An fMRI Investigation of the Neurobehavioral Impact of Sleep Deprivation and Stimulus Degradation on a Working Memory Task

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Senior Thesis

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Abstract

In an fMRI sleep deprivation study employing a variant of the Sternberg task, Habeck et al. (2004) found a pattern of brain expression for the probe phase that was correlated with performance decrements. This pattern, whose expression decreased for most subjects and decreased even more strongly for Sleep Deprivation (SD)-sensitive subjects, included a ventral visual processing area. In order to further elucidate the role of this visual processing area and its possible relation to SD-induced performance decrements, we did a similar study in which the probe was presented at three levels of visual degradation. We investigated the neural substrate of performance decrements by having subjects perform the degraded Sternberg task in an fMRI scanner pre- and post-48 hours of sleep deprivation. Because Habeck et al.'s findings suggested that sleep deprivation had a significant effect on visual processing; we expected that the increasing difficulty of visual processing, by using a degraded Sternberg task, would interact with sleep deprivation on both reaction time and discriminability (a measure of accuracy that removes selection bias). These behavioral interactions were not observed. Using network analysis, we found a pattern of co-varying activation whose expression decreased with sleep deprivation for the probe interval ($p = .04$) and expression of this pattern pre-SD was predictive of the expression post-SD with a correlation of 0.91 ($p < .001$). The change in our subjects' pattern expression from pre- to post-SD was not correlated with behavioral changes from pre- and post-SD. However, this pattern did bear resemblance to Habeck et al.'s in that it included the anterior cingulate and thalamus. Interestingly the correlation of activation was opposite in our case. Together, these results indicate that these two regions are involved in SD but the nature of their interaction remains unclear.

1. Introduction

Sleep deprivation generally causes cognitive slowing, lapsing, memory effects, and time-on-task effects (i.e., the subject's performance on the task decreases over time) (Dinges and Kribbs, 1991). More recently, brain imaging has been used to find neural correlates to these performance decrements. As of yet, few studies have been done using fMRI, and many of these studies have been done by Drummond and his colleagues [1999, 200, 2001, 2004] Drummond's and others' neuroimaging studies have shown mixed results regarding the brain's reaction to SD. From pre-sleep deprivation to post-sleep deprivation "task-related" brain areas (i.e. brain areas used for the task under rested conditions) activated or deactivated and "new " brain areas (i.e. areas that are not typically used for the task under rested conditions) activated in response to sleep deprivation.

Effects of Sleep Deprivation on Brain Activation/Deactivation

Several neuroimaging studies have investigated whether sleep deprivation is accompanied by both changes in brain activation from pre- to post- sleep deprivation and performance decrements. Both Drummond et al. (Serial Subtraction Task: 1999) and Thomas et al. (Serial Addition/Subtraction task: 20000) found that sleep deprivation resulted in performance decrements and fMRI deactivations in task-related brain regions. Conversely, in other studies, Drummond and colleagues (Verbal Learning task: Drummond et al. 2000, Divided Attention task: Drummond et al. 2001) and Portas et al. (Attentional task: 1998) found performance to be similar before and after SD, and observed SD-induced brain activations in task-related brain regions. Additionally, the Drummond et al. studies (2000, 2001) showed activation of "new areas" with SD. All the foregoing

studies suggest that increases in activation may have compensated for the effect of sleep deprivation.

The Effects of Task Difficulty and Sleep Deprivation on Brain Activation/Deactivation

Another manipulation (other than SD) employed in neuroimaging studies in which challenge-induced brain activation is often related to performance is task difficulty. Typically, increased brain activation with increasing task difficulty is observed (i.e. Jovicichi et al., 2001, Culham, 2001). Drummond et al. (2000, 2001) manipulated both task difficulty and SD and found that increasing task difficulty was accompanied by a cerebral compensatory response to sleep deprivation. He suggested that increasing task difficulty may have facilitated a compensatory neuronal activation. More specifically, Drummond et al. (2004) suggests that the SD-related decrease in temporal lobe activation was compensated for by bringing the parietal lobes "on-line" which might account for the reduced SD-related decrement in performance relative to subjects which did not show additional activating in the parietal lobe after SD. Drummond et al. (2001) also suggests that the nature and duration of the task may affect how the brain compensates for sleep deprivation. Increasing task difficulty may also reduce affects of monotony, decreased motivation or arousal that may cause performance decrements.

1.1 Neuroimaging of SD (network analysis)

The type of analysis used (i.e. voxel-wise vs. network) is an important issue in fMRI research (Habeck et al., 2003). Voxel-wise analysis was used by the aforementioned neuroimaging studies of SD, and is most compatible with a "modular-theory" of the brain whereby specific areas of the brain are related to the specific functions. On the other hand,

spatial covariance (or "network") analysis is more compatible with the idea that the brain uses a network of interacting brain regions to perform a task. One major type of network analysis attempts to identify covarying a spatial pattern of activation/deactivation, and assesses the magnitude of that pattern's expression between conditions and/or subjects (Habeck et al. 2003).This covariance analysis is more attuned to the relation of activation of areas with the activation in other areas. It is possible that the neural instantiation of sleep deprivation is represented less well by the task-related response of individual brain areas, (as would be measured by a voxel-wise analysis), than by the task-related response of a network of covarying activation. If this is true, a network analysis would be the better tool to detect such an effect.

Habeck et al.'s 2004 experiment

One example of a study that used a network analysis approach to find neural correlates of SD and behavioral performance was Habeck et al. (2004). They used a delayed match-to-sample (DMTS) task, which has been used extensively to test working memory. A DMTS task consists of 3 phases: (1) the stimulus phase, in which a stimulus is presented, (2) the retention phase, in which the stimulus is removed and subjects must retain the information, and (3) the probe phase, in which subjects must identify whether probe information matches with the test stimulus of the stimulus phase. The DMTS task has been used with MRI to identify the regions of activation used for various forms of working memory employed in facial recognition, auditory memory, and verbal recognition tasks [Horwitz and Braun 2004, Habeck et al. 2004, Tanaka et al. 2002, Garavan et al. 2000, Mcintosh 1999, Tagamets and Horwitz 1998]. More recently, Habeck et al. used fMRI on a DMTS task to test subjects' working memory during sleep deprivation. Habeck et al.

found a covarying pattern of activation in the probe phase whose expression increased with sleep deprivation (2004).[1] SD was associated with several negative aspects of performance in the DMTS task, including decreased recognition accuracy, increased reaction time variability, and increased non-responses. Habeck et al. (2004) also found that those subjects who evidenced greater SD-related change in the pattern expression had greater SD-induced performance decrements in reaction time variability and decrease in percent accuracy due to sleep deprivation.

1.2 Sleep Deprivation Decrements and the Visual System

The Habeck pattern whose expression distinguished between SD-tolerant and SD-sensitive subjects included a ventral visual processing area (see area circled in Fig. 1). This indicated that poor performance after sleep deprivation may be in part due to decreased performance in the visual system. In functional terms, it seems possible that, relative to SD-tolerant subjects, these SD-sensitive subjects are having trouble very early in the processing stream – i.e., in the visual detection and identification of the probe.

