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Time-Varying Coupling of EEG Oscillations Predicts Excitability Fluctuations in the Primary Motor Cortex as Reflected by Motor Evoked Potentials Amplitude: An EEG-TMS Study

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Abstract: Purpose: Motor evoked potentials (MEPs) elicited by a train of consecutive, individual transcranial magnetic stimuli demonstrate fluctuations in amplitude with respect to time when recorded from a relaxed muscle. The influence of time-varying, instantaneous modifications of the electroencephalography (EEG) properties immediately preceding the transcranial magnetic stimulation (TMS) has rarely been explored. The aim of this study was to investigate the influence of the pre-TMS motor cortex and related areas EEG profile on time variants of the MEPs amplitude. **Method:** MRI-navigated TMS and multichannel TMS-compatible EEG devices were used. For each experimental subject, post-hoc analysis of the MEPs amplitude that was based on the 50th percentile of the MEPs amplitude distribution provided two subgroups corresponding to "high" (large amplitude) and "low" (small amplitude). The pre-stimulus EEG characteristics (coherence and spectral profile) from the motor cortex and related areas were analyzed separately for the "high" and "low" MEPs and were then compared. **Results:** On the stimulated hemisphere, EEG coupling was observed more often in the high compared to the low MEP trials. Moreover, a paradigmatic pattern in which TMS was able to lead to significantly larger MEPs was found when the EEG of the stimulated motor cortex was coupled in the beta 2 band with the ipsilateral prefrontal cortex and in the delta band with the bilateral centro-parietal-occipital cortices. **Conclusion:** This data provide evidence for a statistically significant influence of time-varying and spatially patterned synchronization of EEG rhythms in determining cortical excitability, namely motor cortex excitability in response to TMS. *Hum Brain Mapp 35:1969–1980, 2014.* © **2013 Wiley Periodicals, Inc.**

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INTRODUCTION

Human brain functions are mostly characterized by transient and time-varying interactions of topographically distributed networks within the brain. These networks dynamically connect and disconnect over time, have varying mechanisms of binding/unbinding, and link together adjacent and/or remote cortical neuronal assemblies via cortico-cortical "fragile" connections [Kandel, 2008; Shepherd and Erulkar, 1997; Siegel et al., 2012; Varela et al., 2001]. Within this model, the transient synchronization of neuronal firing has been proposed as one of the most effective mechanisms for the dynamic linkage of separate and widely distributed neuronal assemblies within a unique and functionally coherent frame. For example, this linkage occurs in sensory and motor areas for sensorimotor coordination and integration [Engel et al., 1991; Fries et al., 2001; Mioche and Singer, 1989; Roelfsema et al., 1997; Singer et al., 1997; Uhlhaas and Singer, 2006].

Theoretically, the level of output from the primary motor cortex in response to identical consecutive stimuli could be used as an indicator of connectivity strength and of short-term changes in the network governing M1 excitability, and the level of output could be largely indicative of changes in synaptic efficacy within network connections [Destexhe and Marder, 2004; Erchova and Diamond, 2004; Johnson et al., 2012; Steinke and Galán, 2011]. Over the last 25 years, a number of specific methods have been developed to identify transient modifications in the functional coupling of distributed neuronal assemblies via electroencephalography (EEG) and magnetoencephalographic (MEG) recordings [Andrew and Pfurtscheller, 1996; Bressler et al., 1993; Lachaux et al., 1999; Määttä et al., 2010; Rodriguez et al., 1999; Vecchio et al., 2010; Zeitler et al., 2006] or by transcranial magnetic stimulation [TMS; Barker et al., 1985; Basso et al.,2006; Hallett, 2000; Kujirai et al., 1993; Rossini et al., 1994].

It is well known that the amplitudes and latencies of motor evoked potentials (MEPs) during motor cortex TMS are driven by a combination of excitatory and inhibitory events that simultaneously occur at different neural levels in the motor-related brain networks and along the cortico-spinal pathway [Amassian et al., 1989; Barker et al., 1985; Ferreri et al., 2006, 2011b, 2012; Hallett, 2000; Kujirai et al., 1993; Rossini et al., 1991, 1994, 2010]. Within this framework, one intriguing phenomenon is that, when recorded from a fully relaxed muscle, MEPs elicited by a consecutive series of individual TMS stimuli show a clear fluctuation in amplitude with respect to time despite having stable spatial and physical stimulus characteristics [Amassian et al., 1989; Ellaway et al., 1998; Mitchell et al., 2007; Mäki and Ilmoniemi 2010; Rossini et al., 1991, Kiers et al., 1993; van der Kamp et al., 1996]. This finding has been previously ascribed to the so-called "uncertainty" of the excitability of the cortical pyramidal neurons and their local field potential (postsynaptic activity) that continuously fluctuate in time. This "uncertainty" has been previously described in pioneering historical experiments [Adrian and Moruzzi, 1939]. After reviewing the TMS literature, we conclude that the view that primary motor cortex (M1) stimulation only activates cortico-spinal pathways is no longer tenable. In fact, several studies combining PET and fMRI have shown that TMS on M1 produced several "activations" in the adjacent and remote motor-related brain areas that belong to a patterned network [Bestmann et al., 2004, 2008; Laird et al., 2008; Siebner et al., 2009]. Moreover, relatively recent TMS-EEG literature has demonstrated the existence of quite a few EEG wavelets elicited by TMS on M1 at different scalp sites both psi- and contralateral, which have a latency of milliseconds and are therefore compatible with direct neural connectivity. The bulk of this data suggests that M1 is strongly connected with other brain areas, that TMS simultaneously excites cortico-spinal tracts and that the motor-related cortico-cortical connectivity network and M1 excitability to TMS might be partially modulated by the strength of the connectivities within this network.

