The Effect of Co-activation of Antagonist Muscles on Motor Cortex Excitability: A Transcranial Magnetic Stimulation Study

Kapka Mancheva[1], Diana I. Stephanova[1], Werner Wolf[2], Andon Kossev[1*]

[1]*Institute of Biophysics and Biomedical Engineering*
Bulgarian Academy of Sciences, Sofia, Bulgaria
E-mails: kapka_mancheva@abv.bg, dsteph@bio.bas.bg, kossev@bio.bas.bg

[2]*Institut für Infomationstechnik*
Universität der Bundeswehr München, Neubiberg, Germany
E-mail: Werner.Wolf@UniBw.de

[*]*Corresponding author*

Received: September 19, 2017 **Accepted: May 11, 2018**

Published: June 30, 2018

Abstract: *The effect of unilateral tonic muscle activity with and without co-activation of the antagonists on motor cortex excitability has been studied in seven right handed healthy volunteers. Contralateral motor evoked potentials (MEPs) were recorded from the first dorsal interosseous muscles of right hands in response to transcranial magnetic stimulation (TMS) during relax, isometric index finger abduction and antagonistic co-activation. The intracortical facilitation (ICF), short- and long-latency intracortical inhibition (SICI and LICI) were investigated by paired-pulse TMS.*

The unilateral tonic activation of the right hand facilitated MEPs in response to single-pulse TMS. The increase of MEP amplitudes was significantly greater during isometric index finger abduction compared to co-activation of antagonist muscles. During paired-pulse TMS with short interstimulus intervals, the SICI (interstimulus interval of 3 ms) was not influenced by the unilateral tonic activity while ICF (interstimulus interval of 13 ms) was suppressed. During paired-pulse TMS with longer interstimulus interval (100 ms) the LICI was not influenced during isometric index finger abduction while during antagonistic co-activation the LICI was significantly less pronounced.

The decreased LICI is assumed to reflect mechanisms underlying the co-activation of antagonists.

Keywords: *Transcranial magnetic stimulation, Motor evoked potential, Intracortical facilitation, Short-latency intracortical inhibition, Long-latency intracortical inhibition, Co-activation.*

Introduction

The main result of muscle activity is the generation of torque and a movement of some joint segments or the whole body in the surrounding space. Another important function of muscle activity is to keep body position by adaptation of mechanical impedance of joints to external perturbations by co-activation of antagonist muscles [5, 19]. The co-activation increases joint stiffness and provides mechanical stability in holding posture [11] and during limb movement [1, 19]. The co-activation of antagonist muscles occurs in anticipation of predictable movements and in motor learning [17, 18]. Also, increased co-activation of antagonist muscles is counted among the requirements for higher accuracy of multi-joint movements [4]. The co-activation can vary over a wide range of values while maintaining zero net torque at a joint [12, 21, 22]. Several studies provide evidences that maximal muscle activity during

co-activation with zero net torque at the ankle is lower than the maximal muscle activity during reciprocal activation of muscles [13]. The physiological mechanism responsible for a limited muscle activity during co-activation may involve a postsynaptic inhibition at spinal level or may originate from central voluntary commands. The "common drive" of some motor units of agonist and antagonist muscles during voluntary co-activation is consistent with the idea of centrally originated co-activity [3, 6, 15].

In our previous study using transcranial magnetic stimulation (TMS) we have failed to find the effect of co-activation on motor cortex excitability as well as on short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF) concerning contralateral responses [2]. In that study we have used circular stimulation coil and very low level of muscle activity – in range from 5% to 10% of maximal voluntary activity. The aims of the present study were: (i) to repeat the investigation, now using focal stimulating coil and higher level of co-activity and to find out if there is any possible effect of co-activation on SICI and ICF, and (ii) to extend the investigation concerning long-latency intracortical inhibition (LICI).

