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Sleep deprivation-induced reduction in cortical functional response to serial subtraction

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THIRTEEN normal volunteers were studied with fMRI during arithmetic performance after a normal night of sleep and following sleep deprivation (SD). Aims included determining whether the prefrontal cortex (PFC) and the parietal lobe arithmetic areas are vulnerable to the effects of SD. After a normal night of sleep, activation localized to the bilateral PFC, parietal lobes and premotor areas. Following SD, activity in these regions decreased markedly, especially in the PFC. Performance also dropped. Data from the serial subtraction task are consistent with Horne's PFC vulnerability hypothesis but, based on this and other studies, we suggest the localized, functional effects of SD in the brain may vary, in part, with the specific cognitive task. *NeuroReport* 10:3745–3748 © 1999 Lippincott Williams & Wilkins.

Key words: fMRI; Mathematics; Parietal lobe; Prefrontal cortex; Sleep deprivation

Introduction

Sleep deprivation (SD) interferes with the performance of a variety of cognitive tasks, including working memory tasks [1]. However, the neurophysiological substrates of performance deficits following SD have not been thoroughly studied. Horne [2] and others [3–6] have suggested the prefrontal cortex (PFC) is particularly vulnerable to SD and this proposed susceptibility may underlie some performance deficits. These studies reported only behavioral data, however, and did not test the functional or metabolic response of the PFC to SD. Therefore, the question of the neurophysiological response of the PFC to SD remains open.

Only four functional brain imaging studies of SD have been reported [7–10], and only one used a working memory task. In a preliminary study, Thomas *et al.* [9], utilizing a serial arithmetic task, reported a decrease in absolute levels of glucose metabolism within the PFC after 24 h SD. However, the long duration of the task in this PET study (i.e. about 30 min) suggests that successful performance relied heavily on sustained attention, in addition to arithmetic accuracy. Furthermore, it remains unclear whether arithmetic or working memory regions of the parietal lobes are adversely affected by SD, as the authors did not report glucose metabolism for these areas.

This study used fMRI to simultaneously study arithmetic performance and cerebral activation after a normal night of sleep and after 35 h of total SD. We hypothesized that SD would reduce activation in response to this working memory task within the PFC as well as the parietal lobes and other brain regions involved in arithmetic. An arithmetic working memory task was chosen because it is sensitive to SD [9,11]. Others have reported that arithmetic reliably activates the executive centers of the PFC as well as the parietal lobes and the premotor areas [12–14]. Activation of brain regions was measured with fMRI and defined as the response of the blood oxygen level dependent (BOLD) signal to the behavioral task.

Materials and Methods

Thirteen normal healthy subjects (mean age 27.2 years, range 21–35 years; mean education 16.5 years, range 14–18 years) participated after providing written informed consent. Subjects performed four separate cognitive tasks twice at the same time of day in a counterbalanced order while undergoing fMRI scans: once after a normal night of sleep and once

after a mean of 35 h total SD. We report here only the results of the arithmetic task.

The behavioral trial was similar to that reported by others [12] but was modified to acquire behavioral data. Briefly, each trial alternated between four experimental and five baseline blocks, starting and ending with a baseline block (each block = 40 s; total trial = 360 s). During each experimental block, subjects saw a series of random three-digit numbers and were required to serially subtract either 6, 7, 8, or 9 (randomly chosen for each subject) from them. Specifically, the 'seed' number was presented for 1 s. This was followed by a second three-digit number presented for 1.5 s. The subjects determined, and responded via a button box, whether the second number was the correct answer to the question 'Does the seed number minus (6, 7, 8, or 9) equal the second number?' Then, a third number appeared for 1.5 s and the subjects answered the same question, but used the second number as the new seed. The baseline blocks were identical visually, but subjects counted forward by one. The proportions of arithmetic problems answered correctly, incorrectly, and omitted, as well as reaction times, were recorded. Behavioral data was lost for three subjects due to mechanical malfunctions, leaving 10 subjects available for the behavioral data analyses. Subjects also rated their subjective level of sleepiness at each scanning session with the Stanford Sleepiness Scale [15].

