Neuroscience Letters 647 (2017) 141–146

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

Age related differences in functional synchronization of EEG activity as evaluated by means of TMS-EEG coregistrations

Florinda Ferreri[a,b,*,1], Fabrizio Vecchio[c,1], Andrea Guerra[a], Francesca Miraglia[c], David Ponzo[a], Luca Vollero[d], Giulio Iannello[d], Sara Maatta[b], Esa Mervaala[b], Paolo Maria Rossini[c,e], Vincenzo Di Lazzaro[a]

[a] Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, Università Campus Bio-Medico di Roma, via Álvaro del Portillo 21, 00128 Rome, Italy
[b] Department of Clinical Neurophysiology, Kuopio University Hospital, University of Eastern Finland, Kuopio, Finland
[c] Brain Connectivity Laboratory, IRCCS San Raffaele Pisana, Rome, Italy
[d] Department of Computer Science and Computer Engineering, University Campus Bio-Medico, Rome, Italy
[e] Institute of Neurology, Catholic University, Rome, Italy

HIGHLIGHTS

- M1-prefrontal coupling in the beta-2 band led to larger MEPs both in the young and the elderly.
- M1-parietoccipital coupling in the delta band effectively led to significantly larger MEPs in the young but not in the elderly.
- In elderly delta coherence is high both for high and for low MEPs. M1 excitability is led by the coupling of specific EEG rhythms depending on age.

ARTICLE INFO

Article history:
Received 28 October 2016
Received in revised form 23 February 2017
Accepted 13 March 2017
Available online 18 March 2017

Keywords:
EEG
Navigated transcranial magnetic stimulation
TMS-EEG co-registration
EEG coherence
Cortical connectivity
Cortical excitability
Aging

ABSTRACT

It was recently demonstrated that the characteristics of EEG rhythms preceding a transcranial magnetic stimulation (TMS) of the motor cortex (M1) influence the motor-evoked potential (MEP) amplitude with a peculiar pattern, thus reflecting the M1 functional state. As physiological aging is related to a decrease in motor performance and changes in excitability and connectivity strength within cerebral sensorimotor circuits, we aimed to explore whether aging affects EEG-MEP interactions. Using MRI-navigated TMS and multichannel EEG, we compared the EEG-MEP interactions observed in healthy aged subjects with those observed in young volunteers. We divided the MEPs amplitude into two different subgroups consisting of "high" and "low" MEPs, based on the 50th percentile of their amplitude distribution. Then we analysed the characteristics of the pre-stimulus EEG from M1 and correlated areas separately for the "high" and "low" MEPs, comparing the two conditions. In both young and old subjects, significantly larger MEPs were evoked when the stimulated M1 was coupled in the beta-2 band with the homolateral prefrontal cortex. Conversely, only in young participants was the MEP size modulated when the M1 and homolateral parieto-occipital cortices were coupled in the delta band. The elderly didn't show this kind of pattern. Importantly, this coupling was significantly higher in elderly brains than in young brains, both for high and low MEPs. Our results suggest an age-related significant influence of time-varying coupling of spatially patterned EEG rhythms on motor cortex excitability in response to TMS.

1. Introduction

The transcranial application of magnetic stimuli (TMS) on the primary motor cortex (M1) not merely activates the corticospinal tract but also determines activations in adjacent and distant brain regions that are a part of the motor networks [5,20,73]. Brain functions are, in fact, subtended by time-varying interactions of networks that are spatially distributed and able to connect and

* Corresponding author at: Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, Università Campus Bio-Medico di Roma, via Álvaro del Portillo 21, 00128 Rome, Italy.
E-mail address: f.ferreri@unicampus.it (F. Ferreri).
[1] Equally-contributing authors

