



Imaging brain fatigue from sustained mental workload: An ASL perfusion study of the time-on-task effect

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ARTICLE INFO

Article history:

Received 6 May 2009

Revised 16 September 2009

Accepted 10 November 2009

Available online 24 November 2009

Keywords:

Time-on-task effect

psychomotor vigilance test

ASL perfusion fMRI

Fronto-parietal network

ABSTRACT

During sustained periods of a taxing cognitive workload, humans typically display time-on-task (TOT) effects, in which performance gets steadily worse over the period of task engagement. Arterial spin labeling (ASL) perfusion functional magnetic resonance imaging (fMRI) was used in this study to investigate the neural correlates of TOT effects in a group of 15 subjects as they performed a 20-min continuous psychomotor vigilance test (PVT). Subjects displayed significant TOT effects, as seen in progressively slower reaction times and significantly increased mental fatigue ratings after the task. Perfusion data showed that the PVT activates a right lateralized fronto-parietal attentional network in addition to the basal ganglia and sensorimotor cortices. The fronto-parietal network was less active during post-task rest compared to pre-task rest, and regional CBF decrease in this network correlated with performance decline. These results demonstrate the persistent effects of cognitive fatigue in the fronto-parietal network after a period of heavy mental work and indicate the critical role of this attentional network in mediating TOT effects. Furthermore, resting regional CBF in the thalamus and right middle frontal gyrus prior to task onset was predictive of subjects' subsequent performance decline, suggesting that resting CBF quantified by ASL perfusion fMRI may be a useful indicator of performance potential and a marker of the level of fatigue in the neural attentional system.

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Introduction

Sustaining attention to a taxing cognitive task often comes at a cost, known in the literature as the “vigilance decrement,” or “time-on-task effect” (Mackworth, 1948, 1968). Behaviorally, this effect manifests itself in failures in target detection (Davies and Parasuraman, 1982), also known as “lapses” (Dinges and Powell, 1989), increasing reaction times (Boksem et al., 2005) and escalating reaction time variability, as well as an increasing sense of subjective fatigue over the course of a mentally challenging task. Although this effect was documented early in the psychological literature, it has not been the subject of much investigation in the field of neuroimaging, and the neural correlates of the phenomenon are not well understood.

The real world consequences of fatigue and the time-on-task effect are serious and pervasive. For example, many accidents involving truck drivers and medical personnel have been attributed at least in part to sleepiness, fatigue and lapses in vigilant attention (Landrigan et al., 2004; Arnedt et al., 2005). Because of this, the time-on-task effect has been of special interest to researchers in multiple disciplines who seek to understand the effects of brain function on human work

capacity. In particular, the emerging field of neuroergonomics aims to study the neural basis of cognitive and physical work in order to optimize mental functioning (Parasuraman, 2003; Parasuraman and Wilson, 2008). Viewed through the framework of neuroergonomics, the time-on-task effect arises because the workload associated with tasks requiring vigilance is high and consumes mental resources that cannot immediately be replenished (Warm et al., 2008). This stands in contrast to traditional views of this phenomenon, which attributed the decrement to boredom or motivational decline (Frankmann and Adams, 1962; Mackworth, 1968).

Logically, neural regions associated with time-on-task effects should correspond with areas active during optimal engagement of attention. Studies of attention using positron emission tomography (PET) have implicated regions associated with successful task performance, including the anterior cingulate cortex (ACC), right middle and inferior prefrontal cortex, right inferior parietal regions, and the thalamus (Kinomura et al., 1996; Paus et al., 1997; Coull et al., 1998; Sturm et al., 1999; Lawrence et al., 2003). These regions can be differentiated into areas of “bottom-up” attention or detecting signals that are intrinsically alerting, and “top-down” attention, including processes such as biasing attention towards specific signal features, inhibiting unwanted distractions from the task, or modulating attention via motivation (Corbetta and Shulman, 2002; Sarter et al., 2001, 2006). It is thought that the inferior parietal cortex, temporal-

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parietal junction and the thalamus provide bottom-up input, while dorsolateral prefrontal cortex and ACC perform top-down functions under conscious control (Kinomura et al., 1996; Foucher et al., 2004; Fan et al., 2005).

There have been relatively few studies on neurobiological mechanisms underlying the time-on-task effect. Coull et al. (1998) compared tasks of selective and non-selective attention and found time-on-task effects exclusively in the latter. These effects were accompanied by decreased regional cerebral blood flow (rCBF) in the right inferior parietal cortex and inferior frontal cortex. Although both selective and non-selective tasks activated this fronto-parietal network and showed no significant difference when averaged over time, activation to the selective task was preserved across the run, suggesting top-down modulation was involved in maintaining performance. The authors hypothesized that decreasing activation in the non-selective task was due either to habituation or diminished attentional resources. In another experiment, Paus et al. (1997) studied subjects performing a 60-min continuous auditory vigilance task and reported decreased CBF in the thalamus, which was related to diminishing levels of arousal. Right-lateralized areas of the frontal, parietal and temporal cortex also showed decreasing activity over the course of the task, which were related to shifts in task strategy from controlled to automatic processing. However, both of these studies were analyzed at the group level (over time) and did not examine the relationships between brain activity and behavioral performance or inter-subject variability.

One of the challenges in carrying out neuroimaging studies of sustained attention arises from methodological limitations. Early studies such as those identified above have typically employed PET to measure absolute levels of cerebral blood flow. However, PET has poor temporal and spatial resolution, and cannot provide information about brain activity to individual events within a task block. Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) can overcome some of these problems, yet it is limited by the poor sensitivity to track slow neural activity changes over a time scale longer than a few minutes (Aguirre et al., 1997, 2002). As short tests mostly fail to elicit significant decrements in human performance over time, it is critical to select an imaging method capable of measuring slow varying neural activity with a high level of spatial and functional resolution.

