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BIOLOGICAL PSYCHIATRY - ORIGINAL ARTICLE

Methylphenidate (MPH) promotes visual cortical activation in healthy adults in a cued visuomotor task

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Abstract Seeking for the mechanisms by which methylphenidate (MPH) improves behavior has demonstrated that MPH modulates excitability in the primary motor cortex. However, little is known about the influence of MPH on top-down controlled mechanisms in the sensory domain. The present study explored the effects of MPH on the activation of visual cortices in healthy adults who performed a cued visuo-motor task in a double-blind placebo-controlled crossover design. Two distinct measures, posterior alpha power and occipital slow cortical potentials (SCPs), were used to reflect raise in excitability and attention-based activation of visual cortical areas. According to the results, performance parameters (reaction time, response variance and error rate) were not affected by MPH. At the neurophysiologic level reflected by reduced alpha power, MPH increased the overall excitability of the occipital cortex, but not the parietal cortex. Before the cued response, MPH reduced alpha power and increased SCPs only before right hand responses, mostly at the right occipital location. It can be concluded that in visuo-motor tasks, MPH has the potency of adjusting the background excitation/inhibition balance of visual areas. Additionally, MPH may raise the attention controlled activation of visual cortical regions, especially during increased response control.

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Introduction

Methylphenidate (MPH) is a psychostimulant drug, which affects catecholamine neuromodulation in both cortical (prefrontal and fronto-parietal) and subcortical (posterior noradrenergic/locus coeruleus) networks (Arnsten 2006; Andrews and Lavine 2006; Tomasi et al. 2011; Kuwahata et al. 2002). MPH is widely used in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children. Its application consistently reduces hyperactivity and improves attention in both children and adults with ADHD (The MTA Cooperative Group 1999; Rapport and Kelly 1993; Pietrzak et al. 2006).

Major evidence for MPH effects on motor cortical functioning has been accumulated by using transcranial magnetic stimulation (TMS). TMS studies have revealed that MPH affects the primary motor cortices of healthy and ADHD subjects by altering mainly the intracortical inhibition and interhemispheric balance between excitation and inhibition during both passive and task-processing conditions (Moll et al. 2000, 2003; Buchmann et al. 2006, 2010; Richter et al. 2007; Schneider et al. 2007; Kratz et al. 2009; Linssen et al. 2011). Electroencephalographic (EEG) studies also have assessed the effects of MPH in the motor domain by using the contingent negative variation (CNV), a slow negative cortical potential generated by a top-down preparatory control over motor cortical neurons (Brunia 1999; Bastiaansen and Brunia 2001). In conditions with cued responses, MPH medication in healthy adults

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(Linssen et al. 2011) and children with ADHD (Kratz et al. 2012) has produced CNV amplitude enhancement and reaction speeding, reflecting an improving MPH effect on the efficiency of movement preparation.

Far less is known, however, about whether MPH modulates top-down controlled mechanisms in the sensory domain. Such mechanisms can be best evaluated in conditions, where internal attention is directed by a warning signal to an expected stimulus appearance (Thut et al. 2006; Sylvester et al. 2007). EEG studies have revealed that sensory anticipation elicits a negative slow potential shift at modality-specific cortical areas (stimulus-preceding negativity), which reflects a top-down controlled pre-activation of perceptual mechanisms (Brunia and van Boxtel 2001; Damen and Brunia 1987; Brunia et al. 2011). Recently, alpha (8–14 Hz) EEG activity has been validated as another relevant index of sensory cortical activation (Pfurtscheller and Lopes da Silva 1999; Klimesch et al. 2007; Jensen and Mazaheri 2010). Decreased posterior alpha oscillations have been associated with functional activation and improved visual perception (Thut et al. 2006; Romei et al. 2008). In contrast, enhanced occipital alpha oscillations have been related to an inhibitory mechanism preventing the intake of visual information in task-irrelevant visual areas (Worden et al. 2000; Kelly et al. 2006; Rihs et al. 2007). In visual spatial tasks, parieto-occipital alpha activity has manifested a lateralized pattern, with alpha being smaller at areas contralateral and larger at areas ipsilateral to the side of attention (Worden et al. 2000; Sauseng et al. 2005; Kelly et al. 2006; Thut et al. 2006; Romei et al. 2008). Top-down controlled lateralization patterns of alpha EEG activity correlating with discrimination performance also have been found in the somatosensory modality (Haegens et al. 2010, 2011). Thus, it has been suggested that performance efficiency is mediated by a gating alpha mechanism increasing the information flow in task-relevant and decreasing the information flow in task-irrelevant sensory regions (Klimesch et al. 2007; Jensen and Mazaheri 2010).

