NeuroImage 77 (2013) 105–113

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Distinct neural correlates of time-on-task and transient errors during a visuomotor tracking task after sleep restriction

Govinda R. Poudel [a,b,c,*], Carrie R.H. Innes [a,b], Richard D. Jones [a,b,d,e]

[a] New Zealand Brain Research Institute, Christchurch, New Zealand
[b] Department of Medical Physics and Bioengineering, Christchurch Hospital, Christchurch, New Zealand
[c] Monash Biomedical Imaging, Monash University, Australia
[d] Department of Electrical and Computer Engineering, University of Canterbury, Christchurch, New Zealand
[e] Department of Medicine, University of Otago, Christchurch, New Zealand

ARTICLE INFO

Article history:
Accepted 18 March 2013
Available online 1 April 2013

Keywords:
Sleep restriction
fMRI
Sleepiness
Lapses
Visuomotor tracking

ABSTRACT

Sleep loss leads to both time-on-task slowing of responsiveness and increased frequency of transient response errors. The consequences of such errors during real-world visuomotor tasks, such as driving, are serious and life threatening. To investigate the neuronal underpinning of time-on-task and transient errors during a visuomotor tracking task following sleep restriction, we performed fMRI on 20 healthy individuals when well-rested and when sleep-restricted while they performed a 2-D pursuit-tracking task. Sleep restriction to 4-h time-in-bed was associated with significant time-on-task decline in tracking performance and an increased number of transient tracking errors. Sleep restriction was associated with time-on-task decreases in BOLD activity in task-related areas, including the lateral occipital cortex, intraparietal cortex, and primary motor cortex. In contrast, thalamic, anterior cingulate, and medial frontal cortex areas showed overall increases irrespective of time-on-task after sleep-restriction. Furthermore, transient errors after sleep-restriction were associated with distinct transient BOLD activations in areas not involved in tracking task per se, in the right superior parietal cortex, bilateral temporal cortex, and thalamus. These results highlight the distinct cerebral underpinnings of sustained and transient modulations in alertness during increased homeostatic drive to sleep. Ability to detect neuronal changes associated with both sustained and transient changes in performance in a single task allowed us to disentangle neuronal mechanisms underlying two important aspects of sustained task performance following sleep loss.

Introduction

Loss of sleep leads to impaired alertness during sustained-attention tasks, which is manifested as transient errors (Chee et al., 2008; Dinges and Kribbs, 1991; Doran et al., 2001) and increased time-on-task related reduction in performance (Oken et al., 2006). These effects can be observed even when sleep is only reduced to 4–6 h in bed, particularly during monotonous conditions (Åkerstedt et al., 2005; Devoto et al., 1999; Stutts et al., 2003). Performance errors compromise individual and public safety, particularly in occupations which require continuous monitoring or visuomotor control, such as truck drivers, locomotive drivers, pilots, air-traffic controllers, and process-control workers (Sagberg, 1999).

A continuous visuomotor task, such as pursuit tracking, can be used to capture moment-to-moment changes in alertness (Huang et al., 2008; Peiris et al., 2006; Poudel et al., in press). A pursuit-tracking task is also a good surrogate of an everyday monitoring/visuomotor task, such as driving, which is difficult to deliver in an imaging environment, and has been used to detect effects of behavioural microsleeps and eye-closures during continuous tasks (Poudel et al., 2010, in press). In a continuous task, both transient and sustained changes in performance can be recorded in near real-time, allowing for detection of errors with a high temporal accuracy (Davidson et al., 2007; Huang et al., 2008; Peiris et al., 2011). Furthermore, such visuomotor tasks engage brain networks involved in attention, motor control, and eye–hand coordination (Grafton et al., 2008; Grefkes et al., 2004), allowing us to probe multiple pathways using a single task. The most dominant visuomotor pathway is the dorsal stream that connects the striate and extrastriate cortices to the posterior parietal area and has anterior projections into the frontal motor system (Nishitani et al., 1999). This pathway is involved in transformation of visual information into motor behaviour and is continuously engaged throughout visuomotor performance (Fogassi and Luppino, 2005). The attentional network has its origin in the prefrontal cortex and is involved in allocating attentional resource and biasing of attention towards a target via its top-down connections to the parietal and visual cortices (Desimone and Duncan, 1995; Kastner et al., 1998). The fronto-parietal attentional system tends to be more active during the early stages of a complex visuomotor task and shows a progressive decrease in activity with time-on-task (Floyer-Lea and Matthews, 2004).

* Corresponding author at: New Zealand Brain Research Institute, 66 Stewart Street, Christchurch, 8011, New Zealand. Fax: +64 3 3786080.
E-mail address: govinda.poudel@nzbri.org (G.R. Poudel).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.03.054

Sleep restriction increases time-on-task and transient errors or lapses during visuomotor tasks (Lim and Dinges, 2010). Given the multiple networks engaged during visuomotor tasks, it is reasonable to suggest that some of these networks are modulated by sleep-restriction. There have been no neuroimaging studies of visuomotor tracking following sleep loss, but studies measuring BOLD fMRI during discrete vigilance tasks, which require button presses following a stimulus, have reported localized modulation in frontal and parietal cortical attention regions and thalamic regions when attention and alertness are compromised following sleep loss (Chee et al., 2008; Chee and Tan, 2010; Drummond et al., 2005a; Tomasi et al., 2008). In particular, thalamic and visual processing capacity declines following sleep loss leading to attentional lapses during a selective attention task (Chee et al., 2008; Chee and Tan, 2010). Sleep loss also reduces the capacity to downregulate medial frontal and posterior cingulate activity leading to prolonged reaction times in a vigilance task (Drummond et al., 2005b). The cortico-thalamic alertness network also shows compensatory response to sleep loss not only during complex tasks (Drummond et al., 2001; Tomasi et al., 2008) but also during an awake but resting state (Poudel et al., 2012).

To identify neural correlates of both sustained and transient changes in alertness after sleep restriction, we scanned participants performing a blocked design fixation vs 2-D pursuit-tracking task during rested and sleep-restricted sessions. Specifically, we investigated effects of a single night of acute sleep-restriction on performance during a pursuit tracking task and on BOLD activity. We hypothesized that sleep-restriction would (1) increase both sustained and transient errors in performance, (2) alter the BOLD response in visuomotor and arousal networks with time-on-task, and (3) elicit a distinct pattern of BOLD responses during transient errors.

Materials and methods

Participants

Twenty right-handed volunteers (10 males and 10 females, aged 20 to 37 years, mean age 24.9 years) with no history of neurological, psychiatric, or sleep disorder participated in the study. For inclusion in the study, participants had to report a usual time to bed between 10 and 12 pm and a usual time in bed of between 7.0 and 8.5 h. Ethical approval for the study was obtained from the New Zealand Upper South B Regional Ethics Committee.

Study procedure

All participants visited the laboratory three times. On the first visit, they were briefed on the experimental protocol and provided with an Actiwatch (Respironics Inc., PA, USA) and a detailed sleep diary to record their sleep habits for 6 days and 5 nights prior to each of the two experimental sessions. They also recorded time of intake of caffeine, alcohol, and food in the diary. The second and third visits involved rested and sleep-restricted sessions, the order of which was counterbalanced across the participants. The sessions were 1 week apart to minimize residual effects of sleep restriction in participants who were sleep-restricted during the first session.

The participants were asked to sleep normal hours during the week prior to the rested session. They were asked to do likewise for the sleep-restricted session except for the immediately preceding night in which their time-in-bed was restricted to 4 h (3:00–7:00 am). Participants were requested not to engage in any safety-sensitive tasks (such as driving) following the sleep restriction. They were also asked not to consume any stimulants or depressants, such as alcohol, caffeine, and nicotine, on the day of either experimental session.