Using magnetically labelled water in arterial blood as a diffusible tracer, arterial spin labeling (ASL) perfusion fMRI (Detre and Wang, 2002) provides a non-invasive imaging method of quantifying cerebral blood flow (CBF) at task-free resting baselines (Rao et al., 2007a, 2007b) as well as during the performance of cognitive tasks (Wang et al., 2005; Kim et al., 2006; Olson et al., 2006; Rao et al., 2007c). ASL perfusion imaging also offers reliable measures of CBF with excellent reproducibility over long time periods (Aguirre et al., 2002). These features suggest that ASL perfusion fMRI may provide a highly suitable method for imaging the time-on-task effect over long durations. The present study, therefore, used ASL perfusion fMRI to examine the neural correlates of the time-on-task effect during the performance of a highly-demanding attentional task – the psychomotor vigilance test (PVT). The PVT is a simple reaction time task in which subjects are instructed to respond as rapidly as possible to a single stimulus presented at short, random intervals. We selected this test as our measurement instrument for a few reasons. First, it has been shown that the PVT is a simple, reliable and highly sensitive task for measuring attentional and performance deficits due to fatigue. Second, the PVT is free of aptitude and leaning effects which may confound the effects of TOT. Finally, the attentional requirements in the PVT are undiluted by elements of selectivity such as spatial orientation or executive decision-making. As stimulus saliency is held constant throughout the task, the maintenance of optimal performance on the PVT is almost completely mediated by top-down processes. These task features allowed us to isolate the

time-on-task effect and minimize the confounding effects of differing visual stimuli, aptitude, strategy shifts or learning. In this current study therefore, we aimed to characterize neural activity associated with time-on-task decline not only during the continuous performance of PVT but also at resting baseline periods before and after the 20-min task.

Materials and methods

Participants

Fifteen healthy undergraduate and graduate students (eight male, mean age = 23.2 ± 3.6 years) from the University of Pennsylvania participated in this study. Written consent was obtained from all participants according to the University of Pennsylvania Institutional Review Board. Each participant was paid \$35 in compensation for their effort and time.

Prior to enrolment in the experiment, all participants were screened to ensure that they had no history of chronic physical or mental illness, were right-handed, and did not habitually consume more than 250 mg of caffeine a day. Participants who qualified for enrolment were instructed to obtain between 6.5 and 8 h of sleep during the two nights prior to the experiment and not to consume caffeine, alcohol, or any other psychoactive substances during the 24 h before the study. We took special care to control for baseline levels of sleepiness, as the PVT is typically used in the context of sleep deprivation experiments (Dorrian et al., 2005; Durmer and Dinges, 2005; Lim and Dinges, 2008) and is exquisitely sensitive to the sleep propensity of the test-taker.

Task parameters

The psychomotor vigilance test (Dinges et al., 1997) was used as the sustained attention task in this study. This test is a simple reaction time test with varying and random inter-stimulus intervals (ISI) which range from 2 to 10 s (including a 1 s delay after each button press for subjects to read their reaction time). A Windows-compatible version of the PVT was used to display the stimuli in this study (Pulsar Informatics, Philadelphia, PA). Before the experiment, subjects were instructed to focus their attention on a red, rectangular box subtending 2×1.3 degrees of visual angle in the middle of a black screen, and monitor the space for the appearance of a millisecond counter. They were told to react to and stop the counter with a button press, after which their reaction time would be displayed. Participants were instructed to respond as quickly as possible to the stimuli while avoiding “false starts” or responses when the counter was not on the screen. The length of a standard PVT administration is 10 min; however, in order to elicit a greater time-on-task effect and increase between-subject variability in performance, we imaged subjects as they underwent a 20-min PVT bout. In order to boost motivation, we emphasized to subjects the importance of giving their best effort “throughout the task” without any reference to the strenuous nature of the test.

We extracted the following variables from each test as a measure of overall level of performance: median reaction time (RT), standard deviation of reaction times and number of lapses (RT > 500 ms). To assess the time-on-task effect, we divided the PVT bout into 4-min quintiles and obtained the median RT in each of those time bins, as well as computing the percentage change in reaction times from the first to the last quintile for each subject.

Directly before and after administration of the PVT, subjects were asked to rate their subjective fatigue on a 9-point visual analogue scale. To control for other potential confounds, we also obtained data on recent sleep quality and history using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), baseline levels of sleepiness using the Epworth Sleepiness Scale (ESS), and a scale containing questions

where subjects were asked to provide a subjective rating of their own performance.

Data acquisition

Functional imaging was conducted on a Siemens 3.0T Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a product eight-channel array coil. All fMRI scans were conducted in the Hospital of the University of Pennsylvania, between 1400 and 1700 h. Before entering the magnet, subjects were given a brief 1-min opportunity to practice performing the PVT. As the PVT is a highly challenging task with negligible learning effects (Dorrian et al., 2005; Lim and Dinges, 2008), we did not allow participants to practice the task for a lengthier period of time.

A pseudo-continuous ASL sequence (Wu et al., 2007; Dai et al., 2008) was used for the perfusion scan. Arterial spin labeling was implemented with a series of selective RF pulses (Hanning window, peak/average RF, amplitude $B = 5.3/1.8 \mu\text{T}$, duration = 500 μs) applied at 9 cm beneath the center of the imaging slices. Interleaved images with and without labeling were acquired using a gradient echo-planar imaging (EPI) sequence. The tagging/control duration was 1.77 s. A delay of 1 s was inserted between the end of the labeling pulse and image acquisition to reduce transit artifact. Acquisition parameters consisted of the following: FOV = 22 cm, matrix = 64×64 , TR = 4 s, TE = 17 ms, flip angle = 90° . Sixteen slices (7 mm thickness with 1.4 mm gap) were acquired in an inferior to superior direction in sequential order. The perfusion scanning protocol of PVT performance lasted 20 min and consisted of 300 acquisitions. An additional two 4-min perfusion scanning protocols consisting of 60 acquisitions were collected while subjects were at rest before and after the PVT to assess resting baseline CBF levels. During these resting times, subjects were asked to relax, keep their eyes open and stay awake. After the functional scans, high-resolution T1-weighted anatomic images were obtained using a 3D-MPRAGE sequence (TR = 1620 ms, TI = 950 ms, TE = 3 ms, flip angle = 15° , 160 contiguous slices of 1.0 mm).

Data analysis

Functional imaging data processing and analyses were carried out with Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, UK, implemented in Matlab 6, Math Works, Natick, MA). In house SPM add-on scripts (online at <http://www.cfn.upenn.edu/perfusion/software.htm>) developed by two authors (H.R. and J.W.) were used to quantify CBF values and reconstruct CBF maps for perfusion analysis.

