli, increase in frequency for some but not all persons after sleep deprivation (SD). To identify patterns of task-related brain activation that might explain differences in vulnerability to SD, we performed fMRI on participants during a visual, selective attention task. We analyzed the correct responses in a trial-by-trial fashion to model the effects of response time. Stimulus contrast was varied to modulate perceptual difficulty. Attentional lapses and low-contrast stimuli were independently associated with increased signal in fronto-parietal regions associated with biasing attention. Sleep-deprived vulnerable individuals showed reduced top down fronto-parietal signal across all levels of image contrast and this reduction was particularly significant during lapses. There was concurrent reduction in extrastriate cortex and thalamus activation. Non-vulnerable persons showed a trend towards higher top-down biasing of attention and preserved visual cortex activation during SD lapses. A major contributor to performance degradation in SD appears to be a reduction in top-down biasing of attention that is independent of task difficulty.

Introduction

Serious industrial catastrophes, transportation accidents, and medical errors result from lapses of attention that occur when sleep-deprived individuals fail to stay alert while fighting the tendency to fall asleep (Mitler et al., 1988; Dinges, 1995; Barger et al., 2006; Philip and Akerstedt, 2006). Lapses can manifest as delayed responses to well-defined target stimuli (Dorrian et al., 2005; Weissman et al., 2006; Chee et al., 2008), response errors (Padilla et al., 2006) or failure to respond (Peiris et al., 2006). We recently showed that lapses resulting from a delayed response in the setting of sleep deprivation (see Methods for an elaboration) differ from lapses of equivalent duration recorded after a normal night of sleep by (1) an attenuated response of frontal and parietal control regions with an accompanying (2) reduction in extrastriate visual cortex activation, and (3) reduced thalamic activation during lapses that contrasts with the elevated thalamic activation during non-lapse periods (Chee et al., 2008).

These findings raised two questions addressed in the present study. The first relates to whether or not these results generalize across individuals who differ in their vulnerability to sleep deprivation. The second question involves the relative contribution of reduced top-down control of attention in the sleep-deprived state vis-à-vis regional failure of the extrastriate visual cortex to adequately capture sensory information.

It is well established that selective attention results in enhanced responses to stimuli within the attended location, driven by top-down signals originating in frontal and parietal regions (Desimone and Duncan, 1995; Reynolds and Chelazzi, 2004). As such, a possible explanation for the reduced extrastriate activation associated with lapses during sleep deprivation is that it merely reflects weakened parietal and frontal biasing signals.

However, an alternative explanation is that use-dependent homeostatic effects (Huber et al., 2004; Huber et al., 2006) could impair the ability of visual cortex to respond appropriately to salient stimuli independent of attention driven effects. The affected extrastriate cortex could also be manifesting "local sleep" whereby cortical areas that were particularly taxed during wakefulness show greater propensity to manifest sleep-like properties (Pigarev et al., 1997; Krueger et al., 2008).

To distinguish between these alternative explanations for reduced extrastriate cortex activation during lapses in SD, we manipulated image contrast to vary the perceptual difficulty of the task. Increasing perceptual difficulty has been shown to elevate activation in fronto-parietal regions involved in mediating cognitive control (Marois et al., 2004). This has the effect of increasing the apparent contrast of the stimulus—making a low contrast stimulus more likely to be perceived. We have previously suggested that lapses in SD might result from a compounded loss of top-down cognitive control superposed on existing deficits that occur when

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lapsing in the rested state. Under this framework, if reduced visual cortex activation was the product of a decrease in top-down influences, we would expect a concurrent state-related reduction in both fronto-parietal and visual sensory activation across different levels of stimulus contrast. We might additionally expect that such a decline in top-down control of visual attention to be more severe in those vulnerable to the effects of sleep deprivation than in those resistant to its effects.

Conversely, should local sleep or use-dependent degradation of visual cortex function be at fault, we might expect vulnerable individuals to show a disproportionate reduction of visual cortex activation at low levels of stimulus contrast and a concurrent increase in top-down biasing signals arising from fronto-parietal control regions with these low-contrast stimuli (Fig. 1).

Methods

Participants

Twenty right-handed, healthy adults (15 females, mean age = 21.5 years, stdev = 2.0 years) participated in the study after giving informed consent. Participants were selected from a pool of university students who responded to a web-based questionnaire. They had to: (1) be right-handed, (2) be between 18 and 35 years of age, (3) have habitual good sleeping habits (sleeping no less than 6.5 h each night for the past 1 month), (4) not be on any long-term medications, (5) have no symptoms associated with sleep disorders, and (6) have no history of any psychiatric or neurologic disorders. The sleeping habits of all participants were monitored throughout the 2-week duration of the study and only those whose actigraphy data indicated habitual good sleep (i.e., they usually slept no later than 1:00 AM and woke up no later than 9:00 AM) were recruited for the study. All participants indicated that they did not smoke, consume any medications, stimulants, caffeine or alcohol for at least 24 h prior to scanning.

Study procedure

Participants visited the laboratory three times. In the first visit, they were briefed on the study protocol and practiced the study task. At the end of this session, participants were each given an actiwatch (Actiwatch, Philips Respironics, USA) and were issued sleep diaries on which they were to record the onset and offset of all sleep bouts. Sleep history was inspected prior to each of the fMRI scanning sessions, and participants who did not comply with a regular sleep schedule (>6.5 h of sleep/night; sleep time no later than 1:00 AM; wake time no later than 9:00 AM) were excluded. The second and third visits involved the actual in-scanner fMRI experiments. The first scanning session took place approximately 1 week after the initial visit. The order of the two sessions (rested wakefulness (RW) and sleep deprivation (SD)) was counterbalanced across all the participants and the sessions were separated by 1 week. This was to minimize residual effects of sleep loss in participants whose SD session preceded the RW session. The RW session commenced at about 8:00 AM. For the SD session, participants were monitored in the lab from 7:00 PM onward and scanning took place the next morning at approximately 5:00 AM. Participants remained awake overnight in the laboratory under the constant supervision of a research assistant and were allowed to engage in non-strenuous activities such as reading and watching videos. For 10 min every hour from 7:00 PM until 5:00 AM, participants completed the Psychomotor Vigilance Task, a test of sustained attention that is sensitive to SD (Dinges et al., 1997; Doran et al., 2001), and rated their subjective sleepiness using the Karolinska Sleepiness Scale. Vigorous physical activity prior to the scans was not permitted.