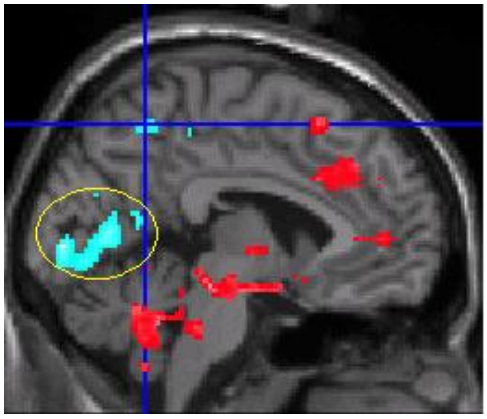

Figure 1. Pattern observed by Habeck et al. (2004). Decreasing activation in the visual processing areas (blue area, yellow circled) was correlated with increasing activation of various other areas (red), including anterior cingulate.

[1] Habeck looked for at the neural effects specifically in the probe phase because it tests for memory scanning, binary decision, response selection and motor output processes, as well as for the practical reason that responding in the probe phase indicated that the subject was awake.

1.3 Current Study

The questions we wanted to address in this study, was whether stimulus detection/identification was impaired by sleep deprivation, whether this SD-related decrease is sensitive to interpersonal differences, and whether the degree of using the visual system is correlated to SD-related performance decrements. This will provide stronger evidence for whether interpersonal differences in SD-tolerance are due to interpersonal differences in activation of the visual system during sleep deprivation.

We did a modified version of Habeck's experiment in which we manipulated the probe's properties to differentially challenge the perceptual processes that may be relevant to the SD effects. Like Habeck et al. (2003), we used a version of the Sternberg task, which is a DMTS item-recognition task testing for verbal working memory (Sternberg, 1966). We manipulated the visual processing demand by presenting the subject with a probe that had a low, medium, or high level of degradation (white noise contamination, see methods section). We hypothesize that there will be a decrease in performance due to sleep deprivation (as observed by Habeck et al. 2004 and others), and a decrease in performance with increasingly degraded probes (due to the increased demand on visual processing areas). Additionally, because we believe that SD performance decrements are caused in part by decrements in visual processing efficiency, we predict there will be an interaction between these two main effects such that sleep deprived subjects will perform significantly worse when presented with a highly degraded probe than would be predicted by the two main effects alone. A previous study done by Sanders et al. (1982) showed such an interaction between sleep deprivation and stimulus degradation on reaction time.

Hypotheses

To see if inter-individual differences in network expression would help explain inter-individual differences in performance (i.e. people whose performance is relatively resistant to SD versus people whose performance suffers with SD) we used fMRI. Habeck et al. (2004) found a pattern of covariation whose expression changed with sleep deprivation, and that people who expressed this neural pattern of sleep deprivation more strongly showed larger performance decrements in a DMTS task. We hypothesized that we would find a similar pattern of covariation whose expression would change with sleep deprivation, and that people who showed this pattern of sleep deprivation more strongly would show larger performance decrements. Furthermore, we hypothesize that during SD, these performance decrements will be augmented by a highly degraded stimulus, since the visual system may play a large role in these decrements. We believe that these effects will be super-additive (i.e., that there will be an interaction). In our study we are most concerned with the probe phase, especially since this is the stage where we degraded the stimulus to elucidate the effects of visual processing on sleep; however, we will look for activation patterns elicited by the study stimulus and retention intervals as well. In this manner, we hoped to find inter-individual differences in activation patterns to help explain inter-individual differences in performance during sleep deprivation. Assuming such a pattern is observed, inspection of its components will allow us to identify interacting brain areas which may be associated with SD-related performance decrements.

2. Methods

All subjects were right-handed and screened to ensure that none had a history of drug abuse, medical disorder, psychiatric disorder, neurological disorder or sleep disorder. Fifteen (3 female) subjects, between the ages of 21 and 29 years, participated in two sessions of an efMRI DMTS task similar to the one in Habeck et al. (2004). The fMRI data from two of the subjects failed to demonstrate positive controls (visual activity in response to the study stimulus, see Results section) due to large amounts of movement, and one sleep-deprived subject timed out of the majority of the DMTS trials, presumably due to excessive sleepiness. Thus, in all, twelve subjects provided useable data. Subjects did not drink caffeine 24 h prior to study participation or for the duration of the study. Subjects maintained a sleep log for 2 weeks prior to the study. The sleep logs revealed that all subjects had at least 6 h of sleep on both nights prior to the experiment. Subjects were supervised at all times, and polysomnographic monitoring confirmed that they remained awake during the sleep deprivation period. 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.

After the initial fMRI session subjects underwent 48 hours of prolonged wakefulness. In order to control for confounding circadian rhythm effects, both the initial fMRI session and the follow-up session occurred at 9 AM.

2.1 DMTS task

The DMTS task was similar to the one presented in Habeck et al. (2004), with the major exception that there was no manipulation of study set size in the current experiment.

Subjects were presented with 3 blocks, each of which consisted of 30 trials (5 'old' probes at each of the three levels of probe degradation, and 5 'new' probes at each level of degradation). Each trial consisted of a blank screen presented for 3 seconds, a study stimulus (6 letters) presented for 3 seconds, a 7 second retention interval, and then a probe stimulus presented for 3 seconds (Fig. 2). During the 3 second probe presentation subjects pressed one button to indicate that the probe was in the study list (old), and a different one to indicate that the probe was not in the study list (new). Responses made after the three-second probe phase ("time-outs") were considered invalid and not included in the analysis. There were also thirty-four 4 s. blank ITI periods interspersed between trials randomly, for a total block length of ~11 minutes.

Figure 2. A DMTS trial consists of one of the probe degradation levels shown in the bottom row.

2.2 fMRI acquisition and processing

Functional images were acquired using a 1.5-T magnetic resonance scanner (Philips). A gradient echo EPI sequence [TE=50 ms; TR=3 s; flip =90°] and a standard quadrature head coil was used to acquire T2*-weighted images with an in-plane resolution of 3.124×3.124 mm (64×64 matrix; 20 cm^2 field of view). Based on T1 "scout" images,

seventeen 8-mm transaxial slices were acquired. Following the fMRI runs, a high (in-plane) resolution T2 image at the same slice locations used in the fMRI run was acquired using a fast spin–echo sequence [TE=100 ms; TR=3 s; 256×256 matrix; 20 cm2 field of view]. Task administration and data collection were controlled by a Macintosh computer running custom software written in Psycope. Task stimuli were back-projected onto a screen located at the foot of the MRI bed using an LCD projector. Subjects viewed the screen via a mirror system located in the head coil and made button presses on a Lumitouch button pad.

All image pre-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. The T2* images within each block were intensity normalized to allow comparison between blocks. All functional volumes in a given subject were realigned to the first volume from the first run of each study. The T2 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 (7×8×7 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 2×2×2 mm).

