Modafinil Activates Cortical and Subcortical Sites in the Sleep-Deprived State

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Subject Objectives: To assess the effect of the wake-promoting drug modafinil on working memory and brain activation in the executive network, following a single night of sleep deprivation.

Design: Randomized, placebo-controlled, 4-arm, double-blind evaluation of a single 200-mg dose of modafinil on working memory (1-, 2-, and 3-back)-related functional brain activation and performance following overnight sleep deprivation.

Setting: General Clinical Research Center, Biomedical Imaging Center.

Subjects: Eight medication-free men, aged 21 to 35 years.

Interventions: Overnight sleep deprivation, single-dose 200-mg modafinil, functional magnetic resonance imaging

Measurements and Results: Brain activation patterns and regional signal intensity based on the blood-oxygen level-dependent signal were assessed. The following reaction times were used as measures of performance: (1) attention in the scanner before functional scanning, (2) "back" responses during the active-task block, and (3) attention during the base-

line task block. Contrast of activation maps among conditions revealed sleep-deprivation and drug effects, and their interactions. Performance in the deprived state was enhanced by modafinil only at an intermediate (2-back) level of task difficulty and was associated with the recruitment of increased cortical activation volumes. Strong and consistent individual differences in performance were noted on the working memory tasks.

Conclusions: Modafinil effectively counters the adverse effects of overnight sleep deprivation on working memory but only when task difficulty is moderate, recruiting extensive areas in the executive network to do so. Interindividual differences in working-memory performance are stable trait characteristics.

Keywords: Sleep deprivation, modafinil, functional magnetic resonance, working memory

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INTRODUCTION

SLEEP DEPRIVATION AND SLEEP FRAGMENTATION IMPAIR PERFORMANCE ON TASKS OF "EXECUTIVE FUNCTION." 1 THESE COGNITIVE CONTROL PROCESSES include flexibility in problem solving, planning, response inhibition, allocation of attention, maintenance and manipulation of information over time, and self-regulation of goal-directed behavior. 2,3 Sleep has important potential restorative effects on prefrontal cortex activity and function. 4 Working memory is an important executive process used for temporary storage, active monitoring, and manipulation of information. 5 Several abnormalities described after sleep deprivation suggest impaired executive control, such as an increased rate of forgetting, slow responses to simple mathematical calculations, and false responses. 6 It is possible that impaired working memory is a fundamental abnormality in the state of excessive sleepiness regardless of etiology.

Modafinil is a nonamphetamine wake-promoting drug that is approved for the treatment of excessive sleepiness associated with narcolepsy, shift work sleep disorder and residual sleepiness in positive airway pressure-treated obstructive sleep apnea. 7,8 It is clinically effective in preventing or reversing the effects of acute sleep deprivation and shift-work--induced performance decrements 9,10 and in improving executive function in narcoleptics. 11 Functional neuroimaging of executive functions, including working memory, has consistently demonstrated activation in an interconnected and distributed network of cortical areas that include the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate in the medial wall (AC), and the posterior parietal cortex (PPC). 11,14 We hypothesized that modafinil would reverse sleep deprivation-induced activation reductions in the executive network, especially in the prefrontal cortex. We used functional magnetic resonance imaging (fMRI) with 3 levels of difficulty on a verbal working-memory task—1, 2, and 3-back 15—to assess the functional neurobiology of executive function in sleep-deprived adults treated with 200 mg of modafinil or placebo.

METHODS

The subjects were 8 medication- and disease-free healthy men aged 21 to 35 years who were recruited from the local community. All subjects had an initial telephone or e-mail contact with 1 author (RJT), followed by a formal sleep clinic evaluation. This included detailed questioning about sleep, sleepiness, sleep habits, past or current neurologic or psychiatric symptoms; administration of the Epworth Sleepiness Scale; and a clinical examination, including examination of the upper airway.

Subjects who habitually consumed more than 2 cups of coffee daily were excluded. An honor system was used to provide a drug-, tobacco-, caffeine-, and alcohol-free lead-up period to each scan session; drug screens were not done. The mean age of the subjects was 26 ± 2 years. Women were excluded to eliminate confounding from effects of estrogen on working memory.
fMRI activation across the menstrual cycle.\textsuperscript{16} Sleep deprivation was performed with constant attendance in the General Clinical Research Center at the Beth Israel Deaconess Medical Center, Boston, Massachusetts. Ambient light was low (<50 lux) during the deprivation period. Lights off was at 10:00 PM; lights on was at 6:00 AM. Subjects were allowed to watch movies, use a laptop computer, and engage in conversation with the research assistant. They could stretch but not exercise. Use of caffeine- or theobromine-containing beverages or snacks was not permitted for the 48 hours prior to each experiment or during sleep deprivation. A standard meal of 800 calories was provided to all subjects. A shower was permitted before lights out but not in the morning.

Functional imaging was performed at the Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts; both Institutional Review Boards approved the protocol, and all subject provided written informed consent. To minimize circadian effects, subjects were selected who habitually kept a 10:00 AM to 6:00 AM schedule, as determined by personal reports, sleep logs, and actigraphy, and scanning was performed between 8:00 and 10:00 AM. Subjects were randomly assigned to 1 of 4 conditions (sleep deprived + a single dose of modafinil or placebo at 6:00 AM, rested + modafinil or placebo). The sleep-deprived condition involved approximately 28 hours of continuous wakefulness, and the rested condition included 8 hours of scheduled sleep opportunity. Each subject was tested 4 times; all subjects were studied in each condition (32 separate experiments), counterbalanced, with a minimum delay (washout) period of 1 week. Modafinil was thus administered about 2 hours before the start of imaging, to allow adequate time for absorption.

