

Identification and Differential Vulnerability of a Neural Network in Sleep Deprivation

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The study aimed to identify task-related brain activation networks whose change in expression exhibits subject differences as a function of differential susceptibility to sleep deprivation. Brain activity during a non-verbal recognition memory task was investigated in an event-related functional MRI paradigm both prior to and after 48 h of sleep deprivation. Nineteen healthy subjects participated. Regional covariance analysis was applied to data. An activation network pattern was identified whose expression decreased from pre- to post-sleep deprivation in 15 out of 19 subjects ($P < 0.05$). Differential decrease in expression correlated with worsening performance in recognition accuracy ($P < 0.05$). Sites of de-activation were found in the posterior cerebellum, right fusiform gyrus and precuneus, and left lingual and inferior temporal gyri; increased activation was found in the bilateral insula, claustrum and right putamen. A network whose expression decreased after sleep deprivation and correlated with memory performance was identified. We conclude that this activation network plays a role in cognitive function during sleep deprivation.

Keywords: cognitive function, covariance analysis, functional imaging, neural networks, non-verbal recognition memory, sleep deprivation

Introduction

Sleep deprivation significantly impacts human functioning (Pilcher and Huffcutt, 1996), negatively affecting levels of alertness and cognitive performance (Harrison and Horne, 2000; Thomas *et al.*, 2000). It has been demonstrated that sleep-deprived individuals experience increased reaction times and reduced vigilance relative to those with normal sleeping patterns (Harrison and Horne, 2000; Thomas *et al.*, 2000). Changes in cerebral blood flow may account for the cognitive deficits observed during sleep (Horne, 1993; Drummond *et al.*, 2001). Neuroimaging studies, using positron emission tomography (PET) (Wu *et al.*, 1991; Thomas *et al.*, 2000) or functional magnetic resonance imaging (fMRI) (Drummond *et al.*, 2000, 2001) have shown that changes in cerebral activation occur as a function of sleep deprivation, and that these changes are associated with changes in cognitive performance. Specifically, in studies utilizing PET, significant decreases in overall glucose metabolism following 24 h (Thomas *et al.*, 2000) and 32 h (Wu *et al.*, 1991) of sleep deprivation were observed and shown to correlate with declines in performance. Decreases in regional glucose activity have been observed primarily in the thalamus (Wu *et al.*, 1991; Thomas *et al.*, 2000), temporal (Wu *et al.*, 1991), prefrontal and parietal cortices (Thomas *et al.*, 2000).

Using fMRI, Drummond *et al.* (Drummond *et al.*, 2001) reported an increase in cerebral activation of the bilateral prefrontal cortex and parietal lobes following 35 h of sleep deprivation. Further, less impairment on a divided attention task, involving both a verbal learning and an arithmetic component, was associated with greater activation of the left inferior parietal/superior temporal gyri and the right inferior parietal gyri. On a verbal learning task, greater activation of the bilateral parietal lobe was associated with better task performance (Drummond *et al.*, 2000).

Most of these studies relied on group- and voxel-wise analyses to determine brain functional patterns without taking into account subject differences. As such, the individual behavioral and brain functional variability in response to sleep deprivation is not known. Subject differences may exist that are masked in the expression of group-specific functional patterns, and these differences important to an improved understanding of the impact of sleep deprivation on cognition and behavior. Our goal was to evaluate individual variability in susceptibility to sleep deprivation as a function of differential neural network changes in sleep deprivation. The analytic method we employ in the present study establishes regional covariance patterns of neural networks that are affected in sleep deprivation and quantifies the extent to which they are affected in each subject. If, in addition, these changes in network expression across individuals correlate with changes in cognitive performance, they provide a plausible explanation for how sleep deprivation acts on the brain to affect cognition. While of interest in and of itself, this might also aid the search for remedies that might lessen the detrimental effects of sleep deprivation. To the best of our knowledge, this is the first study to employ this type of analyses within an event-related functional magnetic resonance imaging design.

Materials and Methods

Nineteen healthy young adults (14 male, 5 female; mean education = 14.9 ± 1.84 years), between the ages of 21 and 30 years (mean = 25.05 ± 2.7 years), participated in an event-related functional magnetic resonance imaging (efMRI) paradigm both prior to and after 48 h of sleep deprivation. All subjects were right-handed and carefully screened to insure that they had no history of medical, psychiatric, neurological, or sleep disorder. Subjects maintained a sleep log for 2 weeks prior to study participation and reported sleeping an average of 6–8 h per night. Subjects were instructed to stop drinking caffeine 24 h prior to study participation and for the duration of the study. All subjects passed substance abuse screening tests. Polysomnographic monitoring confirmed that subjects remained awake during the sleep deprivation period.

During the sleep deprivation period, all subjects followed a standardized behavioral testing protocol (away from the scanner) consisting of test of simple RT (every 6 h), source memory (every 12 h), Sternberg memory scanning (every 12 h), and choice timing (every 24 h). Subjects also completed a neuropsychological profile on day 1 and the Beck Depression Inventory and Epworth Sleepiness Scale on both day 1 and day 3. Body temperature was measured every 6 h and blood pressure every 12 h. Television (with DVD), Sony PlayStation II, and Internet access were also available at all times.

Informed consent, as approved by the Internal Review Board of the College of Physicians and Surgeons of Columbia University, was obtained prior to study participation and after the nature and risks of the study were explained. Subjects were paid for their participation in the study.

Non-verbal Recognition Task

Two conditions of a nonverbal recognition test were included in the current analysis. The basic task consisted of the serial presentation of one or more single novel shapes, which we refer to as study items, followed by a series of the same number of recognition test probes or test items (see Fig. 1). The test items were distinguished from study items by a circumscribed rectangular frame. Subjects were instructed to make a 'new' or 'old' response for each test item by pressing with the index finger of the right or left hand, respectively, on a LUMItouch response device. A 'new' response was appropriate for test items that were not previously presented within the study items. An 'old' response was appropriate for test items that were presented and studied within the list of study items. Instructions were to stress accuracy over speed. New and old test items occurred with the frequency of 50%. Test items were pseudo-randomized so that no more than four consecutive trials required the same response.

Each shape was used only once for each subject. Loop shapes were used since their level of complexity made verbal encoding difficult. The stimuli were pre-screened to insure that they could not easily be given a name.

Subjects underwent two study conditions: low demand and high demand. In the low demand condition, the study list size (SLS) was 1 (i.e. one study shape followed by one recognition/test probe). The titrated demand condition used a subject-specific SLS that was predetermined to elicit a recognition accuracy of 75%. Prior to the initial fMRI scan, each subject completed a standardized training session and then two 15 min titration sessions. During these sessions, the particular SLS value at which the subject achieved 75% accuracy

was determined using a staircase method of SLS adjustment. This SLS value was then used in the titrated demand condition on both days of scans.

fMRI data for all conditions were acquired over three separate sessions (i.e. runs). In each session, the titrated demand condition lasted 240 s (15 trials), and the low demand condition 112 s (seven trials).

Each low demand trial was 16 s long: trials began with a 600 ms inter-trial interval (ITI), followed by the studied stimulus for 3400 ms, the test item for an additional 3400, followed by an 8600 ms resting baseline. (The purpose of the baseline was to increase signal:noise for the comparison of titrated and low demand. Though this might seem non-intuitive, it is related to the low frequency noise seen in fMRI data. Baseline periods were not similarly intercalated into the titrated demand condition because that would have disturbed its psychological structure.)

