Now I am Ready—Now I am not: The Influence of Pre-TMS Oscillations and Corticomuscular Coherence on Motor-Evoked Potentials

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There is a growing body of research on the functional role of oscillatory brain activity. However, its relation to functional connectivity has remained largely obscure. In the sensorimotor system, movement-related changes emerge in the α (8–14 Hz) and β (15–30 Hz) range (event-related desynchronization, ERD, before and during movement; event-related synchronization, ERS, after movement offset). Some studies suggest that β-ERS may functionally inhibit new movements. According to the gating-by-inhibition framework (Jensen and Mazaheri 2010), we expected that the ERD would go along with increased corticomuscular coupling, and vice versa. By combining transcranial magnetic stimulation (TMS) and electroencephalography, we were directly able to test this hypothesis. In a reaction time task, single TMS pulses were delivered randomly during ERD/ERS to the motor cortex. The motor-evoked potential (MEP) was then related to the β and α frequencies and corticomuscular coherence. Results indicate that MEPs are smaller when preceded by high pre-TMS β-band power and low pre-TMS α-band corticomuscular coherence (and vice versa) in a network of motor-relevant areas comprising frontal, parietal, and motor cortices. This confirms that an increase in rhythms that putatively reflect functionally inhibited states goes along with weaker coupling of the respective brain regions.

Keywords: corticomuscular coherence, ERO/ERS, gating by inhibition, motor network, TMS

Introduction

Similar to other sensory brain regions, sensorimotor areas at rest exhibit characteristic rhythmic activity in the α and β frequency range, which is reduced upon movement or the preparation for movement (Jasper and Penfield 1949; Chatrian et al. 1959). Currently, the exact functional role of such dominant resting activity is still an area of exploration. However, notions that this reflects functionally irrelevant “idling” are becoming increasingly doubtful (Pfurtscheller et al. 1996a, 1996b). An alternative view is that dominant resting rhythms in sensorimotor systems reflect the current excitatory inhibitory balance of underlying neuronal cell assemblies, with low power in the α or β range indicating an “excitatory” state and high power indicating an “inhibitory” state (Neuper and Pfurtscheller 2001; Klimesch et al. 2007; Jensen and Mazaheri 2010; Weisz et al. 2011). This notion has recently been given direct evidence in a study showing an inverse relationship between α power and firing rate in sensorimotor regions of the monkey brain (Haegens et al. 2011).

At rest that is, in the absence of stimulation or anticipatory pattern of any task it appears plausible that sensorimotor systems reside within a metastable equilibrium, in which inhibitory and excitatory influences are finely balanced, thus allowing for functionally adaptive modulations. An unresolved issue within this framework is the relationship between changes in equilibrium in relatively “local” sensorimotor regions and their impact on long range communication. Recently, Jensen and Mazaheri (2010) described an intriguing model of how the modulation of dominant resting rhythms “gates” information flow within a distributed network by, for example, functionally blocking task irrelevant pathways. Even though the focus in their article was on visual α activity, this mechanism could in principle constitute a general mechanism across sensory and motor modalities. The model suggested by Jensen and Mazaheri (2010) are an extension to previous conceptions (Thut and Minnussi 2009) which propose that modulations of occipito-parietal α oscillations or α/β band oscillations over motor areas generated via cortico-cortical and thalamo-cortical interactions adjust local gain for in or outputs from the respective region. Due to the fact that the primary motor cortex is closely connected to the peripheral musculature even via monosynaptical pathways (Schinke et al. 2009), the motor system appears to be an ideal model for investigating the relationship between local power modulations and long range connectivity (while also circumventing certain well known methodological issues such as volume conduction). However, another factor makes the motor system a suitable model for investigating this issue. Apart from the aforementioned movement related event related desynchronization (ERD) during the preparation for and execution of body movements, the termination of the movement is followed by a robust and sustained synchronization of α and β frequency power above baseline level (event related synchronization, ERS) a phenomenon called “postmovement rebound” (Salmenlin and Hari 1994; Salmenlin et al. 1995; Pfurtscheller et al. 1996a, 1996b). This means that within a single movement trial, one is able to track the relationship between motor oscillatory activity and corticomuscular connectivity across relatively “excited” as well as “inhibited” states.