In this framework, the present study assessed the effects of MPH on anticipatory sensory activation. A warned visuomotor task was used, in which an S1 stimulus warned about the side of response (left or right), while a subsequent imperative S2 stimulus required either response execution (Go) or response inhibition (NoGo). The task was performed in conditions with either MPH or placebo application. One objective was to evaluate if MPH modulated top-down controlled allocation of processing resources to sensory areas during visual target expectation in the S1–S2 interval. Occipital EEG alpha activity was analyzed to reflect preparatory facilitation/inhibition of sensory input (Pfurtscheller and Lopes da Silva 1999; Haegens et al. 2011), and EEG occipital slow cortical potentials (SCPs) were analyzed to reflect the degree of attention-based preactivation of visual cortical regions under MPH (Rektor et al. 2006; Bastiaansen and Brunia 2001; Filipovic et al. 2000). It was hypothesized that if MPH induced an unspecific increase in excitability of visual areas, alpha power decrease would be detected both before S1 and S2, and this decrease would not differ between pre-S1 and pre-S2 epochs. If, however, MPH leads to an attention-based sensory pre-activation, alpha reduction and SCPs with specific temporal dynamics can be expected only before S2.

Another objective was to explore if MPH would boost the interactions between sensory (visual) and motor cortical areas during spatial motor attention (Bedard et al. 2004; Lubow et al. 2005). It was tested if the spatial attention to motor preparation manipulated here on a trial-by-trial basis can be transferred to the sensory domain such as to induce a lateral asymmetry in the activation of the visual cortical regions prior to S2 (Thut et al. 2006). It was hypothesized that if MPH amplifies sensorimotor associations, lateralization effects in alpha activity at visual cortical areas corresponding to the side of response would emerge or would be strengthened under MPH.

Methods

Subjects

In the present study, a subset of the data reported in Kratz et al. (2009) was used. Twelve healthy subjects (5 males) aged 20–40 years participated in the study. None reported of any chronic neurologic, psychiatric or somatic disease. All subjects were right-handed, as determined by the Edinburgh Handedness Inventory (Oldfield 1971) with normal or corrected to normal vision. Participants were free of any psychotropic medication. Written informed consent was obtained from each individual in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committees of the University of Erlangen-Nürnberg, Erlangen, Germany.

Medication

Each subject underwent two experimental sessions 1 week apart from each other at the same time of day. At 60 min before the experimental session, either 20 mg dl of MPH or placebo was orally administered in a double-blind counterbalanced manner.

Task and conditions

A warned visual motor task was implemented in separate blocks (details of the overall experimental design are presented in Kratz et al. 2009 and Hoegl et al. 2011). Subjects

Fig. 1 Experimental paradigm: Go/NoGo task (S1–S2 paradigm). The Go/NoGo task consisted of control, Go-left, NoGo-left, Go-right and NoGo-right trials (see text for more details)

were seated comfortably in an armchair with a distance between the eyes and a 17-in. monitor of approximately 100 cm and were given instructions for a Go/NoGo task performance. Responses were produced by spreading the fingers of the right or left hand (excluding the thumb). The index, middle, ring and little fingers were linked via a plastic loop to a switch, which could be activated by finger spreading, transmitting the signal to the recording computer. The task was set on Presentation® software (Version 11.0, Neurobehavioral Systems, Albany, CA, USA), which also recorded the behavioral data (Fig. 1). Trials consisted of a warning stimulus (S1, 250-ms duration) followed by an imperative stimulus (S2, 250-ms duration) with a fixed interval of 1,750 ms between their onsets. S1 was a horizontal blue arrow (4.5 cm/2.58° visual angle) pointing either to the left or to the right and instructing the participant which hand to spread in case a Go-signal was presented as S2. Accordingly, S2 was either a Go (green check) requiring a motor response, or a NoGo (red X-mark) requiring response inhibition. The visual angle of Go and NoGo stimuli was also 2.58°. Hence, there were four stimulus–response types (Go-left/right and NoGo-left/right) presented with equal probability of $p = 0.25$. Each trial started with a central fixation cross in the middle of the visual field followed by S1 that appeared at the same position. The intertrial interval varied randomly between 5 and 6 s. Thus, a total of 60 trials (comprising 24 Go and 24 NoGo trials as well as 12 control trials not analyzed here) were presented and the experimental block lasted about 8 min.