For each subject, functional images were first realigned to correct for head motion, co-registered with the anatomical image and smoothed in space using a three-dimensional, 6-mm full width at half maximum (FWHM) Gaussian kernel. The perfusion weighted image series was then generated by pair-wise subtraction of the label and control images, followed by conversion to an absolute CBF image series based on a single compartment CASL perfusion model (Wang et al., 2004). Thus, the resulting CBF data sets contained 210 acquisitions (30 acquisitions for pre-task resting baseline, 150 acquisitions for PVT, and 30 acquisitions for post-task resting baseline) with an effective TR of 8 s. One mean CBF image was generated for every 4-min perfusion scan for each individual subject. Thus, each subject had one CBF image for pre-task resting baseline, five CBF images for the PVT, and one CBF image for post-task resting baseline. These CBF images were normalized to a $2 \times 2 \times 2 \text{ mm}^3$ Montreal Neurological Institute (MNI) template using bilinear interpolation and then entered into the whole brain voxel-wise general linear model (GLM) analysis using the PET model in SPM. The GLM model included an adjustment for global CBF differences. Contrasts were defined to compare the PVT with rest baselines (PVT

vs. Rest), the post-task resting baseline with the pre-task resting baseline (Rest2 vs. Rest1), and the last 4-min quintile of PVT with the first 4-min quintile of PVT (PVTq5 vs. PVTq1). For the contrasts of PVT vs. Rest and Rest2 vs. Rest1, activation clusters were identified at a significance level of $p < 0.05$ (FDR corrected across comparisons for the whole brain) and cluster size larger than 30 voxels. For the contrast of PVTq5 vs. PVTq1, no area survived the whole-brain correction and a small volume correction ($p < 0.05$) was applied to regions in the right fronto-parietal network.

Region of interest (ROI) analysis was also conducted to calculate quantitative regional CBF changes and discover whether regional CBF changes were correlated with behavioral time-on-task deficits. These ROIs were determined *a priori* to be the brain regions comprising the fronto-parietal network that mediates sustained attention, including the thalamus, anterior cingulate cortex (ACC), right middle frontal gyrus (MFG), and right inferior parietal lobe (IPL) (Kinomura et al., 1996; Paus et al., 1997; Coull et al., 1998; Sturm et al., 1999; Lawrence et al., 2003). In addition to the functional ROIs which were defined by the activation clusters from the contrast between the PVT and resting baselines, we also used structure-based ROIs which were independent of the PVT activations to further confirm the relationship between CBF activity and behavioral performance changes and make the findings more generalizable. The structure-based ROIs were defined from an automated anatomical-labeling ROI library (Tzourio-Mazoyer et al., 2002). Quantitative CBF changes in each voxel of each ROI were averaged and read out by the Marsbar toolbox (Brett et al., 2002), which provides routines for region of interest analysis (online at <http://marsbar.sourceforge.net>). Finally, correlation analyses were performed between performance changes and quantitative regional CBF values (after adjusting for global CBF differences) in these ROIs during the pre-PVT resting baseline.

Results

Behavioral data

Mean (SD) reaction time (RT) to the PVT across all subjects was 293.5 (28.3) ms. Participants were attentive to the task, as shown by the relatively small number of lapses (reaction times > 500 ms) committed overall (mean = 2.1, SD = 3.0). Performing the PVT elicited a clear time-on-task effect, with most participants showing steadily increasing RT over the course of the run (Fig. 1a). One-way analysis of variance (within subject repeated measures) of mean RT in the 4-min quintiles revealed a significant effect of time-on-task (Fig. 1a, $F_{4,70} = 2.34$, $p < 0.05$). Tukey's post-hoc comparisons showed significant differences between reaction time in the first and last quintile only ($p < 0.05$). However, there was no significant effect of time-on-task on the standard deviation of RT over the run ($F_{4,70} = 0.50$, n.s.), suggesting that this slowing was not confounded with a change in the stability of the attentional system.

Time-on-task vulnerability was quantified by calculating the percentage change in mean reaction times from the first to last quintile of the PVT for each subject. These values ranged from -0.2% to 30.7%. There were noticeable inter-individual differences in the extent of this vulnerability. Fig. 1b shows the RT time series of four subjects over the 20-min PVT, with two subjects (s1 and s4) demonstrating little increase in reaction times (<3%) from the first to the last minute of the PVT and the other two subjects (s2 and s3) showing marked performance decrements (>18%).

Subjects reported being mentally fatigued by performing the PVT, with subjective ratings on the 9-point fatigue scale increasing significantly from pre- to post-task (Fig. 1c, $p < 0.001$). There was no significant correlation between objective performance decline and either increases in self-rated fatigue (Fig. 1d, $r = 0.06$, n.s.), or levels of fatigue prior to engaging in the task ($r = 0.33$, n.s.). Sleep quality (as