Cognitive Testing (Working Memory) Protocol

A block-design protocol was used, with 60 seconds on task alternating with 30 seconds off task. On task, random letters were presented in the center of the visual field every 4 seconds, 15 for each 60-second block, and each stimulus lasted 500 milliseconds (total of 6 active-task blocks). Three levels of difficulty were tested—1-, 2-, and 3-back. A small ramp up was present (e.g., for the 2-back task, the first and second stimuli could only be nontargets but had to be retained in working memory to determine the nature of the third and subsequent stimuli). Thus, the load on working memory was the ordering, retention, updating, and manipulation of 1, 2, or 3 letters and consideration of their relationship with the third (new) presented letter, which, for example, in a 2-back sequence, could be a target (e.g., an m-f-m sequence) or a nontarget (e.g., a y-t-b sequence).

Subjects made responses to all presented stimuli. A total of 14 alphabets were used, and sequences that made “word sense” (e.g., b-a-d) were excluded. Based on our prior experience during protocol development of the testing of performance following sleep deprivation and in patients with sleep apnea, we chose an intertrial interval of 4 seconds to capture the whole range of slowing. It is our observation that patients with sleep disorders or subjects with excessive sleepiness find the 2-back test relatively difficult. One third of the presented alphabets were targets. Only subjects who demonstrated high accuracy (> 90%) during a pretesting session were enrolled. During the screening process, 3 subjects were excluded for this reason. During the “off” periods, vigilance was monitored and reaction times to the discrimination of randomly occurring symbols + and * were determined. During this task, either symbol was present continuously, while the task requirement was to note a change to the other, which occurred at randomly occurring intervals but, on average, every 5 seconds (twice in a 10-second period). The task could thus be considered a variant of the Psychomotor Vigilance Test and did require sustained attention. The working-memory component of the task required significant “online” maintenance and manipulation of the alphabet stream and sustained attention, whereas the baseline task required sustained attention. The task sequence during each experimental session was fixed: 1-2-3-2-3-1 (back). Two complete scan runs were collected at each level of difficulty, and reaction times (90 per subject in the 2-back, 84 per subject in the baseline, per run) were obtained using a scanner-compatible button box. Reaction times were averaged over the 2 runs to provide a single composite number per subject per task level per condition. If there was a concern that the subject fell asleep (>2 missed responses), the scanning was stopped and repeated.

During anatomic scanning, a modified continuous 10-minute attention task (nearly identical to the Psychomotor Vigilance Test but for absence of performance feedback) was run to obtain a measure of vigilance in the scanner—in this instance, the “+” symbol appeared at random (mean intertrial interval of 5 seconds, range 2-10 seconds) but disappeared on button press; it also served to keep subjects awake when functional data were not being collected. Thus, the study provided 3 related but distinct behavioral measures: 2-back, attentional “baseline” during the functional run, and attentional performance during anatomic scanning. The reported mean reaction times included all responses (correct and incorrect). A composite subjective sleepiness and general sense of well-being score was determined just before and after the scanning session and averaged (0 = worst [can barely stay awake, feel down, miserable, unable to function], 10 = best [feel wide awake, alert, motivated, rested]).

Functional Imaging and Data Analysis

Imaging was performed on a 3.0 Tesla Siemens scanner. Behavioral performance responses were monitored continuously to discard runs in which the subjects may have transiently fallen asleep, as determined above. A button-box response was required at least once every 4 seconds, reaction times were observed in real time, and the subjects were checked on between each scan run. This ensured that what data were obtained reflected performance while sleepy and not functional activation of mixed sleep and wakefulness. Structural images and echoplanar functional images were acquired over a 90- to 120-minute session. The 3-dimensional structural anatomic image had a 1-mm resolution and a 256-mm field of view. A gradient echo T2*-weighted sequence (TR: 2000 msec, TE: 30 msec, flip angle: 90°) was used to obtain BOLD contrast data. Functional data sets had 16 slices, each 5 mm with a 1-mm gap, 285 time points, 200 mm field of view, and a 64 × 64 matrix. Inplane voxel X/Y resolution was 3.125 mm. An identical-slice high-resolution T1-weighted scan was used as an intermediate step for functional overlays prior to transformation into 3-dimensional space, reducing the effect of echoplanar anatomical distortion. Slices were obtained approximately parallel to the anterior commissure-posterior commissure line.

Preprocessing included 3-dimensional motion correction, spatial smoothing using a 6-mm Gaussian filter for individual subject analysis and a 10-mm filter for group averaging, linear trend re-
moval, and temporal high-pass filtering using the Brain Voyager 2000 (Brain Innovation, Maastricht, The Netherlands) software package. Statistical correlation maps were generated using a general linear model, as implemented within the software, and incorporated into the 3-dimensional anatomic data set through interpolation of the functional voxels to the same resolution as the anatomic voxels [1 × 1 × 1 mm]. In the design matrix, the reference function was defined by convolving a boxcar with a gamma function. Stereotaxic transformation of data into a standardized space (Talairach) was performed for neuroanatomic localization of activated foci. Following estimation of whole-brain activation corrected for multiple comparisons (Bonferroni p ≤ .05), we tabulated volume of activation (number of contiguous activated voxels reflected the sum total of both halves of the brain in the areas of interest) and mean percentage BOLD signal (the signal time course over all activated voxels in the area was extracted and a mean value of percentage of signal change was computed by the software) from the following 3 areas: (1) dorsolateral prefrontal cortex (Brodmann Area [BA] 46/9), (2) anterior cingulate cortex (BA 24), and (3) inferior parietal lobule in the posterior parietal cortex (BA 40). Given the normal variability in cortical anatomy, this localization is only approximate.

