Publication I

H. Mäki and R. J. Ilmoniemi. The relationship between peripheral and early cortical activation induced by transcranial magnetic stimulation. *Neuroscience Letters*, 478, 24–28, 2010.

Neuroscience Letters 478 (2010) 24–28

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

The relationship between peripheral and early cortical activation induced by transcranial magnetic stimulation

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ARTICLE INFO

Article history:
Received 17 February 2010
Received in revised form 21 April 2010
Accepted 25 April 2010

Keywords:
TMS–EEG
Cortical excitability
Motor evoked potential

ABSTRACT

The purpose of this study was to assess the relationship between peripheral muscle responses (motor evoked potentials, MEP) evoked by transcranial magnetic stimulation (TMS) and the early components of the TMS-evoked EEG response, both of which reflect cortical excitability. Left primary motor cortex of five healthy volunteers was stimulated with 100% of the motor threshold. The relationship between MEP amplitudes and the peak-to-peak amplitudes of the N15–P30 complex of the evoked EEG signal was determined at the single-trial level. MEP and N15–P30 amplitudes were significantly correlated in all five subjects. The results support the view that the amount of direct activation of neurons in M1 evoked by TMS affects both subsequent cortical activation and the activation of the target muscle. Cortical excitability is altered in some neuronal disorders and modulated locally during various tasks. It could thus be used as a marker of the state of health in many cases and as a method to study brain function. The present results improve our understanding of the early components of the TMS-evoked EEG signal, which reflect cortical excitability, and may thus have widespread use in clinical and scientific studies.

Cortical excitability reflects the state of neurons. It is altered in many neuronal disorders, such as Alzheimer's disease [1,7,9,30], multiple sclerosis [5], and Huntington's disease [34], and modulated during various tasks [4,11,13,16,17,28]. Thus, it informs us both about the state of health and about information processing during a task; the excitability of each neuron depends on its instantaneous membrane potential [20]. Transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) in combination with electromyographic (EMG) recording of the motor evoked potential (MEP) in the target muscle has been used to study corticospinal excitability [2]. Combining TMS with electroencephalography (EEG) has provided an effective tool for studying cortical excitability [14], allowing one to probe also areas other than M1 [6,12,22,26,31] and to use stimulation intensities below the threshold required to activate peripheral muscles [20,21].

In addition to the task-dependent or long-term fluctuations in cortical excitability, also the spontaneous moment-to-moment fluctuations are expected to affect the evoked responses. Indeed, MEPs elicited by identical consecutive stimuli vary largely in amplitude. Although part of the variability results from varying synchrony of the descending action potentials [24,32] and spinal excitability changes, also cortical excitability is believed to play a role [18,25,33,38]. It is a reasonable assumption that a stronger initial TMS-induced excitatory activation of the cortex leads to both stronger subsequent activation of the cortex and stronger activation of the target muscle. Thus, a correlation between MEP and evoked EEG signal can be expected even when stimulation strength is constant. Paus et al. [29] found a significant correlation between MEP amplitude and a negative deflection in the TMS-evoked EEG signal peaking around 100 ms after the pulse (N100), whereas in a study by Nikulin et al. [28], no relationship between MEP and N100 was found. However, the early deflections in the evoked EEG would serve as more direct measures for studying the excitability of the stimulated area. Particularly, as the conduction time between the brain and small hand muscles is about 20 ms, in case of M1 hand area stimulation the deflections peaking approximately 40 ms after the stimulus and later may be affected by the somatosensory feedback resulting from the target muscle activation. Bonato et al. [3] reported non-significant correlation coefficients $r = 0.13$ and 0.46 between the average amplitude of MEPs and the average amplitude of deflections peaking at 18 ms (N15; negativity over the stimulation site) and 28 ms (P30; widespread positivity), respectively, using the average values of five series of responses of all the six subjects averaged over trials and channels. To our knowledge, the correlation between MEPs and the early deflections of the TMS-evoked EEG response has not been studied at the single-trial level within subjects. Altogether, the early components of the TMS-evoked EEG response have not been studied extensively, partly because of the challenges in recording artefact-free signals imme-

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doi:10.1016/j.neulet.2010.04.059

diately after the TMS pulse. The electromagnetic artefact can be minimized with an EEG system using gain-control and sample-and-hold circuits [37] or slew-rate-limited amplifiers that do not become saturated during the pulse [15].

