The influence of peripheral electromagnetic solenoid - type vibration on motor cortical excitability : a navigated transcranial magnetic stimulation study

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Diploma thesis

Academic year:
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LIST OF ABBREVIATIONS

TMS – Transcranial magnetic stimulation

TES – Transcranial electric stimulation

MRI – Magnetic resonance imaging

fMRI – Functional magnetic resonance imaging

MEP – Motor evoked potential

ISI – Inter-stimulus interval

rTMS – Repeated TMS

EMG – Electromyography

MT – Motor threshold

CMCT – Central motor conduction time

M1 – Primary motor cortex (in this paper)

CSP – Cortical silent period

GABA – Gamma-aminobutyric acid

ALS – Amyotrophic lateral sclerosis

MS – Multiple sclerosis

DLPFC – Dorsolateral prefrontal cortex

CNS – Central nervous system

ADM – m. abductor digiti minimi

CMAP – Compound muscle action potential

VF – Vibration frequency

ECR – m. extensor carpi radialis

FCR – m. flexor carpi radialis

SEP – Somatosensory evoked potential

SOL – m. soleus

TA – m. tibialis anterior

H-reflex – Hoffman reflex

N20 – A specific somatosensory evoked potential

APB – m. abductor pollicis brevis

RMT – Resting motor threshold

rANOVA – Repeated analysis of variance

LMN – Lower motor neuron

UMN – Upper motor neuron

AVR – Antagonist vibration response

1. INTRODUCTION

1.1 Transcranial magnetic stimulation

1.1.1 Technological overview and neurophysiological effects

Transcranial magnetic stimulation (TMS) is a method used to indirectly cause electrical stimulation and depolarization of neural tissues such as the brain, spinal nerve roots, and peripheral nerves (1). Its use in stimulating the human cerebral cortex was first demonstrated by Barker in 1985 (2). TMS is based on Faraday's principle of electromagnetic induction, which allows for a non-invasive mode of operation (1). This is made possible by passing a sufficiently strong, but short-lived current pulse through a coil over a person's head. Rapidly changing magnetic pulses then penetrate the skull and induce electric activity in the brain. Hence, the magnetic aspect of TMS is not the direct cause of the tissue effects, but rather serves as a means to generate *in vivo* electric fields non-invasively (3).

The essence of the TMS instrument is a coil consisting of circular turns of copper wire connected to a large electric capacitance (3). It usually takes the form of a hand-held probe that extends via cables from a bigger installation responsible for tasks related to signal processing, power generation, and coil cooling. A switch allows discharge of the capacitance through the coil with a current flow of several thousand amperes for a short duration of less than 1 ms (4). The peak magnetic flux generated from this event is 1-2 T. A monophasic pulse configuration of the current translates to one phase of current flow in the brain, while a biphasic configuration results in two phases of physiologically significant current fluxes in the same or opposite direction. The most basic mode of pulse application of TMS is in the form of a single discrete pulse (1). The other modes of application deliver multiple pulses in succession. Paired-pulse stimulation involves two discrete pulses separated by a variable inter-stimulus interval (ISI), while in repetitive TMS (rTMS) a train of repetitive stimuli is delivered at various frequencies ranging from 1 Hz to 20 Hz or more.

The point of TMS is to stimulate specific topographical areas of brain tissue, but the brain anatomy of individual subjects is difficult to discern based on gross exterior landmarks alone (4). Iterative methods based on correlation of coil placement and degree of resulting physiologic response can be employed to guide coil positioning over the scalp, and these are accurate to within a few centimeters. An improved method is stereotactic neuronavigation using MR images, in which the brain anatomy of individual subjects can be coregistered in a common reference space with anatomical land marks in real-time. This method has a spatial accuracy of a few millimeters, and reduces the variability of induced electric fields between trials.

Various coil configurations are available depending on the intended use case (3). The simplest configuration is that of a single circular coil. It penetrates well into the cerebral cortex and induces a widely distributed electric field potentially reaching both hemispheres, but thus lacks the focality offered by the newer 'figure-8' coil. In the latter, two circular coils are placed side-by-side, and the direction of current in each is opposite to the other. The magnetic field is directed perpendicularly to the long axis of the figure-8 coil and is maximum directly under the center of the coils, but the secondarily induced current tends to be maximum near the outer edge of the coil. Thus, the induced currents flow in one direction, and the resultant electric fields are added together and peak below the junction point. The figure-8 coil, however, has reduced penetration compared to a simple circular coil owing to smaller side loops.

