Invited review article

Insights into motor learning from a viewpoint of transcranial magnetic stimulation

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Abstract

Several protocols of non-invasive transcranial magnetic stimulation have been developed in the past decades. Single-and paired-pulse transcranial magnetic stimulation are painless, and non-invasive tools to evaluate cortical and corticospinal excitability in cerebral cortex compared with transcranial electric stimulation. Motor evoked potential induced by paired-pulse transcranial magnetic stimulation can particularly assess changes of the cortical excitability after motor learning, such as motor skill and motor practice in sports and functional recovery in rehabilitation. However, the effect of electric current in transcranial magnetic stimulation on pyramidal neuron and interneuron in gray and white matters is not actually understood well yet in the field of sports and rehabilitation sciences. Here, we show the important basic knowledge of neurophysiology and transcranial magnetic stimulation and introduce some studies of cortical plasticity and motor learning by using transcranial magnetic stimulation.

Introduction

In recent years, human brain science has gathered cumulative findings in non-invasive transcranial brain stimulation (NIBS). These findings have benefited several areas, such as physical education, sports, and rehabilitation, dedicated to the use of motor learning to enhance motor skills, motor control, and functional recovery. The NIBS methods are typically transcranial magnetic stimulation (TMS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and transcranial electrical stimulation (TES) in brain function research.

TMS is particularly useful to evaluate changes in cortical and corticospinal excitability in the cerebral cortex for basic studies of dynamic and static movement, muscle contraction, motor skill, and motor practice. This article focuses on the neurophysiological mechanisms of cortical and corticospinal excitability, evoked by single-and paired-pulse TMS.

Here we introduce TMS characteristics, the basic terminology related to TMS technology, the mechanisms of intracortical excitability and paired-pulse TMS, motor learning and cortical plasticity and reduced short-interval intracortical inhibition (SICI) induced by paired-pulse TMS, and three case studies of motor learning and SICI.

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TMS characteristics

Baker et al. [1] presented the first basic and clinical studies using TMS. Since then, the use of this technique has spread to the fields of neurophysiology, neurology, neurosurgery, and rehabilitation medicine, mostly because it is a painless, non-invasive method, which can be used in conscious humans, allowing brain stimulation through the scalp. Recently, TMS has also been applied to the fields of motor learning and motor skills, physical education, and sports science.

In a relaxed condition, motor evoked potential (MEP) occurs to stimulate the motor cortex by TMS. According to Faraday's law of electromagnetic induction, currents can only be induced by a changing or time-varying magnetic field. In a primary circuit, the coil current generates a magnetic field, through which the stimulator drives current pulses that stimulate the body, which in turn generates the electric current of the secondary circuit in the brain (Eddy's current) and records MEP in some muscles (Figure 1A). The current produced by TMS flows parallel to the superficial layer of the gray matter and trans-synaptical to interneurons. Some authors have provided detailed description of the relation between the current strength in the coil and in the stimulated brain sites. Hess et al. [2] indicated that the magnetic field falls off rapidly with increasing distance from the coil; with a typical 12-cm diameter round coil, the strength falls by half at 4–5 cm from the coil surface. Rothwell [3] explained that because the cerebral cortex can be 1–2 cm from the scalp surface and because the central sulcus itself can be 2-cm deep in humans, the stimulation is severely attenuated at deep sites, such as the basal ganglia or the thalamus. In an extensive study of the relationship between the electric direction of TMS and stimulation of pyramidal neurons and interneurons in gray matter, Laakso et al. [4] illustrated that the component directions are approximated based on the anatomy of the white and gray matters, as

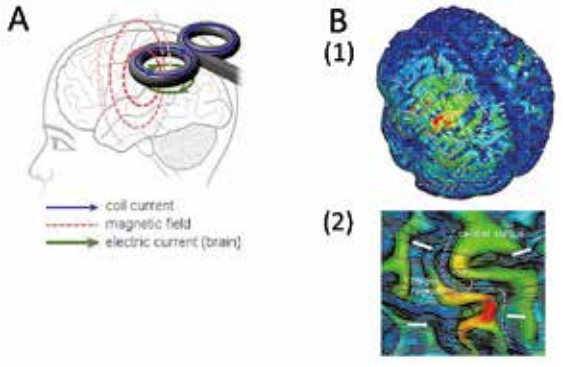

Figure 1.

A: Schemas of coil current of primary circuit (blue solid line), magnetic field (red dash line), and the electric current (green solid line) of secondary circuit in brain through TMS stimulator.