The activity of pyramidal cortical neurons, which contribute to the excitability level of the related neuronal assemblies, can be inferred by EEG scalp characteristics, such as spectral frequency profile, topography of various rhythms, and phase coherence of the EEG oscillations [Ferreri et al., 2011a,b, 2012; Klimesch et al., 2007; Lopes da Silva, 1991; Neuper and Pfurtscheller, 2001; Rossini and Ferreri, 2012].

Until now, relatively little attention has been paid to the relationship linking the EEG properties immediately preceding the moment of TMS delivery to the motor cortex with the MEPs amplitude characteristics. The aim of this study was to expand on previous data [Ellaway et al., 1998; Lepage et al., 2008; McAllister et al., 2011; Mitchell et al., 2007; Mäki and Ilmoniemi, 2010; Rossini et al., 1991; Sauseng et al., 2009] regarding pre-TMS motor cortexes and related areas' EEG parameters influence on MEPs amplitude characteristics. This influence was studied by using special amplifiers that allow for the continuous coregistration of EEG during TMS [Ferreri et al., 2011b, 2012;

Ilmoniemi et al., 1997; Lepage et al., 2008; Massimini et al., 2005; Mäki and Ilmoniemi, 2010; Rossini and Ferreri, 2012] and by evaluating the connectivity of the stimulated brain area by measuring the phase coherence of the pre-stimulus EEG of the stimulated site with the other scalp recording sites of the EEG signals.

MATERIALS AND METHODS

Subjects

Eight healthy young female volunteers (age range, 18–30 years) participated in the study during the luteal phase of their menstrual cycle to avoid any confounding effects of the ovarian cycle on motor cortex excitability [Smith et al., 2002] After approval by the Ethics Committee, written informed consent was obtained before the experiment began. Subjects were instructed to abstain from caffeine, alcohol, and medication and to maintain their regular sleep-wake schedule for 3 days prior to the experimental session. All subjects were right-handed (handedness score 0.70) as evaluated by the Handedness Questionnaire. The exclusion criteria established by international safety standards for TMS were followed [Rossi et al., 2009, Rossini et al., 2010].

Transcranial Magnetic Stimulation

During the EEG recording, suprathreshold (120%) single pulse TMS of the left M1 was performed according to standardized international guidelines [Rossini et al., 1994] using TMS MAGSTIM 200 equipment (Magstim Company Limited, Whitland, South West Wales; biphasic pulse configuration). The equipment had an eight-shaped coil with an inner diameter of 70 mm for each wing oriented to elicit a posterolateral-anteromedial current flow in the brain. The virtual cathode of the coil was placed over the "hot spot" of the hand area of the left M1, which was defined as the point from which TMS of minimal intensity triggered MEPs of maximal amplitude and shortest latency in the target hand muscle. Then, the resting motor threshold was identified, and according to international guidelines, was defined as the stimulator's output that was able to elicit reproducible MEPs (at least 50 μV in amplitude) in ~50% of 10–20 consecutive stimuli [Rossini et al., 1994]. As this experiment involved stereotactic TMS–EEG, the Cartesian head coordinates, the EEG electrode scalp positions, and the coil position/orientation were determined and transformed to the same coordinate system with magnetic resonance (MR) images [Krings et al., 1997]. In this way, the TMS was continuously targeted to the hot spot as the coil was hand-held and was adjusted manually throughout the entire recording procedure. We did not use any means of coil/head stabilization because they are not necessary when using the navigation system. In fact, even minimal displacements from the "hot spot" would have inhibited the stimulus discharge. Each subject underwent a 15-min session consisting of a series of 120 TMS single pulses, and any two consecutive stimuli were separated by a 4–6 s interval to avoid habituation [Kujirai et al., 1993; Sanger et al., 2001; Ziemann et al., 1996]. The subjects were seated in an armchair with their elbows flexed at 90° and their prone hands in a relaxed position. Their eyes were fixed on a target that was on the opposite wall. The TMS-elicited compound EMG responses were recorded bilaterally from the first dorsal interosseus muscle (FDI) via Ag/AgCl coated disk electrodes filled with conductive jelly in a belly/tendon montage. The skin/electrode resistances were <10 K Ohm. The amplitudes of the MEPs were measured semiautomatically between the two major and stable peaks of opposite polarity. The latencies of the MEPs were measured automatically at the onset of the first reproducible deflection from the baseline.