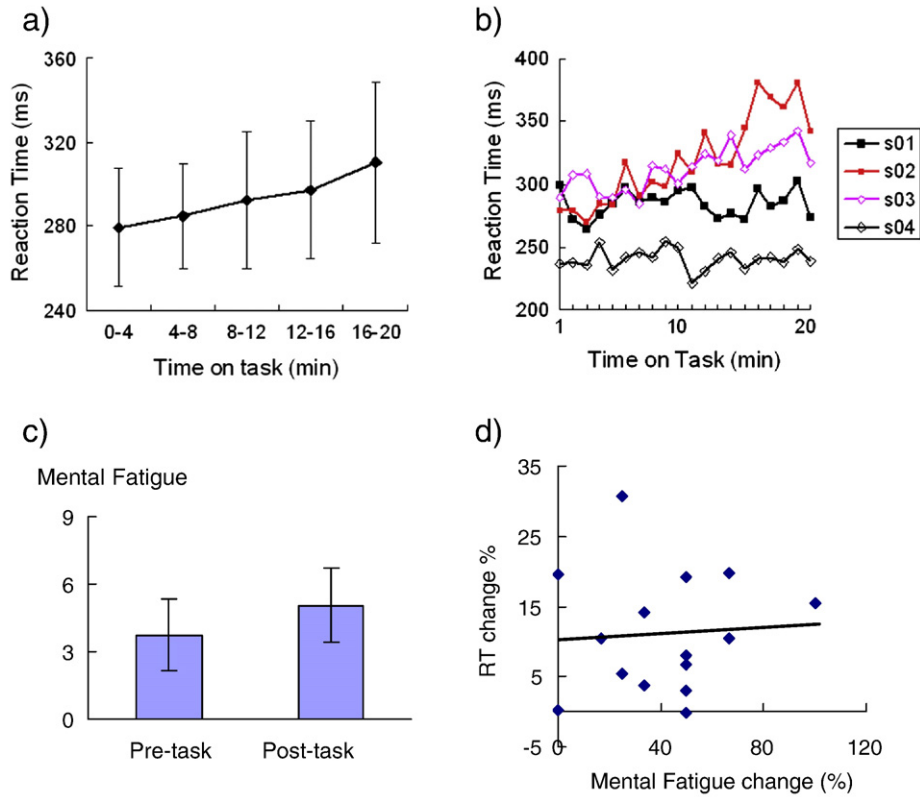


Fig. 1. (a) Means and standard deviations of reaction time (RT) from the first to the last 4-min quintiles. (b) RT time series of four subjects from the first minute to the last minute of the 20-min PVT. Note that there were robust individual differences in the rate of RT increases. (c) Mean mental fatigue scales reported by subjects before and after the PVT. Note both RT and mental fatigue scales showed significant time-on-task effects. (d) Self-reported mental fatigue scale changes showed no correlation with RT changes ($r = 0.66, p > 0.9$).

measured by the PSQI), subjective performance ratings, and ratings on the ESS were not significant predictors of time-on-task decline (data not shown) and were not subject to any further analysis.

Imaging results

Quantitative CBF maps

With the exception of a single subject who showed poor labeling and abnormally low global CBF values, and who was excluded from further analysis, all individual quantitative CBF maps for the task and resting baseline scans were of high quality. As an example, the quantitative CBF image from a representative subject is illustrated in Fig. 2a. Perfusion in brain regions was visualized with good sensitivity, and clear contrast between gray and white matter was observed in the perfusion intensity. The mean whole brain (global) CBF values of remaining 14 subjects (mean \pm SD, in mL/100 g/min) were 67.0 ± 12.0 , 65.8 ± 12.2 , and 70.3 ± 13.7 for the pre-PVT resting period, the PVT, and the post-PVT resting period, respectively. There were no global CBF differences between the pre-PVT resting baseline and post-PVT resting baseline or between the PVT and the resting baselines, nor correlations between global CBF changes and RT changes (all $p > 0.1$).

PVT task-related CBF changes

Compared to the resting baseline periods, continuous performance of the PVT increased CBF in right middle frontal gyrus and inferior frontal cortex (MFG/IFC), right inferior parietal lobe (IPL), bilateral supplemental motor area/anterior cingulate cortex (SMA/ACC), bilateral basal ganglia/insula, and left sensorimotor cortex (Fig. 3a, Table 1). We also observed slight CBF activation in the left MFG/IFG.

However, no CBF change was seen in the thalamus. The PVT also induced significant deactivation (CBF decreases) in bilateral occipital cortex and precuneus/posterior cingulate cortex (PCu/PCC).

Quantitative CBF analysis on the functional ROIs revealed that regional CBF increased 8.4% (SD = 5.1%, $p < 0.001$) in the right MFG, 6.7% (SD = 6.4%, $p = 0.002$) in the right IPL, and 7.3% (SD = 5.7%, $p < 0.001$) in the ACC during the PVT comparing to the baseline. However, no correlations were found between RT changes and these regional task-induced activations in the attentional network. Quantitative CBF analysis on the independent structural ROIs confirmed that there were no correlations between RT changes and regional CBF activations in the right MFG and right IPL but showed significant correlations between RT changes and CBF changes in the thalamus and ACC (both $p < 0.05$). However, these correlations disappeared (both $p > 0.1$) when the outlier (RT change = 30.7%) was removed.

CBF changes in resting baseline after task

Compared to the pre-task resting baseline, post-task resting baseline scans showed robust deactivation (CBF decreases) in bilateral ACC, MFG, superior temporal cortex (STC), and right IPL/cuneus (Fig. 3b; Table 2). The MFG deactivation overlapped with the PVT activated MFG/IFG regions, but the ACC deactivation was more anterior and inferior, and the right IPL deactivation was more posterior and inferior to the PVT activated regions, respectively. Quantitative CBF analysis on the functional ROIs revealed that regional CBF decreased significantly in the right MFG ROI (mean = -5.4%, SD = 6.5%, $p = 0.008$). Although CBF decreases in the ACC (mean = -1.4%, SD = 10.1%) and right IPL (mean = -2.9%, SD = 11.2%) did not reach significance (both $p > 0.1$), CBF changes in these three functional ROIs all showed significant correlations with RT changes during the 20-min PVT (all $p < 0.05$, Fig. 4a). Quantitative CBF

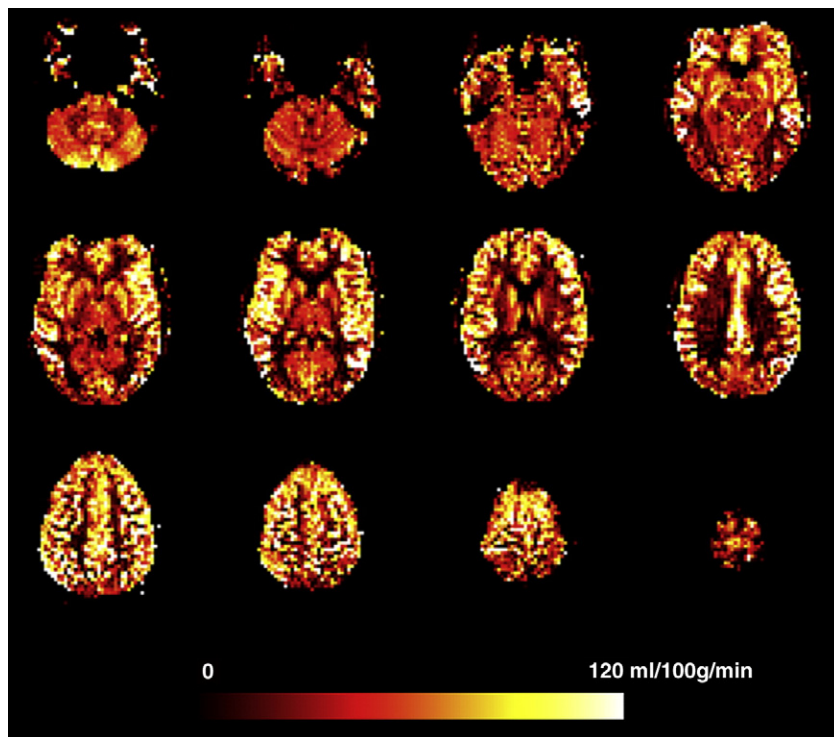


Fig. 2. Quantitative CBF maps from a representative subject.

analysis on the independent structural ROIs confirmed significant correlations between RT changes and regional CBF deactivations in the ACC, right MFG and right IPL (Fig. 4b). These results indicated that better-preserved performance over the 20-min PVT (smaller RT increases) was associated with smaller CBF decreases in the fronto-parietal network after the task.

