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ORIGINAL ARTICLE

The Influence of Alertness on the Spatial Deployment of Visual Attention is Mediated by the Excitability of the Posterior Parietal Cortices

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Abstract

With a reduced level of alertness, healthy individuals typically show a rightward shift when deploying visual attention in space. The impact of alertness on the neural networks governing visuospatial attention is, however, poorly understood. By using a transcranial magnetic stimulation twin-coil approach, the present study aimed at investigating the effects of an alertness manipulation on the excitability of the left and the right posterior parietal cortices (PPCs), crucial nodes of the visuospatial attentional network. Participants' visuospatial attentional deployment was assessed with a free visual exploration task and concurrent eye tracking. Their alertness level was manipulated through the time of the day, that is, by testing chronotypically defined evening types both during their circadian on- and off-peak times. The results revealed an increased excitability of the left compared with the right PPC during low alertness. On the horizontal dimension, these results were accompanied by a significant rightward shift in the center and a bilateral narrowing in the periphery of the visual exploration field, as well as a central upward shift on the vertical dimension. The findings show that the manipulation of non-spatial attentional aspects (i.e., alertness) can affect visuospatial attentional deployment and modulate the excitability of areas subtending spatial attentional control.

Key words: alertness, eye tracking, posterior parietal cortex (PPC), transcranial magnetic stimulation (TMS), visuospatial attention

Introduction

In everyday life, we are confronted with a stream of visual information from our environment, and we need to select only the relevant portion for ongoing behavior. In this process, we deploy visual attention in space overtly, that is, we selectively attend to an object in the environment by aligning it with the fovea of the retina, a form of spatial attention (e.g., Posner and Petersen 1990). Besides its spatial aspects, attention also encompasses non-spatial components, such as alertness, that is, the general wakefulness and preparedness to respond to stimuli (Sturm and Willmes 2001). These spatial and non-spatial aspects of attention are thought to interact with each other, whereby non-spatial attention can modulate the deployment of visual attention in space. In fact, previous research has shown that, with a reduced level of alertness (triggered by different manipulations, such as sleep deprivation, circadian rhythmicity, or increasing time-on-task), healthy participants typically show a rightward shift when deploying visual attention in space (e.g., Manly et al. 2005; Fimm et al. 2006; Dufour et al. 2007; Heber et al. 2008; Matthias et al. 2009; Benwell et al. 2013; Newman et al. 2013; Dorrian et al. 2015; Paladini et al. 2016). However, to date, the neural basis of this interaction between spatial and non-spatial attentional aspects is poorly understood, and the neurophysiological substrate of the above-mentioned rightward attentional shift with a reduced level of alertness is largely unknown.

On a neural level, the spatial deployment of visual attention has consistently been shown to rely on a bilateral dorsal fronto-parietal network, including the posterior parietal cortex (PPC) and the frontal eye field (FEF) as key nodes (e.g., Corbetta and Shulman 2002, 2011). The fronto-parietal networks of the 2 hemispheres are thought to compete with each other to direct attention to the contralateral hemifield, thereby exerting reciprocal inhibition (Kinsbourne 1987, 1993). The activity within each network thus determines the resulting strength of the antagonistic attentional vectors and, therefore, how visual attention is deployed in space. A current hypothesis holds that a low alertness level would differentially affect the activity within the dorsal fronto-parietal networks, that is, result in an increased activity of the left hemisphere and thus in a rightward attentional shift (Corbetta and Shulman 2011).

In the present study, we investigated how a systematic alertness manipulation would affect the activity of a key node of the fronto-parietal network of each hemisphere, namely the PPC. This was achieved by directly assessing the excitability of these areas in the left and the right hemisphere, by means of a transcranial magnetic stimulation (TMS) twin-coil approach. TMS twin-coil stimulation provides a valid method for the direct assessment of the connectivity between cortical brain regions and of the excitability of cortical brain areas, such as the PPC, connected to the primary motor cortex (e.g., Murase et al. 2004; Koch et al. 2006, 2007, 2008; Rothwell 2011; Kuppuswamy et al. 2015). Thus, as the PPC and the primary motor cortex are connected through cortico-cortical pathways (Makris et al. 2005), the application of a TMS pulse over the PPC temporarily increases the excitability of these cortico-cortical pathways and of the connected primary motor cortex (M1; see e.g., Koch et al. 2007). The amplitude of motor evoked potentials (MEPs)—elicited by a second, ensuing TMS pulse over M1—will thus be increased, as compared with the case of a single TMS pulse over M1 without prior stimulation of the PPC. Depending on the level of excitability of the PPC, the increase of excitability in the connected M1 will differ. Thus, the changes in amplitude of the MEPs elicited after a prior stimulation of the PPC can serve as a valid indicator of the excitability of the PPC itself (see, e.g., Koch et al. 2007, 2008). In the present study, this technique thus allowed for the assessment of the excitability of both the left and the right PPCs during high and low alertness states.

Participants' level of alertness was manipulated by means of the synchronicity effect between chronotype and time of the day (May and Hasher 1998). This synchronization between the time of the day during which testing takes place and the individual circadian on- and off-peak times provides a valid method to manipulate participants' alertness level (e.g., Smith et al. 2002; Cazzoli et al. 2014; Dorrian et al. 2015).

Previous research showed that the cortical representations of eye movements and of the deployment of visuospatial attention closely overlap (e.g., Corbetta et al. 1998; Nobre et al. 2000). We therefore applied a free visual exploration task with concurrent eye movement recording to assess the deployment of visuospatial attention (e.g., Karnath 1998; Sprenger et al. 2002; Pflugshaupt et al. 2004; Malhotra et al. 2006; Nyffeler et al. 2008; Müri et al. 2009; Cazzoli et al. 2015) and to relate the alertness level and excitability parameters of the PPCs with the spatial deployment of visual attention.

Methods

Participants

Twenty healthy subjects with a mean age of 26 years (SD = 3.8, range = 21–32) participated in the study. Fourteen were female and 17 were right-handed, according to their score in the Edinburgh Handedness Inventory (Oldfield 1971).

