1 **Cortical Brain States and Corticospinal Synchronization**

2 **Influence TMS-evoked motor potentials**

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20 Running Head: EEG and EMG State and Synchronization Influence MEP

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Abstract

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 showed 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 electromyogram (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.

Introduction

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 (Nunez and Srinivasan, 2010; Dalal et al., 2011) 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) (Van Dijk et al., 2008; Romei et al., 2010) 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 (Mathewson et al., 2009; Busch and Vanrullen, 2010) 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; (Schroeder and Lakatos, 2009; Stefanics et al., 2010; Ng et al., 2012; Henry and Obleser, 2012), 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 TMS. TMS-evoked visual perceptions, so-called phosphenes, are perceived more readily when TMS is applied in a period of low alpha power compared to a period of high alpha power (Romei et al., 2008; Hartmann et al., 2011). 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 (Siebner et al., 2004) showed that pre-conditioning the primary motor cortex with low frequency (1 Hz) transcranial direct current stimulation (tDCS) could modulate the MEP. Related to this, Bergmann and colleagues showed state-dependent modulations of MEP amplitude (Bergmann et al., 2012). During global depolarization, indexed by up-states of neocortical slow oscillations (<1Hz) as recorded by EEG, TMS evoked significantly larger MEPs compared to TMS during down-states. 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

98 correlation with MEP amplitude. In addition to cortical power, the phase of ongoing
99 oscillatory EMG activity also influences the effect of TMS. Van Elswijk and colleagues
100 (van Elswijk et al., 2010) showed that TMS-evoked synaptic input from the cortex to the
101 hand muscles is most effective when it arrives at the rising flank of the EMG beta
102 frequency (18 Hz) oscillation. The synchronization between EEG and EMG activity,
103 quantified as the so-called corticomuscular coherence (Hari and Salenius, 1999), also
104 influences the amplitude of a TMS-evoked MEP. Schulz and colleagues (Schulz et al.,
105 2013) showed that reduced communication between cortex and hand muscles as
106 marked by low corticomuscular coherence in the alpha band (5-15 Hz) is associated
107 with small MEP amplitudes, whereas optimal communication was associated with large
108 MEP amplitudes.

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

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

127

Materials and Methods

Participants: Twenty-five right-handed participants (mean age 24, range 18–31 years, 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., under review), 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 1080 trials (6 conditions × 180 trials) at an average duration of 3.5 s, the experiment took approximately 1 hour, 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 focussed on the "motor involuntary" condition in the current analysis. Whereas previous studies (van Elswijk et al., 2010; Schulz et al., 2013) 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

160   in the "involuntary" conditions. Therefore, no instruction to contract the muscles was
161   feasible.

162   *EEG recording and TMS application:* During EEG recordings, participants were seated
163   comfortably and were instructed to move as little as possible and to fixate their gaze on
164   a grey cross, displayed on a black computer screen, in order to reduce eye movements.
165   Stimulus generation and acquisition of behavioural responses were controlled using
166   MATLAB (The MathWorks, www.mathworks.com) and the Cogent2000 toolbox
167   (www.vislab.ucl.ac.uk/cogent_2000.php). Participants were instructed to rest the index
168   and middle finger of their right hand relaxed on a piezoresistive response pad controlled
169   by an Arduino microcontroller board (www.arduino.cc). TMS pulses were applied every
170   2.5 to 4.5 s (mean 3.5 s). Only trials in which a response (i.e. change in force applied to
171   the response pad) could be elicited were used for data analysis.

172   TMS was applied with a Rapid2 system with a hand-held 70-mm figure-eight coil
173   delivering biphasic pulses (Magstim, www.magstim.com). A Brainsight 2 neuro-
174   navigation system (Rogue Research, www.rogue-research.com) was used to aid
175   localizing and verifying the TMS target position. We registered a magnetic resonance
176   image of a template head to the head of each participant. The neuro-navigation system
177   tracked the relative positions of the TMS coil and the participant's head during the
178   experiment and displayed anatomical locations on the template brain corresponding to
179   the current coil position. The approximate location of the left primary motor cortex was
180   identified on the template brain. Initially, the coil was placed at a 45° angle relative to
181   the parasagittal plane (Mills et al., 1992). The biphasic pulse induces a M-shaped current
182   waveform in the cortex. In the first phase, the biphasic pulse therefore induces an
183   anterior-posterior current flow, which is reversed to posterior-anterior in the second
184   phase, and again reversed in the third and fourth phase (Sommer et al., 2006). The
185   position of the coil was then adjusted so that a TMS pulse produced a motor potential in
186   the right first dorsal interosseous muscle. This muscle abducts the index finger and is
187   involved in stabilizing the metacarpophlangeal joint and in the voluntary finger
188   movement that participants executed when pressing the button. Muscle activity was
189   recorded with an electromyography system integrated with the EEG system. The
190   intensity of the TMS stimulation during the experiment was set to 110% of the smallest
191   intensity that produced a motor potential and a visible finger movement. The threshold
192   intensity was determined using an adaptive staircase paradigm (Awiszus, 2003).