B: Illustration of whole (1) and expanded (2) flowlines of the current and the absolute value (red color in high value) of the electric field on the white matter and grey matter boundary in the vicinity of the target region by TMS [4].

shown in Figure 1B. The horizontal component of the electric field is defined as being perpendicular to the vertical directions. The cortex is the most sensitive to fields oriented perpendicular to the cortical layers, whereas it is relatively insensitive to fields parallel to them (Figure 2). Apparently, inducing TMS through gray area's anatomical area 4 is favorable to excite pyramidal neurons (Betz cell) and interneurons, although the high intensity of TMS may also excite some neurons in the white matter. Following TMS, the occurrence of MEP, as recorded by electromyography (EMG), corresponds to the sum of the excitation states of many pyramidal cells and synapses. For example, when recording the amplitude of MEP in distal muscles (finger, hand or leg, foot muscles), the recorded MEP reflects the total excitation status of the corresponding sites of pyramidal cells and synapses.

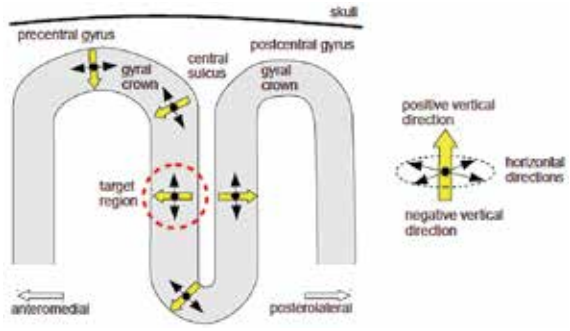

Figure 2. Definition of the 'vertical' and 'horizontal' component directions of the electric field. Note that the horizontal directions also included the directions towards and away from the reader [4].

Basic terminology related to TMS technology

When performing and reporting TMS studies, being familiar with the relevant terminology is crucial. This section describes the most important terms.

The target of TMS refers to the neural network connected to the large corticomotor neurons that are monosynaptically linked to spinal motoneurons. *Threshold* may reflect an anatomical feature, such as the number of corticomotor neurons, the density of the network targeting the corticomotor neurons, or a physiological feature such as the excitability level of the corticospinal system. *Motor Threshold* refers to the measure of cortical excitability in the motor cortex as well as the lowest intensity of the TMS stimulator. The motor threshold may present two conditions: resting or active. The *resting motor threshold (RMT)* is defined as the minimum stimulation intensity over the motor hotspot, required to evoke a MEP ≥50 μV in five of 10 trials performed in a relaxed sitting condition [5]. The *active motor threshold (AMT)* is defined as the lowest intensity required to evoke a MEP of 200 μV in more than five of 10 consecutive trials, while the subjects maintain approximately 5% maximum voluntary contraction (MVC) of the target muscle in the same conditions as RMT [6].

It is important to understand the definition of *D(direct)-wave* and *I(indirect)-wave* of the pyramidal tract. Patton and Amassian [7] indicated that TES applied at threshold to the skull recruited a single descending volley in the pyramidal tract, identified as a D-wave. At higher intensities of stimulation, this volley was followed by others, with a periodicity of approximately 1.5 ms. These volleys were termed I-waves (Figure 3). It suggested that the initial volley was produced by direct stimulation of the pyramidal tract axons (D-wave), whereas the later volleys were produced by synaptic activation of the same pyramidal tract neurons, as I-waves. The I-wave comprised I_1-, I_2-, and I_3-waves, with a periodicity of 1.5–2.0 ms; it is likely that the mechanism underlying the I_3-or later waves was different from that of I_1-wave [8-10] and that it was related to SICI by paired-pulse TMS [6] and TMS and drugs [11]. As will be

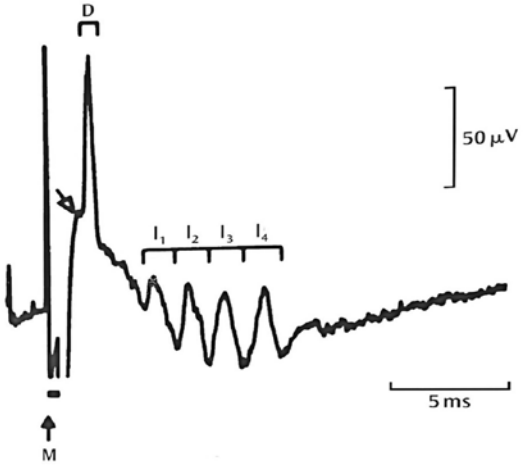

Figure 3. Single-sweep recording of volleys was excited by figure of eight coil TMS in squirrel monkey. Recording made from the surface of dorsolateral funiculus at C8-Th1 segment. After D-wave, the later volleys, I-wave made up I_1, I_2, and I_3-waves etc. periodicity by 1.5-2.0ms, D; direct wave, I; indirect wave, M; TMS stimulation time [8].

discussed below, later I-wave components have a deep relationship with motor leaning and synaptic plasticity.

