

# The Neural Basis of the Psychomotor Vigilance Task

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**Study Objective:** To identify brain regions underlying the fastest and slowest reaction times on the Psychomotor Vigilance task (PVT) under well-rested conditions, as well as brain regions related to particularly poor performance after sleep deprivation.

**Design:** Subjects took the PVT twice while undergoing functional magnetic resonance imaging: once 12 hours after waking from a normal night of sleep and once after 36 hours of total sleep deprivation (TSD). Session order was counterbalanced.

**Setting:** UCSD J. Christian Gillin Laboratory for Sleep and Chronobiology (the sleep core of the General Clinical Research Center) and UCSD Magnetic Resonance Institute.

**Patients or Participants:** Twenty right-handed healthy adults (8 women; age = 27.4 ± 6.7 years; education = 15.6 ± 1.5 years.)

**Measurements and Results:** After a normal night of sleep, optimal performance was related to greater cerebral responses within a cortical sustained attention network and the cortical and subcortical motor systems.

Slow reaction times, particularly after TSD, were associated with greater activity in the “default mode network” consisting of frontal and posterior midline regions.

**Conclusions:** Optimal performance on the PVT appears to rely on activation both within the sustained attention system and within the motor system. Poor performance following TSD may result from a disengagement from the task and related inattention, and brain regions responsible for this localize within midline structures shown to be involved in the brain’s “default mode.” Finally, particularly poor performance after TSD may elicit a subsequent attentional recovery that manifests as greater activation within the same regions normally responsible for fast reaction times.

**Keywords:** Sleep deprivation, cognitive function, functional magnetic resonance imaging, PVT, sustained attention, default mode network

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## INTRODUCTION

THE PSYCHOMOTOR VIGILANCE TASK (PVT) WAS ORIGINALLY DEVELOPED IN 1985 AS A MEASURE OF SUSTAINED ATTENTION.<sup>1</sup> SINCE THAT TIME, A LARGE number of studies have demonstrated its sensitivity to sleepiness in clinical, experiment, and operational contexts,<sup>2</sup> making it one of the most widely used neurobehavioral tests in studies of sleep and circadian rhythm research.<sup>2</sup> As examples, studies have shown the PVT to be sensitive to, among other things, alterations in the homeostatic<sup>3-6</sup> and circadian systems,<sup>4,7</sup> as well as work schedules,<sup>8</sup> age,<sup>9</sup> and sleepiness countermeasures such as naps,<sup>10</sup> bright light,<sup>11</sup> and caffeine.<sup>11</sup>

PVT results are generally interpreted as reflecting the arousal and attentional state of the individual. Comparisons are made both across conditions (eg, well rested vs sleep deprived) and within a given test administration. Across conditions, the PVT has proven to be a very sensitive measure of sleep loss.<sup>3,5,12</sup> With-

in a given test bout, changes in performance (ie, reaction time [RT]) may reflect what has been termed “state instability,” which refers to PVT performance variability produced by the influence of homeostatically controlled sleep-initiating mechanisms on the endogenous capacity to maintain alertness and utilize executive attention.<sup>2</sup> State instability is evident in the waxing and waning of attention and arousal over time (ie, milliseconds to minutes), especially during periods of sleep deprivation.<sup>12</sup> As a result, when an individual’s arousal and attention are relatively normal, so too is PVT performance. However, when attention and arousal wane due to elevated homeostatic sleep drive, PVT performance changes such that RTs reflect commingling of errors of omission (lapses) and errors of commission (false responses). Depending on the degree of sleep deprivation, the fastest RTs on the PVT do not change or change only modestly relative to the well-rested state, which reflects the fact that individuals experience instances of relatively normal attention and arousal levels even when sleep deprived. On the other hand, the slowest RTs can lengthen dramatically after sleep deprivation, reflecting instances when individuals experience markedly reduced levels of attention and arousal.<sup>2,12</sup>

Despite the plethora of behavioral data collected with the PVT, there have been no published functional neuroimaging studies examining the cerebral correlates of PVT performance. Thus, little is known about the cerebral substrates underlying fast and slow performance on the PVT. Reports of electroencephalographic (EEG) measures of brain function related to PVT performance have either not collected the EEG and PVT performance data simultaneously<sup>6</sup> or have not reported correlations between EEG and PVT performance measures.<sup>8</sup> Some possible insight into brain systems subserving PVT performance can be gained, though, by examining related literature on attention. For example, neuroimaging studies during well-rested states have revealed a network related to sustained attention that includes the

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right middle frontal gyrus and inferior parietal lobe, as well as, possibly, the left inferior parietal lobe and bilateral thalamus.<sup>13-16</sup> Neuroimaging studies of (nonsustained) attention tasks during sleep deprivation have reported greater responses in either the bilateral ventral lateral thalamic nuclei (for short-term attention)<sup>17</sup> or right prefrontal and left inferior parietal regions (for divided attention)<sup>18</sup> after total sleep deprivation (TSD). One could therefore reasonably posit that optimal PVT performance (ie, fast RTs) would rely on some or all of these attention-related regions.