Participants' chronotype was determined with the Morningness-Eveningness-Questionnaire (German version, D-MEQ, Griefahn et al. 2001; originally developed in English by Horne and Östberg 1976). Recruitment addressed participants who considered themselves to be evening types, since evening types demonstrate more pronounced differences in subjective alertness across the day (Smith et al. 2002). Of the 20 participants, 5 participants were categorized as "definite evening types" (score ≤ 30), and 15 as "moderate evening types" (score from ≤ 31 to ≤ 41). All of these 20 participants completed 2 eye tracking sessions during which their deployment of visuospatial attention was assessed. In addition to these 2 eye tracking sessions, 10 of the 20 evening types (2 definite and 8 moderate evening types) also completed 2 separate TMS twin-coil sessions during which the excitability of the PPCs was assessed, that is, they completed a total of 4 sessions overall.

All participants had normal or corrected-to-normal visual acuity, and gave written informed consent prior to the beginning of the study. The study was approved by the Ethics Committee of the State of Bern, and was conducted in compliance with the latest version of the Declaration of Helsinki.

Stimuli and Materials

Subjective Alertness

Participants' subjective level of alertness was assessed through a visual analogue scale (VAS). Participants were instructed to indicate how alert they felt, by drawing a vertical mark on a 100 mm horizontal line, ranging from "not at all alert" to "very alert."

Objective Alertness

The objective alertness assessment was performed by means of a modified and prolonged version of a validated attention test battery (Testbatterie zur Aufmerksamkeitsprüfung, TAP;

Zimmermann and Fimm 1993) encompassing a tonic and a phasic alertness component, each comprising 40 trials. Stimuli were presented on a 21.3-inch computer screen (Samsung SyncMaster 213 T with a resolution of 1600 × 1200 pixels, a color depth of 32 bit, and a refresh rate of 60 Hz using E-Prime software (Psychology Software Tools, Inc.). During the tasks, participants were presented with a central fixation cross with varying random duration (3000–5000 ms), which was then replaced by a central target, that is, an "x." In the phasic alertness task, the target stimulus was additionally preceded by an alerting tone at a variable, randomly determined time interval (650–1240 ms). For both tasks, participants were instructed to press a button as quickly as possible upon appearance of the target stimulus, which was placed centrally in front of them.

As healthy individuals' pupil size has previously been shown to be reduced with a decreasing level of alertness (Morad et al. 2000), participants' pupil size was also measured during the free visual exploration task as an additional objective alertness measure.

Deployment of Visuospatial Attention with Eye Tracking

The assessment of the deployment of visuospatial attention was performed by means of a prolonged free visual exploration task with concurrent eye movement recording. Stimuli consisted of 78 full color pictures depicting landscapes. The pictures were divided into 3 blocks, each containing 26 stimuli. The order of the pictures within each block was randomized for each participant. For each trial, the presentation of a central fixation for 1.5 s was followed by the presentation of a picture for 10 s. For this task, participants were instructed to freely explore the presented pictures with their eyes, while avoiding head movements (i.e., "please look at the pictures that will be presented to you on the computer screen without moving your head. Look at the pictures naturally, as you would look at photographs in an album. Before each picture, you will see a fixation point in the center of the screen. Please always look at this point."). After each block of 26 pictures, participants were allowed a short break of 3 min, which enabled the recalibration of the eye tracking system. All of the 78 pictures were presented during each session.

Landscapes were selected based on their saliency maps, as assessed by an algorithm, which, by taking different aspects such as the orientation, color, and intensity of features within a picture into account, allows for the computation of salient regions within that picture (Itti et al. 1998). This enabled the balancing of the overall saliency between the left and the right halves of the pictures. Pictures containing people or writing were not included. The stimuli were presented full-screen on a 20-inch computer display (Dell UltraSharp, Dell Inc.), with a resolution of 1600 × 1200 pixels, a refresh rate 60 Hz, and a color depth of 32 bit, subtending a visual angle of approximately 31 × 24°.

Excitability of the Left and the Right PPCs

The excitability of the left and the right PPCs was assessed by means of a TMS twin-coil procedure (based on Koch et al. 2007, 2008; see Fig. 1). In general, electromyographic (EMG) responses resulting from a single TMS pulse over the primary motor area (M1; in the shape of MEPs) are contrasted with the MEPs resulting from the combined application of a conditioning pulse over the PPC and a subsequent test pulse over M1 (e.g., Koch et al. 2007). As the PPC and M1 are connected through cortico-cortical pathways (Makris et al. 2005), the pulse over the PPC enhances M1 excitability, and the elicited MEPs are larger compared with the ones resulting from a single test pulse over M1. The MEPs elicited after a prior PPC stimulation therefore provide an index for the excitability of the PPC (Koch et al. 2007, 2008).

In the present study, EMG recordings in the shape of MEPs were obtained from the first dorsal interosseous (FDI) muscle, by means of Ag/AgCl surface tab electrodes with a diameter of 5 mm (Medtronic Ltd.). The active electrode was placed over the belly of the FDI muscle, the reference electrode over the proxima interphalangeal joint of the index finger, and the ground electrode over the proxima interphalangeal joint of the thumb (see Fig. 1). The signal was amplified and recorded with a sampling rate of 48 kHz, and bandpass filter limits were set to 2 Hz and 10 kHz.

In a first step, the resting motor threshold (RMT) was determined, defined as the lowest intensity necessary to elicit at least 5 muscle twitches in a series of 10 TMS pulses. Whenever pulses were delivered over the primary motor cortex (M1), the coil was placed 45° tangentially to the scalp midline. For the pulse delivery over the PPC (henceforth referred to as the conditioning stimulus, CS), intensity was then set to 90% RMT. The coil was placed over the right or the left PPC, equivalent to the P4 or P3 position of the 10-20-system, respectively (e.g., Koch et al. 2008; Nyffeler et al. 2008). More precisely, the positions of P3 and P4 correspond, on average, to the projection on the scalp of the left and right inferior parietal lobules, respectively, proximal to the posterior intraparietal sulci (Hilgetag et al. 2001; Herwig et al. 2003; Rushworth and Taylor 2006). The intensity of the CS over the PPC was set at 90% RMT, as this, in combination with an inter-pulse-interval of 4 ms, has been shown to potentiate the MEPs (Koch et al. 2007, see also Ziemann et al. 1996).