In the present study, we examine the early components of the TMS-evoked EEG response following M1 stimulation in five subjects. We show that the peak-to-peak amplitude of the N15–P30 complex measured over the stimulated area correlates significantly with MEP amplitude in all of these subjects at the single-trial level. The early components of the TMS-evoked EEG provide a way to assess cortical excitability even at non-motor sites.

We studied five healthy right-handed subjects (females: S1–S3, aged 24; males: S4–S5, 20 and 24), who gave their written informed consent before the experiment. The study was approved by the Ethics Committee of the Helsinki University Central Hospital and was in compliance with the Declaration of Helsinki. The subjects sat comfortably on a reclining chair and were instructed to keep their hands relaxed and eyes open.

The Nexstim eXimia TMS stimulator with its figure-of-8 focal monophasic coil (loop average diameter 59 mm) and MRI-guided navigated brain stimulation system eXimia NBS (Nexstim Ltd., Helsinki, Finland) were used to deliver and target the stimuli to the left primary motor cortex. The stimulation location and orientation (anterior–medial direction, about 45° from the midline) were further adjusted to produce maximal MEPs from the right abductor pollicis brevis (APB). A total of 60–100 TMS pulses were delivered at random 2–3-s intervals at 100% of the resting motor threshold (RMT; 5/10 responses >50 μV) of the APB. The NBS system tracking the positions of the coil and the head in real time was used to control that the coil position was maintained within 2 mm from the initially defined stimulation site. For subjects S1, S2, and S4, the deviation was less than 1 mm.

EEG was recorded with a 60-channel TMS-compatible Nexstim eXimia EEG device, which uses sample-and-hold circuits to block the electromagnetic stimulus artefact. In order to further increase the quality of the signal, the contacts between the scalp and the electrodes were carefully prepared; the impedances were kept below 5 kΩ. The signal was referenced to an electrode behind the right ear. The ground electrode was placed over the right cheek bone. EOG was recorded to monitor eye movements. The signals were bandpass filtered at 0.1–350 Hz, digitized at 1450 Hz and analyzed offline.

As the TMS pulse is accompanied with a loud click that produces an auditory response in the EEG [27,36], the subjects wore earphones damping external noise and listened to masking white noise, which was adjusted so that they did not perceive the coil click. Bone conduction of the sound was reduced with a thin piece of foam plastic between the coil and the head [26].

The MEPs were recorded from the right APB 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 and the signal was digitized at 20 kHz. The voltage resolution was 1 μV.

Offline analysis of the EEG and EMG data was performed using MATLAB (The Mathworks, Inc., Natick, Massachusetts, USA). The data were visually inspected; disconnected channels and channels with visible artefacts were discarded (no more than 4 per subject). Trials containing blinks, artefacts, or baseline EMG activity revealing preactivation of the muscle were omitted. For the rest of the trials (on average, 76) peak-to-peak MEP amplitudes were determined. The EEG data were zero-phase filtered using a second-order Butterworth bandpass (2–80 Hz) filter (roll-off 20 dB/dec), resulting in a time resolution of about 6 ms, and average-referenced. In order to determine the average latencies of the early deflections peaking around 15 and 30 ms after the stimulus (N15 and P30), the data were averaged over trials from −100 ms prestimulus to 500 ms poststimulus. The average latencies at each channel were determined manually from the averaged responses. The amplitudes of single filtered and average-referenced EEG trials at these latencies were determined automatically and the peak-to-peak amplitudes of the N15–P30 complex were calculated for each trial.

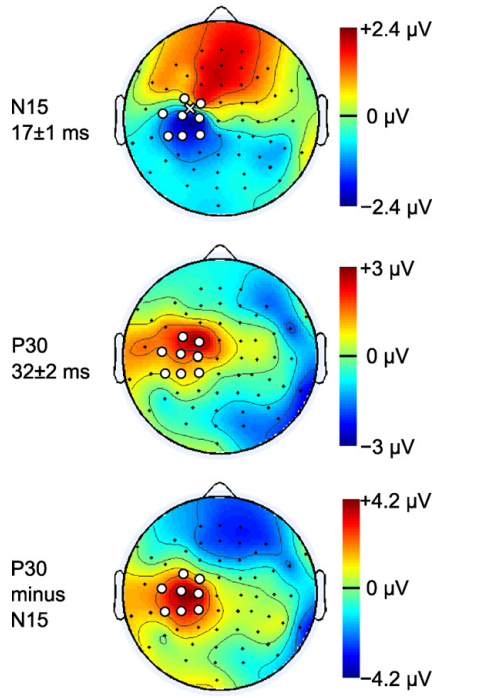

Fig. 1. Grand average potential distributions at the average latencies of N15 and P30 deflections and the difference between them (P30 minus N15). The electrodes from which the N15–P30 amplitude was determined are marked with white circles. The average stimulation site is marked with a white cross.