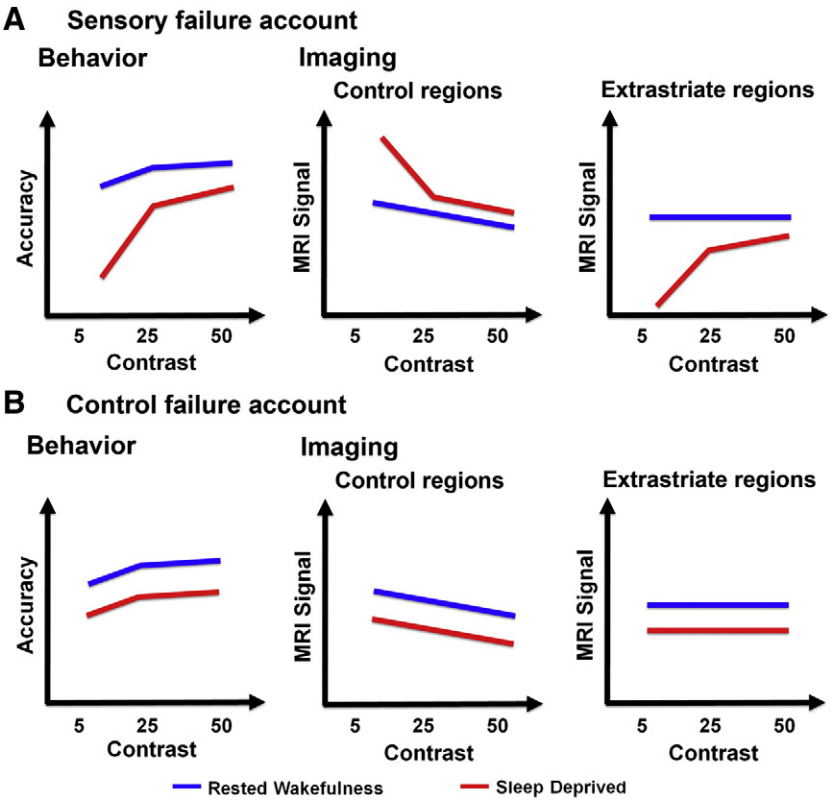

Fig. 1. Schematic showing the expected relative accuracy and BOLD signal values in cognitive control and visual sensory areas, at different levels of luminance contrast, in the "top-down control failure" and "sensory failure" accounts of lapsing while sleep deprived.

Experimental task

The task stimuli were single large, global letters (H or S; 3.3°×2.1°) composed of several, smaller local letters (H or S; 0.6°×0.4°) (Navon, 1977). The global letter and the local letters were either congruent (i.e. a global H made up of local Hs or a global S made up of local Ss) or incongruent (i.e. a global H made up of local Ss or a global S made up of local Hs). Three different levels of luminance contrast were used in creating the stimuli: 5%, 25% and 50% of the original luminance (Fig. 2). In each trial, a stimulus was presented in the center for 200 ms and participants identified the smaller, local letters by pressing one of two buttons. The buttons represented either H or S.

There were 6 runs of this task and each run contained 96 trials. Each run lasted 441 s and there were 294 time points per run. Within each run, there were equal numbers of congruent and incongruent stimuli. As such there were a total of 576 trials per subject per state or 144 trials per contrast condition per state. This large number of trials ensured data fidelity even in the event of increased lapses in SD. The order of presentation of the different trial types was counterbalanced. The inter-trial interval (ITI) ranged from 3 to 9 s (mean ITI = 4.2 s) using an exponential distribution that favored short ITI (Hagberg et al., 2001).

Training runs were half the length of actual experimental runs, and participants had to practice the task until they surpassed an accuracy threshold of 70%. Most participants succeeded on the first training run.

Imaging procedure and analysis

Participants viewed stimuli through a set of MR-compatible LCD goggles (Resonance Technology, Los Angeles, USA) and responded using their right hand via a MR-compatible button box. Participants' performance was continually monitored through the use of an in-scanner camera and they were prompted to respond if they missed three consecutive responses or if their eyelids were closed for more than the duration of a slow blink. Foam padding was used to restrict head motion. Images were acquired on a 3 T Tim Trio system (Siemens, Erlangen, Germany) fitted with a 12-channel head coil. A gradient echo-planar imaging sequence was used with a TR of 1500 ms, TE of 30 ms, field of view of 192×192 mm and a matrix size of 64×64. Parallel image reconstruction with GRAPPA was enabled and an acceleration factor of 2× was engaged. Twenty-eight oblique axial slices (4 mm thick with a 0.4 mm inter-slice gap) parallel to the AC-PC line covering the whole brain were acquired. High-resolution coplanar T1 anatomical images were also obtained. For the purpose of image display in Talairach space, a further high-resolution anatomical reference image was acquired using a 3D-MPRAGE sequence.

The functional images were processed using Brain Voyager QX version 1.10.3 (Brain Innovation, Maastricht, Netherlands). Intra-session image alignment to correct for motion across runs was performed using the first image of the final functional run as the reference image. Inter-slice timing differences attributable to slice acquisition order were adjusted using cubic spline interpolation. Gaussian filtering was applied in the spatial domain using a smoothing kernel of 8 mm FWHM for group level activation maps. Following linear trend removal, a high-pass filter of period 147 s was applied. The T1 images were used to register the functional data set to the volunteers' own 3D image and the resulting aligned dataset was transformed into Talairach space.