193   Average motor threshold intensity across all participants was 83.36 % of maximum
194   stimulator output. Due to the increased distance between the TMS coil and the scalp
195   introduced by the EEG electrodes, we used relatively high stimulator intensity. A trigger
196   was generated whenever the exerted force (as measured continuously by the response
197   pad) deviated by a set amount from the reference value, which was defined as the
198   weight of the relaxed finger on the pad. Significant movements that led to button presses
199   were elicited in 81 % (standard deviation: 14.27 %) of involuntary trials. Participants
200   were instructed to hold their hand relaxed while TMS stimulation to avoid possible
201   corrections of button presses, which were too soft. It is important to note that this
202   instruction could be seen as a "no-go" task. Therefore, participants likely exerted a mild
203   tonic force to keep the hand still.

204   Electroencephalographic activity was recorded continuously throughout the experiment
205   with a SynAmps2 amplifier (Neuroscan, www.neuroscan.com) and TMS-compatible
206   sintered Ag/AgCl electrodes from 64 positions on the scalp, including the left and right
207   mastoid (M1, M2). Electromyographic data was recorded with the same amplifier
208   system from right first dorsal interosseus muscle. In addition, a ground electrode was
209   placed on the forehead, and a reference electrode was placed on the tip of the nose. Eye
210   movements were monitored with bipolar recordings from electrodes placed above and
211   below the left eye (vertical electro-oculogram, VEOG) and lateral to the outer canthi of
212   both eyes (horizontal electro-oculogram, HEOG). The EEG and EOG signals were
213   sampled at 2000 Hz with an online lowpass filter of 200 Hz. In clinical settings, an online
214   lowpass filter of 2000 Hz is usually used. This was not possible in our recording
215   environment.

216   *Data processing:* Epochs of 3 seconds around the TMS pulse were extracted from the raw
217   data of the "motor involuntary" condition. A linear trend was removed from each epoch
218   and power line noise was removed by rejecting the 60 Hz bin from the epoch's spectrum
219   using a discrete Fournier transform. Resulting epochs were inspected for artefacts and
220   channels with excessive noise or flat lines were interpolated. The EMG signal was
221   rectified and high-pass filtered (10 Hz, 4th order Butterworth filter, one pass).
222   Subsequently, the peak of the TMS artefact was identified and trials with a temporal
223   aberration were excluded. MEP amplitude was computed as the difference between
224   minimum and maximum between 30 ms and 200 ms after the TMS artefact. The EEG and
225   EMG signal was band-pass filtered for the frequency of interest (17 – 19 Hz, 8th-order

226   Butterworth filter, one pass). In order to extract power and phase angles, a Hilbert
227   transform was computed on three cycles of the 18 Hz frequency of interest prior to the
228   up-ramp of the TMS artefact. Power values were computed from the absolute of the
229   Hilbert transformed signal. We could not determine the exact phase at which the pulse
230   arrived, because the up-ramp of the TMS artefact required us to insert a small delay (5
231   ms) between the extracted phase and the recorded TMS pulse.

