

# Influence of acute sleep loss on the neural correlates of alerting, orientating and executive attention components

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## SUMMARY

The Attention Network Test (ANT) is deemed to assess the alerting, orientating and executive components of human attention. Capitalizing on the opportunity to investigate three facets of attention in a single task, we used functional magnetic resonance imaging (fMRI) to assess the effect of sleep deprivation (SD) on brain responses associated with the three attentional components elicited by the ANT. Twelve healthy volunteers were scanned in two conditions 1 week apart, after a normal night of sleep (rested wakefulness, RW) or after one night of total sleep deprivation. Sleep deprivation was associated with a global increase in reaction times, which did not affect specifically any of the three attention effects. Brain responses associated with the alerting effect did not differ between RW and SD. Higher-order attention components (orientating and conflict effects) were associated with significantly larger thalamic responses during SD than during RW. These results suggest that SD influences different components of human attention non-selectively, through mechanisms that might either affect centrencephalic structures maintaining vigilance or ubiquitously perturb neuronal function. Compensatory responses can counter these effects transiently by recruiting thalamic responses, thereby supporting thalamocortical function.

## INTRODUCTION

A single night of sleep deprivation is detrimental to a number of cognitive abilities, ranging from phasic alertness (Doran *et al.*, 2001) to executive functions (Harrison *et al.*, 2000). Deteriorating attention is usually believed to participate in this decline in cognitive performance. However, attention is a heterogeneous concept (Oken *et al.*, 2006) and sleep deprivation has been shown to affect various aspects of attention, such as phasic alertness (Drummond *et al.*, 2005), selective (Horowitz *et al.*, 2003) and divided attention (Drummond *et al.*, 2001). A persistent issue is therefore whether sleep deprivation affects various components of attention selectively and differentially or whether the decrease in alertness is the core phenomenon that can explain the failure of the other attention systems (Lim and Dinges, 2010). Operational

definitions of vigilance, phasic alertness and attention are detailed in Data S1.

A cognitive model assumes that human attention is supported by three main functions which are associated specifically with independent brain circuits and neuromodulators (Posner and Petersen, 1990). Following this model, the alerting component is defined as the ability to prepare and sustain alertness to process high-priority signals (Posner and Petersen, 1990). It would involve thalamic, frontal and parietal areas (Fan *et al.*, 2005). The orientating component would allow one to attend to target items overtly or covertly, thereby improving their processing efficiency (Posner and Petersen, 1990). Orientating would involve the superior parietal lobe, temporo-parietal junctions and superior frontal cortex (Fan *et al.*, 2005). A third, executive attention component would be involved in conflict resolution and would recruit

the anterior cingulate cortex and the lateral prefrontal cortex (Fan *et al.*, 2005).

The attention network test (ANT) was designed to probe the efficiency of these three attention networks within a single task (Fan *et al.*, 2005). Therefore, it would be a particularly appropriate task to address whether sleep deprivation has a differential and selective influence on the various components of attention. In this study, using functional magnetic resonance imaging (fMRI) and a within-subject design, we assessed brain responses related to the three main effects (alerting, orientating and conflict effects) during rested wakefulness and after sleep deprivation.

## MATERIALS AND METHODS

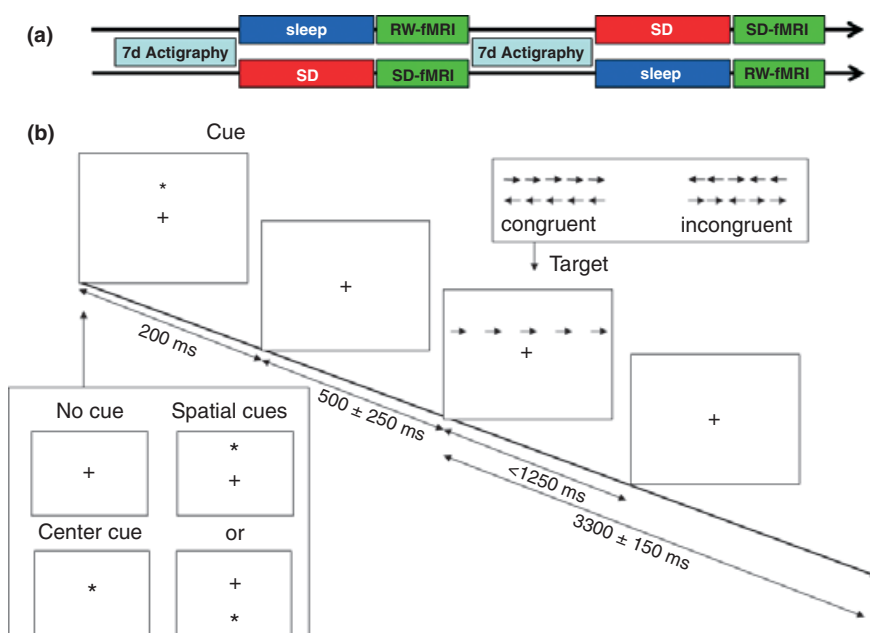
### Subjects

Young, healthy subjects ( $n = 14$ , seven female; age range 19–27 years; mean age = 21) gave their written informed consent to participate in this study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. They received financial compensation for their participation. An interview established the absence of medical, traumatic, psychiatric or sleep disorders. All volunteers were right-handed (Oldfield, 1971), free from medication, non-smokers and moderate caffeine and alcohol consumers. None had worked on night shifts during the previous year or travelled through more than one time zone during the last 2 months. Extreme morning and evening types, as assessed by the Horne–Ostberg questionnaire (Horne and Ostberg, 1976), were not included. None complained of excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale (score < 11) (Johns, 1991) or of sleep disturbances as determined by the Pittsburgh Sleep Quality Index Questionnaire (score < 7) (Buysse *et al.*, 1989).