Eight channels (C1, C3, C5, CP1, CP3, CP5, FC1, FC3) were chosen for further analysis because of their location close to the stimulation site and on the basis of the potential distributions at the average latencies of N15 and P30 (see electrodes marked with white circles in Fig. 1). The potential distributions were visualized by the EEGLAB toolbox [8]. The N15–P30 amplitudes (P30 amplitude minus N15 amplitude) were averaged over these channels. The use of this differential measure decreases the possible effect of varying polarization of the electrode–electrolyte interface that may cause shifts in the baseline of the EEG signal. Visual inspection of the data revealed that the relationship between MEP and N15–P30 amplitudes is not linear. Thus a non-parametric measure of dependency, Spearman's rank correlation coefficient [35], was calculated between the single-trial values of the MEP and N15–P30 amplitudes. Instead of testing linear dependency, Spearman's rank correlation coefficient measures how well a monotonic function describes the dependency between two variables. To visualize the relationship between MEP and evoked EEG amplitudes, the EEG signals were separately averaged over trials corresponding to 1/3 of the smallest and 1/3 of the largest MEPs.

Even though EEG amplifier noise is low, unaveraged EEG traces are variable as, in addition to the evoked responses, they also reflect the ongoing activity of the brain. Thus, the observed correlation

between MEP and EEG responses is lower than the underlying correlation. However, the amount of these EEG background fluctuations and thus also the correlation coefficient in the absence of them can be estimated. We assumed that the variance of the N15–P30 amplitudes ($\sigma^2_{\mathrm{N15-P30}}$) consists of the following uncorrelated components: background fluctuations in the EEG signal (σ^2_{EEG}), variance that is explained by the correlation between MEP and EEG responses (σ^2_{corr}) and the remaining variance (σ^2_{rem}):

$$\sigma^2_{\mathrm{N15-P30}} = \sigma^2_{\mathrm{EEG}} + \sigma^2_{\mathrm{corr}} + \sigma^2_{\mathrm{rem}}. \quad (1)$$

σ^2_{EEG} was estimated from the baseline signals from −250 to −20 ms with respect to the stimuli separately for each subject. In order to estimate σ^2_{corr}, the variation in N15–P30 amplitudes that is explained by variation in MEPs needed to be estimated; this variation cannot be directly deduced from the rank correlations. N15–P30 amplitudes were normally distributed (Lilliefors test; $p > 0.32$) and MEP amplitude distribution had its maximum close to zero (see [25], Fig. 2 for typical MEP amplitude values at 100% RMT), so the smaller-amplitude MEPs were more numerous than larger-amplitude MEPs. This imbalance between MEP and N15–P30 amplitude distributions seems to be the reason for the nonlinearity between MEP and N15–P30 amplitudes. Nevertheless, MEP ranks and N15–P30 amplitudes seem to be linearly correlated (Pearson's correlation coefficients: S1: $r = 0.30$; S2: $r = 0.30$; S3: $r = 0.31$; S4: $r = 0.31$; S5: $r = 0.27$). As these correlation coefficients were similar to the Spearman's rank correlation coefficients between MEP and N15–P30 (S1: $r = 0.26$; S2: $r = 0.30$; S3: $r = 0.30$; S4: $r = 0.29$; S5: $r = 0.29$), the best-fitting linear function f_{corr} describing the dependency of N15–P30 amplitudes on MEP ranks was assumed to correspond to the underlying dependency between MEP and N15–P30 responses. σ^2_{corr} was estimated as the variance of the values of f_{corr} at each MEP rank. The correlation between MEP and N15–P30 responses that would be obtained in the absence of EEG background fluctuations was estimated using simulations. In each simulation, random normally distributed noise with variance σ^2_{rem} determined from Eq. (1) was added on f_{corr}. Spearman's correlation coefficient between MEP ranks and the simulated noisy f_{corr} values was determined from each simulation. The correlation in the absence of EEG background fluctuations was determined from the distribution of Spearman's correlation coefficients obtained in 1000 simulations.