For the titrated condition, study and test periods were repeated as many times as possible (depending on the SLS) over the course of the 240 s interval, with new study and test lists presented on each iteration. The number of stimulus presentations at each study and test period was the SLS established for each subject. Both study and test trials began with a 600 ms ITI followed by stimuli for 3400 ms. Again, test trials were distinguished by study trials by the presence of a circumscribed rectangular frame. Subjects were instructed to study the object for the entire 3400 ms on study trials. Presentation of the test list (3400 ms per test stimulus) followed immediately after presentation of the study list.

fMRI Acquisition and Processing

Functional images were acquired using a 1.5 Tesla magnetic resonance scanner (General Electric) retrofitted for echoplanar imaging. A gradient echo EPI sequence ($T_E = 50$ ms; $T_R = 3$ s; flip angle = 90°) and a standard quadrature head coil was used to acquire T_2^* weighted images with an in-plane resolution of 3.124 mm \times 3.124 mm (64×64 matrix; 20 cm² field of view). Based on T_1 'scout' images, 8 mm transaxial slices (15–17) were acquired. Following the fMRI runs, a high (in-plane) resolution T_2 image at the same slice locations used in the fMRI run was acquired using a fast spin echo sequence ($T_E = 105$ ms; $T_R = 2500$ ms; 256×256 matrix; 20 cm² field of view).

All image processing and analysis was done using the SPM99 program (Wellcome Department of Cognitive Neurology) and other code written in Matlab 5.3 (Mathworks, Natick, MA). fMRI time series were corrected for order of slice acquisition. All functional volumes in

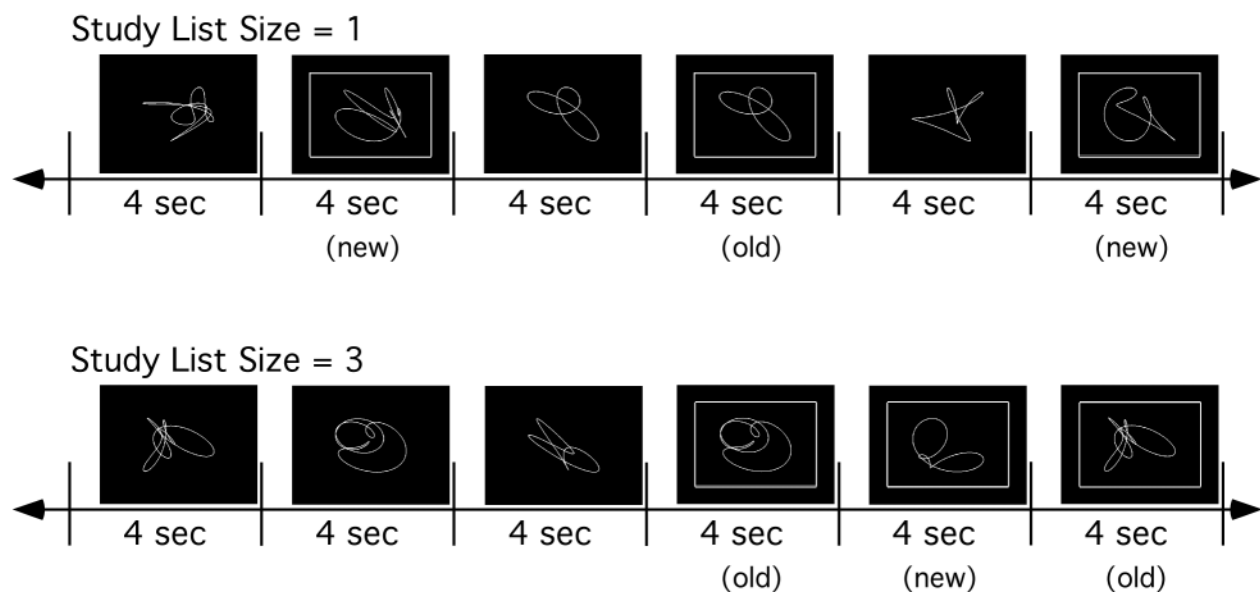


Figure 1. Schematic sketch explaining the task procedure. The upper part of the figure shows the low demand task condition with study and test on one item, whereas the lower part shows study and test on a list of three items.

a given subject were realigned to the first volume from the first run of each study. The T_2 anatomical image was then co-registered to the first functional volume, using the mutual information co-registration algorithm implemented in SPM99. This co-registered structural image was then used in determining non-linear spatial normalization ($7 \times 8 \times 7$ nonlinear basis functions) parameters for a transformation into a Talairach standard space defined by the Montreal Neurological Institute template brain applied with SPM99. These normalization parameters were then applied to the functional data (using sinc-interpolation to reslice the images to $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$).

