

TITLE

Working memory load modulates time-of-day and chronotype effects on task-related BOLD activity.

AUTHORS

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INTRODUCTION

During the day, the circadian alertness signal continuously increases to counteract accumulating homeostatic sleep pressure (Dijk and Czeisler 1994). In humans, differences exist in the ability to maintain optimal performance levels over the day. As compared to evening types, morning types find it more difficult to maintain performance in the evening hours (Horne, Brass et al. 1980). Circadian typology partially originates from differences in circadian and homeostatic sleep-wake regulatory processes. We recently observed with fMRI that optimal sustained attention-related hypothalamic activity of extreme morning and evening types was negatively related to sleep homeostasis (Schmidt, Collette et al. 2009). Moreover, task complexity appears to impact on brain activity observed under different homeostatic sleep pressure conditions (Chee and Choo 2004). Here, we investigated the cerebral correlates of time-of-day and chronotype effects according to task difficulty using the n-back task for which we created different difficulty levels by manipulating memory load.

METHODS

Sixteen extreme evening types and 16 extreme morning types participated. Each subject underwent 2 fMRI sessions, one 1h30 (morning) and the other 10h30 (evening) after wake-up. A visual n-back task was performed. The experimental stimuli consisted of pseudorandom sequences of consonants and subjects had to indicate whether or not the probe letter matched the stimulus presented n-back trials ago (2 trials for the 2-back; 3 trials for the 3-back). For the 0-back task, subjects had to indicate whether the presented stimulus matched a predetermined letter: K. Five blocks were performed for each condition and series of stimuli (30 letters; presentation time: 2000ms) were constructed with 30% positive answers. Rest periods lasting 12-17 seconds were interspersed between each condition block. Only subjects whose performance level in terms of correct responses was greater than 70% for all difficulty levels were included in the analysis (11 evening types and 10 morning types). MRI data were acquired from a 3T Allegra MRscan (Siemens; 32 slices, voxel size: 3.4x3.4x3, TR:2130 ms, TE:40 ms, FA:90°). For anatomical reference, a high-resolution T1-weighted image was acquired (3D MDEFT; repetition time = 7.92ms, echo time = 2.4ms, inversion time = 910ms, flip angle = 15°, field of view 256 x 224 mm², matrix size = 256 x 224 x 176, voxel size = 1x1x1 mm³; (Deichmann, Schwarzbauer et al. 2004)). Data were analyzed using SPM5 (<http://www.fil.ion.ucl.ac.uk>). Individual fMRI time series were modeled using a general linear model which assessed the brain response to onset of the experimental blocks of the task (0-, 2-, and 3-back condition). Linear contrasts assessed the main effect of the task, time of day and their interaction. The individual summary statistical images were used in a second level analysis, corresponding to a random effect analysis where comparisons were made at the group level according to chronotype. Statistical inferences were

made at $p < 0.05$, corrected for multiple comparisons over small volumes of interest. Here, only the comparison between the 3-back and the 0-back condition will be considered.

RESULTS

Although a repeated-measures ANOVA on accuracy performance including the three variables of interest (working memory load*chronotype*time of day) did not reach significance ($F(1,19) = 2.19$; $p = .16$) Figure 1 indicates that, for the 3-back condition, morning and evening types differed in their performance levels according to time of day. When we performed an ANOVA on the 3-back condition separately, there was a trend toward an interaction between chronotype and time of day ($F(1,19) = 4.1986$, $p = .054$), with evening types' performance improving from the morning to the evening hours (LSD Fisher post hoc; $p < .05$). We also observed a trend toward higher performance levels during the evening hours for evening types than for morning types (LSD Fisher post hoc; $p = .078$). From a functional neuroimaging point of view, our preliminary findings indicate that activity in a thalamic region ($x = -6$; $y = -6$; $z = 4$; z -score = 3.26) predominantly projecting to the prefrontal cortex (thalamic connectivity atlas: <http://www.fmrib.ox.ac.uk/cgi-bin/thalamus.pl>) is simultaneously modulated by all three variables [(morning/evening session)*(morning/evening type)*(0-back/3-back)]. This triple interaction effect indicates that the chronotype-dependent time-of-day modulation in performance acts differentially depending on the working memory load (see Figure 1). Globally, higher thalamic activity was observed in the high-working memory load condition (3-back) than in the control condition (0-back; no memory load). Interestingly, parameter estimates shown in Figure 1 indicate that evening types present increased thalamic activity differences between the 3- and 0-back condition from the morning to the evening session, whereas morning types show the reverse profile. BOLD activity in frontal brain areas such as the left middle ($x = -24$; $y = 48$; $z = 12$; z -score = 4.39) and right superior ($x = -8$; $y = 10$; $z = 62$; z -score = 3.41) frontal gyrus behave similarly.