The general linear model that we used to conduct our trial-by-trial analyses included three main sets of predictors, which had separate vectors for each contrast and for each of the two states SD and RW:

$$h_{\mathrm{RT,contrast\_}x,\mathrm{state}}(t) = h_{0,\mathrm{contrast\_}x,\mathrm{state}}(t) + (RT - \overline{RT})h_{1,\mathrm{contrast\_}x,\mathrm{state}}(t) + m(t)_{\mathrm{combined\_state}} + \varepsilon \quad (1)$$

The first set of predictors ($h_{0,\mathrm{contrast\_x,state}}(t)$) modeled the average RT-indifferent hemodynamic response to each trial type across time and used 12 finite-impulse-response regressors per contrast (subscript contrast_x) and for each state (subscript state). The second set of predictors $(RT\text{-}\overline{RT})h_{1,\mathrm{contrast\_}x,\mathrm{state}}(t)$ consisted of 12 regressors that modeled the contribution of RT to the average hemodynamic response at each time-point of each trial type's average response. Again, this was computed per contrast and for each state. For these RT regressors, the relative RT for each trial was the mean-subtracted RT for correct trials (Weissman et al., 2006). This second set of predictors was completely orthogonal to the first set of predictors at each time-point. Incorrect trials, trials with an omitted response, and trials with RTs greater than 3 s or less than 0.3 s were modeled separately as misses ($m(t)$) and were not analyzed further.

The complete model therefore contained 168 predictors; 24 predictors being associated with each state and contrast respectively and 12 predictors each for separately modeled misses for each state.

For each participant, multiple linear regression analyses yielded two sets of fMRI response curves per state per contrast level. One set of response curves reflect the average cortical response to the stimuli across all RTs which is referred to as "task-related brain activation"—the terms modeled by ($h_{0,\mathrm{contrast\_x,state}}(t)$). Comparing task-related brain activation in the RW and SD states at each level of contrast allowed us to determine whether, on average, different patterns of brain activation were present in the SD and RW states. The second set of response curves ("delay-related response") reflect the change in BOLD signal corresponding to a unit delay in responding relative to the mean RT for that state and for each level of contrast—the terms modeled by $(RT\text{-}\overline{RT})h_{1,\mathrm{contrast\_x,state}}(t)$.

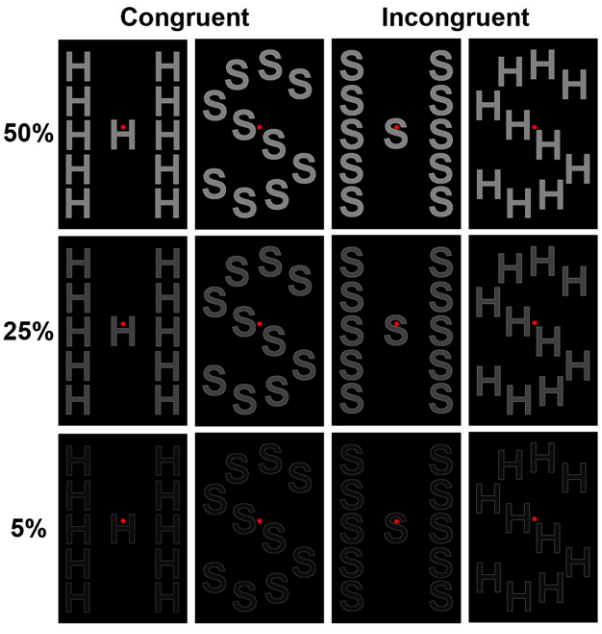

Fig. 2. Task stimuli used in the experiment were single large, global letters (H or S) composed of several smaller local letters (H or S). The global letter and the local letters were either congruent (global H made up of local Hs and global S made up of local Ss) or incongruent (global H made up of local Ss and global Ss made up of local Hs). The stimuli were constructed at three different levels of contrast: 5%, 25% and 50%. A red fixation dot was displayed at the centre of the screen throughout each run, and the experimental stimuli were presented in the surrounds of the fixation dot. Participants identified the smaller, local letters by pressing one of two buttons.

To determine the *overall effect* of the task on cortical activation at each state for each level of contrast, we *summed* the "task-related activation" curve, with the product of the RT delay and the second "delay-related" response curve (Suppl Fig. 1):

$$h_{\mathrm{LAPSE(contrast\_x)}}(t) = h_{0,\mathrm{contrast\_x}}(t) + 0.5h_{1,\mathrm{contrast\_x}}(t) \quad (2)$$

Although lapses are conceptually defined as delayed responses, their identification, that is, determining what constitutes a delayed response, is less clear, if not arbitrary. This is illustrated by the unimodal RT histograms of this experiment (Suppl. Fig. 2), those of our previous study (Chee et al., 2008), and the gamma distribution plots shown in a review on sleep deprivation and vigilant attention (Lim and Dinges, 2008), reflecting the absence of a second peak that represents a distinct delineation of delayed responses from the mean RT. In other words, while lapses correspond to less efficient or disrupted information processing, there does not seem to be a discrete "failure point." Although the probability of a negative behavioral outcome increases with increasing RT, it remains that very brief departures from median (say 25 ms) are unlikely to result in untoward consequences, making the application of a cut-off sensible.

We labeled responses that were at least 0.5 s longer than the mean RT "lapses." This served to demarcate lapses as *substantial* response delays, differentiating them from lesser, possibly less significant, temporal deviations (Lim and Dinges, 2008).

The "mean + 0.5 s" definition we used for lapses represents rare events that comprised approximately 3.5% of actual SD responses, averaged across subjects in the current study and about 2% in our original study (Chee et al., 2008). We analyzed between-state differences in brain activation at this particular time delay (0.5 s + mean RT) to compare lapses of comparable duration across RW and SD.

Additionally, to assess the appropriateness of using linear modeling for the delayed responses, we previously ran a separate model using the fastest and slowest 10% of response times and found the two analyses to give largely similar findings (Chee et al., 2008).