The α and β band modulations observed within the context of a movement might, however, differ with respect to their temporal behavior and have different underlying generators, as suggested by electroencephalography (EEG) and magnetoencephalography (MEG) source reconstructions: whereas α modulations were mainly located in postcentral somatosensory areas and related more to somatosensory processing, β modulations, and especially the postmovement β rebound were located in most studies to the precentral gyrus (Hari and Salmenlin 1997; Lee et al. 2003; Jurkiewicz et al. 2006; Parkes et al. 2006; Dalal et al. 2008). However, in MEG and electrocorticography (ECoG) data, a wider spread of movement related β modulations going beyond the primary motor and somatosensory cortices has been reported, including the supplementary motor area (SMA), cingulate cortex, and...
dorsolateral prefrontal and premotor cortex (Sochurkova et al. 2006). The \( \beta \) rebound has also been shown in the ECoG data of Putamen. Strong \( \beta \) band rebound seems to reflect a stabilization process in motor related areas (Caetano et al. 2007), shielding from external input and the activation of new motor sets (Gilbertson et al. 2005). The suppression of somatosensory processing and sensory afferences of motor actions have been reported for the period during \( \beta \) band rebound (Cassim et al. 2001; Parkes et al. 2006). Studies on patients with Parkinson’s disease have also shown that a pathological increase in \( \beta \) band accompanies pathological slowness or poverty of movement and a deficit in initiating new movements (Schnitzler and Gross 2005). van Wijk et al. (2009) suggest that \( \beta \) band oscillations in the motor cortex are responsible for response selection, comparable with \( \alpha \) band activity during atentional modulation. Pogosyan et al. (2009) showed that the entrainment of 20 Hz rhythms via alternating current stimulation in the motor system led to slower voluntary movements. A vast amount of studies have been conducted with regards to a long range corticospinal connectivity (Hari and Salenius 1999; Salenius and Hari 2003). Isometric contractions generate corticospinal synchrony in the 20 Hz range (Gross et al. 2000). Furthermore, Gross et al. (2002) showed significant coherences in the 6-9 Hz frequency range, which spanned a cerebellothalamocortical network in a healthy motor behavior. Additionally, an increase in coherence in the thalamocortical loop particularly in 3-10 Hz frequencies in Parkinson’s disease could be related with tremor symptomatology (Schnitzler and Gross 2005). The latter studies illustrate that whereas local modulations on the level of the motor cortex are mainly pronounced in the \( \beta \) range, synchronization between the central and peripheral motor systems can take place at significantly lower frequencies.

A relationship between \( \alpha/\beta \) oscillatory activity and behavior has been also suggested by studies relating transcranial magnetic stimulation (TMS) induced motor evoked potential (MEPs; Barker et al. 1985; Pascual Leone et al. 1999; Hallett 2007; Di Lazzaro et al. 2008) to pre TMS oscillatory activity. Maki and Ilmoniemi (2010) found that MEPs elicited by TMS were smaller in amplitude after higher pre TMS midrange \( \beta \) band power in the stimulated motor area and were related to the \( \beta \) band phase in occipital areas. Lepage et al. (2008) reported similar results in tasks in which subjects had to execute, observe, or imagine movements while at rest. In studies conducted by Sauseng et al. (2009) and Zarkowski et al. (2006), MEPs were elicited more easily when pre TMS \( \alpha \) band power was low in motor areas at rest and vice versa. Contrary to these studies, Mitchell et al. (2007) were unable to find pre TMS correlations on the level of the EEG in a voluntary movement task, even though this was evident for the EMG signal. Suppressions to the TMS induced MEP studies mentioned above further studies have been performed relating EEG and MEPS during active movement. Leocani et al. (2000) found that MEP amplitude is larger prior to a simple reaction in a simple reaction time task, but the authors could not show a relation between ERD/ERS and TMS induced responses (Leocani et al. 2001). van Elswijk et al. (2010) also were not able to show relations between cortical \( \beta \) band modulations and MEP size, but showed relations between \( \beta \) band phase and MEP gain modulation in the EMG signal. There is also evidence that prior in tension can modulate M1 inhibitory processes and resultant cortical responses to TMS (Bonnard et al. 2009).

To summarize this section, the vast majority of evidence using diverse approaches indicates an inverse relationship between \( \alpha \) or \( \beta \) power in the sensorimotor system and behavioral outcomes and studies in patients indirectly point to a relationship between local synchronization in the \( \beta \) band and corticomuscular coherence at lower frequencies. However, no study to date has directly investigated these putative relationships in a single experiment.

In our study, we investigated a simple reaction time task in cluding a squeezing movement to elicit ERD and ERS “within” a single trial, modulating the inhibitory components in the motor system over time. This procedure thus offers us the opportunity to track the relationship between local levels of synchronization with long range corticomuscular connectivity in detail. According to the framework outlined above (Jensen and Mazaheri 2010), we expected that the ERD goes along with increased corticomuscular coupling, whereas the ERS (i.e. rebound) would be marked by decreased corticomuscular coupling. Another aim of the study was to investigate the relationship of both that is, local activity levels in the brain and long range synchronization and their influence on behavioral motor output by applying single pulse TMS in a subset of trials. Resulting MEP parameters were subsequently related to prestimulus activation in the EEG on a single trial level, similar to some previously described studies (Mitchell et al. 2007; Lepage et al. 2008), with the difference, however, of also explicitly taking corticomuscular coupling into account.

Materials and Methods

Subjects

Sixteen volunteers (6 males; mean age 24 years, standard deviation [SD] = 3.74) participated in the study. All participants were right handed according to the Edinburgh Handedness Inventory (Oldfield 1971) and had normal or corrected to normal vision and no reported history of neurological or psychiatric illness. All participants were recruited via a notice posted on the campus of the University of Konstanz. After a detailed explanation of the procedures, they provided their written informed consent and received €25 compensation. The Ethics Committee of the University of Konstanz approved the study. One participant had to be excluded due to very noisy EEG data quality.

Task and Experimental Procedure

All stimuli were presented via Psychosoftware (Cohen et al. 1995; http://psy.ckm.sissa.it/), an open source environment for the design and control of behavioral experiments. Stimuli were presented on the center of a screen (diagonal dimensions of the screen were 71.12 cm) placed ∼1 m in front of the participant. The session consisted of 2 blocks lasting ∼12 min. Each block comprised 30 control trials containing no TMS stimulation and 60 TMS Trials in randomized order. Figure 1 depicts an example of a single trial including EMG activity (Fig. L4). As can be seen in Figure 1B, each trial started with an intertrial interval of 3000-3500 ms. During this period, no TMS was applied. After the end of the intertrial period, 3 crosses emerged for 80 ms and directed subjects to squeeze a towel roll with their right hand as quickly and strongly as possible. The movement was intended to induce a consistent \( \beta \) band rebound. In TMS Trials, a single TMS pulse was randomly applied between 50 and 4450 ms after the offset of the cross. In control trials, no TMS pulse was applied, and the procedure was equally terminated after 50-4450 ms. With the exception of the cross, an instruction to keep fingers relaxed was consistently presented on the screen.