An additional consideration is the nature of the task itself. Although the PVT is used as a behavioral measure of sustained attention, it relies on simple RT as the output measure. Consequently, the neuroanatomic correlates of RT velocity (eg, fast vs slow) as measured by simple RT tasks may also play a role in the sensitivity of PVT performance to elevated sleep drive. Using several sensory modalities, Naito et al<sup>19</sup> reported that faster RTs were associated with greater cerebral blood flow in the primary motor cortex, primary somatosensory cortex, supplementary motor area, and the motor region of the cingulate cortex. Oguz et al<sup>20</sup> compared subjects with an overall fast RT response to those with an overall slow RT response. They reported a greater activation volume for fast responders within left sensorimotor and left visual cortices. In a follow-up experiment, this group reported significant negative associations between RT and blood oxygenation level dependent (BOLD) amplitudes within bilateral occipital and left sensorimotor areas (ie, smaller/faster RTs related to greater activation).<sup>21</sup> Studies of visuomotor tracking have indicated the basal ganglia play a role in speed of response.<sup>22</sup>

Understanding the neural basis of PVT performance may provide insights into brain regions that are particularly sensitive to sleep loss. Although PVT performance has not been directly studied with functional neuroimaging techniques, related literatures on the neural basis of attention and RT suggest that optimal PVT performance while well rested may rely primarily on a right hemisphere frontoparietal sustained attention network along with cortical and subcortical motor systems. Optimal performance during TSD may further require recruitment of thalamic nuclei. To test these predictions and establish the neural basis of increased PVT slowing during elevated sleep drive, we studied individuals performing the PVT while undergoing functional magnetic resonance imaging (fMRI) studies both well rested and following 36 hours of TSD. We addressed 3 specific questions and associated hypotheses: (1) Which brain regions discriminate between the fastest and slowest RTs in a well-rested state? We hypothesized that faster RTs would be related to greater cerebral responses within sustained attention regions of the right middle frontal gyrus and inferior parietal lobe, as well as cortical and subcortical motor system regions. (2) How does the cerebral response during fast versus slow RTs change with sleep deprivation? We hypothesized that obtaining fast RTs after TSD would require greater activation in sustained attention areas and in the bilateral ventral lateral thalamus, relative to the well-rested condition. This would be consistent with the compensatory recruitment model of successful cognitive performance during TSD we previously reported.<sup>23,24</sup> (3) Can we identify brain regions where the activity (or lack thereof) predicts particularly slow performance after TSD? We did not have specific hypotheses for this question, but believed that increasingly slower RTs during sleep deprivation would be related to reduced cerebral responses within sustained-attention regions of the cortex and thalamus.

## METHODS

### Subjects

Subjects for this report included 22 young adults who participated in 1 of 2 concurrent protocols. Of these 22, 2 were not included in the analyses here because 1 was found to be ineligible after participation and 1 had excessive movement artifact in the fMRI data. Each protocol consisted of the same eligibility and screening procedures, as well as a normal night of sleep followed by an evening fMRI scanning session and 36 hours of TSD followed by an fMRI scanning session. The 2 scanning sessions were at the same time of day, between 6:00 pm and 8:00 pm, and were conducted in a counterbalanced order. The only difference between the 2 protocols is that 1 of them (n=15) also contained a second sleep-deprivation period that included administration of modafinil and the other (n=5) did not. There were no differences in demographics, performance, or imaging data between subjects drawn from the 2 protocols. The final sample consisted of 20 right-handed adults (8 women; mean  $\pm$  SD, age = 27.4  $\pm$  6.7 years; education = 15.6  $\pm$  1.5 years). All subjects reported habitual sleep times between 7 and 9 hours, with typical sleep windows starting at 10:00 pm to 12:00 am and ending between 6:00 am and 8:00 am. Mean Horne-Ostberg Morningness Eveningness Questionnaire scores were 52.7  $\pm$  8.9, and extreme chronotypes on this measure were excluded. Subjects conformed to an agreed upon sleep-wake schedule (based on their habitual schedule) and completed daily sleep diaries for 7 to 10 days prior to the Normal sleep night in the lab. Subjects reported obtaining a mean of 7.7  $\pm$  0.4 hours of sleep per night over that time. Prior to the first experimental night, subjects underwent a full polysomnogram to rule of intrinsic sleep disorders.

### Experimental Nights

All subjects spent 2 experimental nights in the UCSD General Clinical Research Center's J. Christian Gillin Laboratory for Sleep and Chronobiology (GCRC-LSC). One night was a normal night of sleep, and the other was a period of 36 hours of TSD. Generally, 2 subjects were studied in the same condition on a given night. The order of the 2 nights was counterbalanced across subjects. For the Normal night, subjects slept according to their habitual sleep schedule. The fMRI and cognitive testing session was scheduled for 12 hours after awakening. On the TSD night, subjects reported to the GCRC-LSC at approximately 11:00 pm and remained supervised and on the unit until the scanning session scheduled for 36 hours after awakening. Caffeine intake and napping were prohibited. Mean TSD at the time of scanning was 35.9  $\pm$  0.7 hours.

### fMRI and Cognitive Testing Sessions

All fMRI sessions took place on a Siemens 1.5T Signa scanner (Siemens Medical Solutions, Erlangen, Germany). During scanning, subjects performed the PVT. The task was identical to the PVT typically administered outside of the scanner, other than having the presentation modified for the fMRI environment. Stimuli were projected from a laptop computer via an LCD projector to a screen at the foot of the scanner. Subjects saw the stimuli through a mirror mounted on the head coil just above their eyes, and they responded via a button box designed spe-

cifically to interface with the PVT program (Current Designs, Philadelphia, Penn). During the task, subjects saw a blank box in the middle of the screen. At random intervals, a millisecond counter started to scroll, and subjects had to press a button to stop the counter as quickly as possible. After pressing the button, the counter displayed the achieved RT for 1 second, providing the subject with feedback on performance. Interstimulus intervals were distributed randomly from 2 to 10 seconds (Normal night mean:  $6.1 \pm 0.6$  seconds; TSD mean:  $6.0 \pm 0.7$  seconds), and the task lasted 10 minutes. Immediately after each task, subjects verbally completed the Stanford and Karolinska Sleepiness Scales and a series of 10-point Likert scales assessing subjective levels of task difficulty, motivation to perform the task well, concentration on the task, effort put into the task, and effort required by the task.

fMRI images measured the BOLD signal.<sup>25</sup> Functional scans consisted of 600 gradient echo EPI images (TR: 1.0 seconds, TE: 35 ms, FOV: 256 mm, 4 mm x 4 mm in-plane resolution) of twelve 6-mm axial slices anchored to the top of the brain. Slice coverage typically extended to the bottom of the orbital frontal cortex, and the included diencephalon, but not the brain stem or cerebellum. Whole brain coverage was not possible given the rapid volume acquisition time required for this event-related task. Functional data were aligned with high-resolution anatomic images (MPRAGE: 1mm<sup>3</sup> resolution).