CONCLUSION

According to a previous study performed in the context of total sleep deprivation and using a similar paradigm (Choo, Lee et al. 2005), three variables can be considered to be involved here: the state (morning vs. evening session), the trait (morning vs. evening types) and the memory load (0-, 2- vs. 3-back condition). In their study, Choo et al. observed that the left prefrontal region and thalamus showed load-dependent activity modulation interacting with the state. Our preliminary results show a similar state by load interaction. They further indicate that this interaction is modulated by the individual's trait, i.e. the chronotype of the subject and argue in favour of the assumption that interindividual differences have to be considered while studying state effects in task-related brain activity.

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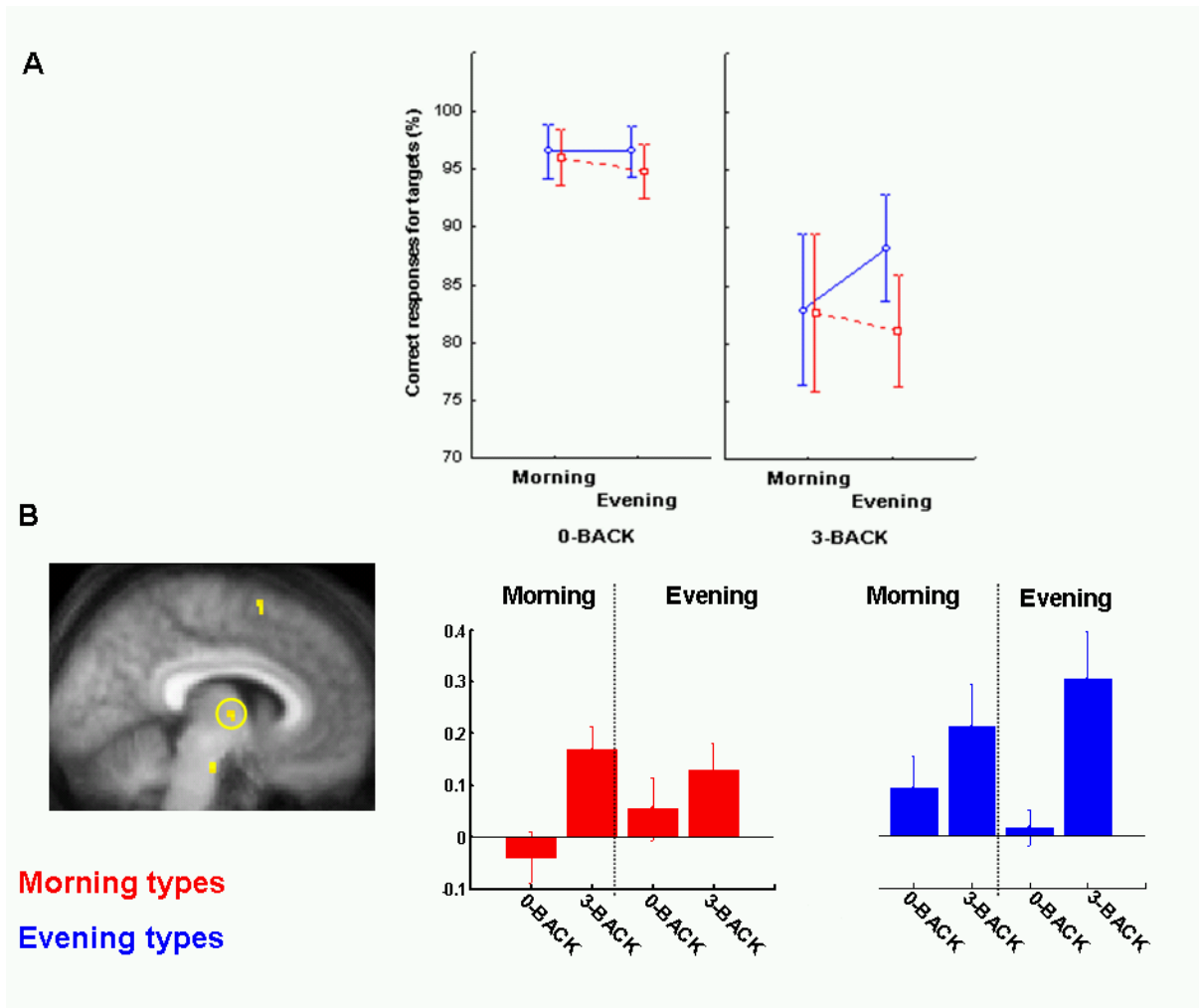


Figure 1. (A) Correct responses on the n-back task according to the working memory load condition (0- and, 3-back), time of day (morning, evening) and chronotype (morning type, evening type). **(B)** Thalamic response in morning as compared to evening types during the morning and evening sessions and according to the working memory load (triple interaction effect [(morning*evening session)*(morning*evening type)* (0-back*3-back)]. Functional results are displayed at $p < .001$, uncorrected threshold, over the mean normalized structural MR image of the population. Corresponding parameter estimates are plotted beside the display (arbitrary units).