232   In order to evaluate the 18 Hz effect in relationship to other frequencies, we performed
233   a broad-band analysis. Therefore, we computed power, phase and coherence on the
234   Fourier transform of a single, three cycle wide time window between 2 Hz and 50 Hz in
235   2 Hz steps, tapered using a single Hanning window. This resulted in spectral smoothing
236   of 2 Hz for each frequency. The computation of coherence is based on the cross-
237   correlation of two signals and requires an estimate of variance. It can therefore not be
238   performed on single trials (Bullock and McClune, 1989). Single trials were thus sorted
239   by the MEP amplitude and partitioned into quartiles for the analysis of corticomuscular
240   coherence. To investigate the influence of the intensity of communication between the
241   first dorsal interosseus muscle and the brain on the resulting MEP peak-to-peak
242   amplitude, we statistically analyzed the linear trend between corticomuscular coherence
243   prior to TMS and MEP size. From the complex Fourier values, coherence was computed
244   between all EEG channels and the EMG channel (see Fig. 1 for details). Preprocessing
245   and time-frequency analysis was accomplished using the FieldTrip open-source Matlab
246   toolbox (Oostenveld et al., 2011).

247   *Statistical analysis:* Single trial EEG and EMG data were correlated with the amplitude of
248   the MEP of each single trial. Angular-linear correlations between phase and MEP
249   amplitude were computed (Eq. 27.47, (Zar, 2010)) as implemented in the circular
250   statistics   toolbox   for   Matlab
251   (www.mathworks.com/matlabcentral/fileexchange/10676).   Because   circular
252   correlation values can only take values between 0 and 1, subject-wise correlation values
253   were converted to rational arcsine units (RAU; Studebaker, 1985) prior to statistical
254   analysis. Correlation between power and MEP amplitude were computed using the
255   Matlab built-in function for Pearson's linear correlation coefficient. Pearson's
256   correlation values were Fisher-z-transformed in order to assure a normal distribution.
257   Correlation values between EEG data and MEP amplitude were tested against zero with
258   an independent-samples t-test with Monte-Carlo randomization and cluster-based

259   correction for multiple comparisons (Maris and Oostenveld, 2007). Correlation values

260   between EMG-data and MEP amplitude were tested against zero with a one-samples t-

261   test. Coherence values were linearized and also converted to rational arcsine units

262   (RAU) for the statistical analysis using linear tests. It was assumed that increased

263   corticomuscular coherence in the pre-TMS period would lead to increased MEP

264   amplitude. Therefore we statistically analyzed the linear trend between corticomuscular

265   coherence prior to TMS and MEP size.

266

267

268   **Results**

269   We found a significant correlation between EEG beta frequency activity estimated for 3

270   cycles of oscillatory activity prior to the TMS pulse and MEP amplitude. Cortical beta

271   frequency (18 Hz) phase prior to TMS onset in a fronto-central electrode cluster showed

272   a significant correlation with MEP (rho $\sim$ 0.2, $p < 0.001$, Fig. 2 A and C). As we had

273   applied TMS to the left hand area, located approximately below the C1 electrode of the

274   10-20 EEG electrode system, it is of note that C1 was among the electrodes that showed

275   the strongest correlations.

276   We also found a significant correlation between EEG beta band power and MEP

277   amplitude. Beta frequency (18 Hz) power prior to TMS onset in a parietal electrode

278   cluster showed a negative correlation with MEP ($r \sim -0.1$, $p < 0.01$, Fig. 2 B and D). We

279   found a significant correlation between 18 Hz EMG phase and MEP ($t(24) = 5.53$, sd =

280   9.49, $p < 0.001$, Fig. 2 E). There was a no significant correlation between EMG power and

281   MEP, ($t(24) = 1.67$, sd = 0.19, $p = 0.11$, figure 2 E). Therefore, we conclude that the

282   power level was identical over trials and the current results are not due to a trivial effect

283   of motor pre-activation.

284   A clearly bimodal distribution of MEP amplitudes was observed, when analyzing them

285   with respect to beta oscillatory phase at time of TMS pulse: TMS on the peak or trough of

286   the beta frequency oscillation ($\sim$90° and $\sim$270°) led to the largest MEP amplitudes (Fig.

287   3). Stimulation at these "optimal" EEG phase angles was followed by a 34% increase in

288   MEP amplitude compared to an angle of 0° (109.09 µV vs. 71.61 µV). Stimulation at the

289   optimal EMG phase angle lead to a 17% increase in MEP amplitude (123.60 µV vs.

290 101.95 µV). A state of low parietal EEG beta frequency power was followed by a 14 %
291 increase in MEP amplitude compared to a state of high beta frequency power (105.44 µV
292 vs. 90.40 µV).