CBF changes during the 20-min PVT

No CBF differences were found when comparing the first quintile to the last quintile of the PVT using a whole brain corrected threshold. Using a more liberal threshold of uncorrected $p < 0.001$ and cluster-size larger than 30 voxels, regional CBF showed significant decreases in bilateral

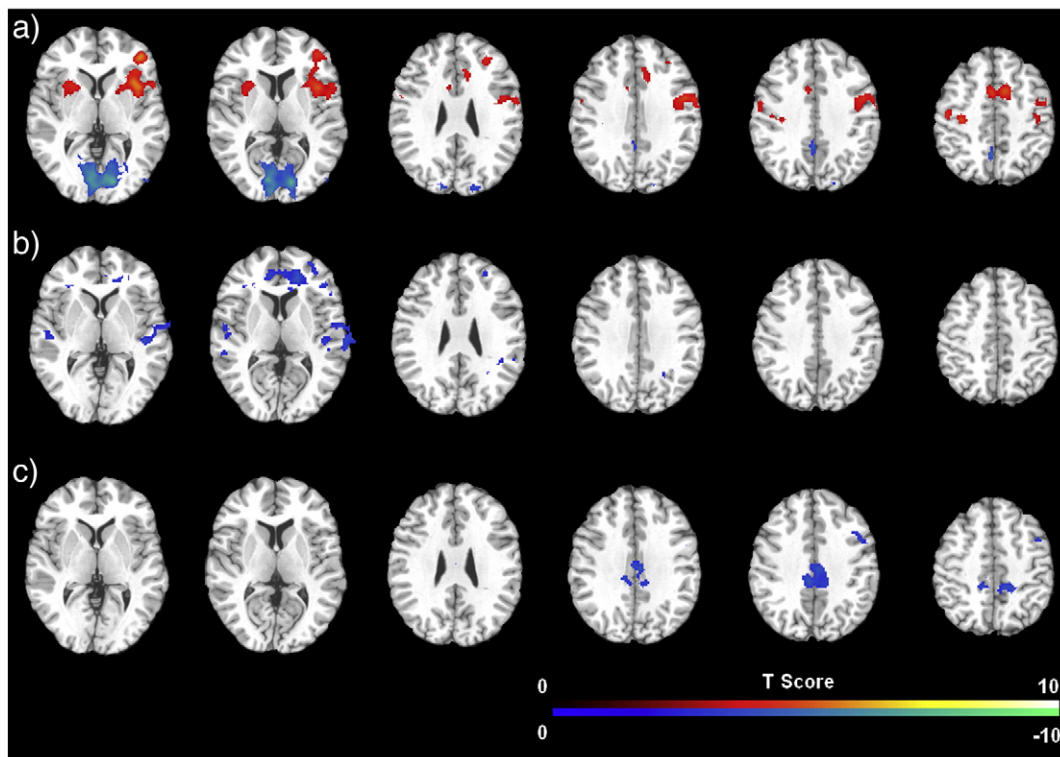


Fig. 3. Brain areas associated with (a) the comparison of PVT versus resting baselines, (b) the comparison of post-task resting baseline versus pre-task resting baseline, and (c) the comparison of the last quintile of PVT versus the first quintile of PVT. The threshold of display was set as FDR or small volume corrected $p < 0.05$.

Table 1
Brain areas showing significant activation (CBF increases) and deactivation (CBF decreases) to the PVT compared to resting baseline.

Region	Cluster size	MNI coordinates			Peak Z	Peak p (corrected)
		x	y	z		
<i>(A) CBF increases</i>						
R. middle frontal cortex, inferior frontal cortex, insula, putamen	3104	42	44	2	5.42	0.001
		36	14	2	5.25	0.001
		32	36	20	4.76	0.002
B. supplementary motor area, anterior cingulate cortex	655	8	8	48	4.71	0.002
L. sensorimotor cortex	574	-4	4	50	4.66	0.002
		-34	-22	50	4.60	0.002
		-56	2	18	4.46	0.003
		-50	-16	48	4.24	0.004
L. insula, putamen	325	-30	14	6	4.25	0.004
R. anterior cingulate cortex	157	8	26	26	3.93	0.008
L. middle frontal cortex	66	-24	32	22	3.61	0.014
		-34	36	22	3.33	0.025
R. inferior parietal lobe	127	60	-40	42	3.42	0.021
		54	-48	48	3.02	0.044
<i>(B) CBF decreases</i>						
B. occipital	3234	12	-84	6	6.56	<0.001
		-12	-82	8	6.08	<0.001
L. posterior cingulate cortex	196	-6	-56	46	4.72	<0.001

The threshold was set as whole brain FDR-corrected $p < 0.05$. L, left; R, right; B., bilateral.

posterior cingulate cortex (PCC), right MFG, right SMA, and right STC from the first to the last quintile of the PVT (Fig. 3c; Table 2). The right MFG deactivation overlapped with the PVT activated MFG/IFG regions and it survived the small volume correction using a structure-based ROI of MFG. Quantitative CBF analysis on the functional ROIs revealed that regional CBF decreased 12.8% (SD = 11.1%, $p = 0.001$) in the right MFG with no significant CBF changes in other functional or structural ROIs, and no correlation between regional CBF changes and RT performance changes.