http://dx.doi.org/10.1016/j.neulet.2017.03.021
0304-3940/

disconnect over time via cortico-cortical "fragile" connections [32,43,72,74,82]. In this frame, the temporary synchronization of neuronal firing has been suggested to be an efficient means of functionally linking distinct and broadly distributed neuronal clusters. In theory, the primary motor cortex (M1) output to stereotyped and sequential stimuli may be utilized as a probe of fluctuations in the connectivity strength within the network subtending M1 excitability and its distributed connections [18,23,27,41,78]. The amplitude of motor-evoked potentials (MEPs) produced by stereotyped and sequential transcranial magnetic stimuli (TMS) changes across time, while the spinal reflexes elicited in the same muscles do not vary in amplitude [68]. This variability is thus considered as induced, at least partially, by the transient changes in M1 excitability and connectivity strength [1,6,7]. Natural oscillations in cortical layers have unveiled rhythmic fluctuations of membrane potential that subtend changes in neuronal assemblies excitability [44]. Neurons of the corticospinal tract account for an essential portion of the cerebral oscillatory system, and their firing is in part phase-locked to such oscillations, thus denoting a recurring modulation in the excitability of these cells [55]. Several kinds of synaptic plasticity can be significantly influenced by the level of the excitability in a network that has been suggested as a probe of network connectivity strength [18,23,41,78]. Then the temporary synchronization of post synaptic potentials, primarily contributing to the electroencephalogram signals, has been proposed to be an efficient mechanism for governing the transient time-varying binding/unbinding phenomena that coordinate the connection of distinct but functionally related neuronal clusters [22,54,64,75]. It could then be speculated that, if fluctuations of the spontaneous EEG oscillation and MEPs amplitude reveal the level of cortical excitability, then their modulations in time may be related to each other. Within this theoretical model, we have effectively verified in recent experiments [28,32,84] that the MEPs amplitude is related to the functional coupling of the EEG rhythms, instantaneously foregoing distinct TMS stimuli in particular brain regions, whereas the EEG power spectrum for such rhythms plays only a minimal role in controlling M1 excitability. In healthy young subjects we demonstrated the existence of a definite pattern in which TMS elicits larger MEPs if the EEG of the stimulated M1 is coupled in the delta rhythm with the parietal and occipital cortices and in the beta 2 rhythm with the homolateral prefrontal cortex [28]. Thus, the purpose of the present experiment was to extend our previous results regarding the role of pre-TMS motor networks' EEG rhythms on MEPs amplitude, observing the behaviour of the paradigmatic pattern identified in normal aging. Physiological aging is related to a decline in motor performance and reduced, as well as improved, connectivity strength in the sensorimotor networks [4,47,65,71,81,89]. Long-range connectivity, in particular, has been found to be decrease, whereas short-range connectivity increases, suggesting strongly age-related modulations of the overall brain functional connectivity architecture [81]. Whether and how these functional modifications dynamically affect the motor output is unknown [19,58] and could be highlighted by this kind of neurophysiological approach.

2. Material and methods

2.1. Subjects

Eleven healthy aged volunteers (mean age 67.7, ranging between 57 and 81 years) participated to the protocol and were compared to 8 healthy young volunteers (mean age 24.6, ranging between 18 and 30 years) from the previous study [28]. All but two of the aged volunteers were retired from work. All had a good level of general health and well being and could completely independently perform the instrumental activities of daily living. All subjects were right handed (handedness score $\geq$+ 70), as evaluated by the Handedness Questionnaire.

We followed the exclusion criteria established by the international methodological/safety standards for TMS [66]. An ethics committee approved the protocol, and written informed consent was obtained from all subjects before the experiment.

2.2. Transcranial magnetic stimulation

During a multi-channel EEG recording, the experimental subjects underwent a fifteen-minute session of 100 supra-threshold (120%) single pulse TMS of the dominant primary motor cortex (left), while seated with their eyes open in a relaxed position with their hands prone and their elbows flexed. The stimulation was made in accordance with the international guidelines [66], using MAGSTIM 200 equipment with a monophasic pulse configuration (Magstim Company Limited, Whitland, South West Wales) and a 70 mm butterfly-shaped coil. The coil's cathode was located over the "hot spot" of the hand area of the left-side M1. Habituation due to stimulations repeated was reduced by using a 4–6 s intertrials interval [46,69,90]. White noise was used to mask the coil-generated clicks [51]. MEPs were bilaterally recorded from the first dorsal interosseus muscle (FDI), and their amplitude was measured semi-automatically between the two higher peaks opposite in polarity.

2.3. EEG recordings

EEG recordings were performed by means of a device that permits continuous data recording (BrainAmp 32MRplus, BrainProducts GmbH, Munich, Germany) and does not necessitate pinning the preamplifier output to a constant level during the TMS discharge [24].

The EEG activity was acquired from 19 TMS-compatible Ag/AgCl-coated electrodes placed in accordance with 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; filtered at 0.1–500 Hz with a sampling rate of 2.5 kHz). The ground was placed in Oz to take the greatest distance from the coil. The linked mastoid was the reference for all electrodes. Skin/electrode impedance was always below 5kOhm. Electro-oculograms (EOG) were recorded in order to detect horizontal and vertical eye movements [26].

2.4. Data analysis

The EEG recordings were analysed and off-line fragmented into 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 trials contaminated by environmental noise, muscle activity, or eye movements were rejected – along with their corresponding MEPs-. Similarly, trials contaminated by involuntary FDI muscle activation were also eliminated. For the evaluation of the MEP, each trial was baseline-corrected (100 ms pre-stimulus) and average-referenced.

For each subject within the two groups, at the end of the MEPs acquisition session, the trials were divided into two sub-groups of *high* and *low* MEP amplitudes, based on the 50th percentile of the distribution: the mean value of the trials was about 40 in both the *high* and *low* MEP amplitude conditions.

The frequency domain analyses were performed using the EEG data reported as a common reference ("common average") obtained by subtracting sample-by-sample the corresponding average value of all electrode sites. This procedure removes the effects of electrode reference in EEG data. The power spectrum and the spectral coherence was computed at the following bands of interest: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha