

# Cortical brain states and corticospinal synchronization influence TMS-evoked motor potentials

Julian Keil, Jana Timm, Iria SanMiguel, Hannah Schulz, Jonas Obleser and Marc Schönwiesner

*J Neurophysiol* 111:513-519, 2014. First published 6 November 2013; doi:10.1152/jn.00387.2013

## You might find this additional info useful...

---

This article cites 46 articles, 21 of which can be accessed free at:

</content/111/3/513.full.html#ref-list-1>

Updated information and services including high resolution figures, can be found at:

</content/111/3/513.full.html>

Additional material and information about *Journal of Neurophysiology* can be found at:

<http://www.the-aps.org/publications/jn>

---

This information is current as of December 16, 2014.

# Cortical brain states and corticospinal synchronization influence TMS-evoked motor potentials

Julian Keil,<sup>1,2</sup> Jana Timm,<sup>1,3</sup> Iria SanMiguel,<sup>1,3</sup> Hannah Schulz,<sup>4</sup> Jonas Obleser,<sup>5</sup>  
and Marc Schönwiesner<sup>1</sup>

<sup>1</sup>International Laboratory for Brain, Music, and Sound Research (BRAMS), Department of Psychology, University of Montréal, Canada; <sup>2</sup>Department of Psychiatry and Psychotherapy, Charité Berlin, Germany; <sup>3</sup>Institute of Psychology, University of Leipzig, Germany; <sup>4</sup>Department of Psychology, University of Konstanz, Germany; and <sup>5</sup>Max Planck Research Group “Auditory Cognition,” Max Planck Institute for Human Cognitive and Brain Science Leipzig, Germany

Submitted 28 May 2013; accepted in final form 5 November 2013

**Keil J, Timm J, SanMiguel I, Schulz H, Obleser J, Schönwiesner M.** Cortical brain states and corticospinal synchronization influence TMS-evoked motor potentials. *J Neurophysiol* 111: 513–519, 2014. First published November 6, 2013; doi:10.1152/jn.00387.2013.—Transcranial magnetic stimulation (TMS) influences cortical processes. Recent findings indicate, however, that, in turn, the efficacy of TMS depends on the state of ongoing cortical oscillations. Whereas power and phase of electromyographic (EMG) activity recorded from the hand muscles as well as neural synchrony between cortex and hand muscles are known to influence the effect of TMS, to date, no study has shown an influence of the phase of cortical oscillations during wakefulness. We applied single-pulse TMS over the motor cortex and recorded motor-evoked potentials along with the electroencephalogram (EEG) and EMG. We correlated phase and power of ongoing EEG and EMG signals with the motor-evoked potential (MEP) amplitude. We also investigated the functional connectivity between cortical and hand muscle activity (corticomuscular coherence) with the MEP amplitude. EEG and EMG power and phase in a frequency band around 18 Hz correlated with the MEP amplitude. High beta-band (~34 Hz) corticomuscular coherence exhibited a positive linear relationship with the MEP amplitude, indicating that strong synchrony between cortex and hand muscles at the moment when TMS is applied entails large MEPs. Improving upon previous studies, we demonstrate a clear dependence of TMS-induced motor effects on the state of ongoing EEG phase and power fluctuations. We conclude that not only the sampling of incoming information but also the susceptibility of cortical communication flow depends cyclically on neural phase.

EEG; EMG; corticospinal coherence; power; phase

CORTICAL OSCILLATORY ACTIVITY plays a crucial role for information processing in the brain (Wang 2010). Different frequency ranges of cortical oscillation are associated with different functions (Dalal et al. 2011; Nunez and Srinivasan 2010) and with stimulus processing in different modalities (Thut et al. 2011).

Studies of visual perception indicate that near-threshold stimuli are more likely to be perceived when low-level visual cortex is in a desynchronized state, reflecting an increased excitability of visual regions. For example, alpha-band power (Hanslmayr et al. 2007; Romei et al. 2010; Van Dijk et al. 2008) has been robustly reported to influence the perception of visual stimuli. These findings suggest that alpha rhythms (~10

Hz) reflect an excitatory-inhibitory balance, in which strong alpha-band power indicates an inhibitory state (Klimesch 2012) and predicts perception. Alpha-band phase (Busch and Vanrullen 2010; Mathewson et al. 2009) has been reported to influence the perception of visual stimuli as well. Thus, in addition to power, the phase of cortical oscillations critically influences perception. Similar effects have been found in auditory perception, which is influenced by theta and delta phase (~1–6 Hz) (Henry and Obleser 2012; Ng et al. 2012; Schroeder and Lakatos 2009; Stefanics et al. 2010), and in somatosensory perception, which is influenced by local beta-band (10–40 Hz) power over primary and secondary somatosensory cortex (Lange et al. 2011). One current interpretation of these results is that ongoing oscillations create periodic windows of facilitated information processing (Busch and Vanrullen 2010; Vanrullen et al. 2011). In a similar manner, cortical oscillations have been suggested to temporally organize incoming speech signals and thereby segregate information into smaller units (Giraud and Poeppel 2012).

Ongoing oscillatory activity also influences the effect of transcranial magnetic stimulation (TMS). TMS-evoked visual perceptions, so-called phosphenes, are perceived more readily when TMS is applied in a period of low alpha power compared with a period of high alpha power (Hartmann et al. 2011; Romei et al. 2008). Phosphenes are also more readily perceived depending on the phase of occipital alpha within 400 ms prior to TMS (Dugué et al. 2011). Siebner and colleagues (2004) showed that preconditioning the primary motor cortex with low frequency (1 Hz) transcranial direct current stimulation could modulate the motor-evoked potential (MEP). Related to this, Bergmann and colleagues (2012) showed state-dependent modulations of MEP amplitude. During global depolarization, indexed by upstates of neocortical slow oscillations (<1 Hz) as recorded by electroencephalogram (EEG), TMS evoked significantly larger MEPs compared with TMS during downstates. These studies showed that the state of the motor system influences the effect of TMS.

The motor cortex communicates with spinal cord neurons via synchronized oscillations in the beta-band (Schoffelen et al. 2005). Cortical beta frequency power (18 Hz) influences the amplitude of the MEP (Schulz et al. 2013). Prior to TMS stimulation, posterior electrodes with an associated source in left parietal cortex exhibited a negative correlation with MEP amplitude. In addition to cortical power, the phase of ongoing oscillatory EMG activity also influences the effect of TMS.