2.3 Data analysis

The fMRI responses were fit to separate sets of predictor variables (Zarahn, 2000). There were between 18 and 36 event types in each subjects' set of predictor variables. All

models had at least 3 (stimulus, probe, retention) *3 (low, medium, high probe degradation) * 2 (old, new probe) event types. All of these events could be "valid" trials (in which a subject made a response in the time allotted) or "time out" trials, (in which the subject did not). Thus, the number of event types depended on the subject's performance. The time out trials were analyzed separately to restrict inferences to valid trials – they are not included in any of the reported results. The set of event types and onsets was convolved with a canonical hemodynamic response waveform (a sum of two gamma functions, as specified in the SPM99 program [24]) whose beginnings were marked by the appropriate onset vector for each epoch and event type. The resulting time series vectors were used in the design matrix for the within-subjects model estimation. The high-pass filtered fMRI time series at each voxel were regressed onto these predictor variables.

At every voxel in the image, contrasts assessed the amplitudes (normalized regression coefficients) of the components of the event-related responses that matched the canonical hemodynamic response waveform for the whole scanning session. This method of time-series modeling and contrast estimation at each voxel reduces the number of images to one per subject per condition. The resulting parametric maps images were smoothed using an isotropic Gaussian kernel (FWHM=8 mm) and used as the data in the subsequent analysis. These parametric maps serve as the dependent variables for the subsequent population-level multivariate analysis.

2.6. Multivariate analysis (summarized from Habeck [2004])

Ordinal Trend Canonical Variates Analysis (OrT CVA) [Habeck et al. 2003, 2002, 2003] was performed on the data. This analysis is similar to other regional covariance analyses techniques, notably Partial Least Squares, to the extent that it applies principal

components analysis (PCA) to the data matrix that is transformed using a matrix representing the experimental design (McIntosh et al. 1996 and Worsley et al. 1997). OrT CVA was designed to identify a covariance pattern in the MR signal utilizing each voxel, the expression of which decreases for as many subjects as possible from PRE to POST sleep deprivation. We will describe OrT CVA here only in brief – a more detailed account of the method can be found in Habeck et al., 2004.

Rather than examining differences in functional connectivity between conditions, we were interested in changes in regional activation induced by sleep deprivation that keep the functional connectivity unchanged from PRE to POST, and could therefore be captured in one covariance pattern. In our case, a single covariance pattern represents set of brain regions the connections of which are not changing from PRE to POST. Rather, subject expression of the covariance pattern varies from subject to subject with the additional constraint of a change from PRE to POST in the same direction (increase or decrease) for as many subjects as possible. This means that most people are showing the same mutually correlated regional activation and de-activation in response to sleep deprivation, with individual differences in the degree to which these changes are expressed.

The property of a systematic within-subjects change of pattern expression across task conditions (beyond mere mean trends) is called an "ordinal trend". The number of subjects who violate the rule of decreasing expression from PRE to POST can be used as a statistic to test the null hypothesis of the absence of an ordinal trend in the data. Monte Carlo simulations of regional noise that is independently and identically distributed according to a Gaussian generate the p level for the value of the number-of-exception criterion observed in our subject sample. For these simulations we used 12 subjects and

350 regional resolution elements in accordance with our experimental parameters. A significant ordinal trend lends additional credence to the claim that an activation pattern was obtained through the experimental design manipulation (=sleep deprivation in this case), rather than a significant change on the mean across conditions that might have come about as a result of overly influential subject outliers.

Activation patterns resulting from multivariate analysis assign different weights to all voxels included in the analysis, depending on the salience of their covariance contribution. Voxel weights that are positive indicate a positive correlation between the subject expression value and the associated regional activation, whereas negative weights indicate a negative correlation. This means that as the expression of a pattern increases, activation in the positively weighted regions increases as well, whereas activation in the negatively weighted regions decreases. The absolute magnitude of a regional weight determines the slope of this change: for instance, a region whose weight is twice is large as that of another also changes its activation twice as steeply. Whether a voxel weight is reliably different from zero is assessed by a bootstrap estimation procedure correcting for multiple comparisons.

Individual subject's expression of the activation pattern during the PRE and POST sessions is quantified with the subject-scaling factor (SSF). The SSF is obtained by the operation of an inner product (=covariance across brain regions) between the covariance pattern in question and a subject's task scan. It quantifies to what extent a subject expresses the activation pattern in a task scan with a single number, which can be used for further analysis. Change in pattern expression for each subject as a function of sleep deprivation was measured by the PRE–POST difference of that subject's SSFs.

Once an activation pattern was identified that systematically decreased in expression as a function of sleep deprivation, we examined the correlation between individual change in network expression from PRE to POST sleep deprivation and change in their scores on the task performance measure

3. Results

3.1 Behavioral Results

Each subject's memory for the study set (measured by response discrimination between old and new probes [d']) and median reaction time for correct responses was calculated for each level of probe degradation, pre and post SD.

An ANOVA on discriminability found a main effect of sleep deprivation ($F [1, 11] = 42.8$, $p < .001$) but no effect of probe degradation ($F=1$) or interaction ($F<1$, Fig. 3). Figure 4 shows individual mean discriminability from pre-to post-SD collapsed across the three levels of probe degradation.

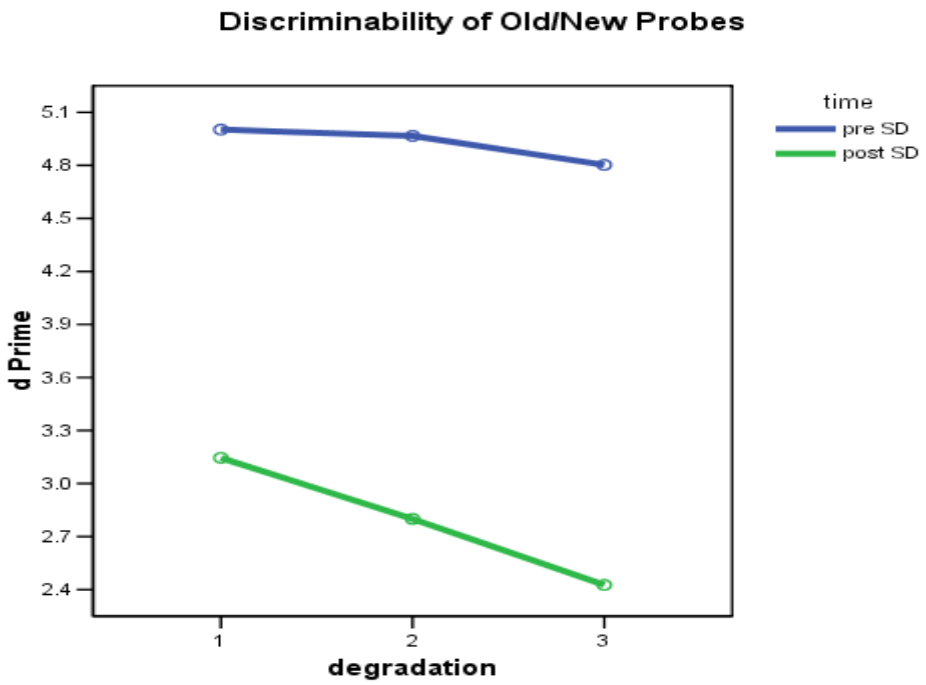

Figure 3.

