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EEG oscillations and magnetically evoked motor potentials reflect motor system excitability in overlapping neuronal populations

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ABSTRACT

Objective: To understand the relationship between neuronal excitability reflected by transcranial magnetic stimulation (TMS) evoked motor potentials (MEPs) and spontaneous oscillation amplitude and phase.
Methods: We combined spontaneous EEG measurement with motor cortex TMS and recorded MEP amplitudes from abductor digiti minimi (ADM).
Results: Midrange-beta oscillations over the stimulated left motor cortex were, on average, weaker before large- than small-amplitude MEPs. The phase of occipital midrange-beta oscillations was related to the MEP amplitudes.
Conclusions: The present results support the view that MEP and Rolandic beta oscillation amplitudes are associated with motor cortical excitability. However, oscillations seen in EEG reflect the excitability of a large population of cortical neurons, and MEP amplitude is affected also by spinal excitability and action potential desynchronization. Thus, MEP and EEG oscillation amplitudes are not strongly correlated. In addition, even during rest, motor system excitability appears to be related to activity in occipital areas at frequency ranges associated with visuomotor processing.
Significance: The ability of spontaneous oscillations and MEPs to inform us about cortical excitability is clarified. For example, it is suggested that oscillatory activity at non-motor sites might be related to motor system excitability at rest.

1. Introduction

Transcranial magnetic stimulation (TMS; Barker et al., 1985) is a noninvasive method for activating cortical neurons. TMS of the primary motor cortex (M1) evokes activation in target muscles that can be recorded as motor evoked potentials (MEPs). MEP amplitudes vary strongly between responses elicited by identical consecutive stimuli. It has been suggested that fluctuations in cortical and spinal motor neuron excitability (Brasil-Neto et al., 1992; Kiers et al., 1993) as well as motor neuron response desynchronization (Magistris et al., 1998; Bühler et al., 2001; Rösler et al., 2008) cause this variability.

Spontaneous oscillations measured with EEG and MEG reflect rhythmic changes in the membrane potential, and thus excitability, of neuronal populations. Periods of large-amplitude spontaneous oscillations at frequencies characteristic of different cortical areas reflect an idling state of the part of the cortex in question. Posterior alpha range (8–13 Hz) oscillations are related to the visual system (Adrian and Matthews, 1934), while pericentral (Rolandic) alpha and beta (12–30 Hz) oscillations are associated with a resting state of the primary sensory and motor cortex, respectively (Stancák and Pfurtscheller, 1995; Salmelin and Hari, 1994; Ritter et al., 2009).

If fluctuations in both MEP and spontaneous oscillation amplitudes reflect cortical excitability changes, these measures could be expected to correlate. This question has been assessed with controversial results. Zarkowski et al. (2006) and Sauseng et al. (2009) found a significant negative correlation between MEP and Rolandic alpha oscillation amplitudes when the target muscle was at rest, whereas MEP and beta band oscillation amplitudes were not correlated. In contrast, Lepage et al. (2008) found a non-significant negative correlation between MEP and Rolandic alpha oscillation amplitudes during movement imagery, observation and execution, as well as rest, whereas in an exploratory analysis (not corrected for multiple comparisons) they found significant correlations between MEP and low-to-midrange-beta (12–18 Hz) oscillation amplitudes. Mitchell et al. (2007) failed to find a relationship between MEP amplitudes and spontaneous oscillations during a precision grip task known to promote Rolandic beta oscillations.

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We combined motor cortex TMS with spontaneous EEG measurement to examine the role of spontaneous oscillations in modulating cortical excitability, and to measure to what extent the fluctuations in ongoing oscillations and MEP amplitudes reflect the excitability of the same neuronal population. Considering the nature of spontaneous oscillations reflecting periodic fluctuations in membrane potentials, it seems plausible that in addition to the amplitude of the ongoing activity, also the phase has an effect on the evoked responses. Thus, the effect of spontaneous oscillation phase on MEP amplitude, which to our knowledge has not been studied before, was also examined.

The results suggest that left Rolandic midrange-beta oscillations and MEP amplitudes are weakly related suggesting that the neuronal populations contributing to these measures overlap, but are not identical. While no significant relationship was found between MEPs and the Rolandic oscillation phase, MEP amplitudes were related to the phase of occipital midrange-beta oscillations, which have been associated with visuomotor processing.

2. Methods

2.1. Subjects

Sixteen healthy right-handed subjects (14 male; 21–29 years old, mean age 25, SD 2.4) participated in the study. All gave their written informed consent before the experiment. The study was approved by the Ethics Committee of Helsinki University Central Hospital and was in compliance with the Declaration of Helsinki. The data of 14 subjects were included in the analysis of MEP amplitudes and spontaneous oscillations: one subject was excluded because of stimulation coil movement and another because of a decreasing trend in MEP amplitudes despite coil position stability. All 16 subjects were included in the analysis of motor threshold and spontaneous oscillations.

2.2. TMS

The subjects sat on a reclining chair with their hands relaxed and eyes open. TMS was delivered using a Nexstim eXimia TMS stimulator (Nexstim Ltd., Helsinki, Finland) and a figure-of-8 focal monopulse coil (loop outer diameter 70 mm). MRI-guided navigation (Nexstim eXimia NBS) was used to target the hand area of the left primary motor cortex and further adjusted to maximize MEP amplitudes from the right abductor digiti minimi (ADM). The induced current was directed anteromedially. A minimum of 60 TMS pulses were given at random 2–3 s intervals at 100% of the resting motor threshold of the ADM. The location-controlled stimulation feature of the NBS system was used, meaning that pulses were only delivered when the coil position deviated less than 2 mm from the initially defined stimulation site.

2.3. EEG

A 60-channel TMS-compatible Nexstim eXimia EEG device was used to record the EEG. The signal was referenced to an electrode behind the right ear; the ground electrode was over the right cheek bone. EOG was recorded to monitor eye movements. The signals were band-pass filtered at 0.1–350 Hz, digitized at 1450 Hz and analyzed offline.

2.4. EMG

The MEPs were recorded from abductor digiti minimi (ADM) using a Medtronic Keypoint EMG device (Medtronic, Inc., Minneapolis, Minnesota, USA). The electrodes were taped in a muscle belly–tendon montage; the ground electrode was placed on the back of the hand. The analog bandwidth was 0.1–3000 Hz; the signal was digitized at 20 kHz.