EEG recording and data processing

Electroencephalogram (EEG) data acquisition was performed with Brainamp recording system (Brain Products GmbH, Gilching, Germany). EEG records were made with Ag–AgCl disc electrodes (Abralyt 2000 electrolyte) located at 23 standard positions according to the 10/20 International system (left, midline and right at the prefrontal, frontal, central, temporal, parietal and occipital locations). EEG signals were referenced online to Cz, with CPz serving as a ground electrode. During the recordings, impedances were kept below 10 kΩ. Additionally, the electrooculogram (EOG) was recorded to detect both vertical and horizontal eye movements. The cutoff frequencies of EEG amplifiers were set to 0.016 and 1,000 Hz (−3 dB/octave). The amplified signals were sampled with a frequency of 5,000 Hz and further recorded on a PC.

Data processing was performed with Brain Vision Analyzer software (Brain Products GmbH, Gilching, version 1.05). After off-line re-referencing to linked mastoids, the EEG data were down-sampled to 250 Hz and filtered with a 50-Hz notch filter. The total length of the analysis epoch was 3,500 ms including 750 ms before S1, 1,750 ms between S1 and S2, and 1,000 ms after S2. EEG traces were visually inspected for gross EOG, EMG or other non-EEG artifacts and contaminated trials were discarded. The number of excluded epochs did not exceed 20 % of the total number of trials per condition. The random presentation of Go and NoGo stimuli allowed to increase the number of trials used for averaging by pooling together trials for Go and NoGo conditions. Further, the influence of blinks and other eye movements on the EEG was corrected by a linear ocular correction procedure (Gratton et al. 1983).

Parameterization

Two independent measures of cortical activation were suggested to reflect the effect of MPH. (1) Alpha total power was measured as an index of the ongoing cortical excitability before S1 and S2 (Romei et al. 2008; Thut et al. 2006). (2) Top-down modulation of activation of visual cortices was assessed by SCPs (e.g., Brunia 1999; Hopf and Mangun 2000) at O1 and O2 prior to S2.

Alpha band activity

Background (750 ms before S1) and anticipatory alpha activities (750 ms before S2) were evaluated at parietal (P3 and P4) and occipital (O1 and O2) sites. Single EEG epochs from each of the four stimulus–response types were subjected to a continuous wavelet transform (CWT, Mallat 1999; Samar 1999). As a basis function, complex Morlet wavelet was applied, which has a symmetrical Gaussian distribution in both time and frequency domains (for details, see Tallon-Baudry et al. 1996; Yordanova et al. 2004). Alpha total power (TOTP) was obtained by

averaging single-sweep power values derived from the 8–12 Hz CWT scale (Tallon-Baudry et al. 1996; Tallon-Baudry and Bertrand 1999). Alpha TOTP was measured as the mean value of 250-ms long time windows within the 750-ms epochs before S1 and S2.

Slow cortical potentials

The same artifact-free epochs selected for analysis of alpha band activity were used. To improve the SCP signal, data were filtered with a digital low-pass filter (cutoff frequency 12 Hz, 24 dB/oct) and were baseline corrected according to the mean value of 250-ms pre-S1 periods. Similar to alpha TOTP, SCPs were measured as the mean value of 250-ms time windows within the analysis epoch before S2.

Statistical analysis

Repeated measures analyses of variance (ANOVA) were used.

Analysis 1 Measures from the two hands were pooled together since this analysis was designed to test the effects of MPH on alpha TOTP as a major index of activation of visual cortical areas (factors: Medication, Placebo vs. MPH). To explore if MPH affects specifically attention-based activation, analysis included epochs before S1 and S2 (factor: Stimulus). To search for anticipation-related dynamics of activation, each 750-ms long epoch was divided into three time windows of 250 ms each (factor: Time, T1 vs. T2 vs. T3), for which mean alpha TOTP values were measured. Alpha TOTP measures from parietal and occipital regions formed the factor Region (parietal vs. occipital) and measures from bilateral locations formed the factor Laterality (left vs. right). Thus, the overall ANOVA included within-subjects factors: Medication × Stimulus × Time × Region × Laterality.