293 The similarity of the EEG and EMG phase effect suggests that effective communication
294 between cortex and hand muscles may increase MEP amplitude. To test this hypothesis,
295 we divided trials according to MEP amplitude into four quartiles and computed
296 corticomuscular coherence for three cycles of oscillatory activity in each quartile.
297 Following our last hypothesis, we tested the hypothesis of a linear trend in which
298 smaller values of corticomuscular coherence in the alpha band (10-15 Hz) would be
299 associated with the smaller MEP. Contrary to our hypothesis, we did not find an effect in
300 the alpha band, but post-hoc testing showed a linear trend in the high beta band (34 Hz,
301 $F(1,24) = 6.05$, $p < 0.05$, uncorrected, Fig. 4). This incidental finding is not statistically
302 significant after Bonferroni correction for multiple comparisons, but its centro–parietal
303 topography fits with that of the linear relationship between alpha-band power and MEP
304 described by Schulz and colleagues (Schulz et al., 2013). Thus, there was some indication
305 that trials with optimal communication between cortex and muscle, as indicated by
306 increased corticomuscular coherence, exhibited the largest MEP amplitude.

307

Discussion

309 The goal of the present study was to relate ongoing cortical oscillatory processes prior
310 to neurostimulation with TMS to the amplitude of the motor evoked potential (MEP).
311 Participants placed their right middle and index finger on a pressure-sensitive response
312 pad while we recorded EEG and EMG data. During this relaxed period, we stimulated the
313 contralateral primary motor cortex with TMS above the motor threshold to elicit a
314 motor-evoked potential. We hypothesized, that 1) cortical beta band power, but also
315 phase over the primary motor cortex influence MEP amplitude; 2) EMG phase and
316 power in the beta band influence MEP amplitude; and 3) a linear trend of the effect of
317 corticomuscular coherence on MEP amplitude in the way that optimal communication
318 entails the largest muscular response.

319 *Cortical beta band power and phase over the primary motor cortex influence MEP*
320 *amplitude*

321 Two important studies on the role of cortical states marked by slow oscillations indicate
322 an influence of the neocortical state on TMS-evoked MEP amplitude (Siebner et al.,
323 2004; Bergmann et al., 2012). To our knowledge no prior study established a
324 relationship between local cortical oscillations and TMS-evoked MEP amplitude during
325 wakefulness. We found a significant correlation between oscillatory phase in the beta
326 band range, centered at 18 Hz, and MEP amplitude. The MEP amplitude varied
327 depending on the phase of local beta band activity in a fronto-central electrode group.
328 The stimulation was most effective at a phase of approximately $\pm \pi$. A similar phase
329 relationship, albeit only for the EMG signal, was reported by Van Elswijk and colleagues
330 (van Elswijk et al., 2010). Previous results on the influence between the phase of cortical
331 oscillations and visual (Mathewson et al., 2009; Busch et al., 2009) and auditory
332 perception (Neuling et al., 2012; Ng et al., 2012; Henry and Obleser, 2012; VanRullen
333 and McLelland, 2013) suggest a widespread relevance of the peak and trough phase in
334 various, usually slower, oscillation frequencies for perception. The present results
335 support the general notion that oscillatory phase acts as a periodic process that gates
336 perception in primary sensory cortices (Busch and VanRullen, 2010) and higher order
337 cognition (Giraud and Poeppel, 2012), but extend it to sensori–motor processes and,
338 congruently (Engel and Fries, 2010), to the beta-band range: Our results demonstrate
339 that beta band phase in the primary motor cortex gates incoming motor commands.
340 Thus the same principle of periodic information processing may apply to the motor
341 system.

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

351 An alternative, but related, explanation for the effects in posterior parietal cortex could
352 be the guidance and preparation of actions. A number of animal studies have shown
353 direct connections between posterior and frontal cortical areas (Johnson et al.,

354   1996);(Battaglia-Mayer et al., 2001). Moreover, Andersen et al. (Andersen and Buneo,
355   2002) have shown the presence of maps related to the formation of movement
356   intentions. The parietal-frontal connections might serve as projections of intentions
357   formed within posterior parietal cortex. An "active" cortical state as indicated by
358   decreased parietal beta band power might thus represent a state in which an intention
359   to move has already been formed.