EEG Recordings

TMS-compatible EEG equipment and electrodes (BrainAmp 32 MRplus, BrainProducts GmbH, Munich, Germany) were used, allowing for continuous data recording without saturation of the EEG signals and without pinning the preamplifier output to a constant level during TMS [Bonato et al., 2006; Veniero et al., 2009, Ferreri et al., 2011b]. The EEG activity was continuously acquired from 19 scalp sites using electrodes positioned according to the 10–20 International System (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). Additional electrodes were used as ground and reference. The ground electrode was positioned in Oz to provide maximal distance from the stimulating coil. The linked mastoid served as the common reference. The EEG signal was bandpass filtered at 0.1–500 Hz and was digitized at a sampling rate of 2.5 kHz. To minimize any potential overheating of the electrodes from the stimulating coil, TMS-compatible Ag/AgCl-coated electrodes were used. Skin/electrode impedance was maintained below 5 k Ohm. Horizontal and vertical eye movements were detected by recording the electrooculogram. The voltage between the two electrodes located to the left and right of the external canthi recorded horizontal eye movements. The voltage between the reference electrodes and the electrodes located beneath the right eye recorded vertical eye movements and blinks. The epochs of the TMS-related scalp, EEG responses were selected for off-line evaluation (see below).

To ensure stable wakefulness throughout the recording sessions, subjects were required to keep their eyes open and to fixate on a target that was on the opposite wall. Additionally [Conte et al., 2008], the lapses of attention of the subjects were controlled by a signal detection task during the experiment [Chee et al., 2008]: brief tones were played through headphones at infrequent random intervals compared to the number of TMS pulses (from 3 to 6 tones during each block). The subjects were instructed to count the tones and to report the number of tones at the end of the block. The error rate was always below 5%.

Data Analysis

The recorded EEG data were analyzed and fragmented off-line in epochs of 6 s (3 s before and 3 s after the TMS stimulus). All EEG–TMS trials were visually inspected in each channel, and any trials contaminated by environmental noise, muscle activity, or eye movement were rejected together with the corresponding MEPs. Similarly, trials contaminated by involuntary FDI muscle activation were also eliminated. For the evaluation of the MEP, the EEG signals were baseline corrected (100 ms prestimulus) and were referenced to the average. Of note, visual inspections were made in all of the 6 s EEG epochs, but the trials were rejected when artifacts were found in the period of interest or very close to that period, which are represented in this experiment as one second before the stimulus (−1050 – −50 ms) for the EEG data and one second after the stimulus (100–1100 ms) for MEPs.

On an individual basis, at the end of the MEP acquisition session, the trials were divided into two subgroups of high and low MEP amplitudes that were based on the 50th percentile of the MEP amplitude distribution. About 40 MEPs, for each subject, were acquired in both the high and low amplitude conditions. Frequency domain analyses were performed from the EEG data that were reported to the common reference ("common average") by subtracting, sample-by-sample, the corresponding average value of all electrode sites to remove the effects of the reference electrode. The power spectrum and spectral coherence were computed at the following bands of interest: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz), and gamma (30–40 Hz). A 50 ms epoch prior to TMS stimulus was discarded to avoid possible artifact effects, and thereafter, the analyses of the EEG data were computed over a period of one second lasting from 1050 to 50 ms before the stimulus.

Spectral Analysis of the EEG Data

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed the power density of the EEG rhythms with a 1 Hz frequency resolution. Before making any band analyses or frequency evaluations, the power spectrum was normalized with respect to all the frequency bins and for all the electrodes; each value was divided by the mean values obtained by averaging the power at all the frequency bins and for all the electrodes. In this analysis, the electrodes Fp1, Fp2, O1, and O2 were discarded due to possible muscular activity contamination.

Functional Connectivity: Between-Electrode EEG Coherence Analysis

Spectral coherence is a normalized measure of the coupling between two (EEG) signals at a given frequency [Leocani and Comi, 1999; Pfurtscheller and Andrew, 1999; Rappelsberger and Petsche, 1988]. The coherence values were calculated for each frequency bin by the following equation

$$Coh_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda) f_{yy}(\lambda)}.$$

This equation is the extension of the Pearson's correlation coefficient for complex number pairs. In this equation, f denotes the spectral estimate of two EEG signals x and y for a given frequency bin (λ). The numerator contains the cross-spectrum for x and y (fxy), while the denominator contains the respective autospectra for x (fxx) and y (fyy). For each frequency bin (λ), the coherence value (Cohxy) was obtained by squaring the magnitude of the complex correlation coefficient R. This procedure returned a real number between 0 (no coherence) and 1 (max coherence).