## Data Analysis

The following PVT variables were analyzed: median RT, mean of the fastest 10% RT, mean of the slowest 10% reciprocal RTs, SD of the RT, and number of lapses (RT > 500 ms). The main effect of Night was examined for each of these variables with a 2-tailed paired-samples *t* test. Subjective questionnaire data were also analyzed for the main effect of Night.

The fMRI data were analyzed in a 2-step procedure (individual time series analysis and group analysis) with the AFNI library.<sup>26</sup> After motion coregistration, individual time-course BOLD signal data were fit to a design matrix using the general linear model.<sup>27</sup> Parameters estimated from the design matrix represented the constant, linear drift, 6 motion-correction parameters derived from the motion coregistration step (3 relational and 3 translational movement directions) and 2 reference functions. The reference functions coded for the cerebral response during the stimuli associated with the fastest 10% of RTs (Fast) and the slowest 10% of RTs (Slow). The 2 reference functions were obtained separately based on a subject-driven event-related model where a stimulus onset was coded when the PVT clock turned on for a stimulus of interest (ie, one that turned out to be one of the fastest or slowest 10% of RTs). The series of stimulus onsets were then convolved with an idealized hemodynamic response to obtain the reference functions.<sup>28</sup> Thus, the parameters associated with the reference functions measure the magnitude of the brain's response during a fast (or slow) RT relative to the magnitude of the brain's response during a typical RT. In this way, we were able to identify brain regions that were significantly more active or inactive during the fastest (or slowest) RTs relative to the level of activity in that same region during a standard RT. Following the time-series analysis, all brains were individually transformed into standard atlas space.<sup>29</sup>

Group analyses used a search region of interest strategy.<sup>30</sup> Two

search regions were defined. One focused exclusively on the subcortical regions of thalamus, basal ganglia, putamen, globus pallidus, and surrounding structures. Analysis of this search region was conducted without any spatial smoothing of the data in this region. The other search region focused on the cortex and was conducted after spatially smoothing the individual data with a 4-mm full-width half-maximum Gaussian kernel. Statistical analyses focused on the 3 main questions stated above. To determine which brain regions discriminate between Fast and Slow responses during a well-rested state, we first computed within each subject the difference contrast between the cerebral responses during Fast RTs and Slow RTs. We then tested the significance of these difference scores with a 1-sample *t* test. To determine if the brain regions discriminating these 2 response types change with TSD, we tested specifically the interaction term from a 2 x 2 (Night x Speed) mixed effects analysis of variance, in which Night (Normal vs TSD) and Speed (Fast vs Slow) were treated as fixed effects and Subject was treated as a random effect. Follow-up analyses for regions showing an interaction effect examined the main effect of Night for each Speed using paired samples *t* tests. Finally, to investigate the neural substrate underlying particularly slow responses during TSD, we regressed the cerebral response to Slow RTs after TSD onto each individual's mean slowest 10% reciprocal RT after TSD.

To protect against Type I error in the fMRI analyses, we used a cluster threshold method.<sup>31</sup> For both analyses, this required any given voxel to be statistically significant at the  $P < .05$  level. For the subcortical regions, we report only clusters of at least 4 contiguous activated voxels (256 mm<sup>3</sup>), and for the cortical regions we report only clusters of at least 12 contiguous activated voxels (768 mm<sup>3</sup>). Together, this protects the whole-brain  $\alpha$  level at  $P = .05$ .

## RESULTS

### Behavioral Data

Table 1 lists PVT performance on each night. As is typically found, subjects became slower and experienced more lapses with TSD. Table 2 lists responses on the subjective questionnaire administered immediately after PVT performance during the scanning sessions. Subjects reported an increase in sleepiness, decrease in concentration, and slight decrease in motivation after TSD.

### fMRI Data

Table 3 lists the brain regions in which the magnitude of the BOLD response showed significant differences between the Fast and Slow responses after the Normal night of sleep. Brain regions underlying Fast responding included the bilateral putamen, caudate body, and inferior parietal lobes, as well as the right dorsolateral prefrontal cortex and several medial or bilateral motor regions (Figure 1). Three medial frontal regions showed greater responses during Slow RTs than during Fast RTs (Figure 1).

Table 3 also shows the brain regions that showed a significant interaction between Night (Normal vs TSD) and Speed (Slow vs Fast). Six of the 7 areas showing an interaction (the 3 subcortical regions and 3 of the cortical regions) are the same as those that showed greater responses during Fast versus Slow RTs on

the Normal night of sleep. Follow-up analyses revealed the same pattern of interaction for all 7 regions, 4 of which are shown in Figure 2. Cerebral activation associated with Fast RTs in these clusters did not significantly change between the Normal night of sleep and TSD. During Slow RTs, however, activation within these clusters increased significantly following TSD, relative to after Normal sleep. Thus, these regions always responded the same during Fast RTs but showed a greater response after TSD than after Normal sleep during Slow RTs.

Table 4 lists the brain regions showing a significant relationship with the speed of the slowest responses after TSD. These regions included both anterior and posterior midline regions, as well as subcortical nuclei with connections to those areas (Figure 3). For all clusters in Table 4, greater levels of activation were associated with slower reciprocal RT, except left precentral gyrus, which showed the opposite pattern.