EEG and EMG Recordings

Participants sat in a comfortable seat with their arms placed upon a table attached to their chair. They were told to keep their eyes open
and to close their left hand in a loose fist while loosely holding a small fabric roll with their right hand. A 128 channel and TMS compatible EEG device (Advanced Neuro Technology, Enschede, the Netherlands) was used to record the EEG and EMG signal. A ground electrode was attached to the subjects’ right ear (contralateral to TMS stimulation). The signal was digitized at a 2048 Hz sampling rate and impedances were held <5 kΩ. Electromyography was recorded in a belly tendon montage bilateral from the first dorsal interosseous (FDI) muscle using 2 disposable surface bipolar electrodes (Ambu Blue Sensor N) for each hand.

**TMS Stimulation**

TMS pulses were delivered using a Magstim Rapid 2000 (Magstim Company) and a figure of eight coil. Neuronavigation (Polaris Spectra Northern Digital Inc.) with the individual MRI was used to assist finding the ideal point to elicit the MEP. Single pulse TMS (60% of stimulator output, if no ideal point was found, stimulator output was increased) was applied to the left handknob area (Yousry et al. 1997) to TMS stimulation. The signal was digitized at a 2048 Hz sampling rate and impedances were held <5 kΩ. Electromyography was recorded in a belly tendon montage bilateral from the first dorsal interosseous (FDI) muscle using 2 disposable surface bipolar electrodes (Ambu Blue Sensor N) for each hand.

**Data Analysis**

**Preprocessing and Artifact Rejection**

For data analysis, the Matlab (MathWorks, Natick, MA) based Fieldtrip package was used (http://www.ru.nl/fcdonders/fieldtrip; (Oostenveld et al. 2011)).

Sixty epochs of control trials ranging from 2 s prior to movement offset to 4 s following movement offset were extracted. Movements were defined as the period in which the EMG signal of the right FDI muscle rose above 1.5 standard deviations of the relaxed muscle signal prior to the visual cue. Apart from this, corresponding trials around the visual cue ( 3 to +3 s) were cut out for later baseline correction. One hundred twenty epochs of TMS Trials ranging from 2 s prior to TMS stimulus to 2 s following TMS stimulus and again corresponding trials around the visual cue ( 2 to +2 s) were cut out for later time frequency power normalization.

To reduce DC components in our data, all epochs were demeaned by subtracting the mean of a data interval of about 1.5 s. In TMS Trials, the mean of respective TMS artifact free data was subtracted (for TMS Trials 1.5 0.01 s prior to TMS). In control trials, the mean of respective movement related activity free interval 2 to 0.5 s prior to movement offset was subtracted and in visual trials (used for actual baseline correction of time frequency data; see below) the mean of data from 1.5 to 0 s prior to visual cues was subtracted. TMS artifacts were removed (for further details, see the next section). Trials contaminated by large nonphysiological artifacts such as electrode jumps or residual TMS artifacts were sorted out by visual inspection. Trials in which overall EMG activity was abnormally high were additionally rejected. Additionally, EEG data were cleaned from EOG and obvious muscle artifacts using independent component analysis.

**Calculation of Peak to Peak MEP Amplitude**

To estimate the influence of prestimulus EEG activity on muscle output, parameters of TMS evoked MEPs were extracted from right EMG channel activity. EMG channel activity was 10 Hz high pass filtered. Peak to peak amplitude was defined as the range between maximal and minimal amplitude, found in the time interval between 15 and 60 ms post TMS. MEP onset was defined as the inflection point prior to maximum and offset was defined as the inflection point after minimum. MEP parameters were automatically determined in a customized Matlab function and were additionally visually inspected for ensuring proper values (see Fig. 1G).


**Estimation of Movement Related Relative Power Change and Corticomuscular Coherence Analysis at the Electrode Level.** We first analyzed relative spectral power at the electrode level for TMS free control trials and corresponding baseline intervals (to cover the time window of the whole “rebound period” control trials were epoched from 1000 ms prior to movement offset to 3000 ms following movement offset; baseline intervals were chosen from 1 to 0 s prior to the visual cue). Subsequently, we estimated the sources of oscillatory activity with an adaptive spatial filtering algorithm (Gross et al. 2001). At the electrode level, we proceeded as follows: prior to time frequency analysis, the number of baseline and activation trials were individually equalized. In our next step, we estimated the spectral power for each individual subject. Time frequency representations of oscillatory power were calculated for each individual trial using spectral analysis applied to short sliding time windows (Percival and Walden 1993). Frequency bands from 3 to 40 Hz in steps of 2 Hz were analyzed. We applied an adaptive Hanning tapered window of 5 cycles per frequency of interest in steps of 5 ms and separately estimated power values for each electrode location. Relative power change compared with baseline was calculated for each individual trial. Average baseline was subtracted from the active period the result was then divided by the averaged baseline period (a value of zero, therefore indicating no change with respect to baseline. Corresponding baseline intervals for power normalization were chosen from 1 to 0 s prior to the visual cue.