2.5. Analysis

Offline analysis of EEG and EMG was performed using MATLAB (The Mathworks, Inc., Natick, Massachusetts, USA). The data were visually inspected; trials containing blinks, artefacts, or baseline EMG activity revealing preactivation of the muscle were omitted. For the rest of the trials, peak-to-peak MEP amplitudes were determined. Four EEG channels over the left M1, four over the right M1, six over the occipital cortex, and six over the frontal lobe were chosen for further analysis (see Fig. 1).

To analyze prestimulus oscillation amplitudes, the temporal spectral evolution (TSE) method (Salmelin and Hari, 1994) was used. Single-trial 1000-ms prestimulus EEG traces were filtered at either alpha (8–12.5 Hz), low-beta (12–15 Hz), midrange-beta (15–18 Hz), or high-beta (18–30 Hz) range using a second-order Butterworth band-pass filter; the filtered trials were rectified. The signals were then averaged over channels within each channel group and a time period before TMS pulse corresponding to three oscillatory cycles at the middle frequency of the range in question (alpha: 293 ms, low-beta: 222 ms, midrange-beta: 182 ms, high-beta: 125 ms). The resulting value indicates the spontaneous activity amplitude at a given frequency range during, on average, three oscillatory cycles preceding the TMS pulse.

The filtered and rectified signals were smoothed and downsampled for visualization purposes so that each data point was an average over one oscillation cycle at the middle frequency of the range in question (alpha: 98 ms, low-beta: 74 ms, midrange-beta: 61 ms, high-beta: 42 ms).

Spearman's correlation coefficients within each subject were calculated between MEP amplitudes and the single-trial EEG oscillation amplitudes determined with the TSE method. In order to study the difference in oscillation amplitudes between groups of trials with small and large MEP amplitudes, the trials were sorted and averaged separately over the trials corresponding to 1/3 of the smallest and 1/3 of the largest MEPs. As a result, one oscillation amplitude value was obtained for each subject, frequency range, channel group (area), and MEP size group. Statistical analysis was performed using paired *t*-tests: statistical significance of the difference in oscillation amplitudes preceding small and large MEPs was calculated separately for each area–frequency range pair. Bonferroni correction was applied to correct for multiple comparison effects. In addition, in order to assess the specificity of the

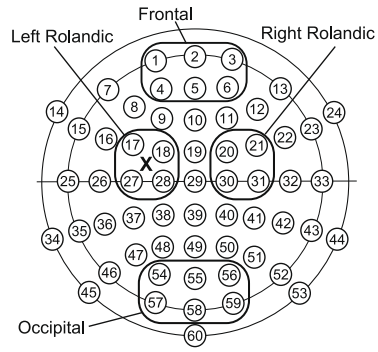

Fig. 1. EEG channel layout and the channel groups chosen for analysis. The cross marks the stimulation site.

dependency between MEP and oscillation amplitudes, three-way repeated measures ANOVA with within-subject factors 'MEP size' (small, large), 'frequency range' (alpha, low-beta, midrange-beta, high-beta), and 'area' (left Rolandic, right Rolandic, occipital, frontal) followed by Bonferroni-corrected simple-effects post hoc tests was performed. Mauchly's test was performed to test the validity of the sphericity assumption, and Greenhouse–Geisser correction of degrees of freedom was applied when necessary. Temporal specificity of a significant effect shown by the *t*-tests was assessed with two-way repeated measures ANOVA with factors 'MEP size' and 'Time' for a given frequency-range–area pair. Factor 'time' had four levels, TSE averaged over oscillatory cycles 1–3, 4–6, 7–9 and 10–12 (at the middle frequency of the frequency range) before the stimulus (1 is the last complete cycle before the stimulus, etc.).

Pearson's correlation coefficient was calculated between the subjects' motor thresholds and the mean spontaneous oscillation amplitudes measured over each area at each frequency range. Single-trial 706-ms (1024 data points) prestimulus EEG traces were multiplied with a Hamming window, zero padded to 8192 data points to increase apparent frequency resolution and Fourier transformed. The amplitude spectra of the Fourier transforms were averaged over trials, channels within the channel group, and the frequency range.

To estimate the phase of spontaneous oscillations at the time of stimulation, the dominant frequency of each subject at each frequency range was first determined. Single-trial 706-ms (1024 data points) prestimulus EEG traces were filtered using a 200th-order Kaiser-windowed FIR band-pass filter (at the relevant frequency range), multiplied with a Hamming window, zero padded to 8192 data points, and Fourier transformed. The amplitude spectra of single-trial Fourier transforms were averaged, and the dominant frequency was chosen as the frequency corresponding to the maximum of the averaged amplitude spectrum.

Single-trial 1000-ms prestimulus EEG traces were again filtered using a 200th-order Kaiser-windowed FIR band-pass filter and averaged over channels of each channel group. A 1.5-cycle sinusoid at the dominant frequency was fitted to the filtered signals just before the TMS pulse, and the phase of the best-fit sinusoid at the time of the stimulation was determined. A FIR filter introduces a known linear phase shift to the signal, so the obtained phase was corrected by the phase delay at the dominant frequency.

The complex phase values were projected to two different axes marking instantaneous oscillation amplitude normalized to range [−1,1], −1 corresponding to wave through, and 1 to wave peak, and instantaneous oscillation slope also normalized to range [−1,1], −1 corresponding to maximal negative slope (crossing the time axis with negative slope) and 1 to maximal positive slope (crossing the time axis with positive slope).

Spearman's correlation coefficients within subjects were calculated between MEP amplitudes and instantaneous amplitude values, as well as MEP amplitudes and instantaneous slope values. In order to study the difference in oscillation phase between groups of trials with small and large MEP amplitude, the instantaneous amplitude and slope values were averaged separately over trials corresponding to 1/3 of the smallest and 1/3 of the largest MEPs. Statistical analysis was performed separately on the instantaneous amplitude and slope values using paired *t*-tests: statistical significance of the difference in oscillation phase between trials with small and large MEPs was calculated separately for each area–frequency range pair. Bonferroni correction was applied to correct for multiple comparison effects. In addition, in order to assess the specificity of the dependency between MEP and oscillation phase, three-way repeated measures ANOVA with within-subject factors 'MEP size' (small, large), 'frequency range' (alpha, low-beta, midrange-beta, high-beta), and 'area' (left Rolandic, right Rolandic, occipital, frontal) followed by Bonferroni-corrected simple-effects post hoc tests was performed separately for instantaneous amplitude and slope. Mauchly's test was performed to test the validity of the sphericity assumption, and Greenhouse–Geisser correction of degrees of freedom was applied when necessary.