Further precautions were taken to minimize false positives. Data sets that had movement-correlated signals mimicking true activation, nonphysiologic BOLD signal-change amplitudes (≥ 5% increases), and extracerebral activation were discarded. The minimum activation cluster size should be set large enough to make it unlikely that a cluster of that size would occur by chance, assuming that falsely activated voxels should be randomly distributed. This relies on the assumption that areas of true neural-signal activity tend to stimulate signal changes over contiguous voxels, and clusters of 200 or more voxels (0.2 cm³) were identified. Activation maps of individual subjects in all 4 states were generated, followed by a fixed-effects analysis. Group activation maps were rested + modafinil, rested + placebo, sleep deprived + placebo, and sleep deprived + modafinil. Contrasts of different task levels were not the focus of this manuscript. The following contrasts were estimated between conditions: rested-deprived, deprived-rested, rested-drug, drug-rested, deprived-drug, and drug-deprived. Activation maps had a pseudocolor code of correlations. The radiologic convention was used, with the right side of picture equal to the left side of brain.

**Statistical Methods**

Summary statistics for various measures of performance and activation were means and standard deviations (STATA SE8, Stata Corporation, TX). Analysis of variance was used for estimating differences in the 4 experimental conditions by subject or drug state and session effects. A randomized-block procedure was used to assess effects of drug on performance, with subject as a blocking factor, because interindividual variability in subject performances were large but consistently in a restricted range for the individual subject. This way, most of the variation observed in the performance of the subjects could more directly be attributed to the treatment, rather than being masked by other factors. Tukey multiple comparisons were computed for significance of differences in performance between the 4 states (sleep deprived vs rested, modafinil vs placebo) for subjective and objective measures of sleepiness and performance. Multiple regression with step-wise backward elimination was used to estimate correlations between task performance at the 2- and 3-back level, subjective sleepiness and attention tasks, in relation to the percentage of signal or volume of activation in the lateral prefrontal, anterior cingulate, and posterior parietal cortex. Intraclass correlations (ICC) were computed to assess the distribution of variance in performance between and within subjects. The ICC values were interpreted using published benchmark ranges, which can be interpreted as corresponding to increasing stability of observed interindividual differences: “slight” (0.0–0.2), “fair” (0.2–0.4), “moderate” (0.4–0.6), “substantial” (0.6–0.8), and “almost perfect” (0.8–1.0).

**RESULTS**

Average total sleep times per night the week prior to each scanning session were 7 ± 0.2 hours, as estimated from sleep logs and actigraphy.

<p>| Table 1—Sleepiness and performance |</p>
<table>
<thead>
<tr>
<th>State</th>
<th>SS</th>
<th>ATTN</th>
<th>1-back</th>
<th>1-baseline</th>
<th>2-back</th>
<th>2-baseline</th>
<th>3-back</th>
<th>3-baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Rested + modafinil</td>
<td>8.1 ± 0.6</td>
<td>387 ± 94</td>
<td>545 ± 164</td>
<td>481 ± 144</td>
<td>688 ± 250</td>
<td>421 ± 67</td>
<td>855 ± 429</td>
<td>459 ± 124</td>
</tr>
<tr>
<td>2 = Rested + placebo</td>
<td>8.1 ± 0.8</td>
<td>384 ± 41</td>
<td>552 ± 146</td>
<td>439 ± 97</td>
<td>692 ± 246</td>
<td>471 ± 65</td>
<td>894 ± 310</td>
<td>462 ± 72</td>
</tr>
<tr>
<td>3 = Deprived + placebo</td>
<td>4.4 ± 1.1</td>
<td>716 ± 350</td>
<td>529 ± 116</td>
<td>435 ± 30</td>
<td>867 ± 252</td>
<td>538 ± 115</td>
<td>849 ± 354</td>
<td>569 ± 156</td>
</tr>
<tr>
<td>4 = Deprived + modafinil</td>
<td>7.4 ± 0.5</td>
<td>422 ± 31</td>
<td>548 ± 131</td>
<td>449 ± 32</td>
<td>705 ± 217</td>
<td>476 ± 75</td>
<td>840 ± 354</td>
<td>469 ± 97</td>
</tr>
<tr>
<td>ANOVA state</td>
<td>F3,28 = 40.5</td>
<td>F3,28 = 7.02</td>
<td>F3,28 = 0.04</td>
<td>F3,28 = 0.44</td>
<td>F3,28 = 0.97</td>
<td>F3,28 = 2.68</td>
<td>F3,28 = 0.03</td>
<td>F3,28 = 1.66</td>
</tr>
<tr>
<td>by subject</td>
<td>p &lt; .001</td>
<td>p = .001</td>
<td>p = .98</td>
<td>p = .72</td>
<td>p = .42</td>
<td>p = .07</td>
<td>p = .99</td>
<td>p = .19</td>
</tr>
<tr>
<td>Significant differences</td>
<td>F3,21 = 39.67</td>
<td>F3,21 = 7.39</td>
<td>F3,21 = 0.32</td>
<td>F3,21 = 0.57</td>
<td>F3,21 = 17.64</td>
<td>F3,21 = 2.88</td>
<td>F3,21 = 0.35</td>
<td>F3,21 = 1.74</td>
</tr>
</tbody>
</table>

SS refers to subjective sleepiness, scale of 0 - 10, see text. All reaction times are in milliseconds. ATTN refers to the mean response times for attention task during anatomic scanning before functional runs; baseline is the mean response times for attention task within the functional run. Drug-induced performance increment during the various levels of the n-back task is significant only in the 2-back condition and only when blocked by subject. Attention and subjective sleepiness are strongly modulated by state and drug, rather than individual differences. ANOVA, analysis of variance.
Subjective Sleepiness and Task Performance

Subjective sleepiness and reaction times during the attention task before the start of the functional imaging were strongly modulated by sleep deprivation (increased) and the use of modafinil (increase prevented, Table 1). During the baseline periods of the scanning blocks, reaction times were not significantly different across conditions: 451 ± 86, 477 ± 90, and 489 ± 120 milliseconds, respectively, on the 1-, 2-, and 3-back (F3,29 = 1.22, p = .30). Increasing task difficulty was associated with significant slowing of performance speed, being 544 ± 134, 749 ± 235, and 865 ± 363 milliseconds on the 1-, 2-, and 3-back conditions, respectively (F2,29 = 12.35, p < .001). Reaction times on the 1- and 3-back were not significantly different in the 4 states but, in the 2-back condition, was significant only when blocked by subject.