In a second step, the stimulator output used to deliver pulses over M1 (henceforth referred to as the test stimulus, TS) was determined, defined as the minimal intensity needed to

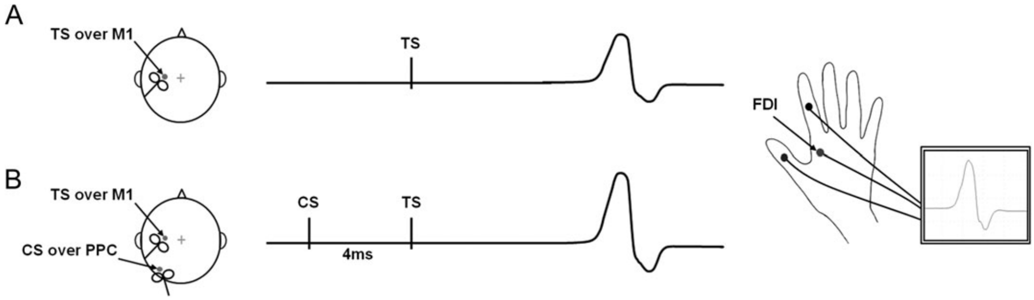

Figure 1. Schematic depiction of the TMS twin-coil procedure. The excitability of the left and the right PPCs was assessed by contrasting: (*A*) the MEPs elicited by the test stimulus (TS) alone; and, (*B*) the MEPs elicited after the combined application of a conditioning stimulus (CS) over the PPC and, 4 ms later, a TS over the primary motor cortex (M1); see also Koch et al. 2007) This figure shows an exemplary depiction of the TMS twin-coil procedure for the left hemisphere, whereby in the study, the excitability was assessed for the PPCs of the left and the right hemisphere. MEPs were obtained from the first dorsal interosseous (FDI) muscle.

elicit a MEP with a peak-to-peak amplitude of approximately 1 mV ($M = 0.96$, SEM $= 0.1$).

Subsequently, single and double TMS pulses were applied in a random order, whereby each single or double pulse trial was followed by an inter-trial-interval of approximately 5 s. A single pulse comprised a TS pulse over M1 only, whereas a double pulse encompassed a CS pulse over the PPC and, 4 ms later, a TS pulse over M1. Overall, 20 MEPs elicited by single pulses and 20 MEPs elicited by double pulses were obtained for each hemisphere.

Apparatus

Eye Tracking

Participants' eye movements were recorded using an infrared, video-based eye tracking system (Eyelink 1000, SR Research Ltd.), with a sampling rate of 1000 Hz, a spatial resolution of typically 0.01°, and a gaze position accuracy of typically 0.25°–0.5° (largely dependent on calibration accuracy). A chin- and forehead-rest ensured a constant viewing distance of 70 cm.

Transcranial Magnetic Stimulation

Two Magstim 200 Mono Pulse stimulators (Magstim Ltd.), connected to a Magstim BiStim System, as well as 2 figure-of-eight TMS-coils (outer diameter: 70 mm) were used in the present study. EMG recordings were obtained using the Dantec Keypoint G4 Workstation (Neurolite) and the Keypoint.net Software to measure the muscle twitches elicited by the TMS pulses.

Procedure

Deployment of Visuospatial Attention with Eye Tracking

All participants completed a total of 2 identical eye tracking sessions, the order of which was counterbalanced across participants, and separated by 1 week. One session took place at 8 a.m. (low alertness session), and the other session at 5 p.m. (high alertness session), as previous studies (e.g., May 1999; Smith et al. 2002; Cazzoli et al. 2014) have shown differences in alertness and cognitive performance in evening types between these time points. The experiment was conducted in a dimly lit room. Participants first indicated their subjective level of alertness on the VAS. They then completed the tonic, followed by the phasic reaction time task, in order to assess their objective level of alertness. Subsequently, to assess their deployment of visuospatial attention, participants completed the prolonged free visual exploration task during which their eye movements were recorded. Finally, all participants filled in a standardized sleep questionnaire (Schlaffragebogen SF-A/R, Görtelmeyer 2011), which contains 25 questions regarding how participants had slept the previous night. This enabled the assurance of equal sleep duration prior to the low and the high alertness sessions.

Excitability of the Left and the Right PPCs

The TMS twin-coil sessions were conducted at 8 a.m. (i.e., during low alertness), and at 5 p.m. (i.e., during high alertness). The assessment of the deployment of visuospatial attention and the excitability of the left and the right PPCs took place on separate days, as a combined assessment would have taken several hours, thus rendering our alertness manipulation, which strongly depends on the time of the day, less effective. The sessions were separated by 1 week, and the order of the sessions was counterbalanced across participants. Upon arrival, participants completed the tonic and the phasic reaction time tasks. Afterwards, they were seated in a chair and instructed to relax during the TMS twin-coil procedure. Then, after obtaining the 20 MEPs elicited by single, and the 20 MEPs elicited by double pulses over one hemisphere, the same TMS twin-coil procedure was repeated for the other hemisphere. The order of the hemispheres was counterbalanced across subjects, as was the order of the TMS twin-coil sessions (high and low alertness session, respectively).

Data Analysis

Deployment of Visuospatial Attention with Eye Tracking

Based on the data of the sleep quality questionnaire, the number of hours each participant had slept prior to the 2 eye tracking assessments was calculated. A paired samples *t*-test was performed to compare the values of the high and the low alertness sessions.