To test if baseline EMG activity affected the evoked responses, Spearman's correlation coefficient was calculated between the root mean square EMG activity at −100...0 ms with respect to the stimulus and the MEP as well as the N15–P30 amplitudes. Also the correlations between MEP and prestimulus spontaneous oscillation amplitudes at alpha (8–12.5 Hz), low beta (12–15 Hz), midrange-beta (15–18 Hz), and high-beta (18–30 Hz) ranges were studied at the single-trial level following the analysis described in Ref. [25].

In line with previous studies [3,10,19,20,26,27,29], deflections identified as P5, N15, P30, N45, P60, and N100 peaking at 4 ± 1, 17 ± 2, 32 ± 2, 46 ± 2, 65 ± 3, and 103 ± 7 ms, respectively, were seen in the TMS-evoked EEG responses following left M1 stimulation. Inspection of the unfiltered data (not shown) revealed that the first component (P5) may partly reflect the electrode polarization artefact, and was thus not included in the analysis. Deflections peaking later than about 40 ms after the TMS pulse might be affected by the somatosensory potentials resulting from target muscle contraction. Thus, components N15 and P30 were chosen for further analysis. Grand average potential maps at the average latencies of the N15 and P30 deflections, as well as the potential difference map between P30 and N15, are presented in Fig. 1. The potential topographies of N15 and P30 were similar to those reported in previous studies [3,14,19,20,29]; the N15 pattern was dipolar with negativity posterior and positivity anterior to the stimulation site and the P30 potential map had positivity over the stimulation site. The difference between N15 and P30 was thus largest in the electrodes over the stimulation site and slightly posterior to it.

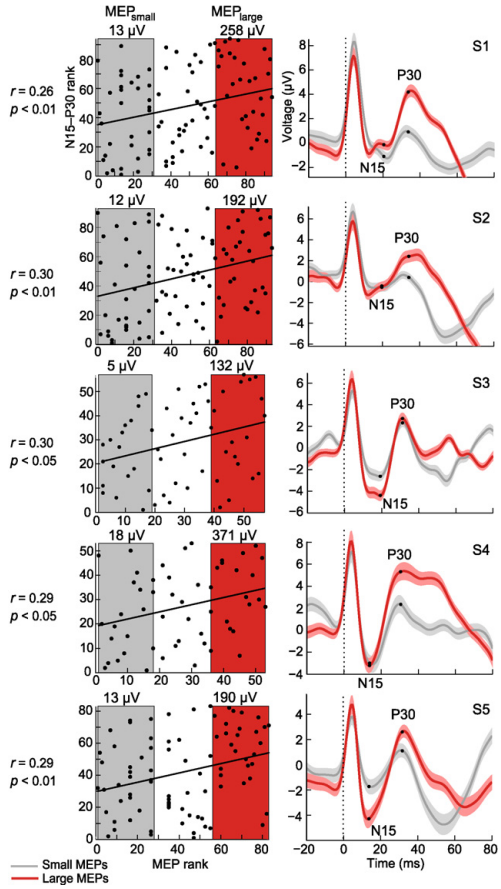

Fig. 2. Rank correlation between the MEP and the N15–P30 amplitudes (left) and the EEG responses (±SEM) averaged over trials with 1/3 of the smallest and 1/3 of the largest MEPs (right) of all subjects (S1–S5). The average latencies of the N15 and P30 deflections are marked with dots (right). $\mathrm{MEP_{small}}$ and $\mathrm{MEP_{large}}$ (on top of the rank plots) refer to the average amplitude of the 1/3 of the smallest and 1/3 of the largest MEPs. The differences between some of the small amplitudes fall within the voltage resolution of the EMG device. Thus, some of the small MEPs share the same rank. The dotted line indicates stimulus time ($t = 0$).

In all subjects, there was a significant correlation (Spearman's rank correlation coefficients: $r = 0.26$ to 0.30, $p < 0.05$) between the amplitudes of MEP and the peak-to-peak amplitudes of the N15–P30 complex averaged over the chosen channels. The rank correlation plots and EEG responses averaged over trials with 1/3 of smallest and those with 1/3 of largest MEPs are shown in Fig. 2.