Analysis 2 The second analysis tested the effect of MPH on attention-based top-down pre-activation of visual areas. Alpha TOTP and SCPs were analyzed only at occipital locations and only before S2 as representing a task-relevant anticipatory period. The effect of Response side was tested to explore if directing attention to the responding hand may alter asymmetrically sensory activation and if MPH may contribute to such effects. The same three time windows before S2 (T1, T2, and T3) were used. Thus, the within-subjects variables were Medication × Time × Laterality (O1, Oz, O2) × Condition (respond left vs. respond right).

In a control analysis, the effects of MPH on top-down motor preparation were tested. Pre-S2 SCPs at the left and right centro-parietal locations where response preceding negativity is mostly expressed were subjected to a Medication × Time × Region (central vs. parietal) × Laterality (left vs. right) × Condition ANOVA.

Reaction times (RTs) from Go trials, coefficients of RT variance [CV = SD/(mean RT)] and error rate were used as performance indices. They were subjected to a Medication × Condition ANOVA. A Greenhouse-Geisser correction was applied whenever sphericity assumption was violated for within-subjects variables with more than two levels.

Results

Behavioral results

Table 1 illustrates the performance data (reaction time and coefficient of variation). Although right-hand responses were faster than left-hand responses, this difference did not reach statistical significance under Placebo [$F(1,11) = 3.1$, $p = 0.1$] or MPH [$F(1,11) = 3.2$, $p = 0.1$]. Accordingly, MPH-induced speeding of responses (Table 1) was not significant [Medication, $F(1,11) = 0.61$, $p = 0.45$] in either the respond-left or respond-right condition [Condition × Medication, $F(1,11) = 0.014$, $p = 0.9$]. Similarly, no main or interactive effects of Condition and Medication were found for coefficients of RT variance (Table 1) and error rate.

Electrophysiological results

Analysis 1 A significant main effect of Stimulus was found for alpha TOTP [$F(1,11) = 15.4$, $p = 0.003$]. Power dynamics and topography maps in Fig. 2a, b demonstrate that alpha TOTP was significantly smaller before S2 than before S1. Also, only before S2 did alpha power decrease with time, i.e., as a function of S2 expectation (Stimulus × Time [$F(1,11) = 4.59$, $p = 0.03$].

No significant main effect of MPH was found [Medication, $F(1,11) = 0.23$, $p = 0.64$]. However, there was a

Table 1 Mean values of behavioral parameters reaction time (RT) and coefficient of variation (CV) under placebo and medication

	Placebo		Methylphenidate	
	RT ± SD (ms)	CV ± SD	RT ± SD (ms)	CV ± SD
Respond left	332.1 ± 21	0.125 ± 0.040	328.0 ± 22	0.131 ± 0.048
Respond right	324.2 ± 17	0.115 ± 0.032	319.4 ± 26	0.140 ± 0.044

