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CORTICOSPINAL INTEGRATION IN HEALTHY HUMANS

by

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A capstone project submitted to the Graduate Faculty in Physical Therapy in partial fulfillment of the requirements for the degree of Doctor of Physical Therapy, The City University of New York

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Abstract

CORTICOSPINAL INTEGRATION IN HEALTHY HUMANS

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Synchronized arrival of neuronal signals from the periphery and motor cortex has been associated with neuronal plasticity and motor learning. The main objective of this study was to examine neuronal interactions following excitation of descending motor axons from the primary motor cortex (M1) and spinal neuronal circuits via transcranial magnetic stimulation (TMS) and transcutaneous electric stimulation of the spine (tsESS) in 15 healthy humans while seated semi-prone. TMS was delivered below or above the resting motor evoked potential (MEP) threshold, for the tibialis anterior (TA) muscle, while tsESS was delivered at the lowest stimulation intensity that evoked responses in most or all leg muscles. TMS was delivered either alone or with tsESS at different interstimulus intervals ranging from negative 50 ms to positive 50 ms. tsESS induced a biphasic excitability pattern of MEPs recorded from the distal ankle muscles of the right leg with negative interstimulus intervals showing depression of MEPs followed by a non significant effect at the interstimulus interval of 0 ms, and potentiation of MEPs at positive interstimulus intervals. These findings suggest that 1) cortical descending motor volleys can either be potentiated or depressed based on the time that cortical and spinal signals meet at the

spinal cord level, and 2) MEPs and tsESS-induced compound action muscle potentials likely share common neuronal pathways. These findings constitute the first evidence that synchronized neuronal signals from the primary motor cortex and spine can potentiate corticospinal motor output.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is a non-invasive tool for excitation of neuronal tissue, including cerebral cortex, spinal roots, and cranial and peripheral nerves (Kobayashi, 2003). It is a painless, non-invasive technique that has been used in neuroscience for over 20 years for the study of motor control in health and disease (Barker et al., 1985; Berardelli et al., 1991; Rothwell, 1991; Rossini et al., 1994; Edgley et al., 1997; Di Lazzaro et al., 2008; Knikou, 2012). TMS creates a quick, high-intensity magnetic field that passes a brief electrical current through a magnetic coil, causing excitation or inhibition of a small segment of the brain (Hallett 2007). A single pulse of TMS can depolarize neurons and evoke compound action muscle potentials (CMAPs) and modulatory effects depending on the frequency of the stimulus (Hemond, 2007; Kobayashi, 2003).

Transcutaneous electric stimulation of the spine (tsESS) at the thoracolumbar region produces CMAPs in lower limb muscles in humans while at rest and during walking (Knikou, 2013a, b; Dy et al., 2010). These CMAPS are not susceptible to spinal inhibitory mechanisms postulated for the soleus Hoffmann (H-) reflex (Knikou, 2013a, b; Einhorn et al., 2013; Knikou 2008). For example, a distinguished characteristic of the monosynaptic H-reflex is that it is profoundly depressed when primary muscle spindle Ia afferents are activated with low stimulation frequencies (Knikou, 2008). This type of depression is not present in CMAPs induced by tsESS. This is likely because tsESS excites likely the axons of the motor roots near their exit at the intervertebral foramina rather than neural elements within the spinal cord (Schmid et al., 1990). The purpose of this study was to establish corticospinal neuronal interactions in humans. Specifically, we established the motor evoked potentials (MEP) input-

output curve as well as to what extent the MEPs recorded from leg muscles are influenced by tsESS in healthy human subjects while seated.

METHODS

Subjects

The experimental protocol was approved by the City University of New York (New York, NY, USA) Institutional Review Board and was conducted in compliance with the Declaration of Helsinki. Each subject signed an informed consent form before participating in the study. Fifteen adult subjects (8 male, 7 female) free of any neuromuscular or orthopedic disorders and between the ages of 21 and 55 participated in the study. Subjects with tooth implants, assistive hearing devices, pacemaker, history of seizures, and medications known to alter central nervous system excitability were excluded from the study. To reduce TMS-related discomfort, all subjects wore a mouth guard and ear plugs during testing.