On the day of each scan, participants arrived at the laboratory an hour before the scanning session. Sleep habits recorded by the actiwatch and in the sleep diary were inspected prior to each of the scanning sessions to confirm compliance with the sleep schedule required for inclusion in the study. The sleep diary was used to confirm that participants did not consume any prohibited substances (caffeine and alcohol) on the day of scanning. Participants were provided with a lunch of hot noodles. They were also able to rate their current subjective sleepiness using the Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990) and Stanford Sleepiness Scale (SSS) (Hoddes et al., 1972) before entering the scanner room. Their self-rated propensity to fall asleep during the day was estimated using the Epworth Sleepiness Scale (ESS) (Johns, 1991). The participants entered the scanner between 1:00 pm and 2:30 pm.

Experimental task

Each participant undertook a 12-min pursuit-tracking task in a blocked design (Fig. 1). During each of the 12 30-s tracking epochs, they had to manoeuvre an MRI-compatible finger-based joystick (Current Designs, Philadelphia, PA, USA) to pursue a 2-D random target moving continuously on a computer screen (Fig. 1.). The target (yellow disc) and the joystick response (red disc), generated by a custom-designed software, were presented via MRI-compatible goggles (Avotec, Stuart, FL, USA) with a resolution of 1024 × 768 pixels and a field of view of 30° × 23°. The target waveform was pseudorandom in nature with period of 30 s so that the complexity of the target was the same for all 30-s epochs of tracking but varied within each block. During the 12 30-s fixation epochs, the participants fixated on a fixed target and response disc in the centre of the screen with a grey background. Participants were familiarized with the tracking task for 2 min both inside and outside the scanner. They were instructed to control the

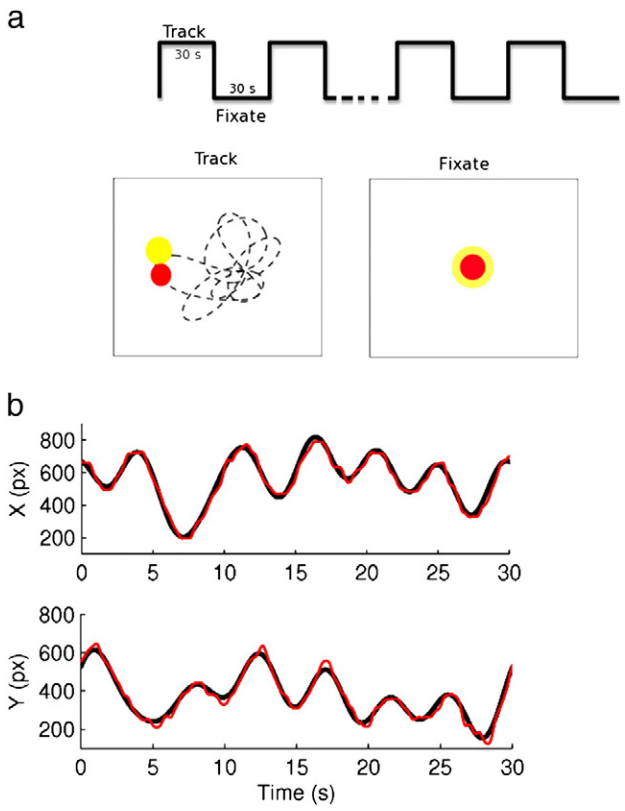

Fig. 1. The pursuit-tracking task. (a) During the 12 tracking blocks, participants used a finger-based joystick to track the displayed yellow target disc moving in a quasi-random trajectory (dotted line) with a red cursor disc. During the 12 fixation blocks, participants looked at the centre of the screen. (b) Accurate tracking led to the movement of the response disc along the same trajectory as the target disc as displayed in the target (smooth black line) and response (jerky red line) position for one cycle (30-s) of tracking. The units are in pixels (px).

joystick position so that the response disc was as close as possible to the centre of the moving target at all times. The nature of the tracking task was such that both sustained attention and finer visuomotor control were required to keep the response disc as close as possible to the target. Baseline periods involved motor grasps (to hold the joystick) and at least a low level of attention to keep fixation on the centre of the screen. Foam support was placed below the right elbow for subject comfort and to minimize hand movement during tracking. Eye-video was used to monitor participant wakefulness during the tracking task.

Imaging procedure

All subjects were imaged using a Signa HDx 3.0 T MRI Scanner (GE Medical Systems) with an eight-channel head coil. High-resolution anatomical images of the whole brain were acquired using T1-weighted anatomical scans (repetition time: 6.5 ms; echo time: 2.8 ms; inversion time: 400 ms; field of view: 250 × 250 mm; matrix: 256 × 256; slice thickness: 1 mm). Functional images were acquired using echo-planar-imaging (repetition time: 2.5 s; echo time: 35 ms; field of view: 220 × 220 mm; slice thickness: 4.5 mm; number of slices: 37, matrix: 64 × 64, number of repetitions: 293 TR). The first five images of each session were discarded to allow for T1 equilibration. A magnetic fieldmap was acquired for each subject to reduce the functional image distortions (echo time: 4.0 ms and 6.2 ms). Participants were provided with ear plugs to lessen the high-volume acoustic noise from the scanner.

Preprocessing of MRI data

The MRI data were preprocessed using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and custom Linux Shell and Matlab scripts (Matlab 7.6.0, R2008a, Mathworks, MA, USA). fMRI preprocessing included motion correction (Jenkinson et al., 2002), field map-based unwarping (Jenkinson, 2003), slice-time correction, spatial smoothing with a 7-mm Gaussian kernel (full width at half maximum), and high-pass filtering with a cut-off of 128 s. The structural images were registered to the MNI152 standard space using a non-linear registration tool (FNIRT). Registration parameters produced by the non-linear registration process were then used to warp the fMRI images into a standard $2 \times 2 \times 2$ mm^3 Montreal Neurological Institute (MNI) template.

Transient tracking errors

The positions of the response and target discs were continuously recorded at 60 samples/s. The time series of disc screen coordinates were converted into a tracking error time series, defined as the Euclidian distance between the target disc and response disc. To identify episodes of transient errors in performance within each 30-s block of tracking, second-to-second average tracking error was calculated and any time period in which the response disc was substantially far from the target disc (defined as tracking error > 2*Diameter of Target Disc (i.e., 50 px)) was marked as a transient error (Fig. 2). Tracking errors below 50 px were considered to be task-related errors. Task-related errors were normalized for complexity within task blocks by dividing the error time-series by a speed time series.

Data analysis

Subjective and objective performance data were analysed using parametric statistical tests. Paired t-tests were used to determine the effect of sleep-restriction on subjective sleepiness, average tracking performance, and transient errors in tracking. ANOVA was used to look for any interaction between time-on-task and prior-night-sleep state (rested vs. sleep-restricted) on tracking performance.