### Protocol

Participants completed the protocol on two separate experimental days (Fig. 1a), 1 week apart. Before each visit, they followed a 7-day regular and individual sleep schedule, including an 8-h sleep period, as assessed by sleep diaries and wrist actigraphy (Actiwatch, Cambridge Neuroscience, UK). Two volunteers were excluded because they did not comply with this schedule. Volunteers were requested to refrain from caffeine- and alcohol-containing beverages and intense physical activity 7 days preceding each visit. At least a week before the first visit, a short behavioural training session outside the scanner familiarized the participants to the task.

During one of the visits [sleep deprivation (SD)], participants came to the laboratory in the evening (19:00 h) and spent the entire night in a dim light environment (<10 lux) under constant supervision by two staff members. They were allowed one snack every 3 h. They were kept in a sitting position except to visit the bathroom. In the morning, starting from 09:00 h, volunteers underwent an fMRI session during which they carried out the ANT. The scanning sessions took place between 09:00 h and 17:00 h, corresponding to a sleep deprivation of 25–33 h, depending on the volunteer. During this time, volunteers were monitored continuously by one experimenter. For the other visit [rested wakefulness (RW)], participants followed exactly the same protocol but after a normal night of sleep at home. For each volunteer, fMRI sessions took place at the same time of day during both visits. Half the participants started with the SD session, the other half with the RW session. Subjective sleepiness was estimated immediately before scanning using the Karolinska sleepiness scale (KSS; Åkerstedt and Gillberg, 1990).



**Figure 1.** (a) Experimental design. (b). Description of a trial.

## Task

The Attentional Network Task (ANT), developed originally by Fan and collaborators (Fan *et al.*, 2005), was adapted to fMRI acquisitions (Fig. 1b). Stimuli were coded using COGENT version 2000 (<http://www.vislab.ucl.ac.uk/cogent.php>) implemented in MATLAB version 6.1 (Mathworks Inc., Natick, MA, USA).

Participants were instructed to fixate the central cross for the entire experiment. Stimuli consisted of a row of five aligned horizontal black arrows ( $0.58^\circ$  in size, separated by  $0.06^\circ$ ; the five arrows row covered a total of  $3.27^\circ$ ), pointing either to the left or right, presented against a grey background,  $1.06^\circ$  above or below a fixation cross. The target, i.e. the central arrow, could point either in the same direction as the other four flanker arrows (congruent condition) or in the opposite direction (incongruent condition). The participants were asked to determine as quickly and accurately as possible the direction of the central arrow of a stimulus by pressing one of two buttons on a keyboard. In one-third of the trials, the stimulus was preceded by a visual cue (an asterisk) presented at the centre of the screen for  $550 \pm 250$  ms (central cue). In another third of the trials, the stimulus was preceded by a visual cue presented above or below the central fixation cross for  $550 \pm 250$  ms (spatial cue), which indicated that the five-arrow-stimulus would appear in the upper or lower part of the screen, respectively. The spatial cue was always predictive of the place where the target would appear. In the remaining third of the trials, the stimulus was not preceded by any visual cue (no cue condition). The stimulus was presented for a maximum of 1250 ms, disappearing when the response was made. The intertrial interval was set to  $3300 \pm 150$  ms. A total of 252 trials (36 for each trial type) were presented in random order and the fMRI session lasted approximately 21 min.

According to Fan *et al.* (2005), three attention components were evaluated behaviourally by measuring the influence of cue and target conditions on reaction times (RTs), relative to a reference condition:

- the alerting effect, by subtracting the mean RTs of the centre cue condition from the mean RT of the no cue condition;
- the orientating effect, by subtracting the mean RTs of the spatial cue condition from the mean RTs of the centre cue condition; and
- the conflict effect, by subtracting the mean RTs of all the congruent trials from the mean RTs of all the incongruent trials.

The objective of the fMRI analysis was to characterize the effects of SD on the alerting, orientating and conflict effects. Because SD was expected to affect attention processes, we considered the responses associated with optimal and global performance separately for RW and SD. Distributions of reaction times were computed separately for each of the six different trial types. We defined optimal performance as the condition corresponding to the trials associated with RTs

below the 30th percentile of the RT distribution during a given state (RW or SD). Global performance corresponded to the trials for RTs which were between the 30th and 70th percentiles. The slowest trials were above the 70th percentile of RTs. This strategy was adopted to eschew the problematic situation in which trials with the fastest response times are selected mainly from the sleep group, as would be observed if the RT distribution was computed across RW and SD conditions. The strategy also avoided some trials, corresponding to optimal vigilance during SD, being compared with intermediate RT trials in the RW condition.

## Behavioural analysis

Only accurate trials were included in the analyses. Trials were split into the fastest RTs (below the 30th percentile of all RTs), slowest RTs (above the 70th percentile) and intermediate RTs (between the 30th and 70th percentiles). For each trial class (percentile 30, intermediate, percentile 70), a repeated-measures analysis of variance (ANOVA) was conducted with 'condition' (RW versus SD), 'cue' (no cue versus centre cue versus spatial cue) and 'target' (congruent versus incongruent) as within-subject factors. Degrees of freedom were adjusted using the Greenhouse–Geisser method. Uncorrected *F*-values were reported together with the Greenhouse–Geisser epsilon and corrected *P*-values.

In a second analysis, alerting, orientating and conflict effects were derived by subtracting the mean RTs of each condition to its reference condition, as described above. A paired *t*-test was used to assess the session effect. Inferences were conducted at  $P < 0.05$  after Bonferroni correction for multiple comparisons ( $n = 3$ ).

## fMRI data acquisition and analysis

Magnetic resonance (MR) imaging was performed on a 3T MR scanner (Allegra, Siemens, Erlangen, Germany). Multi-slice T2\*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation (32 transverse slices; voxel size =  $3.4 \times 3.4 \times 3.0$  mm<sup>3</sup> with a 30% of interslice gap; matrix size =  $64 \times 64 \times 32$ ; TR/TE: 2130/40 ms; FoV:  $220 \times 220$  mm<sup>2</sup>; flip angle =  $90^\circ$ ). A high-resolution T1-weighted structural MR scan was obtained for each participant (3D MDEFT; 176 sagittal slices; TR/TE/TI: 7.92/2.4/910 ms; flip angle =  $15^\circ$ , field of view  $256 \times 224$  mm<sup>2</sup>, matrix size =  $256 \times 224 \times 176$ , voxel size =  $1 \times 1 \times 1$  mm<sup>3</sup>).