Data Analysis

The fMRI response to stimulus presentation in each condition (i.e. either low or titrated demand) and period (i.e. either study or test) was modeled with an appropriately timed rectangular 3400 ms pulse convolved with a canonical hemodynamic response function (the default in SPM99). Contrast images, which compare the relative amplitudes of these fMRI responses to a no-stimulus baseline, were estimated in each subject. Specific contrasts included the titrated and low demand for both the study and test periods versus the baseline. Prior to population hypothesis testing these contrast images were divided by the mean EPI image for that subject (i.e. they were intensity-normalized) in order to eliminate artifactual differences in signal range across datasets due to scanner calibration/data reconstruction issues. The intensity-normalized images were then spatially smoothed with an isotropic Gaussian kernel (full-width-at-half-maximum = 8 mm).

Even though the purpose of the titration procedure was to constrain accuracy at 75% in the titrated demand condition, there were residual variations from this target value. Therefore, recognition accuracy (per cent correct) for the titrated demand condition was included as a covariate to obviate confounding of the reserve variables and task performance. Titrated demand SLS (orthogonalized with respect to the other variables) was also initially included as a covariate to explain other possible variance components of the data in order to increase sensitivity.

Regional Covariance Analysis

Ordinal Trend Canonical Variates Analysis (OrT CVA) (Habeck *et al.*, 2002) was performed on the data. This analysis is methodologically similar to other current regional covariance analyses techniques (McIntosh *et al.*, 1996; Worsley *et al.*, 1997; Alexander *et al.*, 1999) and was designed to identify a covariance pattern that shows an ordinal trend as a function of sleep deprivation, i.e. whose expression decreases for as many subjects as possible from pre to post sleep deprivation. The number of subjects violating the rule of decreasing expression from pre to post can be used as a statistic to test the null hypothesis and check for the presence of an ordinal trend (Habeck *et al.*, 2002).

Once a covariance pattern was identified that systematically decreased in expression as a function of sleep deprivation, we examined the correlation between individual subjects' change in network expression from pre to post sleep deprivation and change in their scores on the task performance measures.

Covariance patterns assign different regional weights to all regional resolution elements (RESELS) included in the analysis, depending on the salience of their covariance contribution. Whether its regional weight is statistically significant (i.e. reliably different from zero) is assessed by a bootstrap estimation procedure (Efron and Tibshirani, 1994) for every voxel. This involved sampling from the subject pool with replacement and repeating the analysis steps that yielded the point estimate results on the re-sampled data many times (>500 iterations). This procedure provides an estimate of the variability of the regional weights in the topography. A regional weight is considered stable when there is small variability about the point estimate. As such, a regional weight contribution to the covariance pattern can be generalized to the population from which the subject sample was drawn with low type I error probability.

As an indication of a stable regional contribution to the covariance pattern, we required the ratio of the point estimate w to the standard deviation of the re-sampled estimates s_w , the inverse coefficient of variation (ICV), to fulfill the following relationship:

$$\left| \frac{w}{s_w} \right| > 1.64$$

Interpreting the ratio of point estimate to its standard deviation as a normally distributed variable means the above equations fulfills the one-tailed requirement of $P < 0.05$.

Results

Behavioral Performance

On the baseline day, performance accuracy on the low demand task as indicated by a per cent correct was $90 \pm 6.04\%$. The mean reaction time was 1076 ± 251 ms. As intended, the titration procedures prior to the scan session produced a performance accuracy of $75 \pm 11.53\%$ on the titrated demand condition during the fMRI session. The reaction time for the titrated demand was 1671 ± 249 ms.