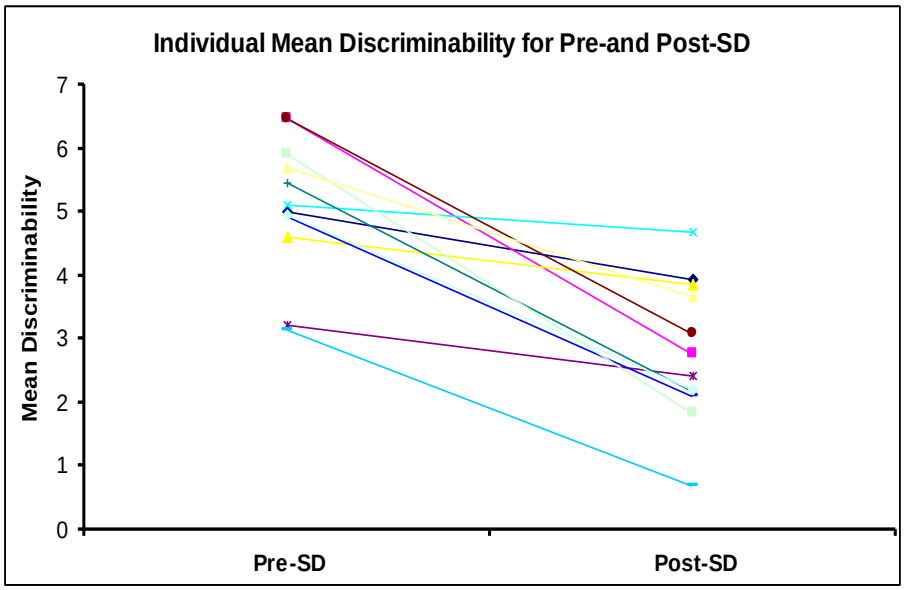

Figure 4.

The ANOVA on median reaction time for correct responses found only a marginal main effect of sleep deprivation ($F [1, 11] = 4.8$, $p = .051$), but a robust effect of probe degradation ($F(2,22) = 10.0$, $p = .001$, see Fig. 5). Contrary to our hypothesis, however, we observed no interaction ($F<1$). Figure 6 shows individual mean of median reaction

time from pre-to post-SD collapsed across the three levels of probe degradation.

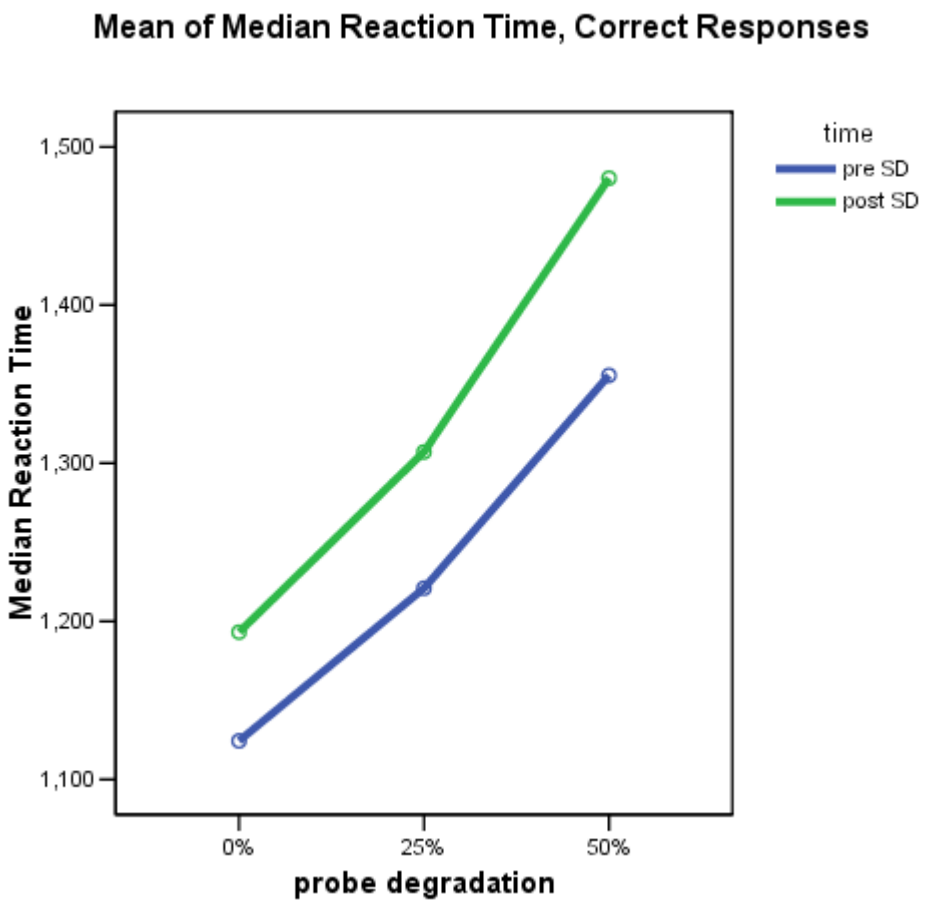

Figure 5.

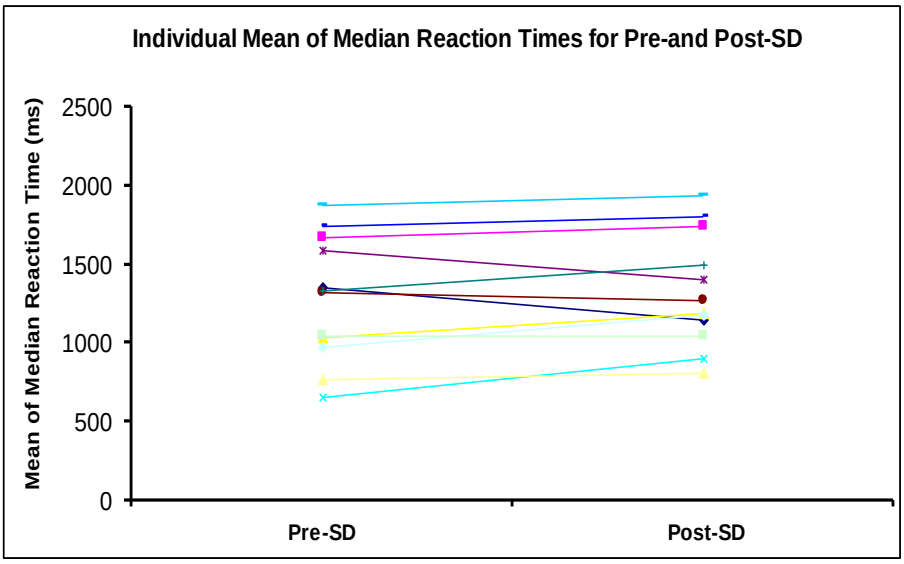

Figure 6.

We also examined subjects' response bias with SD and probe degradation. Beta decreased with sleep deprivation (indicating a more liberal response bias; subjects were more likely to say the probe was old), but not significantly so ($F [1, 11] = 3.1$, $p = .1$, see Fig. 7). There was no effect of probe degradation or interaction between sleep deprivation and probe degradation (Both $Fs < 1$).