All images were acquired with a 1.5 T GE Signa scanner equipped with a local head gradient and RF head coil designed for rapid switching [16]. Functional scans consisted of 90 repetitions of echo planar images (TR = 4000 ms, TE = 40 ms, FOV = 24 cm, image matrix = 64×64, in-plane size = 3.75 mm^2, slice thickness = 6 mm, no interslice gap, image acquisition time = 40 ms) acquired continuously on 20 slices in an interleaved fashion in the sagittal plane. For anatomical images, 128 1.5 mm contiguous images were collected as a volume acquisition using MPRAGE protocol (256×256 matrix, FOV = 24 cm, flip angle 10°).

Analyses were conducted with AFNI software [17]. After motion correction, the functional time-course data from each voxel were correlated with a series of 13 reference functions, one seed reference function representing the alternating time course of the behavioral trial and the same reference function shifted in 1 s increments six times both forward and backward in time [18]. All individual datasets were then transformed into standard atlas space [19] and spatially smoothed with a Gaussian kernel equal to 3.75 mm full width half maximum. Analyses focused on two issues. First, areas of significant activation were identified for each night separately. Second, the two nights were directly compared to identify regions that were significantly more responsive to the arithmetic task after one night compared to the other. Since we were interested in activation during serial subtraction, we only examined positive activations. A cluster thresholding method [19] was used to protect against Type I errors. We report areas of significant activation only if they contain at least six contiguous voxels (cluster volume = 506 mm^3), each individually activated at an *a priori* $p < 0.025$ (one-sided). This resulted in a final per-voxel p-value of 0.0005 (one-sided).

Results

Subjects showed an overall decrease in the proportion of correct responses to the arithmetic problems (0.89 ± 0.09 after normal sleep *vs* 0.84 ± 0.12 after SD, $p < 0.05$) and an overall increase in the number of omitted responses (i.e. non-responses; 0.03 ± 0.04 *vs* 0.08 ± 0.05, $p < 0.02$). The statistical interaction between task condition and experimental night was not significant. Subjects reported a significant increase in subjective sleepiness following SD (3.5 ± 1.1 *vs* 4.5 ± 0.7, $p < 0.007$).

After the normal night of sleep (Fig. 1, top panel), activation was seen in the bilateral dorsolateral PFC (Brodmann areas (BA) 9,10,45,46), left premotor region and cingulate gyrus (these two areas merged into one cluster during the spatial smoothing process: BA 6,24,32), right premotor region (BA 6), bilateral inferior and superior parietal lobes (BA 7,40), and bilateral visual regions (BA 17,17,19). After SD (Fig. 1, bottom panel) only one of these areas was activated: the left superior parietal lobe (BA 7). The only other areas of activation after SD were in the left premotor region (BA 6) and the left superior parietal lobe/lateral occipital gyrus (BA 7,19), both of which overlap in BAs, but not physically, with the normal night activation. Table 1 shows the regions that were significantly more responsive to the arithmetic task after one night than the other.

Discussion

The task used here compared a serial subtraction experimental condition to a rote counting baseline condition. As expected, after the normal night of sleep, serial subtraction activated regions within the bilateral PFC, parietal lobes, and premotor areas (Fig. 1). The PFC has been implicated in working memory [21,22], especially manipulation of information within working memory [22,23]. Following SD, on the other hand, no regions within the PFC were responsive to the cognitive demands of the arith-