The analyses of the VAS, of the objective alertness tasks, as well as of the measured pupil size, served as a validation for the alertness manipulation used in the present study. For the VAS, the distance between the left extreme of the horizontal line and the participants' mark was measured in mm. Lower values thus indicate a lower level of subjective alertness. A paired samples *t*-test was performed to compare the VAS scores of the high and low alertness sessions. For the tonic and the phasic reaction time tasks, both the mean reaction time as well as the standard deviation were analysed, as previous studies have found both an increasing mean reaction time as well as an increasing variability in reaction times with a decreasing level of alertness (e.g., Lim et al. 2010; Jung et al. 2011; Wang et al. 2014). Hence, we computed both the mean reaction time across trials for each task, as well as the mean standard deviation of reaction times, for each participant and task. Two separate repeated-measures analyses of variance (ANOVAs) were then conducted on the data concerning mean and standard deviation of reaction times, with the within-subjects factors "alertness session" (levels: high, low) and "task" (levels: tonic, phasic).

Concerning the pupil size, as the accuracy of this measurement during eye tracking is affected by pupil position, the assessment should take place when participants do not move their eyes (e.g., Gagl et al. 2011). For this reason, the mean pupil area was assessed only during central fixation, that is, during the 1.5 s preceding each picture, and was then averaged across each alertness session (high, low) for every participant. A paired samples *t*-test was then conducted to compare the results of the low alertness session with the ones of the high alertness session.

Regarding the allocation of attention in space, participants' exploration behavior was quantified by means of the number of fixations made during the task on defined regions of the screen. As observed in previous studies (e.g., Cazzoli et al. 2014), when focussing on participants' overall fixation behavior during the high and the low alertness session, a comparison of participants' mean fixation duration revealed a higher mean fixation duration for the low compared with the high alertness session ($t_{19} = 3.74$; $P = 0.001$), and thus a lower mean number of fixations during the low compared with the high alertness session ($t_{19} = 2.95$, $P = 0.008$). Thus, to account for the differing number of fixations and to compare the changes in the fixation distribution of participants, subsequent analyses of participants' exploration behavior were performed by means of their mean % of fixations. Thereby, the number of fixations per session equalled 100%. In a first step, we analysed participants' exploration behavior on the horizontal axis. The 100 most central pixels of the pictures were thereby excluded from the analysis, in order to avoid spatial distortions in the results due to calibration inaccuracies. The pictures were divided into 4 equal vertical columns: left peripheral, left central, right central, and right peripheral column (375 pixels each; see Fig. 2A), and the overall mean % of fixations per column was calculated separately for the low and the high alertness session. The data were then analysed by means of a repeated-measures ANOVA, with the within-subjects factors “alertness session” (levels: high, low) and “column of the screen” (levels: left peripheral, left central, right central, right peripheral). In a second step, we analysed participants’ exploration behavior on the vertical axis. Again, the 100 most central pixels of the pictures were excluded from the analysis, in order to avoid spatial distortions in the results due to calibration inaccuracies. The pictures were divided into 4 equal horizontal rows: uppermost, upper central, lower central, and lowermost row (275 pixels each, see Fig. 2B), and the overall mean % of fixations per row was calculated separately for the low and the high alertness session. The data were then analysed by means of a repeated-measures ANOVA, with the within-subjects factors “alertness session” (levels: high, low) and “row of the screen” (levels: uppermost, upper central, lower central, lowermost).

Excitability of the Left and the Right PPCs

To validate the absence of a difference in participants’ alertness level during the assessment of participants deployment of visuospatial attention and the assessment of the excitability of the left and the right PPCs, 2 separate repeated-measures ANOVAs with mean reaction time and mean standard deviation of reaction times, respectively, as the dependent variables, and with the within-subjects factors “assessment” (levels: deployment of visuospatial attention, excitability of PPCs), “alertness session” (levels: high, low), and “task” (levels: tonic, phasic) were performed.

Regarding the TMS twin-coil procedure, the individual mean peak-to-peak amplitudes of the MEPs were measured separately, and subsequently averaged for single and double pulses for each hemisphere, for the high and the low alertness session, respectively. To quantify the excitability of the left and the right PPCs for each time point, the % difference in MEP amplitudes after the single and the double TMS pulses was then calculated, and a mean was computed over all subjects, for each hemisphere, and each time point. A repeated-measures ANOVA with the within-subjects factors “hemisphere” (levels: left PPC, right PPC) and “alertness session” (levels: high, low) was calculated.

For all analyses, when the sphericity assumption was not met in the repeated-measures ANOVAs, the degrees of freedom, and thus the *P*-values, were corrected according to the Huynh–Feldt procedure. All post hoc analyses were conducted by means of Tukey HSD tests.

Results

Deployment of Visuospatial Attention

Regarding participants’ sleep duration, the paired samples *t*-test revealed no significant differences between the high and the low alertness session ($t_{19} = 1.17$, $P = 0.26$). Hence, participants’ sleep duration prior to the eye tracking sessions did not differ significantly.

Concerning participants’ subjective level of alertness, as rated through the VAS, there was a significant difference between the high and the low alertness session ($t_{19} = 5.8$, $P < 0.001$). Participants felt significantly more alert during the high compared with the low alertness session (see Fig. 3A). Similarly, for the objective alertness task, when focussing on mean reaction times, the repeated-measures ANOVA revealed a significant main effect of the factors “alertness session” ($F_{1,19} = 18.62$, $P < 0.001$) and “task” ($F_{1,19} = 13.32$, $P = 0.002$), as well as a significant interaction of these factors (“alertness session $*$ task”: $F_{1,19} = 4.4$, $P = 0.049$; see Fig. 3C). Participants reacted significantly slower in the tonic reaction time task during the low compared with the high alertness session. Furthermore, reaction times were significantly increased in the tonic reaction time task during the low alertness session compared with the phasic reaction time task both during the high and the low alertness sessions. Concerning the mean standard deviation of reaction times, the repeated-measures ANOVA revealed no significant main effect of the factor “alertness session” ($F_{1,19} = 0.192$, $P = 0.667$), nor of the factor “task” ($F_{1,19} = 1.337$, $P = 0.262$). However, there was a significant interaction of the 2 factors (“alertness session $*$ task”: $F_{1,19} = 12.521$, $P = 0.002$). Post hoc tests revealed a significantly increased mean standard deviation of reaction times in the tonic alertness task during the low compared with the high alertness session. Furthermore, during the low alertness session, the mean standard deviation of reaction times was significantly larger in the tonic alertness task than in the phasic alertness task (see Fig. 3D).