3. Results

3.1. MEP amplitudes

In line with previous studies, there was a large variability in MEPs even though the stimulation parameters remained virtually unchanged. Fig. 2 shows MEP amplitudes of a representative subject (subject 3) sorted according to their size. The average amplitude of 1/3 of the smallest and 1/3 of the largest MEPs of each subject are presented in Table 1.

3.2. Spontaneous oscillation amplitudes

The TSE waveforms are presented in Fig. 3(A–D). Midrange-beta oscillation measured over the stimulated left motor cortex was stronger preceding stimuli that elicited small MEPs compared to stimuli eliciting large MEPs ($p < 0.05$). No significant dependencies were found between MEP and spontaneous oscillation amplitudes at other frequency ranges or measured over other areas (see Table 2 for *p*-values). The oscillation amplitudes (mean ± SEM over subjects) are presented in Fig. 3(E).

ANOVA for spontaneous oscillation amplitudes indicated a significant 3-way interaction 'MEP size' × 'frequency range' × 'area' [$F(9, 117) = 3.72$, $p = 0.016$; Greenhouse–Geisser correction applied (GG)]. The 2-way repeated-measures ANOVA follow-up test revealed a significant interaction 'MEP size' × 'area' at alpha band [$F(3, 39) = 4.74$, $p = 0.007$] and a tendency for an interaction at the midrange-beta band [$F(3, 39) = 2.20$, $p = 0.10$]. There were no 2-way interactions at the other frequency bands [low-beta: $F(3, 39) = 0.74$, $p = 0.54$; high-beta: $F(3, 39) = 0.92$, $p = 0.44$]. The paired *t*-tests, however, did not show significant simple main effects at alpha band [occipital: $p = 0.056$, $p_{BC} = 0.9$ (Bonferroni-corrected *p*-value); left Rolandic: $p = 0.28$, $p_{BC} = 1$; right Rolandic: $p = 0.45$, $p_{BC} = 1$]. At midrange-beta band, the oscillations measured above left Rolandic areas were stronger before trials with small MEPs compared to trials with large MEPs ($p = 0.0026$, $p_{BC} = 0.042$), whereas the midrange-beta oscillations measured above the other sites were not significantly related to MEP size (occipital: $p = 0.21$, $p_{BC} = 1$; right Rolandic: $p = 0.067$, $p_{BC} = 1$). The fact that the two-way 'MEP size' × 'area' interaction at midrange-beta band failed to reach significance implies that the phenomenon is not necessarily specific to left Rolandic sites (e.g., looking at Fig. 3 and *p*-values in Table 2, also right Rolandic and frontal

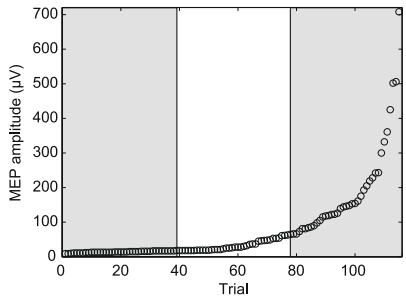

Fig. 2. MEP amplitudes of a representative subject (subject 3) sorted according to size. The shaded areas indicate the 1/3 of smallest and largest MEPs.

Table 1
Average amplitude (μV) of 1/3 of smallest and 1/3 of largest MEPs.

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Small	13	13	14	12	22	31	13	12	40	39	10	13	30	12
Large	254	154	161	154	107	195	152	198	400	439	94	161	143	115

midrange-beta oscillations might be weakly, and in this dataset non-significantly, related to MEP size), or the measure at the other sites is too noisy to draw conclusions about them.

The temporal evolution of the relationship between left Rolandic midrange-beta oscillation and MEP amplitude was further studied with a two-way ANOVA with factors 'MEP size' and 'time'. TSE was averaged over oscillatory cycles 1–3, 4–6, 7–9 and 10–12 (0–182 ms, 182–364 ms, 364–546 ms and 546–728 ms) before the stimulus. The difference in oscillation amplitude between MEP size groups was different at different time ranges, as shown by the significant 'MEP size' × 'time' interaction [$F(3, 39) = 3.32$, $p = 0.030$]. Tukey's post hoc test revealed that the relationship between oscillation and MEP amplitudes was significantly stronger ($p < 0.05$) in the period right before the stimulus (1–3 cycles prestimulus) than during the two earliest periods tested (7–9 and 10–12 cycles prestimulus). Also, the relationship between the oscillation and MEP amplitudes was stronger 4–6 than 10–12 cycles before the stimulus ($p < 0.05$).

The correlation analysis on single-trial level between MEP amplitudes and spontaneous oscillation amplitudes within subjects did not show consistent significant dependencies for oscillations measured over any area or at any frequency range, as shown by the non-significant Spearman's correlation coefficients. The mean correlation coefficients for each frequency range and area are shown in Table 3.

In order to increase the proportion of signal originating from the neurons controlling the target muscle, the analysis was repeated by replacing the left Rolandic channel group with the channel closest to the stimulation site (27 = C3) and replacing the right Rolandic channel group with the channel corresponding to C3 on the contralateral hemisphere (31 = C4). The results did not change much compared to the analysis using four channels on both sides (data not shown).

The correlation between motor threshold and spontaneous oscillation power was strongest for left Rolandic midrange-beta, although not statistically significant (correlation coefficient = 0.18, $p = 0.5$). The correlation coefficients and the respective p-values (not corrected for multiple comparisons) are presented in Table 4.