360   *EMG phase, but not power, in the beta band influences MEP amplitude*

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

370   *Corticomuscular coherence and MEP amplitude*

371   We analysed information transfer from cortex to hand muscle in the last step of our
372   analysis. Functional connectivity is the basis of communication between distant cortical
373   regions, but also between the cortex and distal muscles, and it can be expressed in
374   corticomuscular coherence (Gross et al., 2004; Schoffelen et al., 2005). We found a linear
375   relationship between corticomuscular coherence and MEP amplitude in the high beta
376   band (30–35 Hz). The trials with the smallest coherence values also contained the
377   smallest MEP amplitudes and trials with largest coherence values contained the largest
378   MEP amplitudes. In contrast to our results, which show the strongest effect in the beta
379   band, previous studies found correlations between MEP and corticomuscular coherence
380   in the alpha band (Gross et al., 2002; Schulz et al., 2013). However, participants in these
381   studies were engaged in an active task, whereas our participants were stimulated while
382   keeping the hand relaxed. Muscle activity may shift the spectrum of corticomuscular
383   coherence away from a rhythm related to mild tonic force in the beta band to an active
384   suppression rhythm in the alpha band. This notion is consistent with the gating-by-
385   inhibition framework (Jensen and Mazaheri, 2010). Whereas the individual correlations

386 between phase, power, and MEP amplitude are small they have consistent scalp
387 topography and agree with the results of the coherence analysis. Participants were
388 instructed to keep their hand relaxed in the blocks of trials we analysed, but to actively
389 move the hand in the remaining blocks. It is therefore possible that subjects perceived
390 this as a "no-go" task. In this light, the ongoing activity prior to TMS could reflect a tonic
391 stabilizing force, which in turn influences corticomuscular coherence. Our results
392 therefore may not generalize to experimental setups in which the target muscle is fully
393 relaxed and does not generate measurable EMG activity. Corticomuscular coherence
394 cannot be estimated without sufficient EMG activity. In the present data, the EEG and
395 EMG power spectra are not flat and don't exhibit the signature broadband or 1/f power
396 spectra expected from noise. Thus, we conclude that the small yet present EMG activity
397 has an influence on corticomuscular communication.

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

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535

536   **Figure Captions**

537   Figure 1: Overview of the data analysis steps. We computed MEP amplitude from the
538   difference between maximum and minimum amplitude following the TMS pulse. The
539   raw EEG and EMG signals were bandpass filtered and Hilbert-transformed to extract
540   instantaneous phase and power shortly before the onset of the TMS. Depicted on the left
541   side are single trial data from the first subject. We used a Fourier transform to estimate
542   the frequency and coherence spectra of EEG and EMG signals for three cycles per
543   frequency. Depicted on the right side are group averages for power and phase at
544   electrode C1 and coherence between electrode CP2 and the EMG electrode.

545

546 Figure 2: Results of the correlation analysis between EEG and EMG 18 Hz phase and
547 power and MEP amplitude (circular–linear and linear correlations, respectively). Top
548 row: Topographic distribution of mean correlation coefficients between 18 Hz EEG and
549 EMG phase (A) and power (B) and MEP amplitude. Bottom row: Topographic
550 distribution of statistically significant correlation clusters between 18 Hz EEG phase (C)
551 and power (D) and MEP amplitude. Statistical comparisons were computed on RAU- or
552 z-transformed data, respectively. T-values are masked for statistical significance.
553 Circular-linear correlations are by definition only positive. Therefore, different color
554 ranges are used for the circular-linear and linear correlations. Electrode C1, which is
555 close to the TMS stimulation site and the hand motor area, is circled in (A) and (C). (E)
556 Mean correlation coefficients (± SEM) for the correlation between EMG 18 Hz phase and
557 power and MEP amplitude.