Current induced in the target tissue is proportional to the time derivative of the magnetic flux density (dB/dt) (3). Efficiency of stimulation is optimized by maximizing the voltage of the instrument while minimizing individual pulse duration. Increasing duration of pulses is not efficient, since the initial charge on axonal membranes dissipates quickly. Efficiency of energy transfer from TMS coils to the tissue is on the order of 0.0001%, which is part of the explanation for the high power requirement and ensuing risk of equipment overheating. The induced electric field decreases exponentially at increasing distance from the coil, and near the center of the head it falls towards zero. Majority of the induced current flows parallel to the brain surface. It follows from the last two points that induced electric field strength is strongest in the crown of the gyrus, although there can be certain hot spots within subcortical white matter (4).

The brain consists of white matter, gray matter, and cerebrospinal fluid, and these conduct electric currents inhomogeneously (3). For the purposes of TMS however, the practical consequences of these differences are negligible, and the brain can be treated as a homogeneous conductor. Other factors determining the physiologic effects of TMS in addition to the time derivative of flux density mentioned earlier, include duration of TMS application, and volume and location of the stimulated tissue. The efficacy of tissue stimulation at a given location depends on the orientation of cell bodies and axons relative to induced current flow (5). The capacity of TMS to depolarize neurons is higher when the spatial derivative of the electric field along the nerve is maximal (6). Anatomically this entails that the preferential point of stimulation is where a nerve curves out of the electric field. TMS typically activates pyramidal cells in one of two ways, depending on the orientation of the induced current, with each giving rise to distinguishable patterns of motor evoked potentials (MEPs) (7, 8). One way is by indirect activation through trans-synaptic stimulation, which evokes I-waves. The other is by direct activation at their axon hillock, which evokes D-waves. Higher intensity of TMS is needed for

evoking D-waves compared to I-waves (4). Large-diameter myelinated axons are the main targets of TMS, with fast-conducting axons >75 m/s having lower thresholds for direct activation, and slow-conducting axons < 55 m/s having lower thresholds for indirect activation (1, 4). There seems to be a predilection for activating the axons of excitatory intracortical interneurons which in turn stimulate the pyramidal neurons (4). Neuronal activity following TMS is not just limited to the site of stimulation, but is also observed at anatomically connected sites distant from the coil (5).

Several safety considerations exist when using TMS, often overlapping with those for magnetic resonance imaging (MRI) as both involving magnetic field exposure (3). Implanted metal devices, acoustic devices, and intracranial metal such as aneurysm clips may be absolute or relative contraindications for TMS depending on the circumstances. A history of epileptic seizures should also warrant caution, as there is concern of triggering epileptiform activity during TMS. Acoustic noise, although never documented to have caused hearing impairment, is an obvious feature of TMS that can easily be mitigated with hearing protection. Other considerations of safety include overheating of the coil as well as shock hazard. Modern navigated TMS equipment (e.g. from Nexstim, Finland) incorporate a cooling unit that reduces chances for coil overheating, which is especially important in long-running experiments.

1.1.2 Physiological phenomena related to TMS

1.1.2.1 Motor evoked potentials

Stimulation of the cerebral motor cortex with TMS gives rise to MEPs, which can be detected using EMG at the somatotopically corresponding muscle (3). The amplitude of recorded MEPs is influenced by three physiological mechanisms: first, the number of motor neurons recruited in the spinal cord; secondly, the number of neurons that discharge more than once in response to the stimulus; and lastly, the degree of synchronization of the neural discharges. The relationship between TMS stimulation intensity and resulting MEP amplitude can be described by a sigmoid curve termed the stimulus-response curve, which gets its shape due to progressively higher corticospinal recruitment and temporal dispersion of descending volleys (4). However, maximal MEP amplitudes following very strong TMS stimulation do not reach the levels seen after maximal peripheral stimulation (3). This constraint is due to the fact that a single TMS pulse to the primary motor cortex (M1) gives rise to a series of temporally dispersed descending corticospinal volleys, and the resulting desynchronization of motor neuron discharges entails phase cancellation of motor unit potentials (4). The stimulus-response

relationship for MEPs also varies across different muscles, and between individual subjects. It is also known that intrinsic fluctuations in the nervous system contribute to the variability in MEP amplitude.