In line with previous works [Babiloni et al., 2006a,b; Rossini et al, 2006; Vecchio et al., 2007], the spectral coherence between the electrode pairs was calculated by a in-house software program developed under Matlab 6.5 (Mathworks, Natrick, MA; an extension of Pearson's correlation coefficient to complex number pairs; 1-Hz frequency resolution).

For the evaluation of the intrahemispheric and interhemispheric synchronization of the EEG frequency bands of interest, the spectral coherence was evaluated between the C3 versus F3, Fz, Cz, Pz, P3, O1, and P7 electrodes. As a control condition, the contralateral (nonstimulated) hemisphere was investigated between the C4 versus F4, Fz, Cz, Pz, P4, O2, and P8 electrodes. Finally, another control analysis estimated the functional coupling between the C3 and C4 electrodes.

Topographic Mapping of Spectral Coherence

For illustrative purposes, topographic maps (256 colors) of the spectral coherence (for each electrode with respect to either C3 or C4) were obtained on a 3D cortical model using a spline interpolating function [Babiloni et al., 1996]. This model was based on the MR characteristics of 152 subjects digitized at the Brain Imaging Center of the Montreal Neurological Institute (SPM96, www.mni.mcgill.ca), and it is commonly considered an acceptable template for the rendering of group neuroimaging data.

STATISTICAL ANALYSIS

To test the working hypothesis that time-varying MEP amplitude fluctuations could be related to changes in functional networks as marked by changes in EEG coherence topography, an analysis of variance (ANOVA) was used to evaluate the variance of the coherence values (dependent variable). The ANOVA design included the following factors: Condition (high MEP, low MEP), Hemisphere (left,

TABLE I. Four-way ANOVA, hemisphere, electrode pairs, band, and condition (high and low MEP)

	F	df	*P*-value
Hemisphere	3.653	1, 7	0.098
ElectrodePairs	135.682	6, 42	0.000
Condition	4.101	1, 7	0.083
Bands	1.950	6, 42	0.095
Hemisphere * Electrode Pairs	1.165	6, 42	0.343
Hemisphere * Condition	16.921	1, 7	0.004
ElectrodePairs * Condition	1.639	6, 42	0.160
Hemisphere * ElectrodePairs * Condition	.287	6, 42	0.940
Hemisphere * Bands	1.356	6, 42	0.255
ElectrodePairs * Bands	6.540	36, 252	0.000
Hemisphere * ElectrodePairs * Bands	1.587	36, 252	0.023
Condition * Bands	1.455	6, 42	0.217
Hemisphere * Condition * Bands	0.870	6, 42	0.525
ElectrodePairs * Condition * Bands	1.479	36, 252	0.046
Hemisphere * Electrode Pairs * Condition * Bands	1.165	36, 252	0.248

right), Electrode Pairs (C3-F3, C3-Fz, C3-Cz, C3-Pz, C3-P3, C3-O1, C3-P7 for the left, and the homologues for the contralateral nonstimulated hemisphere), and Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma). The factor of interest was Condition because the working hypothesis was that the coherence values would differ according to the MEP size by hemisphere (left and right), by spatial position (electrode pairs), and by frequency bands (from delta to gamma).

Mauchly's test evaluated the sphericity assumption. In any cases of violation, the degrees of freedom were corrected according to the Greenhouse-Geisser procedure. Sidak's sequential procedure was used for post-hoc comparisons ($P < 0.05$). Finally, to test whether eventual changes of spectral coherence were merely a reflection of the power spectrum, an ANOVA was performed using the normalized power spectrum as a dependent variable. The ANOVA factors were Condition (high MEP and low MEP), Electrodes, and Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma).

RESULTS

The four-way ANOVA with hemisphere, electrode pairs, band, and condition (high and low MEP) is reported in Table I. As a main factor, MEP size was marginally significant ($P = 0.083$), which suggests that brain coherence was slightly higher with respect to the high MEP values. The first interaction of interest was the interaction of Hemisphere with MEP size ($P = 0.004$). The difference in coherence between the *high* and the *low* MEPs was globally