SD standard deviation

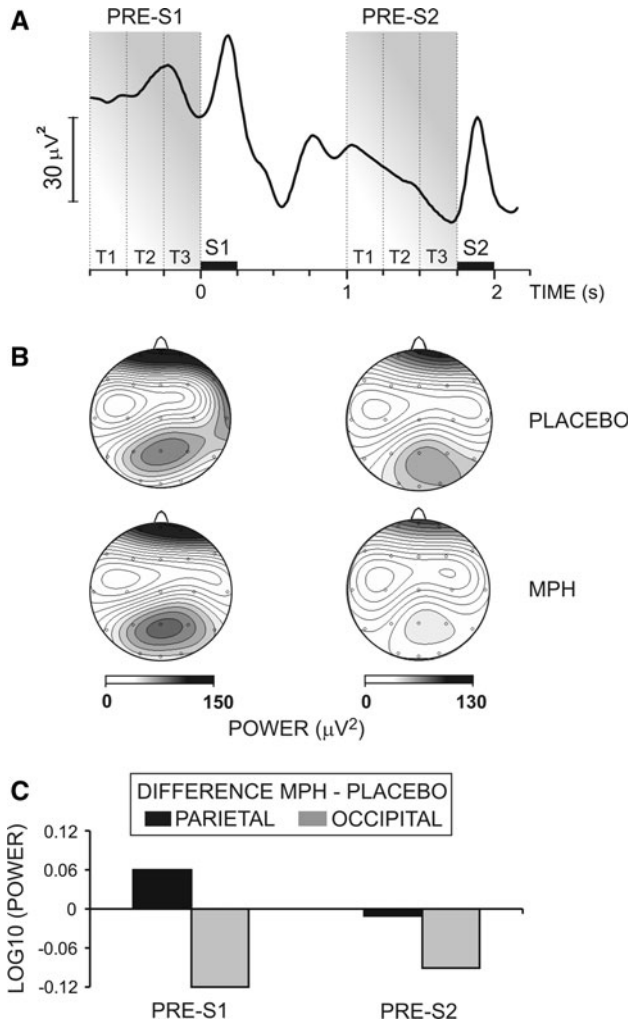

Fig. 2 Overall effect of MPH on alpha total power (TOTP). **a** Grand mean time course of alpha TOTP (all medication, stimulus–response conditions and electrodes are pooled together). The three 250-ms long time windows (*T1*, *T2*, *T3*) used for measurements are shown as shaded areas. **b** Group mean topography maps corresponding to *pre-S1* and *pre-S2* intervals as in (**a**). Three time windows are pooled together. **c** Group mean differences obtained by subtracting alpha TOTP under Placebo from alpha TOTP under MPH at parietal and occipital electrodes for *pre-S1* and *pre-S2* intervals as in (**a**). Three time windows are pooled together

significant Medication × Stimulus × Region interaction [$F(1,11) = 5.3$, $p = 0.04$]. To illustrate this interaction, Fig. 2c shows the changes in alpha power induced by medication for the pre-S1 and pre-S2 periods at the parietal and occipital regions. It is shown that prior to S1, MPH led to an increase of parietal alpha TOTP, while prior to S2 no changes were found at parietal locations [Stimulus × Medication at P3 and P4, $F(1,11) = 4.9$; 8.4, $p = 0.05$; 0.01]. In contrast, alpha TOTP tended to decrease for the two stimulus types S1 and S2 at the occipital regions, but this effect did not reach significance.

Analysis 2 Analysis of occipital alpha power preceding S2 for the respond-left and respond-right conditions revealed a significant Medication × Lead × Condition interaction [$F(2,22) = 4.9$, $p = 0.03$]. As shown in Fig. 3, MPH reduced alpha TOTP only in the respond-right condition and only at the right occipital O2 location [$F(1, 11) = 4.4$, $p = 0.05$] ipsilateral to the side of response, but it did not affect significantly alpha TOTP at the contralateral O1 location [$F(1,11) = 0.3$, $p = 0.66$]. In contrast, for the respond-left condition, MPH did not alter either ipsilateral [O1, $F(1,11) = 0.05$, $p = 0.8$] or contralateral alpha TOTP [O2, $F(1,11) = 1.0$, $p = 0.3$]. These effects were further verified by a Medication × Condition interaction that was non-significant at O1 [$F(1,11) = 0.43$, $p = 0.5$] and significant at O2 [$F(1,11) = 4.7$, $p = 0.05$].

Figure 3 further demonstrates that under placebo, occipital SCPs remained positive along the whole anticipatory period and even increased in positivity with time. Only in the respond-right condition did MPH elicit negative SCPs, which tended to increase in negativity with time, in contrast to both respond-left and Placebo conditions [Medication × Condition × Time, $F(2,22) = 3.88$, $p = 0.05$].

Control analyses Figure 4 demonstrates motor SCPs for left- and right-hand responses under Placebo and MPH at contra- and ipsilateral electrodes. Control analyses of motor SCPs revealed a significant effect of Medication [$F(1,11) = 4.5$, $p = 0.05$] reflecting an overall increase of preparatory motor SCPs under MPH (mean = −3.5 μV, SD = 0.85) relative to Placebo (mean = −1.28 μV, SD = 0.53). Effects of MPH tended to be larger for the right-hand responses [Condition × Medication, $F(1,11) = 3.2$, $p = 0.09$]. There was a main effect of Laterality [$F(1,11) = 5.17$, $p = 0.04$] due to overall smaller SCPs at left than right electrodes. The expected Condition × Laterality interaction [$F(1.11) = 25.1$, $p < 0.001$] was due to larger negative SCPs at motor regions contralateral than ipsilateral to the response (contra vs. ipsi for the right hand, −2.3 μV, SD = 0.82 vs. −1.7 μV, SD = 0.72, for the left hand, −3.8 μV, SD = 0.36 vs. −1.6 μV, SD = 0.63). It also reflected a major decrease in contralateral SCPs for right as compared to left responses. An additional control analysis Condition × Medication × Time was performed for SCPs only at Cz, in which, confirming the findings of Hoegl et al. (2011), no significant effect of MPH was yielded.