3.3. Spontaneous oscillation phase

No significant effect of the phase of Rolandic spontaneous oscillations was found on MEP size. Instead, the difference in the instantaneous slope value of occipital midrange-beta oscillation

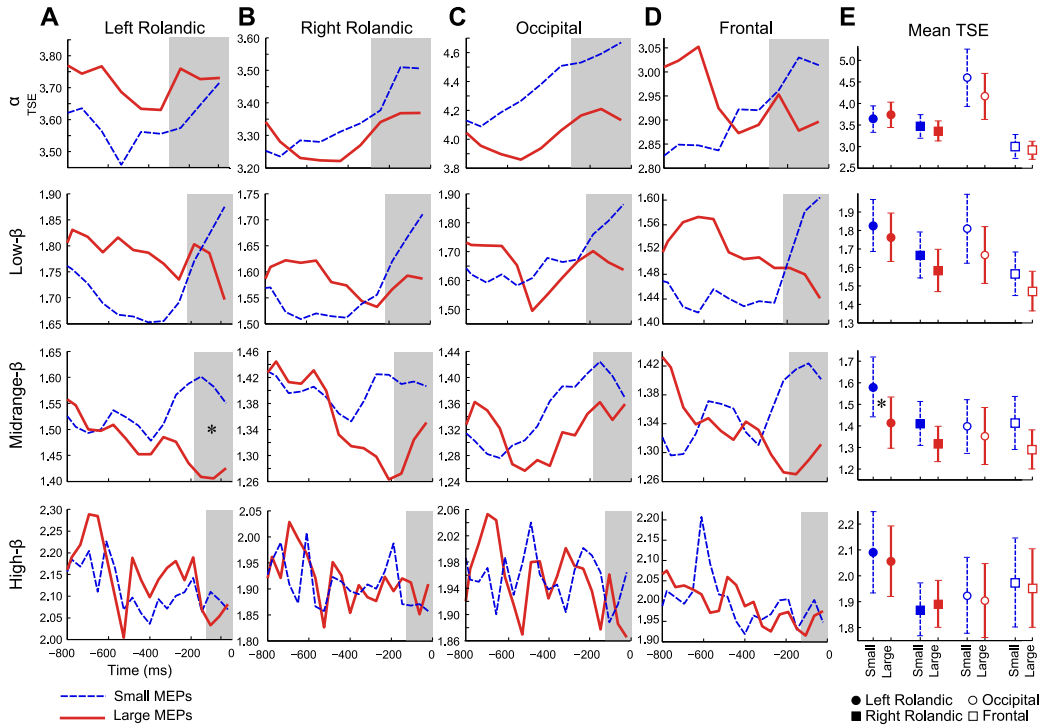

Fig. 3. Grand average TSE waveforms (A–D) calculated separately for trials with small- and those with large-amplitude MEPs. The shaded area indicates the time period over which the TSE values were averaged. The averaged values (±SEM over subjects) are shown in column E. The asterisk (*) indicates a significant difference at the confidence level $p < 0.05$ in spontaneous oscillation amplitudes (averaged TSE value) between trials with small and large MEPs.

Table 2
Bonferroni-corrected (A) and uncorrected (B) p-values of the paired t-tests showing the difference in spontaneous oscillation amplitudes between trials with small and those with large MEPs. The asterisk (*) indicates a significant difference at the confidence level $p < 0.05$.

	Left Rolandic	Right Rolandic	Occipital	Frontal
A	*Bonferroni-corrected p-values*			
α	1	1	0.90	1
Low-β	1	1	1	0.88
Midrange-β	0.042*	1	1	0.35
High-β	1	1	1	1
B	*Uncorrected p-values*			
α	0.45	0.28	0.056	0.48
Low-β	0.35	0.20	0.15	0.055
Midrange-β	0.0026*	0.067	0.21	0.022
High-β	0.41	0.53	0.67	0.58

was significant between the trials with small and those with large MEPs; the oscillation had negative rather than positive slope at the time of stimuli producing larger MEPs, and vice versa at the time of stimuli producing smaller MEPs ($p < 0.05$). For the other frequency ranges and areas, no significant dependencies were found (see Table 5(A–B) for p-values). MEP size did not significantly depend on the instantaneous amplitude of spontaneous oscillations at any frequency range or measured over any area (see Table 5 (C–D)). The instantaneous amplitude and slope values (mean ± SEM over subjects) are presented in Fig. 4.

ANOVA for the instantaneous slope showed a significant interaction 'MEP size' × 'frequency range' [$F(3, 39) = 5.18$, $p = 0.012$ (GG)], indicating that the difference in oscillation phase between small and large MEP groups was different at different frequency ranges. There was, however, no three-way 'MEP size' × 'frequency range' × 'area' interaction [$F(9, 117) = 1.08$, $p = 0.38$], suggesting that the effect did not differ significantly between areas. The follow-up test of the two-way interaction (paired t-test separately on different frequency ranges; areas pooled) showed a slight tendency for a simple main effect of 'MEP size' at midrange-beta ($p = 0.13$) and high-beta ($p = 0.14$) bands, whereas the effect was clearly non-significant at the other frequency ranges (alpha, $p = 0.23$; low-beta, $p = 0.41$). Since the paired t-tests showed a significant dependency between MEP amplitude and the instantaneous slope of the midrange-beta oscillation measured above occipital ($p = 0.002$, $p_{BC} = 0.032$) but not the other sites (left Rolandic: $p = 0.23$, $p_{BC} = 1$; right Rolandic: $p = 0.26$, $p_{BC} = 1$, frontal: $p = 0.94$, $p_{BC} = 1$), the spatial specificity of the effect was further tested with a two-way ANOVA with factors 'MEP size' and 'area' at the midrange-beta band. Still, only a tendency for an interaction was found [$F(3, 39) = 2.68$, $p = 0.060$], the largest difference being between occipital and frontal sites. The results suggest that the effect is not necessarily specific to occipital sites, or that the measure at the other sites is too noisy to draw conclusions about them. The lack of significant interaction might imply that there is a weak relationship between Rolandic midrange-beta oscillation phase and MEP amplitudes, although this should be further studied in future experiments. The paired t-tests and ANOVA showed no significant relationship between the instantaneous oscillation amplitude and

Table 3
Spearman's correlation coefficients (mean ± SD over subjects) between MEP and spontaneous oscillation amplitudes.

	Left Rolandic	Right Rolandic	Occipital	Frontal
α	+0.02 ± 0.10	−0.02 ± 0.08	−0.05 ± 0.11	+0.01 ± 0.16
Low-β	−0.08 ± 0.15	−0.07 ± 0.01	−0.05 ± 0.11	−0.07 ± 0.09
Midrange-β	−0.07 ± 0.09	−0.03 ± 0.10	−0.05 ± 0.11	−0.07 ± 0.08
High-β	+0.04 ± 0.13	+0.03 ± 0.11	−0.03 ± 0.13	+0.004 ± 0.09

Table 4
Pearson's correlation coefficients (r) and respective p-values (not corrected for multiple comparisons) between motor thresholds and spontaneous oscillation amplitudes.