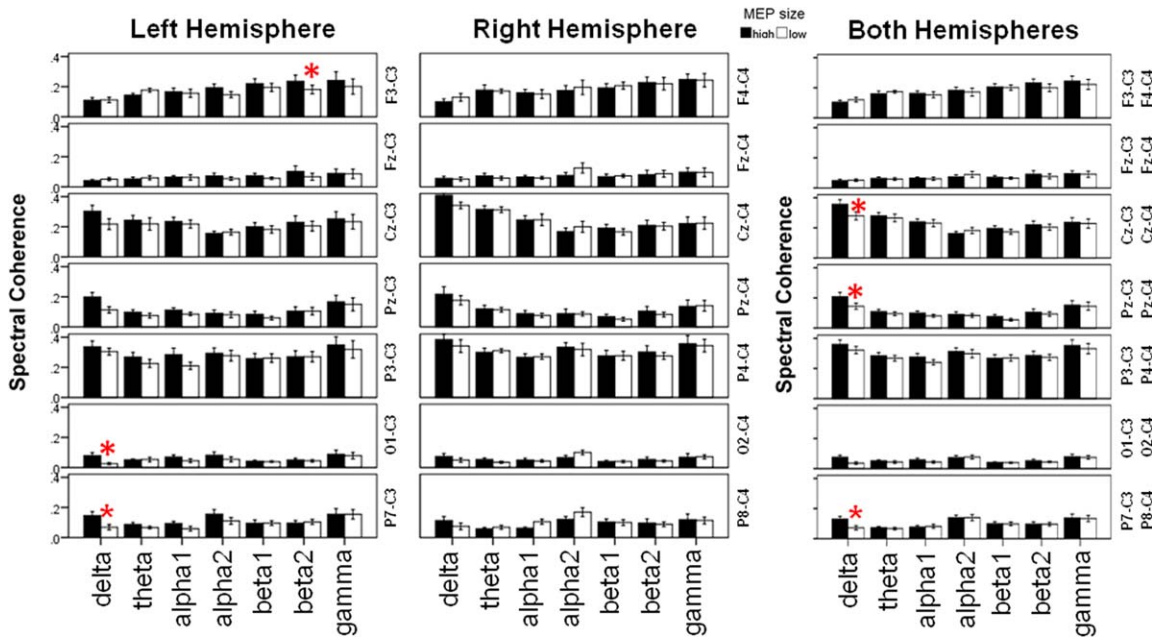

Figure 1.

Mean values and 95% confidence intervals of coherence values according to MEP size, hemisphere, band, and electrode pairs. The right panel ("both hemispheres") represents the band by electrode pairs by condition interaction with higher coherence in higher MEPs, specifically for the delta band in the connections Cz-C3, Pz-C3, and P7-C3. The left panel reveals further hemispheric specificities in the left hemisphere. *Indicates significant differences after Sidak's post-hoc adjustments. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

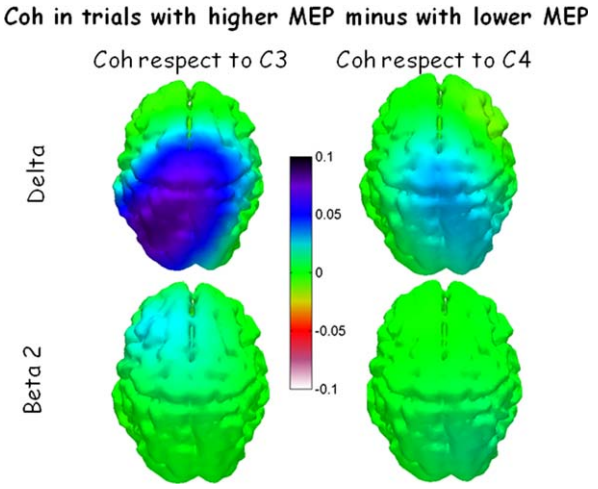

Figure 2.
Topographical maps of the difference between the high and low MEP Conditions for the delta and beta 2 frequency bands in both C3 and C4 coupling versus the other recording electrodes. In general, the maps of the left hemisphere (coupling with respect to C3) were characterized by an evident increase of posterior coupling of the delta band. Of note, the maps for the nonstimulated hemisphere (coupling with respect to C4) were lower in amplitude in both frequency bands. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

larger in the left than in the right hemisphere. Sidak's post-hoc analysis indicated that the left hemisphere EEG coherence was larger when the MEP was high ($P < 0.01$) and that no difference was observed in the right hemisphere. No other significant interactions that would have been determined by two-way interactions with condition were found. However, a three-way interaction of electrode pairs by band by condition was significant ($P = 0.046$). This effect is represented in Figure 1 (right panel, "both hemispheres" column). The differences in coherence between high and low MEP were dependent on the electrode pairs in addition to band frequency. In particular, Sidak's post-hoc analysis indicated that in the delta band, the coherence of Pz-C3 and contralaterally of Pz-C4 and Cz-C3, Cz-C4, and P7-C3 and P8-C4 were significantly larger in the high MEP condition compared with the low MEP. The pattern represented in Figure 1 (right panel) was not significantly different in the two hemispheres (four-way interaction, $P = 0.248$). Strictly speaking, a more focused analysis should have been performed. However, our analysis was hampered by a low power to detect such types of combined effects. To overcome this limitation despite an increased risk of false positive findings, we performed two separate blocks of three-way ANOVAs. The first block was comprised of seven 3-way ANOVAs for each electrode pair to reveal eventual hemispheric/band specificities, and the second block was comprised of seven 3-way ANOVAs for each band to reveal eventual hemispheric/electrode specificities.