For each subject and session, general linear model (GLM) based analysis was used to identify the pattern of BOLD activity associated with the tracking task, task-related errors, and transient errors. The GLM comprised of: (i) two task regressors modelling BOLD activity during tracking versus fixation in the first half and second half of the 12-min tracking task, (ii) a normalized task-related error regressor modelling scan-to-scan BOLD fluctuations during scan-to-scan changes in tracking error, (iii) an impulse regressor to model episodes of transient error, (iv) a regressor modelling block-to-block changes in tracking error, and (iv) six motion parameters. Regressors modelling average BOLD activity during the first and second half of the 12-min tracking task were square waves with unit height during tracking blocks and zeros during fixation blocks. The normalized tracking error regressor modelled average error during tracking for each TR (2.5 s) divided by average target speed during that time. Time periods during which transient error (>2 * target diameter) occurred were also excluded from the normalized task-related error regressors. The normalized tracking error regressor was demeaned so that it only captured error-related activity and was orthogonal to task-related regressors. The regressor modelling block-to-block changes in tracking error was used to model tonic changes in performance with amplitude during tracking blocks set to average error in tracking during the block (30 s) and amplitude during fixation set to zero. This regressor was also demeaned so that it only captured fluctuations in BOLD signal due to tonic changes in performance and was orthogonal to task-related regressors. Transient errors were modelled in subjects who had at least one transient error. Dummy regressors were used for subjects with no transient errors. All regressors were convolved with double-gamma haemodynamic response functions to model appropriate BOLD signal change. Appropriate contrasts were used to identify BOLD activity during the first and second half of the tracking task, the average activity during total task duration, the activity correlated with task-related errors, and the activity during transient errors.

A group-level analysis was carried out to investigate the effect of sleep-restriction on BOLD activity. FMRIBS's Local Analysis of Mixed Effects type 1 (FLAME 1, FSL) was used to estimate the group-level model which tested for the main effect and differences between sessions. Statistical maps were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P < 0.05$.

Region of interest (ROI) analyses were used to further probe the effects of time-on-task on task-related BOLD activity. ROIs from the dorsal stream, thalamus, anterior cingulate, and medial frontal cortex were selected as they represented key task-related and arousal-related brain areas. Parameter estimates from ROIs were subjected to a 2 × 2 ANOVA to investigate the effect of time (First Half vs Second Half) and session (Rested vs Sleep-restricted) on the BOLD signal. $P < 0.05$ was considered significant for the ROI analyses.

Results

Behaviour

Three subjects were excluded from analysis due to movement during fMRI scanning. Based on actigraphy analysis, we determined that the remaining participants ($N = 17$) had 7.84 ± 0.93 (mean ± SD) hours of sleep during the night before the rested scan and 3.55 ± 0.21 h of sleep before the sleep-restricted scan. Compared to the rested session, participants reported being more sleepy during the sleep-restricted session as assessed by both SSS (3.06 vs 1.76, paired *t*-test, $t_{16} = 6.15$, $P < 0.001$) and KSS (5.21 vs 2.88, $t_{16} = 6.43$, $P < 0.001$).

The number of transient errors increased following sleep restriction compared to the rested session (46.6 vs 16.52, $t_{16} = 2.42$, $P < 0.05$). There was a significant interaction ($F_{11,352} = 2.58$, $P < 0.01$) on average tracking error between session (rested/sleep-restricted) and time on task (see Fig. 2b). There was a time-on-task effect ($P < 0.05$) following sleep-restriction but not when rested.

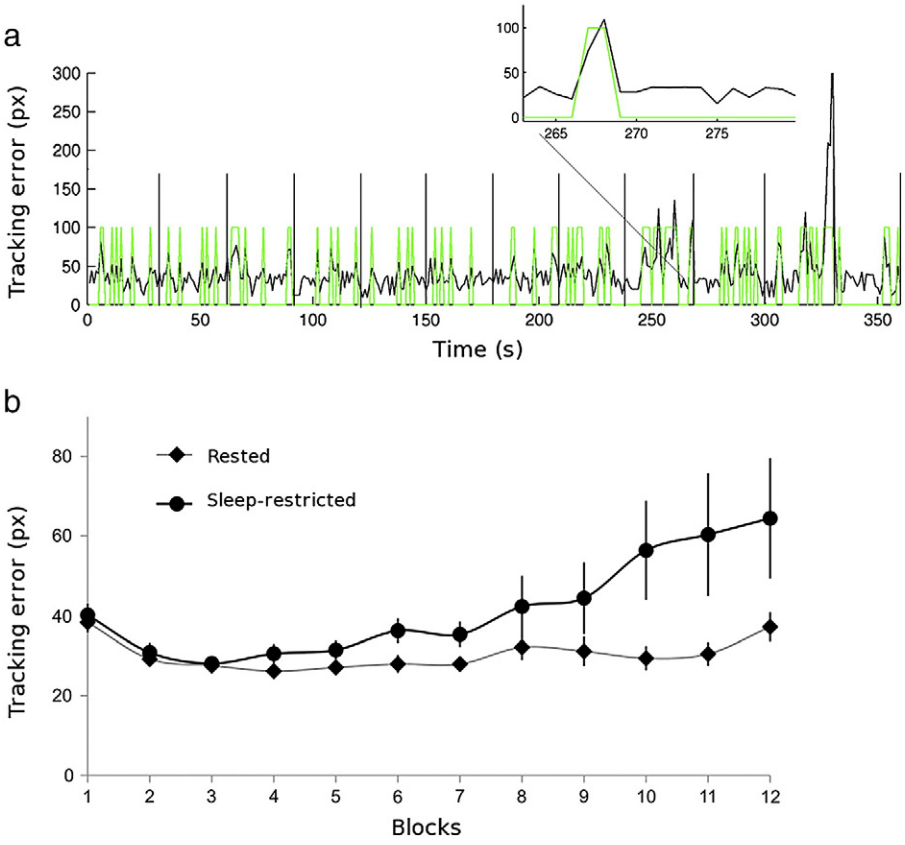

Fig. 2. Transient and sustained changes in performance. (a) The top panel (black line) depicts second-to-second changes in tracking error during tracking blocks in a representative subject. The green line indicates the location of transient errors. The vertical black lines indicate the onset of each block of tracking. The expanded inset illustrates the transient nature of the error identified as episodes with >2× diameter of target (i.e., >50 px) at time 267 s. (b) The bottom panel illustrates time-on-task effect in sustained tracking performance during sleep-restricted and rested conditions. The tracking errors in each block of tracking were averaged across subjects (N = 17) in each condition. The vertical bar represents standard error. The units are in pixels (px).

BOLD activity during tracking and effect of sleep restriction

In contrast to fixation, performance of the tracking task while rested increased ($Z > 2.3$, $P < 0.05$, cluster corrected for family-wise-error) brain BOLD activity bilaterally in a number of visual, motor and attentional regions (listed in Table 1). Bilateral cortical activity was observed in the lateral occipital cortex, superior parietal cortex, postcentral cortex, and precentral cortex (Fig. 3). Sub-cortical activity was observed in the bilateral thalamus, putamen, and cerebellum. The spatial pattern of activity during the tracking task in a sleep-restricted session was similar to that observed during the rested session. Deactivation ($Z > 2.3$, $P < 0.05$, cluster-corrected) during tracking was observed in the left inferior frontal gyrus in both rested and sleep-deprived sessions.

When activity while tracking during the sleep-restricted session was compared to activity while tracking when rested, greater activity was observed bilaterally in the thalamus, caudate, and right middle frontal and medial frontal areas following sleep restriction (Table 2). Whole-brain analysis did not show a significant decrease ($Z > 2.3$, $P < 0.05$, cluster-corrected) in average BOLD activity during the tracking task after sleep restriction.

Time-on-task effects on ROIs

A number of regions of interest were further probed to investigate the effect of time-on-task on average task-related activity (Fig. 4). Average activity in the first and last six blocks of tracking were compared during rested and sleep-restricted sessions using a 2 × 2 ANOVA. A significant time × session interaction was observed in the lateral occipital cortex (extrastriate) ($F_{1,16} = 21.6$, $P < 0.01$) and the superior parietal lobule ($F_{1,16} = 10.1$, $P < 0.01$). In contrast, the thalamus, anterior cingulate, and medial frontal gyrus ROIs showed only a significant effect ($P < 0.05$) of session in task-related BOLD activity. In the lateral occipital cortex, BOLD increased with time-

Table 1
Clusters showing increased BOLD activity during 2-D pursuit tracking compared to fixation at $Z > 3.8$, $P < 0.05$ (cluster-corrected). The brain regions with no corresponding cluster size are part of the larger cluster. The anatomical locations correspond to MNI coordinates (mm).