**Table 1—Psychomotor Vigilance Test Performance Data**

Variable	Normal	Total Sleep Deprivation	P value	Effect size
Median RT	.269 ± .033	.295 ± .031	< .001	.585
Fastest 10% RT	.217 ± .019	.231 ± .019	.001	.423
SD RT	.139 ± .275	.180 ± .176	NS	.018
Lapses	1.55 ± 2.62	3.85 ± 3.95	.015	.274
Slowest 10% reciprocal RT	2.58 ± .616	2.09 ± .693	.002	.401

RT refers to reaction time, measured in ms; reciprocal RT, 1/RT.  
P-value is for paired samples t test of Night effect; effect size =  $\eta^2$  (variance accounted for by night)

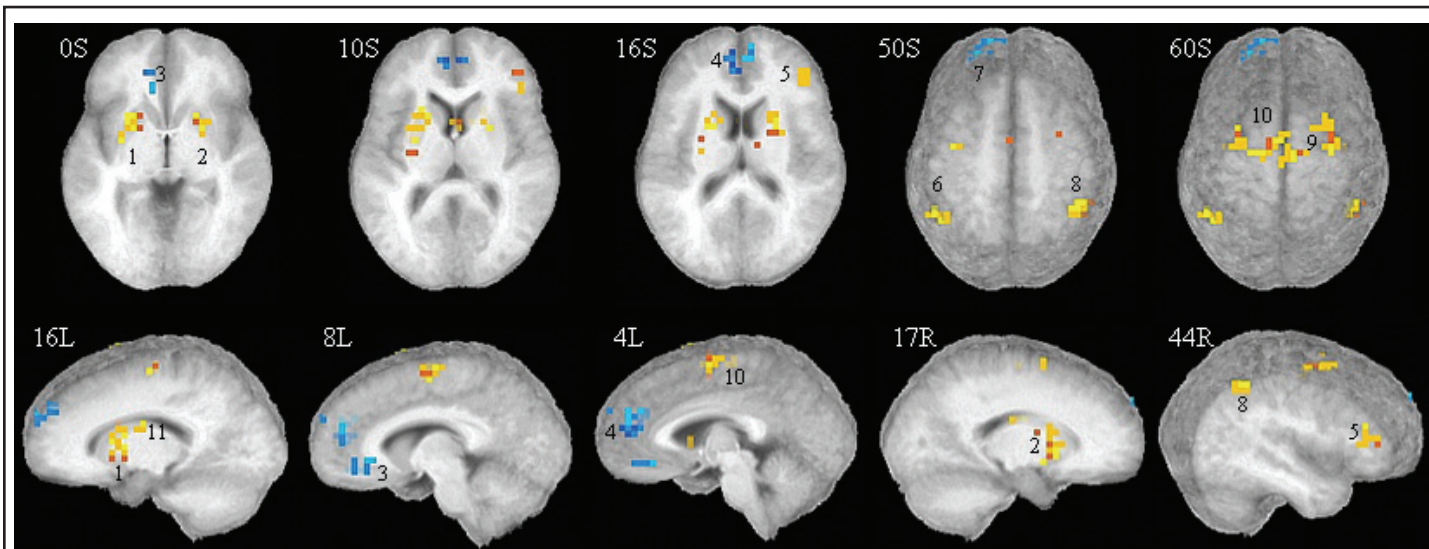
## DISCUSSION

This was the first study, to our knowledge, to examine brain regions underlying PVT performance with functional neuroimaging techniques. We used fMRI to identify cerebral correlates of the fastest and slowest RTs in well-rested young adults, how the differential response to Fast and Slow RTs changed with 36 hours TSD, and which brain regions are most related to slow performance following TSD. As hypothesized, greater BOLD responses were seen in sustained attention and motor regions during Fast RTs, relative to Slow RTs, after Normal sleep. However, results did not support our hypothesis that compensatory

**Table 2—Subjective Measures of Performance**

Variable	Normal	Total Sleep Deprivation	P value	Effect size
Stanford Sleepiness Scale	2.0 ± 0.7	4.5 ± 1.7	< .001	.637
Karolinska Sleepiness Scale	3.3 ± 1.5	6.6 ± 2.4	< .001	.524
Concentration (1-10)	7.6 ± 1.6	5.3 ± 1.8	< .001	.579
Difficulty (1-10)	4.4 ± 2.7	5.0 ± 3.1	NS	.041
Effort required (1-10)	5.2 ± 2.9	6.6 ± 3.2	NS	.131
Effort put in (1-10)	7.8 ± 1.7	7.5 ± 1.6	NS	.016
Motivation (1-10)	8.1 ± 1.4	7.2 ± 2.0	.018	.264

P value is for paired samples t test of Night effect; effect size =  $\eta^2$  (variance accounted for by night)



**Figure 1**—Brain regions showing a differential response during Fast versus Slow reaction times (RTs). Images show brain regions exhibiting greater responses during Fast (hot colors) and Slow (cold colors) RTs after a Normal night of sleep. Fast RTs were associated with greater responses within cortical and subcortical motor systems, as well as cortical areas, implicated in sustained attention. Several of these regions also showed a significant Night-by-Speed interaction effect (see Table 3). Slow RT's were associated with greater activation within frontal midline structures.

For all images, clusters surviving our cluster threshold method are overlaid in color on top of the group average anatomic image, with the slice location listed relative to the Talairach atlas origin. The color corresponds to the effect size,  $\eta^2$ , corresponding to the amount of variance accounted for by the Fast vs Slow contrast.