Address for reprint requests and other correspondence: J. Keil, AG Multi-sensory Integration, Dept. of Psychiatry and Psychotherapy, Charité Medical School at St. Hedwigs Hospital, Große Hamburger Straße 5-11, Raum E 307, 10115 Berlin, Germany (e-mail: julian.keil@charite.de).

Van Elswijk and colleagues (2010) showed that TMS-evoked synaptic input from the cortex to the hand muscles is most effective when it arrives at the rising flank of the EMG beta frequency (18 Hz) oscillation. The synchronization between EEG and EMG activity, quantified as the so-called corticomuscular coherence (Hari and Salenius 1999), also influences the amplitude of a TMS-evoked MEP. Schulz and colleagues (2013) showed that reduced communication between cortex and hand muscles as marked by low corticomuscular coherence in the alpha-band (5–15 Hz) is associated with small MEP amplitudes, whereas optimal communication was associated with large MEP amplitudes.

In summary, EEG power, EMG power and phase, and the synchronization between EEG and EMG signals have all been found to influence the amplitude of motor potentials evoked by TMS. However, to our knowledge no study reported a link between ongoing EEG phase and MEP amplitude during wakefulness. Given the ubiquitous role of oscillatory phase in windowing of stimulus processing, EEG phase should also influence the effectiveness of TMS in a quasi-periodic manner.

On the basis of the above-mentioned results, we speculated that the phase of cortical activity influences the effect of TMS stimulation on motor output. To test this hypothesis, we applied TMS pulses to the finger region of the left motor cortex and correlated cortical and muscle activity prior to a TMS pulse with the motor activity evoked by the pulse. In line with the results by van Elswijk and colleagues (2010) and Schulz and colleagues (2013), we hypothesized that pre-pulse cortical beta-band power and phase, measured with EEG over the primary motor cortex, influence MEP amplitude. We further hypothesized that pre-pulse EMG phase and power in the beta-band influence MEP amplitude. Finally, we expected a linear trend in the influence of communication between cortex and hand muscle, as indexed by corticomuscular coherence in the alpha-band, on MEP amplitude such that optimal communication entails larger muscular responses.

## MATERIALS AND METHODS

**Participants.** Twenty-five right-handed participants (mean age 24, range 18–31 yr, 9 male) without a history of neurological or psychiatric disorders took part in the experiment conducted at the International Laboratory for Brain, Music, and Sound Research (BRAMS) at the University of Montréal. All participants gave their written informed consent and were compensated for their participation. The experiment was carried out in accordance with the ethical standards of the Declaration of Helsinki and was approved by the local ethical committee. All the accepted recommendations for the use and safety of TMS were applied.

The current data were collected as part of a larger research project (Timm et al., unpublished data), investigating auditory self-generation effects of voluntary and involuntary movements and their relation to the sense of agency. In brief, the experiment consisted of a block-wise presentation of three voluntary conditions (“motor-auditory voluntary,” “motor voluntary,” and “auditory voluntary”) and three involuntary conditions (“motor-auditory involuntary,” “motor involuntary,” and “auditory involuntary”). All conditions involved EEG recording and the involuntary conditions involved TMS. The auditory involuntary condition involved sham TMS with the TMS coil tilted by 90°. In the voluntary conditions, participants were instructed to press a button. In the involuntary conditions, we applied a single TMS pulse to the left primary motor cortex that elicited an involuntary finger movement of the participants, leading to a button press. The TMS-induced movements were similar, but, of course, not identical to the

voluntary movements. In all conditions, the experimenter was present in the laboratory. Each of the six conditions was presented in four blocks of 45 trials (180 trials per condition). With 1,080 trials (6 conditions  $\times$  180 trials) at an average duration of 3.5 s, the experiment took  $\sim$ 1 h, excluding subject preparation and breaks. Blocks for voluntary and involuntary conditions were always followed by the respective auditory-only and motor-only blocks. Apart from this constraint, the order of the voluntary and involuntary conditions was counterbalanced across participants. We focused on the motor involuntary condition in the current analysis. Whereas previous studies (Schulz et al. 2013; van Elswijk et al. 2010) required hand muscle contraction during which the stimulation occurred, participants in this study were asked to press the button at will in the voluntary conditions, but to rest the hand on the response pad in the involuntary conditions. Therefore, no instruction to contract the muscles was feasible.

**EEG recording and TMS application.** During EEG recordings, participants were seated comfortably and were instructed to move as little as possible and to fixate their gaze on a gray cross, displayed on a black computer screen, to reduce eye movements. Stimulus generation and acquisition of behavioral responses were controlled using MATLAB (The MathWorks, www.mathworks.com) and the Cogent2000 toolbox (www.vislab.ucl.ac.uk/cogent\_2000.php). Participants were instructed to rest the index and middle finger of their right hand relaxed on a piezoresistive response pad controlled by an Arduino microcontroller board (www.arduino.cc). TMS pulses were applied every 2.5–4.5 s (mean 3.5 s). Only trials in which a response (i.e., change in force applied to the response pad) could be elicited were used for data analysis.