Brain regions	Peak Z	Cluster size (voxels)	MNI coordinates		
			x	y	z
Activations					
L. Postcentral gyrus	6.74	2860	−34	−38	44
R. Precentral gyrus	5.15		22	−24	56
R. Precentral gyrus	5.15		22	−24	56
L. Precentral gyrus	4.98		−22	−28	52
L. Superior parietal lobe	6.23	1229	−30	−56	46
L. Lateral occipital cortex	5.04		−20	−78	46
Supplementary motor area	5.36	973	6	−18	50
R. Cingulate gyrus	4.60	145	14	−32	32
L. Cingulate gyrus	4.61	162	−12	−32	36
R. Lateral occipital cortex	5.53	749	30	−70	46
L. Occipital fusiform gyrus	5.17	891	−36	−72	−10
L. Lateral inferior occipital cortex	4.49		−30	−86	2
R. Occipital fusiform gyrus	4.40	722	32	−78	−6
L. Putamen	6.05	1291	−20	−16	4
L. Thalamus	5.42		−16	−26	6
L. Lateral geniculate	4.80		−14	−16	−14
R. Putamen	5.14	627	24	−2	2
R. Thalamus	3.79		14	−20	2
Deactivations					
L. Inferior frontal gyrus	3.95	249	−50	28	16

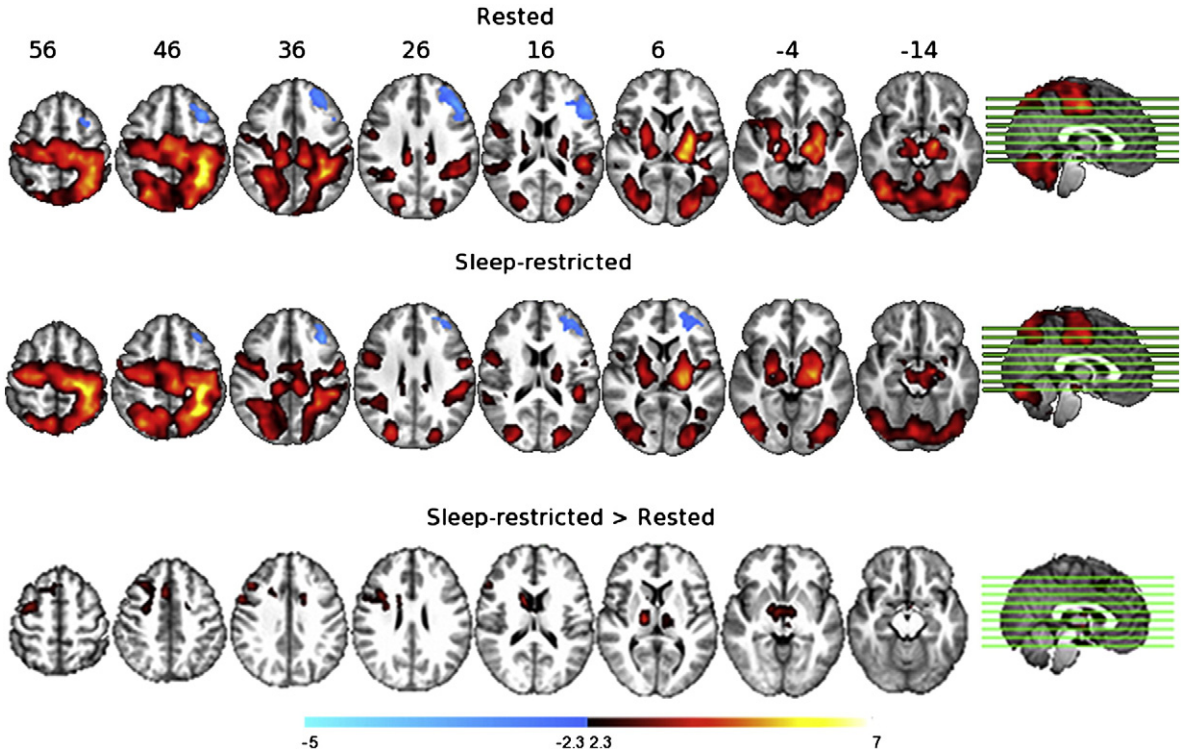

Fig. 3. Group-level significant (Z > 2.3, $p < 0.05$, family-wise-error corrected) pattern of activation during tracking when in the rested and sleep-restricted conditions. Spatial patterns of increased task-related BOLD activity when sleep-restricted compared to rested are shown in the third panel. Activations are shown overlaid on average structural slices. Red–yellow colour represents activation and blue–light blue colour represents deactivation during tracking. The group-level pattern was obtained from the 17 participants. The slices are presented in radiological convention.

on-task (P < 0.05) when rested but decreased (P < 0.01) with time-on-task when sleep-restricted. In the superior parietal cortex and primary motor cortex, BOLD decreased (P < 0.05) with time-on-task when sleep restricted but showed no change over time when rested.

Error-related activity

A positive correlation between task-related tracking error and BOLD signal was observed in the cortical visuomotor regions (listed in Table 3) during both rested and sleep-restricted sessions. The strongest modulation was observed in the lateral occipital, inferior temporal, and posterior parietal areas (Fig. 5). A group-level comparison revealed no significant difference between the rested and the sleep-restriction session after whole brain family-wise error correction.

Transient BOLD responses during transient tracking errors

Large transient tracking errors (>50 px) following sleep-restriction were modelled separately in subjects who had sufficient numbers (>10) of such errors (N = 12). When BOLD activity underlying these errors was analysed, we observed significant transient activity in both cortical and subcortical brain regions (Fig. 6). Clusters of transient activity were observed in the right superior parietal cortex, postcentral cortex, bilateral temporal cortex, and thalamus. The transient responses in the cortical areas followed a typical impulse BOLD response profile with a peak at approximately 10 s (Fig. 6). In contrast, thalamic activity showed a decreased BOLD signal immediately after the error onset, followed by hyperactivation.

Table 2
Increased BOLD activity during the tracking task following sleep-restriction. The clusters were identified by thresholding the statistical maps at Z > 2.6, P < 0.05 (cluster corrected). The anatomical locations correspond to MNI coordinates (mm).

Brain regions	Z	Cluster size (voxels)	MNI coordinates		
			x	y	z
R. Thalamus	4.00	823	14	−16	6
R. Caudate	3.79		14	8	16
L. Thalamus	2.80	67	−8	14	4
R. Middle frontal gyrus	3.72	215	44	24	38
R. Middle frontal gyrus	3.68		36	14	30

Discussion

This is the first study to have used neuroimaging to investigate changes in activation in the brain during a tracking task following sleep-restriction. This allowed us to reveal a distinct pattern of BOLD activity associated with time-on-task decline in performance and transient episodes of errors after sleep-restriction. We found that sleep-restriction led to opposing changes in BOLD activity in the posterior visuomotor and anterior arousal networks with time-on-task. That is, while the occipital cortex, superior parietal cortex, and primary motor areas all showed decreased activity with time-on-task after sleep-restriction, thalamic, anterior cingulate, and medial frontal areas showed an overall increase in BOLD signal. Furthermore, transient tracking errors observed after sleep-restriction were associated with impulse-type BOLD signals in a specific brain network encompassing posterior parietal, superior/middle temporal, and thalamic brain regions.