	Left Rolandic		Right Rolandic		Occipital		Frontal	
	r	p	r	p	r	p	r	p
α	0.12	0.6	0.13	0.6	0.04	0.9	−0.02	0.9
Low-β	−0.007	1	−0.04	0.9	−0.12	0.7	−0.01	1
Midrange-β	0.18	0.5	0.08	0.8	0.03	0.9	0.06	0.8
High-β	0.0009	1	0.01	1	0.10	0.7	−0.09	0.8

MEP amplitude. However, the uncorrected p-value showing the difference in instantaneous amplitude of right Rolandic midrange-beta oscillations between small and large MEP groups is quite low ($p = 0.0084$), but because of the large number of comparisons the Bonferroni-corrected p-value is non-significant ($p_{BC} = 0.13$). Thus, this finding should be confirmed or rejected with another dataset before drawing conclusions.

There were no significant within-subject correlations on single-trial level between MEP amplitude and spontaneous oscillation phase at any frequency range or area (see Table 6 of Spearman's correlation coefficients). The results did not change much when data from only one channel above both motor areas was included in the analysis (left Rolandic: 27 = C3, right Rolandic: 31 = C4; data not shown).

4. Discussion

In the present study, the relationship between spontaneous EEG oscillations and TMS-evoked MEPs was studied. The amplitude of spontaneous oscillations in the midrange-beta band measured over the stimulated (left) motor cortex was, on average, smaller before stimuli producing large MEPs than before stimuli producing small MEPs. Only oscillation amplitudes measured just before the stimulus were related to MEP amplitudes, indicating that the fluctuations in excitability occur on a subsecond timescale. Oscillation amplitudes measured over occipital, frontal or contralateral (right) motor cortex and oscillations at alpha, low-beta, or high-beta band did not have a significant effect on MEP amplitudes. The single-trial analysis within subjects did not reveal consistent correlations between MEP amplitude and oscillation amplitude or phase at any frequency range or measured over any brain area. The phase of Rolandic oscillations was not shown to affect MEP amplitudes, but, surprisingly, the difference in occipital midrange-beta oscillation phase between trials with small- and those with large-amplitude MEPs was significant; the oscillation had negative rather than positive slope at the time of stimuli producing large-amplitude MEPs. The lack of interaction between stimulation sites regarding the relationship of MEPs with both the amplitude and instantaneous slope leaves open the question if the effect is specific to Rolandic areas on the stimulated hemisphere in case of oscillation amplitude and occipital areas in case of oscillation phase. For example, Fig. 3 suggests that there might be a relationship between MEP amplitudes and midrange-beta oscillations measured above right Rolandic and frontal areas, but if there is an effect, it is so weak that it was not statistically significant in the present dataset. There might also be a small non-significant relationship between the MEP amplitude and midrange-beta oscillation instantaneous slope measured above both Rolandic areas.

The relationship between spontaneous oscillations and cortical excitability has been studied using other modalities. Some studies combining spontaneous measurements with evoked responses have revealed an inverse relationship between spontaneous oscillation amplitudes and evoked responses in several modalities

Table 5
Bonferroni-corrected (A and C) and uncorrected (B and D) *p*-values of the paired *t*-tests showing the difference in spontaneous oscillation phase (instantaneous amplitude: A–B, instantaneous slope: C–D) between trials with small and those with large MEPs. The asterisk (*) indicates a significant difference at the confidence level $p < 0.05$.

	Left Rolandic	Right Rolandic	Occipital	Frontal
Instantaneous amplitude				
A	Bonferroni-corrected *p*-values			
α	1	1	1	1
Low-β	1	1	1	1
Midrange-β	1	0.13	1	1
High-β	1	1	1	1
B	Uncorrected *p*-values			
α	0.42	0.57	0.65	0.27
Low-β	0.33	0.35	0.59	0.13
Midrange-β	0.18	0.0084*	0.74	0.17
High-β	0.27	0.070	0.69	0.30
Instantaneous slope				
C	Bonferroni-corrected *p*-values			
α	1	1	1	1
Low-β	1	1	1	1
Midrange-β	1	1	0.032*	1
High-β	1	1	1	1
D	Uncorrected *p*-values			
α	0.36	0.17	0.18	0.50
Low-β	0.80	0.35	0.31	0.39
Midrange-β	0.23	0.26	0.0020*	0.94
High-β	0.16	0.071	0.19	0.66

including visual evoked potentials (VEP; Brandt and Jansen, 1991; Rahn and Basar, 1993a), somatosensory evoked potentials (SEP; Ploner et al., 2006), auditory evoked potentials (AEP; Rahn and Basar, 1993b), and TMS-evoked phosphenes (Romei et al., 2008a,b). In contrast, also positive correlations between evoked responses and ongoing activity have been found using optical imaging (Arieli et al., 1996), SEP (Nikouline et al., 2000), and VEP (Brandt et al., 1991). In addition, an inverse relationship between occipital alpha activity and visual perception has been shown (Thut et al., 2006; Hanslmayr et al., 2007; Romei et al., 2008a,b; van Dijk et al., 2008). Studies on the relationship between the prestimulus oscillation phase and cortical excitability have also been conducted with modalities other than TMS–EEG. Kruglikov and Schiff (2003) detected a dependency of AEP on prestimulus broad-band phase (there was a prominent alpha band power in many of the traces studied, though), as did Haig and Gordon (1998) and Barry et al. (2004) between AEP and alpha phase. In many studies, a dependency between prestimulus alpha phase and VEP has been found (Trimble and Potts, 1975; Valera et al., 1981; Jansen and Brandt, 1991; Makeig et al., 2002). A problem with comparing evoked responses averaged over groups of responses with different prestimulus oscillation phases – a method that has been used in many of these studies – is that the underlying ongoing activity, if not suppressed or reset by the stimulus, will not average to zero and thus affects the evoked response. Also, if the phase is estimated using Fourier transform or wavelets with poststimulus data included in the analysis, the variations in the evoked response affects the estimate of the prestimulus phase. Kirschfeld (2005) and Risner et al. (2009) used methods to subtract the ongoing activity from the evoked responses and failed to find a relationship between prestimulus alpha phase and VEP. However, Busch et al. (2009) and Mathewson et al. (2009) showed that visual perception depends on the phase of occipital alpha.