Regarding participants’ pupil size, the paired samples *t*-test revealed a significantly increased mean pupil area during the high compared with the low alertness session ($t_{19} = 2.377$, $P = 0.028$; see Fig. 3B).

To sum up, these results confirm the efficacy of our alertness manipulation by demonstrating a decreased level of participants’ subjective and objective (i.e., reaction times and pupil size) level

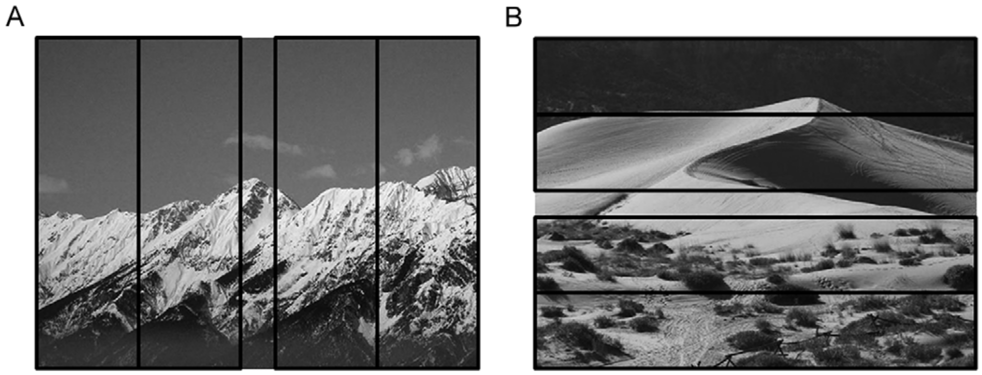

Figure 2. Examples of pictures of the free visual exploration task, with demarcated regions of interest. (*A*) Example of a picture with vertical columns, depicting the regions of interest for the analysis of horizontal asymmetries. (*B*) Example of a picture with horizontal rows, depicting the regions of interest for the analysis of vertical asymmetries. Note that pictures were presented in color in the free visual exploration task.

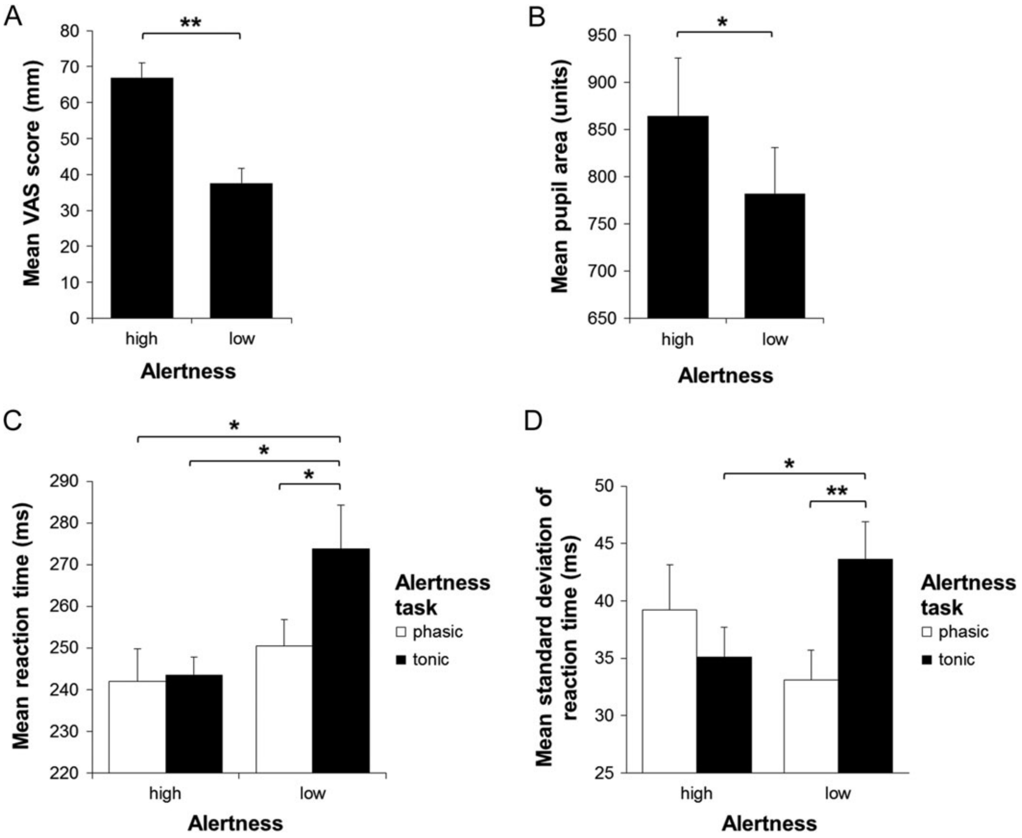

Figure 3. Results of the subjective and the objective alertness assessments. (*A*) Results of the subjective rating of participants' alertness through the VAS. Higher scores indicate a higher level of alertness. (*B*) Results of the analysis of participants' pupil size, which serves as an objective indicator of participants' alertness level. (*C*) Mean reaction times, and (*D*) mean standard deviation of the reaction times in the tonic and phasic reaction time tasks, separated according to alertness session, used to objectively measure participants' alertness level. Error bars represent the standard error of the mean (SEM). Significant post hoc tests are depicted by means of asterisks (*$P < 0.05$, **$P < 0.01$; Tukey HSD corrected).

of alertness during the low compared with the high alertness session.