558

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

568

569 Figure 4: (A) Linear relationship between the 34 Hz corticomuscular coherence in a
570 centro-parietal sensor group and the MEP amplitude. (B) This trend was strongest in the
571 high beta band between 30 and 35 Hz. (C) Increasing corticomuscular coherence in the
572 beta band was associated with increased MEP amplitude. Electrode CP2 is circled in (A)
573 and was used for illustrative purposes in (B) and (C).
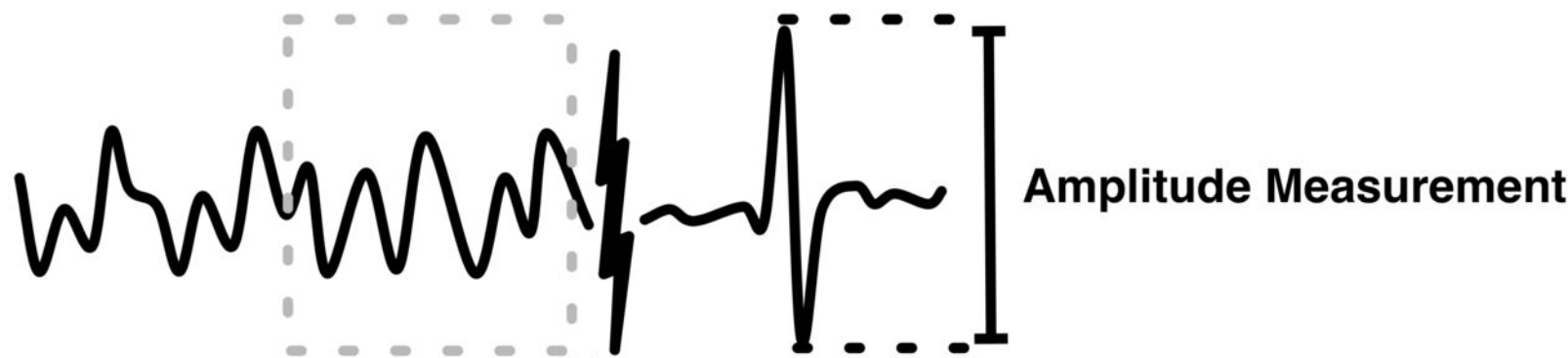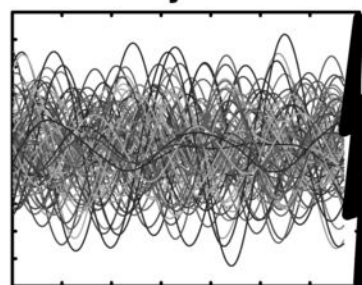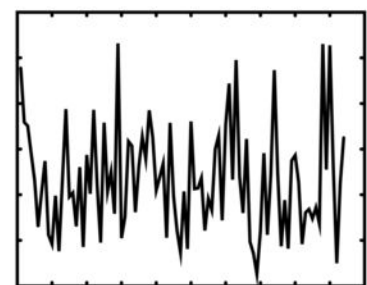
574

Raw Signal   *TMS*   **MEP**

Amplitude Measurement

Bandpass Filter

3 cycles

TMS

Fourier Transform

EEG

40 μV^2

Frequency (Hz)

Hilbert Transform

Power

3 μV^2

1   Trials   94

Phase

π

$-\pi$

1   Trials   94

EMG
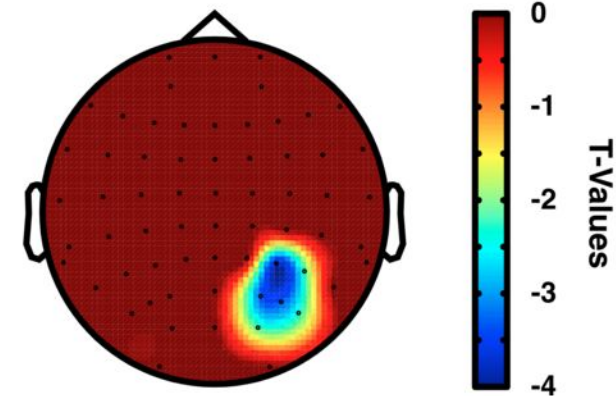
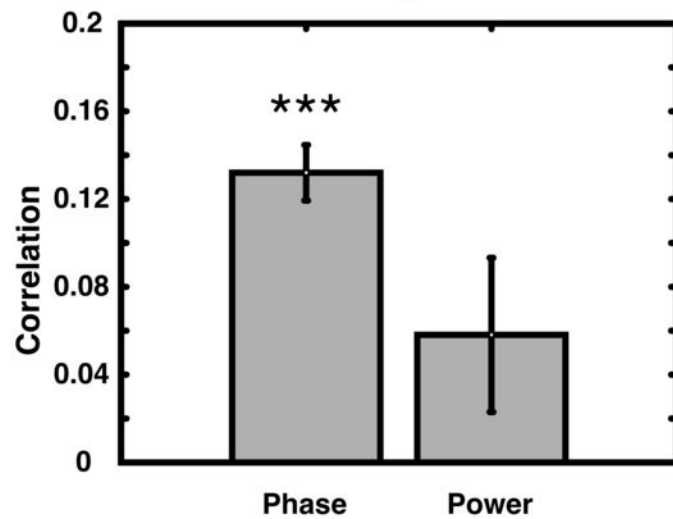400 μV^2