Intracortical excitability and paired-pulse TMS

The paired-pulse TMS was first developed by the Kujirai and Rothwell group [6]. The method involves the use of two TMS apparatuses and a figure of eight shaped coil that generates stimulus pulses through the TMS apparatuses. Stimulus intensities in paired-pulse TMS were set with a supra-threshold evoked at 1–1.5 mV of MEP amplitude for the test stimulus (TS) and a sub-threshold of either 70%–90% RMT or 80%–90% AMT for the conditioning stimulus (CS). Inter-stimulus intervals (ISIs) were set to 1–15 ms. For example, for an ISIs of 2, 3, 7, and 10 ms, each block of 10 trials consisted of five different conditions: TS alone and TS + CSs at four different ISIs. Test and conditioning stimuli at different intervals were randomly intermixed and presented at intervals of 4–5 ms. Kujirai et al. [6] and Ziemann et al. [12] indicated that very short intervals in the range of 1–5 ms resulted in the inhibition of CS MEP (/MEP_{TEST}) and that CS MEP turned from inhibition to facilitation at longer ISIs (10–20 ms). These terms represented the percent ratio to control MEP size (MEP_{TEST}) (Figure 4). Intracortical excitability induced by paired-pulse TMS resulted in SICI and facilitation (ICF) in the motor cortex. There were three reasons evidencing that the effect of the sub-threshold CS on the size of control MEP originated at the motor cortical level and that there was no significant contribution of subcortical or spinal mechanisms [6] : 1) the effect of CS on the excitability of the spinal motoneuron pool, probed by H-reflex testing, showed no change in H-reflex size for inhibitory and facilitatory ISIs, 2) if control MEP was elicited by a small electrical TS in an active hand muscle, the inhibition disappeared. That is, the failure to inhibit an MEP elicited by TES pointed toward an intracortical mechanism with

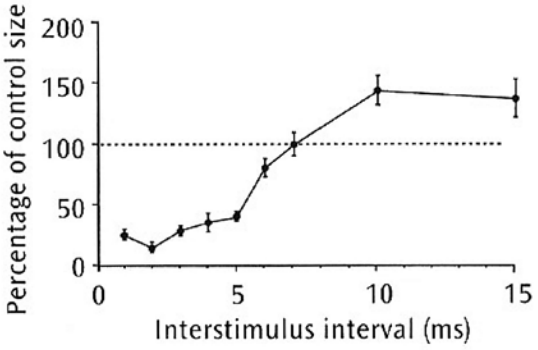

Figure 4. At each interstimulus interval (ISI), the size of the conditioned responses is expressed as a percentage of the control response (MEP_{TEST}). The CS had an inhibitory effect at ISIs of 1-5 ms and a facilitatory effect at ISI of 10–15 ms [6].

paired-pulse TMS, and 3) in the previous experiment of producing corticospinal volleys with cervical epidural electrodes, CS intensity below AMT produced no recognizable descending volley in the spinal cord, whereas a supra-threshold TS evoked indirect (I) waves. At ISIs of 1–4 ms, CS induced a significant inhibition of MEP and all I-waves, except the I_1-wave. Taken together, these findings indicated that the inhibition took place in the motor cortex, upstream of the corticospinal neurons. The selective effect of CS on later I-waves, but not the I_1-wave, was confirmed independently [13,14]. Ilic et al. [15] clarified that paired TMS has greatly advanced our understanding of the underlying mechanisms of excitability in the human motor cortex. They tested the effects of CS and TS intensities on the interaction between CS and TS at short ISIs of 2–5 ms, using surface EMG, single motor unit recordings, and an oral dose of the $GABA_A$ receptor agonist diazepam (DZP). SICI was mediated through a threshold $GABA_A$ receptor-dependent inhibitory pathway, and the sum of the CS's inhibitory postsynaptic potentials (IPSP) and

the TS's excitatory postsynaptic potentials (EPSPs) at the corticospinal neurons.