Total sleep-deprivation of a night or longer is associated with increased instability in distinct wake and sleep-promoting processes in the brain, resulting in impaired cognitive, psychomotor, and visuomotor behaviour (Devoto et al., 1999; Dinges and Kribbs, 1991; Dinges et al., 1997; Doran et al., 2001; Horne et al., 2003; Lim and Dinges, 2010; Tucker and Johns, 2005; Van Dongen et al., 2003). In this study, we observed that a less severe sleep-restriction of 4-hour time-in-bed causes a time-on-task deterioration in performance not seen when rested as well as increased transient errors during a short duration (12-min) monotonous visuomotor task. Increased time-on-task effects have been observed in previous studies, mainly after a night of total sleep

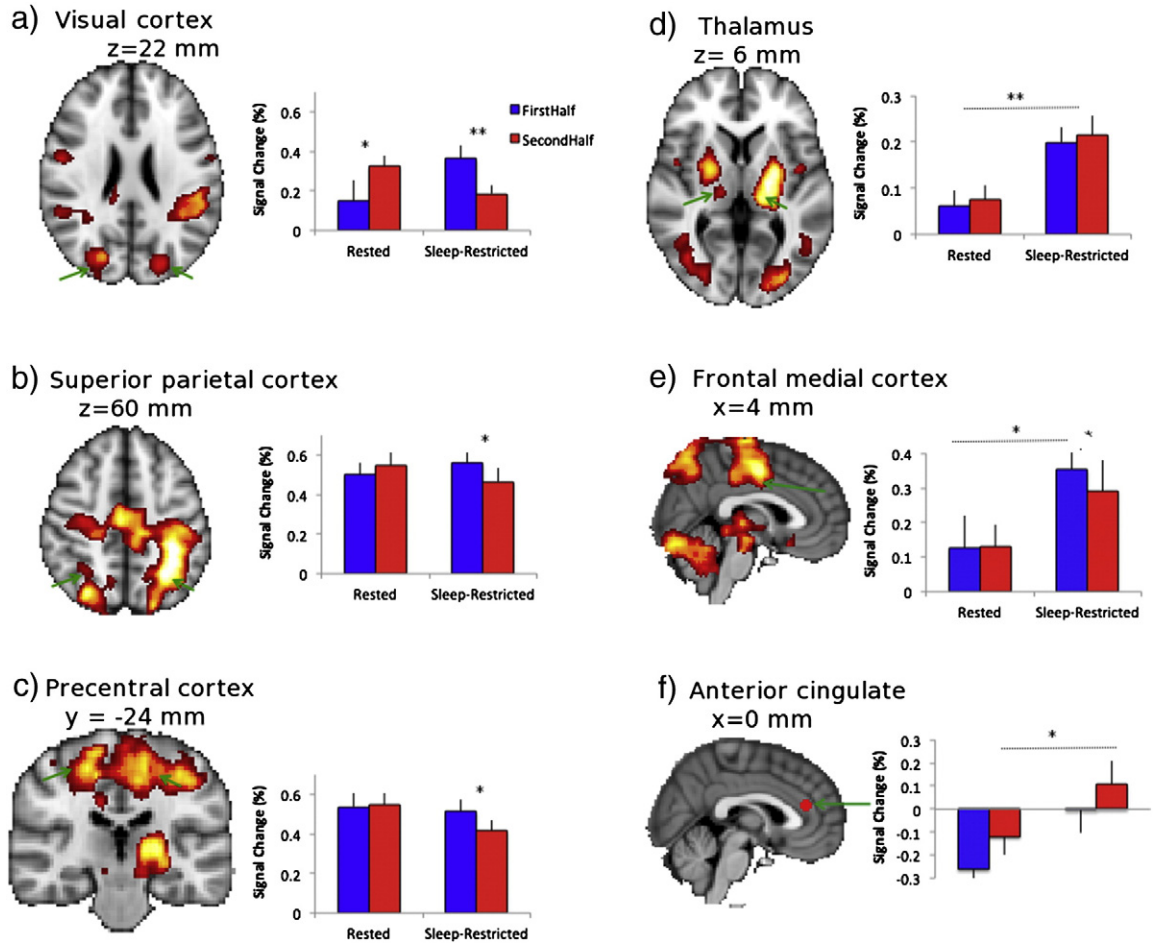

Fig. 4. Effect of time (First Half vs Second Half) and state (Rested vs Sleep-restricted) on task-related BOLD activity in the regions of interest. ROIs were centred on the local maxima brain regions of interest listed in Table 1 (and shown using green arrows). There was a significant interaction between effect of time (first half vs second half) and session (rested vs sleep-restricted) on task-related BOLD activity in the visual cortex. There was reduced activity in the second half of the tracking following sleep-restriction in the superior and precentral ROIs. Thalamic, anterior cingulate, and medial frontal ROIs showed increased activation but no significant interaction with time-on-task. *P < 0.05, **P < 0.01.

deprivation (Dinges and Kribbs, 1991; Lisper and Kjellberg, 1972; van der Hulst et al., 2001). Other studies have shown that time-on-task errors can appear early during monotonous tasks (Thiffault and Bergeron, 2003; Vakulin et al., 2007). In a driving task, which is similar to the task used in the current study, increased time-on-task was observed after 4 h of sleep (Vakulin et al., 2007).

Furthermore, sleep-restriction increased transient errors during tracking blocks. This is in-line with previous studies showing increased frequency of lapses following sleep loss (Anderson et al., 2010; Banks et al., 2010; Kamdar et al., 2004). Transient errors have been documented in previous studies of performance on an extended task, even when well-rested (Huang et al., 2008; Peiris et al., 2006; Poudel et al., in press). However, such transient errors when rested are often the result of fatigue on prolonged (>30 min) tasks. In contrast, the transient errors observed in a much shorter task in the current study are more likely to reflect a disturbed wake-sleep control system due to lack of sleep.

Table 3
Brain regions showing positive correlation between continuous tracking error and BOLD fMRI in the rested session. The clusters were identified by thresholding the statistical maps at Z > 3.2, P < 0.05 (cluster corrected). The anatomical locations correspond to MNI coordinates (mm).

Brain regions	Z	Cluster size (voxels)	MNI coordinates		
			x	y	z
L. Postcentral gyrus	4.18	477	−38	−24	48
R. Superior parietal lobe	3.51	441	32	−52	48
L. Lateral occipital cortex	3.65	402	−48	−68	−4
L. Superior parietal lobe	3.39	325	−28	−52	48
Supplementary motor area	3.65	235	2	−8	46
R. Lateral occipital cortex	4.33	180	26	−88	18
R. Precentral gyrus	4.60	139	32	−26	56
R. Postcentral gyrus	3.48	46	34	−26	52

The biological basis of the time-on-task effect is not well understood. A key finding from this study is of two divergent neural processes after sleep loss: (i) decreased activity in task-related cortical brain areas which is decreased further by time-on-task and (ii) increased thalamic and anterior cingulate activity which is time-on-task independent. The fronto-parietal attentional and thalamo-cortical arousal networks have long been established as important in the maintenance of sustained attention and arousal (Corbetta and Shulman, 2002; Sturm et al., 1999). Our data have extended our understanding of the role of these networks in several ways. First, BOLD fMRI has uncovered modulations of task-related neural activity with time-on-task. That is, in task-related visual, parietal, and frontal areas, sleep-restriction led to decreased BOLD activity following time-on-task, suggesting that the ability to respond to task demands is relatively intact in these areas during early phases of task performance even after restricted sleep. Previous studies suggest that, even when rested, increased task duration and repetition can deplete cognitive resources in these areas, ultimately increasing fatigue and time-on-task effects (Coull et al., 1998; Lim et al., 2010). On the other hand, sleep-restriction has a profound effect due to increased homeostatic drive to sleep, leading to early drowsiness in task-related areas and disruption in neural processes (Doran et al.,