Visual Exploration on the Horizontal Dimension

Regarding participants' fixation distribution on the horizontal dimension during the free visual exploration task, the repeated-measures ANOVA revealed a significant main effect of the factor "column of the screen" ($F_{2.09,39.65} = 55.19$, $P < 0.001$). Furthermore, there was a significant interaction between the factors "column of the screen" and "alertness session" ($F_{1.68,31.89} = 19.26$, $P < 0.001$). As confirmed by post hoc analyses, during the low compared with the high alertness session, participants showed a lower mean % of fixations both in the left and the right peripheral columns, and a higher mean % of fixations in the right central column. Moreover, when focussing on participants' exploration distribution in the central field of visual exploration, there was no asymmetry between left and right during the high alertness session. However, during the low alertness session, there was a significant central asymmetry, as participants' mean % of fixations was significantly higher in the right central compared with the left central column (see Fig. 4).

Visual Exploration on the Vertical Dimension

The repeated-measures ANOVA revealed a significant main effect of the factor "row of the screen" ($F_{3,57} = 113.32$, $P < 0.001$), as well as a significant interaction of the factors "alertness session" and "row of the screen" ($F_{3,57} = 7.605$; $P < 0.001$). Post hoc analyses showed a significantly higher mean % of fixations in the upper central row during the low compared with the high alertness session, and no significant differences between the low and the high alertness session for the lowermost, the uppermost, or the lower central row. Moreover, whilst there was no significant difference between the lower and the upper central row during the high alertness session, participants showed a significant asymmetry during the low alertness session, with a significantly higher mean % of fixations in the upper central row (see Fig. 5).

To sum up, on the horizontal dimension, participants showed a significant bilateral decrease in the mean % of fixations in the peripheral columns and an increase in the right central column, that is, a shift to the right, during the low compared with the high alertness session. On the vertical dimension, participants demonstrated a significant increase in the mean % of fixations in the upper central row during the low compared with the high alertness session, that is, a shift towards the upper visual field.

Excitability of the Left and the Right PPCs

To confirm the absence of a difference in participants' alertness level during the assessment of the deployment of visuospatial attention and the assessment of the excitability of the left and the right PPCs, participants' performance in the phasic and the tonic reaction time tasks (mean reaction times and mean standard deviation of the reaction times) were compared. Concerning

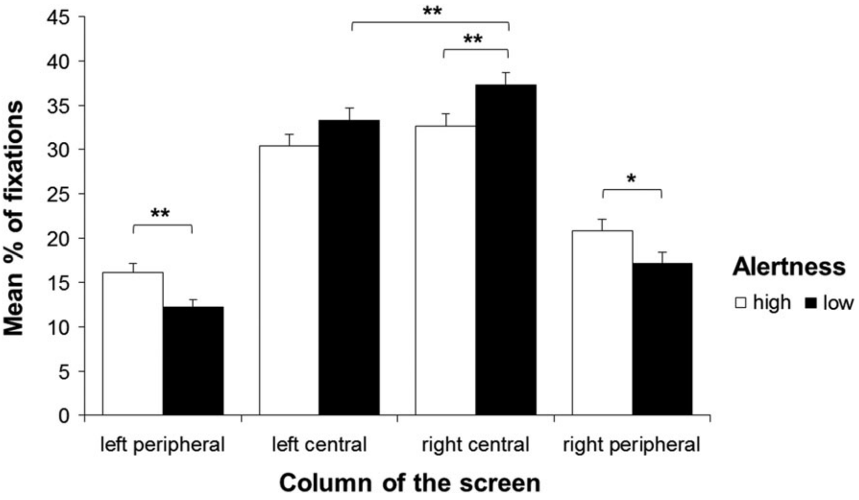

Figure 4. Participants' horizontal fixation distribution during the free visual exploration task. Mean % of fixations are depicted separately for each column, and for the high and the low alertness sessions. Error bars represent the SEM. Significant post hoc tests are depicted by means of asterisks (*$P < 0.05$, **$P < 0.01$; Tukey HSD corrected).

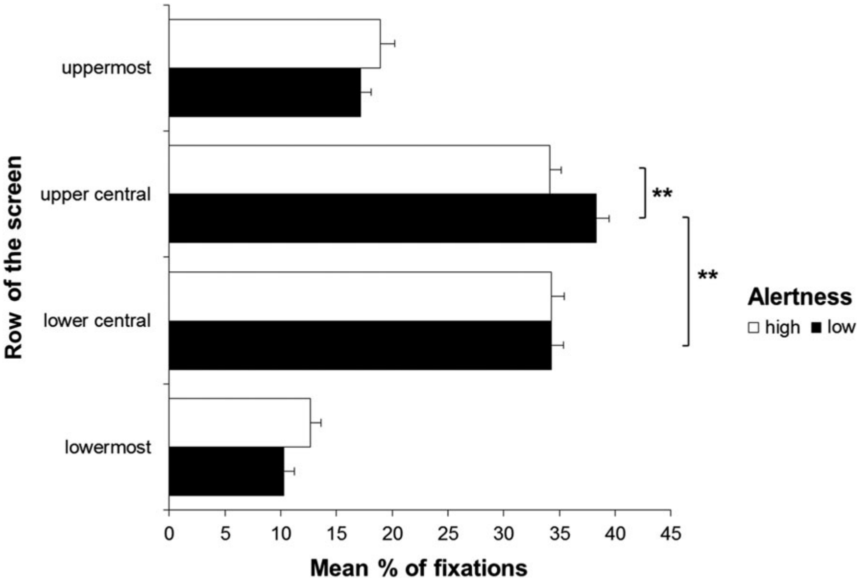

Figure 5. Participants' vertical fixation distribution during the free visual exploration task. Mean % of fixations are depicted separately for each row, and for the high and the low alertness sessions. Error bars represent the SEM. Significant post hoc tests are depicted by means of asterisks (**$P < 0.01$; Tukey HSD corrected).