To statistically underline movement related power changes in control trials, we tested relative power change across the whole time and frequency range against the null hypothesis in a nonparametric cluster based, permutation dependent samples t statistic across all participants (Maris and Oostenveld 2007). In the cluster based permutation test, we accounted for the multiple comparison problem and the resulting familywise error rate, which originate from the fact that EEG data have a spatiotemporal structure and that a large number of statistical comparisons therefore have to be calculated when 2 conditions are compared. In the Monte Carlo cluster based permutation test, the probability of 3D clusters (i.e. time, frequency, and space) is calculated by permuting data many times (here 1000 times) between relative power change and no change as well as by taking into account highly correlated neighboring channels as well as points in time frequency space. By this means, the empirically observed metric of each cluster (i.e. the sum of t values) can be compared against a distribution of the same metric under the assumption that the condition with no change has no influence. We considered a cluster of P < 0.05 in a 2 tailed test as significant; on average, each channel possesses 6 neighboring channels.

To study oscillatory synchrony between the signal of the hand muscle and the brain, corticoomuscular coherence was analyzed. The EMG signal was 3 Hz high pass filtered and rectified (Myers et al. 2003). Corticoomuscular coherence was computed by using the cross spectral density matrix of the time frequency analysis between EMG channels and EEG channels. The cross spectral density matrix was calculated over time and frequency in the frequency range from 3 to 40 Hz in steps of 2 Hz. We applied an adaptive Hanning tapered window of 5 cyles in steps of 5 ms. The magnitudes of the summed cross spectral density matrix were then normalized through their respective power values. Resulting coherence values reflect linear dependency (considering both phase and amplitude relationships) between the EMG and EEG signals in different time and frequency bands (Schoffelen et al. 2005). For control trials, corticomuscular coherence over all trials for each individual participant was computed from 1 to 5 s surrounding movement offset.

In our data driven approach (see below), we found significant effects in the α (5-15 Hz) range and in the β (15-25 Hz) band between MEP amplitude and prestimulus coherence in TMS Trials. In control trials, we therefore descriptively compared grand averages of the time series of averaged β power changes (15-25 Hz) and time series of average α coherence (5-15 Hz) and β coherence (15-25 Hz). As we found modulations in the broad α band, but not in the β band, coherence, we focused our further analysis on the broad α band. We tested the temporal evolution of baseline coherence (1.5 to 0.5 s prior to visual cue) against the evolution of coherence in the active period (0.5 to 1.5 s after movement offset) with a dependentsamples t test corrected for multiple comparisons.

**Analysis at the Source Level.** For the identification of neuronal sources, we used a spectral domain beam forming approach (Gross et al. 2001). Sources were calculated for the time and frequency domains that were statistically most prominent on electrode level. Dynamic imaging of coherent sources (DICS) is an adaptive procedure because it uses the cross spectral density matrix to construct spatial filters for each individual grid point. For a frequency band of interest, the power can be optimally calculated for a certain location while suppressing activity from all other locations. A 3D grid (grid resolution: 10 mm) covering the whole brain volume and the respective grid matrix for each grid point were calculated using a standard boundary element model and standard electrode positions were supplied by the EEG manufacturer (http://www.ant neuro.com/). A common spatial filter from the cross spectral density matrix of the EEG signal was calculated for each grid point at the frequency of interest over the active and baseline periods. We used data epochs from baseline and activation intervals, which were not ICA cleaned to avoid rank deficiency issues that can lead to unreliable filter estimations. Prior to this step, the raw data were rigorously inspected for artifacts such as blinks and muscle activity. We then applied the spatial filters to the ICA cleaned cross spectral density matrix of Fourier transformed data (multitaper analysis, DPSS window) for the frequency and time window of interest. The resulting activation volumes were normalized to a template MNI brain provided by the SPM2 toolbox (http://www.fil.ion.ucl.ac.uk/spm/software/ spm2)

For control trials, the source localization of power between 15 and 25 Hz (as obtained from the electrode level nonparametric cluster per mutation analysis) was calculated for a time window of 500 1000 ms after movement offset as the active period. As a baseline interval, the source localization ranging from 500 ms prior to the visual cue until its appearance was calculated. Source power during the rebound period was then normalized by the respective baseline activation. A group statistic (paired t test) of power change against no change over all voxels was then calculated and images were thresholded with P < 0.05.

To scrutinize the neuronal origins of corticomuscular coherence, we calculated DICS using the EMG channel as a reference channel. We chose an active period from 0.25 to 0.25 seconds (as broadly obtained from sensor analysis) surrounding movement offset, for which we descriptively found the strongest corticomuscular coherence in the range. The baseline period for source normalization was calculated from 500 ms prior to the onset of the visual cue. The cross spectral density between the EEG and EMG channels at the frequency of interest at 10 ± 5 Hz was then calculated. To reveal voxels of high coherence, we compared relative coherence change to no change. Images were thresholded with P < 0.05.

**Estimation of Relation Between Movement Related Power and Corticoomuscular Coherence.** In order to estimate the sequential relationship between power and corticomuscular coherence, we cross correlated the signal around movement offset. To do this, we first normalized corticomuscular coherence by a baseline interval ranging from 500 to 0 ms prior to the onset of the visual cue, as had also been done for spectral power normalization. Second, we again averaged z scored power and coherence spectra across frequencies (α: 5-15 Hz for coherence and β: 15-25 Hz for power) and extracted data from 250 to 250 ms surrounding movement offset. We then cross correlated the signal for each channel in each individual subject. We finally calculated the grand average of the cross correlation and the signal lag across all subjects.