TMS was applied with a Rapid2 system with a hand-held 70-mm figure-eight coil delivering biphasic pulses (Magstim, www.magstim.com). ABrainsight 2 neuro-navigation system (Rogue Research, www.rogue-research.com) was used to aid localizing and verifying the TMS target position. We registered a magnetic resonance image of a template head to the head of each participant. The neuro-navigation system tracked the relative positions of the TMS coil and the participant’s head during the experiment and displayed anatomical locations on the template brain corresponding to the current coil position. The approximate location of the left primary motor cortex was identified on the template brain. Initially, the coil was placed at a 45° angle relative to the parasagittal plane (Mills et al. 1992). The biphasic pulse induces an M-shaped current waveform in the cortex. In the first phase, the biphasic pulse therefore induces an anterior-posterior current flow, which is reversed to posterior-anterior in the second phase, and again reversed in the third and fourth phase (Sommer et al. 2006). The position of the coil was then adjusted so that a TMS pulse produced a motor potential in the right first dorsal interosseous muscle. This muscle abducts the index finger and is involved in stabilizing the metacarpophalangeal joint and in the voluntary finger movement that participants executed when pressing the button. Muscle activity was recorded with an electromyography system integrated with the EEG system. The intensity of the TMS stimulation during the experiment was set to 110% of the smallest intensity that produced a motor potential and a visible finger movement. The threshold intensity was determined using an adaptive staircase paradigm (Awiszus 2003). Average motor threshold intensity across all participants was 83.36% of maximum stimulator output. Due to the increased distance between the TMS coil and the scalp introduced by the EEG electrodes, we used relatively high stimulator intensity. A trigger was generated whenever the exerted force (as measured continuously by the response pad) deviated by a set amount from the reference value, which was defined as the weight of the relaxed finger on the pad. Significant movements that led to button presses were elicited in 81% (SD 14.27%) of involuntary trials. Participants were instructed to hold their hand relaxed during TMS stimulation to avoid possible corrections of button presses, which were too soft. It is important to note that this

instruction could be seen as a “no-go” task. Therefore, participants likely exerted a mild tonic force to keep the hand still.

Electroencephalographic activity was recorded continuously throughout the experiment with a SynAmps2 amplifier (Neuroscan, www.neuroscan.com) and TMS-compatible sintered Ag/AgCl electrodes from 64 positions on the scalp, including the left and right mastoid (M1, M2). Electromyographic data was recorded with the same amplifier system from the right first dorsal interosseus muscle. In addition, a ground electrode was placed on the forehead, and a reference electrode was placed on the tip of the nose. Eye movements were monitored with bipolar recordings from electrodes placed above and below the left eye (vertical electro-oculogram) and lateral to the outer canthi of both eyes (horizontal electro-oculogram). The EEG and EOG signals were sampled at 2,000 Hz with an online low-pass filter of 200 Hz. In clinical settings, an online low-pass filter of 2,000 Hz is usually used. This was not possible in our recording environment.

**Data processing.** Epochs of 3 s around the TMS pulse were extracted from the raw data of the motor involuntary condition. A linear trend was removed from each epoch, and power line noise was removed by rejecting the 60-Hz bin from the epoch’s spectrum using a discrete Fourier transform. Resulting epochs were inspected for artefacts, and channels with excessive noise or flat lines were interpolated. The EMG signal was rectified and high-pass filtered (10 Hz, 4th-order Butterworth filter, one pass). Subsequently, the peak of the TMS artefact was identified, and trials with a temporal aberration were excluded. MEP amplitude was computed as the difference

between minimum and maximum between 30 ms and 200 ms after the TMS artefact. The EEG and EMG signal was band-pass filtered for the frequency of interest (17–19 Hz, 8th-order Butterworth filter, one pass). To extract power and phase angles, a Hilbert transform was computed on three cycles of the 18-Hz frequency of interest prior to the upramp of the TMS artefact. Power values were computed from the absolute of the Hilbert transformed signal. We could not determine the exact phase at which the pulse arrived, because the upramp of the TMS artefact required us to insert a small delay (5 ms) between the extracted phase and the recorded TMS pulse.

To evaluate the 18-Hz effect in relationship to other frequencies, we performed a broad-band analysis. Therefore, we computed power, phase, and coherence on the Fourier transform of a single, three-cycle wide time window between 2 Hz and 50 Hz in 2-Hz steps, tapered using a single Hanning window. This resulted in spectral smoothing of 2 Hz for each frequency. The computation of coherence is based on the cross-correlation of two signals and requires an estimate of variance. It can therefore not be performed on single trials (Bullock and McClune 1989). Single trials were thus sorted by the MEP amplitude and partitioned into quartiles for the analysis of corticomuscular coherence. To investigate the influence of the intensity of communication between the first dorsal interosseus muscle and the brain on the resulting MEP peak-to-peak amplitude, we statistically analyzed the linear trend between corticomuscular coherence prior to TMS and MEP size. From the complex Fourier values, coherence was computed between all EEG channels and the EMG channel (see Fig. 1 for details). Preprocessing and time-frequency analysis was accomplished