Materials and methods

Seven healthy right-handed volunteers (Edinburgh Handedness Inventory [16]), aged 24-67, gave their informed consent and participated in the study approved by the local ethics committee. The subjects were seated with right arm gently fixed in slight abduction from the trunk (20°) and flexion in the elbow (110°). The right hand and forearm were pronated and fixed on horizontal supports. The index finger was placed on manipulandum, and was securely clamped by two pads; the axis of the manipulandum was positioned to align the axis of rotation of index finger. The torques in abduction – adduction as well as in direction of index finger flexion during isometric contractions were measured using appropriately placed transducers.

Motor evoked potentials (MEPs) were recorded from the first dorsal interosseous muscle (FDI) using two conventional surface Ag/AgCl disc electrodes (8 mm diameter) and differential techniques. One electrode was fixed on the muscle belly and the second on distal tendon at the index finger base. Electromyographic signals (EMG) were amplified (band pass 10 Hz - 1 kHz) and digitized (sampling rate 2 kHz). Epochs of 1 s duration (starting 0.5 s prior to the test stimulus) were stored on a disk. The EMG activity as well as the force signals were continuously monitored to control the level of tonic activity.

Two MagStim 200 stimulators connected to the eight-shaped stimulating coil (mean diameter 7 cm) through a BiStim module were used [20]. The BiStim module was used to combine the single pulses from the two stimulators to a paired-pulse configuration delivered through the coil, with a possibility to control the interstimulus interval (ISI) between both pulses in steps of 1 ms. All of the used TMS intensities are percentage of maximum stimulator output. The coil was adjusted over the left hemisphere to evoke optimal responses from the right FDI. Motor threshold (MT) was determined at relax condition as the lowest stimulus intensity which elicited three MEPs of at least 0.05 mV peak to peak amplitude in five consecutive TMS with interval between trials 5-10 s. When a focal TMS is used (eight-shaped stimulating coil) the test stimulus intensity usually is 130% of MT which is somewhat higher compared to non-focal stimulation (circular coil) where the stimulation area is larger [14].

Five single pulse stimuli with an intensity of 130% of the MT were applied to obtain control MEPs in the relaxed muscle. Then, ten paired-pulse stimuli (five with ISI of 3 ms and five with ISI of 13 ms) were applied with 5-10 s interval between trials. The different ISIs were

applied in random order. The intensity of the conditioning and test stimuli were 80% and 130% of the MT, respectively. The same stimulation procedure was repeated during tonic isometric index finger abduction and co-activation of antagonist muscles without external force production (controlled by visual force feedback). During antagonistic co-activation the mean value of rectified EMG was the same as the corresponding value during isometric abduction (20% of maximal voluntary contraction). In the second part of the experiment, after five single pulse stimuli with an intensity of 130% of the MT, five paired-pulse stimuli with ISI of 100 ms were applied. The intensity of both conditioning and test stimuli were 130% of the MT.

Data analysis was performed off-line; only trials showing similar levels of tonic EMG (mean rectified EMG) activity during the 400 ms prestimulus period in both co-activation and isometric abduction were considered. The measured parameter was peak to peak amplitude of MEPs. For single-pulse stimulation data were normalized to the individual mean values recorded at relax and then pooled for all subjects. For paired-pulse TMS with short ISIs (3 and 13 ms) the conditioned MEP amplitudes were normalized to the corresponding unconditioned responses (single-pulse TMS). For paired-pulse TMS with long ISI (100 ms) the MEP amplitudes of the test stimulus (responses to the second pulse) were normalized to the corresponding MEP amplitudes in response to the first pulse. Values are given by means ± standard error. The differences between control and test values were assessed using a Wilcoxon matched-pair signed-rank test. Probability values (p) less than 0.05 were considered significant and indicated by asterisks in the diagrams. The effect of tonic muscle activity (relax, co-activity and abduction) was assessed by ANOVA and in case of significance its locus was identified by Wilcoxon matched-pair signed-rank test.

Results

At rest (i.e. relaxed muscle), the MT of the left hemisphere ranged from 45% to 58% of the maximum output of the stimulator for the different subjects (mean ± SD: 52.2 ± 3.8%).