Discussion and conclusions

The aim of the present study was to explore the effects of MPH on the activation of sensory cortical regions. A visuomotor warned reaction (S1–S2) task was used to differentiate between effects of unspecific raise in excitability and attention-based activation of visual areas. Also, it was

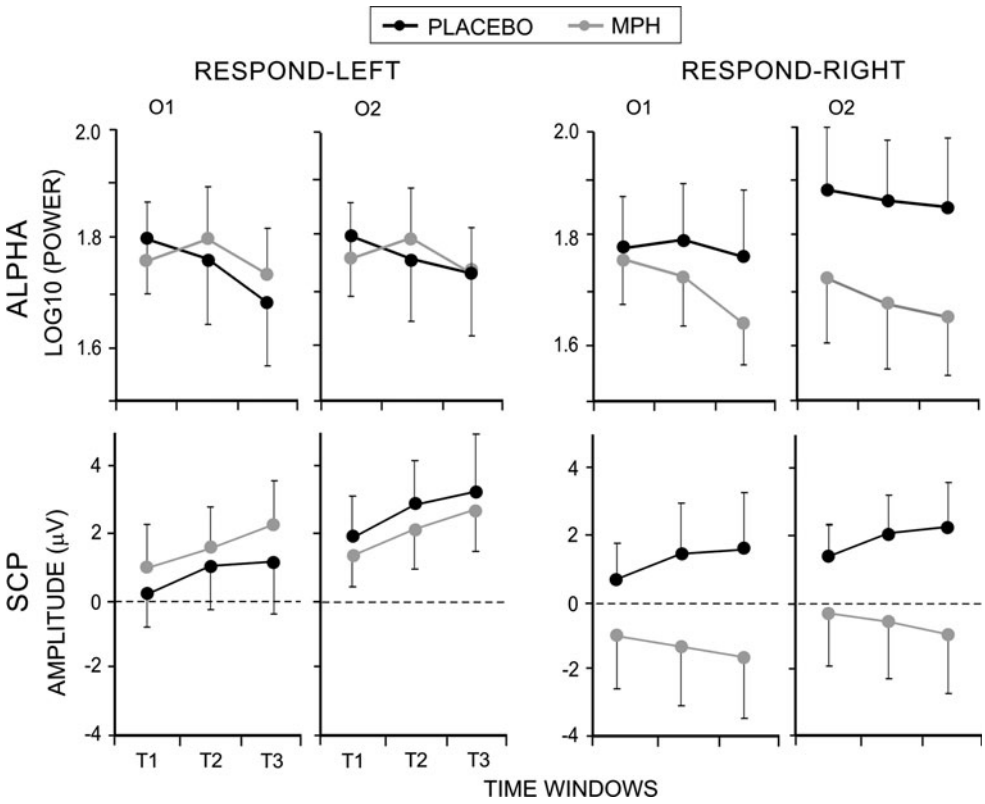

Fig. 3 The effect of MPH on alpha total power and slow cortical potentials (*SCP*). The time dynamics of mean alpha power and SCPs within three consecutive time windows (*T1*, *T2*, *T3*), each 250-ms long, at electrodes *O1* and *O2* is presented for respond-left and respond-right conditions. *Error bars* present standard error