Functional volumes were preprocessed and analysed using Statistical Parametric Mapping (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB version 7.4.0 (Mathworks Inc.). The first three volumes were discarded to account for saturation effects. Images were realigned, coregistered to the structural image, normalized spatially to a template conforming to the Montreal Neurological Institute (MNI) space, and smoothed spatially with a Gaussian kernel of 8-mm full width at half maximum.

The fMRI data analysis, based on a mixed-effects model, was conducted in two serial steps, taking into account fixed and random effects (respectively, intra- and interindividual variance). At the first level, event types were defined according to the presence and position of the cue (no cue, central cue, 'spatial' cue), congruency of the target (congruent, incongruent) and the distribution of reaction times (<percentile 30, >percentile 70, intermediate RTs). This resulted in 18 different trial types. Two further trial types of no interest (error and lapses) were also included in the design matrix.

For each subject, changes in brain regional responses were estimated using a general linear model, in which the activity evoked by each trial type was modelled as a function representing its onset, convolved with a canonical haemodynamic response function. Movement parameters estimated during realignment and a constant vector were also included in the matrix as variables of no interest. High-pass filtering was implemented in the matrix design using a cutoff period of 128 s to remove low-frequency drifts from the time-series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus a white noise model and a restricted maximum likelihood algorithm.

Linear contrasts estimated the three main effects of interest (alerting, orientating, executive effects) for each session (sleep versus sleep deprivation) separately as well as the differences in these effects between sessions (i.e. the sleep status  $\times$  effect interaction) separately for each class of reaction times. We focused on the effects corresponding to the fastest and intermediate RTs. The slowest RTs, although modelled explicitly, were not investigated further, given that they could result from several potential factors [sleepiness, perceptual, attentional or executive deficit, task disengagement (Drummond *et al.*, 2005)]. With regard to behavioural analyses, trials associated with intermediate RTs (percentile  $30 < \text{RTs} < \text{percentile } 70$ ) were considered to be corresponding to an average alertness level, to which we will refer as 'global' alertness. In contrast, trials associated with the fastest RTs (RTs < percentile 30) relative to the intermediate RTs were denoted as an 'optimal' alertness level (Schmidt *et al.*, 2009). The resulting set of voxel values for each contrast constituted maps of the  $t$ -statistics [SPM(T)]. Summary statistic images were then further smoothed (6-mm FWHM Gaussian kernel) and entered into the second-level analysis, which corresponded to one-sample  $t$ -tests probing the experimental effects tested at the first level. Statistical inferences were performed after correction for multiple comparisons on small spherical volumes (SVC; 10-mm radius) at a threshold of  $P_{\text{SVC}} = 0.05$ , around a priori locations of activation in structures of interest, taken from the literature (see Tables 2–4).

## RESULTS

### Behavioural results

Subjective sleepiness was increased significantly in SD, relative to the RW condition (KSS, RW:  $2.41 \pm 0.79$ ; SD:

**Table 1** Mean reaction times [and standard deviations (SD) in milliseconds] for the different trial types during the two conditions

| Trial type              | Sleep deprivation |    | Rested wakefulness |    |
|-------------------------|-------------------|----|--------------------|----|
|                         | Mean              | SD | Mean               | SD |
| No cue congruent        | 612               | 77 | 560                | 63 |
| No cue incongruent      | 674               | 66 | 616                | 58 |
| Central cue congruent   | 570               | 61 | 532                | 60 |
| Central cue incongruent | 686               | 94 | 607                | 54 |
| Spatial cue congruent   | 575               | 87 | 515                | 59 |
| Spatial cue incongruent | 632               | 48 | 601                | 65 |

$5.33 \pm 1.55$ , paired  $t$ -test:  $t_{(11)} = 7.7$ ,  $P < 0.001$ ). All volunteers maintained a response accuracy of between 97 and 98% (percentage of given responses) in both conditions.

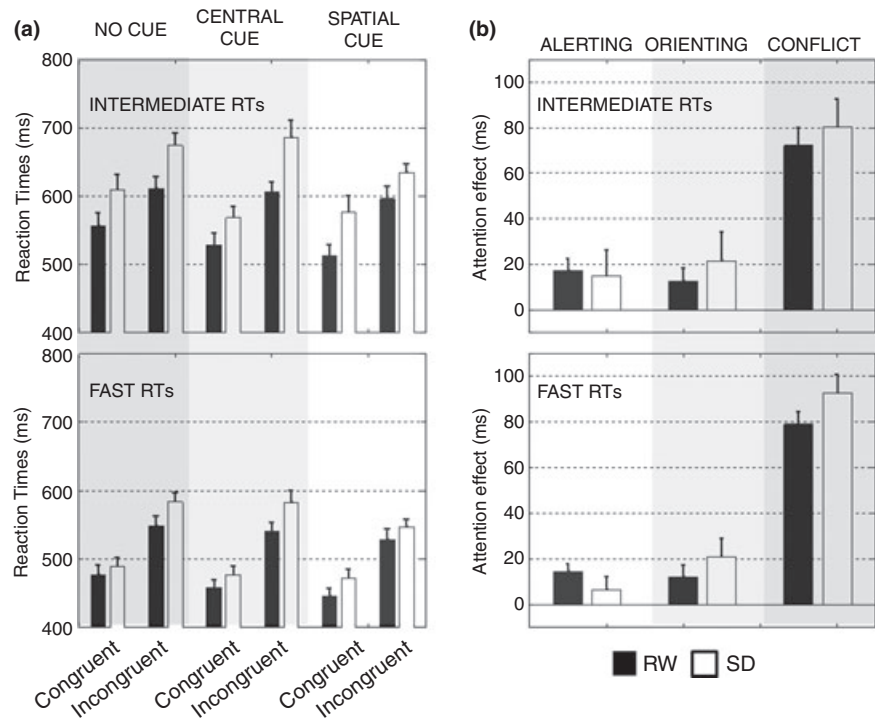
For the sake of completeness, we first detail the effects of sleep, cue and target conditions on RTs for intermediate, fast and slow trials. In a second step, statistics on the alerting, orientating and conflict effects are summarized for the three categories of RTs. Mean values and standard deviations of each trial type appear in Table 1.