Some previous studies have used an approach similar to the one used here to study the excitability of the motor cortex with MEP and spontaneous oscillation amplitudes but with inconsistent results (see Thut and Miniussi (2009) for a review of TMS and spontaneous oscillations). Zarkowski et al. (2006) found a significant negative correlation between the power in alpha range and MEP measured from a resting abductor pollicis brevis (APB) muscle in a single-trial analysis. The coil position alterations were not controlled, however, and there was a relationship between MEP amplitude and time, so the correlations resulting from simultaneous coil movement and other factors changing over time, e.g., subject fatigue, cannot be ruled out. Likewise, the results of Sauseng et al. (2009) indicated a significant difference in alpha power preceding MEPs measured from the first dorsal interosseous (FDI) with sub- vs. supra-threshold amplitude (50 μV was chosen as threshold according to the motor threshold criterion). The alpha power was greater preceding smaller MEP amplitudes only at sites over the motor cortex, as compared with prefrontal and occipital sites. The effect was also restricted in terms of frequency, as Sauseng et al. failed to find any relationship between MEPs and other frequencies studied ranging from delta (0–4 Hz) to high gamma (46–70 Hz). The beta ranges studied were low-beta (12–20 Hz) and high-beta (20–30 Hz). Also in the study of Sauseng et al., the target muscle was at rest. Lepage et al. (2008) observed a negative, but non-significant, correlation between Rolandic alpha power and MEP amplitude in a resting FDI, as well as during observation, visualization, and execution of movement. Instead, in an exploratory analysis, they found significant (not corrected for multiple comparisons) negative correlations between MEPs and spontaneous Rolandic oscillations in the low-to-midrange-beta band (12–18 Hz) during the execution and rest conditions. Mitchell et al. (2007) used a precision grip task known to promote oscillations in the beta band, but no correlation between MEPs measured from FDI and EEG oscillations at any frequency was shown.

In addition, Chen et al. (1999) observed a reduction of TMS-evoked MEP amplitudes following median nerve stimulation, the time course of which was consistent with the rebound of Rolandic 20-Hz rhythm associated with the peripheral stimulation, which, however, was not measured during the experiment. Rossini et al. (1991) showed an increase of MEP amplitude evoked by right M1 stimulation and decrease of alpha-range activity measured over left M1 when subjects kept their eyes closed and performed mental arithmetic, as compared with eyes-closed and mental inactivity condition. In addition, Brignani et al. (2008) showed that 1-Hz rTMS to M1 (known to have an inhibitory effect) increased Rolandic alpha activity along with decreased MEP amplitudes. The results of Chen et al. (1999), Rossini et al. (1991), and Brignani

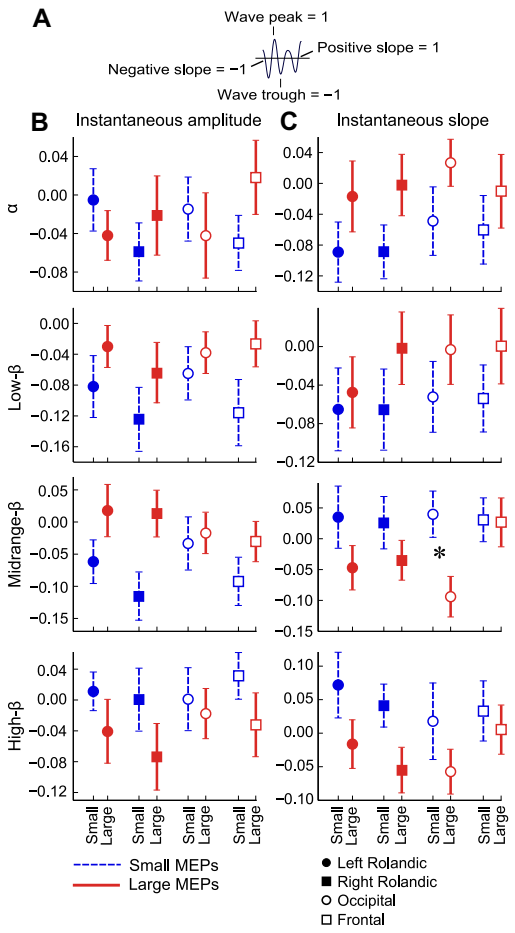

Fig. 4. (A) Naming of the phases of an oscillatory cycle. The complex phases have been projected separately to instantaneous amplitude and instantaneous phase axis and normalized to range [−1,1], −1 corresponding to wave trough/maximal negative slope and 1 to wave peak/maximal positive slope. (B) Spontaneous oscillation instantaneous amplitude values. (C) Spontaneous oscillation instantaneous slope values (mean ± SEM over subjects). The asterisk (∗) indicates a significant difference at the confidence level $p < 0.05$ between phases of trials with small and those with large MEPs.

Table 6
Spearman's correlation coefficients (mean ± SD over subjects) between MEP amplitudes and spontaneous oscillation phase (instantaneous amplitude (A) and instantaneous slope (B) values).

	Left Rolandic	Right Rolandic	Occipital	Frontal
A. Instantaneous amplitude				
α	−0.02 ± 0.11	+0.03 ± 0.16	−0.01 ± 0.13	+0.04 ± 0.14
Low-β	+0.03 ± 0.13	+0.04 ± 0.13	−0.00 ± 0.12	+0.05 ± 0.10
Midrange-β	+0.05 ± 0.12	+0.11 ± 0.08	+0.02 ± 0.11	+0.05 ± 0.09
High-β	−0.01 ± 0.12	−0.04 ± 0.09	+0.00 ± 0.09	−0.03 ± 0.14
B. Instantaneous slope				
α	+0.04 ± 0.16	+0.05 ± 0.13	+0.02 ± 0.11	+0.01 ± 0.16
Low-β	+0.01 ± 0.14	+0.05 ± 0.15	+0.01 ± 0.10	+0.04 ± 0.14
Midrange-β	−0.04 ± 0.14	−0.02 ± 0.12	−0.05 ± 0.09	−0.01 ± 0.13
High-β	−0.07 ± 0.15	−0.08 ± 0.10	−0.05 ± 0.15	−0.03 ± 0.12

et al. (2008) suggest that cortical excitability does have an effect on MEP amplitude and that spontaneous oscillations are related to MEPs, but they do not clarify to which extent the changes in cortical excitability account for the fluctuations in MEP amplitude and spontaneous oscillations within a condition and if these measures are correlated.