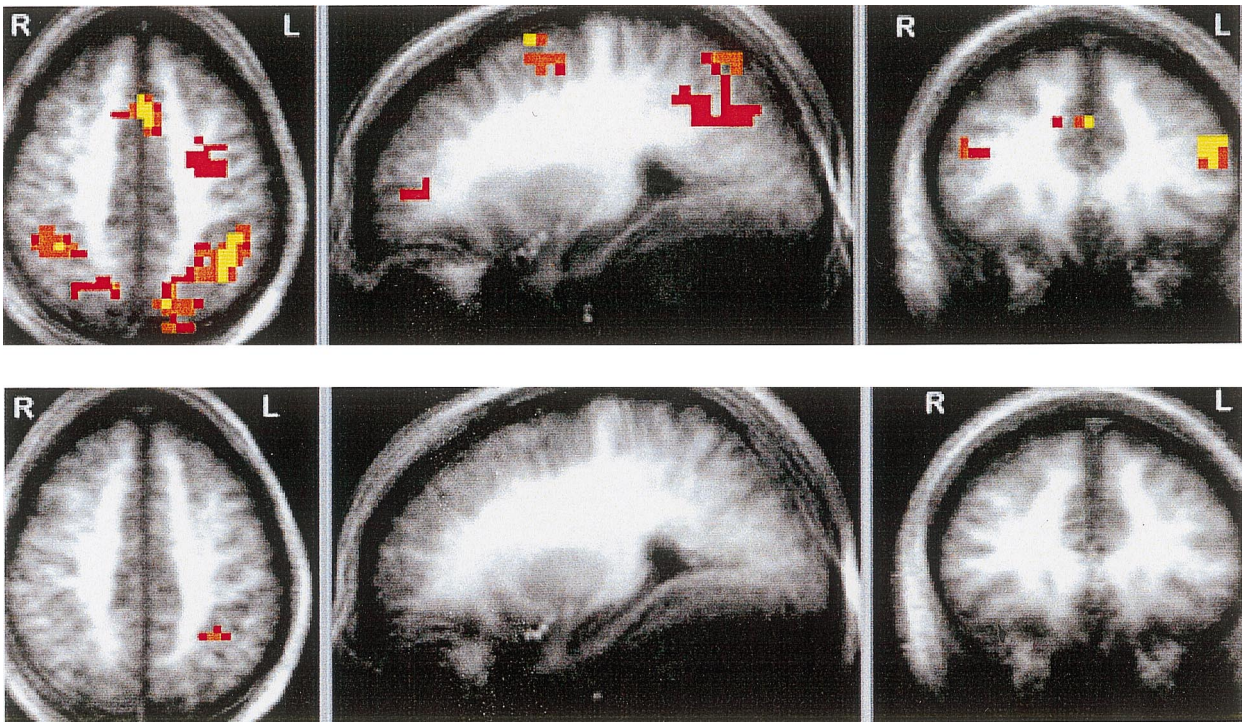

FIG. 1. Activation during the arithmetic task after a normal night of sleep (top) and following sleep deprivation (bottom). Significant activation in color is overlaid onto the mean Talairach anatomical image averaged across all 13 subjects. Yellow represents the most intense activation, red the least intense. Slices are the following distances from the center point: 41 mm superior (axial), 25 mm right (sagittal) and 29 mm anterior (coronal). Axial and coronal slices are in radiological orientation (left and right are reversed).

Table 1. Results of the direct comparison of the two nights. Each entry corresponds to one significant cluster. Clusters covering more than one area are so designated

Analysis	Cluster location	Talairach centroid coordinates
Normal night > sleep deprivation	L. premotor region (BA 6)	29L, 1P, 60S
	L. premotor region/cingulate gyrus (BA 6/32)	3L, 11A, 46S
	L. pulvinar nucleus of thalamus	15L, 25P, 15S
	B. inferior parietal lobe (BA 40)	42L, 45P, 41S
		33R, 37P, 38S
	B. superior parietal lobe (BA 7)	16L, 80P, 46S
		22R, 66P, 52S
	B. calcarine gyrus/middle occipital gyrus/cuneus (BA 17/18/19)	4R-19L, 96P, 4S
	L. cuneus (BA 18)	2L, 78P, 19S
	L. lingual gyrus (BA 19)	20L, 57P, 0S
	R. superior occipital gyrus (BA 19)	32R, 69P, 33S
	R. middle occipital gyrus/cuneus (BA 18/19)	29R, 94P, 6S
	R. fusiform gyrus (BA 37)	46R, 52P, 2S
		33R, 64P, 1I
Sleep deprivation > normal night	R. insula/precental operculum (BA 4,6)	38R, 1P, 13S