There was a negative effect of sleep deprivation on performance. Specifically, per cent correct for each task condition was significantly poorer following sleep deprivation (low demand = $64 \pm 20.8\%$, PRE-POST comparison: paired $t = 5.50$, $P < 0.0001$; titrated demand = $52 \pm 16.27\%$, PRE-POST comparison: paired $t = 8.71$, $P < 0.0001$), with increased between-subject variability. Reaction times for both task demands did not change significantly from PRE to POST sleep deprivation (low demand mean RT = 1200 ± 289 ms, POST-PRE comparison: paired $t = 1.18$, $P = 0.87$; titrated demand mean RT = 1582 ± 219 ms, POST-PRE comparison: paired $t = -1.75$, $P = 0.10$).

fMRI data

The first principal component of the OrT CVA displayed ordinal trend properties for the titrated demand condition of the test phase. Fifteen of 19 subjects decreased their pattern expression ($P < 0.05$), suggesting a clear neural correlate of sleep deprivation. A covariance pattern was not found for the low demand condition of the test phase or for either condition in the study phase (Fig. 2).

Brain regions that decreased in activation for the majority of subjects from the pre to post sleep deprivation transition were the bilateral posterior cerebellum, right fusiform gyrus and precuneus, and the left lingual and inferior temporal gyri. Brain

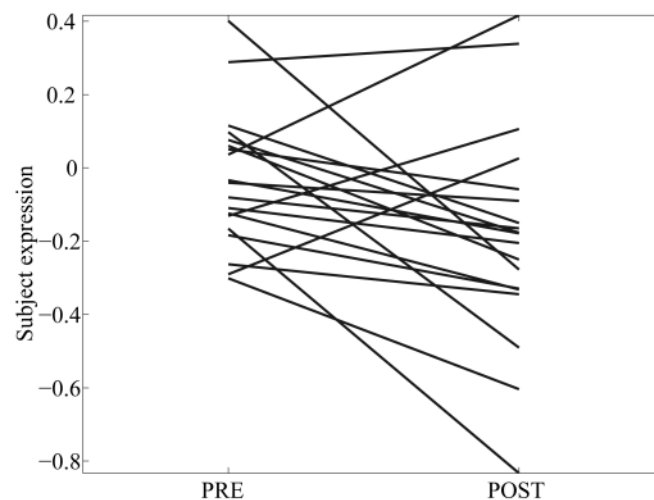


Figure 2. Difference of pattern expression from PRE to POST sleep deprivation. Fifteen of 19 subjects displayed a decrease in pattern expression ($P < 0.05$), affording good confidence that the activity related to the identified covariance pattern is successfully manipulated by the experimental design.