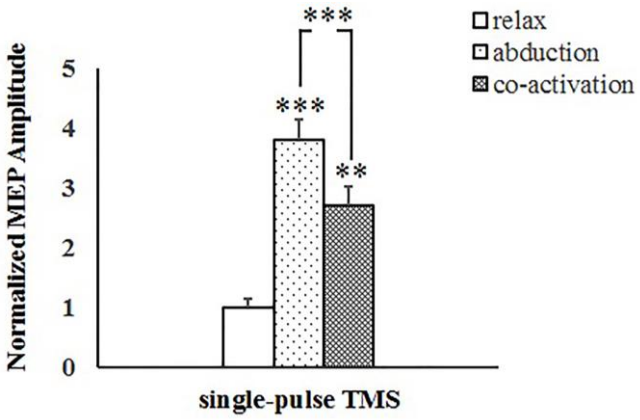

Fig. 1 Mean values of MEP amplitudes (± standard error) in response to single-pulse TMS normalized to the corresponding mean values at rest (i.e. relaxed muscle). The asterisks indicate the level of statistical significance (** $p < 0.01$ and *** $p < 0.001$).

At relax conditions and single-pulse TMS the mean MEP amplitude for the investigated subjects was 2.53 ± 1.27 mV ($n = 7$). During tonic muscle activity the amplitudes of MEPs were significantly increased (Fig. 1). The effect of unilateral muscle activity (relax, co-activity, abduction) on MEP amplitude was significant (ANOVA, $p < 0.01$).

The augmentation of MEPs during abduction of the index finger was significantly stronger compared to co-activation of the antagonist muscles ($p < 0.001$).

Paired-pulse TMS during relax conditions well revealed both the SICI and ICF. The amplitude of responses was significantly decreased ($p < 0.01$) at ISI of 3 ms and significantly increased ($p < 0.05$) at ISI of 13 ms (Fig. 2, open columns). There was no effect of tonic muscle activation (co-contraction or abduction) on SICI (Fig. 2, middle columns). In contrast, ICF was not pronounced during tonic muscle activity (Fig. 2, right columns).

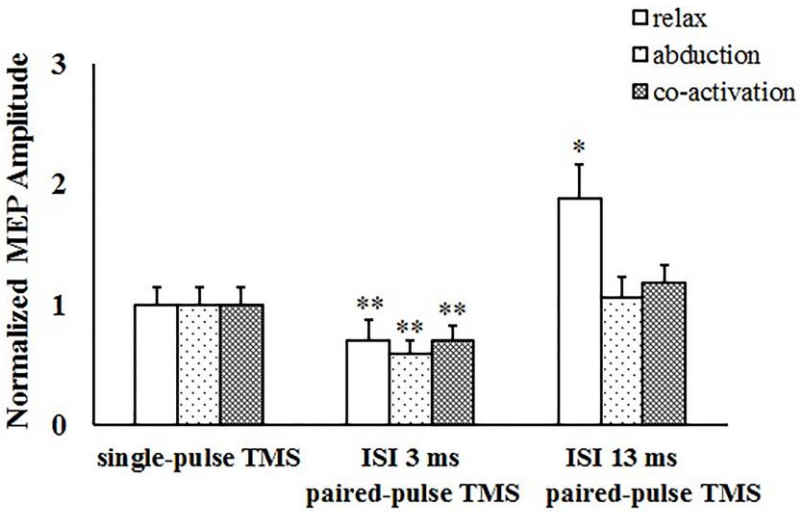

Fig. 2 Mean values of MEP amplitudes (± standard error) in response to paired-pulse TMS with ISI of 3 and 13 ms. The MEP amplitudes in response to the first pulse were normalized to the corresponding unconditioned responses (single-pulse TMS). The asterisks indicate the level of statistical significance (* $p < 0.05$ and ** $p < 0.01$).