Task-related activation was determined by identifying voxels showing a significant difference in BOLD signal between the peak and post-peak undershoot phases of the average hemodynamic response to the stimuli in the RW state. Specifically, two time-points from the peak (4.5 and 6 s) and two time-points from the nadir (12 and 13.5 s) of this *average, RT-indifferent* fMRI response were contrasted. To control for Type I error, voxels were processed using an iterative cluster size thresholding procedure (Goebel et al., 2006) that considered the spatial smoothness of functional imaging data when generating activation maps based on a corrected cluster threshold ($p<0.05$). A random effects analysis of the aforesaid contrast was conducted and the resulting t-map was thresholded at $p<0.001$. The reasons for using the RW state as a reference point to base further analyses have been previously discussed (Choo et al., 2005).

ROI analysis

Five sets of significantly activated regions relevant to our predictions were chosen for ROI analyses based on prior work using the same experimental paradigm (Weissman et al., 2006; Chee et al., 2008). These ROIs were (1) medial frontal cortex, (2) left and right inferior frontal gyrus, (3) left and right intraparietal sulcus (IPS), (4) left and right lateral occipital cortex and (5) left and right thalamus. Each ROI was centered at a local maximum in the task-related activation statistical map and had a minimum volume of 1 cm^3. For bilateral ROI, activations in the left and right hemispheres were averaged to give a single figure.

We evaluated differences in activation across state and response delay by comparing the elicited BOLD signal between 3 and 9 s following stimulus onset under the different contrast conditions. Where there was a phase shift in the BOLD response as in the case of the thalamus, the lapse (delayed responses) response curves were shifted so as to align the response maxima for comparison. Statistical significance of these differences was evaluated using one-way and two-way ANOVA as appropriate.

Vulnerability to SD and its effect on cortical and thalamic activation

To determine how vulnerability to performance decline influenced brain activation, the 20 subjects were median split into Vulnerable and Non-vulnerable groups, according to their change in performance accuracy after sleep deprivation. This change in performance accuracy was averaged across the three levels of contrast. Vulnerable persons showed a more pronounced deterioration in performance accuracy in SD relative to RW when compared to Non-vulnerable persons. Note that although there was a trend, RT during sleep deprivation did not differ significantly across these two subgroups (Table 1, Suppl. Fig. 2). Additionally, we correlated change in accuracy and change in activation with SD in various ROI for each level of stimulus contrast.

Results

Behavioral findings

There was a strong main effect of contrast ($F_{(2,36)}=41.77$, $p<0.001$) and state ($F_{(1,18)}=22.75$, $p<0.001$) on performance accuracy. Subjects were less accurate in the low contrast conditions and during SD (Table 1). There was no interaction between contrast and state ($F_{(2,36)}=0.70$, n.s.). There was an interaction between vulnerability and state ($F_{(1,18)}=36.82$, $p<0.001$) in which Vulnerable subjects were less accurate after SD compared to Non-vulnerable subjects.

Subjects were slower in responding to lower contrast stimuli ($F_{(2,36)}=73.47$, $p<0.001$) but although there was a trend, their responses were not significantly slower after SD ($F_{(1,18)}=1.60$, n.s.). There was no interaction between state and contrast with respect to reaction time ($F_{(2,36)}=0.20$, n.s.). Additionally, vulnerability to SD did

Table 1
Behavioral data after a normal's night sleep (RW) and after 24 h of sleep deprivation (SD). Figures in parentheses indicate standard deviation.

Stimulus Contrast	RW			SD		
	5%	25%	50%	5%	25%	50%
Accuracy (%)						
Overall	84.55 (8.86)	94.13 (3.61)	94.65 (3.69)	78.72 (14.50)	87.81 (8.67)	90.73 (6.36)
Non-vulnerable	83.47 (9.82)	93.33 (3.26)	95.07 (4.00)	86.67 (13.61)	94.10 (4.14)	95.49 (2.97)
Vulnerable	85.63 (8.18)	94.93 (3.93)	94.24 (3.51)	70.76 (10.85)	81.53 (7.33)	85.97 (5.12)
Correct RT (ms)						
Overall	732 (93)	668 (88)	659 (89)	746 (93)	685 (83)	680 (83)
Non-vulnerable	696 (113)	637 (102)	630 (104)	707 (92)	646 (93)	650 (101)
Vulnerable	767 (53)	698 (62)	688 (65)	785 (79)	725 (50)	709 (49)

not have a significant effect on reaction time ($F_{(1,18)}=4.17$, n.s.). There was no vulnerability by state interaction ($F_{(1,18)}=0.10$, n.s.).

RT histograms in the SD state (Suppl. Fig. 2) did not show a clearly noticeable rightward shift. This is because unlike the conventional PVT distribution, non-responses, RT>3 s and incorrect responses were excluded from analysis. Instead, what we observed is a lowering of the peak of the RT distribution in Vulnerable compared to Non-vulnerable volunteers.

Perceptual difficulty and its effect on fronto-parietal activation

Across the entire study group and collapsed across state, there was a borderline main effect of contrast on activation. As activation in the fronto-parietal regions of interest that were identified through a whole brain analysis were symmetrical across hemispheres, analyses were performed by averaging activation magnitude across both left and right inferior frontal as well as IPS regions.

Considering data collapsed across all subjects and both RW and SD, lower contrast stimuli elicited marginally greater activation than high contrast stimuli in the bilateral inferior frontal ($F_{(2,36)}=4.83$, $p<0.05$) and superior parietal (around the intraparietal sulcus; IPS) regions ($F_{(2,36)}=4.45$, $p<0.05$; Fig. 3, Table 2). At this level of analysis, the effect of contrast was diluted by increased variance in activation relating to state and vulnerability to sleep deprivation.

To unpack, the effect of contrast on task-related activation was primarily a result of observations made after a normal night of sleep (RW: IPS: $F_{(2,36)}=3.18$, $p=0.05$; Inferior frontal: $F_{(2,36)}=3.71$, $p<0.05$)). The effect of contrast was not apparent following sleep deprivation (SD: IPS: $F_{(2,36)}=1.37$, n.s.; Inferior frontal: $F_{(2,36)}=0.83$, n.s.). More importantly, the effect of contrast on activation was significant for Non-vulnerable subjects (IPS: $F_{(2,18)}=9.96$, $p<0.001$; Inferior frontal: $F_{(2,18)}=18.34$, $p<0.001$) but was either not significant (IPS: $F_{(2,18)}=1.96$ n.s.) or less significant (Inferior frontal: $F_{(2,18)}=3.94$, $p<0.05$) in Vulnerable subjects.