These findings suggested that neurophysiological mechanisms of SICI and ICF induced by paired-pulse TMS involved intracortical (cortico-cortical) excitability within the motor cortex, without spinal motoneurons. SICI indicated that the excitability of inhibitory interneurons evoked by 80%–90% AMT at a low intensity of CS and ISIs of 2–5 ms stimulates the neurotransmitter of cortical $GABA_A$ receptors.

Motor learning and cortical plasticity in reduced SICI

In this section, we present a summary of motor learning acquisition through practice and report three case studies that involve motor learning: 1) typing practice and cortical plasticity, 2) neuroplasticity and grip touch in a racket player, 3) observing the actions of an expert baseball player and mirror neurons through TMS.

1) Typing practice and cortical plasticity. Motor programs are refined continuously by motor learning. There are changes in cortical motor output of programs as motor behavior progresses from being novel to being automatic. Proficiency in motor behavior may require modulation of the cortical motor output to accommodate the new skill. Acquiring new skills is therefore associated with learning-induced cortical plasticity. The synaptic strength of cortical horizontal connections was improved by long-term potentiation (LTP) and long-term depression (LTD). Strong evidence gathered from rodent models showed that motor learning reduced subsequent LTP, but increased LTD, in the primary motor cortex [16,17]. Bounomano and Merzenich [18] reviewed the mechanisms of synaptic plasticity in excitatory pathways, clarifying that LTP and LTD of EPSPs underlined the balance between excitatory and inhibitory inputs. This plasticity might be observed in EPSPs from an excitatory cell onto an inhibitory cell and / or in IPSPs between an inhibitory cell and an excitatory cell. In studies with macaque models, the activity-dependent modifications of the visual cortex were accompanied by a significant reduction of cortical $GABA_A$ receptors and GABA, indicating that sensory experiences can produce activity-dependent long-term modifications in inhibitory transmission [19]. Motor learning and cortical excitability in the human brain have been studied using techniques of functional magnetic resonance imaging (fMRI), positron emission topography (PET), and TMS. Studies of fMRI and PET were suitable to detect changes of cortical excitability before, during, and after motor skill learning, and presented the enhancements of brain activity / network under different conditions, such as the complex motor task of finger movement, short- and long-term experience, dominant and non-dominant hand movements for asymmetry, motor learning-related changes in piano players, and changes in the sensorimotor area during bimanual skill acquisition [20-25].

There are previous studies of human motor skill learning and the related cortical plasticity. SICI by paired-pulse TMS is a functional and suitable measure of excitability of the motor cortex GABAergic interneurons, which are involved in processes of LTP and LTD of cortical synapses. We examined how SICI was affected by periods of short-term practice (SP), long-term practice (LP), and no practice (NP) using a keyboard finger task [26]. The participants had little previous experience of typing on a keyboard; hence, they were at the beginner level of the skill. SICI was measured in the dominant FDI and ADM of 10 non-typists using paired-pulse TMS with a CS of 90% AMT and ISIs 2, 3 (SICI), and 10–15 ms (ICF). The typing performance was assessed based on the typing speed and the number of missed characters per session. Subjects were considered as LP after 30 days of practice. After LP, SP was assessed again and repeated after a NP interval of 30 days. Results were presented in Figure 5. As expected, training improved skill performance. SP led to an