Significant Hemisphere by Band by Condition interactions were found for "O1-C3, O2-C4," and for "P7-C3, P8-C4." Compared with the low MEP condition, the delta coherence was larger in the high MEP condition. This effect was observed either only in the left hemisphere (O1–C3) or was greater in the left hemisphere (P7–C3) compared with the homologous pairs in the right hemisphere.

A significant hemisphere by electrode pairs by condition interaction was found only for the beta 2 band. This effect was mainly due to a specific coherence increase between F3 and C3 with respect to the contralateral pair, and this difference was not observed in the other pairs.

Figure 1 (left panels) shows the patterns for each hemisphere. In summary, we found an increased bilateral centro-parietal-occipital delta coherence (slightly more evident in the left hemisphere for O1 and P7) and increased left frontal beta 2 coherence in the trials corresponding to the MEPs of larger amplitude (Figs. 2 and 3).

Of note, the apparent differences observed in Figure 1 in the C3-P3 alpha 1 coherence were not significant ($P = 0.085$ with a *t*-test analysis), but it should be regarded as a trend that would be better evaluated with a greater number of subjects.

Control Analysis

The control data analysis was carried out to understand whether changes in the spectral coherence could be explained by eventual modifications of the power spectrum. Figure 4 shows the profile and magnitude of the EEG spectral power density. This profile and the related statistics confirmed that there were no significant differences ($P < 0.9$) between the high and low MEP conditions in the EEG frequency distribution and suggests that the changes in functional coupling cannot be simply explained by changes in the power of the EEG frequency bands. Finally, we also reevaluated the main ANOVA using the power spectrum as a covariate, and we obtained the same principal results.

DISCUSSION

It is now widely accepted that TMS of M1 not only activates cortico-spinal pathways but also produces activations in adjacent and remote brain areas belonging to the motor-related brain networks. Moreover, it is well known that the amplitude of MEPs is clearly influenced by cortical excitability [Ferreri et al., 2006; Nikulin et al., 2003; Rossini and Ferreri, 2012; Rossini et al., 1991]. In fact, amplitudes of MEPs vary across time in responses elicited by identical consecutive TMS stimuli, while motor responses in the same "target" muscle of spinal reflex origin do not change [Rossini et al., 1991]. Therefore, fluctuations in motor cortex

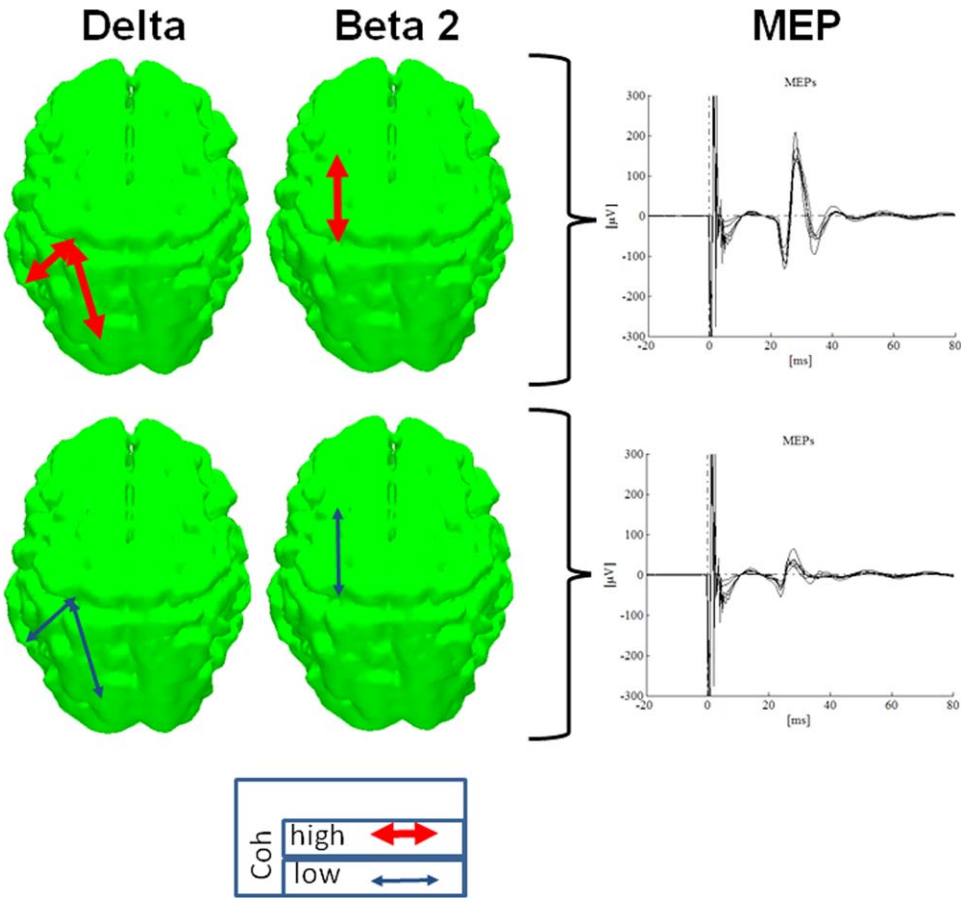

Figure 3.