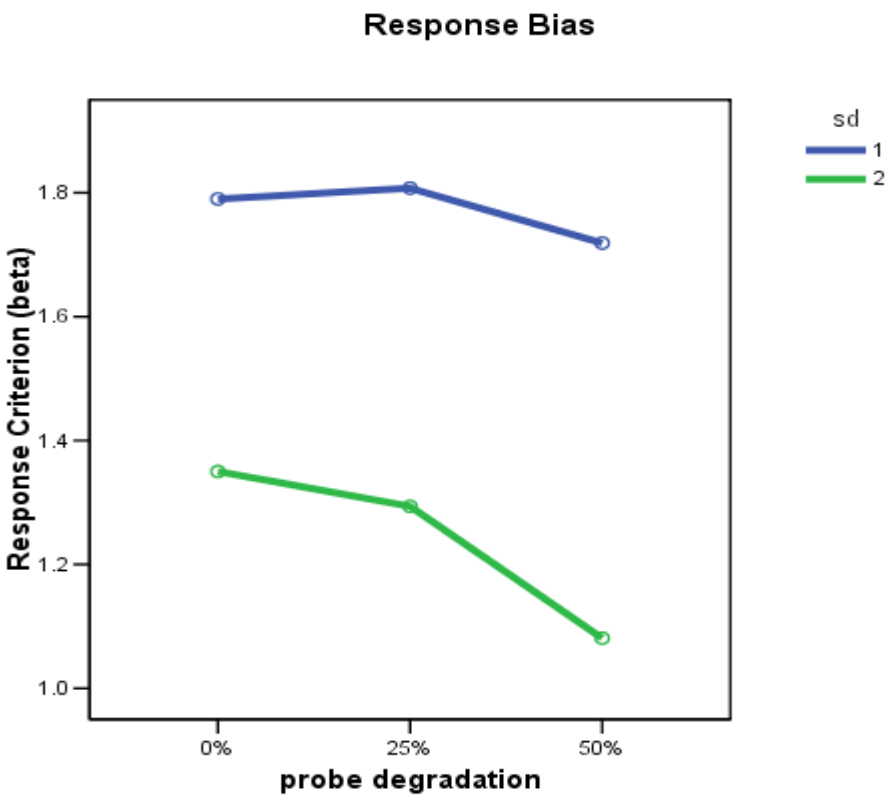

Figure 7.

We also observed a significant increase in the number of lapses from an average of 2.5 trials (3% of trials) pre-sleep deprivation to 30.1 trials (33% of trials) post sleep deprivation ($t[11] = 6.9$, $p < 0.001$). The large increase in number of lapses after sleep deprivation may have overshadowed performance decrements in both discriminability and reaction time (see discussion).

3.2 fMRI Results

The positive control analysis for the twelve subjects is shown in Figure 8. This shows the voxel-wise visual activity elicited by the study stimulus. Activity shown is significant at $p<.0005$, uncorrected.

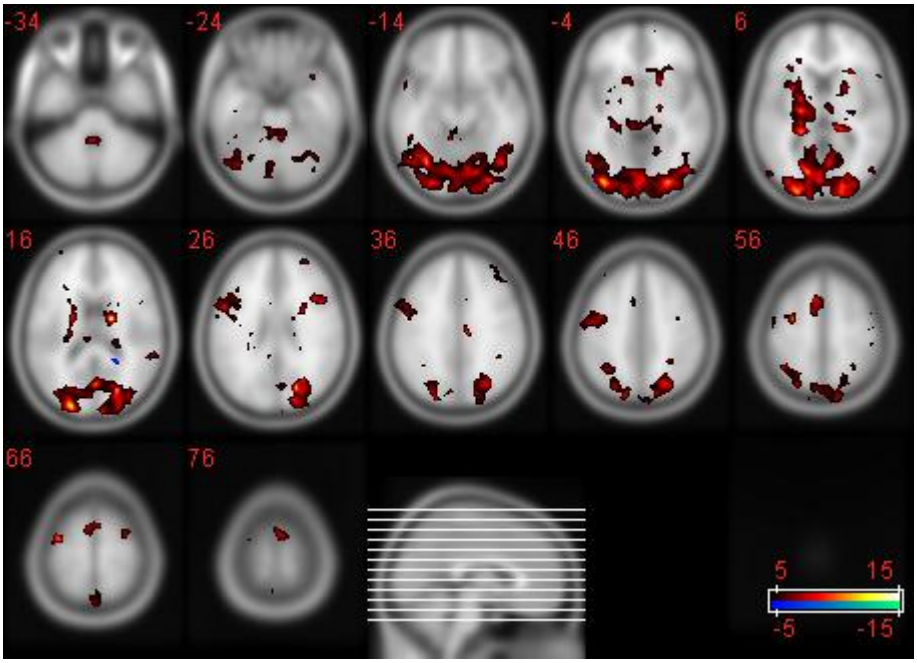

Figure 8. Voxel-wise positive control. Activation to the study stimulus, collapsing across probe degradation levels and pre-/post-SD, ($|t| > 4.8$, uncorrected $p < .0005$).

Despite the failure to find the hypothesized behavioral result, we explored the CVA analysis of the study stimulus, retention, and probe phases separately. As explained in 2.6, this analysis attempted to identify a covarying pattern of spatial activation whose expression changes, in the same direction, from pre- to post-SD for a number of subjects greater than would be expected by chance.

The OrT CVA for the study stimulus identified a pattern whose expression increased for 9 out of 12 subjects, which was not significant ($p = .14$, see Figure 9a & 9b for the covariance pattern and the pattern expression levels for each subject, pre- and post-SD).

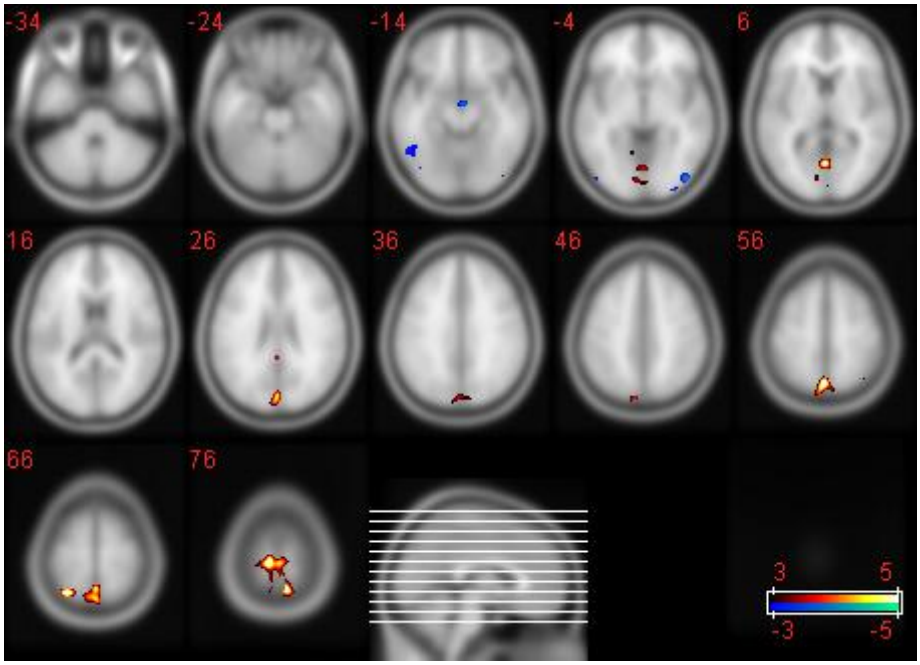

Figure 9a. Areas most robustly contributing to the spatial covariance pattern at study stimulus (|z| > 3).