The significant correlations between MEP and alpha oscillation amplitudes (Zarkowski et al., 2006; Sauseng et al., 2009) might be explained by the fact that the excitability of the somatosensory cortex plausibly manifested as Rolandic alpha oscillations might be related to the state of the primary motor cortex via the connections between these two functionally related systems. Still, Rolandic oscillations in the beta band linked to the state of the motor cortex would serve as a more likely candidate for modulating motor cortical excitability. Our results showing a relationship between MEP and midrange-beta oscillation amplitudes and those of Lepage et al. (2008) showing an effect of low-to-midrange-beta oscillations on MEP amplitude are in line with this view. The different choice of frequency ranges might explain the different results of Sauseng et al. (2009).

In the studies of Zarkowski et al. (2006), Mitchell et al. (2007), and Lepage et al. (2008), the relationship was analyzed on single-trial basis. In contrast, Sauseng et al. (2009) divided the trials in two groups according to MEP amplitude and analyzed the differences in spontaneous oscillation amplitudes between the groups. In the present study, both approaches were used, with the difference that trials with 1/3 of the smallest and 1/3 of the largest MEPs were compared. Consistent significant correlations on the single-trial level within subjects were not found even for left Rolandic midrange-beta oscillations, which showed a significant effect on MEP amplitude in the analysis between MEP size groups. The results indicate that part of the fluctuations in MEP and Rolandic midrange-beta oscillation amplitudes reflect the excitability fluctuations in the same neuronal population, which becomes evident when averaging the oscillation amplitude values over several trials. However, the amplitudes of MEPs, spontaneous oscillations or both are strongly affected by other factors that, on the single-trial level, mask the effect of fluctuations in the neuronal population affecting both measures.

The EEG signal reflects neuronal activity in large cortical areas including neurons that control different muscles, while the cortical excitability component of MEP amplitude fluctuations is specific to the neurons controlling the target muscle. Yet, at rest, MEPs measured from pairs of muscles in the same or opposite upper limbs are correlated (Ellaway et al., 1998; Pearce et al., 2005). In contrast, during voluntary activation of the target muscle or even a remote upper limb muscle when the target muscles are at rest, the correlation between MEPs of opposite upper limbs is reduced, whereas that between within-limb MEPs is only slightly reduced during target muscle contraction (Pearce et al., 2005). Pearce et al. suggested that the correlation between within-limb muscles is explained by shared corticomotoneuronal projections, whereas rhythmic oscillations in cortical excitability could explain the between-limb results. They proposed that Rolandic beta rhythms, which are synchronous between hemispheres during rest (Nikouline et al., 2001) and attenuated during movement (Stancák and Pfurtscheller, 1995), could account for the interhemispheric correlations in cortical excitability.

In order to reduce the contribution from other sources than the neurons controlling the target muscle to the EEG signal, the results in the present study were recalculated using only data from the channel closest to the stimulation site and the corresponding channel on the contralateral hemisphere. The results remained virtually the same as with data from the four closest channels.

Based on the fact that both within- and between-limb MEPs and Rolandic beta oscillations between hemispheres are correlated at

rest, MEP and oscillation amplitudes measured above the motor cortex of both hemispheres would be expected to correlate also on the single-trial level if both spontaneous oscillations and MEPs mostly reflected motor cortical excitability. However, in addition to cortical excitability fluctuations, MEP amplitude is also affected by fluctuations in spinal excitability as well as variable synchrony; in case of desynchrony, there is phase cancellation of the descending action potentials. Magistris et al. (1998) showed that with precontraction and high-intensity TMS activating nearly all motor neurons innervating the target muscle (ADM), most of the variability is due to varying desynchronization. With such stimulation intensities above the threshold of all motor neurons involved, the changes in cortical and spinal excitability do not have an effect on the MEPs. In a study by Rösler et al. (2008) with lower stimulation intensities, about 1/3 of the ADM MEP amplitude variability was caused by varying desynchronization and 2/3 by variable number of activated motor neurons resulting from excitability fluctuations. They used stimulation intensities around 170% of MT with the target muscle at rest, and 100% of MT during 5% and 20% of maximum voluntary contraction of the target muscle. Stimulation at 170% of MT activated, on average, approximately half of the motor neurons. In the present study with even lower stimulation intensity (100% of MT), a smaller proportion of motor neurons is activated indicating that both fluctuations in excitability (cortical and spinal) and varying action potential synchrony contribute to the variability of MEPs. The lack of correlation between MEP and spontaneous oscillation amplitudes on single-trial level suggests that either varying action potential synchrony or spinal excitability fluctuations dominate, or spontaneous oscillation amplitude measured over the stimulated hand area reflects mostly excitability of neurons that do not control ADM, or both.

To locate the source of variability related to excitability, Rösler et al. (2008) also evoked MEPs using magnetic stimulation at the level of brainstem using a method described by Ugawa et al. (1994). The variability in MEPs evoked by TMS and in those evoked by brainstem stimulation, which is not assumed to be affected by cortical excitability, was approximately the same. Similarly, the difference in MEP variability between small hand muscles and foot muscles, which are strongly controlled by cortical and spinal input, respectively, was of the same order. Based on these observations, Rösler et al. concluded that the number of activated motor neurons mainly varied according to spinal segmental excitability changes. Nevertheless, because the brainstem stimulation caused contractions of neck muscles, head movements with respect to the stimulation coil could not be totally avoided. This might be a factor increasing the variability of MEPs evoked by brainstem stimulation. Also, the variability of foot muscle MEPs was slightly, but not statistically significantly, smaller than that of small hand muscle MEPs. As Rösler et al. note, the results do not rule out the possibility of cortical excitability changes affecting the MEPs. In addition, the results of Kiers et al. (1993) are in conflict with those of Rösler et al. (2008), as they found larger variability for MEP than for H-reflex, which is believed to reflect spinal motor neuron excitability.

Indeed, there are several facts supporting the view that fluctuations in cortical excitability have an effect on MEP amplitude: transcranial electrical stimulation (TES) preferably evokes D-waves resulting from direct activation of corticospinal neurons, whereas TMS at threshold intensities evokes more readily indirect activation (I-waves), by exciting corticospinal neurons transsynaptically (Nakamura et al., 1996; Edgley et al., 1997; Di Lazzaro et al., 1998). Probably because of this difference, TMS-evoked MEPs are more sensitive to conditioning stimuli that induce short-lasting modulation of cortical excitability (Ferbert et al., 1992; Kujirai et al., 1993), and in contrast to TMS, the variability of TES-evoked MEPs is small (Burke et al., 1995). Furthermore, the threshold for evoking I-waves is more labile than the D-wave threshold (Edgley et al., 1997). In addition to conditioning TMS pulses, several mental or physical actions affecting corticospinal excitability facilitate MEPs. These include muscle contraction (Hess et al., 1987), movement preparation (Hoshiyama et al., 1996), observation (Fadiga et al., 1995), imagery (Kasai et al., 1997), muscle stretch (Day et al., 1991), non-specific tasks like sticking out the tongue and counting aloud (Hufnagel et al., 1990), as well as recognition of self (Keenan et al., 2001). Although these maneuvers might also affect spinal excitability, which is undoubtedly the case with voluntary contraction (Berardelli et al., 1985), there is evidence that spinal excitability changes alone do not account for the MEP facilitation (Flament et al., 1993; Kasai et al., 1997; Di Lazzaro et al., 1998).