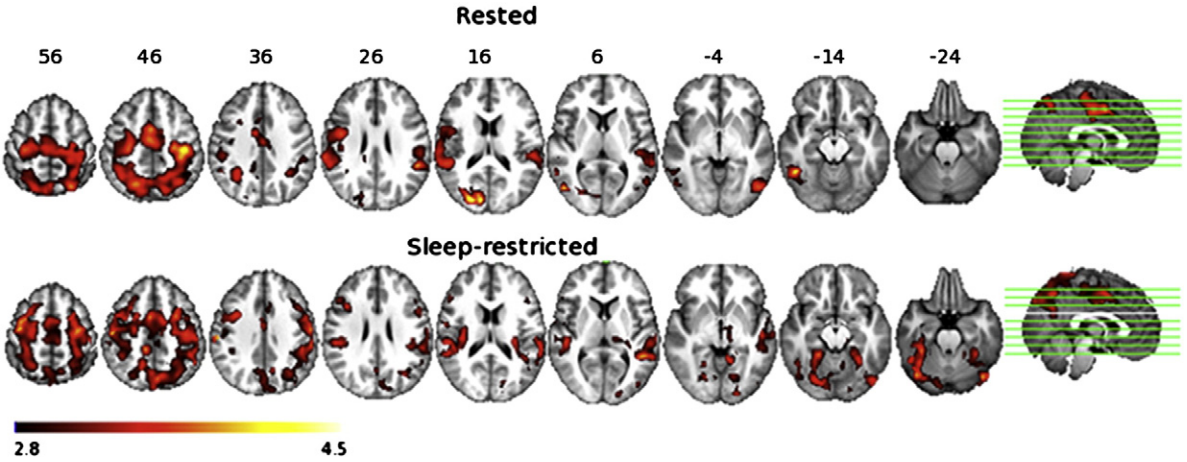

Fig. 5. Error-related brain activity. Brain regions showing a positive linear relationship ($Z > 2.8$, cluster $P < 0.05$, cluster-based FWE correction) between moment-to-moment tracking error and BOLD activity during blocks of tracking when rested and sleep-restricted. Activations are shown overlaid on average structural slices. The group-level pattern was obtained from the 17 participants. There was no significant difference in average error-related activity between rested and sleep-restricted sessions. The slices are presented in radiological convention.

2001; Van Dongen et al., 2011; Vyazovskiy et al., 2011). This effect is manifested in a sleep-deprived reduction in regional metabolism (Thomas et al., 2000; Thomas et al., 2003; Wu et al., 1991, 2006) and blood oxygenation signal (Chee et al., 2008; Chee and Tan, 2010; Drummond et al., 1999, 2005b; Mu et al., 2005; Tomasi et al., 2008) in task-related areas. However, most of these previous studies provided evidence for overall deactivation following total sleep deprivation in contrast to the current study where we observed only time-on-task related decline in activation in task-related areas. Lack of overall deactivation is likely to be due to the sleep-restriction protocol of 4-h time-in-bed not being enough to drive the deactivations. This notwithstanding, sleep-restriction protocol allowed us to observe both intact activation during earlier phase and reduced activation in the later phase, uncovering the dynamics of neural signal changes in a single task. It has also been suggested that, after sleep-deprivation, task performance is degraded by local, use-dependent sleep in neuronal groups, underpinning the cognitive processes associated with the task at hand (Van Dongen et al., 2011; Vyazovskiy et al., 2011). We postulate that the time-on-task decreases in visuomotor brain regions observed when sleep-restricted in the current study may be due to clustered local sleep in task-related neuronal population.

Second, the thalamo-cortical arousal network has increased activity during an active task after sleep-restriction irrespective of time on task. Although PET studies have reported decreases in thalamic activity after severe sleep deprivation of 24 h or more (Thomas et al., 2000; Wu et al., 1991, 2006), our finding is largely consistent with fMRI studies which have found increased thalamic response following sleep loss (Chee and Tan, 2010; Chuah et al., 2006; Portas et al., 1998; Tomasi et al., 2008). The thalamus is involved in mediating the interaction of attention and arousal during demanding tasks, with a greater level of attention-related activity in the thalamus following sleep deprivation (Portas et al., 1998; Tomasi et al., 2008). During a simple visual task after sleep loss, increased transmission has been observed in the thalamo-cortical cholinergic afferent network (Chuah and Chee, 2008). Therefore, it is likely that the increased BOLD response in thalamic, anterior cingulate, and medial frontal areas represents the sub-cortical drive to stay awake when local cortical areas go offline.

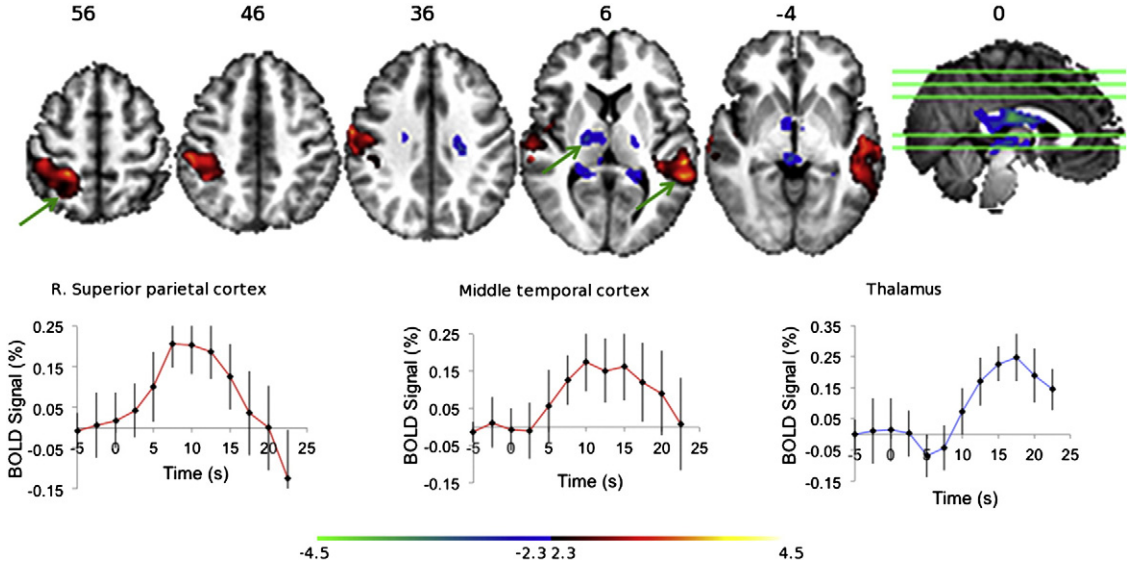

Fig. 6. Brain regions showing transient BOLD activity ($Z > 2.3$, $P < 0.05$, cluster-based FWE correction) during large transient tracking errors following sleep-restriction. The group-level pattern was obtained from the 12 participants with a sufficient number of transient errors. The average transient-error-related time-courses obtained from different regions illustrate the temporal nature of the activity. Transient BOLD activity was time-locked (at 0 s) to the onset of transient error. The vertical bars represent standard deviation in the average transient BOLD signal. Activations are shown overlaid on average structural slices.