Taken together, these observations support the notion that activation in fronto-parietal regions relates to top-down biasing of visual attention that was weakened following sleep deprivation in Vulnerable individuals. This inference on these particular ROI is buttressed by the fact that the peak voxels showing the effect of contrast coincided with those activated by the task, confirming their functional relevance. Finally, these results concur with work showing greater engagement of the fronto-parietal control regions with higher visual perceptual demands (Marois et al., 2004) in well rested subjects.

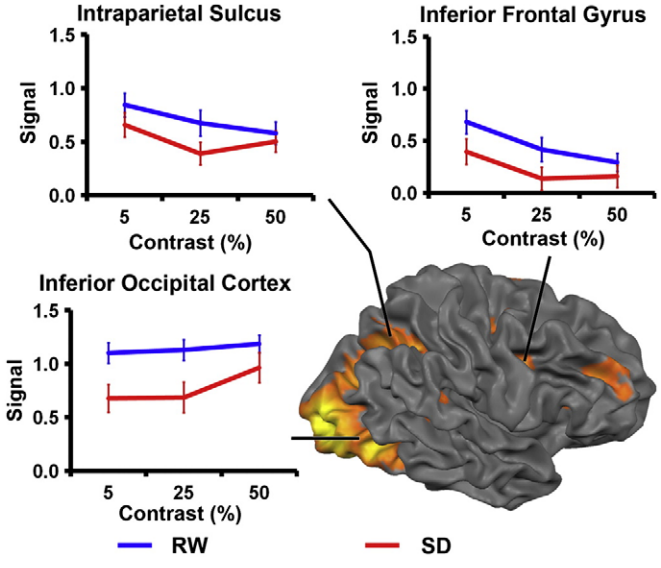

Fig. 3. Plots depicting the magnitude of activation at the mean RT for rested wakefulness after a normal night's sleep (RW) or sleep deprivation (SD) in the intraparietal sulcus (IPS; top-left panel), inferior frontal gyrus (top-right panel) and inferior occipital cortex (bottom-left panel). The bottom-right panel shows areas activated during the task across all three contrasts during RW (threshold $p<0.001$ uncorrected). BOLD signal in the IPS and inferior frontal gyrus scaled linearly with contrast change during both RW and SD. BOLD signal was significantly lower during SD in the occipital and frontal regions.

Table 2
Talairach co-ordinates of regions that showed significant task-related activation (thresholded at $p<0.001$ uncorrected). Regions that showed an effect of contrast are marked with an asterisk.

	BA	Talairach coordinates			t value	
		x	*y*	*z*	RW	SD
L medial frontal cortex	6	−3	−1	55	8.80	6.92
R medial frontal cortex	6	4	2	52	7.98	6.30
L inferior frontal gyrus*	6	−39	2	31	4.34	2.45
R inferior frontal gyrus*	6	39	−1	31	6.55	3.58
L middle frontal gyrus	9	−30	41	28	6.25	6.53
R middle frontal gyrus	9	30	44	31	5.42	4.28
L insula*	13	−33	14	13	6.77	3.09
R insula*	13	27	29	10	5.17	3.52
L intraparietal sulcus*	7/40	−24	−64	34	7.91	5.94
R intraparietal sulcus*	7/40	27	−52	40	5.58	4.34
L inferior occipital lobule	18	−39	−73	−14	11.19	6.44
R inferior occipital lobule	18	36	−82	−5	7.73	5.99
L thalamus		−15	−19	13	7.65	8.93
R thalamus		9	−10	13	5.81	6.55

Perceptual difficulty and its effect on visual cortex activation

In keeping with prior work concerning the effect of contrast on visual cortex activation (Tootell et al., 1995), we found a parametric effect of image contrast on primary visual cortex ($F_{(2,36)}=15.84$, $p<0.001$; represented in the medial occipital, pericalcarine area) activation (Fig. 4) and contrast insensitivity in the extrastriate cortex ($F_{(2,36)}=1.36$, n.s.; represented in the inferior / lateral occipital cortex) following a normal night of sleep (Malach et al., 1995).

Lapses result in elevation of fronto-parietal activation across both states

In agreement with prior findings that lapses result in an elevation of top-down biasing signals (Weissman et al., 2006; Chee et al., 2008), lapses were associated with higher intraparietal sulcus, inferior frontal and medial frontal activation relative to mean task-related activity (IPS: $F_{(1,18)}=41.04$, $p<0.001$; inferior frontal: $F_{(1,18)}=51.28$, $p<0.001$; medial frontal: $F_{(1,18)}=35.57$, $p<0.001$) in this study. At the whole group level, lapse-related signal elevation was not significantly affected by SD as reflected by the absence of an interaction between state and delay (IPS: $F_{(1,18)}=0.01$, n.s.; inferior frontal: $F_{(1,18)}=3.29$, n.s.; medial frontal: $F_{(1,18)}=0.01$, n.s). Additionally, there was no significant contrast by delay interaction (highest $F_{(2,36)}=1$, n.s.), indicating that on average, perceptual difficulty did not modulate the increase in top-down control signal associated with lapsing.

Sleep deprivation disproportionately impairs extrastriate visual cortex activation

In concert with SD-related reduction in mean, task-related activation within top-down control regions, there was a main effect of state on visual extrastriate activation in the inferior occipital region ($F_{(1,18)}=6.98$, $p<0.05$, Fig. 3).

