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Research report

fMRI activation during failures to respond key to understanding performance changes with sleep deprivation

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ABSTRACT

Study objectives: During sleep deprivation (SD), failures to respond (FR) increase across a variety of tasks. This is the first systematic investigation of neural correlates of FR during SD. We use multivariate analysis to model neural activation separately for FR and responses (R) at each trial phase.
Setting: In two experiments a delayed letter recognition task was performed in a 1.5T scanner at 9:30 am after two nights of total SD. Participants were continuously monitored in the laboratory.
Participants: Healthy young adults from two SD experiments (combined $n = 37$; aged 25.55 ± 3.86 years).
Materials and methods: Multivariate linear modeling (MLM) was used to find networks of activation that differed between FR and R. At each of three trial phases—encoding, retention, and test—two networks were expressed. In the encoding phase, the second network was seen during FR and was not seen during R. This network constituted widespread deactivations (~26,000 voxels) of fronto-parietal and thalamic areas concomitant with activation of extrastriate cortex and hippocampus. In a multiple regression including activation during FR and R from all networks and all trial phases, expression of this encoding-phase network during FR was the key predictor of SD-related performance impairment, operationalized as greater %FR ($\eta_p^2 = 0.33$), lower d' and larger median RT ($\eta_p^2 = 0.17$).
Conclusions: FR were most associated with neural disruptions occurring at the encoding phase when subjects must attend to and encode items. Further, expression of this FR-related encoding-phase network made the largest independent contribution to predicting vulnerability to overall SD-related impairment.

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1. Introduction

Failures to respond, or non-responses (sometimes called errors of omission), have been noted to increase during sleep deprivation on a variety of tasks: serial subtraction [1], psychomotor vigilance [2], arrow flanker [3], semantic judgment [4], as well as working memory tasks [5–8]. Understanding such failures to respond would seem to provide much insight into the disproportionate number of real-world accidents that have been attributed in part or in whole to sleep deprivation [9]. This is the first report focused on the neural correlates of failures to respond during sleep deprivation.

Two previous articles reported on failures to respond during sleep deprivation, although this was not the main focus of either article [4,5]. Non-responses seemed to be associated with less activation of task-relevant areas as well as less activation of some additional areas. In these studies, however, activation was pooled across responded to and non-responded to trials, which may have obscured any neural activation that is only present during failures to respond.

We report here the first systematic investigation of neural correlates of failures to respond during sleep deprivation. Specifically, we examine networks of expression that differ between responded to and non-responded to trials on a delayed letter recognition task. The event-related design allows us to separate the encoding, retention, and test phases of each trial. We further investigate how

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expression of responded to and of non-responded to trials at each of these trial phases correlates with the performance decrement with sleep deprivation in terms of speed, accuracy, and non-responses.

2. Materials and methods

2.1. Participants

Participants were from two sleep deprivation (SD) experiments ($n = 17$ and $n = 20$). While changes were made to other experimental tasks, the delayed letter recognition task (DLR) was run according to the same protocol in each study. Younger adults were recruited from the community using flyers; age range was 20–35 (25.55 ± 3.86; 30 male, 7 female). All participants were right-handed with normal or corrected-to-normal vision and screened for medical and psychiatric disorders, the presence of a sleep disorder, and/or any substance abuse. Partial data from subjects from the first and/or second experiment were used in the cited reports, none of which focused on the present topic [5,10–13]. The experiment was performed with the understanding and written consent of each subject.

2.2. Task

The critical experimental factor for this DLR task was set size, which is the number of letters (either 1, 3, or 6) to be remembered on each trial. Set size was varied pseudo-randomly across trials. Each of three experimental blocks contained 10 trials at each of the three set sizes, with five true negative (i.e., non-matching) probes and five true positive (i.e., matching) probes per set size. In sum, there were a total of 30 trials at each of the three blocks for a total of 90 experimental trials per subject.

The sequence of trial events was as follows: first, a fixed blank inter-trial interval (ITI) of 3 s; then, a memory set of 1, 3, or 6 letters was presented for 3 s; next, there was a delay of 7 s during which the memory set had to be retained; finally, the probe was on the screen until the participants responded or 3 s had passed, whichever came first. In addition to the 3 s ITI, there were also 70 two-second intervals per block that were inserted in a random fashion between trials. For more details see [5].

2.3. Protocol

Participants were continuously monitored in the laboratory. They were required to abstain from caffeine for 24 h prior to study participation and for the duration of the study. Participants kept sleep logs for two weeks prior to laboratory entry. Participants in the first SD study slept 7.8 ± 1 h per night; in the second SD study one subject had missing data, the other participants slept 8.1 ± 0.7 h per night. For both studies, the protocol for the DLR was the same. All participants received one training session with feedback prior to the initial scanned session. At this session they received 7 blocks of 30 trials; for the first 6 blocks feedback was provided while for the final block no feedback was provided. Then, the initial scanning session occurred at 9 am and the follow-up scanning session occurred at the same time 48 h later, to control for known circadian influences on the effects of sleep deprivation [14]. For more details of the protocol see [15].