For intermediate RTs (Fig. 2a), a repeated-measures ANOVA with session (RW versus SD), cue (no cue, central or spatial cue) and target (congruent versus incongruent) as within-subject factors showed a main effect of session ( $F_1 = 10.29$ ,  $P = 0.008$ ), cue ( $F_2 = 10.75$ ,  $P = 0.001$ ) and target ( $F_1 = 72.82$ ,  $P < 0.001$ ). The cue  $\times$  target interaction was significant ( $F_{(2,22)} = 6.09$ ,  $P = 0.008$ ,  $\epsilon = 0.82$ ), due to an unexpectedly smaller conflict effect in the no cue condition ( $F_{1,11} = 12.93$ ,  $P = 0.004$ ), independent of the sleep condition. The session  $\times$  cue and session  $\times$  target interactions were not significant ( $F_2 = 0.42$ ,  $P = 0.664$ ;  $F_1 = 0.73$ ,  $P = 0.410$ , respectively), whereas the session  $\times$  cue  $\times$  target interaction tended to be significant ( $F_2 = 3.80$ ;  $P = 0.06$ ,  $\epsilon = 0.67$ ).

For fast RTs (Fig. 2a), a repeated-measures ANOVA with session (RW versus SD), cue and target as within-subject factors showed a main effect of session ( $F_1 = 5.1$ ,  $P = 0.045$ ), cue ( $F_2 = 17.4$ ,  $P < 0.001$ ) and target ( $F_1 = 191.5$ ,  $P < 0.001$ ). The session  $\times$  target interaction was significant ( $F_1$ ,  $F = 5.0$ ,  $P = 0.048$ ), due to a larger difference in RTs between congruent and incongruent trials during SD, relative to the RW condition. The session  $\times$  cue, the cue  $\times$  target and the session  $\times$  cue  $\times$  target interactions were not significant ( $F_2 = 0.62$ ,  $P = 0.48$ ;  $F_1 = 1.57$ ,  $P = 0.23$ ;  $F_2 = 2.35$ ,  $P = 0.13$ ,  $\epsilon = 0.86$ ).

For slow RTs (not shown), a repeated-measures ANOVA with session, cue and target as within-subject factors showed a main effect of session ( $F_1 = 19.71$ ,  $P = 0.001$ ), cue ( $F_2 = 9.06$ ,  $P < 0.001$ ) and target ( $F_1 = 20.96$ ,  $P < 0.001$ ). None of the interactions were significant.

Essentially, these results showed a global slowing of RTs after SD, relative to RW, irrespective of the cue or target condition. The only exception was a larger effect of target incongruence during SD for the fastest responses. These



**Figure 2.** (a) Reaction times (ms) for each trial types, following cue and target conditions, during rested wakefulness (RW) and deprivation (SD). (b) Alerting, orientating and conflict effects (ms) during RW and SD. Black bars: RW; white bars: SD. Error bars stand for standard error of the mean. Statistical results are detailed in the text.

results do not provide compelling evidence for a selective and differential effect of SD onto the different attention components.

To investigate this aspect further, we analysed the effect of SD on alerting, orientating and conflict effect (Fig. 2b). This analysis corresponded to the effects investigated in fMRI. There was no significant change in any of these effects from RW to SD (alerting effect,  $P = 0.93$ ; orientating effect,  $P = 0.94$ ; conflict effect,  $P = 0.61$ ). Again, these results indicate that sleep deprivation slowed RTs globally in every trial category.

### Functional MRI results

First, we report the neural correlates of the alerting, orientating and conflict effects during the RW session, to allow for comparison with the literature. For this analysis, all trials (i.e. fast, intermediate and slow RTs) were considered together. In a second step, we address the effects of sleep deprivation. Because of the performance instability that characterizes sleep deprivation, these contrasts assessed fast and intermediate trials separately. Therefore, we detail separately the responses for the three attention effects, for fast and intermediate trials, during RW and SD sessions. Finally, we describe separately the session  $\times$  effects interaction (i.e. between-session comparisons) for each attention effect, for fast and intermediate trials. Results are summarized in Tables 2–4.

#### Responses during rested wakefulness – all trials

The alerting effect was associated with a distributed set of brain areas, including bilateral occipito-temporal regions,

right anterior inferior frontal gyrus, medial prefrontal cortex and left intraparietal sulcus (Table 2). The orientating effect elicited a significant response in the posterior middle frontal gyrus. Finally, the conflict effect was associated with significant responses in bilateral occipito-temporal areas, left inferior and posterior frontal gyrus, left precentral gyrus and left superior parietal cortex.

#### Responses during rested wakefulness and sleep deprivation – intermediate trials

During RW, the alerting effect was associated with significant responses in the right inferior frontal gyrus, the right superior temporal sulcus and in bilateral temporo-occipital cortices (Table 3). In contrast, no significant response survived correction for multiple comparisons during the SD sessions. This is related probably to a larger signal variance: at a lenient threshold ( $P_{\text{uncorrected}} < 0.001$ ), responses were detected in the same bilateral occipito-temporal areas as during wakefulness. In addition, no region showed a differential alerting effect between sessions (RW  $>$  SD or SD  $>$  RW).

During RW, the orientating effect was associated with responses in the left temporo-parietal junction and the precuneus (Fig. 4). In contrast, during SD, the orientating effect resulted in a significant response in the right thalamus. The only difference in response between sessions was a larger right thalamic response during SD, relative to RW.