10   Frequency (Hz)   50

Coherence

4 F-values
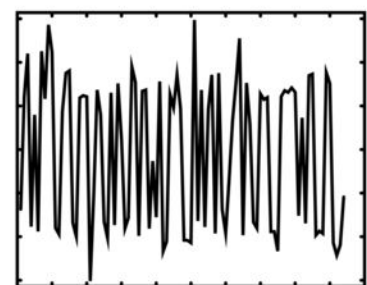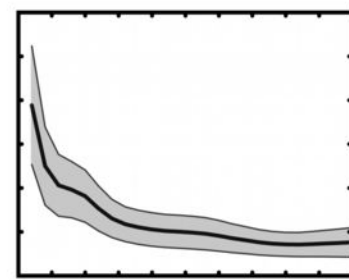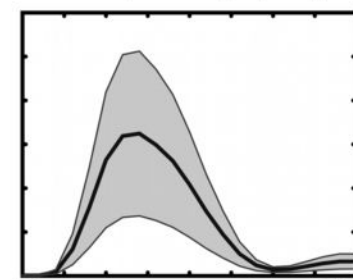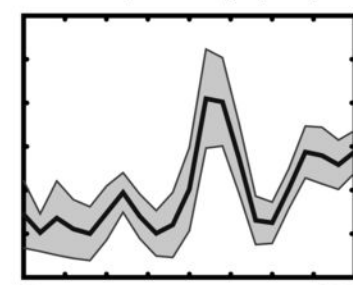
10   Frequency (Hz)   50