The greater sensitivity of extrastriate cortex, referring to the more lateral part of the inferior occipital lobe, to sleep deprivation was evidenced by the absence of a significant effect of state on medial occipital (corresponding to primary visual cortex) activation at the whole-group level ($F_{(1,18)}=1.03$, n.s.). Additionally, we found strong

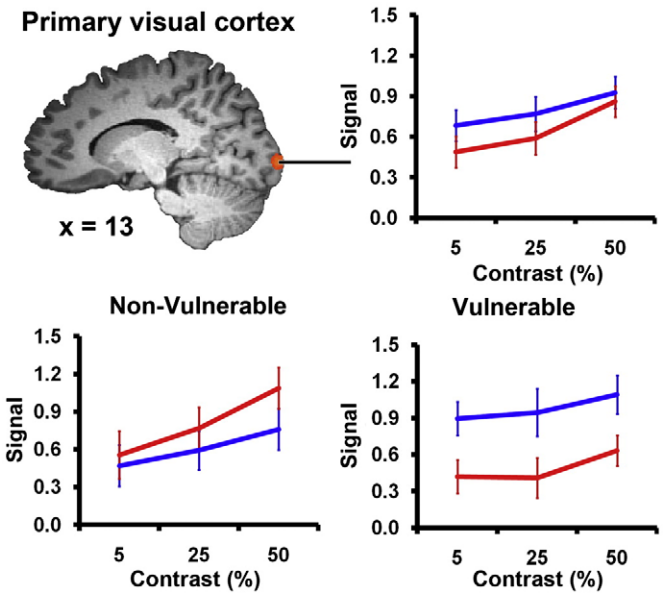

Fig. 4. Plots depicting signal associated with the mean RT across all three levels of contrast after a normal night's sleep (RW) and after sleep deprivation (SD) in the primary visual cortex. The top-left panel shows the region in the primary visual cortex that showed the strongest BOLD signal modulation with contrast during RW (threshold $p<0.001$, uncorrected). Overall, BOLD signal in the primary visual cortex (top-right panel) scaled linearly with contrast change during both RW and SD but there were no state effects in this region. The bottom panel illustrates the magnitude of activation in the primary visual cortex when Vulnerable and Non-vulnerable subjects were plotted separately. The Vulnerable subjects but not the Non-vulnerable subjects showed significantly lower signal during SD compared to RW.

correlations between state-related change in intraparietal sulcus and inferior occipital signal across all three-stimulus contrasts (5% contrast: $r=0.82$, 25% contrast: $r=0.75$, 5% contrast: $r=0.81$; Suppl. Fig. 3).

Vulnerability to sleep deprivation reduced top-down biasing signal which affects extrastriate activation

Overall, sleep deprivation resulted in a lowering of mean task-related activity in the inferior frontal ($F_{(1,18)}=7.84$, $p<0.05$) and inferior occipital cortical regions bilaterally ($F_{(1,18)}=6.98$, $p<0.05$) (Fig. 5). Non-vulnerable subjects responded as though they were not sleep deprived—showing neither a state related reduction in top-down biasing signal (highest $F_{(1,9)}=1.05$, n.s.) nor a state-related reduction in lapse-related signal elevation (largest $F_{(1,9)}=2.39$, n.s.). Instead, it was the Vulnerable subjects who showed a significant reduction of mean task related activity in regions that bias visual attention (IPS: $F_{(1,9)}=13.43$, $p<0.01$; inferior frontal: $F_{(1,9)}=34.76$, $p<0.001$; medial frontal: $F_{(1,9)}=21.73$, $p<0.001$). Additionally Vulnerable subjects showed a smaller increase in lapse associated biasing signal following SD—a state by delay interaction (IPS: $F_{(1,9)}=8.57$, $p=0.01$, inferior frontal $F_{(1,9)}=17.36$, $p<0.01$; medial frontal: $F_{(1,9)}=5.12$, $p<0.05$, Fig. 5).

Reinforcing evidence that top-down bias in visual attention influences extrastriate cortex activation, Non-vulnerable subjects showed comparable inferior occipital activation across both RW and SD for mean (average RT) and lapse trials ($F_{(1,9)}=0.40$, n.s.). In contrast, Vulnerable subjects showed a reduction in mean and lapse-related inferior occipital signal after SD ($F_{(1,9)}=17.63$, $p<0.01$).

To investigate whether these findings regarding top-down biasing might generalize across different levels of performance decline (as opposed to being confined to a median split analysis), we examined the association between change in accuracy across state and the corresponding change in cortical activation, at different levels of stimulus contrast. We found significant correlations between behavioral change and activation in inferior occipital signal across all three-stimulus contrasts (5% contrast: $r=0.61$, $p<0.01$; 25% contrast: $r=0.49$, $p<0.05$; 50% contrast: $r=0.55$, $p<0.05$). In the IPS, the

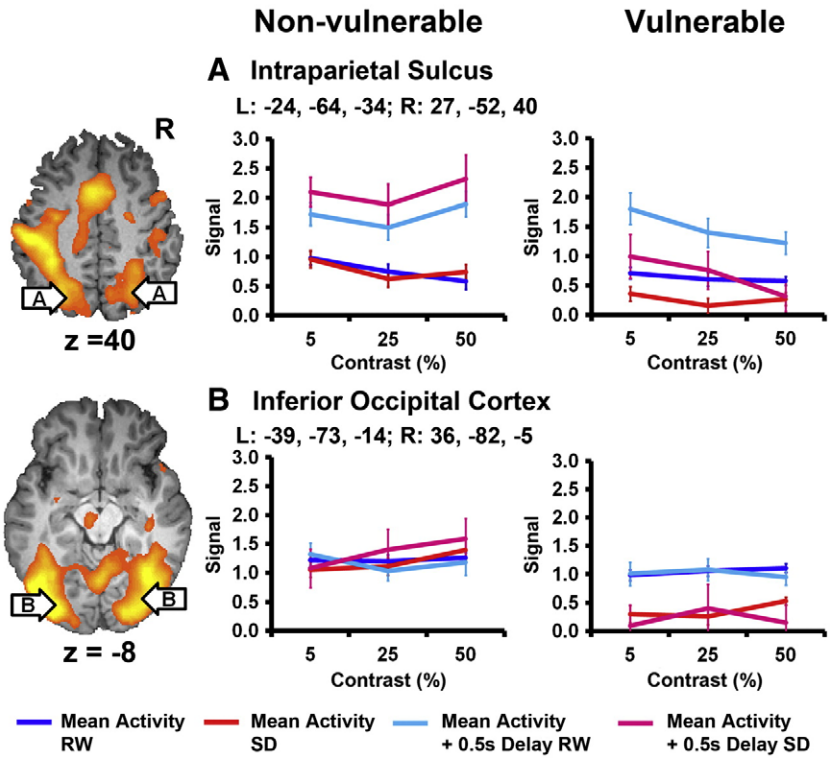

Fig. 5. State-specific mean and lapse associated BOLD signal in the intraparietal sulcus (IPS) and inferior occipital cortex across all three levels of contrast. Lapses were associated with higher signal in the bilateral intraparietal sulcus during both RW and SD. In both of these regions, there was a decline in activation following SD across all three contrasts for the Vulnerable but not for the Non-vulnerable group.