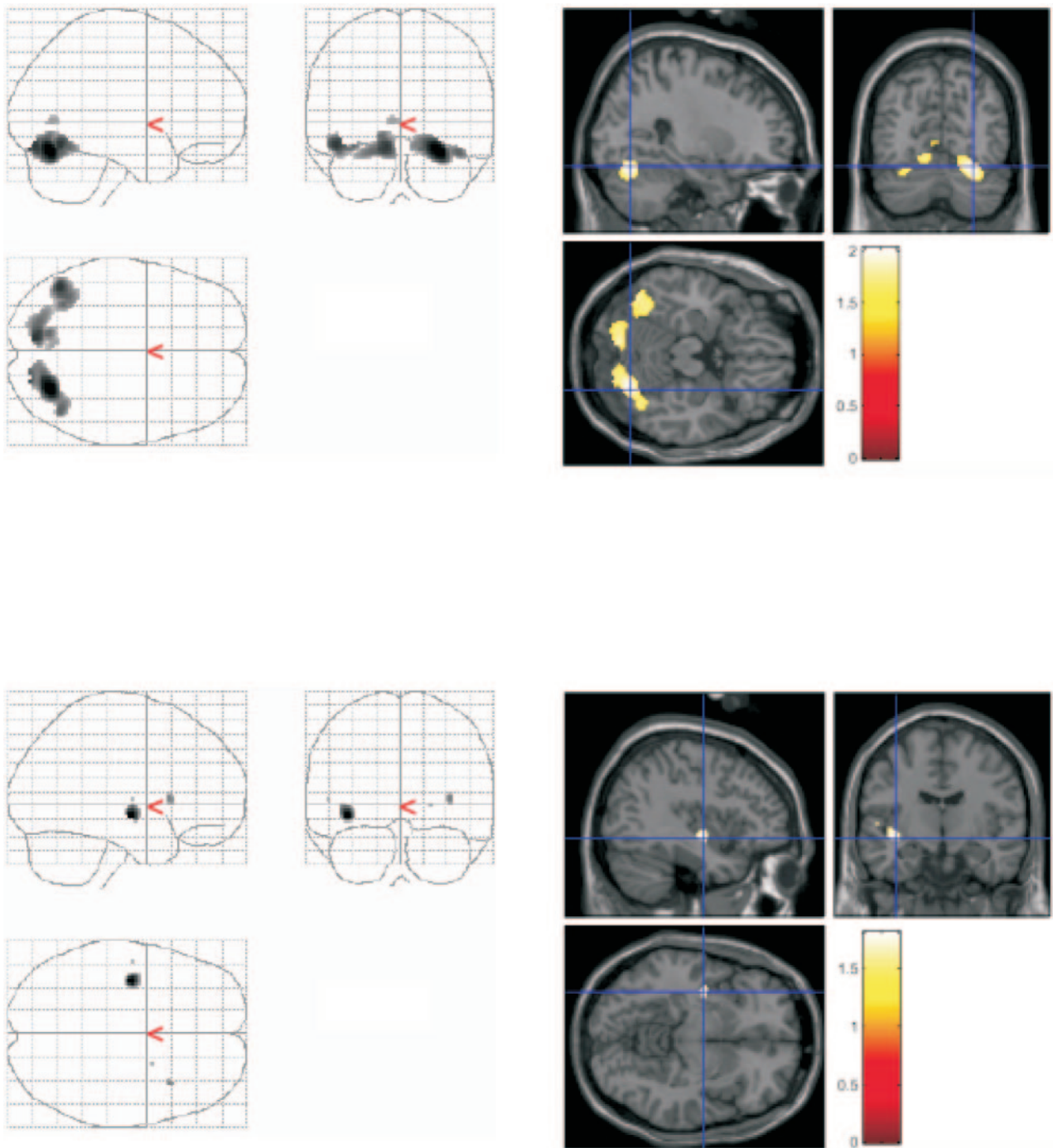


Figure 3. Upper half: glass brain projections and sectional view of selected brain regions that have a significant positive loading ($P < 0.05$) (i.e. associated activity decreases for the majority of subjects from PRE to POST) as ascertained by the bootstrap resampling test. Lower half: glass brain projections and sectional view of selected brain regions that have significant negative loadings ($P < 0.05$).

regions that increased in activation from pre to post for the majority of subjects were the bilateral insula, claustrum, and right putamen (Fig. 3; Table 1 and Table 2).

We then tested whether pattern expression could also predict behavioral performance and found that sleep-induced decrease from pre to post sleep deprivation was predictive of the decrease in recognition accuracy (i.e. % correct) (see Fig. 4).

The significant brain-behavior correlation provides further confirmation of having established a true neural correlate of sleep deprivation and its effects on cognitive performance.

Discussion

To our knowledge, this is the first study to investigate individual differences in susceptibility to sleep deprivation using a

Table 1
Talairach locations of areas with significant de-activation from PRE to POST ($P < 0.05$) as ascertained by a bootstrap resampling test (Talairach Demon Client 1.1, Research Imaging Center, University of Texas Health Science Center at San Antonio)