A Phase by MEP Correlation
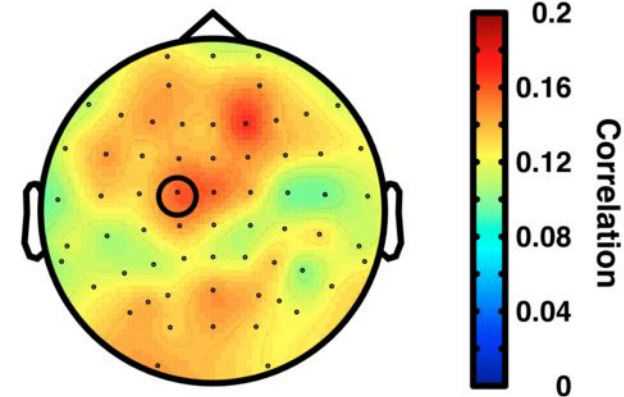
B Power by MEP Correlation
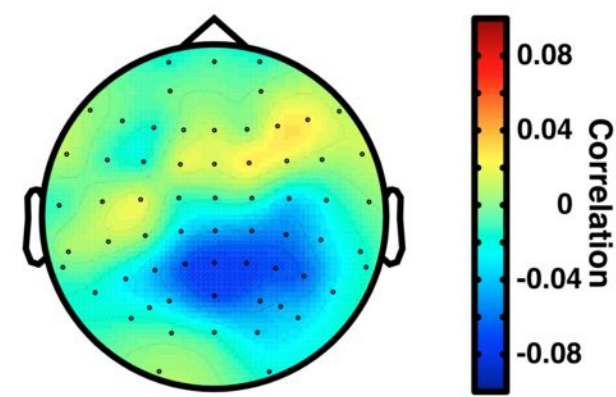
C Phase by MEP Correlation
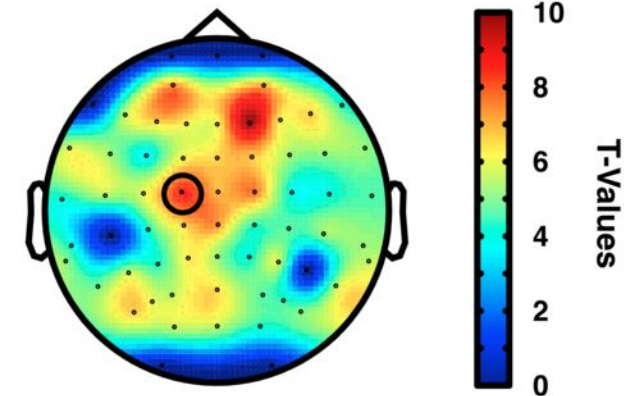
D Power by MEP Correlation
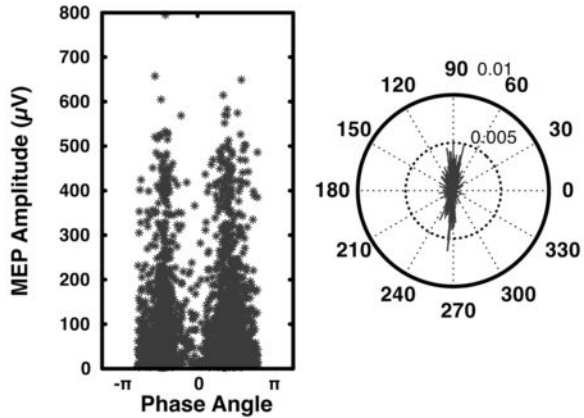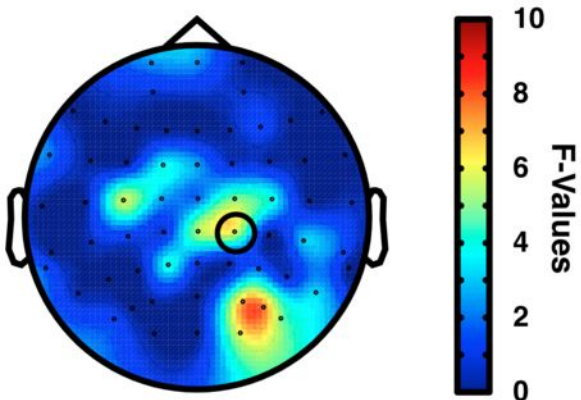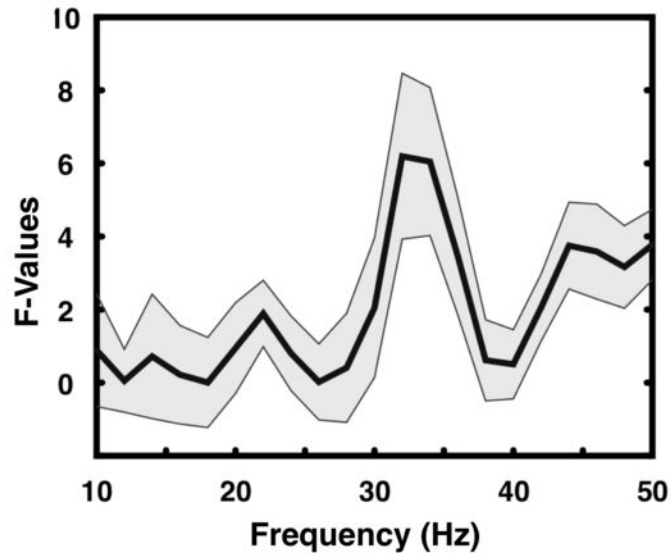
E EMG Phase and Power by MEP Correlation

A   EEG Channel C1 by MEP Amplitude
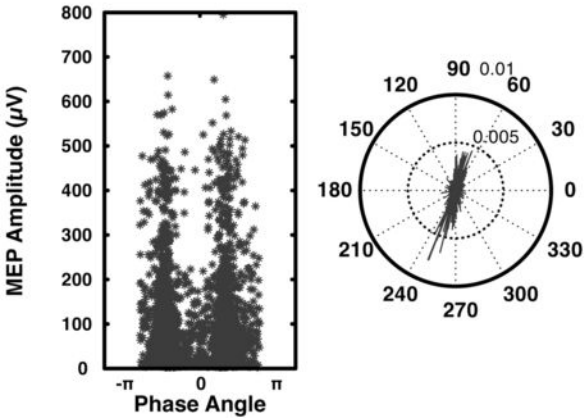
B   EMG Channel by MEP Amplitude

A Topography at 34 Hz

B F-Values (± STD) at CP2

C Coherence at CP2 (± SEM) by MEP Amplitude