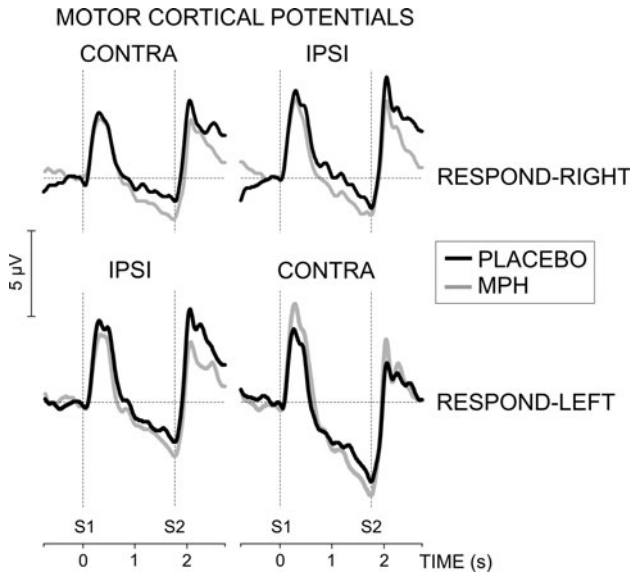

Fig. 4 Effects of MPH on motor cortical potentials. Grand average contra- and ipsilateral SCPs (at central and parietal electrodes pooled together) are shown for the right-hand (*respond-right*) and left-hand (*respond-left*) responses for both conditions, placebo and MPH. Negativity is plotted downwards

tested if MPH would affect fundamental spatial attention mechanisms by boosting a link between spatial motor preparation and perceptual expectation, which would induce or enhance a lateral asymmetry of visual cortex activation corresponding to the side of the prepared response.

Alpha power and occipital SCPs as distinct measures of visual cortical activation

Two distinct measures of cortical activation were used, posterior alpha power and occipital SCPs. According to the results, posterior alpha power was significantly reduced during active stimulus anticipation (pre-S2 relative to pre-S1). This observation confirms previously established relationships between focused attention and alpha power suppression (Pfurtscheller and Lopes da Silva 1999; Jensen and Mazaheri 2010; Thut et al. 2006; Sylvester et al. 2007). The progressive alpha decrease in the course of anticipation further indicates the sensitivity of alpha power to modulations by top-down control mechanisms (Romei et al. 2008; Kelly et al. 2006). Given this functional dynamics of alpha activity, the lack of pronounced negative shifts of occipital SCPs before S2 demonstrates the distinct functional significance of alpha power and SCPs for top-down control (Rektor et al. 2006; Bastiaansen and Brunia 2001; Filipovic et al. 2000). Thus, in the current motor attention experiment (Rushworth et al. 1997, 2001; Leuthold 2003), the preparatory state of the visual cortex appears to be dominated by a task-related increase in the readiness for intake, spreading and communication of visual information as reflected by alpha suppression

(Rektor et al. 2006; Mathewson et al. 2011) rather than by a direct depolarization of visual receptive neurons as reflected by occipital SCPs (Rockstroh 1989; Brunia et al. 2011). Such a preparatory functional state of the visual cortex corresponds to the current task demands directing attention to the side of the motor response, with equal probabilities of Go and NoGo outcome.

Effects of MPH on behavior

In the current study, MPH application in healthy adults did not affect significantly performance measures—reaction time, response variance and error rate. These observations are generally in line with previous reports, according to which MPH is less effective in speeding up reactions in healthy adults (Moll et al. 2003; Coons et al. 1981) than in ADHD children (Kratz et al. 2012; Epstein et al. 2011; DeVito et al. 2009; Spencer et al. 2009) and adults (Aron et al. 2003). However, in the same cued response Go/NoGo task, Kratz et al. (2009) demonstrated a right versus left hand advantage as well as a significant reduction of RT by MPH in blocks with TMS application at the left motor cortex. Here, a no-TMS subset of Kratz et al. (2009) data was used. The present performance results confirmed the observations of Kratz et al., with the lack of statistical significance possibly due to less statistical power stemming from a smaller number of trials analyzed here relative to those of Kratz et al. (2009).

Effects of MPH on visual cortical activation

Major results of the present study provide evidence for the activating effects of MPH on visual cortical areas. First, the observation that under MPH alpha power tended to decrease both before S1 and S2 at occipital electrodes but increased before S1 at parietal electrodes points out that the MPH may not act as a non-specific excitatory agent. The region-specific correlates of simultaneously increased excitation and inhibition imply that similar to the effects of MPH in the motor domain (Moll et al. 2003; Kratz et al. 2009; Buchmann et al. 2010), in the current cued visuo-motor task, MPH may adjust the excitation/inhibition balance in task-relevant visual areas (Kounios et al. 2008). Further, the slight reduction of occipital alpha power both before S1 and S2 shows that MPH effects are not limited to the active anticipation preceding S2. MPH may therefore alter the functional preparedness and processing capacity of visual cortical regions through a mechanism that is not directly mediated by the top-down anticipatory control. This conclusion is supported by the lack of consistent enhancing effects of MPH on occipital negative SCPs that are basically modulated by a top-down pre-activation of cortical neurons (Rockstroh 1989; Rockstroh et al. 1982). Thus, independently of time-structured attentional control, MPH appears to optimize and tune the background excitation/inhibition balance in task-related visual areas.