The conflict effect was related to response in the left intraparietal sulcus during RW and in the left temporo-occipital cortex and left thalamus during SD. Similarly to the

**Table 2** Results obtained during rested wakefulness (RW) (all trials included)

| Area                                | x   | y   | z  | Z-score | P <sub>svc</sub> | References                    |
|-------------------------------------|-----|-----|----|---------|------------------|-------------------------------|
| <b>Alerting effect</b>              |     |     |    |         |                  |                               |
| R. lateral temporo–occipital cortex | 48  | –68 | 6  | 3.88    | 0.011            | (Coull <i>et al.</i> , 2001)  |
| L. lateral temporo–occipital cortex | –42 | –66 | 6  | 4.19    | 0.004            | (Fan <i>et al.</i> , 2005)    |
| R. superior medial frontal cortex   | 4   | 32  | 34 | 3.51    | 0.030            | (Fan <i>et al.</i> , 2005)    |
| R. inferior frontal gyrus           | 50  | 28  | 4  | 3.42    | 0.038            | (Konrad <i>et al.</i> , 2005) |
| L. anterior intraparietal sulcus    | –30 | –42 | 34 | 4.21    | 0.004            | (Thiel <i>et al.</i> , 2004)  |
| <b>Orientating effect</b>           |     |     |    |         |                  |                               |
| Left MFG                            | –44 | 2   | 48 | 3.16    | 0.049            | (Thiel <i>et al.</i> , 2004)  |
| <b>Conflict effect</b>              |     |     |    |         |                  |                               |
| R. occipito–temporal cortex         | 44  | –60 | –2 | 3.47    | 0.033            | (Fan <i>et al.</i> , 2005)    |
| L. occipito–temporal cortex         | –46 | –68 | –2 | 3.31    | 0.049            | (Fan <i>et al.</i> , 2005)    |
| L. inferior frontal sulcus          | –34 | 32  | –4 | 3.25    | 0.05             | (Konrad <i>et al.</i> , 2005) |
| L. precentral gyrus                 | –36 | –10 | 50 | 3.64    | 0.022            | (Fan <i>et al.</i> , 2005)    |
| L. superior parietal cortex         | –44 | –36 | 52 | 3.31    | 0.049            | (Coull <i>et al.</i> , 2001)  |

Coordinates (x, y, z) are expressed in mm in the Montreal Neurological Institute (MNI) space. P<sub>svc</sub>: probability of rejecting the null hypothesis of no activation after correction for multiple comparisons over small volumes of interest taken from the literature (reference in the last column). R., right; L., left; MFG, Middle Frontal Gyrus.

**Table 3** Results obtained during rested wakefulness (RW) and deprivation (SD) (intermediate trials)

| Area                                 | x   | y   | z  | Z-score | P <sub>svc</sub> | References                   |
|--------------------------------------|-----|-----|----|---------|------------------|------------------------------|
| <b>Alerting effect RW</b>            |     |     |    |         |                  |                              |
| R. inferior frontal gyrus            | 44  | 22  | 18 | 3.29    | 0.046            | (Fan <i>et al.</i> , 2005)   |
| R. superior temporal sulcus          | 52  | –46 | 12 | 4.31    | 0.003            | (Fan <i>et al.</i> , 2005)   |
| R. lateral temporo–occipital cortex  | 50  | –70 | 2  | 4.17    | 0.004            | (Coull <i>et al.</i> , 2001) |
| L. lateral temporo–occipital cortex  | –42 | –68 | 6  | 3.88    | 0.010            | (Fan <i>et al.</i> , 2005)   |
| <b>Orientating effect RW</b>         |     |     |    |         |                  |                              |
| L. precuneus                         | –16 | –50 | 34 | 3.47    | 0.050            | (Thiel <i>et al.</i> , 2004) |
| L. temporo–parietal junction         | –58 | –60 | 35 | 3.45    | 0.050            | (Coull <i>et al.</i> , 2001) |
| <b>Orientating effect SD</b>         |     |     |    |         |                  |                              |
| R. thalamus                          | 8   | –16 | 0  | 3.24    | 0.036            | (Fan <i>et al.</i> , 2005)   |
| <b>Orientating effect SD &gt; RW</b> |     |     |    |         |                  |                              |
| R. thalamus                          | 8   | –16 | 0  | 5.45    | 0.032            | (Fan <i>et al.</i> , 2005)   |
| <b>Conflict effect RW</b>            |     |     |    |         |                  |                              |
| L. intraparietal sulcus              | –26 | –48 | 50 | 3.40    | 0.039            | (Coull <i>et al.</i> , 2001) |
| <b>Conflict effect SD</b>            |     |     |    |         |                  |                              |
| L. temporo–occipital cortex          | –42 | –68 | –6 | 3.77    | 0.039            | (Coull <i>et al.</i> , 2001) |
| L. thalamus                          | –14 | –28 | 8  | 3.24    | 0.05             | (Fan <i>et al.</i> , 2005)   |
| <b>Conflict effect SD &gt; RW</b>    |     |     |    |         |                  |                              |
| R. thalamus                          | 18  | –28 | 4  | 3.92    | 0.01             | (Fan <i>et al.</i> , 2005)   |
| L. thalamus                          | –12 | –26 | 4  | 3.28    | 0.05             | (Fan <i>et al.</i> , 2005)   |

Coordinates (x, y, z) are expressed in mm in the Montreal Neurological Institute (MNI) space. P<sub>svc</sub>: probability of rejecting the null hypothesis of no activation after correction for multiple comparisons over small volumes of interest taken from the literature (reference in the last column). R., right; L., left.

orientating effect, the only difference in responses between sessions was a larger conflict-related activity in bilateral thalamic nuclei during SD, relative to RW (Fig. 5).