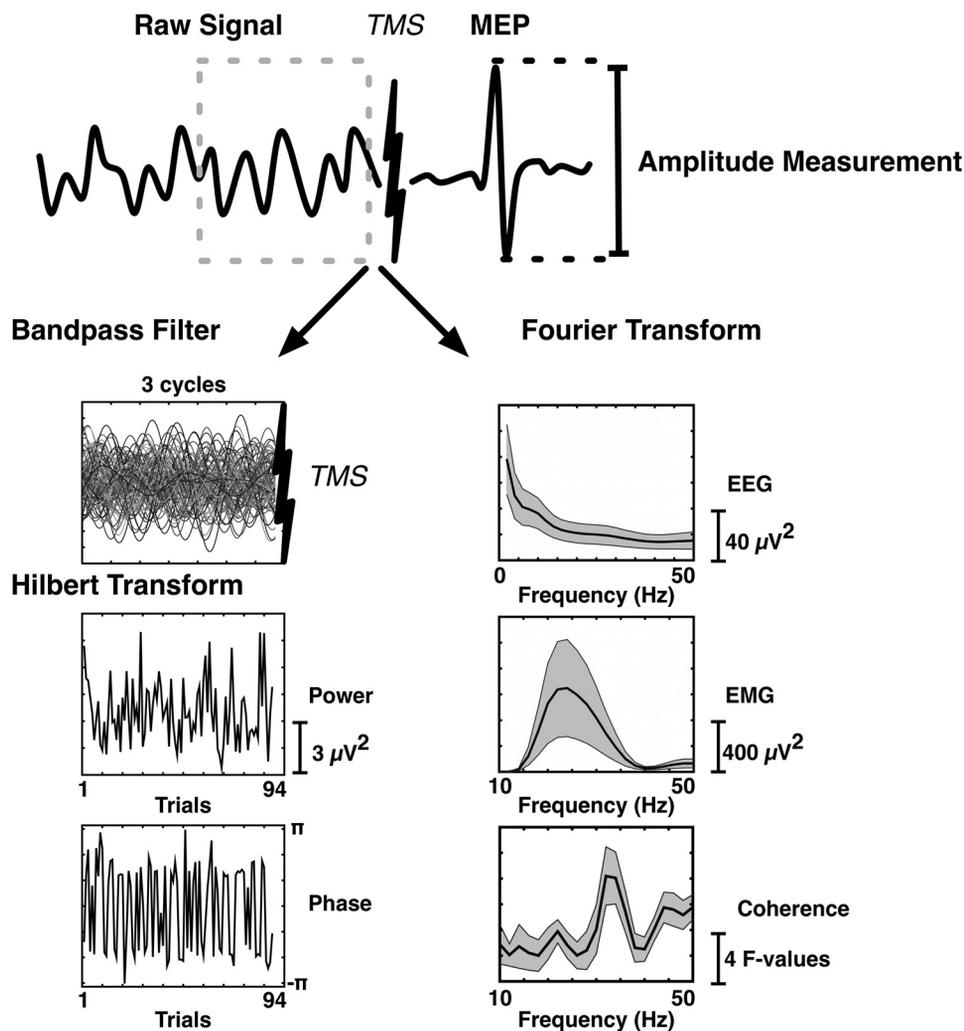


Fig. 1. Overview of the data analysis steps. We computed motor-evoked potential (MEP) amplitude from the difference between maximum and minimum amplitude following the transcranial magnetic stimulation (TMS) pulse. The raw electroencephalogram (EEG) and EMG signals were bandpass filtered and Hilbert-transformed to extract instantaneous phase and power shortly before the onset of the TMS. Depicted at *left* are single trial data from the first subject. We used a Fourier transform to estimate the frequency and coherence spectra of EEG and EMG signals for 3 cycles per frequency. Depicted at *right* are group averages for power and phase at electrode C1 and coherence between electrode CP2 and the EMG electrode.

using the FieldTrip open-source Matlab toolbox (Oostenveld et al. 2011).

**Statistical analysis.** Single trial EEG and EMG data were correlated with the amplitude of the MEP of each single trial. Angular-linear correlations between phase and MEP amplitude were computed (Zar 2010, Eq. 27.47) as implemented in the circular statistics toolbox for Matlab ([www.mathworks.com/matlabcentral/fileexchange/10676](http://www.mathworks.com/matlabcentral/fileexchange/10676)). Because circular correlation values can only take values between 0 and 1, subject-wise correlation values were converted to rational arcsine units (RAU) (Studebaker 1985) prior to statistical analysis. Correlation between power and MEP amplitude were computed using the Matlab built-in function for Pearson's linear correlation coefficient. Pearson's correlation values were Fisher-z-transformed to assure a normal distribution. Correlation values between EEG data and MEP amplitude were tested against zero with an independent-samples *t*-test with Monte-Carlo randomization and cluster-based correction for multiple comparisons (Maris and Oostenveld 2007). Correlation values between EMG-data and MEP amplitude were tested against zero with a one-samples *t*-test. Coherence values were linearized and also converted to RAU for the statistical analysis using linear tests. It was assumed that increased corticomuscular coherence in the pre-TMS period would lead to increased MEP amplitude. Therefore, we statistically analyzed the linear trend between corticomuscular coherence prior to TMS and MEP size.

## RESULTS

We found a significant correlation between EEG beta frequency activity estimated for three cycles of oscillatory activity prior to the TMS pulse and MEP amplitude. Cortical beta frequency (18 Hz) phase prior to TMS onset in a fronto-central electrode cluster showed a significant correlation with MEP ( $\rho \sim 0.2$ ,  $P < 0.001$ , Fig. 2, A and C). As we had applied TMS to the left-hand area, located approximately below the C1 electrode of the 10–20 EEG electrode system, it is of note that C1 was among the electrodes that showed the strongest correlations.

We also found a significant correlation between EEG beta-band power and MEP amplitude. Beta frequency (18 Hz) power prior to TMS onset in a parietal electrode cluster showed a negative correlation with MEP ( $r \sim -0.1$ ,  $P < 0.01$ , Fig. 2, B and D). We found a significant correlation between 18-Hz EMG phase and MEP [ $t(24) = 5.53$ ,  $SD = 9.49$ ,  $P < 0.001$ , Fig. 2E]. There was no significant correlation between EMG power and MEP [ $t(24) = 1.67$ ,  $SD = 0.19$ ,  $P = 0.11$ , Fig. 2E]. Therefore, we conclude that the power level was identical over trials, and the current results are not due to a trivial effect of motor preactivation.

A clearly bimodal distribution of MEP amplitudes was observed when analyzing them with respect to beta oscillatory phase at time of TMS pulse: TMS on the peak or trough of the beta frequency oscillation ( $\sim 90^\circ$  and  $\sim 270^\circ$ ) led to the largest MEP amplitudes (Fig. 3). Stimulation at these “optimal” EEG phase angles was followed by a 34% increase in MEP amplitude compared with an angle of  $0^\circ$  ( $109.09 \mu\text{V}$  vs.  $71.61 \mu\text{V}$ ). Stimulation at the optimal EMG phase angle led to a 17% increase in MEP amplitude ( $123.60 \mu\text{V}$  vs.  $101.95 \mu\text{V}$ ). A state of low parietal EEG beta frequency power was followed by a 14% increase in MEP amplitude compared with a state of high beta frequency power ( $105.44 \mu\text{V}$  vs.  $90.40 \mu\text{V}$ ).