The second key finding from the current study was that transient errors during tracking after sleep restriction are associated with distinct transient BOLD responses in cortical and thalamic areas. Although previous studies have reported that lapses during an attentional task can trigger increased BOLD activity in the frontoparietal cortex, possibly as a mechanism to compensate for less efficient perceptual processing (Chee et al., 2008; Weissman et al., 2006), these lapse-related activations were localized in the task-related areas. Here, we observed transient BOLD activations in bilateral temporal cortices and the right superior parietal cortex, which were not active during the task relative to resting fixation. In a previous study of lapses during tracking in rested participants (Poudel et al., in press), we showed that microsleeps generate transient BOLD signals in wide-spread cortical areas, including parietal visuomotor areas and the bilateral temporal cortices. In this study, we were not able to model transient errors during the well-rested condition due to insufficient transient errors. However, when transient tracking errors during sleep-restriction were modelled as orthogonal to task-related activation, distinct patterns of activity in the cortex and thalamus emerged. Furthermore, there were a number of differences in the temporal profile of the thalamic and cortical BOLD responses. While the cortical BOLD responses followed a typical impulse BOLD signal, the thalamic BOLD response had a strong initial deactivation followed by a hyperactivation, suggesting that thalamic activity largely decreases at the onset of error but increases during recovery phase. It is important to note that transient errors during lowered arousal can often be accompanied by other complex behavioural changes including slow-eye-closures and behaviours related to the recovery process, such as eye-movement and a large motor response. These behavioural changes have been associated with transient changes in BOLD signal in parietal and motor cortex (Ohlendorf et al., 2010; Poudel et al., 2010), the areas where some of the transient activations were observed in the current study. This notwithstanding, our findings suggest a complex interaction of events in the brain relating both to the causation of, and response to, substantial transient dips in performance during a tracking task.

A number of important factors should be considered in light of our results. Firstly, a blocked version of a pursuit tracking task was used instead of continuous pursuit tracking to enable measurement of relative change in BOLD signal due to task performance compared to baseline. The baseline period between tracking epochs may have provided periods of rest to the participants, hence reducing time-on-task effects and related BOLD signal change following sleep restriction. Secondly, due to the infrequent nature of brief-eye-closures, we did not systematically mark or investigate these episodes. Although transient errors during tracking were documented and modelled as events of interest, participants may have had microsleeps during the baseline, causing transient BOLD activations (Poudel et al., in press) and, hence, reducing relative signal change during tracking. Thirdly, we used six motion parameters as covariates to control for linear effects of motion on the BOLD signal. However, non-linear effects of motion on T2* were not accounted for in the analysis. Although careful consideration was given to reduce transient motions and jerks during tracking, even smaller motion may have induced artefactual relative signal change during both task and transient events. Notwithstanding, the time courses during transient events followed the profile of a typical BOLD signal, suggesting that transient activations were unlikely to be artefactual.

Taken together, our study provides a new insight into the cerebral correlates of time-on-task and transient errors after sleep-restriction. Different patterns of cerebral activation were found in both the occipito-parietal visuomotor and thalamo-cortical arousal networks following sleep restriction. Transient errors were also found to be associated with distinctive BOLD responses in cortical areas not directly related to the tracking task. These results suggest distinct cerebral underpinnings of sustained and transient modulations in alertness/responsiveness during the increased homeostatic drive to sleep.

Acknowledgments

This work was funded by grants from the Royal Society of New Zealand Marsden Fund, Canterbury Medical Research Foundation, Lottery Health Research, and Accident Compensation Corporation, New Zealand.

References

Akerstedt, T., Gillberg, M., 1990. Subjective and objective sleepiness in the active individual. Int. J. Neurosci. 52, 29–37.
Åkerstedt, T., Peters, B., Anund, A., Kecklund, G., 2005. Impaired alertness and performance driving home from the night shift: a driving simulator study. J. Sleep Res. 14, 17–20.
Anderson, C., Wales, A.W., Horne, J.A., 2010. PVT lapses differ according to eyes open, closed, or looking away. Sleep 33, 197–204.
Banks, S., Van Dongen, H.P., Maislin, G., Dinges, D.F., 2010. Neurobehavioral dynamics following chronic sleep restriction: dose–response effects of one night for recovery. Sleep 33, 1013–1026.
Chee, M.W., Tan, J.C., 2010. Lapsing when sleep deprived: neural activation characteristics of resistant and vulnerable individuals. Neuroimage 51, 835–843.
Chee, M., Tan, J., Zheng, H., Parimal, S., Weissman, D., Zagorodnov, V., Dinges, D., 2008. Lapsing during sleep deprivation is associated with distributed changes in brain activation. J. Neurosci. 28, 5519–5528.
Chuah, L.Y., Chee, M.W., 2008. Cholinergic augmentation modulates visual task performance in sleep-deprived young adults. J. Neurosci. 28, 11369–11377.
Chuah, Y., Venkatraman, V., Dinges, D., Chee, M., 2006. The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. J. Neurosci. 26, 7156.
Corbetta, M., Shulman, G., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 215–229.
Coull, J.T., Frackowiak, R.S.J., Frith, C.D., 1998. Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. Neuropsychologia 36, 1325–1334.
Davidson, P.R., Jones, R.D., Peiris, M.T.R., 2007. EEG-based lapse detection with high temporal resolution. IEEE Trans. Biomed. Eng. 54, 832–839.
Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193–222.
Devoto, A., Lucidi, F., Violani, C., Bertini, M., 1999. Effects of different sleep reductions on daytime sleepiness. Sleep 22, 336–343.
Dinges, D.F., Kribbs, N.B., 1991. Performing while sleepy: effects of experimentally-induced sleepiness. In: Monk, T.H. (Ed.), Sleep, Sleepiness, and Performance. John Wiley and Sons, Oxford, England, pp. 97–128.
Dinges, D.F., Pack, F., Williams, K., Gillen, K.A., Powell, J.W., Ott, G.E., Aptowicz, C., Pack, A.I., 1997. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. Sleep 20, 267–277.
Doran, S., Van Dongen, H., Dinges, D., 2001. Sustained attention performance during sleep deprivation: evidence of state instability. Arch. Ital. Biol. 139, 253–267.
Drummond, S.P., Brown, G.G., Stricker, J.L., Buxton, R.B., Wong, E.C., Gillin, J.C., 1999. Sleep deprivation-induced reduction in cortical functional response to serial subtraction. Neuroreport 10, 3745–3748.
Drummond, S.P.A., Gillin, J.C., Brown, G.G., 2001. Increased cerebral response during a divided attention task following sleep deprivation. J. Sleep Res. 10, 85–92.
Drummond, S.P.A., Meloy, M.J., Yanagi, M.A., Orff, H.J., Brown, G.G., 2005a. Compensatory recruitment after sleep deprivation and the relationship with performance. Psychiatry Res. Neuroimaging 140, 211–223.
Drummond, S.P.A., Grethe, A.B., Dinges, D., Ayalon, L., Mednick, S.C., Meloy, M.J., 2005b. The neural basis of the psychomotor vigilance task. Sleep 28, 1059–1068.
Floyer-Lea, A., Matthews, P.M., 2004. Changing brain networks for visuomotor control with increased movement automaticity. J. Neurophysiol. 92, 2405–2412.
Fogassi, L., Luppino, G., 2005. Motor functions of the parietal lobe. Curr. Opin. Neurobiol. 15, 626–631.
Grafton, S.T., Schmitt, P., Van Horn, J., Diedrichsen, J., 2008. Neural substrates of visuomotor learning based on improved feedback control and prediction. Neuroimage 39, 1383–1395.
Grefkes, C., Ritzl, A., Zilles, K., Fink, G.R., 2004. Human medial intraparietal cortex subserves visuomotor coordinate transformation. Neuroimage 23, 1494–1506.
Hoddes, E., Dement, W., Zarcone, V., 1972. The development and use of the Stanford Sleepiness Scale. Psychophysiology 9, 150.
Horne, J.A., Reyner, L.A., Barrett, P.R., 2003. Driving impairment due to sleepiness is exacerbated by low alcohol intake. Occup. Environ. Med. 60, 689–692.
Huang, R., Jung, T., Delorme, A., Makeig, S., 2008. Tonic and phasic electroencephalographic dynamics during continuous compensatory tracking. Neuroimage 39, 1896–1909.
Jenkinson, M., 2003. A fast, automated, n-dimensional phase unwrapping algorithm. Magn. Reson. Med. 49, 193–197.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841.
Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14, 540–545.
Kamdar, B.B., Kaplan, K.A., Kezirian, E.J., Dement, W.C., 2004. The impact of extended sleep on daytime alertness, vigilance, and mood. Sleep Med. 5, 441–448.
Kastner, S., De Weerd, P., Desimone, R., Ungerleider, L.G., 1998. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. Science 282, 108.