The percentage of correct responses was not significantly different in the 1- and 2-back conditions. In the 1-back condition, the percentage of correct responses for the rested + modafinil, rested + placebo, sleep deprived + placebo, and sleep deprived + modafinil conditions were 95% ± 2.9%, 95.4% ± 1.2%, 96% ± 1%, and 94.5% ± 2.3%, respectively (F1,28 = 0.73, p = .54). In the 2-back condition, it was 94.1% ± 2.6%, 92.3% ± 2.8%, 93.3% ± 5.2%, and 88.4% ± 6.6%, respectively (F1,28 = 1.23, p = .32). In the 3-back condition, an increase in accuracy was seen (86.9% ± 5.2%, 88.4% ± 6.6%, 78.4% ± 6.2%, and 89.3% ± 3.8% correct responses, F1,28 = 6.49, p = .002), being significantly reduced only in the sleep-deprived + placebo condition, relative to all other states. There was no session effect on baseline (F3,92 = 1.99, p = .12) or working-memory (F3,92 = .01, p = .99) performance.

Subjective Pharmacologic Effects

All subjects tolerated the drug well with no discernable side effects. Only 1 of 8 could accurately guess before scanning, following sleep deprivation, if they had received the drug or placebo, but this increased to 3 of 8 by the end of the scanning session. If not sleep deprived, subjects could not discriminate the placebo or modafinil.

Functional Activation Maps

Activation in the classic nodes of the executive network was seen in each subject only in the 2- and 3-back conditions; signal percentage and activation volume data for the 1-back condition were thus incomplete and not presented. In the 2-back condition (Table 2), volumes of activation in the lateral prefrontal, medial wall, and posterior parietal cortices were significantly reduced by sleep deprivation, with a robust increase relative to the deprived state associated with drug use. In the 3-back condition, the lateral prefrontal cortex activation volume increased in the deprived-modafinil relative to the rested-modafinil state, and the posterior parietal activation increased in the deprived-modafinil relative to the deprived-placebo state. The percentage of signal differences, in the posterior parietal cortex, were seen on only the 2- and not the 3-back task.

**Activation Maps**

**Effects of Task Difficulty and State:**

Increasing task load was associated with increasing activity in the known nodes of the executive network (lateral and medial prefrontal, posterior parietal) and in the subcortical areas, especially the thalamus (Figure 1). During the 1-back task, activation was scarce; the rested state had activation in the left middle frontal gyrus (Talairach x, y, z: -47, 13, 17, BA 9) and in the region of the insula (Talairach x, y, z: -33, 22, 11, BA 13). Modafinil use during the 1-back task resulted in new activation centered bilaterally in the inferior parietal lobule (Talairach x, y, z: -44, -35/35, 30, BA 40). Sleep deprivation reduced activation in the 2- and 3-back conditions, and, in the 1-back task, there was no activation seen, as the attention demands on the block baseline periods may have been similar to the active condition. Modafinil use following sleep deprivation seemed to restore activation to rested levels and beyond (during the 2-back task) over contiguous areas.

**Contrasts:**

**Sleep Deprivation vs Rested State:** In the contrast of rested-state activation > sleep deprived or sleep deprived > rested, there was no activation that exceeded the criteria for significance for the 1-back task(Figure 2). Overall patterns of activation during the 2- and 3-back were similar. The rested state had greater activation in the lateral frontal and prefrontal regions (e.g., Talairach x, y, z: 363 - Regional Activation During the 2-Back Task

<table>
<thead>
<tr>
<th>State</th>
<th>% PPC 2-back</th>
<th>% AC 2-back</th>
<th>% PFC 2-back</th>
<th>Voxels PPC 2-back</th>
<th>Voxels AC 2-back</th>
<th>Voxels PFC 2-back</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Rested + modafinil</td>
<td>0.55 ± 0.20</td>
<td>0.53 ± 0.19</td>
<td>0.72 ± 0.38</td>
<td>22908 ± 7846</td>
<td>9210 ± 4439</td>
<td>10919 ± 5724</td>
</tr>
<tr>
<td>2 = Rested + placebo</td>
<td>0.86 ± 0.29</td>
<td>0.78 ± 0.37</td>
<td>0.88 ± 0.40</td>
<td>27133 ± 12061</td>
<td>9983 ± 3853</td>
<td>10892 ± 6851</td>
</tr>
<tr>
<td>3 = Deprived + placebo</td>
<td>0.77 ± 0.20</td>
<td>0.60 ± 0.12</td>
<td>0.54 ± 0.30</td>
<td>41996 ± 15053</td>
<td>12754 ± 7177</td>
<td>19420 ± 11107</td>
</tr>
<tr>
<td>4 = Deprived + modafinil</td>
<td>0.41 ± 0.17</td>
<td>0.47 ± 0.29</td>
<td>0.71 ± 0.20</td>
<td>13337 ± 8247</td>
<td>4255 ± 3015</td>
<td>5189 ± 4586</td>
</tr>
</tbody>
</table>

ANOVA state

F3,29 = 7.04
F3,29 = 2.18
F3,29 = 1.44
F3,29 = 9.07
F3,29 = 4.22
F3,29 = 4.92
p = .001
p = .11
p = .25
p < .001
p = .01
p = .007