metic task. Furthermore, the cingulate gyrus was significantly more responsive to the arithmetic task after the normal night of sleep compared to after SD (Table 1). These findings with arithmetic are consistent with Horne's PFc vulnerability hypothesis [2]. In contrast, we found the PFC showed an increased response to verbal learning after SD than after a rested state during another trial in this study [24] (submitted). Briefly, the superior frontal gyrus (BA8) showed increased activation after SD compared to the normally rested state during a word-memorization task, while several other areas within the PFC, including the cingulate gyrus, showed equivalent activation after SD. Thus, the response of the PFC, and other brain regions, to SD may depend on the nature of the specific cognitive task. Serial subtraction involves maintenance and manipulation of information by the executive centers, while verbal

learning involves speech production and rehearsal. These differential cognitive demands may help explain why the PFC shows decreased responsiveness to our arithmetic working memory task after SD while it appears to compensate during the verbal learning task.

SD also affected brain regions other than the PFC. Several areas reportedly involved in arithmetic performance [12–14] were more activated after the normal night of sleep (and thus less activated after SD), including the bilateral parietal lobes, and left premotor region and lingual gyrus (Table 1). The parietal lobes in particular showed a decreased response to arithmetic performance following SD, though it was not as complete as that of the PFC. In addition to involvement in arithmetic performance, the parietal lobes have been implicated in working memory tasks [25,26]. In our verbal learning trial [24] (submitted), the bilateral parietal lobes were activated following SD but not in the rested condition. Furthermore, parietal lobe activation after SD was correlated with preserved free recall performance. These contrasting findings in the parietal, frontal, and other brain regions suggest that the response of the brain to SD may be cognitive task-specific rather than brain region-specific.

What might these data tell us about the relationship between changes in cerebral activation and changes in behavioral performance after SD? First, the decreased responsiveness of the working memory and arithmetic areas of the brain after SD may account for the decreased behavioral performance after SD. Second, Dehaene and colleagues [14] recently reported that exact arithmetic performance emphasizes language-based representations and more strongly activates the inferior frontal and cingulate gyri. In contrast, approximate arithmetic performance emphasizes visual–spatial representations of numerical magnitudes and more strongly activates the parietal lobes. The lack of prefrontal activation suggests that subjects did not use language based representations to find exact arithmetic answers after SD. Rather, the diminished but statistically significant activation of parietal lobes after SD suggests that subjects might have used a more visually based strategy to find approximate answers.

Conclusion

These arithmetic data are consistent with Horne's PFC vulnerability hypothesis [2]. When those from our verbal learning trial [24] are also considered, we can extend Horne's hypothesis. We propose that the response of the PFC, and the brain in general, to SD is cognitive task-specific. Future research should focus on differential effects of specific tasks and the implications of those differential effects. For example, for the task utilized here, the working memory regions of the brain exhibited a decreased responsiveness to cognitive demands after SD. When one considers the professionals who are often required to work sleep deprived (e.g. pilots, military personnel, doctors, truck drivers, politicians), a deficit in the functioning of the working memory systems may have serious impacts on public safety. Decreased involvement of the frontal executive centers may be especially problematic considering the proposed role of this brain area in originality and flexibility of thought, behavioral inhibition, reasoning, and problem solving. Finally, if the results seen here after SD replicate with other working memory tasks, it may help explain diminished performance during neuropsychological assessment in patient populations commonly experiencing SD (e.g. patients with traumatic head injury and a variety of psychopathologies).

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