Electromyography (EMG) recordings

Following standard skin preparations, single differential bipolar surface EMG electrodes (Motion Lab Systems Inc., Baton Rouge, LA, USA) were placed bilaterally on the rectus femoris (RF), medial hamstring (MH), medial gastrocnemius (MG), soleus (SOL), tibialis anterior (TA), and peroneus longus (PL) muscles, and were secured with 3M Tegaderm transparent film (3M, St. Paul, MN, USA). All EMG signals were filtered with a cut-off frequency of 20-1000Hz (1401 plus running Spike 2; Cambridge Electronic Design, Cambridge, UK).

Transcranial magnetic stimulation (TMS)

Single TMS pulses over the left primary motor cortex (M1) were delivered using a Magstim 200² stimulator (Magstim, Whitland, UK) with a double-cone coil (diameter 110 mm) placed so the current of the coil to flow from a posterior to an anterior direction, and according to procedures we have previously utilized (Knikou et al. 2013). The point where the lines between theinion and glabellum, and the left and right ear tragus met was marked on an EEG cap. The double-cone coil was placed parallel and approximately 1 cm posterior and 1 cm lateral to the left from this intersection point. With the double-cone coil held at this position, the stimulation intensity was gradually increased and the MEPs recorded from the right TA and soleus muscles were observed on a digital oscilloscope (TDS 2014, Tektronix, Beaverton, OR, USA). When in three out of five TMS pulses, MEPs could not be evoked at low stimulation intensities with the subject at rest in the TA muscle only, the magnetic coil was moved by few mm and the procedure was repeated. When the optimal position was determined, the TA MEP resting threshold was established and corresponded to the stimulation intensity that induced repeatable MEPs in size that were approximately 100 μ V of peak-to-peak amplitude (Rossini et al. 1994; Rothwell et al. 1999). All subjects wore a mouth guard and ear plugs to minimize discomfort due to TMS.

Transcutaneous electric stimulation of the nerve roots

Two re-usable self-adhering electrodes of 10.16 x 5.08 cm (anodes; Model EP84169, Uni-Patch, Wabasha, MA), connected to function as one electrode, were placed bilateral on the iliac crests. The thoracic 12 vertebrae was identified via palpation, and a monopolar stainless-steel circular handheld electrode was used to determine the most optimal stimulation site. The optimal

stimulation site was determined when compound muscle action potentials (or spinal evoked potentials) were present in most or all of the leg muscles when stimulation was delivered at low intensities, which were viewed on the oscilloscope (TDS 2014, Tektronix, Beaverton, OR). The monopolar, stainless steel handheld electrode was then replaced by a self-adhering electrode of 10.16 x 5.08 cm, and held under constant pressure throughout the experiment via pre-wrap and athletic wrap. This cathode electrode was placed equally between left and right paravertebral sides and, depending on the height of the subject, spanned between T10 – L4 vertebrae levels. The anode and cathode electrodes were connected to a stimulator (DS7A, Digitimer, Welwyn Garden City, Hertfordshire, UK), that was triggered by an analog-to-digital acquisition system with customized scripts written in Spike 2 with single pulses of 1-ms duration. The stimulation intensity during which CMAPs in the leg muscles were first noted on the oscilloscope were termed spinal evoked potential (SEP) response threshold. The stimulation intensities ranged from 432 – 867 mA (725 ± 147 ; mean \pm SD) across subjects. At these stimulation intensities, subjects reported no pain or discomfort.

Experimental Protocol

With subjects seated, and after cortical and spinal stimulation sites were determined, the MEP input output curve was constructed. The TMS was set at below MEP threshold intensities and was progressively increased until the MEPs reached their maximal amplitude. MEPs were recorded at least at 10 different TMS intensities while at least 4 MEPs were recorded at each intensity. Then, the TMS was set at 1.2 tibialis anterior (TA) MEP threshold, and MEPs were recorded following tsESS at conditioning-test (C-T) intervals that ranged from negative 20 to

positive 20 ms. A negative C-T interval denotes that tsESS was delivered after TMS. At each C-T interval at least 10 MEPs, evoked once every 10 s, were recorded in all subjects.