Significant differences by state

4 > 3
2 > 3
2 > 1

% refers to the percentage increase in the BOLD signal; AC, anterior cingulate; voxels, the number of voxels (0.001 cm3), interpolated that met thresholds described in methods; ±, standard deviation; state, rested or deprived or drug or placebo; ANOVA, analysis of variance. Significant differences in measures of regional activation were modulated by state (drug, sleep deprivation). Modafinil use in the sleep-deprived (vs placebo) state significantly increased activation volumes in medial wall, posterior parietal cortex (PPC), and lateral prefrontal cortex (LPC). Percentage signal differences were seen only in the PPC: (i) Greater activation associated with the drug in the sleep-deprived state, relative to placebo condition. (ii) Less activation in the drug relative to the placebo condition when rested. (iii) Reduction of activation in the drug-free sleep deprived vs rested state—the effect of sleep deprivation.
Activation effects of modafinil > placebo were small in the rested state, with the predominant activation being in the left precuneus (Talairach x, y, z: -9, -69, 27, BA 31) and posterior cingulate grey (Talairach x, y, z: -24, -52, 11, BA 30) during the 2-back task and left inferior frontal gyrus (Talairach x, y, z: -41, 18, 11, BA 45) during the 3-back task (Figure 3). The placebo > modafinil contrast while rested showed activation in the following regions: (1) 1-back: medial frontal gyrus (Talairach x, y, z: 5, 49, 11, BA 10), (2) 2- and 3-back: left middle frontal gyrus (Talairach x, y, z: -32, 41, 26, BA 46) and posterior cingulate grey (Talairach x, y, z: -24, -52, 11, BA 30) during the 2-back task and left inferior frontal gyrus (Talairach x, y, z: -41, 18, 11, BA 45) during the 3-back task (Figure 3). The placebo > modafinil contrast while rested contrast revealed activation in the subgenual anterior cingulate, as discussed below, and in the (predominantly) left middle temporal gyrus (Talairach x, y, z: -47, -64, 27, BA 39) (Figure 4).

**Modafinil Effects When Rested:** Activation effects of modafinil > placebo were small in the rested state, with the predominant activation being in the left precuneus (Talairach x, y, z: -9, -69, 27, BA 31) and posterior cingulate grey (Talairach x, y, z: -24, -52, 11, BA 30) during the 2-back task and left inferior frontal gyrus (Talairach x, y, z: -41, 18, 11, BA 45) during the 3-back task (Figure 3). The placebo > modafinil contrast while rested contrast revealed activation in the subgenual anterior cingulate, as discussed below, and in the (predominantly) left middle temporal gyrus (Talairach x, y, z: -47, -64, 27, BA 39) (Figure 4). The modafinil > placebo contrast showed no significant differ-

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**Figure 1**—Activation maps, state and task difficulty. Fixed-effects average-activation maps during the 1-, 2-, and 3-back tasks, of 8 subjects in 4 different conditions—A, alert / rested; P, placebo; M, modafinil; SD, sleep deprivation. Activation in the thalamus and executive network are similar to that reported in the literature. When used in the rested state, modafinil has small effects on activation, better visualized on the contrast maps. Sleep deprivation results in an overall reduction in activation, especially in frontal and prefrontal areas. There is a nearly complete loss of thalamic activation at the 2-back level of difficulty and a reduction at the 3-back level in the SD + P condition. When used after sleep deprivation, modafinil results in extensive recruitment of subcortical-thalamic and cortical (executive network) areas, most evident at the 2-back level of difficulty, along with maintained activation in the thalamus (see text for discussion). In all figures: L refers to the left and R to the right side of the brain. Pseudocolor coding: yellow: t: 8.0, red: t: 4.87, corrected for multiple comparisons, p: < .05. In all sets of images, the Talairach z is 27 and 11, left and right panels respectively.

**Figure 2**—Rested and sleep deprivation contrasts under placebo. The 1-back level has no significant activation. There is greater activation when rested relative to deprived in prefrontal areas and greater activation in the posterior components of the executive network when sleep deprived relative to rested. L refers to the left and R to the right side of the brain. Pseudocolor coding: yellow: t: 8.0, red: t: 4.87, corrected for multiple comparisons, p: < .05. In all sets of images, the Talairach z is 27 and 11, left and right panels respectively.

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26, 42, 27, right superior frontal gyrus, BA 10; Talairach x, y, z: -41, 38, 22, left middle frontal gyrus, BA 46) and activation in the left middle frontal gyrus (Talairach x, y, z: -41, 18, 11, BA 45) and bilateral inferior parietal lobule (Talairach x, y, z: -59/-55, -21, 26, BA 40) and supramarginal gyrus (Talairach x, y, z: 57/-59, -49, 27, BA 40).

**Modafinil Effects When Sleep Deprived:** The placebo > modafinil contrast revealed activation in the subgenual anterior cingulate, as discussed below, and in the (predominantly) left middle temporal gyrus (Talairach x, y, z: -47, -64, 27, BA 39) (Figure 4). The modafinil > placebo contrast showed no significant differ-

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BA 9), and a marked increase in regions within and contiguous to the executive network during the 2-back task. This could suggest increased efficiency of information processing by the drug (and thus reduced inefficiency of information processing by the drug (and thus reduced 

to the percentage increase in the BOLD signal; AC, anterior cingulate; voxels, the number of voxels (0.001 cm3, interpolated) that met thresholds described in methods; ±, standard deviation; state, rested or deprived or drug or placebo; ANOVA, analysis of variance. There were no significant differences in % signal change from the regions of interest across conditions. Prefrontal cortex (PFC) activation volumes were increased in the deprived + modafinil vs rested + modafinil state; posterior parietal cortex (PPC) activation volumes were increased in the deprived + modafinil vs. deprived + placebo state.

Strong clustering of performance was seen on the 1-, 2-, and 3-back tasks but not on the baseline or attention task (including the number of responses ≥ 500 ms, a "lapse" on the standard Psychomotor Vigilance Test). The ICC were 0.88, 0.84, and 0.92 for 1-, 2-, and 3-back levels of difficulty, respectively (Table 4)—the majority of the difference in performance could be explained by intersubject variability, a reflection of relatively fixed individual differences in performance space. The only other high ICC was for percentage of posterior parietal activation during the 3-back task (0.86).