Correlations between pre-task resting CBF and performance decline

Interestingly, quantitative CBF analysis of pre-task resting CBF in the functional ROIs revealed that resting CBF activity in the right MFG before PVT performance was predictive of the extent to which subjects' performance declined over the course of the 20-min task. Lower regional CBF in the right MFG at pre-task resting baseline was associated with smaller reaction time increases during the PVT (Fig. 5a, $r = 0.69$,

$p = 0.007$). Quantitative CBF analysis on the independent structural ROIs confirmed significant correlations between performance decline and right MFG resting CBF (Fig. 5b, $r = 0.64$, $p = 0.01$), and further revealed that pre-task resting CBF activity in the thalamus was also predictive of the reaction time increases during the PVT (Fig. 5c, $r = -0.59$, $p = 0.03$). Removing the outlier did not change these results.

Discussion

In this experiment, we induced time-on-task deficits by asking subjects to perform the psychomotor vigilance test for 20 min. As expected, subjects reacted significantly slower to target stimuli as the task proceeded and reported higher fatigue ratings after the task. Additionally, we observed a substantial amount of inter-individual variation in the degree to which subjects showed this effect. While some participants were able to perform relatively consistently over the course of the 20-min period, others showed markedly worse performance by the end of the test.

Table 2
Brain areas showing significant CBF decreases for the post-task resting baseline comparing to pre-task resting baseline (Rest2–Rest1) and for the last quintile of the PVT comparing to first quintile of the PVT (PVTq5–PVTq1).

Regions	Cluster size	MNI coordinates			Peak Z	Peak p (corrected)
		x	y	z		
<i>(A) CBF decreases: Rest2–Rest1</i>						
R. anterior cingulate cortex, middle frontal gyrus, inferior frontal cortex	1008	18	48	10	5.12	0.005
		2	42	14	5.02	0.005
		18	38	6	4.98	0.005
L. superior temporal cortex	313	-54	-22	0	4.56	0.006
		-52	-34	10	4.29	0.009
R. inferior parietal lobe/cuneus	82	26	-56	28	4.48	0.007
L. anterior cingulate cortex	70	-12	44	12	4.40	0.008
R. superior temporal cortex	477	62	-32	8	4.12	0.011
L. middle frontal gyrus	46	-36	46	6	4.05	0.013
<i>(B) CBF decreases: PVTq5–PVTq1</i>						
B. posterior cingulate cortex	565	-6	-32	40	4.23	0.010
		2	-18	36	4.12	0.011
R. middle frontal gyrus	105	44	10	46	3.81	0.03

Thresholds were set as whole brain FDR corrected $p < 0.05$ and small volume corrected $p < 0.05$, respectively. L, left; R, right; B., bilateral.

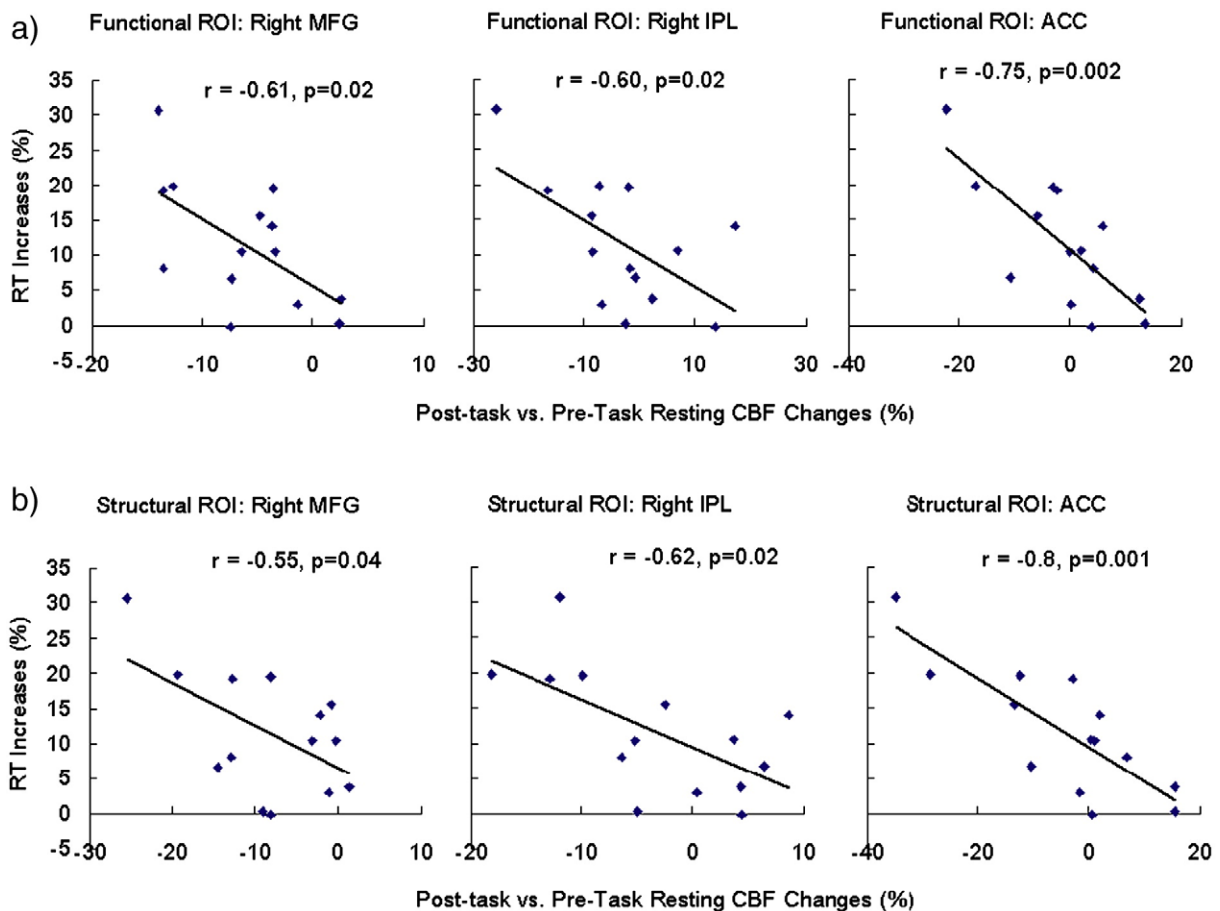


Fig. 4. Region of interest (ROI) analysis on the functional (a) and structural ROIs (b) showing that RT increases (%) during the PVT negatively correlated with post-task regional CBF changes in the ACC, right MFG, and right IPL.