Data analysis

All compound muscle action potentials recorded with subjects seated were measured as the area of the rectified waveform. The stimulation intensities (as a % of the maximum stimulator output) at which MEPs were recorded across the recruitment curve were normalized to the intensity corresponding to the MEP threshold. Then, the MEPs recorded from the right TA, SOL, MG, and RF muscles were expressed as a percentage of the maximal MEP and plotted against the multiple of MEP threshold. The mean normalized amplitude of each MEP was grouped across subjects based on multiples of MEP threshold. A sigmoid function $MEP(s) = \frac{MEP_{max}}{(1 + \exp(m(S50 - x)))}$ was used on the normalized MEPs plotted as a function of the normalized stimulation intensities (Carroll et al. 2001; Klimstra and Zehr 2008). The parameters in the above equation denote the maximal MEP (MEP_{max}), the slope parameter of the function (m), the stimulus required to elicit an MEP equivalent to 50% of the MEP_{max} (S50), and the MEP amplitude at a given stimulus value MEP(s).

The MEPs recorded from the right TA, MG, PL, and SOL muscles upon tsESS at different C-T intervals were expressed as a percentage of the mean amplitude of the homologous unconditioned MEPs recorded at $1.2 \times$ MEP threshold. This was done separately for each subject and MEP recorded. Based on the latency of MEPs (~ 30 ms) and the latency of ankles SEPs (~15 ms), at the C-T intervals of -4, -8, -10, and -20 ms, a summation of MEPs and SEPs is possible. To counteract the summation of action potentials and establish the net effect of tsESS on MEPs, at these C-T intervals, the associated SEP was subtracted from the conditioned MEP, and the

resultant value was normalized to the associated control MEP amplitude. Conditioned MEPs were grouped across subject based on muscle and C-T interval, and statistically significant differences of the conditioned MEPs were established with one-way analysis of variance (ANOVA) when data were normally distributed or with a Kruskal-Wallis one-way ANOVA on ranks when data were not normally distributed. When statistical significant difference was found, post hoc Bonferroni tests for multiple comparisons were conducted to establish at which C-T interval the conditioned MEP is statistically significant different. This analysis was done for each MEP separately.

RESULTS

MEP Input-Output Curve

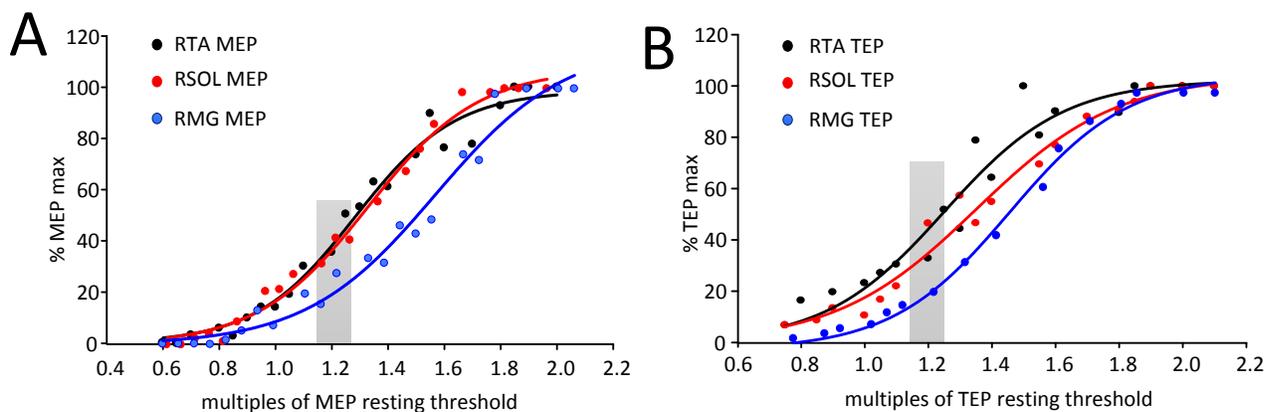


Fig. 1. MEP and SEP Input-Output Curves. (A) MEPs recorded from all subjects while seated are plotted against the stimulation intensities, which were normalized to the MEP resting threshold. The vertical grey column identifies the point with respect to the TA MEP input-output curve that TMS was delivered to evoke and record control and conditioned MEPs. (B) SEPs recorded from 2 subjects while seated are plotted against the stimulation intensities, which were normalized to the SEP resting threshold.

In Figure 1A, the overall amplitude of the TA, SOL, and MG MEPs recorded at different stimulation intensities from all subjects are indicated. MEPs are shown as a percentage of the maximal associated MEP amplitude relative to the multiples of the associated MEP threshold

which is shown on the abscissa. The relationship between the TA, SOL, and MG MEPs amplitude and multiples of MEP threshold intensities were well characterized by a sigmoid function, which is shown as solid lines for each MEP. Further, in Fig. 1A, the grey bar indicates the level of TMS with respect to multiples of MEP threshold when control and conditioned MEPs were recorded. It is apparent that TMS induced activity of the most excitable corticomotoneuronal cells. A similar relationship between TA, SOL, and MG SEPs and stimulation intensities was observed (Fig. 1B), suggesting that recruitment of motor axons occur in a similar pattern for both MEPs and SEPs.