Lim, J., Dinges, D.F., 2010. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. Psychol. Bull. 136, 375–389.
Lim, J., Wu, W.C., Wang, J., Detre, J.A., Dinges, D.F., Rao, H., 2010. Imaging brain fatigue from sustained mental workload: an ASL perfusion study of the time-on-task effect. Neuroimage 49, 3426–3435.
Lisper, H.O., Kjellberg, A., 1972. Effects of 24-hour sleep deprivation on rate of decrement in a 10-minute auditory reaction time task. J. Exp. Psychol. 96, 287–290.
Mu, Q., Mishory, A., Johnson, K.A., Nahas, Z., Kozel, F.A., Yamanaka, K., Bohning, D.E., George, M.S., 2005. Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. Sleep 28, 433–446.
Nishitani, N., Uutela, K., Shibasaki, H., Hari, R., 1999. Cortical visuomotor integration during eye pursuit and eye–finger pursuit. J. Neurosci. 19, 2647–2657.
Ohlendorf, S., Sprenger, A., Speck, O., Glauche, V., Haller, S., Kimmig, H., 2010. Visual motion, eye motion, and relative motion: a parametric fMRI study of functional specializations of smooth pursuit eye movement network areas. J. Vis. 10, 21.
Oken, B., Salinsky, M., Elsas, S., 2006. Vigilance, alertness, or sustained attention: physiological basis and measurement. Clin. Neurophysiol. 117, 1885–1901.
Peiris, M.T.R., Jones, R.D., Davidson, P.R., Carroll, G.J., Bones, P.J., 2006. Frequent lapses of responsiveness during an extended visuomotor tracking task in non-sleep-deprived subjects. J. Sleep Res. 15, 291–300.
Peiris, M.T.R., Davidson, P.R., Bones, P.J., Jones, R.D., 2011. Detection of lapses in responsiveness from the EEG. J. Neural. Eng. 8, 1–15.
Portas, C., Rees, G., Howseman, A., Josephs, O., Turner, R., Frith, C., 1998. A specific role for the thalamus in mediating the interaction of attention and arousal in humans. J. Neurosci. 18, 8979–8989.
Poudel, G.R., Jones, R.D., Innes, C.R., Watts, R., Davidson, P.R., Bones, P.J., 2010. Measurement of BOLD changes due to cued eye-closure and stopping during a continuous visuomotor task via model-based and model-free approaches. IEEE Trans. Neural Syst. Rehabil. Eng. 18, 479–488.
Poudel, G.R., Innes, C.R.H., Jones, R.D., 2012. Cerebral perfusion differences between drowsy and nondrowsy individuals after acute sleep restriction. Sleep 35, 1085–1096.
Poudel, G.R., Innes, C.R.H., Watts, R., Bones, P., Jones, R.D., 2013. Losing the struggle to stay awake: divergent thalamic and cortical activity during behavioural microsleeps. Hum. Brain Mapp. http://dx.doi.org/10.1002/hbm.22178 (in press).
Sagberg, F., 1999. Road accidents caused by drivers falling asleep. Accid. Anal. Prev. 31, 639–649.
Sturm, W., Simone, A.d., Krause, B.J., Specht, K., Hesselmann, V., Radermacher, I., Herzog, H., Tellmann, L., Muller-Gartner, H.-W., Willmes, K., 1999. Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. Neuropsychologia 37, 797–805.
Stutts, J.C., Wilkins, J.W., Scott Osberg, J., Vaughn, B.V., 2003. Driver risk factors for sleep-related crashes. Accid. Anal. Prev. 35, 321–331.
Thiffault, Bergeron, J., 2003. Monotony of road environment and driver fatigue: a simulator study. Accid. Anal. Prev. 35, 381–391.
Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., Wagner, H., Thorne, D., Popp, K., Rowland, L., 2000. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. J. Sleep Res. 9, 335–352.
Thomas, M.L., Sing, H.C., Belenky, G., Holcomb, H.H., Mayberg, H.S., Dannals, R.F., Wagner, J., Henry, N., Thorne, D.R., Popp, K.A., 2003. Neural basis of alertness and cognitive performance impairments during sleepiness: II. Effects of 48 and 72 h of sleep deprivation on waking human regional brain activity. Thalamus Relat. Syst. 2, 199–229.
Tomasi, D., Wang, R.L., Telang, F., Boronikolas, V., Jayne, M.C., Wang, G.-J., Fowler, J.S., Volkow, N.D., 2008. Impairment of attentional networks after 1 night of sleep deprivation. Cereb. Cortex 19, 223–240.
Tucker, A., Johns, M., 2005. The duration of eyelid movements during blinks: changes with drowsiness. Sleep 28, A122.
Vakulin, A., Baulk, S.D., Catcheside, P.G., Anderson, R., van den Heuvel, C.J., Banks, S., McEvoy, R.D., 2007. Effects of moderate sleep deprivation and low-dose alcohol on driving simulator performance and perception in young men. Sleep 30, 1327–1333.
van der Hulst, M., Meijman, T., Rothengatter, T., 2001. Maintaining task set under fatigue: a study of time-on-task effects in simulated driving. Transp. Res. F Traffic Psychol. Behav. 4, 103–118.
Van Dongen, H., Maislin, G., Mullington, J., Dinges, D., 2003. The cumulative cost of additional wakefulness: dose–response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26, 117–126.
Van Dongen, H.P., Belenky, G., Krueger, J.M., 2011. A local, bottom-up perspective on sleep deprivation and neurobehavioral performance. Curr. Top. Med. Chem. 11, 2414–2422.
Vyazovskiy, V.V., Olcese, U., Hanlon, E.C., Nir, Y., Cirelli, C., Tononi, G., 2011. Local sleep in awake rats. Nature 472, 443–447.
Weissman, D., Roberts, K., Visscher, K., Woldorff, M., 2006. The neural bases of momentary lapses in attention. Nat. Neurosci. 9, 971–978.
Wu, J.C., Gillin, J.C., Buchsbaum, M.S., Hershey, T., Hazlett, E., Sicotte, N., Bunney, W.E., 1991. The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. Sleep 14, 155–162.
Wu, J.C., Gillin, J.C., Buchsbaum, M.S., Chen, P., Keator, D.B., Khosla Wu, N., Darnall, L.A., Fallon, J.H., Bunney, W.E., 2006. Frontal lobe metabolic decreases with sleep deprivation not totally reversed by recovery sleep. Neuropsychopharmacology 31, 2783–2792.