The similarity of the EEG and EMG phase effect suggests that effective communication between cortex and hand muscles may increase MEP amplitude. To test this hypothesis, we divided trials according to MEP amplitude into four quartiles and computed corticomuscular coherence for three cycles of oscillatory activity in each quartile. Following our last hypothesis, we tested the hypothesis of a linear trend in which smaller values of corticomuscular coherence in the alpha-band (10–15 Hz) would be associated with the smaller MEP. Contrary to our hypothesis, we did not find an effect in the alpha-band, but post

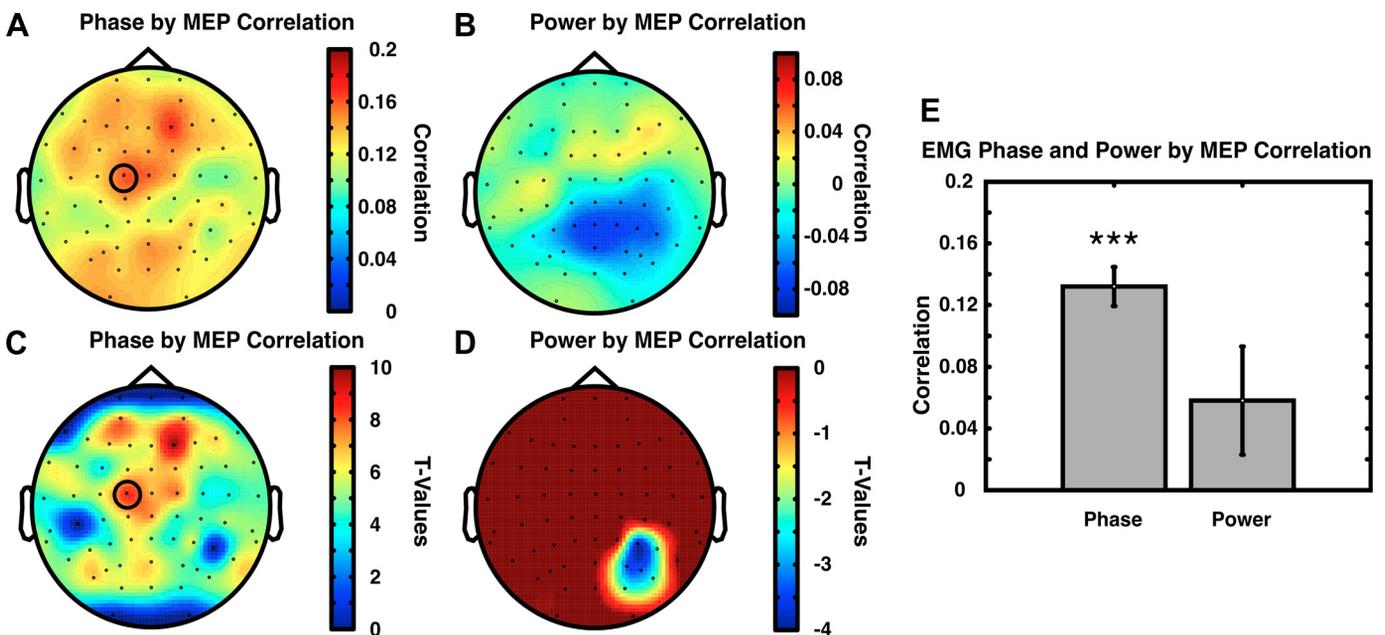


Fig. 2. Results of the correlation analysis between EEG and EMG 18-Hz phase and power and MEP amplitude (circular-linear and linear correlations, respectively). *Top*: topographic distribution of mean correlation coefficients between 18-Hz EEG and EMG phase (A) and power (B) and MEP amplitude. *Bottom*: topographic distribution of statistically significant correlation clusters between 18-Hz EEG phase (C) and power (D) and MEP amplitude. Statistical comparisons were computed on RAU- or z-transformed data, respectively. *T* values are masked for statistical significance. Circular-linear correlations are by definition only positive. Therefore, different color ranges are used for the circular-linear and linear correlations. Electrode C1, which is close to the TMS stimulation site and the hand motor area, is circled in A and C. *E*: mean correlation coefficients ( $\pm$  SE) for the correlation between EMG 18-Hz phase and power and MEP amplitude.

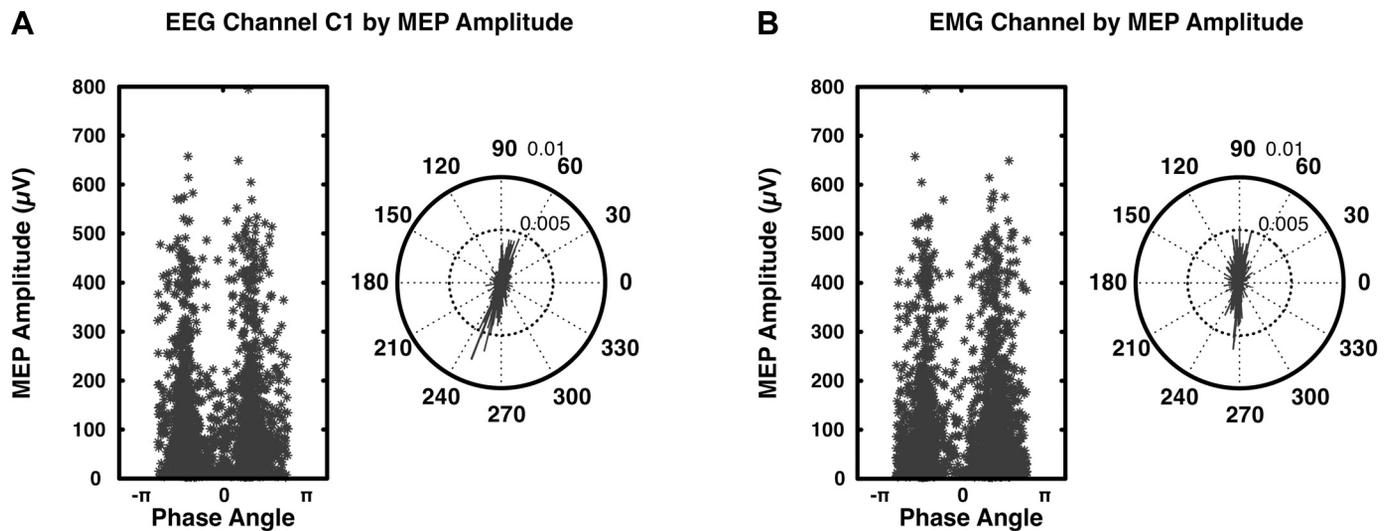


Fig. 3. Single-trial MEP amplitude by EEG (electrode C1) and EMG phase. Electrode C1 was picked as exemplar, because it covers primary motor cortex and is located close to the site of TMS. The  $x$ -axis of the phase-by-amplitude plots depicts the phase of the 18-Hz oscillations. A phase of zero and  $\pm \pi$  indicate the inflection points between peak and trough. Each single point represents a single trail. The same information is depicted on the polar plots, whereby each single trial is represented by a single line, the length of which represents the MEP amplitude. TMS stimulation at the peak or trough of the 18-Hz EEG (A) and EMG (B) oscillation elicited larger MEP amplitudes than at other time points during the oscillatory cycle.

hoc testing showed a linear trend in the high beta-band [34 Hz,  $F(1,24) = 6.05$ ,  $P < 0.05$ , uncorrected, Fig. 4]. This incidental finding is not statistically significant after Bonferroni correction for multiple comparisons, but its centro-parietal topography fits with that of the linear relationship between alpha-band power and MEP described by Schulz and colleagues (2013). Thus, there was some indication that trials with optimal communication between cortex and muscle, as indicated by increased corticomuscular coherence, exhibited the largest MEP amplitude.