#### *Responses during rested wakefulness and sleep deprivation – fast trials*

Similarly to intermediate responses, fast responses corresponding to the alerting effect during RW were associated with increased activity in the bilateral occipito–temporal areas

and right superior temporal gyrus (Fig. 3, Table 4). No significant response was observed during SD, except at a lenient threshold ( $P_{\text{uncorrected}} < 0.001$ ) in the left occipito–temporal cortex. Alerting-related activity in the left precuneus and the right temporo–parietal junction was larger during RW than SD (Fig. 3), whereas no region was more active during SD than RW.

In contrast, for the orientating effect, significant brain activity was detected only during SD in the left temporo–parietal junction and the precuneus (Fig. 4). Intriguingly, these

**Table 4** Results obtained during rested wakefulness (RW) and deprivation (SD) (fast trials)

| Area                                 | x   | y   | z  | Z-score | P <sub>SVC</sub> | References                   |
|--------------------------------------|-----|-----|----|---------|------------------|------------------------------|
| <b>Alerting effect RW</b>            |     |     |    |         |                  |                              |
| R. lateral temporo-occipital cortex  | 42  | -76 | -4 | 3.53    | 0.025            | (Coull <i>et al.</i> , 2001) |
| L. lateral temporo-occipital cortex  | -48 | -60 | 6  | 3.49    | 0.028            | (Fan <i>et al.</i> , 2005)   |
| R. superior temporal gyrus           | 68  | -36 | 16 | 3.65    | 0.019            | (Fan <i>et al.</i> , 2005)   |
| <b>Alerting effect RW &gt; SD</b>    |     |     |    |         |                  |                              |
| L. precuneus                         | -16 | -56 | 36 | 3.72    | 0.014            | (Thiel <i>et al.</i> , 2004) |
| R. temporo-parietal junction         | 52  | -66 | 18 | 3.53    | 0.024            | (Thiel <i>et al.</i> , 2004) |
| <b>Orientating effect SD</b>         |     |     |    |         |                  |                              |
| L. temporo-parietal junction         | -48 | -64 | 24 | 4.3     | 0.002            | (Coull <i>et al.</i> , 2001) |
| L. precuneus                         | -10 | -68 | 44 | 3.28    | 0.044            | (Thiel <i>et al.</i> , 2004) |
| <b>Orientating effect SD &gt; RW</b> |     |     |    |         |                  |                              |
| L. temporo-parietal junction         | -46 | -62 | 20 | 3.75    | 0.015            | (Coull <i>et al.</i> , 2001) |
| <b>Conflict effect SD &gt; RW</b>    |     |     |    |         |                  |                              |
| L. thalamus                          | -6  | -6  | 12 | 3.47    | 0.032            | (Fan <i>et al.</i> , 2005)   |

Coordinates (x, y, z) are expressed in mm in the Montreal Neurological Institute (MNI) space. P<sub>SVC</sub>: probability of rejecting the null hypothesis of no activation after correction for multiple comparisons over small volumes of interest taken from the literature (reference in the last column). R., right; L., left.

areas correspond to those associated with intermediate responses during RW. Responses in the left temporo-parietal area were larger during SD than during RW, whereas no region had a larger orientating-related activity during RW, relative to SD.

Bold responses did not differ between congruent and incongruent trials (conflict effect), either in RW or in SD. Thalamic responses associated with the fastest trials were increased significantly during SD relative to RW (Fig. 5).

## DISCUSSION

We used the ANT to test whether sleep deprivation would influence differentially the alerting, orientating and executive components of attention. Behavioural data did not support this hypothesis and essentially showed a global slowing of RTs for all trial types. Only the conflict effect associated with the fastest RTs was enhanced during SD, relative to RW condition. Functional MRI data did not show significant between-session changes in responses related to the alerting effect, except for those associated with the fastest RTs, which were characterized by increased activity during RW in the precuneus and right temporo-parietal junction. For the orientating effect, the precuneus and left temporo-parietal junction, which were activated during RW, could still be recruited during SD, but only when an optimal alertness level could be achieved. The orientating effect during SD was supported by an enhanced recruitment of the thalamus (intermediate RTs) and right temporo-parietal region (fastest RTs). The conflict effect was also associated with increased thalamic responses during SD relative to RW, for both intermediate and fast RTs.

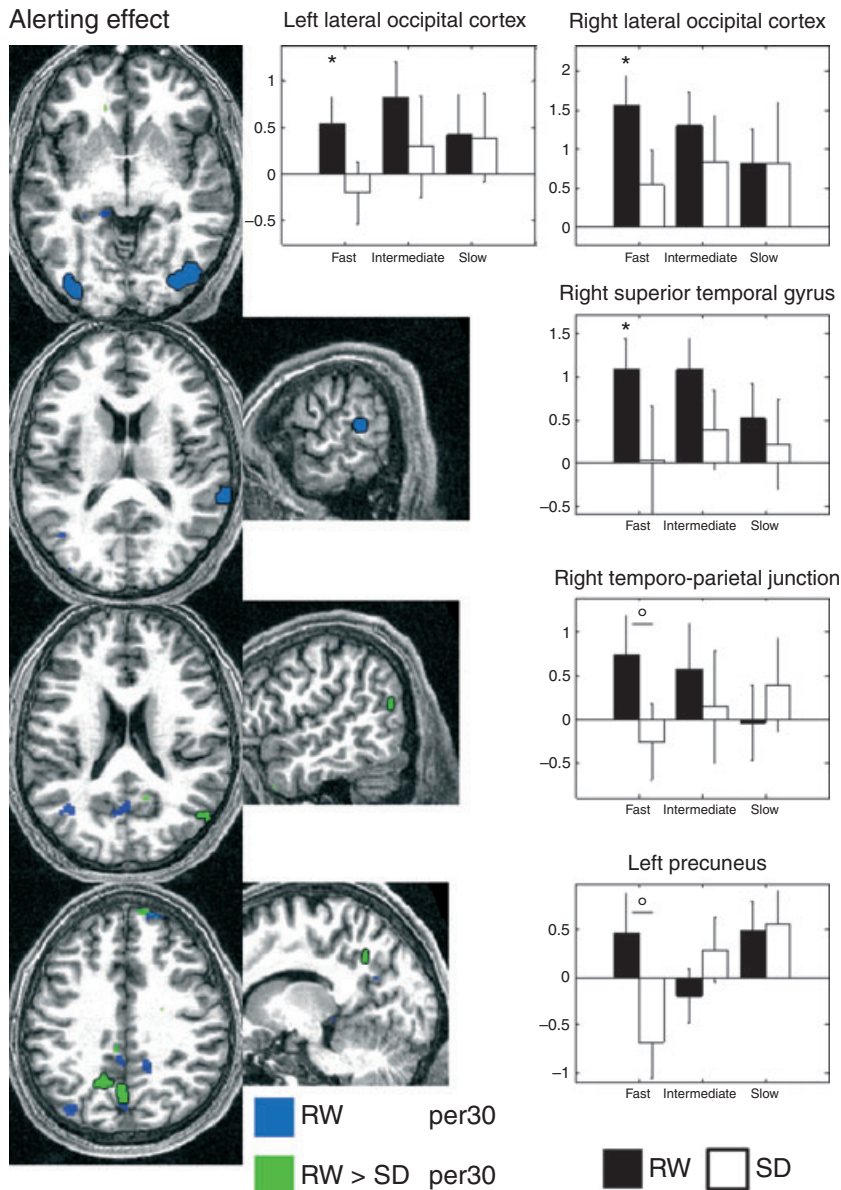
## Maintaining phasic alertness during sleep loss