In Figure 2, the overall amplitude of the RF MEPs recorded at different stimulation intensities from all subjects are indicated. MEPs are shown as a percentage of the maximal associated MEP amplitude relative to the multiples of the associated MEP threshold which is shown on the abscissa. The RF MEP input-output curve relationship was well defined with a sigmoid function, which gave an $R^2 = 0.98$.

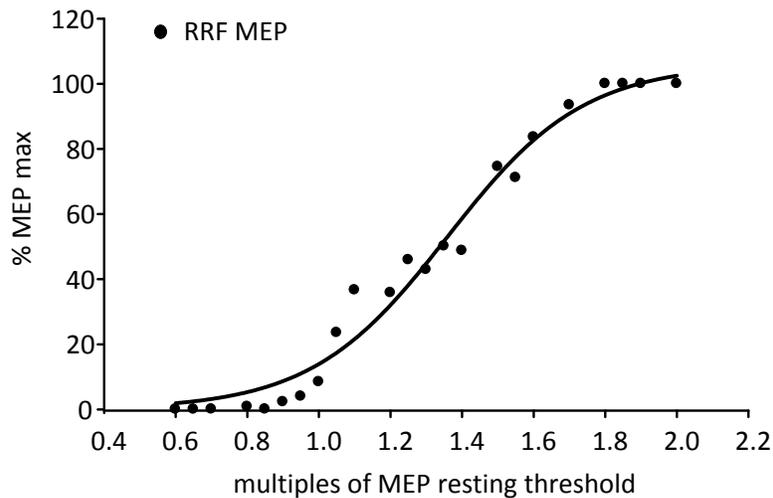


Fig. 2. Right rectus femoris (RF) MEP Input-Output Curve. RF MEP peak-to-peak amplitudes recorded from all subjects while seated are plotted against the stimulation intensities, which were normalized to the MEP resting threshold.

The estimated parameters from the sigmoid function are indicated in Table 1. No statistically significant differences were found between MEPs and SEPs ($P > 0.05$ for all parameters), suggesting that recruitment of neuronal elements engaged in the manifestation of MEPs and SEPs is conducted in a similar order.

Table 1. Sigmoidal recruitment curve relation results¹					
	m	S50	slope	Stim @ th	Stim @ max
Cortical evoked potentials (MEPs)					
TA	5.60	1.28	0.36	0.92	1.64
MG	4.88	1.41	0.41	1.00	1.82
SOL	5.08	1.36	0.39	0.97	1.75
Spinal evoked potentials					
TA	5.32	1.25	0.38	0.87	1.63
MG	5.29	1.44	0.38	1.06	1.82
SOL	4.51	1.35	0.44	0.91	1.79

¹ Parameters estimated from the sigmoidal input-output relation of MEPs and SEPs. m: slope parameter of the function, S50: stimulus at 50% of the maximal evoked compound action muscle potential, slope: MEP or SEP slope estimated as $2/m$, stim @ th: stimulus at MEP or SEP threshold estimated as $S50 - \text{slope}$, stim @ max: stimulus at MEP or SEP estimated as $S50 + \text{slope}$. No statistically significant differences were found between MEPs and SEPs ($P > 0.05$) for any of these parameters.

Spinal Modulation of Motor Evoked Potentials

The MEP threshold ranged from 39 to 79 % of the maximum stimulator output (51.73 ± 12.02 ; mean \pm SD) across subjects. TMS upon control conditions was delivered at 60 ± 10.74 % of the maximum stimulator output, which was equivalent to 1.17 ± 0.11 % of the MEP threshold.