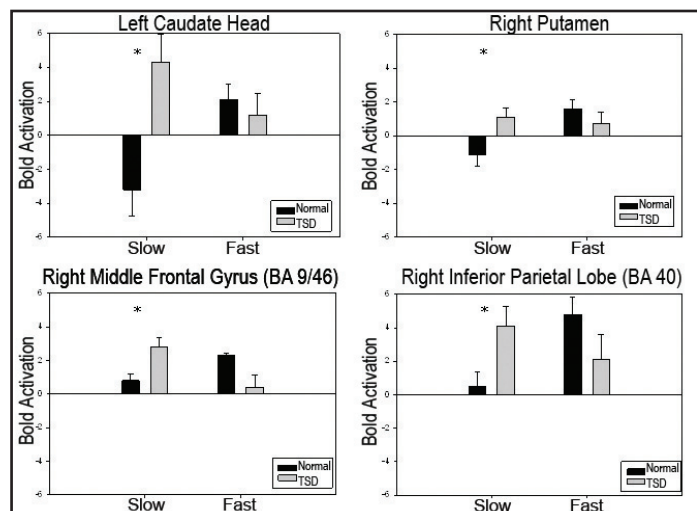
Brain regions shown correspond to the following clusters from Table 3: 1. L putamen; 2. R putamen; 3. L medial frontal and ventral cingulate gyri (10/32); 4. medial frontal gyrus (BA 9); 5. R. middle and inferior frontal gyri (BA 46); 6. L inferior parietal lobe (BA 40); 7. superior and medial frontal gyri (BA 10/9); 8. right inferior parietal lobe (BA 40); 9. R SMA, premotor and precentral areas (BA 6/4); 10. left supplementary motor, premotor, and precentral areas (BA 6/4); 11. L caudate nucleus.

recruitment of even greater responses in these regions would be required to obtain Fast RTs after TSD. In addition, we identified a number of brain regions related to the slowest responses following TSD.

### Brain Regions Underlying Fast Versus Slow RTs

We identified a network of subcortical and cortical brain regions in which greater activation is related to optimal performance (ie, the fastest RTs) in well-rested individuals (Table 3, Figure 1). These regions are known to be responsible for attention and motor function. As hypothesized, Fast RTs were associated with greater involvement of the frontoparietal sustained-attention network. The right middle frontal gyrus and right inferior parietal lobe are the most consistent areas reported as supporting sustained attention,<sup>13-16</sup> and the left inferior parietal lobe has been implicated in allocation of attentional resources.<sup>14,16</sup> Thus, these cortical regions probably reflect top-down modulation of the attention required to sustain focus on the task, thereby allowing individuals to respond quickly when a stimulus appeared. A similar role may have been played by the cortical motor system. Culham and colleagues reported that supplementary motor and precentral regions and the right inferior parietal lobe show stronger responses with greater attentional demands.<sup>16</sup> While we did not manipulate task demands in this study, a parallel situation of an internally generated higher state of attention could be expected to manifest as greater activation in these cortical areas, and that would support faster responding. Supporting this idea is the study by Lawrence and colleagues showing that a greater magnitude of response within the presupplementary motor area correlates with faster response times on an attention task.<sup>13</sup>

With respect to the motor system, our findings following Normal sleep support a relationship between Fast RTs and basal ganglia structures, including the putamen, caudate nucleus, and



**Figure 2**—Brain regions showing a significant Night-by-Speed interaction effect. Graphs are of 4 of the regions showing a Night-by-Speed interaction. For each area showing an interaction effect (including those in Table 3 but not depicted here), the cerebral response during Fast reaction times (RTs) was not significantly different after Normal sleep vs after total sleep deprivation (TSD). However, there was a significant increase in the observed response during Slow RTs following TSD. \* $P < .05$  for comparison of Normal sleep vs TSD.

**Table 3**—Brain Regions Showing a Speed Effect on a Normal Night or a Night x Speed Interaction

Anatomic Location	BA	Fast vs Slow: Normal Night			Night x Speed		
		Volume, mm <sup>3</sup>	Centroid Coordinate	Max eta <sup>2</sup>	Volume, mm <sup>3</sup>	Centroid Coordinate	Max eta <sup>2</sup>
<b>Fast &gt; Slow</b>							
Putamen and lateral globus pallidus	L	3712	-23, 5, 8	.444	768	-23, -1, 12	.414
Putamen	L	384	-28, -14, 11	.297			
	R	2240	20, 6, 6	.447	320	24, 1, 14	.263
Caudate body and thalamus	L	256	-16, -8, 21	.389	256	-6, 7, 6	.239
Middle and inferior frontal	R + AN	512	12, -12, 22	.416			
Middle frontal	R 46	896	40, 34, 17	.309	1216	47, 23, 23	.352
Medial frontal and SMA/pre-SMA	R 9/8				1088	41, 14, 34	.504
PMA and precentral	L 6	1664	-7, -8, 61	.452	3648 (overlaps both Fast-Slow clusters)	2, -5, 57	.470
	R 6	832	3, -16, 61	.493			
	L 6/4	768	-32, -6, 58	.373			
	R 6/4	1344	30, -3, 59	.316			
Inferior parietal lobe	L 40	832	-47, -53, 46	.363			
	R 40	896	43, -49, 50	.432	1280	41, -51, 50	.447
<b>Slow &gt; Fast</b>							
Superior and medial frontal	L 10/9	1216	-17, 54, 29	-.376			
Medial frontal	M 9	2048	-2, 45, 19	-.483			
Medial frontal and ventral cingulate	L 10/32	832	-8, 36, -5	-.507			

All clusters survived the cluster threshold procedure (whole brain  $\alpha P < .05$ ). All regions covered by a cluster are listed. This does not imply the entire region was contained within a given cluster.

SMA, supplementary motor area; PMA premotor area; AN, anterior nucleus of the thalamus (only part of the right caudate cluster); BA, Brodmann's area; L, left; R, right; M, medial; eta<sup>2</sup>, variance accounted for by effect of interest; negative eta<sup>2</sup> means the cluster showed greater blood oxygenation level dependent (BOLD) response during Slow relative to during Fast reaction times.