Scheme of the cerebral patterns of left hemisphere network in the bands of interest (delta, beta 2) for both high and low MEP productions. The higher MEP (top of the figure) is more evident when specific connections are reflected by a strong coupling (red thick arrows); namely, the coherence values at the delta bands between C3 and O1, P7 and at beta 2 in C3-F3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

excitability are believed to be responsible, at least in part, for this variability [Amassian et al., 1989; Brasil-Neto et al., 1992; Britton et al., 1991]. Cortical spontaneous oscillations have revealed rhythmic changes in the membrane potential and thus in the excitability of neuronal populations [Kiers et al., 1993]. Corticospinal neurons are an intrinsic part of the cortical oscillatory network, and their firing is partially phase-locked to such oscillations. This firing pattern presumably indicates a cyclic modulation in the excitability of the cells of origin of corticospinal tracts [Mitchell et al., 2007]. The level of excitability within a network can critically influence some types of synaptic plasticity, and level of excitability was proposed as an indicator of connectivity strength within such a network [Destexhe and Marder, 2004; Erchova and Diamond, 2004; Johnson et al., 2012; Steinke and Galán, 2011]. The transient synchronization of local field potential (postsynaptic activity), which mostly contributes to the EEG signals, has been suggested as one of the most effective mechanisms for determining the rapidly time-varying binding/unbinding phenomena that orchestrate the dynamic linkage of separate and widely distributed neuronal assemblies within a unique and functionally coherent frame [Engel et al., 1991; Mioche and Singer, 1989; Roelfsema et al., 1997; see for review D'Amelio and Rossini, 2012; Singer et al., 1997]. One could speculate that if fluctuations of the MEPs amplitude and of the spontaneous EEG oscillation's power, and/or of functional coupling, reflect cortical excitability levels, then their changes in time could be expected to correlate with each other.

In this article, we presented clear evidence that the amplitude of MEP was correlated in time to the strength and the stochastic dynamics of the functional coupling of the EEG oscillations immediately preceding individual TMS in specific brain areas (Fig. 3). Notably, the EEG rhythmicity, as reflected by the frequency power spectrum, appeared to play a marginal role in modulating the motor cortex

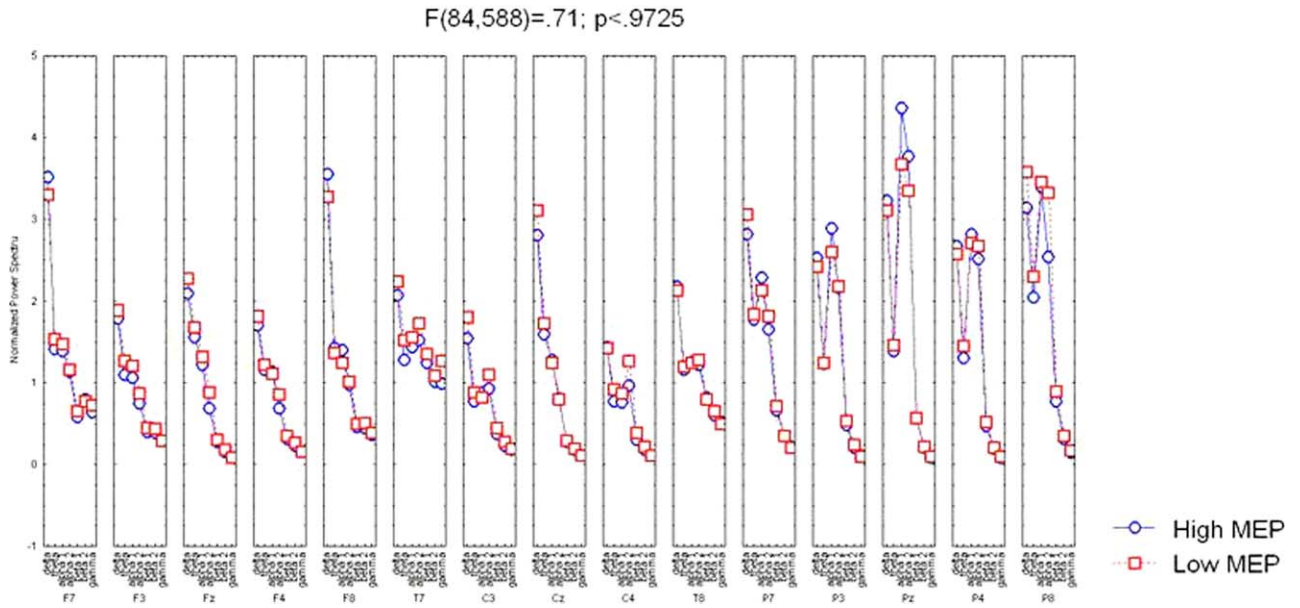

Figure 4.
Normalized electroencephalographic (EEG) spectral power density. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