No significant correlation was observed between self-reported mental fatigue changes and objective performance decline. Intuitively, one would imagine that the better-preserved performance is over time, the greater one's subjective sense of fatigue. Our data suggest that this is not the case. This finding is similar to the results from experiments by [Leprout et al. \(2003\)](#) and [Van Dongen et al. \(2003\)](#), in which there was no significant association between subjective and objective measures of alertness in a group of sleep-deprived subjects. Our finding further extended these results by demonstrating a similar dissociation in well-rested subjects, indicating that subjects may not be aware of the degree of their objective impairment after a period of high cognitive workload.

Although the PVT has been widely used for the accurate neurocognitive assessment of performance during sleep loss and the dynamic expression of waking neurobehavioral integrity, there have been relatively few studies on the brain mechanisms mediating PVT performance when compared to other attentional tasks. The only two neuroimaging studies on the PVT to date both employed an event-related BOLD fMRI design ([Drummond et al., 2005](#); [Schmidt et al., 2009](#)) and contrasted the hemodynamic responses of fast and slow (or average) reaction times to uncover the areas associated with optimal task performance. While this approach yielded some interesting results, it was not a method applicable to studying the process of sustained attention per se. Timely responding on a task of sustained attention may be determined by neural activity antecedent to stimulus onset, something which was not captured by the event-related analysis. Instead of focusing on phasic event-related responses, it is arguable that tonic activity throughout the task

block is a more meaningful marker of the level of vigilance displayed by a subject. While low-frequency artifacts in the BOLD spectrum make such a design impossible, ASL perfusion imaging is able to overcome this problem by canceling low-frequency noise through pair-wise subtraction of tagged and control images. Our current study of the PVT therefore overcomes the limitations associated with analysis of phasic events and gives us greater confidence that regions of activation are associated specifically with sustained attention.

Our ASL fMRI data revealed that performing the PVT engaged a right-lateralized fronto-parietal network of regions, which are reported regularly in tests requiring vigilance and continuous performance ([Cabeza and Nyberg, 2000](#)). Similar activation patterns have been reported in a variety of studies employing comparable attention tasks and different neuroimaging techniques, including monkey electrophysiology ([Colby et al., 1996](#)), human PET ([Corbetta et al., 1993](#); [Nobre et al., 1997](#); [Coull et al., 1998](#)) and fMRI ([Fan et al., 2005](#); [Ogg et al., 2008](#)). More interestingly, our results revealed significant associations between behavioral performance decline and regional CBF activity in the sustained attention network. Specifically, an individual's ability to preserve better performance over time (i.e., demonstrate less RT increase over the 20-min task) was associated with smaller CBF decreases in right MFG, right IPL and ACC from pre-task to post-task baseline and less thalamic and ACC CBF activation during PVT performance. Furthermore, pre-task resting CBF activity in the thalamus and right MFG predicted subsequent performance decline, with better-preserved performance being associated with lower pre-task resting CBF in right MFG and higher resting CBF in the thalamus. These key points of interest are discussed below.

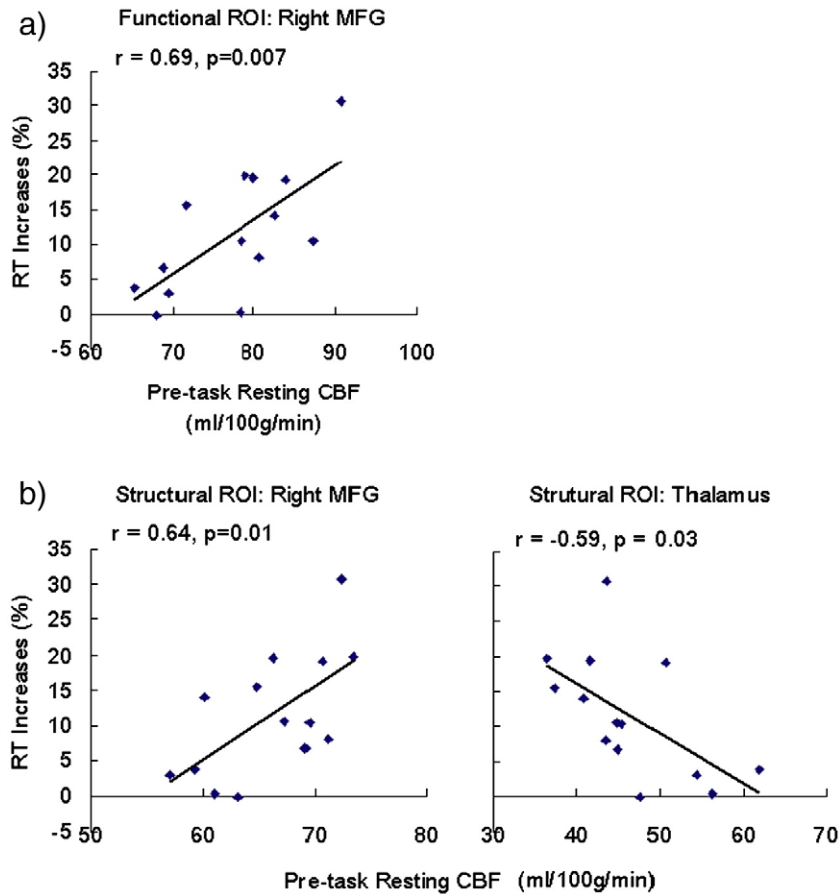


Fig. 5. Region of interest (ROI) analysis on the functional (a) and structural ROIs (b) showing that pre-task resting CBF in the right MFG and thalamus predicted RT increases (%) during the PVT.

Performance decline correlates with CBF decreases from pre- to post-task rest

The first key finding of this study is that brain fatigue in the right fronto-parietal network persists after a period of heavy mental work and that subjects' ability to maintain baseline levels of performance over time was correlated with CBF decrease from pre- to post-task resting activity in this attentional network. Areas in this network have long been established as important in the effortful maintenance of sustained attention (Lewin et al., 1996; Cabeza and Nyberg, 2000). However, our data extended the classic findings in two important ways.