**Table 4**—Brain Regions Showing Significant Correlations With the Slowest 10% Reciprocal Reaction Times After Total Sleep Deprivation

Anatomic Location	BA	Volume, mm <sup>3</sup>	Centroid Coordinate	Max eta <sup>2</sup>
Positive correlation with slowest 10% reciprocal RT				
Pineal gland	B	448	-2, -32, 2	-.417
Geniculate body	R	384	18, 23, 0	-.393
Caudate head	L	320	-9, 20, 3	-.380
Thalamus	L dorsal medial; dorsal lateral	256	-10, -23, 14	-.377
Medial frontal	L 9	1856	-7, 47, 15	-.432
	L 9	896	-9, 57, 28	-.493
	M 8	832	-4, 25, 40	-.328
Cingulate/ Medial frontal	M 32/24/8	4160	4, 35, 21	-.550
Middle frontal	L 46	1344	-46, 35, 18	-.461
PMA	R 6	768	39, 6, 46	-.394
Superior	L 7	1344	-38, -60, 47	-.383
Parietal Lobe	R 7	896	36, -67, 43	-.354
Inferior Parietal Lobe	R 40	1088	49, -44, 40	-.311
Cuneus	L 17/18	4032	-8, -75, 16	-.394
Posterior cingulate	L 31	832	-10, -43, 41	-.361
Negative correlation with slowest 10% reciprocal RT				
Precentral gyrus	L 4	1088	-3, 26, 69	.386

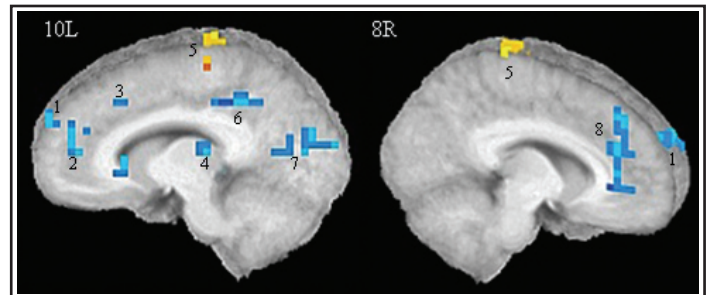
All clusters survived the cluster threshold procedure (whole brain  $\alpha P < .05$ ). All regions covered by a cluster are listed. This does not imply the entire region was contained within a given cluster.

RT refers to reaction times; BA, Brodmann's area; L, left; R, right; B, bilateral; Eta<sup>2</sup>, variance accounted for by effect of interest; PMA, premotor area.

Positive correlations and eta<sup>2</sup> mean that the greater the region was activated during Slow RTs after TSD, the faster the individual was. Negative correlations and eta<sup>2</sup> mean that the greater the region was activated during Slow RTs after TSD, the slower the individual was.

globus pallidus. Numerous studies have implicated the basal ganglia in RT tasks.<sup>32-37</sup> Additionally, increased movement velocity in visuomotor tracking is related to increased activation within the putamen and other related structures,<sup>22</sup> and neuronal recordings of putaminal firing in the monkey show an abrupt increase in response to a cue to initiate movement.<sup>38</sup> Furthermore, the basal ganglia are linked with cognitive processes via their connections to frontal regions. The cortical regions in which greater responses are associated with the Fast RTs also include regions related to motor performance. The premotor and precentral regions control and coordinate the motor sequences.<sup>39,40</sup> The supplementary motor area is involved in motor tasks with a critical timing component<sup>41</sup> and may serve to initiate simple repetitive motor responses under such circumstances (eg, when repeated simple RT responses are required).<sup>42</sup>

Finally, frontal regions involved in executive functioning (eg, BA 9 and 46) have been found to be related to Fast RTs and tend to project to the head of the caudate.<sup>43,44</sup> The motor-related cortical areas (eg, motor cortex, premotor cortex, supplementary motor area) that have been found to be related to Fast RTs project to the putamen.<sup>44,45</sup> Therefore, the sustained attention and motor systems may be working in concert to allow for optimal performance on the PVT.



**Figure 3**—Brain regions related to speed of response during Slow reaction times (RTs) after total sleep deprivation (TSD). Images show brain regions exhibiting a significant relationship after TSD between the speed of the slowest 10% reciprocal RTs and BOLD signal during Slow RTs. Cold colors show regions in which the cerebral response was strongest during Slow RTs in the slowest individuals. These areas included frontal and posterior midline regions involved in the default mode of brain function,<sup>46</sup> as well as associated subcortical regions. For all images, clusters surviving our cluster threshold method are overlaid in color on top of the group average anatomic image, with the slice location listed relative to the Talairach atlas origin. The color corresponds to the effect size, R<sup>2</sup>, corresponding to the amount of variance accounted for by the mean speed of the slowest 10% reciprocal RT.

Brain regions shown correspond to the following clusters from Table 4: 1. medial frontal gyrus (BA 9b); 2. medial frontal gyrus (BA 9a); 3. medial frontal gyrus (BA 8); 4. L thalamus; 5. L precentral gyrus (BA 4); 6. L posterior cingulate (BA 31); 7. L cuneus (BA 17/18); 8. L cingulate and medial frontal gyri (BA 32/24/8).

### Brain Regions Related to Inattention and Task Disengagement

Not all significant activations were related to Fast RTs. We also identified a set of regions in which greater activation was related to an individual's slowest performance. These activations were found within the frontal midline and consisted of the medial frontal, superior frontal, and ventral anterior cingulate gyri. It may seem counterintuitive that larger responses in a particular brain area would correspond to slower RTs. However, these specific regions are involved in what Raichle and colleagues refer to as the "default mode" brain network.<sup>46</sup> The default mode 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. Raichle et al argue that this network represents the baseline working state of the brain that must be suspended or inhibited to actively engage in goal-directed behavior, such as a cognitive challenge.<sup>46</sup> Under this model, the default mode is active whenever the individual is not otherwise cognitively engaged. When the individual then focuses attention to engage in a specific task, resources must be reallocated away from the default mode network and toward the brain regions needed to successfully complete the task at hand.<sup>47</sup> In the context of the PVT, greater activation of these midline brain regions during the slowest RTs may represent a partial disengagement from the task and subsequent failure to allocate resources to the motor and attention systems related to fast responding. It is this attentional disengagement that in turn results in Slow RTs and, at the extreme, a lapse.