**Table 3—Regional Activation During the 3-Back Task**

<table>
<thead>
<tr>
<th>State</th>
<th>% PPC 3-back</th>
<th>% AC 3-back</th>
<th>% PFC 3-back</th>
<th>Voxels PPC 3-back</th>
<th>Voxels AC 3-back</th>
<th>Voxels PFC 3-back</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Rested + modafinil</td>
<td>1.18 ± 0.28</td>
<td>1.05 ± 0.46</td>
<td>1.22 ± 0.42</td>
<td>25758 ± 7897</td>
<td>11728 ± 3899</td>
<td>14818 ± 1958</td>
</tr>
<tr>
<td>2 = Rested + placebo</td>
<td>1.14 ± 0.31</td>
<td>1.21 ± 0.55</td>
<td>1.28 ± 0.38</td>
<td>25096 ± 7624</td>
<td>12884 ± 4049</td>
<td>19210 ± 5303</td>
</tr>
<tr>
<td>3 = Deprived + placebo</td>
<td>1.21 ± 0.51</td>
<td>0.8 ± 0.29</td>
<td>1.23 ± 0.29</td>
<td>22603 ± 7793</td>
<td>14192 ± 5686</td>
<td>16371 ± 2875</td>
</tr>
<tr>
<td>4 = Deprived + modafinil</td>
<td>1.31 ± 0.42</td>
<td>0.92 ± 0.23</td>
<td>1.23 ± 0.37</td>
<td>35201 ± 9303</td>
<td>11332 ± 3586</td>
<td>21947 ± 7924</td>
</tr>
</tbody>
</table>

% refers to the percentage increase in the BOLD signal; AC, anterior cingulate; voxels, the number of voxels (0.001 cm3, interpolated) that met thresholds described in methods; ±, standard deviation; state, rested or deprived or drug or placebo; ANOVA, analysis of variance. There were no significant differences in % signal change from the regions of interest across conditions. Prefrontal cortex (PFC) activation volumes were increased in the deprived + modafinil vs rested + modafinil state; posterior parietal cortex (PPC) activation volumes were increased in the deprived + modafinil vs. deprived + placebo state.

**Table 4—Intraclass Correlation Coefficients**

<table>
<thead>
<tr>
<th>Measure</th>
<th>(F_{2,28})</th>
<th>Significance</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-baseline mean RT</td>
<td>2.33</td>
<td>.06</td>
<td>0.25</td>
</tr>
<tr>
<td>2-baseline mean RT</td>
<td>1.05</td>
<td>.42</td>
<td>0.01</td>
</tr>
<tr>
<td>3-baseline mean RT</td>
<td>1.08</td>
<td>.41</td>
<td>0.02</td>
</tr>
<tr>
<td>1-back mean RT</td>
<td>30.16</td>
<td>&lt;.001</td>
<td>0.88</td>
</tr>
<tr>
<td>2-back mean RT</td>
<td>22.7</td>
<td>&lt;.001</td>
<td>0.84</td>
</tr>
<tr>
<td>3-back mean RT</td>
<td>49.5</td>
<td>&lt;.001</td>
<td>0.92</td>
</tr>
<tr>
<td>Mood</td>
<td>0.15</td>
<td>.99</td>
<td>0</td>
</tr>
<tr>
<td>Attention</td>
<td>0.67</td>
<td>.69</td>
<td>0</td>
</tr>
<tr>
<td>% PPC 2-back</td>
<td>0.91</td>
<td>.51</td>
<td>0</td>
</tr>
<tr>
<td>Voxels PPC 2-back</td>
<td>0.58</td>
<td>.76</td>
<td>0</td>
</tr>
<tr>
<td>% AC 2-back</td>
<td>0.96</td>
<td>.48</td>
<td>0</td>
</tr>
<tr>
<td>Voxels AC 2-back</td>
<td>0.30</td>
<td>.94</td>
<td>0</td>
</tr>
<tr>
<td>% PFC 2-back</td>
<td>1.92</td>
<td>.11</td>
<td>0.19</td>
</tr>
<tr>
<td>Voxels PFC 2-back</td>
<td>0.96</td>
<td>.48</td>
<td>0</td>
</tr>
<tr>
<td>% PPC 3-back</td>
<td>3.58</td>
<td>.009</td>
<td>0.39</td>
</tr>
<tr>
<td>Voxels PPC 3-back</td>
<td>0.90</td>
<td>.52</td>
<td>0</td>
</tr>
<tr>
<td>% AC 3-back</td>
<td>2.16</td>
<td>.08</td>
<td>0.23</td>
</tr>
<tr>
<td>Voxels AC 3-back</td>
<td>0.95</td>
<td>.49</td>
<td>0</td>
</tr>
<tr>
<td>% PFC 3-back</td>
<td>26.50</td>
<td>&lt;.001</td>
<td>0.86</td>
</tr>
<tr>
<td>Voxels PFC 3-back</td>
<td>0.60</td>
<td>.75</td>
<td>0</td>
</tr>
</tbody>
</table>

The n-back task shows strong interindividual differences and high intraclass correlation coefficients (ICC), even though the repeat testing was done in 4 different states of alertness. High posterior parietal cortex (PCC) activation % ICC may reflect individual ceiling effects on activation during performance of the difficult task. RT refers to reaction time; PFC, prefrontal cortex; AC, anterior cingulate.

**Individual Differences:** Strong clustering of performance was seen on the 1-, 2-, and 3-back tasks but not on the baseline or attention task (including the number of responses ≥ 500 ms, a “lapse” on the standard Psychomotor Vigilance Test). The ICC were 0.88, 0.84, and 0.92 for 1-, 2-, and 3-back levels of difficulty, respectively (Table 4)—the majority of the difference in performance could be explained by intersubject variability, a reflection of relatively fixed individual differences in performance space. The only other high ICC was for percentage of posterior parietal activation during the 3-back task (0.86).