X	Y	Z				
28	-69	-12	right cerebellum	posterior lobe	declive	*
22	-82	-11	right cerebrum	occipital lobe	fusiform gyrus	Brodmann area 19
42	-61	-14	right cerebrum	temporal lobe	fusiform gyrus	Brodmann area 37
-10	-78	-10	left cerebrum	occipital lobe	lingual gyrus	*
-14	-68	-5	left cerebrum	occipital lobe	lingual gyrus	Brodmann area 18
-46	-61	-9	left cerebrum	occipital lobe	sub-gyral	*
-34	-59	-11	left cerebellum	posterior lobe	declive	*
-6	-64	5	left cerebrum	occipital lobe	lingual gyrus	Brodmann area 18

Table 2
Talairach locations of areas with significant activation from PRE to POST ($P < 0.05$) as ascertained by a bootstrap resampling test

X	Y	Z				
-38	-10	-6	left cerebrum	sub-lobar	insula	*
36	16	3	right cerebrum	sub-lobar	insula	*
22	4	0	right cerebrum	sub-lobar	lentiform nucleus	putamen
-51	-10	4	left cerebrum	temporal lobe	superior temporal gyrus	Brodmann area 22

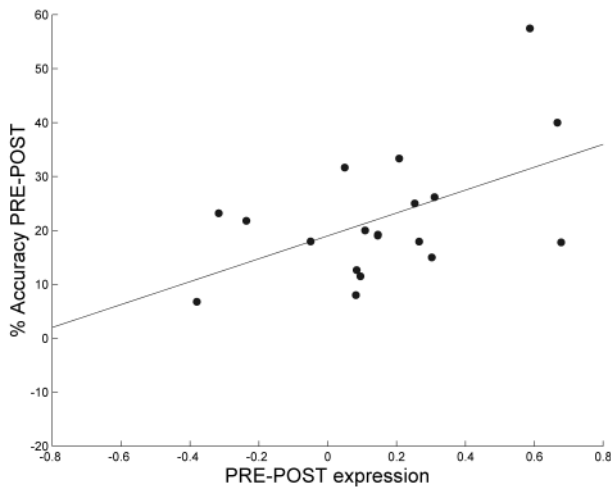


Figure 4. Brain-behavior correlation of pattern expression and worsening recognition accuracy due to sleep deprivation. The bigger subjects' decrease of their pattern expression, the worse their drop in performance.

covariance analysis on data obtained from an efMRI paradigm both prior to and after 48 h of sleep deprivation. This type of analysis can reveal a covariance pattern of neural networks that changed in expression as a function of task performance. Our analyses identified one such pattern, whose expression is disrupted with sleep deprivation. Specifically, the covariance pattern systematically changes in expression from pre to post sleep deprivation during the more demanding test phase of the recognition task that was conducted at two levels of difficulty (= memory load). Further, all but four subjects showed a decrease in the expression of the covariance pattern with sleep deprivation. These results suggest that a neural network

specific to sleep deprivation is identifiable and that change in expression of this network is related to cognitive functioning. The susceptibility of the neural network to sleep deprivation and its effect on cognition was variable across individuals, and those with a greater decrease in the expression of the covariance pattern demonstrated greater decrements in cognitive performance.

The covariance pattern that accounted for the effects of sleep deprivation and the subsequent drop in performance involved a number of visual association areas or 'ventral stream' regions that were identified in previous cognitive neuroimaging experiments involving visual memory and novelty processing tasks of objects' features and imagery (Moscovitch *et al.*, 1995; D'Esposito *et al.*, 1997; Faillenot *et al.*, 1997; Carlson *et al.*, 1998; Menon *et al.*, 2000; Rama *et al.*, 2001). Activation in these areas and the precuneus (BA 7), an area associated with 'dorsal stream' activity previously identified in processing object location (Beauchamp *et al.*, 2001; Burgess *et al.*, 2001; Calhoun *et al.*, 2001), decreased as a function of sleep deprivation for the majority of subjects in our experiment. This decrease was significantly correlated with worsening recognition performance. Additionally it is worth noting that sleep deprivation in our study did not affect the lateral prefrontal cortex, which is an important node in ventral stream processing (e.g. working memory for objects) and known to participate in many vertically segregated cortico-striatal-thalamo-cortical loops.