This idea is further supported by the results of the regression examining brain regions related to the Slow RTs after TSD (Figure 3). Among the areas showing greater responses during Slow RTs in the slowest individuals following TSD are the same midline frontal regions differentially responding to Slow RTs in the

well-rested state. Additional areas showing this relationship included medial areas in the posterior cingulate and cuneus. These areas are also part of the default mode as defined by Raichle and colleagues.<sup>46</sup> Therefore, perhaps not surprisingly, individuals showing the slowest RTs after TSD have associated patterns of brain activity characterized by even stronger activation of the default-mode brain state, suggesting even stronger inattention and disengagement from the task in the slowest individuals. Put the opposite way, those individuals who showed the fastest Slow RTs after TSD showed the least activity within the brain's default-mode network, suggesting that these individuals were better able to reallocate cognitive resources to motor, attention, or both motor and attention systems.

One could speculate that alternative explanations for the pattern of brain responses related to Slow RTs may be that it is actually secondary to eye closures, EEG changes, or even microsleeps. Eye closures are a sensitive measure of lapses during PVT performance<sup>48</sup> and of sleepiness during driving.<sup>49</sup> Certainly, if there was an increase in brief eye closures during TSD, and these occurred in coincidence with stimulus presentations, that would be expected from a behavioral perspective to create the Slow RTs. However, we do not believe that this is responsible for the pattern of brain response during Slow RTs. This is because having eyes closed, relative to eyes open, is associated with decreased BOLD signal in the visual cortex, thalamus, and the lateral geniculate,<sup>50</sup> all of which actually showed increased responses in the slowest individuals. A factor perhaps contributing to the subcortical pattern of response during Slow RTs is a possible increase in alpha EEG rhythm during TSD. While many authors have reported decreased resting alpha power in waking EEG subsequent to sleep loss,<sup>51-53</sup> increased alpha has been reported during RT tasks after TSD.<sup>8, 54</sup> Feige et al<sup>50</sup> and Goldman et al<sup>55</sup> have both reported that greater occipital alpha power is correlated with increased BOLD signal in thalamic nuclei, consistent with the greater thalamic BOLD signal in the slowest individuals here. However, both groups also reported alpha-related decreases in occipital, superior parietal, and/or cingulate regions, all of which showed increases in relation to Slow RTs here. Finally, one must wonder whether some of the slowest RTs were secondary to microsleeps. Again, though, available evidence suggests this is not the case. The slowest RT observed in any subject was 5.6 seconds, and only about 5% of all responses qualifying as 1 of the Slow RTs (ie, 9 responses out of a total of 200 across all 20 subjects) were greater than 2.0 seconds. So, even if these delayed responses represented microsleeps, that accounts for few of the analyzed Slow RTs. Furthermore, if sleep did occur, it could only have been Stage 1 sleep. Kjaer and colleagues<sup>56</sup> have reported that Stage 1 sleep is associated with decreased blood flow (which could be expected to reduce BOLD signal at "rest" if subjects were asleep) in bilateral parietal lobes, the right premotor area, and the left thalamus. As with the eye closure and alpha EEG data, this is the opposite of what we observed here as related to Slow RTs. Overall, then, while we can not definitively rule out the presence of eye closures, changes in EEG alpha power, and microsleeps (since we did not simultaneously measure EEG and fMRI), they do not appear to explain the network of brain regions showing increased responses during Slow RTs nearly as well as the disengagement and inattention hypothesis related to the default-mode network. These data, then, may provide insight into the mechanism underlying poor performance during TSD: an inability to allocate cognitive resources away

from the default brain network and to the brain regions required by the given task demands.

### Night-by-Speed Interaction: Evidence for Attentional Recovery?

The results of the Night-by-Speed interaction analysis did not confirm our original hypothesis. We anticipated that the sustained-attention brain regions showing a differentially greater response to Fast RTs after a Normal night of sleep, plus the thalamus, would show an even greater differential response to Fast RTs after TSD. This hypothesis was based on previous findings that showed (1) increased recruitment of cerebral resources during task performance after TSD when that performance was nearly equivalent to performance while well rested,<sup>17,18,24,57</sup> and (2) even greater compensatory recruitment with harder versions of a given task.<sup>24,58</sup> Based on available behavioral data, we assumed that the speed of Fast RTs would not change dramatically after TSD and, therefore, that maintaining optimal performance after TSD would require compensatory recruitment. However, as Figure 2 shows, this was not the pattern of interaction we found.

Instead, we found that the cerebral response during Fast RTs did not change with TSD, while the response during Slow RTs significantly increased in several regions (Table 3, Figure 2). Interestingly, 6 of the 7 clusters showing this interaction overlap with clusters showing differentially greater responses to Fast RTs, relative to Slow RTs, after a Normal night of sleep. As discussed above, these are regions implicated either in optimal motor function or sustained attention. The seventh area (middle frontal gyrus, BA 9/8), while not showing a significant response after Normal sleep here, has also been implicated in sustained attention.<sup>14</sup> Why might the activation within brain regions normally associated with the fastest RTs actually show increases during Slow RTs after TSD? One possible explanation relates to the recovery of attention and arousal immediately after a Slow RT. Dinges and colleagues reported that, following TSD, lapses (ie, Slow RTs of at least 500 milliseconds) are often commingled with false starts (pressing the response button in the absence of a stimulus or making a response faster than 100 milliseconds).<sup>12</sup> They argue that such errors of commission are anticipatory and reflect subjects' compensatory efforts in response to the feedback that they made a very slow response.<sup>12</sup> In essence, then, a Slow RT may prompt a subject to reengage in the task (ie, increase compensatory effort), thereby momentarily raising his or her alertness and attention levels. This attentional recovery may occur especially strongly during TSD when Slow RTs denote particularly bad performance. After Normal sleep, on the other hand, even an individual's slowest RTs are rarely in the lapse range, and, therefore, the RT feedback may not be as salient an indicator to reengage in the task. Put in the context of the fMRI data reported here, the Night-by-Speed interaction may reveal the cerebral substrate of this attentional recovery to be within not only the cortical sustained attention network, but also the cortico-subcortical motor systems responsible for optimal performance under Normal conditions.