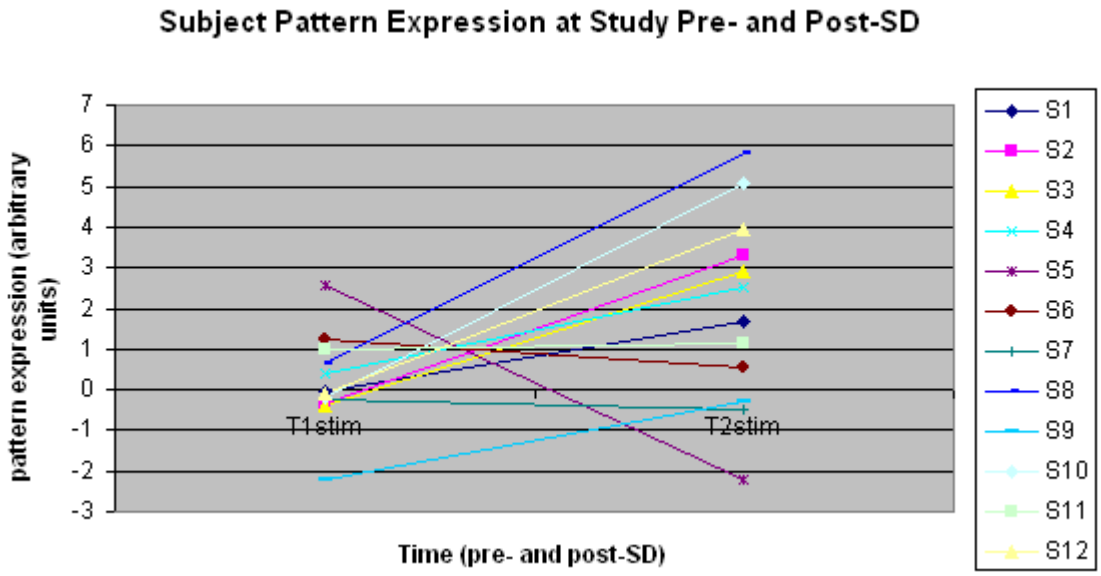

Figure 9b. Subjects pattern expression pre- and post-SD at study.

The OrT CVA for the retention interval identified a pattern whose expression decreased for 9 out of 12 subjects, which was not significant (p = .14, see Figure 10a &

10b for the covariance pattern and the pattern expression levels for each subject, pre- and post-SD). Interestingly, this pattern appears to essentially be the inverse of the pattern found at study. Because expression of the retention interval pattern usually decreased from pre- to post-SD for this pattern and expression increased from pre- to post-SD for the probe pattern, the findings for the probe and study stimulus are essentially the same. However, the three subjects who violated the ordinal trend for the pattern elicited by the study stimulus were not the same subjects who violated the ordinal trend for the pattern elicited by the retention interval). The number of people who violated the ordinal trend in pattern expression was not less than would be expected by chance in any case, so these findings will not be further dwelled upon.

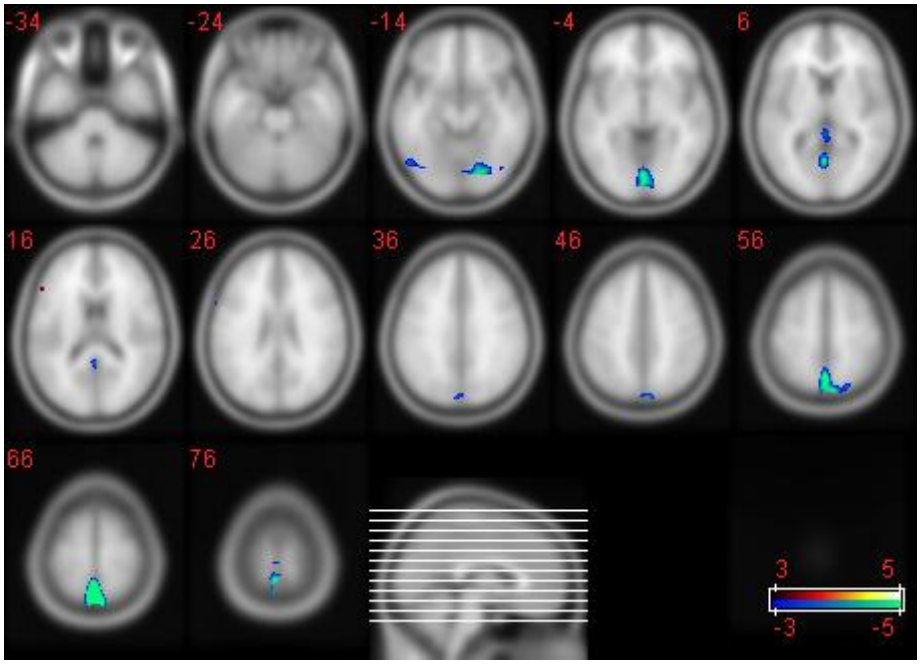

Figure 10a. Areas most robustly contributing to the spatial covariance pattern during the retention interval ($|z| > 3$).

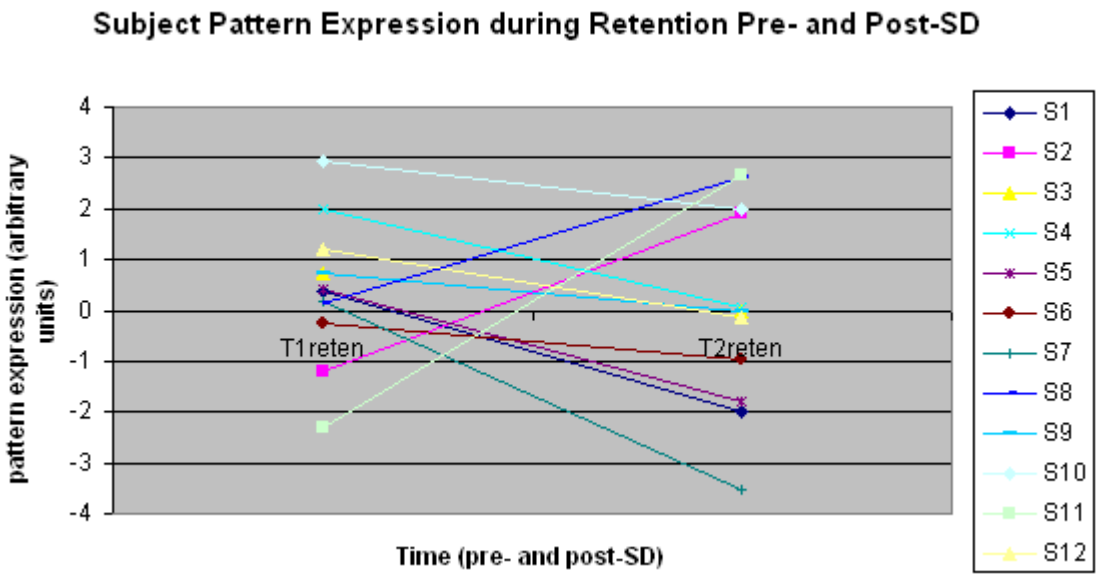

Figure 10b. Subjects pattern expression pre- and post-SD during retention.