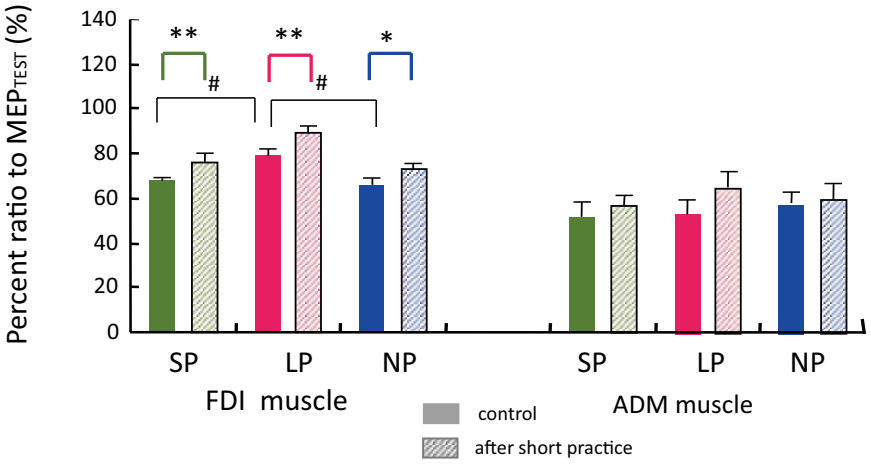

Figure 5. Effect of typing motor learning of short period (SP) for an hour (green filled square in control, green slash square after SP), long term practice (LP) for 10 days (30 min typing practice / day, red filled square in control, red slash square after SP in LP) and no practice(NP) for 30 days (blue filled square in control, blue slash square after SP in NP) on SICI in FDI and ADM muscles each period. Symbols** represents significant differences between control and after practice in SP, LP and NP ($P<0.01$ or $P<0.05$) and Symbols # does significant differences between control in SP and control in LP and between control in LP and control in NP($P<0.05$).

immediate post-practice decrease in the effectiveness of SICI in FDI, but not in ADM. After LP, control SICI remained decreased in FDI and unchanged from baseline in ADM. Subsequent SP further decreased SICI in FDI, but had no effect on ADM. Although the enhancement of typing speed and reduced missed characters were maintained, 30-days NP resulted in a return of SICI to baseline values in FDI.

2) Neuroplasticity and grip touch in a racket player. Sports players, such as tennis, baseball, and golf players make use of their specific sport-related tools, most likely receiving a considerable amount of tool-related information into the brain. We investigated the changes that occurred in the motor and sensory cortices of a racket player, specifically a tennis player who practices daily. The player's grip of the racket's handle provided an enormous amount of sensory information from the cutaneous receptor and tactile sensation, which was relevant to successful performance.

We tested whether the sensation of touching the racket loosely in the hand could itself change to SICI and ICF as well as compared the sensory-motor excitability of short afferent inhibition (SAI) and long afferent inhibition (LAI) in skilled players with a non-player control group. In addition, we compared these effects with those of an imagined touch of the racket and imagined tennis playing [27]. The subjects were nine tennis players with 6–10 years of experience, who play tennis every day, and the control group included eight non-player subjects. Sensory-motor excitability was assessed by measuring the amplitude of single-pulse MEPs, SICI at ISIs of 2 and 3 ms, and ICF at ISIs of 10 and 15 ms in CS intensity of 80% AMT, and SAI at ISIs of 20 ms and LAI at ISIs of 200 ms in median nerve electric stimulation (MNES) at motor threshold in three different conditions, with subjects at rest: (1) control, (2) with the handle of the racket placed in the palm of the hand, (3) with an aluminum baton of the same

diameter as the racket placed in the palm of the hand. In a second set of experiments, expert players were asked to do nothing, imagine touching a racket, or imagine playing with the racket. TS alone elicited MEPs of 1–1.2 mV. Results (see Figure 6 that) indicated that 1) touching the racket, but not the aluminum baton, increased MEPs significantly in racket players but not in controls. It also significantly reduced SICI, SAI, and LAI, but not ICF (Figure 6A); 2) For expert players, to imagine touching the racket did not affect MEP or other parameters, whereas to imagine playing increased MEPs and reduced SICI, but did not affect SAI or LAI (Figure 6B). From these results, we concluded that long-term tennis practice changes the effect exerted by the sensory inputs of the hand on sensory-motor excitability. We speculated that in expert players, the input evokes changes in the system that mimic those required during actual play. Interestingly, imagined playing only evoked