**The Influence of Prestimulus Power and of Prestimulus Corticoomuscular Coherence on MEP Peak to Peak Amplitude Analysis at the Electrode Level.** In TMS Trials, we again analyzed relative spectral power at the electrode level using the same
parameters as described in the section before. An active period lasted from 1.5 s pre TMS to 1.5 s post TMS. Corresponding baseline intervals for power normalization were chosen from 1 to 0 s prior to the visual cue. To analyze relations between prestimulus power spectrums and subsequent MEP size, we z transformed MEP amplitudes and Pearson correlated normalized MEP peak to peak amplitudes with the normalized power spectrum for each individual TMS Trial in each participant. We obtained a matrix with a correlation coefficient for each channel, each time point, and each frequency for every participant.

As we were interested in the influence of prestimulus activity on MEP peak to peak amplitude, statistical analysis was conducted for a time period ranging from 550 to 0 ms pre TMS. Fisher's z transformed distributions of correlations were tested against the null hypothesis in a cluster based nonparametric permutation test, with dependent samples t test as statistic across all participants, for which all parameters were the same as those described above (Maris et al. 2007). To examine the influence of prestimulus corticomuscular coherence on MEP peak to peak amplitude, TMS Trials were separated into terciles ranging from the tercile of trials in which the corresponding MEP peak to peak amplitudes were smallest to the tercile including trials with the highest peak to peak amplitude. For each participant, coherence values for each tercile were calculated 450 0 ms pre TMS. As we hypothesized that the coherence between muscle and brain should be smaller prior to small MEP peak to peak amplitudes than prior to high amplitudes, we calculated a dependent sample test assessing this linear trend. We again corrected for multiple comparisons (same parameters as before) over frequencies ranging from 5 to 40 Hz (Maris et al. 2007).

Analysis at the Source Level. For TMS Trials, a source analysis was calculated for each single trial from 550 to 0 ms before TMS in the 15 35 Hz range (as obtained from electrode analysis) and was then correlated with the corresponding MEP peak to peak amplitude in each individual subject and for each trial. Group statistics (paired t test) between significant Fisher's z transformed correlations against no correlations were calculated. The resulting images were thresholded with P<0.05 to reveal voxels expressing a consistent relationship between oscillatory activity and MEP.

To again scrutinize the neuronal origins of corticomuscular coherence, we also calculated DICS for TMS Trials using the EMG channel as a reference channel. The source analysis for TMS Trials was calculated over all trials from 350 to 0 ms pre TMS and for a frequency range between 5 and 15 Hz. The resulting spatial filters were then applied to the terciles of the ICA cleaned data sorted for electrode analysis. Analogous to the electrode level analysis, a group statistic using a dependent samples t test was then calculated to identify significant voxels in which Fisher's z transformed coherence linearly decreased on the MEP size. Images were thresholded with P<0.05.

Results

Movement related Desynchronization and Synchronization in the α and β Band Power and its Relation to Corticomuscular Coherence

In order to obtain sufficient modulations in α and β band activity to systematically test its relationship with MEP, participants had to perform a reaction time task.

Time frequency analysis of induced responses showed movement related oscillatory activity in α and β frequency bands at central electrodes in the no TMS condition. The grand averaged movement related oscillatory activity over central electrodes is depicted in Figure 2A. It can be seen that, whereas an ERD can be observed for both frequency bands with a slightly different time course (α 15 Hz, ~0.5 Hz; β 15 36 Hz, ~0.25 Hz), the ERS was particularly pronounced for the β band. The topographical representation in

Figure 2B illustrates the central putative motor focus of this rebound but reveals moreover a posterior focus. The nonparametric cluster statistic, which compared relative power change to no change, resulted in a significant negative cluster with P<0.001 containing frequencies between 5 and 40 Hz and ranging from −275 to 1000 ms and peaking at 22 Hz and at 100 ms. Furthermore, a positive cluster spanning the frequencies between 2 and 40 Hz with P<0.001 ranging from 350 to 2500 ms with a peak in the β range at 20 Hz (20 Hz ±7) and from −450 to 0 in the α range (5 ±2) was generated.

DICS source localization for frequencies between 15 and 25 Hz at 500 s 1000 ms revealed significant voxels in the left premotor and motor areas containing voxels in the precentral gyrus (Brodmann area [BA] 4, BA 6, and BA 8 (medial and superior frontal gyrus). There was also a significant power increase in the parietal lobe at BA 7 and BA 5 (superior parietal cortex) and in postcentral gyrus. We additionally identified a more temporal source encompassing the left superior temporal gyrus (BA 40, BA 41, BA 42, and BA 43) and an occipital source (BA 18) (Fig. 2D shows masked source t values with P<0.05). Consistent activity was also evident in the right culmen (cerebellum), in the right BA 18, in a source around right BA 7 and BA 5 and in right prefrontal areas (BA 11 and BA 32).