The OrT CVA for the probe identified a pattern whose expression decreased for 10 out of 12 subjects, which was significant ($p = .04$, see Figure 11a & 11b for the covariance pattern and the pattern expression levels for each subject, pre- and post-SD). Interestingly, the expression of this pattern pre-SD was predictive of the expression post-SD, as the correlation was .91 ($p < .001$). This was even true after excluding the outlying data point from subject #8 ($r = .82$, $p < .001$). However, though there are some similarities, this appeared to be a somewhat different network than that found by Habeck et al. (2004).

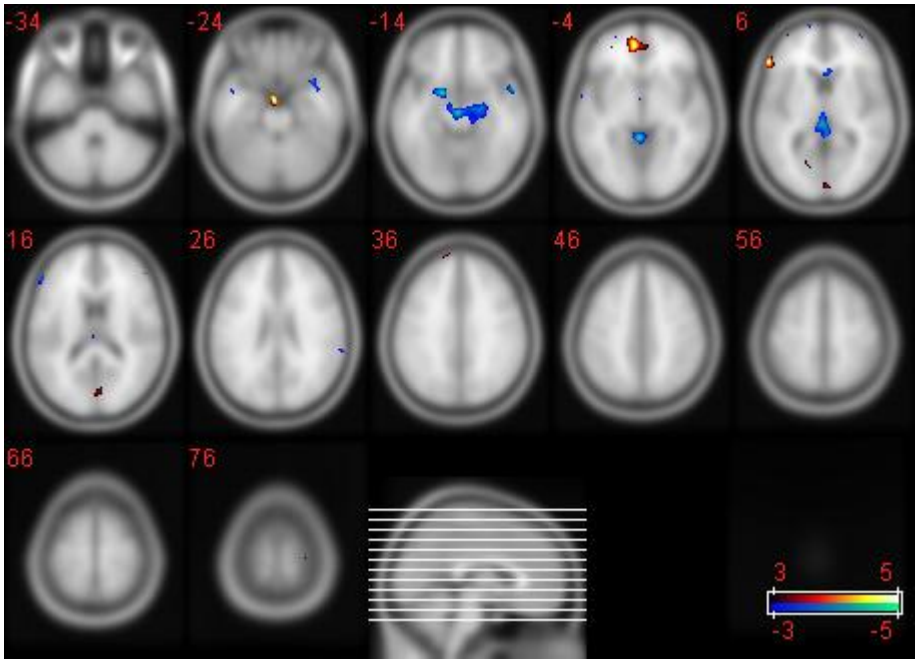

Figure 11a. Areas most robustly contributing to the spatial covariance pattern during the retention interval (|z| > 3).

Figure 11b. Subjects pattern expression pre- and post-SD at probe.

Additionally, unlike Habeck, we did not find a significant correlation between our change in pattern expression from pre- to post-SD in the probe phase and change in

behavior from pre- to post-SD. Habeck found a significant correlation with both accuracy and reaction time variability. We did not find a significant increase in reaction time variability and difference in network expression pre-post (r=-0.07). Similarly, the difference in pattern expression from pre- to post-sleep deprivation did not significantly correlate with discriminability (r= -0.39) or with mean reaction time (r=0.21).

4. Discussion

4.1 Behavioral Results

Contrary to our hypothesis, sleep deprivation and probe degradation did not have an interaction on either reaction time or probe discriminability (i.e. memory). Instead, we saw an additive effect of these two factors on performance. This indicates that the two effects might be affecting independent processes. Our findings are in contrast to a study done by Sanders (1982) which showed an interaction of sleep deprivation and probe degradation on reaction time. Sanders et al. suggests that the degree of degradation of the probe may determine whether or not an interaction is found. If the probe does not reach a certain threshold of degradation, the expected interaction will not be observed. Thus one explanation for the lack of interaction is that the degree of degradation of the letters in our Sternberg task may not have reached a certain threshold. Unfortunately, Sanders does not report the levels of stimulus degradation used in her experiment so it is difficult to compare the degree of degradation of our probes to Sanders' probes.

Task Difficulty and Lack of Interaction in Our Study

The fact that we did not find an interaction between sleep deprivation and probe degradation on behavioral performance may be due to the various conflicting effects of task difficulty on our task. Several studies which varied task difficulty did not find an interaction with sleep deprivation and the difficulty level of the task. For example, in Habeck et al.'s study there were 3 levels of difficulty of the DMTS task where 1, 3, or 6 letters respectively appeared in the stimulus stage. No interaction was found between set size and sleep deprivation on performance. As noted earlier, Drummond et al. (2000, 2001) suggests that increasing the difficulty level may actually facilitate brain activation that

compensates for sleep deprivation. This effect may partially be due to increasing motivation and arousal levels, decreasing the monotonous nature of the task resulting in improved performance (Dahmns, 1996).This is consistent with the fact that Drummond et al. (200,2001) observed SD-induced brain activations in task-related brain regions that were accompanied by maintaining performance level from pre-to post-SD. However, the absence of interaction may be a result of the combination of the various conflicting forces such as the above forces improving task performance, while the actual difficulty level decreases performance.

Lapses May Explain Lack of Interaction

One possible explanation for the absence of interaction of sleep deprivation and probe degradation on discriminability (measure of accuracy that removes selection bias) and reaction time is that these effects were overshadowed by the large number of lapses during sleep deprivation in which subjects failed to respond. The number of lapses were not included in the count of reaction times nor discriminability, but had a large negative impact on performance. This may explain why we saw an effect of both sleep deprivation (although marginal $p=0.051$) and probe degradation on reaction time ($p<0.001$), but did not see an effect of sleep deprivation on discriminability or the subjects' selection criterion.

Common Sleep Performance Decrements

While studies have found sleep deprivation to have an effect on performance accuracy, the most predominant effects are on the speed of the task rather than accuracy (Koslowsky and Babkoff 1992, Thomas et al. 2000). As Hockey (1979 in Sanders 1982) shows, the predominant problem in sleep deprivation is on reaction time and misses which

supports the findings in our study. Lapses and increased reaction time are related in that they may both be caused by the "lapse hypothesis", which posits that sleep deprivation results in microsleeps, in which the subject falls asleep very briefly. Depending on the length of this “microsleep” or “lapse” the subject may increase their reaction time, or miss the probe response phase altogether (Koslowsky and Babkoff 1992). Similarly, while Sanders did find an interaction between sleep loss and signal degradation on mean reaction time, this interaction was not found on accuracy. Sanders explains that this is due to the small number of errors in comparison with missed trials (i.e. lapses) (Sanders 1982). Thus the absence of effect of sleep deprivation on discriminability, an unbiased measure of accuracy, is not inconsistent with previous findings. Others’ observed SD-induced accuracy effects may reflect criterion shifts as much or more than “memory” decrements, though our bias effect was marginal ($p=0.1$).