First, we clearly showed that the residual effects of performing a fatiguing task on brain activity can be detected by ASL perfusion fMRI. Regional activity at rest following task completion decreased in the anterior cingulate cortex, middle prefrontal gyrus and inferior parietal cortex, suggesting that the brain does not immediately “reset” itself following task performance and cognitive resources depleted during demanding tasks cannot be restored within a 4-min post-task window. Second, we showed that larger RT increases were associated with greater post-task CBF decreases, indicating that subjects' ability to better preserve performance may depend on the stability of activity in the attentional system.

The CBF changes associated with time-on-task in our experiment are consistent with those found in previous studies (Paus et al., 1997; Coull et al., 1998), which showed decreases in cortical activation over time. In both of these paradigms, however, decreases in activation were suggested as implying shifts to automaticity. In contrast to oddball paradigms, the PVT demands rapid and timely responding to randomly presented stimuli, and it is not possible for subjects to adapt to the PVT by shifting from controlled to automatic processing and

still maintain optimal performance. We thus reject strategy shifts as a theoretical framework for understanding the changes observed in this experiment. Instead, we posit that there is a physiological ceiling to how well one can perform and that the speed at which these scarce attentional resources get depleted varies widely from person to person and depends on the demands of the task an individual is engaged in.

One possible alternative account of the data is that declines in performance and brain activity are dictated largely by decreasing motivation. Altering motivation by providing monetary incentives has been shown to modulate the time-on-task effect in college students (Tomprowski and Tinsley, 1996). It seems unlikely, however, that differences in motivation could entirely account for the substantial amount of variability in performance shown in our study. All of our subjects volunteered for the study and were paid and treated identically and were only required to perform a simple task with no element of motivation and reward. Nevertheless, certain individuals may “try” harder than others on tasks, based (for example) on individual differences in personality traits, and part of the variance captured in this experiment may reflect effort rather than physiological capacity. Future work is needed to test this hypothesis.

Resting baseline activity predicts subsequent performance decline

Another key finding from the present study was that resting CBF activity in the thalamus and right middle frontal gyrus prior to task onset was predictive of the extent to which subject's performance eventually declined. This result is analogous to various findings in the research on sleep deprivation suggesting that baseline activity is associated with cognitive vulnerability to periods of sleep loss. For

example, Mu and colleagues (2005) found in an fMRI study that sleep deprivation resilient individuals had a significantly greater number of activated voxels globally than sleep deprivation vulnerable individuals when performing a working memory test. Similarly, Caldwell et al. (2005) found that, in a group of well-rested pilots, global fMRI activation (and activation in the left posterior parietal cortex) to a Sternberg working memory task was correlated with subsequent performance measures on a flight simulator after they were sleep deprived.

Why would pre-task resting activity correlate with the level of vulnerability when the attentional system is challenged? We posit that differing levels of resting thalamic activity reflects individual differences related to the amount of sensory filtering the brain performs while in its baseline state. The thalamus has been implicated in worsening performance due to sleep deprivation (Thomas et al., 2000) and as a mediator of attention between different arousal states (Portas et al., 1998). It is conceivable, therefore, that its default state of activity should have some bearing on its efficiency during tasks that require its engagement. Similarly, the prefrontal cortex, an area with known connections to the thalamus, acts in concert with this region to carry out the early filtering of irrelevant information. Our data suggest that individuals for whom this system operates less efficiently at baseline may be less effective in the early selection of relevant information (reflected by lower baseline thalamic activity) and thus require greater top-down control (reflected by higher prefrontal activity) during later processing stages. Hence, when an additional load is placed on this neural system (as in the case of an attention-demanding task), subjects who are already performing near capacity have no spare neural resources and thus show the greatest deficits in performance.

Although it may be argued that resting levels of activity could reflect pre-existing levels of sleep debt, we contend that this was not the case, as we controlled for sleep history prior to the scanning session. We found that subjects were regular sleepers as assessed by the PSQI and neither scores on this questionnaire nor the Epworth Sleepiness Scale correlated with brain activity in any of the attentional regions. We posit therefore, that the observed variability in resting-state activation may reflect a fundamental individual difference trait. Recent perfusion studies showing resting baseline CBF correlating with habitual emotion regulation scores (Abler et al., 2008) and working memory capacity (Beschoner et al., 2008) also support this hypothesis.

Taken together, our main findings highlight the potential importance of resting-state CBF in assessing the degree of taxation on the brain's attentional system, a possibility that has been overlooked by the vast of previous neuroimaging studies for which pre- and post-task activity is taken merely as inseparable "baseline." Future work is needed to determine the time of course of recovery following a period of sustained activity, that is, how long the brain takes to return to its default resting state.

Task-induced activation did not correlate with performance decline

In contrast to the resting-state data, CBF changes during the task in the attentional network regions did not correlate with individual differences in performance decline. This may be due to the mixed CBF signal of both tonic and transient activity changes in this network detected by ASL perfusion while subjects are engaged in a cognitive task. In other words, phasic activity to stimulus responses may have activated regions that overlap with the attentional network (Drummond et al., 2005), thus adding noise to the tonic signal obtained from these areas in our analysis. In general, therefore, the magnitude of activation in perfusion imaging datasets acquired during cognitive task performance should be interpreted with caution, as it may reflect the contribution of multiple sources of variance.

Conclusion

This study demonstrates the utility of ASL perfusion imaging in revealing the neural network associated with tonic activity to a highly demanding sustained attention task. Our results demonstrate the critical role of the right fronto-parietal network in mediating time-on-task effects and that these effects persist and can be measured in the immediate aftermath of a period of heavy cognitive workload. Moreover, our findings reveal that differences in neural activity between the resting periods before and after the demanding task can act as markers of cognitive fatigue and thus contain useful information that has heretofore been neglected in the neuroimaging literature. Most interestingly, pre-task levels of CBF in the thalamus and right middle frontal gyrus appear to be meaningful predictors of subsequent time-on-task decline. These results may help identify neural "risk factors" for accidents and errors due to prolonged task performance and lead to greater safety and work efficiency in populations where fatigue is an ever-present problem.

Acknowledgments

This research was supported by NSF grants BCS 0224007 and 0517935, NIH grants P30 NS045839, R01 NR04281, National Space Biomedical Research Institute through NASA NCC 9-58 and Air Force Office of Scientific Research grant FA9550-05-1-0293.

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