In our data driven approach, we looked at modulations in corticomuscular coherence and descriptively found the strongest modulations in the broad α frequency range from ~5 to 15 Hz. The time course of β power and the coherence modulation showed an inverse relationship (see Fig. 2C). A comparison of baseline and active periods displayed an increase in corticomuscular coherence in the α band from about ~320 to 250 ms surrounding movement offset (positive cluster P<0.01). The cross correlation of the signal ranging from −250 to 250 ms surrounding movement offset suggests a time lag of 5 ms, in which power precedes coherence with a negative correlation of r=−0.22 between (P<0.05) β band power (15 35 Hz) and α band corticomuscular coherence (5 15 Hz) at a central representative electrode averaged across all subjects.

An additional source analysis of corticomuscular coherence in this time window for the frequency band between 5 and 15 Hz revealed the strongest increases compared with baseline in the following areas (illustrated in Fig. 2E): a significant source in premotor areas comprised the left inferior/superior frontal lobe (BA 44, BA 45, BA 46, BA 6, BA 9, and BA 8), left precentral gyrus (BA 4), left superior temporal gyrus (BA 22), one source at the posterior parietal lobe (BA 5, BA 7, and BA 19), as well as in the right hemisphere, in the parietal lobe (BA 5, BA 40, BA 39, and BA 7), precentral gyrus (BA 4), a frontal source comprised BA 9 and in superior temporal gyrus (BA 22).

β Band Correlations at Pre TMS Intervals

In line with our hypothesis that a negative correlation exists between β and/or α band power in the prestimulus period and subsequent MEP peak to peak amplitude, we found a significant negative cluster ranging from ~550 to 0 ms pre TMS. This was most prominent in the β range from 15 to 35 Hz (P=0.033), as illustrated in Figure 3A. This could be divided into an earlier time period (~400 ms pre TMS) dominated by frontal electrodes (see Fig. 3B for topographical illustration)
and a later time period, which was more prominent in posterior electrodes (∼150 ms pre TMS, see Fig. 3C).

Source level statistics of the correlation between MEP peak to peak amplitude and β band activity for the whole period showed multiple significant negative voxels, illustrated in Figure 3D. The strongest effects were found in the left parietal cortex (containing BA 3, BA 4, BA 5, and BA 7). Further negative associations spread into the left motor (precentral gyrus [BA 4]), premotor areas (BA 6), and frontal areas (superior and medial frontal gyri, BA 10, BA 24, and BA 9) and in superior temporal gyrus (BA 39), whereas in the right hemisphere voxels were significant in the region of the superior temporal gyrus (BA 22 and BA 41) (P < 0.05).

Corticomuscular Coherence Dependent Changes in MEP Peak to Peak Amplitude

To investigate the influence of the intensity of communication between the FDI muscle and the brain on the resulting MEP peak to peak amplitude, we statistically analyzed the linear trend between corticomuscular coherence prior to MEP and MEP size. It was assumed that low corticomuscular coherence in the prestimulus period would lead to a smaller MEP amplitude.

The nonparametric permutation statistic of the linear trend pictured in Figure 4 resulted in a significant cluster strongest and most sustained in the α range 150 ms prior to the TMS pulse (positive cluster just prior to TMS P = 0.017).

In line with the result on sensor level as well as with source solutions, rebound and pre TMS correlations, we could disclose a linear trend between the MEP size and corticomuscular coherence in the α band (5–15 Hz) at multiple sources from 350 to 0 ms pre TMS. We found one sensorimotor source including the pre and postcentral gyri (BA 2, BA 3, BA 4, and BA 43) and premotor area (BA 6), a parietal source containing BA 7 and BA 5 and precuneus, a frontal source with a peak at left inferior frontal gyrus (BA 10, BA 45, and BA 46), and a postrerior source peaking at BA 18. In the right hemisphere, we revealed significant voxels at the right BA 40 and in the right posterior cingulum. See Figure 4C for significant voxels.

Discussion

In the current study, we were able to show that prestimulus β band power and prestimulus α band corticomuscular coherence fluctuations predict TMS induced MEP size. In detail, high β band power along with low corticomuscular coherence

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Figure 2. Movement related changes in time frequency power and corticomuscular coherence. (A) grand average of movement related power changes in central representative electrodes. (B) Topography of the “rebound” at 20 Hz at 500 ms after movement offset. (C) Movement related changes in corticomuscular coherence (5–15 Hz) accompanied by relative power changes (15–35 Hz) in a representative electrode. The gray bar indicates where corticomuscular coherence is significant compared with baseline. (D) Significant voxels for relative power change in the 15–25 Hz frequency range (500–1000 ms after movement offset) compared with no change. (E) Significant corticomuscular coherence compared with baseline for 5–15 Hz (250 to 250 ms after movement offset).
in the $\alpha$ band in a sensorimotor network comprised of the frontal, parietal, and primary motor cortices (see Fig. 5) led to smaller muscular responses while low $\beta$ band power and high $\alpha$ band corticomuscular coherence led to large MEPs.

Furthermore, movement related power modulations in the $\beta$ band (ERD/ERS) are accompanied by an inverse evolution of corticomuscular coherence in the broad $\alpha$ band; this relationship is again most prominent in a sensory motor network consisting of the frontal, parietal, and primary motor cortices.

As intended, we replicated Pfurtscheller et al. (1996a, 1996b) and showed movement related ERD/ERS in the $\alpha$ and $\beta$ bands. However, $\beta$ band ERD/ERS was stronger and more sustained than $\alpha$ ERD/ERS. This may be attributed to the movement type used in our task. First, $\beta$ synchronization is stronger in brief, compared with sustained movements (Cassim et al. 2000; Alegre et al. 2003); our task was a brief and not sustained squeezing task. Second, $\alpha$ band modulations are more related to sensory input (Salmelin and Hari 1994; Hari et al. 1997; Lee et al. 2003; Jurkiewicz et al. 2006; Parkes et al. 2006); our task only had moderate sensory input.