Lack of Controls and Practice Effects

One problem with our study is that we did not have a control group that followed the same procedure under rested conditions to attribute for practice effects (though the practice effects may themselves be different under sleep deprivation). Practice effects may be especially critical to control for as Sanders’ study found a stronger interaction between stimulus degradation and sleep deprivation on performance when subjects were first sleep deprived and then slept than the reverse (Sanders 1982). In the reverse group, the subjects were not sleep deprived during the first run, which may have allowed subjects to practice and improve performance on the task. These practice effects may reduce the observed performance decrements after sleep deprivation, as the practice likely improved performance.

Practice Effect on Brain Activation

Practice effects have a significant impact on brain activation, and a control group may have been helpful in analyzing the neural correlates to behavior in the present study. In fact, it is possible that changes in the network's degree of activation and activation of new areas are at least partially due to practice effects, or changes in memory strategies instead of sleep deprivation (Tanaka 2002). In a DMTS study using fMRI, Garavan et al. (2000) found changes in activation without sleep deprivation, simply due to practice effects, in which posterior areas including the occipital and precuneous, left middle frontal gyrus, left precentral gyrus, and right insula decreased activation after practice. This suggests that practice effects should not be confused with the network of interest or network changes. Generally, practice results in decreased activation of brain regions, which is usually thought of as "increased efficiency" as it is correlated with increased performance. Thus practice effects can cause a reduction in activation associated with increased performance in contrast with sleep deprivation instigated decreases associated with decreases in performance which may obfuscate correlating brain activation to behavior. Jansma et al. (2001) discusses this conflict as well whereby increased activity can indicate more effort and thus better performance or decreased activity can indicate more efficiency and thus better performance as well.

On visuospatial working memory, practice effects cause the anterior and posterior cingulate regions (part of the network found in our probe phase) as well as occipital regions (part of the region found in Habeck's pattern), to decrease in activations. Thus one must be careful to avoid incorrectly attributing functional activation to a cognitive process of interest (Garavan 2000). However, one can also argue that subjects have a fixed memory

capacity which can only change slowly (Kurland 1981 in Cooney and Troyer) so performance on the Sternberg task will not change much over a short period of practice.

4.2 fMRI Results

Although we did not observe the expected behavioral interaction between sleep depravation and stimulus degradation, we did identify a significant pattern of expression that decreased from pre-to post- sleep deprivation for the probe interval. Additionally, the expression of this pattern pre-SD was predictive of the expression post-SD. Brain areas active in the pattern included the positively correlated ventral anterior cingulate (vACC) and the negatively correlated thalamus descending into brain stem. Thus, the more subjects' vACC activated the less their thalamus activated, and the degree to which each was activated/deactivated increased with sleep deprivation for 10 out of 12 subjects. This pattern bore resemblance to Habeck et al's in that it included the anterior cingulate and thalamus. However, the directionality was somewhat different. Taking the difference from pre to post sleep deprivation, both patterns showed a decrease in the anterior cingulated. However, our pattern differed from Habeck et al's in that our pattern consisted of an increase in thalamic activity, whereas Habeck et al's pattern consisted of a thalamic activity increase. Finally, we did not observe visual processing areas in our pattern.

Role of the Thalamus

The thalamus, according to previous fMRI studies, plays an important role in sleep and sleep deprivation, specifically in arousal and attention. Several studies have indicated that the thalamus has a role in attention and alertness (i.e. Coull et al. 1997, Mesulam 1990, Roland 1993, Kinomura et al. 1996, and Sturm et al 1999). In a study on sleep deprivation

on an attentional task, Portas et al.(1998) found the thalamus to mediate attention and arousal. In this study the thalamus showed the highest level of activity during conditions of low arousal and subjects were able to keep a steady level of performance for all conditions. This suggests that the thalamus may be "compensating" for the effects of sleep deprivation. Furthermore the thalamus may represent the voluntary modulation of attention (La Berge and Buschaum 1990, La Berge 1995 quoted in Portas et al. 1998). Subjects may have voluntarily attempted to stay awake and thus activated the thalamus (Portas et al. 1998). Furthermore, Portas et al. suggests that the thalamus is specific to attention and not simply a result of passive viewing of a visual stimulus or necessarily performance related. This may explain why changes in thalamus activity in our study were not correlated with behavioral performance.

The Role of the Thalamus in Sleep

The thalamus is indicated in sleep related decreases related to reduced visual vigilance(Wu et al. 1991). Furthermore, the thalamus exhibits change in activation during transition from waking (sustained tonic firing) to sleep onset (bursting mode) (McCormick and Feeser, 1990; Steriade et al. 1993 in Portas et al. 1998). Neuroimaging of light and/or deep nREM sleep finds decreased thalamus activity (Maquet et al. 1990, Buchsbaum et al. 1989) and in general, the largest area of deactivation after 24 hours of sleep deprivation was the thalamus (Wu et al. 1991, Everson 1994, Drummond 1999).

The Role of the Anterior Cingulate

The anterior cingulate, a brain area in our pattern, is involved in task difficulty, memory task, and speed of response (Tomas et. al 1998). The anterior cingulated gyrus also plays a role in attention (Vogt et al 1992). Thomas et al. (2000) found that the ventral

and dorsal anterior cingulate decreases with decreased performance of a task. Furthermore, the anterior cingulate gyrus may be specifically activated by attention but not arousal (Portas et al. 1998). Habeck (2004) noted the role of the anterior cingulated gyrus in evaluative process, and suggested that SD may cause increases in monitoring and evaluating to select the correct response in the probe phase.

Other Study's Results vs. Ours

Although we did find anterior cingulate deactivation from pre to post sleep deprivation, in contrast to our studies, two other studies found a decrease in both the thalamus and anterior cingulate activation from pre to post sleep deprivation (Thomas et al. 2000, Habeck et al. 2003)

Unlike Habeck et al.'s (2004) pattern, whose expression pre- to post-SD correlated with both accuracy and reaction time variability, the observed change in pattern expression in the current study did not correlate to the behavioral performance. This may be due to having only 12 subjects, which limited the power to detect differences that may have been present, and due to the previously mentioned conflicting forces effecting on brain activation. Additionally, the fact that Habeck's pattern was correlated to behavior may have been due to the apparently larger performance decrements found in their subjects.

The degree to which the pattern was expressed pre-SD was predictive of subject expression post-SD. That is to say, subjects who expressed the pattern more pre-SD also expressed it more post-SD. The functional relevance of this correlation is unclear, however, as network expression was not found to correlate to any behavior. Ort CVA is inclined to find such effects--provided they exist--over effects in which there is an ordinal

trend but no correlation between expression at the two observation times (Habeck, personal communication).

Although our findings are in contrast to those found by Habeck et al. (2004), past research on the effects of sleep deprivation seem to indicate similar brain regions to the ones found in our pattern, namely the thalamus and anterior cingulate. More research must be done in terms of the nature of their interaction with each other in relationship to sleep deprivation to reveal inter-individual differences in sleep deprivation tolerance.

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