**Activation Performance Correlations:**

Linear relationships were explored using between baseline or working-memory performance and activation measured by the percentage of BOLD signal in the regions of interest, in each of

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the 4 states. Significant correlations were rare in our relatively small sample, being significant for the percentage of BOLD signal in (1) the posterior parietal cortex and subjective sleepiness (F₁,₃₀ = 8.38, p = .007) and attention task before start of functional imaging (F₁,₃₀ = 4.23, p = 0.48), (2) the lateral prefrontal cortex and 3-back performance speed (F₁,₃₀ = 20.02, p < .001), and (3) the medial wall and response speed on the baseline periods of the 3-back task (F₁,₃₀ = 4.86, p = .035).

**DISCUSSION**

The results of this study show that working-memory performance, as assessed by the n-back task, and the associated executive network activation are sensitive to the effects of sleep deprivation. There are important interactions among state (rested or sleep deprived), task difficulty, and drug. There are several features of the functional activation maps that are of interest. (1) Activation was greater in extent and intensity (% signal) with increasing task load. (2) Activation was minimal at the 1-back level of difficulty. (3) Modafinil use in the sleep-deprived state resulted in a major increase in activation only at the 2-back level of difficulty, at both cortical and subcortical levels. (4) Drug effects in the rested state were relatively minor. (5) Increased medial frontal and rostral anterior cingulate (all task levels) and posterior cingulate (2-back) activation were noted in sleep-deprived + placebo > modafinil and placebo + sleep-deprived > rested contrasts; these regions are important in higher-order autonomic regulation and...
perception of visceral state. (6) There was greater prefrontal activation in the rested versus the sleep-deprived state and greater posterior parietal activation in the sleep-deprived versus the rested state. An important feature was the relatively small effect of modafinil in improving activation and performance associated with tasks of minimal (1-back) or high (3-back) difficulty. At the level of moderate difficulty, the drug enhanced activation and performance in the sleep-deprived state, but at the expense of recruiting connected and adjacent cortical and subcortical areas. Strong interindividual differences in performance speed were noted at 1-, 2-, and 3-back levels of difficulty. Modafinil did reduce activation in the prefrontal and posterior parietal cortices, which may be consistent with improved efficiency of information processing. These results have potentially important implications in understanding the beneficial effects, limitations, and behavioral toxicity of modafinil.

There are similarities and differences in our results relative to those reported in the literature; neither patterns of activation nor direction of signal change have been uniform.22-29 The disproportionate impact of sleep deprivation on the lateral prefrontal cortex in this study is similar to the results of a study using a mental arithmetic task;27 moreover, sleep deprivation reduces resting blood flow in associative cortices.38 We demonstrated possibly compensatory increases associated with sleep deprivation in the posterior parietal cortex, as has been reported using a verbal learning task.29 A recent study on narcoleptics showed progressive reduction of activation with repeated task runs;39 moreover, imaging during the circadian trough (unpublished observations) is associated with profound activation reductions, suggesting that the dominant functional activation theme for the effect of increased sleep debt is reduced activation. Possible explanations for the varied results include task specificity, baseline (active as in our study or passive such as fixation), task duration, single trial versus blocked designs, and modulation by circadian phase. Our studies were performed relatively early in circadian time, after 26 to 28 hours of sleep deprivation, whereas the verbal learning task was evaluated after 35 to 40 hours of sleep deprivation, when circadian drive is higher. Circadian effects on resting cerebral blood flow have recently been described to vary across circadian time and drive.41 In general, imaging early in circadian time following sleep deprivation shows more-consistent reductions (regardless of area involved in activation) than increases in activation. However, the type of cognitive process probed must be equally important. The results reported here also support a critical role, as has been previously described,35 for thalamic mechanisms in alert state performance and may be a target for a range of alertness-promoting drugs.

Insights may be obtained on the neuropharmacology of wakefulness by functional imaging. Clinical stimulants may antagonize adenosine (caffeine), enhance dopaminergic transmission (amphetamine, methylphenidate), or, possibly, acetylcholine (donepezil) and noradrenaline (atomoxetine).35-36 Normal functioning of the working-memory circuit is critically dependent on dopamine and to a lesser extent on glutamate, acetylcholine, and serotonin.37-39 The extensive recruitment of activation with modafinil in the sleep-deprived state at intermediate levels of task difficulty may suggest dopaminergic effects, multiple neurotransmitter-enhancing effects including the orexin system,40 activation of hypothalamic arousal mechanisms,41 or unique effects not yet identified.42 Recruitment of contiguous areas does not prove that they are necessary for task performance, as functionally connected areas may show activation.

Pharmacologic MRI may provide unique insights into brain-behavior-drug relationships. In keeping with our result of enhancement of activation in the impaired state, in a recent randomized double-blind placebo-controlled crossover trial in schizophrenics performing a working-memory task, 100 mg of modafinil significantly increased activation in the anterior cingulate cortex during the task, and this increase correlated with cognitive performance.43

Results with d-amphetamine have shown both decreases44 and increases.45 Although we did not assess dose responses, studies that have done so with d-amphetamine have shown an inverted-U effect, suggesting an optimal range of monoaminergic activity for working-memory performance and activation, either below or above which it is compromised.45,46

The D2 dopamine agonist bromocriptine has been reported to reduce task-related activity.47 During a spatial and object-delayed recognition task, the drug decreased activity in the task network at encoding and increased activity at response, without a definite pattern change in the delay period. These BOLD-signal changes were accompanied by reductions in accuracy and increases in response time.48 With the drug, less-efficient subjects with slower memory-retrieval rates have greater prefrontal activity, whereas more-efficient subjects have less activity.49 Although physostigmine decreased right prefrontal blood flow on a study using positron emission tomography,50 results with cholinergic enhancement have shown increases in task-specific regional (e.g., in the right precuneus and right middle frontal gyrus) activation when used in the condition of cognitive impairment.51,52 Estimating a functional activation and correlated performance dose-response curve with modafinil would be required to determine if nonlinear responses similar to amphetamine are possible.