In Figure 3, the average amplitude of the conditioned TA, PL, SOL, and MG MEPs recorded from all subjects following tsESS is indicated. The C-T interval is denoted on the abscissa while the conditioned MEPs are presented as a percentage of control MEPs. Kruskal-Wallis one-way ANOVA showed that the TA MEP varied significantly across the C-T intervals tested ($H_{10} = 19.1$, $P = 0.039$; Fig. 3A). The same result was also found for the PL MEPs ($F_{10,52} = 2.61$, $P = 0.012$; Fig. 3B), being statistically significant different at negative C-T intervals compared to those observed at positive C-T intervals. Similarly, the SOL MEPs varied significantly across C-T intervals tested ($H_{10} = 19.1$, $P < 0.001$; Fig. 3C), with SOL MEPs at -10 and -8 ms to be significantly significant different compared to those recorded at the C-T interval of 4 ms. A similar result was also found for the MG MEPs ($H_{10} = 19.1$, $P < 0.001$; Fig. 3D). For each MEP, a third order polynomial relationship between conditioned MEP amplitude and C-T intervals tested is indicated along with the R^2 value in Fig. 3. It is apparent that transcutaneous stimulation of the spine induces a biphasic modulation pattern of MEPs, with MEP depression at negative C-T intervals and MEP facilitation at positive C-T intervals.

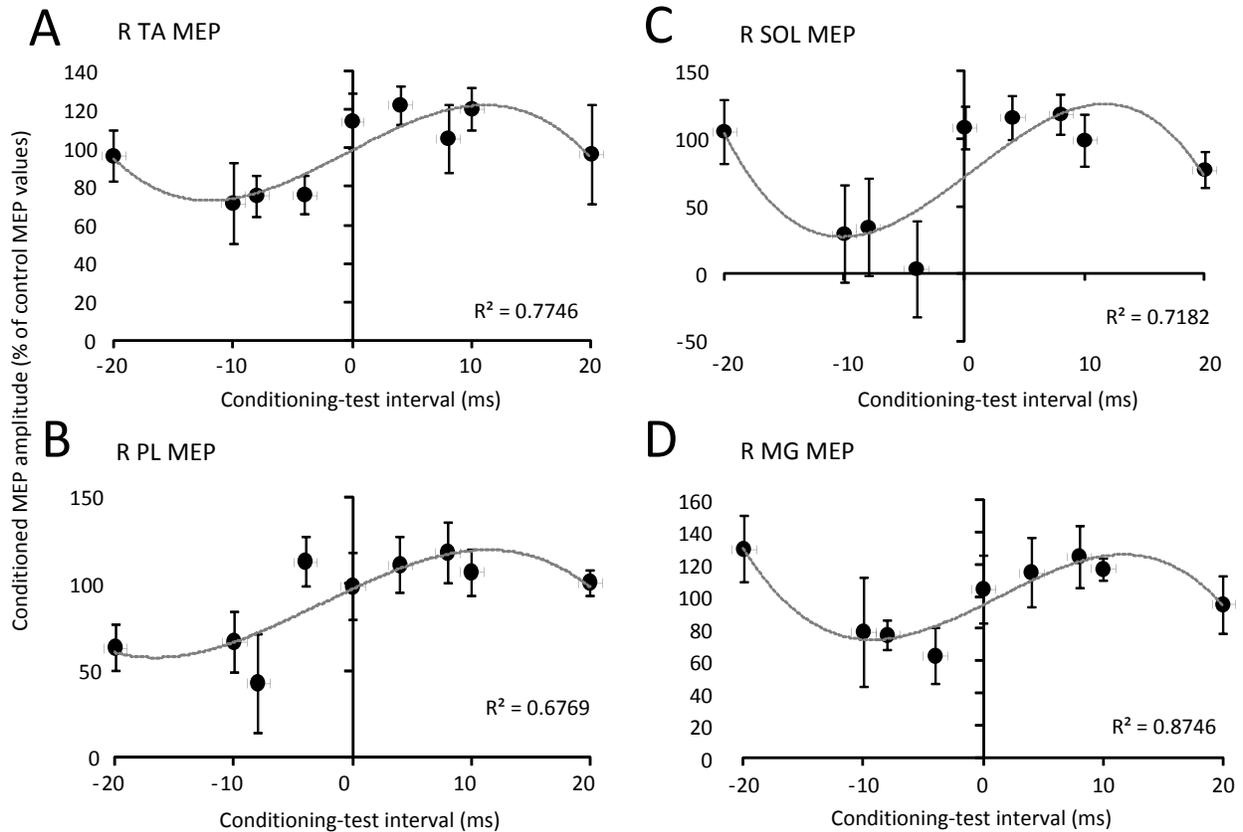


Fig. 3. Spinal modulation of motor evoked potentials. Amplitude of TA, PL, SOL, and MG MEPs from all subjects is indicated for each C-T interval tested. MEP= motor evoked potentials. TA=tibialis anterior. PL: peroneus longus. SOL=soleus. MG: medialis gastrocnemius.