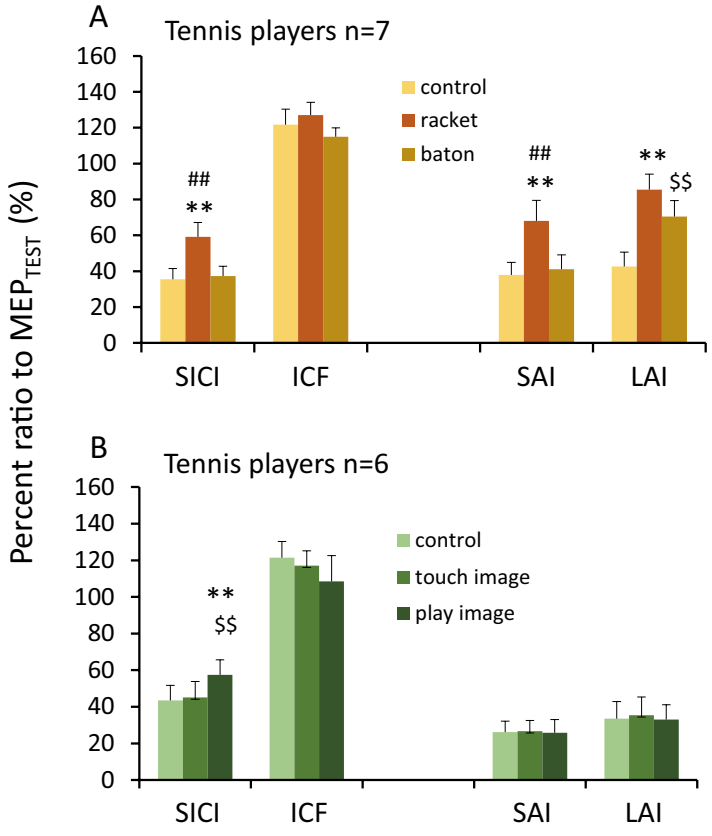

Figure 6. Effect of touch of control (no touch, light yellow), racket (Ocher) and baton (dark yellow) in A and control (light green), touch imagery (TI, green) and play imagery (PI, dark green) in B on SICI, ICF, SAI and LAI in FDI muscle by combination of a paired pulse TMS and NMES in tennis players. Symbol*or** represents significant differences between control and racket (P<0.01 or P<0.05), Symbol ## does significant differences between racket and baton (P<0.01) and Symbols $$ does significant differences between control and baton (P<0.01) in A. Symbol** represents significant differences between TI and PI (P<0.01) and Symbol $$ does significant differences between control and PI (P<0.01) in B.

a subset of these changes (SICI, but not LAI and SAI), whereas imagined touching exerted no effect. Therefore, well-learned sensory input from the handle of a familiar object produces more widespread changes in sensory-motor organization than pure imagination.

3) Observing the actions of an expert baseball player and mirror neurons through two coils and paired-pulse TMS. The process of learning more advanced motor skills generally starts with observation of actions and progresses to imitation of the observed movements and repeated motor practice. Consequently, motor consolidation of the acquired skill occurs in the neural networks, generating neural plasticity for a specific skill and a whole movement. Action observation is a big step for novices to acquire motor skills. Novices are unfamiliar with the skilled motions; hence, their motor and premotor cortices do not possess the neural coding for the new motion or technique. The primary point of the procedure consists of watching the new motion and then copying it. This observation is the beginning of motor learning. Rizzollati et al. [28] indicated that insights into the neural mechanisms of motion understanding came from the discovery of neurons activated during observation of action in the monkey premotor cortex. These neurons were called mirror neurons. Animal and human experiments have shown that the mirror neurons of the ventral premotor cortex (PMv) played a part in understanding as well as learning visually performed movement. Koch et al. [29] suggested that observation also modulated the excitability of the connections between the left PMv and left M1, in a way similar to that observed during self-performed grasping. Importantly, observation of inappropriate grasping movements exerted a reduced effect. It was worth mentioning that because observation controlled self-movement for the enhancement of motor skills, careful observation of some motion or movement pattern might produce the different proficiency in specific sport skills. However, it was unclear how the cortical excitabilities of mirror neurons (PMv) and motor cortex change when a skilled expert sportsman observes some motion or movement on a screen.

To test whether observation of a movement had different effects in skilled and non-skilled subjects, we examined how observing a throwing motion affected motor cortical excitability in skilled baseball players versus non-expert throwers [30]. The subjects were seven expert baseball players (all males), all right-handed, who played baseball almost every day for 8–10 years. The control group included seven non-experts, right-handed subjects (four males and three females). Subjects observed repeated slow-motion videos of right throwing on a 27-inch monitor during TMS measures of motor cortical excitability in the FDI muscle. The data were compared with those obtained at rest, with no screen display. In the first experiment, paired-pulse TMS was used to assess corticospinal excitability, SICI, and ICF [6], with TS alone of 1–1.2 mV and CS intensity of 80% AMT at ISIs of 3 ms for SICI and 10 ms for ICF. In the second experiment of PMv-M1 connection (included six experts and six non-experts in the first experiment), the intensity of CS was individually adjusted to 90% RMT, as evaluated using paired-pulse TMS protocol of Bäumer et al. [31], with TS alone of 1–1.5 mV and a CS intensity of 90% RMT at ISIs of 4 and 6 ms for PMv-M1. In both experiments, the order of presentation of the conditions was randomized by computer. Results indicated that for the TS alone, MEP amplitudes increased during visual observation, in both expert and non-expert players. Furthermore, as shown in Figure 7A and 7B, in both experiments, both SICI and PMv-M1 were reduced during observation in experts, but not in non-experts. However, no changes in ICF were observed in either group. In conclusion, visual observation of a task by expert performers leaded to more pronounced changes in cortical excitability than in the case of non-experts. Particularly, PMv-M1 excitability reduced in

expert performers, because the increased activation of mirror neurons modulated motor cortex excitability from PMv-M1. We suggested that elite sports athletes, who acquired neural consolidation to a proficient movement, most likely possessed enhanced observation skills.