### Limitations and Future Directions

One limitation of this study is the brain coverage we were able to obtain. Due to the speed of acquisition of each brain volume (1 second), we were only able to acquire 12 slices. At 6 mm per slice, this only allowed us to acquire data from a 72mm brick, which does not include the entire brain. This necessitated a trade-

off between dorsal cortical areas and the ventrally located brain stem and cerebellum. Since our TSD-related hypotheses focused on the cortical sustained-attention network and the thalamus, we chose to focus on the more dorsal areas. Clearly, though, it would be important for future studies to examine activation in the more ventral regions to better understand the role of brain-stem arousal centers in PVT performance, as well as possibly cerebellar motor regions.

A limitation of using the PVT in the fMRI environment resides in the timing of the task. We specifically wanted to use the traditional task timing to allow for maximal comparability with the plethora of behavioral studies utilizing the PVT. However, an interstimulus interval of 2 to 10 seconds is insufficient to allow the hemodynamic response to return to baseline after each RT, meaning that the task has no true “baseline.” Due to the linearity of the hemodynamic response,<sup>59</sup> the BOLD signal related to 1 RT was influenced by the BOLD signal from previous RTs. This, in combination with the fact that the task contains only 1 type of stimulus, makes it very difficult to discriminate the brain’s response to consecutive RTs. Indeed, this may have influenced the results of the Night-by-Speed interaction analysis, as discussed above. On the other hand, we were able to discriminate the BOLD signal response to Fast and Slow RTs from all other RTs because Fast and Slow did not typically occur back to back.

The timing of the PVT could be changed slightly to avoid this problem, although the changes may not be ideal, either. For example, the interstimulus interval could be extended to 15 to 16 seconds to allow the hemodynamic response to return to baseline after a given RT. This would afford the ability to detect the brain’s response to each individual stimulus, would better reveal the time course of an “attentional recovery” effect, and would allow for the examination of the brain state before the stimulus onset. The latter, in particular, may be especially valuable in predicting lapses of attention. However, such a long time between stimuli would also increase the probability of subjects actually falling asleep during the task, especially while sleep deprived.<sup>2</sup> Another option would be to alternate the task with blocks of some baseline condition. Such a strategy may allow a more statistically powerful examination of brain regions underlying PVT performance.<sup>60</sup> However, this strategy would also reduce, if not eliminate, the ability to discriminate Fast versus Slow RTs and would actually reduce the sustained-attention demands by providing regular breaks from the task. To fully understand the cerebral substrates of sustained attention and arousal as measured with the PVT, future studies will need to solve these timing issues. Another task-design factor that likely influenced the results here (as well as most published behavioral PVT data) is the fact that subjects received feedback on their RTs. As discussed above, this feedback probably contributes to the attentional recovery often observed behaviorally and for which we identified cerebral correlates. Future studies could contrast Fast versus Slow RTs with and without feedback to determine the extent to which this feedback interacts with subsequent performance, influences cerebral responses, or both.

As with all fMRI studies, these data represent relative cerebral activation and not absolute levels of metabolism. Here, the cerebral response during fastest and slowest 10% of RTs is examined relative to the cerebral response to the middle 80% of RTs. Thus, while data from all RTs are used in the times-series analysis, the middle RTs are used as a baseline against which the Fast and Slow RTs are compared. As stated above, this allows us to report

brain regions that are especially involved in producing 1 of these extreme RTs. Nonetheless, future studies would benefit from the development of analysis techniques that would allow for more precise and dynamic modeling of all individual RTs. The relative measures used in BOLD fMRI also mean we were unable to identify absolute levels of brain activation during the task, as can be done, for example, with positron emission tomography. Previous positron emission tomography studies<sup>61,62</sup> have reported decreased glucose metabolism during TSD, including in some of those areas discussed here. Thus, it is possible that the results reported here occurred against a background of overall decreased cerebral glucose metabolism. However, as we have argued elsewhere, it is unclear how much diminished glucose metabolism would directly influence overall brain-energy utilization or the BOLD signal underlying fMRI.<sup>24</sup>

In conclusion, we used fMRI to study the neurophysiologic correlates of Fast and Slow RTs on the PVT after Normal sleep and following 36 hours of TSD. Results showed that Fast RTs are supported by increased activation within a sustained-attention network and a cortical and subcortical motor network. Slow RTs, on the other hand, were associated with greater activation within midline structures involved in the default brain mode, which we hypothesize to underlie inattention and task disengagement. Furthermore, an interaction analysis showed brain regions possibly involved with recovery after attention lapses. Taken together, these findings may start to provide the neuroanatomic basis for the state instability to which the PVT appears sensitive.<sup>2,12</sup> That is, state instability during PVT performance may be characterized by brain states alternating between activation within areas supporting sustained attention and fast motor responding and activation within the default-mode network suggestive of inattention and task disengagement. The results of the interaction analysis would then capture the change between those 2 states. One implication of these data is that inappropriate activation of the default-mode network, and failure to reallocate resources to other task-related brain regions, may be among the early manifestations of sleep loss and serve as a precursor to more overt manifestations of sleepiness such as microsleeps, eye closure, and, ultimately, sleep onset. It remains to be seen whether the motor regions reported as involved here would be replaced by other tasks-specific networks if other cognitive tasks were studied in similar event-related paradigms. Such a finding in future studies would suggest that the sustained-attention network is the cortical system primarily involved in state instability.

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