Cerebellar regions were also de-activated by sleep deprivation. There is evidence linking the cerebellum to procedural learning and adaptation (Fiez *et al.*, 1992; Nixon and Passingham, 1999, 2000; Nixon, 2003) and it could be that subjects' ability to anticipate the end of the testing sequence is affected adversely by sleep deprivation. With regard to cogni-

tive processes beyond procedural learning and adaptation, the cerebellum has not been found to be a necessary factor for accuracy of performance in spatial working memory or visual associative learning tasks (Nixon and Passingham, 1999), only speed. It is noteworthy however (Middleton and Strick, 1994) that the anatomical connectivity of the cerebellum with the thalamus gives rise to a closed cerebellar-thalamo-cortical loop, and that developmental cerebellar abnormalities in autism (Allen *et al.*, 1997; Allen and Courchesne, 2003) have been shown to cause posterior cerebellar attention-related activation and performance deficits, which might occur during sleep deprivation also.

These results suggest that sleep deprivation may affect the processing of visual object properties at the initial stages of perceptual and attentional processing. To the extent that sleep deprivation impacts working memory processes, sleep deprivation does not appear to differentially activate the frontal regions involved in this cognitive process. This effect may be due to the inability of a sleep deprived subject to sustain their visuospatial attention sufficiently, thereby having a detrimental and differential impact on performance in the relatively early stages of cognitive processing resulting in de-activation in the posterior parts of the brain.

The brain regions associated with increasing activation from pre to post sleep deprivation were located bilaterally in the basal ganglia and insula. The basal ganglia receive input from the visual association areas that were identified with decreased activation, but the portion of the fusiform gyrus located in inferior temporal cortex (BA 37) is the only one of the areas identified in visual association cortex that in turn receives input from the basal ganglia, thus establishing a closed basal ganglia-thalamocortical feedback loop (Middleton and Strick, 1996; Beiser *et al.*, 1997). Increased basal ganglia activation with concomitant inferior temporal de-activation could thus be interpreted as the result of an inhibitory connection between both brain regions. Increased activity in one region would then lead to decreased activity levels in the other region and vice versa. Sleep deprivation might act to shift the equilibrium between the two nodes towards a greater imbalance compared to the baseline when subjects were well rested.

Some of the regions in our covariance pattern have been noted in the context of psychiatric disorders (Liotti *et al.*, 2000; Nofzinger *et al.*, 1999; Wu *et al.*, 2001): striatal and paralimbic areas show increased activation in depressed patients in resting scans, whereas regions in the inferior temporal and parietal cortex show decreased activation. The increased activation in the former brain regions can be brought to normal levels in depressed patients through sleep deprivation, thereby apparently reversing the effect observed in our study for normals. We must point out however that there are several differences that complicate the interpretation: (i) Our study contrasted conditions from a recognition memory task, and did not scan subjects during rest. (ii) We used multivariate analysis to identify a set of regions exhibiting changes in activation that covaried across our subject sample, rather than univariate SPM analyses as in the references quoted above. Our study is therefore more suited to discover widely distributed and correlated changes in activation than SPM, while potentially missing focal effects that do not display correlation with other brain regions in their activation. (iii) Our subjects are healthy, and the noted activation differences in depressed subjects may have unique pathophysiological causes that are absent or reversed in sign in

healthy subjects. It is thus possible that neuromodulatory changes (Wu *et al.*, 2001) that occur in depression (and can be alleviated through sleep deprivation) are also induced by sleep deprivation in normal subjects and persist during performance of a cognitive task, but more confirmatory analysis is needed to substantiate this initial suggestion.

In summary, our analysis identified a neural network that is linked to sleep deprivation and that also changes in expression as a function of differential susceptibility to sleep deprivation. Our data further suggest that this network plays an important role in cognitive processing during sleep deprivation since the extent to which the covariance expression decreased in each subject was predictive of the effect on cognitive performance. This differential impact may help explain differences in susceptibility of maintaining cognitive ability during prolonged hours of wakefulness.

Notes

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