the mean reaction times, the repeated-measures ANOVA revealed a significant effect of the factor "task" ($F_{1,9} = 37.01$, $P < 0.001$), yet no significant effects of the factors "assessment" ($F_{1,9} = 0.28$; $P = 0.61$) or "alertness session" ($F_{1,9} = 2.49$; $P = 0.15$), nor of the interactions "assessment ∗ alertness session" ($F_{1,9} = 3.24$; $P = 0.11$), "assessment ∗ task" ($F_{1,9} = 0.155$; $P = 0.7$), "alertness session ∗ task" ($F_{1,9} = 1.22$; $P = 0.3$), or "assessment ∗ alertness session ∗ task" ($F_{1,9} = 2.97$; $P = 0.12$). Thus, participants' mean reaction times did not differ between the eye tracking sessions and the TMS twin-coil sessions. When comparing participants' mean standard deviation of reaction times, the repeated-measures ANOVA yielded no significant results ("assessment": $F_{1,9} = 0.013$, $P = 0.913$; "alertness session": $F_{1,9} = 0.999$, $P = 0.344$; "task": $F_{1,9} = 0.286$, $P = 0.606$; "assessment ∗ alertness session": $F_{1,9} = 0.116$, $P = 0.741$; "assessment ∗ task": $F_{1,9} = 2.788$, $P = 0.129$; "alertness session ∗ task": $F_{1,9} = 0.001$, $P = 0.982$; "assessment ∗ alertness session ∗ task": $F_{1,9} = 2.607$, $P = 0.141$). Hence, the participants' mean standard deviation of reaction times did not differ between the eye tracking sessions and the TMS twin-coil sessions. Taken together, participants did not show any differences in their alertness level between the 2 assessments.

To ensure the absence of a difference in the excitability of M1 between the left and the right hemisphere, and the high and the low alertness sessions, a repeated-measures ANOVA with the within-subjects factors "hemisphere" (levels: left PPC, right PPC) and "alertness session" (levels: high, low) was conducted. This revealed no significant effects of the factors "alertness session" ($F_{1,9} = 1.74$, $P = 0.219$) or "hemisphere" ($F_{1,9} = 0.736$, $P = 0.41$), nor of the interaction "alertness session ∗ hemisphere" ($F_{1,9} = 0.15$, $P = 0.708$).

When focussing on the excitability of the left and the right PPCs, the repeated-measures ANOVA yielded no significant main effects of the factors "alertness session" ($F_{1,9} = 0.005$; $P = 0.946$) or "hemisphere" ($F_{1,9} = 0.003$; $P = 0.957$). However, there was a significant interaction between the 2 factors ("alertness session $*$ hemisphere": $F_{1,9} = 32.66$; $P < 0.001$). During the high alertness session, the mean excitability of the right PPC was significantly greater than the one of the left PPC; whereas, this pattern was reversed during the low alertness session. Furthermore, the mean excitability of the left PPC was significantly lower during the high compared with the low alertness session; whereas, the opposite excitability pattern was observable for the right PPC (see Fig. 6).

Thus, to sum up, the excitability of the left and the right PPCs differed significantly during the low compared with the high alertness session.

Discussion

In the present study, we investigated the effects of an alertness manipulation on the spatial deployment of visual attention, and on the excitability of the left and the right PPCs. When freely exploring visual stimuli during low alertness, on the horizontal dimension, participants showed a rightward shift in the central field of visual exploration, and a bilateral narrowing in the peripheral field. On the vertical dimension, they showed an upward shift in the central visual field during low alertness. The visual exploration results were accompanied by a lower excitability of the right compared with the left PPC, a pattern that reversed during high alertness.

In the following, we will first discuss the observed horizontal visual exploration results, that is, the observed rightward bias and its putative neurophysiological correlates, followed by a discussion of the bilateral, peripheral narrowing of the field of visual exploration. Finally, we will discuss the vertical visual exploration results.

The neural basis of the rightward shift in spatial attentional deployment after a reduction of participants' alertness level (as obtained with different experimental manipulations; e.g., Manly et al. 2005; Benwell et al. 2013) is largely unknown. With the twin-coil approach applied in the present study, we could investigate the neural underpinnings of this rightward shift by directly assessing the effects of an alertness manipulation on the excitability of the left and the right PPCs, key nodes of the dorsal fronto-parietal network governing the spatial deployment of visual attention (Corbetta and Shulman 2002). Our results were characterized by a lower excitability of the left compared with the right PPC during the high alertness session, and a reversal of this pattern during the low alertness session. This inversion of the excitability pattern could not be accounted for by the sole change in the excitability of either the left or the right PPC alone, as the excitability of each PPC changed significantly between the high and the low alertness sessions. To the best of our knowledge, the present study was the first to directly assess changes in the excitability of the left and the right PPCs, as triggered by an alertness manipulation in healthy individuals, and to link these physiological correlates to changes in behavior. Our findings may be explained within the framework of interhemispheric rivalry (e.g., Kinsbourne 1987, 1993). According to this concept, the 2 PPCs inhibit each other, each competing to direct attention toward the contralateral hemifield. Thereby, a decreased activity of the right PPC would result in an increased activity of the left PPC, and hence an attentional bias towards its contralateral (i.e., right) hemifield, as was observed in the present study. Our results also nicely fit with the ones of previous studies applying inhibitory TMS over the right PPC in healthy participants, and showing that an inhibitory interference with the activity of this area results in a rightward shift in the deployment of visuospatial attention (e.g., Bjoertomt 2002; Nyffeler et al. 2008; Cazzoli et al. 2009a, 2009b; Vesia et al. 2015). Additionally, a recent correlational study using EEG showed that preparatory α-band activity (a proxy of decreased excitability) increased over the right relative to the left parieto-occipital scalp regions with decreasing alertness, and correlated with participants' rightward bias (Newman et al. 2013). Though the present findings and previous research shed light on the neural underpinnings of the rightward attentional shift during low alertness, future studies applying larger sample sizes should also further investigate interindividual differences, and relate them to their neural substrates. In this respect, calculating correlations with residuals have been shown to be a valid method, which, by regressing results obtained in a control condition from a relevant experimental condition, provides individual differences scores that are independent form the control condition per se (see DeGutis et al. 2013).