Paired-pulse TMS with ISI of 100 ms well revealed LICI at relax conditions as well as during tonic muscle activity (Fig. 3). The suppression of MEP amplitude was significant during relax conditions ($p < 0.01$) as well as during abduction of the index finger and muscle co-activation ($p < 0.001$ and $p < 0.05$, respectively). During co-activation of antagonist muscles the LICI was significantly less pronounced compared to index finger abduction ($p < 0.01$).

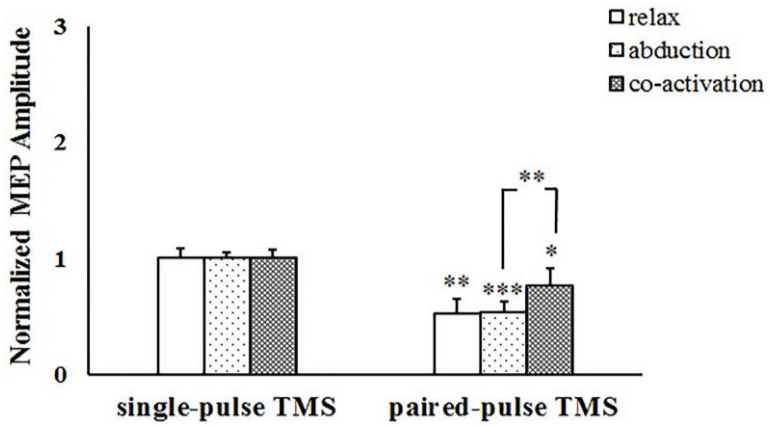

Fig. 3 Mean values of MEP amplitudes (± standard error) in response to paired-pulse TMS with ISI of 100 ms. The MEP amplitudes in response to the second pulse were normalized to the corresponding MEP amplitudes in response to the first pulse. The asterisks indicate the level of statistical significance (* $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$).

Discussion

The paired-pulse TMS is a powerful method to study intracortical neural mechanisms during different motor tasks. It is important to mention, that in the literature all investigations concerning the effect of muscle activity on motor cortex excitability and corresponding intracortical mechanisms have been conducted at reciprocal muscle activation. Up to our knowledge, only our group has studied the different effect of co-activation of antagonist muscles in comparison to reciprocal muscle activation.

The augmentation of MEPs during abduction of the index finger was significantly stronger compared to co-activation of the antagonist muscles. This finding is in line with our previous study [9] and supports the idea for central control of muscle activity during co-activation.

The results of the present study concerning SICI are similar to our previous findings [2] – there is no effect of co-activation on intracortical inhibition. In contrast to SICI we found that the LICI is significantly suppressed during co-activation of antagonist muscles. Cortical inhibition of pyramidal neurons is mediated by gama-amino butyric acid (GABA) receptors [8]. Brain studies in animals and humans have revealed two main phases of inhibition following stimulation: a "fast" phase mediated by ionotropic $GABA_A$ receptors and a "slow" phase mediated by metabotropic $GABA_B$ receptors [10]. Thus SICI and LICI are thought to reflect $GABA_A$- and $GABA_B$-mediated cortical inhibition. The main finding of the present study is that during co-activation of antagonists, $GABA_B$-mediated cortical inhibition is significantly reduced.

Concerning ICF in the present study we found a complete suppression of intracortical facilitation during muscle activity – co-activity or abduction. The level of suppression of ICF is similar to our previous findings [2], although that ICF was completely suppressed only at co-activation of antagonists. We have studied the simultaneous action of ICI and ICF at different intensity of the conditioning pulse [7]. We have shown that ICI threshold is lower compared to ICF threshold and that at 13 ms ISI the MEP in response to the test pulse may reflect the impact effect of both intracortical mechanisms – ICI and ICF. The interaction between both mechanisms is somewhat different for the different subjects. This fact may explain the small differences between our previous and present results concerning ICF.

Conclusion

The main finding of our study is that during co-activation of antagonist muscles, the LICI as well as the motor cortex excitability are significantly reduced compared to those obtained in conditions of isometric index finger abduction.

Acknowledgement

The study was supported by the Grant № DFNP-125/12.05.2016 within the frames of "Program for career development of young scientists in Bulgarian Academy of Sciences".