The temporal evolution with a peak at about 500 ms following movement offset in the $\beta$ band and an $\alpha$ rebound a second later conforms with an MEG tapping task study reported by Caetano et al. (2007), who found a rebound after voluntary movement strongest at 600 ms following movement offset for $\beta$ frequencies and followed by a much smaller $\alpha$ frequency rebound. Task dependent differences in temporal modulations were also reported by Nakagawa et al. (2011).

In sum, we triggered a strong and consistent movement related $\beta$ band rebound that we expected would represent an inhibitory process in sensorimotor areas, as had already been suggested by several authors (Cassim et al. 2001; Parkes et al. 2006; Caetano et al. 2007). Accordingly, we assumed that an increase in $\beta$ band power leads to a reduction in muscular behavior. In line with our hypothesis, we found significant negative correlations between prestimulus $\beta$ band power and peak to peak amplitude of the following MEP in pre motor, motor, parietal, and frontal areas contralateral to the MEP and ipsilateral in temporal areas. Results were similar to those reported by Maki and Ilmoniemi (2010) and Lepage et al. (2008), who found negative correlations between

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**Figure 3.** Significant negative cluster for correlations between spectral power and MEP peak to peak amplitude. (A) Time frequency representation of the significant negative cluster 550 ms prior to TMS. (B) Topography of the early negative cluster (18 Hz, 0.45 s). (C) Topography of the later negative cluster (18 Hz, 0.12 s). (D) Voxels with consistent negative correlations between 15 and 35 Hz spectral power (550 0 ms pre TMS) and MEP peak to peak amplitude ($P < 0.05$).
low to midrange $\beta$ frequency bands (12–18 Hz) at rolandic scalp electrodes and MEP amplitude. Beyond the results reported by these authors who focused their analysis on electrodes, we also demonstrated negative correlations between $\beta$ band power and MEP peak to peak amplitude in source space. We thereby found evidence that these correlations are generated in a sensorimotor network, which we will later discuss in further detail. We could not replicate the findings of Sauseng et al. (2009) and Zarkowski et al. (2006), who reported negative correlations between motor cortex $\alpha$ band power and MEPs when the target muscles were at rest. However, experimental settings (Sauseng et al. 2009) and differences in data analysis (group level vs. single trial analysis) might cause this discrepancy in results. Finally, we cannot completely exclude that some of our results could be related to modulations of neuromuscular or spinal activity levels. It is not yet clear how easy D Waves (more related to spinal activity) and I Waves (stronger cortical contribution) are triggered by our stimulation technique. As there are several methods to account for that problem the most direct method would be to measure in an invasive way the descending potentials and to estimate spinal activity. Another method could be to use the same paradigm and stimulate the periphery and compare F Wave with MEP amplitudes for further discussion (see Siebner and Ziemann 2007). As this information cannot be derived from the present data directly, our results are of correlational nature. Yet they nicely complement previous findings on $\alpha$ and $\beta$ band activity in the motor as well as nonmotor modality. To find out more about possible causal relationships between $\beta$ band power and $\alpha$ band corticomuscular coherence and MEP size, further studies could be done using neurostimulation paradigms to actively "entrain" oscillatory activity as has been done for the auditory (Neuling et al. 2012) or the visual system (e.g., Romei et al. 2011, 2012). Initial works (Pogosyan et al. 2009; Joundi et al. 2012) show that entraining the motor system at different frequencies influences motor output; however, according to our present work, these studies would need to be extended by probing how entrainment influences corticomuscular coherence.

Another point we did not address in our study were behavioral measurements such as reaction times, which could also be influenced by similar mechanisms as reported in our study. To investigate this issue, a similar design without TMS would need to be conducted and compared with our results.

Our results suggest that high $\beta$ band power plays an inhibitory role in a sensorimotor network and correlate with lower behavioral output. Our results support earlier findings about the inhibitory role of $\beta$ band oscillations in the motor system.

Figure 4. Linear relationship between MEP peak to peak amplitude and pre TMS corticomuscular coherence in the $\alpha$ range. (A) Time frequency representation of the significant positive cluster 450 ms prior to TMS indicating the relationship between pre TMS corticomuscular coherence and MEP peak to peak amplitude. (B) Topography of the positive cluster at 10–15 Hz at 150–200 ms pre TMS. (C) Voxels with a consistent positive linear relationship between 5 and 15 Hz corticomuscular coherence (450–0 ms pre TMS) and MEP peak to peak amplitude ($P < 0.05$). (D) Linear relationship between corticomuscular coherence in a precentral representative voxel and MEP peak to peak amplitude. (Bars show means and standard errors for corticomuscular coherence for terciles separated for MEP peak to peak amplitude.)
They point to the fact that this does not represent only an idling process in the motor cortex, as initially suggested (Salmelin and Hari 1994; Salmelin et al. 1995; Pfurtscheller et al. 1996a, 1996b). Rather, \( \beta \) band activity might display a stabilization process in the motor system, as suggested by Caetano et al. (2007). This idea fits well with the findings that an augmented increase in \( \beta \) band power in patients with Parkinson’s disease correlates with akinesia symptoms (Brown 2003; Brown and Williams 2005) and is associated with the maintenance of posture (Brown and Williams 2005; Gilbertson et al. 2005).

A main aim of our study was to track the relationship between local levels of synchronization with long range corticomuscular connectivity in detail. According to the gating by inhibition framework suggested by Jensen and Mazaheri (2010), we expected that the ERD goes along with increased corticomuscular coupling, whereas the ERS (i.e. rebound) would be paralleled by decreased corticomuscular coupling. We found an opposite relationship between high \( \beta \) band power and weaker corticomuscular coupling in the \( \alpha \) range in several areas relevant for motor action. Additionally, we showed that an increase in prestimulus corticomuscular coherence in the \( \alpha \) and \( \beta \) ranges is related to larger MEP peak to peak amplitude.

Examining literature concerned with coherences in the motor system, much evidence that elevated corticomuscular coherences although not task dependent can be found between 5 and 15 Hz; this increase was at the tremor frequencies of the corresponding muscles. The authors concluded that cortical areas were involved in the generation of physiological tremors. An increase in corticomuscular coherence between left sensorimotor areas, the right cerebellum and the right extensor digitorum communis muscle was also reported by Gross et al. (2002): the authors identified a cerebrothalamo premotor motor cortical 8 Hz network underlying movement discontinuities. Vallbo and Wessberg (1993) demonstrated that the velocities of the finger during slow flexion and extension movements exhibit a rhythmic modulation at a frequency of about 8 Hz in the EMG.

An increase in coherence in the low \( \alpha \) range does not just accompany healthy motor activity: the Parkinsonian resting tremor underlies a pathological 8 Hz oscillatory network in the human motor system, including the primary motor cortex, SMA, cingulated motor cortex, premotor cortex, diencephalic structures, the cerebellum, secondary somatosensory cortex and posterior parietal cortex (Timmermann et al. 2003; Schnitzler and Gross 2005; Schnitzler et al. 2006).

To find out more about possible generators of our effects and to see if all effects originated from the same sources, we also performed a source analysis. Surprisingly, we consistently came across the same structures (see Fig. 5).

We found overlapping sources to be active in \( \beta \) band rebound, in movement related increase in \( \alpha \) band corticomuscular coherence, in negative prestimulus \( \beta \) band correlations with MEP size and in linear dependency between \( \alpha \) band corticomuscular coherence and MEP size.

Figure 5. Between analysis concordance, with red indicating significant voxels in 4 of 4 calculations (correlations pre-TMS power/MEP size, relationship between corticomuscular coherence and MEP size, movement related increase in \( \beta \) band power, movement related increase in \( \alpha \) band corticomuscular coherence) and with yellow indicating significant voxels in 3 of 4 calculations.
As expected, fluctuations in prestimulus $\beta$ band power and $\alpha$ band corticomuscular coherence in M1 predicted MEP peak to peak amplitude. M1 controls voluntary movement and participates in motor learning (Sanes and Donoghue 2000). It has narrow connections to the hand muscle via the pyramidal tract and MEP size is influenced by its excitability (for electrophysiological mechanisms see Di Lazzaro et al. 2008). It also has connections to structures such as basal ganglia and premotor areas (Kolb and Wishaw 1996).

We very consistently identified a source in the superior and the inferior parietal cortex (especially BA 5 and BA 7) or seen together, the posterior parietal lobe.

The posterior parietal cortex is viewed as an important structure for sensorimotor integration and for movement planning and intentions (Andersen and Buneo 2002). The superior parietal area seems to play a role in visuomotor integration and is an important structure for visuospatial communciation between the visual and motor systems (Caminiti et al. 1996; Stanley and Miall 2009). Damage to the inferior parietal cortex leads to ideomotor apraxia, a disorder that is characterized by a loss of manipulation knowledge and an inability to produce or recognize gestures associated with using objects (Buxbaum 2001). Furthermore, the posterior parietal cortex has significant connections to the frontal lobe, such as FEF and the premotor cortex, and strong parieto motor connections also exist (Shibasaki and Ikeda 1996; Rizzolatti and Luppino 2001; Koch and Rothwell 2009).

Finally, we also found consistent relevant areas in the frontal gyirus also known as premotor cortex comprised of BA 8 (including the frontal eye field), BA 6, and the medial and superior frontal gyri. The premotor cortex can directly influence motor action via corticospinal synapses and indirectly via M1. It also has strong connections to the posterior parietal lobe (Kolb and Wishaw 1996). Functionally, premotor areas are especially important for movement selection and the programming of movements (Roland et al. 1980). This also goes in line with the idea that an increase in $\beta$ power impairs the activation or selection of a new motor set, as suggested by Gilbertson et al. (2005).

In summary, the results reported here support the idea that elevated $\beta$ band power in areas related to motor action rep resents a “stabilizing” or “inhibitory” mechanism in the motor system and aggravates new motor action. In correspondence with the gating by inhibition model discussed by Jensen and Mazaheri (2010) which states that an increase in local “inhibi tory” activity leads to decreased long range connectivity and to an inhibition of behavior, we showed that local cortical changes in the excitatory inhibitory balance were associated with reverse long range connectivity. The interplay between local power changes and modulations in long range connectivity re sulted in modulations of behavior. This relationship underlines the model suggested by Jensen and Mazaheri (2010) and sup plements it in regards to the sensorimotor system.

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**Notes**

*Conflict of Interest:* None declared.

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