In the present study, the application of a visual exploration task allowed participants to deploy their visual attention freely over an entire portion of the visual space, that is, they were not asked to restrict their attention to specific, often lateralized stimuli (as in, e.g., line bisection or detection tasks). During low alertness, this enabled the detection of not only the above-discussed central, rightward shift, but also of a bilateral, peripheral narrowing of the field of visual exploration. Interestingly, a deterioration of the useful visual field with an increasing time-on-task has previously been found in the context of traffic research, where this phenomenon has been termed "tunnel vision" (e.g., Rogé et al., 2002, 2003). Furthermore, Fimm et al. (2015, 2016) have reported shorter reaction times for targets presented more centrally compared with targets presented more peripherally during low alertness. Previous research applying inhibitory TMS over the right FEF, another crucial node of the dorsal fronto-parietal attentional network, has demonstrated that inhibitory interference with the activity of this area can lead to a bilateral narrowing of attentional deployment in space (Grosbras and Paus 2002; Duecker et al. 2013; Cazzoli et al. 2015). Our findings, entailing both a rightward shift and a bilateral narrowing in the spatial deployment of visual attention during low alertness, may thus reflect a combined decrease of activity in both the right PPC and the right FEF. A decrease in the excitability of the right PPC

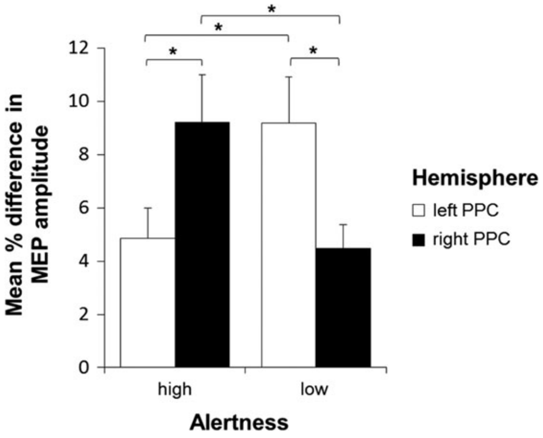

Figure 6. Mean excitability of the left and the right PPCs. Mean % difference in peak-to-peak amplitude between single and double pulse MEPs, for each hemisphere and each time point, as indicators of the excitability of the left and the right PPCs, during the high and the low alertness sessions. Higher scores indicate higher excitability of the PPC. Error bars represent the SEM. Significant post hoc tests are depicted by means of asterisks (*$P < 0.05$; Tukey HSD corrected).

during low alertness was in fact demonstrated by our twin-coil experiment. As to the right FEF, though not directly assessed, a concurrent decrease in the excitability of this area during low alertness seems reasonable, since right PPC and right FEF are strongly interconnected (e.g., Makris et al. 2005; Ptak 2012), and belong to the same dorsal fronto-parietal network controlling the spatial deployment of visual attention (Corbetta and Shulman 2002).

Our findings, obtained by means of an alertness manipulation in healthy participants, also fit well with the findings of studies in patients with attentional disorders after right-hemispheric damage, in particular hemispatial neglect. Patients with neglect not only demonstrate a strong rightward bias in the deployment of visuospatial attention, but also exhibit a reduced level of alertness and difficulties in sustaining attention for a prolonged period of time (Sturm and Willmes 2001; see also Corbetta and Shulman 2011; Langner and Eickhoff 2013). Interestingly, manipulating the level of alertness in neglect patients also triggers changes in the severity of their spatial bias (e.g., Robertson et al. 1997, 1998; Degutis and van Vleet 2010; Chica et al. 2012; van Vleet and Degutis 2013). Based on these findings, Corbetta and Shulman (2002, 2011) postulated the existence of distinct, yet interacting, neural networks controlling spatial and non-spatial attentional aspects. The dorsal fronto-parietal networks of each hemisphere direct spatial attention toward the contralateral hemifield, and interact with each other by means of a reciprocal inhibition. In contrast, non-spatial attentional aspects are governed by a ventral fronto-temporoparietal network, lateralized to the right hemisphere. Thereby, a lesion of the ventral network, typically observed in neglect, is thought to lead to a general right-hemispheric hypoactivity, including a relative hypoactivity in the right dorsal fronto-parietal network. As a result, the reciprocal inhibition between the dorsal fronto-parietal networks is imbalanced, the respective left-hemispheric dorsal fronto-parietal network becomes hyperactive, and attention is biased toward the right hemifield (Corbetta and Shulman 2011). The patterns of excitability observed in the present study after a systematic alertness manipulation in healthy subjects are thus compatible with the predictions of this model.

In addition to the analysis on the horizontal dimension, the free visual exploration task allowed us to investigate whether a change in alertness was also associated with changes in participants' exploration behavior on the vertical dimension, that is, with upper/lower visual field asymmetries. Our results revealed an upward attentional shift in the central visual exploration field during low alertness. Interestingly, it has been previously shown that applying inhibitory TMS over the right PPC in healthy participants resulted in visual extinction of left-sided stimuli that was more sustained when these were presented in the lower visual field (Cazzoli et al. 2009a). Morevover, a vertical bias in the deployment of visuospatial attention has also been found in patients with hemispatial neglect. More precisely, the spatial attentional deficits in hemispatial neglect patients after right-hemispheric stroke have been shown to be particularly pronounced for the left, lower visual field (e.g., Làdavas et al. 1994; Müri et al. 2009; Cazzoli et al. 2011). An upward vertical bias in hemispatial neglect was also found in the processing of vertical mental number lines (Cappelletti et al. 2007).

In conclusion, the present study demonstrates that 1) a manipulation of non-spatial attentional aspects (i.e., alertness) in healthy participants triggers specific changes in the spatial deployment of visual attention; and that 2) these behavioral changes are accompanied by a differential modulation of excitability of the left and right PPCs, key nodes of the dorsal attentional network.

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Notes

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