Notably, MPH did not induce any lateral asymmetry in the contralateral visual areas corresponding to the side of motor attention. This finding does not support a role for MPH in transferring spatial attention from the motor to the sensory domain. Rather, MPH effects on the visual cortex depended on the responding hand, being stronger for the right-hand responses. This was evidenced by both alpha power and SCP measures. Control analyses of centro-parietal SCPs demonstrated a substantially smaller SCP at the left than right electrodes, indicating a weaker pre-activation of the motor cortical regions for right- than left-hand responses. However, performance parameters (RT, response variance and error rate) did not differ between the two hands. Hence, the reduction of motor-preceding negativity at the left motor regions for the precued right hand might be interpreted as reflecting a stronger cognitive control over the balance of excitatory versus inhibitory mechanisms that is needed to maintain performance with the right hand. This interpretation is based on previous observations that the Go tendency prevails in the dominant (right) hand (Kolev et al. 2006; Swinnen et al. 2004), which requires a stronger inhibition of that hand in a task with randomized Go/NoGo trials (Carbonnell et al. 2004). Also, it has been demonstrated that motor-preceding negativity in precued tasks is modulated parametrically by the probability of Go stimuli and is smaller for less predictable targets due to the parallel engagement of inhibitory mechanisms (Leuthold 2003; Scheibe et al. 2009; Wild-Wall et al. 2003; Carbonnell et al. 2004). While the present SCP findings confirm the enhancing effect of MPH on motor preactivation (Linssen et al. 2011; Kratz et al. 2012), they also demonstrate a functional asymmetry of MPH influence on motor activation, which was evidenced by analysis of signals at the hemispheres contralateral to the response. Accordingly, CNV analysis of responses with the two hands at the midline Cz location may be affected by functional asymmetry and yield non-significant effects of MPH (Hoegl et al. 2011).

In addition to refining the asymmetric effects of MPH in the motor domain, the present results further suggest that in case of a stronger involvement of inhibitory control during motor preactivation, MPH also can activate the sensory areas. MPH-related activation of visual sensory areas may engage both a direct increase of visual neurons' excitability by anticipatory attention (as reflected by occipital SCP dynamics for the respond-right condition) and an increase in the readiness for information intake and spreading (as reflected by alpha power decrease for the right-hand condition). The predominant right-hemisphere effect of MPH on occipital alpha power further suggests that MPH may

potentiate visual awareness (Driver and Vuilleumier 2001) as a possible mechanism supporting stimulus selection during increased motor control. In an extended framework, these effects of MPH are consistent with recently found normalizing upregulation by MPH in subjects with ADHD, especially in inhibitory control conditions (interference inhibition and response inhibition): MPH normalized the activation of lateral prefrontal and fronto-striato-thalamic networks during successful inhibition (Bush et al. 2008; Rubia et al. 2011a, b). Thus, the present electrophysiological parameters imply that the beneficial effects of MPH on behavioral inhibition may be at least partly mediated by a top-down sensory pre-activation.

It is a limitation of the present study that a fixed dose of 20 mg MPH was used for all subjects, which did not account for individual pharmacokinetics and body weight. Hence, the magnitude of psychopharmacological effects of MPH was not strictly controlled at the physiological level, in contrast to a recent study of Kratz et al. (2012). Also, the effects of MPH on occipital alpha power were demonstrated for task-processing conditions. It would be relevant to further specify if MPH affects occipital alpha activity in the spontaneous EEG.

From the present findings, it can be concluded that in a cued visuo-motor task, MPH has the potency of adjusting the background excitation/inhibition balance of visual areas. Additionally, during a top-down controlled preparation, MPH may raise the overall functional activation of visual cortical regions, especially in conditions with increased inhibitory control.

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