Finally, we introduce the studies of cortical plasticity estimated by paired-pulse TMS and motor learning acquired through various sport practices. However, the application of paired-pulse TMS for the assessment of motor skills, motor control, and functional recovery relies on careful planning of certain crucial aspects, such as, for example, how the stimulation condition is decided and set in paired-pulse TMS, applied on the course of some task, in which situations do paired-pulse TMS or peripheral electric stimulation stimulate the motor and sensory cortices, and what paired-pulse TMS cortical excitability derives from motor skill proficiency. Paired-pulse TMS is a convenient and noninvasive technique, but it is difficult to get precise, reliable data regarding cortical excitability in the cerebral cortex. To achieve a successful use of TMS, it is therefore recommended to ensure adequate knowledge of neurophysiology and electrophysiology of the central nerves and acquiring deep observations of MEP and good TMS skills.

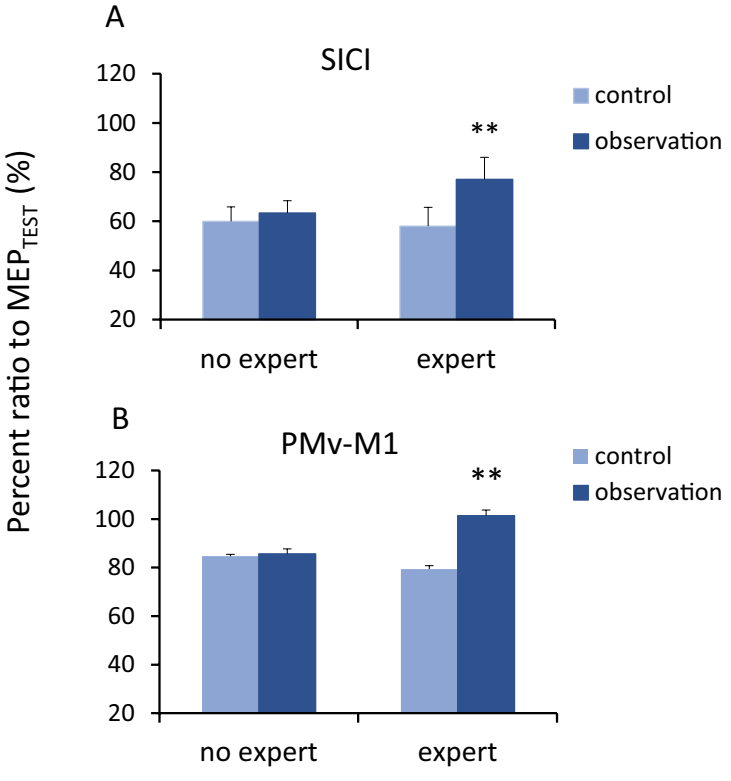

Figure 7. Effect of control (no observation; light blue) and observation (blue) of throwing slow motion in 27- inch monitor on SICI (A) and PMv-M1 (B) in no expert subjects and expert baseball players. Symbol** represents significant differences between control and observation in SIC and PMv-M1 ($P<0.01$).