The motor threshold of the subjects was not found to depend on the amplitude of spontaneous oscillations. Romei et al. (2008b) showed that occipital alpha oscillation power correlates significantly with individual threshold for evoking phosphenes, and noted that the threshold depends also on other factors such as folding of cortical sulci and skull thickness. These factors affect also the MT in a subject-specific way, which may mask the possible relationship between spontaneous oscillations and MT.

Spontaneous oscillations reflect phasic changes in membrane potentials and thus excitability of neuronal populations. In the present study, MEP amplitudes were not found to depend on the phase of Rolandic oscillations. If the neurons controlling the target muscle are involved in the oscillations, as seems to be the case based on the present results concerning the relationship between MEP amplitude and left Rolandic midrange-beta amplitude, also the phase of these oscillations could be expected to affect MEP amplitude. Even if this was the case, the other factors contributing to spontaneous oscillations and MEP amplitude discussed in connection with oscillation amplitudes might mask the effect of phase. Also, the effect of oscillation amplitude might be larger than the effect of phase to the extent that the effect of phase is completely undetectable. In addition, during periods of low-amplitude oscillation, the difference in membrane potentials between different phases is not as large as during high-amplitude oscillation. Thus, studying the effect of phase only during the high-amplitude periods might give more insight into whether oscillation phase has an effect on MEP amplitude. Unfortunately, in this study, the number of trials was too small to conduct such an analysis.

In contrast to Rolandic oscillation phase, a significant difference in occipital midrange-beta phase was found between trials with small and those with large MEPs. When the stimulus coincided with a negative slope of the oscillation, MEP amplitude was likely to be larger than when the stimulus was delivered during a positive slope of the oscillation. Thus, it seems that the excitability of neurons in the motor cortex is modulated by the varying input from occipital areas even at rest, or that both areas receive input from a shared modulator resulting in correlated states. Occipital beta oscillations have been related to visual attention (Wróbel, 2000) and visuomotor processing; a decrease in oscillation amplitude in the lower beta ranges (up to 20 Hz) has been associated with increased preparatory attention (Gómez et al., 2006) and decreased response times (Zhang et al., 2008) in visuomotor tasks. In addition, coherence between visual and motor cortex in the lower beta frequency range (13–21 Hz) has been found to increase during visuomotor tasks (Classen et al., 1998). There is, however, a large body of evidence showing that visual attention is related to occipital alpha rather than beta oscillations (Worden et al., 2000; Sauseng et al., 2005; Kelly et al., 2006; Rihs et al., 2007, 2009; Siegel et al., 2008; Yamagishi et al., 2008) suggesting that the visual–attentional explanation of the coupling between MEP and occipital beta oscillations is not probable. Thus, a more likely explanation is that the processes responsible for the coupling between visual and motor areas during visuomotor processing might – even in the

resting state – have an effect on motor system excitability which is detectable when averaging over several trials, but not strong enough to be seen on the single-trial level. At the time of a stimulus the phase of occipital midrange-beta oscillation might only be related to the state of a small population of neurons in the motor cortex, which would explain why a relationship between MEP amplitude and the phase of Rolandic oscillations was not found. However, the fact that a significant difference in the dependency of MEPs on the midrange-beta instantaneous slope was not found between occipital and Rolandic sites might imply that MEPs are also very weakly related to Rolandic midrange-beta phase, which would not be surprising considering that the link between occipital and Rolandic areas could be seen as phase coupling.

A correlation between activity recorded from occipital and motor sites has been reported in some previous studies during visuomotor tasks, but not during resting state. For example, Kranczioch et al. (2008) showed an increased phase coupling between frontocentral and parieto-occipital areas at alpha and low-beta (<20 Hz) frequencies at the beginning of a movement execution phase. Kilner et al. (2004), in turn, found increased high-beta (20–30 Hz) coherence between occipital and motor electrodes during preparatory period, but decreased coherence compared to baseline during movement execution. In the study of Roelfsema et al. (1997), no direct link between motor and occipital areas was found, but high-beta (>20 Hz) activity was synchronized between occipital and parietal, as well as parietal and motor areas during cat visuomotor coordination task. In addition, errors in visuomotor tasks have been related to simultaneous increases in oscillatory activity at occipital and motor sites. Mazaheri et al. (2009) showed that increased alpha-range activity measured above both occipital and motor areas before a cue stimulus predicted a failure to inhibit motor responses. Huang et al. (2008) found increased power in alpha and beta ranges measured above occipital, somatomotor and supplementary motor areas during errors in a visuomotor tracking task.

Multiple studies have shown that MEPs and spontaneous oscillations reflect cortical excitability. The present results are in line with this view. Particularly, the present results show that Rolandic midrange-beta oscillations and MEP amplitudes reflect the excitability of the human motor system in overlapping but not identical neuronal populations; spontaneous oscillations as seen by EEG are a sum of activity of a large neuronal population, while MEP amplitudes reflect the excitability of the neurons controlling the target muscle, and are also affected by spinal excitability and variable synchrony of the descending action potentials. Neurons controlling the target muscle and probably other neurons modulating them contribute to the oscillations, but in addition to this overlapping neuronal population, both MEPs and spontaneous oscillations are affected by other factors. Thus, MEP and spontaneous EEG oscillation amplitudes are not strongly correlated. In addition, the results suggest that even during rest, motor system excitability is modulated by input from distant non-motor (in this case, occipital) brain areas, or that the excitability is related to activity at occipital areas via a shared modulator. Previous studies have shown that visuomotor tasks have been associated with changes in occipital beta oscillations and phase coupling or co-modulation between visual and motor areas in the beta range, suggesting that processes related to visuomotor processing might explain the relationship between occipital midrange-beta phase and motor cortical excitability as measured with MEPs.

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