References

1. Burdet E., R. Osu, D. Franklin, T. Milner, M. Kawato (2001). The Central Nervous System Stabilizes Unstable Dynamics by Learning Optimal Impedance, Nature, 414, 446-449.
2. Christova M. I., N. G. Pondev, L. G. Christova, W. Wolf, R. Dengler, A. R. Kossev (2006). Motor Cortex Excitability during Unilateral Muscle Activity, J Electromyogr Kinesiol, 16, 477-484.

3. Frysinger R. C., D. Bourbonnais, J. J. Kalaska, A. M. Smith (1984). Cerebellar Cortical Activity during Antagonist Cocontraction and Reciprocal Inhibition of Fore-arm Muscles, J Neurophysiol, 51, 32-49.
4. Gribble P. L., L. I. Mullin, N. Cothros, A. Mattar (2003). Role of Co-contraction in Arm Movement Accuracy, J Neurophysiol, 89, 2396-2405.
5. Hogan N. (1985). The Mechanics of Multi-joint Posture and Movement Control, Biol Cybern, 52, 315-331.
6. Humphrey D. R., D. J. Reed (1981). Separate Cortical Systems for Control of Joint Movement and Joint Stiffness: Reciprocal Activation and Coactivation of Antagonist Muscles. In: Desmedt J. (Ed.), Motor Control Mechanisms in Health and Disease, New York, Raven Press, 347-372.
7. Kossev A. R., S. Siggelkow, R. Dengler, J. D. Rollnik (2003). Intracortical Inhibition and Facilitation in Paired-pulse Transcranial Magnetic Stimulation: Effect of Conditioning Stimulus Intensity on Sizes and Latencies of Motor Evoked Potentials, J Clin Neurophysiol, 20, 54-58.
8. Krnjevic K. (1997). Role of GABA in Cerebral Cortex, Can J Physiol Pharmacol, 75, 439-451.
9. Mancheva K., D. I. Stephanova, W. Wolf, A. Kossev (2016). The Effect of Co-activation of Antagonist Muscles on Recruitment Curve during Transcranial Magnetic Stimulation, Proceedings of the 12th National Medical Physics and Biomedical Engineering Conference NMPEC-2016 with International Participation, Sofia, Bulgaria, 172-182.
10. McCormick D. A. (1989). GABA as an Inhibitory Neurotransmitter in Human Cerebral Cortex, J Neurophysiol, 62(5), 1018-1027.
11. McIntyre J., F. A. Mussa-Ivaldy, E. Bizzi (1996). The Control of Stable Posture in the Multijoint Arm, Exp Brain Res, 110, 248-264.
12. Milner T. E., C. Cloutier (1998). Damping of the Wrist Joint during Voluntary Movements, Exp Brain Res, 122, 309-317.
13. Milner T. E., C. Cloutier, A. B. Leger, D. W. Franklin (1995). Inability to Activate Muscles Maximally during Cocontraction and the Effect on Joint Stiffness, Exp Brain Res, 107, 293-305.
14. Nakamura H., H. Kitagawa, Y. Kawaguchi, H. Tsuji (1997). Intracortical Facilitation and Inhibition after Transcranial Magnetic Stimulation in Conscious Humans, J Physiol, 498(3), 817-823.
15. Nielsen J., Y. Kagamihara (1994). Synchronization of Human Leg Motor Units during Co-contraction in Man, Exp Brain Res, 102, 84-94.
16. Oldfield R. C. (1971). The Assessment and Analysis of Handedness: The Edinburgh Inventory, Neuropsychologia, 9, 97-113.
17. Osu R., D. W. Franklin, H. Kato, H. Gomi, K. Domen, T. Yoshioka, M. Kawato (2002). Short- and Long-term Changes in Joint Co-contraction Associated with Motor Learning as Revealed from Surface EMG, J Neurophysiol, 88, 991-1004.
18. Osu R., E. Burdet, D. W. Franklin, T. E. Milner, M. Kawato (2003). Different Mechanisms Involved in Adaptation to Stable and Unstable Dynamics, J Neurophysiol, 90, 3255-3269.
19. Osu R., N. Kamimura, H. Iwasaki, E. Nakano, C. M. Harris, Y. Wada, M. Kawato (2004). Optimal Impedance from Control for Task Achievement in the Presence of Signal-dependent Noise, J Neurophysiol, 92, 1199-1215.
20. The Magstim Company Ltd, https://www.magstim.com (Last accessed March 31, 2018).
21. Yamazaki Y., H. Itoh, T. Ohkuwa (1995). Muscle Activation in the Elbow-forearm Complex during Rapid Elbow Extension, Brain Res Bull, 38, 285-295.