excitability in wakefulness. It was evident that when the stimulated primary motor cortex was coupled in the beta 2 band with the ipsilateral prefrontal cortex and in the delta band with the bilateral centro-parietal-occipital cortices, TMS led to significantly larger MEPs than when such a patterned coupling was missing (Figs. 2 and 3). In agreement with our results, previous studies with MEG and EEG-fMRI were able to detect a significant association between prefrontal cortex activity and beta rhythm [Hanslmayr et al., 2011]. Beta rhythm is widely recognized to be linked in humans and monkeys with motor behavior and response inhibition, as well as with long-distance signaling along feedback pathways and top-down signaling. A prominent role of beta-band oscillations in top-down projections would corroborate our results and would explain why interareal coherence associated with selective attention [Gross et al., 2005], working memory [Tallon-Baudry et al., 2001], guided search [Buschman and Miller, 2007], object recognition [Sehatpour et al., 2008], perception [Donner et al., 2007], or sensorimotor integration [Brovelli et al., 2004; Brown and Marsden, 2001; Lepage et al., 2008; Witham et al., 2007] is especially conspicuous in the beta frequency range. It may also account for the beta rhythm recorded during attention and motor control in the basal ganglia or in the thalamus [Wróbel et al., 2007] because of inputs from deep layers of cortical areas upstream. Moreover, it is known that even with highly irregular firing of single neurons, the excitatory-inhibitory loop mechanism naturally gives rise to gamma-and beta-band oscillations [for review, see Wang, 2010]. Finally, modeling studies have shown that synchronization can tolerate longer synaptic delays for beta than for gamma oscillation [Buffalo et al., 2011; Jones et al., 2000; Kopell et al., 2000], suggesting that relatively long-distance oscillatory synchronization may be more robustly realized at beta frequencies. The results in the delta band are particularly interesting. It is well known that in the awake brain, alpha rhythms dominate in the posterior areas while delta rhythms are low in amplitude, thus reflecting a condition of likely alpha-delta "reciprocal inhibition" [Rossini et al., 2006]. However, it is also well known that anatomical or functional disconnection from related cortical areas generates spontaneous slow oscillations in virtually all recorded neurons [Gloor et al., 1977]. Based on this theoretical framework, it could be speculated that the widely increased coherence in the delta band immediately preceding a TMS would be able to trigger MEPs of large amplitudes and could underlie a M1 functional disconnection from brain areas with an inhibitory control on the cortico-motor system. Actually, when the cortico-spinal tract is active during voluntary muscle movement, the sensory areas are "gated" via corollary M1-to-S1 inhibitory discharges and respond less to an incoming sensory signal [Narici et al., 1990; Rossini et al., 1999]. Increased coherence in the delta range might therefore partially represent this functional unbinding of the motor cortex from the posterior areas' inhibitory control when a highly excitable or active condition is required [see also the active centro-inhibitory surround organization by Mountcastle et al., 1975].

We are fully aware that these "fragile" time-varying binding/unbinding phenomena are only incomplete hints

of the spatiotemporal spiking activity patterns in the cortex and that they are far from being fully understood [Buzsáki, 2004; Pillow et al., 2008; for review see Wang, 2010]. Furthermore, the sources of variability in network excitability are most likely not reflected by the prestimulus EEG properties. Many potential sources for transient changes in the MEP size, such as coil movement changes in the effectiveness of the stimulation [Reutens et al., 1993] or noise in the recording system [Burke et al., 1995], could be excluded due to the use of an advanced EEG-Navigated TMS coregistration system. Other possible variability sources have been ruled out by previous studies, including the relation of TMS with the phase of the cardiac or respiratory cycles [Amassian et al., 1989; Ellaway et al., 1998; Filippi et al., 2000].

Altogether, the results from the present study demonstrate that analyzing the EEG coherence of candidate brain areas at various scalp sites at different frequencies can help predict instantaneous excitability and hopefully the time-variant performance of the candidate brain areas.

Therefore, it will be of paramount importance to investigate the dynamics of interareal coherence of brain EEG rhythms in healthy brains and in brains suffering from different neuropsychiatric conditions where brain connectivity is possibly altered, such as depression, epilepsy, dementia, and disorders of consciousness [Dal Forno et al., 2006, Ferrarelli et al., 2008; Ferreri et al., 2003, 2011a, 2012; Squitti et al., 2006].

CONCLUSION

The results from the present study provide direct proof for a stochastic linkage of motor-related cortical areas via oscillatory synchronization in selected EEG rhythms in determining primary motor cortex excitability. New developments lay ahead in our quest to understand the nature of the coordinated and gated brain dynamics underlying flexible sensorimotor behaviors. However, it is possible that the mechanisms underlying the response variability could help to understand how the brain optimizes movement control and could possibly provide a new probe to noninvasively test the function and cortico-cortical connectivity in both healthy and neurologically diseased brains.

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