The estimated underlying correlation coefficients between MEP and N15–P30 responses that would be obtained in the absence of EEG background fluctuations varied largely. For subject S3, σ^2_{EEG} was larger than $\sigma^2_{\mathrm{N15-P30}}$ so we were unable to estimate the underlying correlation. For the other subjects, the correlation coefficients and 95% confidence intervals were: S1: $r_{\mathrm{max}} = 0.92$ (0.90–0.95); S2: $r_{\mathrm{max}} = 0.62$ (0.48–0.73), S4: $r_{\mathrm{max}} = 0.88$ (0.82–0.93), S5: $r_{\mathrm{max}} = 0.41$ (0.23–0.59).

There was no significant correlation between baseline EMG activity and MEP amplitudes ($r = -0.26$ to 0.17, $p > 0.05$) or baseline EMG and N15–P30 amplitudes ($r = -0.17$ to 0.11, $p > 0.2$). Furthermore, no significant correlations were found between spontaneous oscillations and MEP amplitudes at any of the frequency ranges ($r = -0.13$ to 0.12, $p > 0.2$).

In each subject, the peak-to-peak amplitude of the N15–P30 complex of the TMS-evoked EEG response following left M1 stimulation correlated significantly with the MEP amplitude recorded from the right APB. This correlation can be expected: the initial activation of neurons by TMS varies depending on the state of the cortex at the time of the stimulus. This leads to trial-to-trial fluctuations in subsequent cortical activation and MEP amplitude. To our knowledge, the present study is the first one indicating a relationship between TMS-induced peripheral and cortical activation measured early after the TMS pulse when the somatosensory feedback from the target muscle has not had time to reach the cortex.

The large intersubject differences in the estimated underlying correlation coefficients suggest that factors other than the excitability of the neuronal population controlling APB have a varying effect on the MEP and EEG responses depending on the subject or experimental conditions. These factors may include spinal excitability changes, varying synchrony of action potentials, and EMG signal noise. If the small stimulation coil movements in these experiments have a notable effect on the electric field observed by the target neurons, the coil movements can have one of the two effects on the correlation coefficients: the coil might move away from the optimal stimulation site reducing both MEP and EEG responses, thus increasing the observed correlation. Alternatively, MEP amplitudes would change along with coil movements while EEG responses would not if the coil moved towards the representation area of another muscle; this would result in weaker correlation. While both scenarios are possible, they are not probable, however, as coil movements were small (1–2 mm) compared to the stimulated area (about 1 cm^2). Since trials with clearly increased prestimulus EMG activity were omitted and no relationship was found between prestimulus EMG and evoked responses, varying preactivation of the muscle and related spinal excitability changes are not likely to explain the variability of the responses.

Spontaneous oscillations also reflect cortical excitability. However, no single-trial correlations between MEP amplitudes and prestimulus oscillations were found at any frequency range. An identical result has been discussed thoroughly in Ref. [25].

The N15 component is generated in the ipsilateral premotor cortex [10,23]. The origin of P30 is less clear, but it has been suggested to reflect activity around ipsilateral sensorimotor/premotor cortex border [10], in the superior wall of the ipsilateral cingulate gyrus or supplementary motor area [23], and in the contralateral cortex [19]. Even though plausibly not reflecting activation in the location directly activated by the stimulus, these components may still inform us about the degree of excitation in M1. With the stimulation coil oriented non-optimally for stimulating M1 (induced current to posterior-medial direction, 45° from the midline), N15 and P30 components were absent, whereas some later components were still present, suggesting that N15 and P30 reflect activation of cortical areas following TMS-induced M1 activation [3]. The amplitudes of these components are also increased after 5-Hz rTMS to M1 inducing long-term potentiation [10].

The present results demonstrate a correlation between MEP and the early components of the EEG response evoked by TMS at the single-trial level. As unaveraged EEG traces are very noisy, they cannot be directly used to study the moment-to-moment fluctuations in cortical excitability. Nevertheless, in contrast to MEPs, which reflect corticospinal excitability and are restricted to studying M1, the early components of the evoked EEG signal reflect the excitability of the stimulated cortical area and the secondary areas activated as a result of the stimulation. The results encourage investigation of the early components of the TMS-evoked EEG signal also when stimulating non-motor sites and using intensities below the motor threshold. This opens up new possibilities to study cortical function and might prove useful in the diagnosis of neurological diseases.

Acknowledgements

This study was supported by the Academy of Finland (grant no. 121167) and International Graduate School in Biomedical Engineering and Medical Physics.