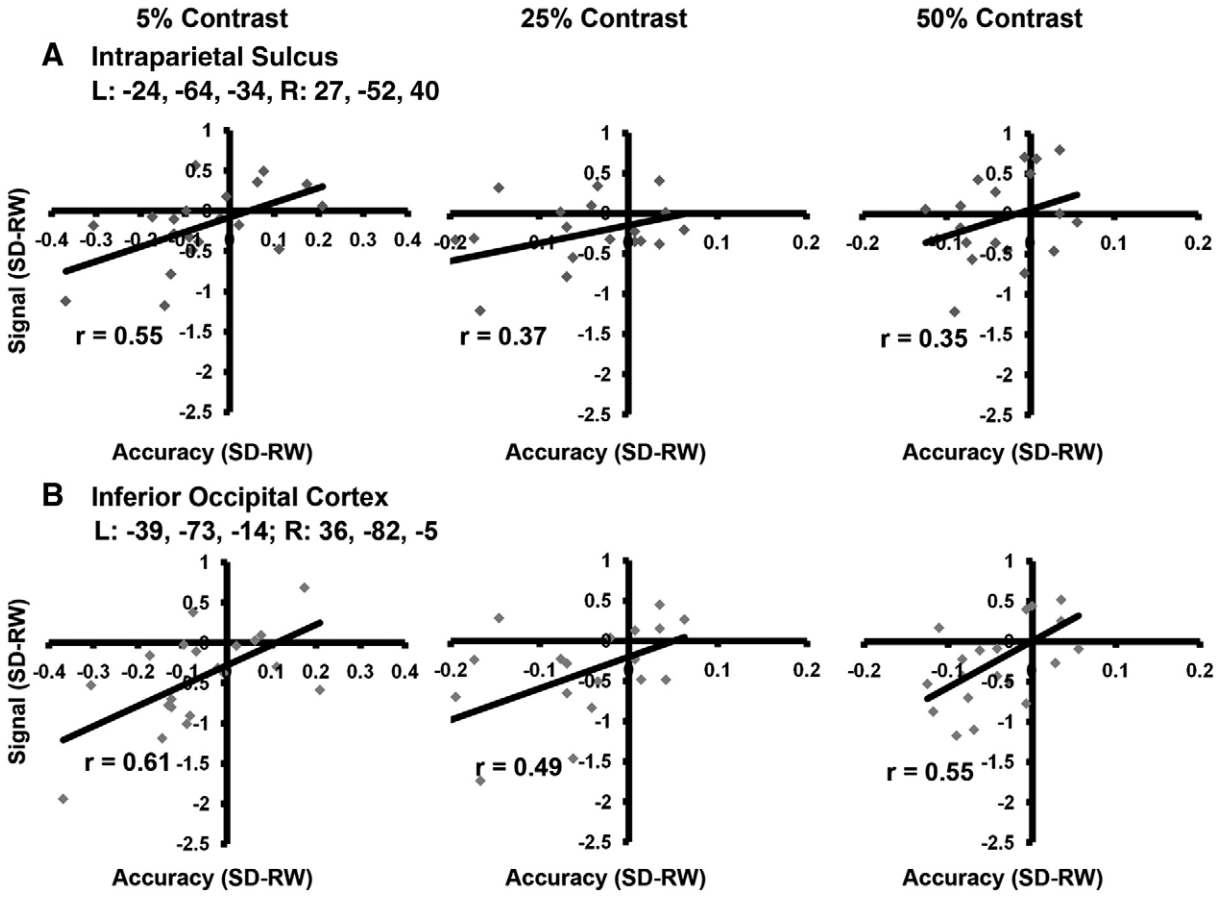

Fig. 6. Correlations between change in performance accuracy and change in BOLD signal across state at each level of luminance contrast for the intraparietal sulcus and inferior occipital regions. Correlation coefficients above 0.47 were significant at $p<0.05$.

behavior–signal correlation was only significant in the 5% contrast condition ($r=0.55$, $p<0.05$; Fig. 6).

Vulnerable subjects showed a pronounced decrease in thalamic activation during lapses

The thalamus is thought to influence arousal, which is distinct from attention modulation (Portas et al., 1998; Fan et al., 2005). Non-vulnerable subjects showed similar levels of thalamic activation during RW and following SD ($F_{(1,9)}=1.71$, n.s.; Fig. 7). In contrast, Vulnerable subjects showed a state by delay interaction ($F_{(1,9)}=13.3$, $p<0.01$). In these subjects, average responses were associated with similar activation across state ($F_{(1,9)}=1.71$, n.s.) whereas lapses in SD were associated with a pronounced reduction in thalamic activation ($F_{(1,9)}=13.11$, $p<0.01$, Fig. 7). Unlike a recent study (Tomasi et al., 2009), we did not find an inverse correlation between thalamus and parietal lobe activation. There was about a 1 TR (1.5 s) phase shift to the right in the BOLD response in SD compared to RW at the mean RT in each state at each level of contrast. The significance of this finding is presently unknown but its detection highlights the advantage of the FIR approach to modeling signal change.