Modafinil did not improve performance speed in the 3-back condition. Thus, when the subjects were capable of performing at this higher level of difficulty, further increases in performance were not possible even with the drug, although accuracy was improved. One possible explanation is subject selection—participants in this protocol had demonstrated the capability to learn and perform the task well; this may have narrowed the range of possible response capabilities at the higher task load. One possible mechanism for improvement in accuracy is what happens when errors are detected—returning to the alphabet stream may have been more difficult in the 3-back condition, a “cognitive stumble.” Reduced function of the anterior cingulate in error monitoring and correction53,54 in the sleep-deprived state is a plausible explanation, but our study was not designed to allow a finer dissection of performance or imaging response characteristics. That would require a single-trial approach.

Modafinil minimally altered activation in the rested state—this may have been due to the fact that the drug does not enhance release of dopamine and norepinephrine, an effect of amphetamine. Thus, the increase in bioamine availability with modafinil may be critically dependent on the degree of ongoing neural activity. If task demands and bioamine release or availability are low, the drug may have minimal effects. If the demands are high and the subject is capable of achieving adequate performance, it may be associated with high degrees of bioamine availability that cannot be further enhanced by modafinil. The effects of the drug may be best seen at intermediate levels of difficulty—when the sys-
tem has a functional reserve that can be enhanced. The relatively modest effectiveness of modafinil in enhancing alertness in those subjects with shift work sleep disorder when tested during the biologic night may reflect a state of bioamine release or availability that can only be minimally influenced by the drug.55

Modafinil facilitates performance on a delayed non–match–to–position swim task in rats.56-57 The drugs induces mild to moderate improvements in mood, motivation, and vigilance in rested individuals.58-60 In this study, there was a major impairment in the "attention" task after sleep deprivation, which was significantly improved by modafinil. Moreover, thalamic activation was reduced when subjects were sleep deprived and showed a small return with modafinil in the 2-back condition. Working-memory impairment or deficits in "executive" functions may be related to attentional deficits, and the result could be interpreted as the drug only improving attention and that the other results are down-stream. This explanation is probably too simple because, during the functional runs themselves, the difference in baseline task speed was not significantly different across conditions. The demonstrated effect of modafinil on activation in the executive network may thus have implications for other sleep disorders and disorders characterized by executive dysfunction and impaired mood. Our results show a functional correlate compatible with the demonstrated positive effect of modafinil in conditions such as sleep apnea, depression, and attention-deficit/hyperactivity disorder.61-67

Interindividual differences are an increasingly recognized biologic phenomenon in sleep research that also directly impacts clinical practice.68-77 We found strong clustering of working-memory performance across our 4 conditions (Table 4). Thus, more than 80% of the variance on the 1-, 2-, and 3-back tasks were from trait-like individual differences. This is all the more remarkable given that the 4 repetitions per subject were under quite different conditions of alertness. Because high ICCs were not noted on the attention tasks or on functional activation measures, it could be that the n-back tasks are more sensitive to such differences, but larger studies will be required to confirm this possibility. The recent demonstration of reduced baseline and post-deprivation prefrontal activation in sleep-deprivation sensitive versus resistant individuals supports further exploration of this approach71 and has the potential to significantly enhance understanding of the individual-difference domain in sleep research.72 Modafinil is not capable of boosting task performance outside the individually determined range—this has implications for any use of this and similar drugs for cognitive enhancement in those who are healthy but "slow."

During the active-task block, sleep deprivation was associated with increased activation in components of what is known as the default mode network.73 This network consists of a set of brain regions that are often found in neuroimaging studies to be more active during passive baseline tasks than corresponding experimental or "activation" tasks and may represent the baseline working state of the brain that must be suspended or inhibited to actively engage in goal-directed behavior. During a task requiring increased cognitive resources, an allocation away from the default-mode network and toward the task-engaged brain regions is required. A study probing the functional neuroimaging correlates of the Psychomotor Vigilance Test showed greater activation of these midline brain regions, the posterior cingulate and the cuneus, during the slowest reaction times.74 It has been suggested that this phenomenon may represent a partial disengagement from the task and subsequent failure to allocate resources to the motor and attention systems related to fast responding. This "attentional disengagement" may then result in the noted slowing of responses. In our study, this may have reflected difficulty in moving resources to the n-back requirement. Seeing that activation was seen only in the sleep-deprived state and increased across increasing task load, makes it unlikely that this is an artifact, as may be seen in the orbitofrontal areas during fMRI. This region and those with close functional connections are also targets for functional imaging studies of depression75 and, more recently, deep brain stimulation for refractory depression.76 Results such as ours may provide a further neuroanatomic and functional basis for overlaps in symptoms in major depression and sleep apnea77 and the antidepressant effects of sleep deprivation.78

In summary, overnight sleep deprivation induced executive dysfunction and generally reduced activation in the executive network. A single 200-mg dose of modafinil reversed subjective estimates of sleepiness and objective performance measures, but this latter effect was evident only at intermediate levels of task difficulty (2-back). Extensive recruitment of contiguous cortical areas was seen predominantly at the 2-back levels of difficulty, in only the sleep-deprived state. This result further supports the use of the drug as a countermeasure in states with sleepiness-induced impairments of attention and executive function but suggests limitations that may be clinically relevant. The demonstrated effects on functional neurobiology offer a possible explanation of its clinical efficacy in subsets of patients with obstructive sleep apnea, attention-deficit/hyperactivity disorder, and depression.

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