22. Yamazaki Y., T. Ohkuwa, H. Itoh, M. Suzuki (1994). Reciprocal Activation and Coactivation in Antagonistic Muscles during Rapid Goal-directed Movements, Brain Res Bull, 34, 587-593.

Kapka Mancheva, Ph.D.
E-mail: kapka_mancheva@abv.bg

Kapka Mancheva graduated from Sofia University "St. Kliment Ohridski" and obtained her M.Sc. degree in Parasitology in 2009. From 2010 she is a full-time Ph.D. student at Institute of Biophysics and Biomedical Engineering – Bulgarian Academy of Sciences (IBPhBME-BAS). She received her Ph.D. in Physiology of Animals and Humans in 2015 and presently she is a Chief Assistant Professor at Motor Control Department of the IBPhBME-BAS. Her fields of interests are human motor cortex physiology, movement control, transcranial magnetic stimulation studies.

Prof. Diana Ivanova Stephanova, D.Sc.
E-mail: dsteph@bio.bas.bg

Diana Stephanova graduated in Atomic Physics at the Sofia University "St. Kliment Ohridski" in 1973. She received Ph.D. (1983) and D.Sc. (2004) degrees in the Institute of Biophysics – BAS. Diana Stephanova is recognized around the world as a top authority in the fields of computational neuroscience. Her recent pioneering research is in the area of mathematical modeling of demyelinating neuropathies and neuronopathies. She has published a book, several book chapters and more than 50 papers in leading scientific journals in the field such as Clinical Neurophysiology, Electromyography and Clinical Neurophysiology, Biological Cybernetics, European Biophysics Journal, Journal of Integrating Neurosciences.

Prof. Werner Wolf, Ph.D.
E-mail: Werner.Wolf@UniBw.de

Werner Wolf received his M.S.E.E. in 1970 and his Ph.D. in 1978, both from the Technical University Munich, Germany. In 1978, he moved to the Institute of Mathematics and Computer Science heading the Biosignal Processing Lab. His main interests are processing of biosignals (e.g. evoked potentials in the electroencephalogram, the electromyogram, etc.) and includes basic research in sensorimotor systems (eye movements, hand and arm movements, etc.). He is author of more than 100 scientific publications, and a member of the IEEE Society of Engineering in Medicine and Biology, the IEEE Society of Signal Processing, the American Society of Neuroscience, and several national scientific societies.

Prof. Andon Kossev, D.Sc.
E-mail: kossev@bio.bas.bg

Andon R. Kossev received the Ph.D. degree (1978) in Neurophysiology from the Institute of Physiology – BAS, and the D.Sc. degree (1993) in Neuroscience from the Institute of Biophysics – BAS. Following a one-year postdoctoral training (1980-1981) at the Technical University of Munich (Clinic of Neurology) he joined the Department of Excitable Structures of the Institute of Biophysics Biophysics – BAS. In 1986-1987 he was a Visiting Professor at the University of Arizona, Tucson (Health Sciences Center), and in 1990-1991 an Alexander von Humboldt Research Fellow at the University of Bonn, Germany (Clinic of Neurology). He is currently a Professor of Biophysics and Physiology, as well as a Director of the Institute of Biophysics and Biomedical Engineering – BAS.