## DISCUSSION

The goal of the present study was to relate ongoing cortical oscillatory processes prior to neurostimulation with TMS to the amplitude of the MEP. Participants placed their right middle and index fingers on a pressure-sensitive response pad while we recorded EEG and EMG data. During this relaxed period, we stimulated the contralateral primary motor cortex with TMS

above the motor threshold to elicit a MEP. We hypothesized that 1) cortical beta-band power, but also phase over the primary motor cortex, influence MEP amplitude; 2) EMG phase and power in the beta-band influence MEP amplitude; and 3) a linear trend of the effect of corticomuscular coherence on MEP amplitude in the way that optimal communication entails the largest muscular response.

*Cortical beta-band power and phase over the primary motor cortex influence MEP amplitude.* Two important studies on the role of cortical states marked by slow oscillations indicate an influence of the neocortical state on TMS-evoked MEP amplitude (Bergmann et al. 2012; Siebner et al. 2004). To our knowledge, no prior study established a relationship between local cortical oscillations and TMS-evoked MEP amplitude during wakefulness. We found a significant correlation between oscillatory phase in the beta-band range, centered at 18 Hz, and MEP amplitude. The MEP amplitude varied depending on the phase of local beta-band activity in a fronto-central

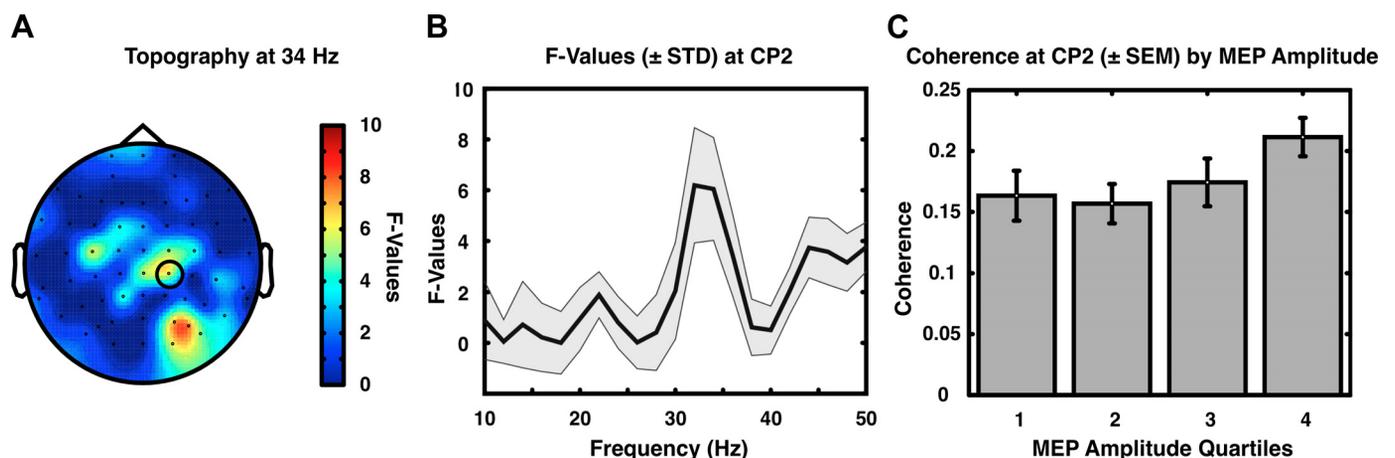


Fig. 4. A: linear relationship between the 34-Hz corticomuscular coherence in a centro-parietal sensor group and the MEP amplitude. B: this trend was strongest in the high beta-band between 30 and 35 Hz. C: increasing corticomuscular coherence in the beta-band was associated with increased MEP amplitude. Electrode CP2 is circled in A and was used for illustrative purposes in B and C.

electrode group. The stimulation was most effective at a phase of approximately  $\pm \pi$ . A similar phase relationship, albeit only for the EMG signal, was reported by van Elswijk and colleagues (2010). Previous results on the influence between the phase of cortical oscillations and visual (Busch et al. 2009; Mathewson et al. 2009) and auditory perception (Henry and Obleser 2012; Neuling et al. 2012; Ng et al. 2012; Vanrullen and McLelland 2013) suggest a widespread relevance of the peak and trough phase in various, usually slower, oscillation frequencies for perception. The present results support the general notion that oscillatory phase acts as a periodic process that gates perception in primary sensory cortices (Busch and Vanrullen 2010) and higher-order cognition (Giraud and Poeppel 2012), but extend it to sensori-motor processes, and, congruently (Engel and Fries 2010), to the beta-band range: our results demonstrate that beta-band phase in the primary motor cortex gates incoming motor commands. Thus the same principle of periodic information processing may apply to the motor system.

EEG beta-band power has been related to movement, with increased beta-band power indicating an idling of motor cortex neurons (Pfurtscheller et al. 1996). In line with our hypotheses and previous results (Schulz et al. 2013), we found that decreased parietal EEG beta-band power correlated with increased MEP amplitude. The parietal topography of the correlation strength suggests a source in posterior parietal cortex, which might be related to attention and coordination (Behrmann et al. 2004; Culham and Kanwisher 2001). An “active” cortical state as indicated by decreased parietal beta-band power might represent a susceptible state open to information processing and stimulation (Jessen et al. 2012).

An alternative, but related, explanation for the effects in posterior parietal cortex could be the guidance and preparation of actions. A number of animal studies have shown direct connections between posterior and frontal cortical areas (Battaglia-Mayer et al. 2001; Johnson et al. 1996). Moreover, Andersen and Buneo (2002) have shown the presence of maps related to the formation of movement intentions. The parietal-frontal connections might serve as projections of intentions formed within posterior parietal cortex. An active cortical state as indicated by decreased parietal beta-band power might thus represent a state in which an intention to move has already been formed.

*EMG phase, but not power, in the beta-band influences MEP amplitude.* Aside from the influence of cortical oscillatory activity on MEP, we also found a strong correlation of the phase of muscular (EMG) oscillations in the beta-band phase with MEP amplitude, at the same frequency of 18 Hz. EMG power in the same frequency was not significantly correlated with MEP amplitude. A recent study (van Elswijk et al. 2010) also linked the phase of EMG beta-band activity to the MEP amplitude. As mentioned above, we found a similar relationship between the time point of stimulation and MEP amplitude. A phase of approximately  $\pm \pi$  entailed the largest gain modulation. This finding underscores the role of beta-band phase in cortical and muscular oscillations as a gating mechanism for information transfer.

*Corticomuscular coherence and MEP amplitude.* We analyzed information transfer from cortex to hand muscle in the last step of our analysis. Functional connectivity is the basis of communication between distant cortical regions, but also be-

tween the cortex and distal muscles, and it can be expressed in corticomuscular coherence (Gross et al. 2004; Schoffelen et al. 2005). We found a linear relationship between corticomuscular coherence and MEP amplitude in the high beta-band (30–35 Hz). The trials with the smallest coherence values also contained the smallest MEP amplitudes, and the trials with the largest coherence values contained the largest MEP amplitudes. In contrast to our results, which show the strongest effect in the beta-band, previous studies found correlations between MEP and corticomuscular coherence in the alpha-band (Gross et al. 2002; Schulz et al. 2013). However, participants in these studies were engaged in an active task, whereas our participants were stimulated while keeping the hand relaxed. Muscle activity may shift the spectrum of corticomuscular coherence away from a rhythm related to mild tonic force in the beta-band to an active suppression rhythm in the alpha-band. This notion is consistent with the gating-by-inhibition framework (Jensen and Mazaheri 2010). Whereas the individual correlations between phase, power, and MEP amplitude are small, they have consistent scalp topography and agree with the results of the coherence analysis. Participants were instructed to keep their hand relaxed in the blocks of trials we analyzed, but to actively move the hand in the remaining blocks. It is therefore possible that subjects perceived this as a no-go task. In this light, the ongoing activity prior to TMS could reflect a tonic stabilizing force, which in turn influences corticomuscular coherence. Our results, therefore, may not generalize to experimental setups in which the target muscle is fully relaxed and does not generate measurable EMG activity. Corticomuscular coherence cannot be estimated without sufficient EMG activity. In the present data, the EEG and EMG power spectra are not flat and don't exhibit the signature broadband or 1/f power spectra expected from noise. Thus, we conclude that the small yet present EMG activity has an influence on corticomuscular communication.

Taken together, our results indicate that neural and neuromuscular beta-band activity significantly influences the amplitude of the TMS-induced motor response (MEP) on different levels. The local state of primary motor cortex at the moment of TMS stimulation, as expressed in beta-band phase and power, and the more global state of functional connectivity with hand muscles critically influence how the stimulus (here: a sweep of neural depolarization extraneously elicited by TMS) will be processed and transmitted. Our results show local power and phase effects in the low beta-band, but corticomuscular coherence effects in the high beta-band. This poses stimulating questions on the functional roles of these frequency bands in sensorimotor processing.

#### GRANTS

This work was supported by the Erasmus Mundus Student Exchange Network in Auditory Cognitive Neuroscience and Grant ERC-2010-StG\_20091209 from the European Union.

#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

#### AUTHOR CONTRIBUTIONS

J.K., J.T., I.S., and M.S. conception and design of research; J.K., J.T., and I.S. performed experiments; J.K. analyzed data; J.K., J.T., I.S., H.S., J.O., and M.S. interpreted results of experiments; J.K. prepared figures; J.K. and M.S.

drafted manuscript; J.K., J.T., I.S., H.S., J.O., and M.S. edited and revised manuscript; J.K., J.T., I.S., H.S., J.O., and M.S. approved final version of manuscript.

## REFERENCES

- Andersen RA, Buneo CA.** Intentional maps in posterior parietal cortex. *Annu Rev Neurosci* 25: 189–220, 2002.
- Awisuz F.** TMS and threshold hunting. *Suppl Clin Neurophysiol* 56: 13–23, 2003.
- Battaglia-Mayer A, Ferraina S, Genovesio A, Marconi B, Squatrito S, Molinari M, Lacquaniti F, Caminiti R.** Eye-hand coordination during reaching. II. An analysis of the relationships between visuomanual signals in parietal cortex and parieto-frontal association projections. *Cereb Cortex* 11: 528–544, 2001.
- Behrmann M, Geng JJ, Shomstein S.** Parietal cortex and attention. *Curr Opin Neurobiol* 14: 212–217, 2004.
- Bergmann TO, Mölle M, Schmidt MA, Lindner C, Marshall L, Born J, Siebner HR.** EEG-guided transcranial magnetic stimulation reveals rapid shifts in motor cortical excitability during the human sleep slow oscillation. *J Neurosci* 32: 243–253, 2012.
- Bullock TH, McClune MC.** Lateral coherence of the electrocorticogram: a new measure of brain synchrony. *Electroencephalogr Clin Neurophysiol* 73: 479–498, 1989.
- Busch NA, Dubois J, Vanrullen R.** The phase of ongoing EEG oscillations predicts visual perception. *J Neurosci* 29: 7869–7876, 2009.
- Busch NA, Vanrullen R.** Spontaneous EEG oscillations reveal periodic sampling of visual attention. *Proc Natl Acad Sci USA* 107: 16048–16053, 2010.
- Culham JC, Kanwisher NG.** Neuroimaging of cognitive functions in human parietal cortex. *Curr Opin Neurobiol* 11: 157–163, 2001.
- Dalal SS, Vidal JR, Hamamé CM, Ossandón T, Bertrand O, Lachaux JP, Jerbi K.** Spanning the rich spectrum of the human brain: slow waves to gamma and beyond. *Brain Struct Funct* (March 25, 2011). doi:10.1007/s00429-011-0307-z.
- Dugué L, Marque P, Vanrullen R.** The phase of ongoing oscillations mediates the causal relation between brain excitation and visual perception. *J Neurosci* 31: 11889–11893, 2011.
- Engel AK, Fries P.** Beta-band oscillations—signalling the status quo? *Curr Opin Neurobiol* 20: 156–165, 2010.
- Giraud AL, Poeppel D.** Cortical oscillations and speech processing: emerging computational principles and operations. *Nat Publish Group* 15: 511–517, 2012.
- Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K, Hommel B, Schnitzler A.** Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. *Proc Natl Acad Sci USA* 101: 13050–13055, 2004.
- Gross J, Timmermann L, Kujala J, Dirks M, Schmitz F, Salmelin R, Schnitzler A.** The neural basis of intermittent motor control in humans. *Proc Natl Acad Sci USA* 99: 2299–2302, 2002.
- Hanslmayr S, Aslan A, Staudigl T, Klimesch W, Herrmann CS, Bäuml KH.** Prestimulus oscillations predict visual perception performance between and within subjects. *NeuroImage* 37: 1465–1473, 2007.
- Hari R, Salenius S.** Rhythmical corticomotor communication. *Neuroreport* 10: R1–R10, 1999.
- Hartmann T, Schulz H, Weisz N.** Probing of brain states in real-time: introducing the conSole environment. *Front Psychol* 2: 36, 2011.
- Henry MJ, Obleser J.** Frequency modulation entrains slow neural oscillations and optimizes human listening behavior. *Proc Natl Acad Sci USA* 109: 20095–20100, 2012.
- Jensen O, Mazaheri A.** Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci* 4: 186, 2010.
- Jessen S, Obleser J, Kotz SA.** How bodies and voices interact in early emotion perception. *PLoS One* 7: e36070, 2012.
- Johnson PB, Ferraina S, Bianchi L, Caminiti R.** Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb Cortex* 6: 102–119, 1996.
- Klimesch W.** Alpha-band oscillations, attention, and controlled access to stored information. *Trends Cogn Sci* 16: 606–617, 2012.
- Lange J, Halacz J, Van Dijk H, Kahlbrock N, Schnitzler A.** Fluctuations of prestimulus oscillatory power predict subjective perception of tactile simultaneity. *Cereb Cortex* 22: 2564–2574, 2012.
- Maris E, Oostenveld R.** Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Meth* 164: 177–190, 2007.
- Mathewson KE, Gratton G, Fabiani M, Beck DM, Ro T.** To see or not to see: prestimulus alpha phase predicts visual awareness. *J Neurosci* 29: 2725–2732, 2009.
- Mills KR, Boniface SJ, Schubert M.** Magnetic brain stimulation with a double coil: the importance of coil orientation. *Electroencephalogr Clin Neurophysiol* 85: 17–21, 1992.
- Neuling T, Rach S, Wagner S, Wolters CH, Herrmann CS.** Good vibrations: oscillatory phase shapes perception. *NeuroImage* 63: 771–778, 2012.
- Ng BSW, Schroeder T, Kayser C.** A precluding but not ensuring role of entrained low-frequency oscillations for auditory perception. *J Neurosci* 32: 12268–12276, 2012.
- Nunez PL, Srinivasan R.** Scale and frequency chauvinism in brain dynamics: too much emphasis on gamma band oscillations. *Brain Struct Funct* 215: 67–71, 2010.
- Oostenveld R, Fries P, Maris E, Schoffelen JM.** FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* 2011: 1–9, 2011.
- Pfurtscheller G, Stancák A, Neuper C.** Event-related synchronization (ERS) in the alpha band—an electrophysiological correlate of cortical idling: a review. *Int J Psychophysiol* 24: 39–46, 1996.
- Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G.** Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. *Cerebral Cortex* 18: 2010–2018, 2008.
- Romei V, Gross J, Thut G.** On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: correlation or causation? *J Neurosci* 30: 8692–8697, 2010.
- Schoffelen JM, Oostenveld R, Fries P.** Neuronal coherence as a mechanism of effective corticospinal interaction. *Science* 308: 111–113, 2005.
- Schroeder CE, Lakatos P.** Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci* 32: 9–18, 2009.
- Schulz H, Ubelacker T, Keil J, Müller N, Weisz N.** Now I am ready—now I am not: the influence of pre-TMS oscillations and corticomuscular coherence on motor-evoked potentials. *Cereb Cortex* (February 8, 2013). doi:10.1093/cercor/bht024.
- Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, Rothwell JC.** Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci* 24: 3379–3385, 2004.
- Sommer M, Alfaro A, Rummel M, Speck S, Lang N, Tings T, Paulus W.** Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. *Clin Neurophysiol* 117: 838–844, 2006.
- Stefanics G, Hangya B, Hernadi I, Winkler I, Lakatos P, Ulbert I.** Phase entrainment of human delta oscillations can mediate the effects of expectation on reaction speed. *J Neurosci* 30: 13578–13585, 2010.
- Studebaker GA.** A “rationalized” arcsine transform. *J Speech Hear Res* 28: 455, 1985.
- Thut G, Schyns PG, Gross J.** Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Front Psychol* 2, 2011.
- Van Dijk H, Schoffelen JM, Oostenveld R, Jensen O.** Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *J Neurosci* 28: 1816–1823, 2008.
- van Elswijk G, Maj F, Schoffelen JM, Overeem S, Stegeman DF, Fries P.** Corticospinal beta-band synchronization entails rhythmic gain modulation. *J Neurosci* 30: 4481–4488, 2010.
- Vanrullen R, Busch NA, Drewes J, Dubois J.** Ongoing EEG phase as a trial-by-trial predictor of perceptual and attentional variability. *Front Psychol* 2: 60, 2011.
- Vanrullen R, McLelland D.** What goes up must come down: EEG phase modulates auditory perception in both directions. *Front Psychol* 4: 16, 2013.
- Wang XJ.** Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol Rev* 90: 1195–1268, 2010.
- Zar JH.** *Biostatistical analysis* (5th ed.). Upper Saddle River, NJ: Pearson Education, 2010.