Sleep deprivation did not selectively modify the alerting component and slow down responses to the same extent to trials with or without a central cue. Whereas the alerting effect was associated with responses in occipital and temporal areas during RW, no statistically significant brain alerting responses were detected after SD. Moreover, the alerting effect was not associated with any significant difference in brain responses between SD and RW for intermediate RTs. These results do not support the view that the neural correlates of phasic alertness are modified specifically by sleep deprivation. On the contrary, they suggest that the main impact of sleep deprivation on brain function is related either to an impaired capacity of centrencephalic structures to maintain vigilance, or to the ubiquitous influence of local sleep pressure on neuronal activity (Krueger *et al.*, 2008).

Intriguingly, for the fastest trials, SD resulted in decreased responses (relative to RW) in the precuneus and right temporo-parietal junction. In the absence of any behavioural correlates, this finding indicates that the activity in these areas might reflect strategies that are adopted primarily under rested conditions but are not critical to the alerting effect. These strategies would buttress a steady cognitive output during RW. In contrast, SD would reduce these cognitive resources and the corresponding brain responses.

The current findings do not confirm recent behavioural data showing, as well as global slowing in RTs, a significant effect of sleep deprivation on alerting effect (Martella *et al.*, 2011). This discrepancy is explained potentially by their

## Alerting effect



**Figure 3.** Brain responses associated with the alerting effect. Row 1: bilateral lateral occipital areas; row 2: right superior temporal gyrus; row 3: right temporo-parietal junction; row 4: left precuneus. Left panels: functional results are displayed at  $P_{\text{uncorrected}} < 0.001$ , over the normalized structural magnetic resonance (MR) scan of a typical subject. Right panels: activity estimates of each area for fast, intermediate and slow reaction times (RTs) (arbitrary units  $\pm$  standard error of the mean). \*Significant within-state effect ( $P_{\text{svc}} < 0.05$ ); °significant state  $\times$  effect interaction ( $P_{\text{svc}} < 0.05$ ).

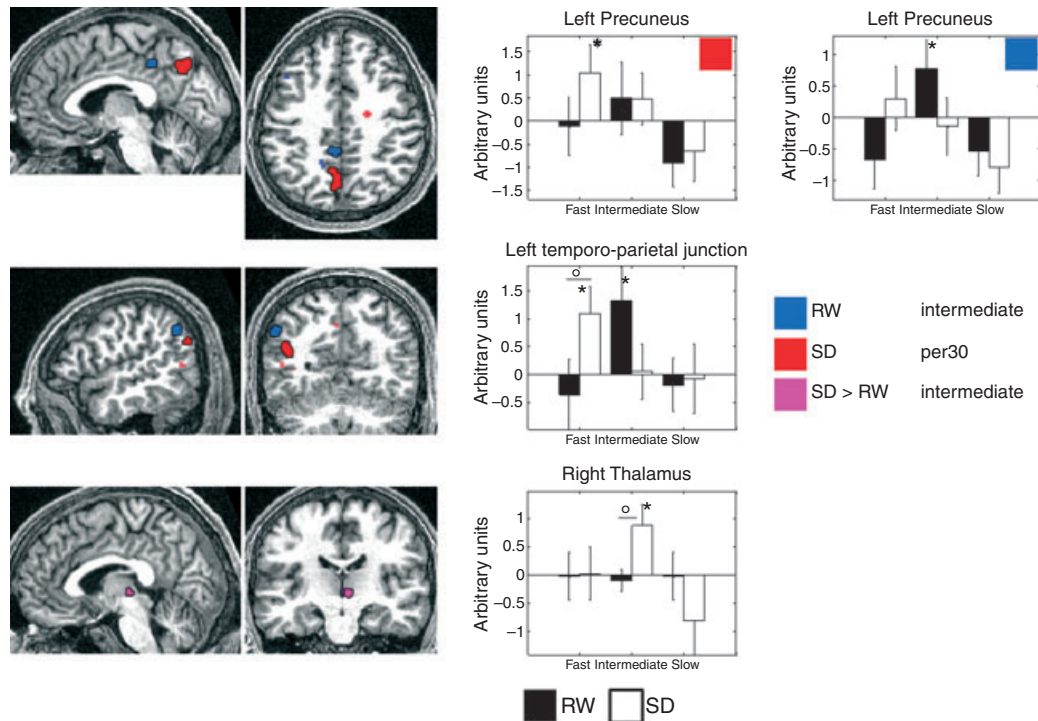
experimental protocol in which SD sessions took place at 04:00 h, a time of day associated with marked circadian decline in alertness (Dijk *et al.*, 1992). It should be noted that this experimental design possibly underestimates the genuine behavioural and neural effects of sleep deprivation, which can be detected more easily in the early morning hours after sleep deprivation. A discussion about the contribution of increased sleep pressure and circadian rhythms on our results can be found in the supporting online information.