References

1. Baker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985; 1: 106-107.
2. Hess CW, Mills KR, Murray NM. Responses in small hand muscles from magnetic stimulation of the human brain. J Physiol. 1987; 388:397-419.
3. Rothwell JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J Neurosci Methods. 1997; 74(2):113-122.
4. Laakso I, Hirata A, Ugawa Y. Effects of coil orientation on the electric field induced by TMS over the hand motor area Physics in Medicine and Biology. 2014; 59(1):203-218.
5. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009; 120(12): 2008-2039.
6. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD. Corticocortical inhibition in human motor cortex. J Physiol. 1993; 471: 501-519.
7. Patton and Amassian (1954) Single and multiple-unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol. 1954; 17(4): 345-363.
8. Maier MA, Olivier E, Baker SN, Kirkwood PA, Morris T, Lemon RN. Direct and indirect corticospinal control of arm and hand motoneurons in the squirrel monkey (Saimiri sciureus). J Neurophysiol. 1997;78(2):721-733.
9. Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Mazzone P, et al. The physiological basis of transcranial motor cortex stimulation in conscious humans. Clin Neurophysiol. 2004; 115: 255-266.
10. Di Lazzaro V, Manganelli F, Dileone M, Notturno F, Esposito M, Capasso M, Dubbioso R, Pace M, Ranieri F, Minicuci G, Santoro L, Uncini A. The effects of prolonged cathodal direct current stimulation on the excitatory and inhibitory circuits of the ipsilateral and contralateral motor cortex. J Neural Transm (Vienna). 2012; 119(12):1499-1506.
11. Ziemann U. TMS and drugs. Clin Neurophysiol. 2004; 115, 1717-1729.
12. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol. 1996; 496(3) :873-881.
13. Di Lazzaro V, Oliviero A, Profice P. Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. Electroencephalogr Clin Neurophysiol. 1998; 109(5):397-401.
14. Ziemann U, Rothwell JC. I-Waves in Motor Cortex. J Clin Neurophysiol. 2000;17(4):397-405.
15. Ilic TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U. Short interval paired-pulse inhibition and facilitation of human motor cortex: The dimension of stimulus intensity. J Physiol. 2002; 545(1): 153-167.
16. Sanes JN, Donoghue JP. Plasticity and primary motor cortex. Annu Rev Neurosci. 2000; 23: 393-415.
17. Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. Science. 2000; 290(5491): 533-536.
18. Buonomano DV, Merzenich MM. Cortical plasticity: From synapses to maps. Annu Rev Neurosci. 1998; 21: 149-186.
19. Hendry SH, Fuchs J, deBlas AL, Jones EG. Distribution and plasticity of immunocytochemically localized $GABA_A$ receptors in adult monkey visual cortex. J Neurosci. 1990; 10(7): 2438-2450.
20. Karni A, Meyer G, Jezzard P, Adams MM, Turner R, Ungerleider LG. Functional MRI evidence for adult motor cortex plasticity

during motor skill learning. Nature. 1995; 377(6545): 155-158.
21. van Mier H, Tempel LW, Perlmutter JS, Raichle ME, Petersen SE. Changes in brain activity during motor learning measured with PET: Effects of hand of performance and practice. J Neurophysiol. 1998; 80(4): 2177-2199.
22. Grafton ST, Hazeltine E, Ivry RB. Motor sequence learning with the nondominant left hand. A PET functional imaging study. Exp Brain Res. 2002;146(3): 369-378.
23. Floyer-Lea A, Matthews PM. Distinguishable brain activation networks for short- and long-term motor skill learning. J Neurophysiol. 2005; 94(1): 512-518.
24. Hund-Georgiadis M, von Cramon DY. Motor-learning-related changes in piano players and non-musicians revealed by functional magnetic-resonance signals. Exp Brain Res. 1999; 125(4): 417-425.
25. Andres FG, Gerloff C. Coherence of sequential movements and motor learning. J Clin Neurophysiol. 1999; 16(6): 520-527.
26. Maruyama A, Takada S, Maeda M, Etoh S, Rothwell JC. Effect of long-term training and detraining on short interval intracortical inhibition (SICI) in human motor cortex. Clin Neurophysiol. 2007; 118: 196.
27. Maruyama A, Takahashi K, Etoh S, Kawahira K, Rothwell JC. Sensory-motor intracortical excitability and imagery of grip touch in racket players. Brain stimulation. 2008;1(3) :245.
28. Rizzolatti G, Fadiga L, Fogassi L, Gallese V. Premotor cortex and the recognition of motor actions. Cogn. Brain Res. 1996; 3: 131-141.
29. Koch G, Versace V, Bonnì S, Lupo F, Lo Gerfo E, Oliveri M, Caltagirone C. Resonance of cortico–cortical connections of the motor system with the observation of goal directed grasping movements. Neuropsychologia. 2010; 48: 3513-3520.
30. Maruyama A, Nuruki A, Yamashiro K, Sato D, Rothwell JC. Changes of short- intracortical inhibition during throwing visual observation in expert baseball players. Clin Neurophysiol. 2011; 122: 191-192.
31. Bäumer T, Schippling S, Kroeger J, Zittel S, Koch G, Thomalla G, Rothwell JC, Siebner HR, Orth M, Münchau A. Inhibitory and facilitatory connectivity from ventral premotor to primary motor cortex in healthy humans at rest--a bifocal TMS study. Clin Neurophysiol. 2009; 120(9): 1724-1731.