2.4. fMRI acquisition and preprocessing

During the performance of each block of the DLR, 207 blood-oxygen-level-dependent (BOLD) images [16,17] were acquired with an Intera 1.5T Phillips MR scanner equipped with a standard quadrature head coil, using a gradient echo echo-planar (GE-EPI) pulse sequence (TE/TR = 50 ms/3000 ms; flip angle = 90; 64×64 matrix, in-plane voxel size = 3.124 mm × 3.124 mm; slice thickness = 8 mm (no gap); 17 trans-axial slices per volume). Four additional GE-EPI excitations were performed before the task began, at the beginning of each run, to allow transverse magnetization immediately after radio frequency excitation to approach its steady-state value; the images corresponding to these excitations were discarded. Data were spatially normalized using a T1-weighted spoiled gradient image (107 slices; 256×256 grid; FOV = 230 mm × 160.5 mm × 183.28 mm).

Task stimuli were back-projected onto a screen located at the foot of the MRI bed using an LCD projector which participants viewed via a mirror system located in the head coil. All participants wore MR compatible glasses as needed to have vision at their best corrected acuity (manufactured by SafeVision, LLC. Webster Groves, MO). Responses were made on a LUMItouch response system (Photon Control Company) using the index fingers of either hand. Task administration and collection of response data were controlled using PsyScope 1.2.5 [18] running on a Macintosh G3 iBook. Task onset was electronically synchronized with the MRI acquisition computer. A Carnegie Mellon Button Box (New Micros, Inc. Dallas, TX) provided digital input–output for the response system and synchronization with the MRI acquisition computer, as well as millisecond accurate timing of responses.

2.5. fMRI time-series (i.e., first-level) modeling

Time series modeling had regressors representing activity of the three trial phases—encoding, maintenance and test—separately for each set size (1, 3, or 6 letters). One rectangular regressor was used for each of the trial components: encoding (3 s in duration), maintenance (7 s in duration), and test (3 s in duration). Failures to respond (FR), which refer to trials without motor responses from the participant during the 3 s test period, were modeled separately. Additionally, trials where an incorrect response was made were modeled separately.

2.6. Multivariate linear modeling (MLM)

The goal of our analysis was to contrast brain activation during R with that observed during FR. As FR were negligible during baseline, this analysis was restricted to the fMRI data collected during sleep deprivation. The spatial networks that differed between R and FR during sleep deprivation were assessed via the application of the multivariate linear modeling (MLM) theory [19]. Specifically, MLM was used to determine if the group-mean contrast images (here the contrast was the slope across set size, which presumably reflects task-specific processes) could be expressed as linear combinations of one or more latent spatial variables, or networks. Singular-value decomposition (SVD) was performed for the encoding, retention, and test phases separately. Each SVD examined 1 effect of interest, which was the group mean contrast images for R and FR trials, respectively, generated by random effect group level General linear modeling (GLM) [20] within SPM5.

Sequential latent root testing, using a global F-test and an alpha level of 0.05, is used to determine the number of significant spatial networks. The maximal number of spatial networks is determined by the dimensionality of the F-contrast. Each F-contrast compares R and FR trials and therefore has a dimensionality of two. Thus, the largest number of potentially significant spatial networks is two for each of the encoding, retention, and test phases.

The areas comprising each MLM network were represented visually, scaled by their singular values, as SPM(t). SPM(t) maps are presented with thresholds of a t-value corresponding to $p < 0.001$ uncorrected for multiple comparisons, and a minimum cluster (k) size of 50 voxels. These values are chosen simply to select the most prominent areas in the spatial networks. The Talairach coordinates and their anatomical labeling based on the template created with automatic anatomical labeling [21] were reported for local maxima of Z-scores in each network.

We calculated the observed expressions of each network by participants for R and FR trials, respectively. We summarized these observed expressions with a single value per participant (the individual subject expression) by taking the inner product of a vector of the observed expression values for that subject and a vector of the predicted expression values over conditions for that subject. In sum, each subject had a single value for network expression during R trials and likewise a single value for network expression during FR trials for each trial phase—encoding, retention, and test. These summarized observed expressions were used as dependent variables in a multiple regression to test hypotheses regarding the association between activation of the networks and behavioral performance impairments with SD (see below).

2.7. Brain–behavior analyses

Two multivariate general linear models were used—the full and the reduced model. For all models our dependent variables (DVs) constituted the change in performance from the first to the second session (i.e., the change in performance with SD) for (1) percent FR, (2) d', a measure of accuracy and (3) median RT. For the full model, the independent variables (IVs) were Group (i.e., the first SD group versus the second SD group), and expression of the spatial networks found in the MLM analysis described above: that is, the expression of each spatial network found in each condition (R versus FR trials) at each phase (encoding, retention, and test). As we found two networks for each of two trial types at three test phases this yielded 12 network expression scores (Encoding Network 1 during R, Encoding Network 1 during FR, etc.). We also initially included the crossing of group with each of the 12 network expression scores as IVs. As none of these crossings were significant, our reduced model dropped these 12 crossings and only retained the main effect of Group. Significance was assessed with the approximate F derived from Wilke's Λ, with $\alpha = 0.05$. If the multivariate F was significant, than any significant univariate Fs were interpreted.

3. Results

3.1. Group behavioral results

As expected, during SD participants were slower, less accurate, and displayed more FR on the DLR. Specifically, participants slowed down an average of 158 ± 32 ms during SD; further, d' values fell by 1.3 ± 0.2, and the percentage of FR increased significantly from $1 \pm 0.4\%$ to $31 \pm 16\%$. The increase in FR was not correlated with the increase in median RT ($r = 0.005$, $p = 0.98$), indicating that the greater number of FR during SD were not just an artifact of slowing. The increase in FR was, however, correlated with the decrease in accuracy ($r = -0.46$, $p = 0.0002$).

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