#### Thalamic and cortical compensatory responses maintain higher-order attention components during sleep loss

For higher-order (orientating and executive) attention components, some brain responses were increased after SD

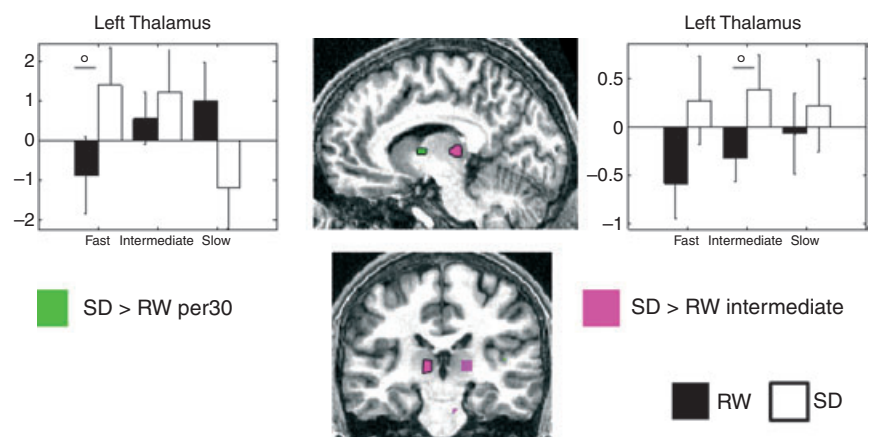
relative to RW. Similar increases were reported for other cognitive tasks (Venkatraman *et al.*, 2007) and are thought to reflect 'compensatory' responses, i.e. brain attempts to recruit neural resources transiently to maintain cognitive output despite increased sleep pressure and/or circadian misalignment (Drummond *et al.*, 2001; Tomasi *et al.*, 2009). Importantly, these 'compensatory' responses were detected in thalamic nuclei for the orientating and executive attention components. The thalamus constitutes a unique interface between vigilance and cognition. Increased thalamic responses were observed during sleep deprivation for working memory (Chee *et al.*, 2008; Vandewalle *et al.*, 2009) and attention tasks (Chee *et al.*, 2008; Portas *et al.*, 1998). These 'compensatory' thalamic responses speak against a selective influence of SD on cortical circuits involved in orientating or executive attention components. In contrast, and in keeping

## Orienting effect



**Figure 4.** Brain responses associated with the orientating effect. Upper row: left precuneus; middle row: left temporo-parietal junction; lower row: right thalamus. Left panels: functional results are displayed at  $P_{\text{uncorrected}} < 0.001$ , over the normalized structural magnetic resonance (MR) scan of a typical subject. Right panels: activity estimates of each area for fast, intermediate and slow reaction times (RTs) (arbitrary units  $\pm$  standard error of the mean). \*Significant within-state effect; °Significant state  $\times$  effect interaction ( $P_{\text{svc}} < 0.05$ ).

## Conflict effect



**Figure 5.** Differential thalamic responses associated with the conflict effect between rested wakefulness (RW) and deprivation (SD). Functional results are displayed at  $P_{\text{uncorrected}} < 0.001$ , over the normalized structural magnetic resonance (MR) scan of a typical subject. Lateral panels: activity estimates for fast, intermediate and slow reaction times (RTs) in each contrast (arbitrary units  $\pm$  standard error of the mean). °Significant state  $\times$  effect interaction ( $P_{\text{svc}} < 0.05$ ).

with the conclusion drawn for alerting effects, these thalamic responses would reflect non-specific mechanisms, which transiently maintain an optimal vigilance level, thereby supporting cortical function and maintaining steady performance.

The only cortical area showing a compensatory response was the left temporo-parietal junction. These findings speak for a phasic recruitment of this area when an optimal vigilance level can be achieved during sleep loss, suggesting

again the importance of vigilance level for the adjustment of cortical responses during sleep loss.

### Does the ANT probe independent and segregated attention components?

The ANT was designed to probe three allegedly independent attention networks, which were segregated in specific brain areas (Fan *et al.*, 2005). The current data acquired during

RW do not support the view that the ANT probes independent sets of brain areas. For instance, the alerting effect elicited significant responses in occipito-temporal areas, in keeping with previous findings, but also in the inferior frontal gyrus, which had been implicated in conflict resolution (Fan *et al.*, 2005). These discrepancies may have various origins, such as different versions of the tasks, the use of different statistical fMRI models or the procedures of statistical inferences (which were conservative in the current work). To maintain short scanning sessions, we transformed the ANT version for fMRI (Fan *et al.*, 2005) in a compact form, whereas Fan and collaborators used a long version allowing them to separate responses to cues from responses to targets (Fan *et al.*, 2005). In the same vein, MacLeod *et al.* (2010) demonstrated recently that the three attention networks do not operate independently at a cognitive level. In any case, the ANT does not seem adapted to our original objective, which was to assess the effects of sleep deprivation on three independent aspects of human attention using a compact design based on a single task.

## CONCLUSIONS

Behavioural and neural data do not support the view of a selective and differential influence of sleep deprivation on alerting, orientating or executive attention components. The recruitment of thalamus during sleep loss to support higher-order (orientating and executive) attention components suggests that sleep deprivation influences attention globally through its impact on the ability to maintain vigilance.

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## DISCLOSURE

The authors have no conflicts of interest to declare.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Alerting, orienting and conflict effects during rested wakefulness.

**Data S1.** Operational definitions of vigilance, alertness, arousal and attention.

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