References

[1] G. Alagona, R. Bella, R. Ferri, A. Carnemolla, A. Pappalardo, E. Costanzo, G. Pennisi, Transcranial magnetic stimulation in Alzheimer disease: motor cortex excitability and cognitive severity, Neurosci. Lett. 314 (2001) 57–60.
[2] A.T. Barker, R. Jalinous, I.L. Freeston, Non-invasive magnetic stimulation of the human motor cortex, Lancet 1 (1985) 1106–1107.
[3] C. Bonato, C. Miniussi, P.M. Rossini, Transcranial magnetic stimulation and cortical evoked potentials: A TMS/EEG co-registration study, Clin. Neurophysiol. 117 (2006) 1699–1707.
[4] M. Bonnard, L. Spieser, H.B. Meziane, J.B. de Graaf, J. Pailhous, Prior intention can locally tune inhibitory processes in the primary motor cortex: direct evidence form combined TMS–EEG, Eur. J. Neurosci. 30 (2009) 913–923.
[5] A. Conte, D. Lenzi, V. Frasca, F. Gilio, E. Giacomelli, M. Gabriele, C.M. Bettolo, E. Iacovelli, P. Pantano, C. Pozzilli, M. Inghilleri, Intracortical excitability in patients with relapsing–remitting and secondary progressive multiple sclerosis, J. Neurol. 256 (2009) 933–938.
[6] Z.J. Daskalakis, F. Farzan, M.S. Barr, J.J. Maller, R. Chen, P.B. Fitzgerald, Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS–EEG study, Neuropsychopharmacology 33 (2008) 2860–2869.
[7] M. de Carvalho, A. de Mendonça, P.C. Miranda, C. Garcia, M. de Lourdes Sales Luís, Magnetic stimulation in Alzheimer's disease, J. Neurol. 244 (1997) 304–307.
[8] A. Delorme, S. Makeig, EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis, J. Neurosci. Methods 134 (2004) 9–21.
[9] V. Di Lazzaro, A. Oliviero, F. Pilato, E. Saturno, M. Dileone, C. Marra, A. Daniele, S. Ghirlanda, G. Gainotti, P.A. Tonali, Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease, J. Neurol. Neurosurg. Psychiatry 75 (2004) 555–559.
[10] S.K. Esser, R. Huber, M. Massimini, M.J. Peterson, F. Ferrarelli, G. Tononi, A direct demonstration of cortical LTP in humans: A combined TMS/EEG study, Brain Res. Bull. 69 (2006) 86–94.
[11] L. Fadiga, L. Fogassi, G. Pavesi, G. Rizzolatti, Motor facilitation during action observation: a magnetic stimulation study, J. Neurophysiol. 73 (1995) 2608–2611.
[12] P.B. Fitzgerald, J.J. Maller, K. Hoy, F. Farzan, Z.J. Daskalakis, GABA and cortical inhibition in motor and non-motor regions using combined TMS-EEG: a time analysis, Clin. Neurophysiol. 120 (2009) 1706–1710.
[13] M. Hoshiyama, S. Koyama, Y. Kitamura, M. Shimojo, S. Watanabe, R. Kakigi, Effects of judgement process on motor evoked potentials in Go/No-go hand movement task, Neurosci. Res. 24 (1996) 427–430.
[14] R.J. Ilmoniemi, J. Virtanen, J. Ruohonen, J. Karhu, H.J. Aronen, R. Näätänen, T. Katila, Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity, NeuroReport 8 (1997) 3537–3540.
[15] J.R. Ives, A. Rotenberg, R. Poma, G. Thut, A. Pascual-Leone, Electroencephalographic recording during transcranial magnetic stimulation in humans and animals, Clin. Neurophysiol. 117 (2006) 1870–1875.
[16] T. Kasai, S. Kawai, M. Kawanishi, S. Yahagi, Evidence for facilitation of motor evoked potentials (MEPs) induced by motor imagery, Brain Res. 744 (1997) 147–150.
[17] J.P. Keenan, A. Nelson, M. O'Connor, A. Pascual-Leone, Self-recognition and the right hemisphere, Nature 409 (2001) 305.
[18] L. Kiers, D. Cros, K.H. Chiappa, J. Fang, Variability of motor potentials evoked by transcranial magnetic stimulation, Electroenceph. Clin. Neurophysiol. 89 (1993) 415–423.
[19] S. Komssi, H.J. Aronen, J. Huttunen, M. Kesäniemi, L. Soinne, V.V. Nikouline, M. Ollikainen, R.O. Roine, J. Karhu, S. Savolainen, R.J. Ilmoniemi, Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation, Clin. Neurophysiol. 113 (2002) 175–184.
[20] S. Komssi, S. Kähkönen, R.J. Ilmoniemi, The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation, Hum. Brain Mapp. 21 (2004) 154–164.
[21] S. Komssi, P. Savolainen, J. Heiskala, S. Kähkönen, Excitation threshold of the motor cortex estimated with transcranial magnetic stimulation electroencephalography, NeuroReport 18 (2007) 13–16.
[22] S. Kähkönen, J. Wilenius, S. Komssi, R.J. Ilmoniemi, Distinct differences in cortical reactivity of motor and prefrontal cortices to magnetic stimulation, Clin. Neurophysiol. 115 (2004) 583–588.