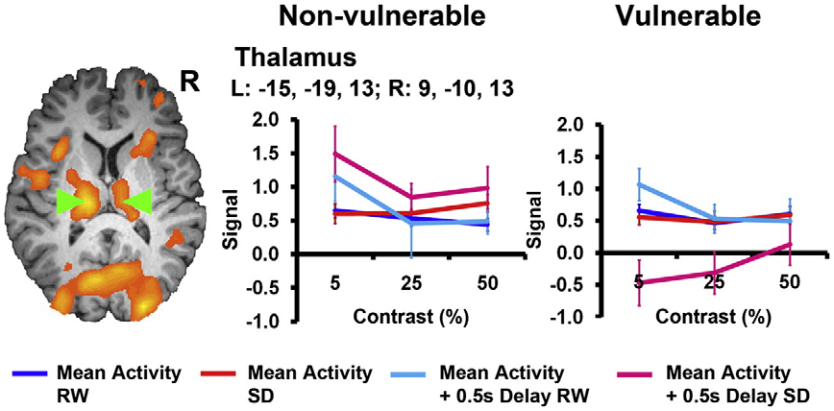

Fig. 7. Task-related fMRI signal associated with responses at the mean RT and lapses in the thalamus. In Vulnerable subjects, lapses significantly attenuated task related thalamic activation during SD but not in RW. This contrasts with the Non-vulnerable subjects, in whom lapses in both states elicited an fMRI signal comparable to that for mean responses.

Discussion

Replicating previous findings, we found that lapses were associated with elevated activation in fronto-parietal control regions that became less pronounced with sleep deprivation. During lapses in SD, Vulnerable persons showed significantly lower signal increases in cognitive biasing regions, a marked drop in visual cortex activation, and reduced thalamic activation. Non-vulnerable persons in contrast, showed higher top-down biasing of attention during lapses in SD, in addition to relatively preserved visual cortex and thalamus activation.

Perceptual difficulty and fronto-parietal and visual cortex activity

Lowering perceptual visibility or increasing interference has been shown to increase activation in a fronto-parietal network of regions similar to the ones indentified in the present study (Marois et al., 2004) and one may conceive of attention as a means of increasing contrast gain for the attended item (Reynolds and Desimone, 2003). This said, while the increase in fronto-parietal activation with lowered stimulus contrast in the present study was significant, it was very modest relative to the overall effect of state on activation. Additionally, SD did not have much impact on the contrast–activation relationship. Had sleep deprivation lowered the effective stimulus contrast, as predicted by a "sensory failure" account of performance degradation, we would have observed significantly reduced visual cortex activation with low-contrast stimuli. However, this was not the case, even for Vulnerable subjects, suggesting that image contrast/perceptual difficulty are relatively inconsequential to performance degradation in SD.

Vulnerable persons are unable to increase fronto-parietal activation when sleep deprived

Both Vulnerable and Non-vulnerable volunteers showed an increase in fronto-parietal activation during lapses, after a normal night of sleep (Weissman et al., 2006; Chee et al., 2008). The propensity to increase activation during lapsing was strikingly attenuated in Vulnerable subjects following SD.

The smaller modulation of fronto-parietal activation during lapsing correlated with the decline in performance accuracy when individuals were sleep deprived. However, as pointed out earlier, there was no significant relationship between state-related change in activation and task difficulty. Similar findings have been reported in experiments evaluating SD-related decline in visual short term memory capacity (Chee and Chuah, 2007), visual tracking (Tomasi et al., 2009) and the effect of cholinergic augmentation on performance (Chuah and Chee, 2008).

In each of these experiments, task difficulty was parametrically varied along a cognitive dimension postulated to be affected by sleep deprivation. However, instead of finding the anticipated association between activation magnitude and difficulty, SD attenuated brain activation independently of task difficulty and at a level well below known capacity limits of the function of interest. This led us to posit that a non-specific effect on cognition, most likely a loss of sustained attention/vigilance, is the dominant mechanism through which SD depresses performance in many tasks. This conclusion was also reached by a meta-analysis of behavioral studies of sleep-deprived individuals (Philibert, 2005).

Loss of top-down biasing affects extrastriate visual cortex activation in sleep-deprived vulnerable persons

The increase in fronto-parietal activation during lapses could plausibly arise through two mechanisms. The first is that these areas serve as accumulators of evidence for perceptual decision making (Shadlen and Newsome, 2001; Ploran et al., 2007). Greater activation with slower responses would be a consequence of less efficient or a reduced number of functional neural circuits kept active for an extended period to facilitate the required perceptual decision. This "time-on-task" account of increased activation with slower responses has been found in several different cognitive experiments (Yarkoni et al., 2009).

An alternative explanation is that refocusing attention to compensate for a degraded sensory input during lapses serves as a stimulus for stronger top-down biasing of the visual cortex (Weissman et al., 2006). The strong correlation between attenuation of parietal and inferior occipital activation during SD favors this latter account. Further, the functional relevance of the observed changes in fronto-parietal activation to behavior is supported by the significant correlation between change in parietal activation and behavior change across state.

Thalamus activation and the complementary role of the arousal system in maintaining performance during sleep deprivation

Although arousal might intuitively be expected to be depressed following sleep deprivation, functional imaging studies evaluating working memory (Chee et al., 2008), visual tracking (Tomasi et al., 2009) and selective attention (Portas et al., 1998; Chee et al., 2010) have shown relative preservation of task-related thalamus activation. In one study, thalamic activation after SD was higher than following a normal night of sleep and inversely correlated with parietal activation, leading the authors to suggest that elevated thalamic activation could be a compensatory mechanism (Tomasi et al., 2009).

Although we did not find elevated thalamic activation overall, the depression of thalamic activation during lapses in Vulnerable individuals combined with the trend towards elevation in Non-vulnerable persons suggests that trial-to-trial modulation of thalamic activation could have a bearing on performance (Chee et al., 2008).

Conclusion

In response to the questions that motivated this study, we found vulnerability to sleep deprivation to significantly modulate brain activation patterns during lapses in this state. We also found that the attenuation of top-down biasing signals rather than a primary deficit in visual cortex function can account for the effects observed in the visual cortex. This could be the predominant mechanism underlying lapses and their associated performance degradation in sleep-deprived persons.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.02.031.

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