DISCUSSION

This study demonstrated for the first time that motor axons are recruited in a similar pattern upon transcortical and transcutaneous stimulation of the spine, and that transcutaneous electric stimulation of the thoracolumbar region induces a biphasic excitability pattern of MEPs recorded from ankle flexor and extensor muscles.

We have recently shown that transcutaneous electric or magnetic stimulation of the spine over the cervicothoracic or thoracolumbar region attenuates significantly flexor carpus radialis (FCR) and soleus H-reflexes in seated and standing healthy human subjects, the compound action potentials recorded upon stimulation of the spine are not susceptible to homosynaptic

depression, and their latency is nearly half of the soleus and/or FCR H-reflex (Knikou, 2013a, b; Einhorn et al., 2013). These findings suggest that neuronal structures involved in manifestation of H-reflexes, SEPs, and likely MEPs at the spinal level are likely different. However, if transcutaneous stimulation of the spine can affect the amplitude of MEPs, with the latter representing the corticospinal axons excitability monosynaptically synapsing onto spinal motoneurons, then SEPs and MEPs may share common neuronal pathways.

In this study, we found that regardless the muscle that the MEP was recorded from (i.e., flexor or extensor), when conditioned by transcutaneous stimulation of the spine the MEPs were either depressed or facilitated depending largely on the interstimulus interval between these two stimulations. Because TMS activates cells with monosynaptic connections to spinal motoneurons, pathways with polysynaptic connections, and the MEP amplitude is sensitive to the excitability state of spinal motoneurons and interneurons (Burke et al., 1993; Nielsen and Petersen, 1995; Geertsen et al., 2010; Nielsen et al., 1999; Schneider et al., 2004), we cannot define the exact neuronal pathway of interaction between MEPs and tsESS.

tsESS generates impulses that travel along the posterior and anterior root fibers exciting the fibers at the spinal cord entry or at their exit from the spinal canal (Ladenbauer et al., 2010). Excitation of dorsal column fibers, motor axons, and antidromic activation of primary muscle spindle afferents (Ia) in the dorsal column may contribute to the generation of these CMAPs (Coburn, 1985; Maertens de Noordhout et al., 1988; Bayoumi and Ashby, 1989; Hunter and Ashby, 1994; Ladenbauer et al., 2010). Because F-waves could be recorded upon concomitant supramaximal peripheral nerve and spinal stimulation, it is likely that the excitation site is distal to the anterior horn cells foramina (Mills and Murray, 1986; Maertens de Noordhout et al., 1988; Ugawa et al., 1989; Chokoverly et al., 1991; Epstein et al., 1991), with nerve roots being excited

near to their exit from the spinal column or near the emergence of the axons from the anterior horn cells (Mills and Murray, 1986). Thus, CMAPs likely represent composite excitatory potentials of different types of afferents as well as efferents.

MEP depression and/or potentiation might have been thus mediated at a presynaptic or postsynaptic level or simultaneously at both synaptic levels, and affected by changes in the excitability of spinal interneurons. Because the latency of CMAPs recorded from the right TA muscle is prolonged by ~2.0 ms compared to the half latency of the TA MEP, polysynaptic spinal reflex pathways had ample time to affect postsynaptically the excitation of alpha motoneurons upon TMS (Ugawa et al., 1995). An altered motor-cortex induced muscle contraction and thalamo-cortical activity following spinal stimulation in anaesthetized rats and mice has recently been shown (Aguilar et al., 2011; Ahmed, 2011).

Clinical application of findings

Invasive dorsal column stimulation in two people with multiple sclerosis improved their motor, reflex, and bladder function (Illis et al., 1976), while continuous epidural stimulation enabled a person with motor complete paraplegia to achieve full-weight bearing and locomotor-like EMG activity (Harkema et al., 2011), consistent to the modulation of spinal locomotor networks of adult spinal rats (Lavrov et al., 2008). These results were obtained with stimulation administered invasively, limiting thus their possibility of application to a larger number of patients. This study showed for the first time that tsESS changed cortical motor output - manifested as MEPs – in ankle muscles. Based on our current and published findings (Knikou, 2013a, b; Einhorn et al., 2013), tsESS can be utilized in upper motor neuron lesions to potentiate cortical motor output.

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