[23] V. Litvak, S. Komssi, M. Scherg, K. Hoechstetter, J. Classen, M. Zaaroor, H. Pratt, S. Kähkönen, Artifact correction and source analysis of early electroencephalographic responses evoked by transcranial magnetic stimulation over primary motor cortex, NeuroImage 37 (2007) 56–70.
[24] M.R. Magistris, K.M. Rösler, A. Truffert, J.P. Myers, Transcranial stimulation excites virtually all motor neurons supplying the target muscle, Brain 121 (1998) 437–450.
[25] H. Mäki, R.J. Ilmoniemi, EEG oscillations and magnetically evoked motor potentials reflect motor system excitability in overlapping neuronal populations, Clin. Neurophysiol. 121 (2010) 492–501.
[26] M. Massimini, F. Ferrarelli, R. Huber, S.K. Esser, H. Singh, G. Tononi, Breakdown of cortical effective connectivity during sleep, Science 309 (2005) 2228–2232.
[27] V. Nikouline, J. Ruohonen, R.J. Ilmoniemi, The role of the coil click in TMS assessed with simultaneous EEG, Clin. Neurophysiol. 110 (1999) 1325–1328.
[28] V.V. Nikulin, D. Kicic, S. Kähkönen, R.J. Ilmoniemi, Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement, Eur. J. Neurosci. 18 (2003) 1206–1212.
[29] T. Paus, P.K. Sipilä, A.P. Strafella, Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study, J. Neurophysiol. 86 (2001) 1983–1990.
[30] G. Pennisi, G. Alagona, R. Ferri, S. Greco, D. Santonocito, A. Pappalardo, R. Bella, Motor cortex excitability in Alzheimer disease: one year follow-up study, Neurosci. Lett. 329 (2002) 293–296.
[31] M. Rosanova, A. Casali, V. Bellina, F. Resta, M. Mariotti, M. Massimini, Natural frequencies of human corticothalamic circuits, J. Neurosci. 29 (2009) 7679–7685.
[32] K.M. Rösler, D.M. Roth, M.R. Magistris, Trial-to-trial size variability of motor-evoked potentials. A study using the triple stimulation technique, Exp. Brain Res. 187 (2008) 51–59.
[33] P. Sauseng, W. Klimesch, C. Gerloff, F.C. Hummel, Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex, Neuropsychologia 47 (2009) 284–288.
[34] S. Schippling, S.A. Schneider, K.P. Bhatia, A. Münchau, J.C. Rothwell, S.J. Tabrizi, M. Orth, Abnormal motor cortex excitability in preclinical and very early Huntington's disease, Biol. Psychiatry 65 (2009) 959–965.
[35] C. Spearman, The proof and measurement of association between two things, Am. J. Psychol. 15 (1904) 72–101.
[36] H. Tiitinen, J. Virtanen, R.J. Ilmoniemi, J. Kamppuri, M. Ollikainen, J. Ruohonen, R. Näätänen, Separation of contamination caused by coil clicks from responses elicited by transcranial magnetic stimulation, Clin. Neurophysiol. 110 (1999) 982–985.
[37] J. Virtanen, J. Ruohonen, R. Näätänen, R.J. Ilmoniemi, Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation, Med. Biol. Eng. Comput. 37 (1999) 322–326.
[38] P. Zarkowski, C.J. Shin, T. Dang, J. Russo, D. Avery, EEG and the variance of motor evoked potential amplitude, Clin. EEG Neurosci. 37 (2006) 247–251.