In the context of TMS applied to the motor cortex, the concept of motor threshold (MT) refers to the lowest intensity of single-pulse stimuli needed to evoke MEPs in the target muscle (4). MT is probably a function of the membrane excitabilites of different neurons along the length of the corticospinal pathway, from various interneurons and other modulatory inputs projecting onto pyramidal cells in the motor cortex, to the final neuron synapsing at the neuromuscular junction in the peripheral muscle.

Excitability of the corticospinal pathway influences the magnitude potential of MEPs, and this excitability can be modulated by a number of diverse processes ranging from voluntary actions such as intentional muscle contractions, visualization of movements, and speech; to externally induced sensory stimulation of receptors in tendons, skin, or muscle (3). Corticospinal excitability is also subject to influence by certain TMS paradigms, typically involving paired-pulse stimulation. For example, paired-pulse TMS stimulation of the motor cortex causes either increased or decreased MEP size depending on the inter-stimulus interval (ISI) chosen and whether the ipsilateral or contralateral hemisphere is stimulated. One practical consequence of the inter-individual variability in corticospinal excitation is that TMS intensity must be fine tuned for each person (4). The standard measure used for such normalization is referred to as the MT, which is taken to mean the minimal intensity of motor cortical stimulation required for reliably producing minimal MEPs in the target muscle (the convention is to require 50 μV in at least 5 out of 10 trials). Figure 1 shows the typical shape of a MEP recorded from a hand muscle by stimulation of the primary motor cortex.

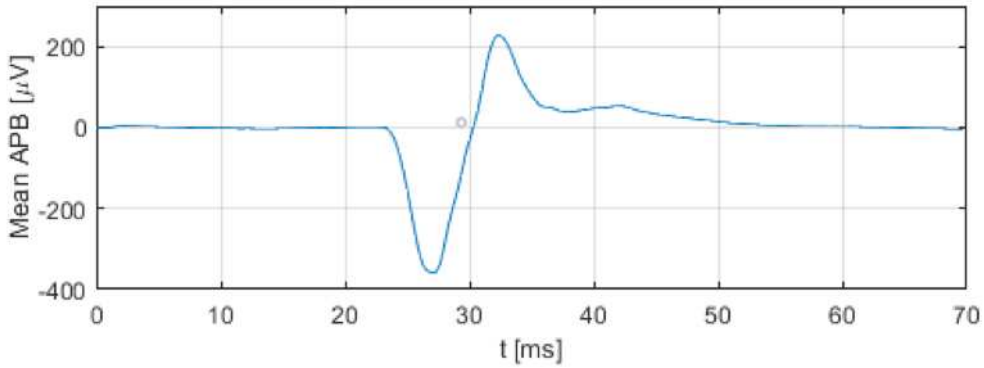

Figure 1. Averaged MEP evoked with stimulation of the primary motor cortex representation for the abductor pollicis brevis (APB) muscle in ten trials.
Source: Laboratory for Human and Experimental Neurophysiology, School of Medicine, Split.

By comparing differences in MEP latencies following TMS stimulation at different points along the corticospinal pathway, it is possible to determine the conduction times of sub-segments of the pathway (1). One example of such a metric is the central motor conduction time (CMCT), which refers to the duration of time a descending volley needs to travel from the motor cortex to the spinal cord. It is obtained by subtracting the MEP latency associated with stimulation of the spinal nerve root from the latency associated with stimulation of the motor cortex.

1.1.2.2 Cortical silent period

A suprathreshold TMS pulse to the motor cortex will not only cause a detectable muscle contraction in the contralateral target muscle, but also leads to an interruption of any underlying voluntary muscle contraction for a short duration (9). This phenomenon is referred to as the cortical silent period (CSP), and manifests as a 100-300 ms period of EMG inactivity following the MEP (3). Its duration depends on TMS intensity and ISI, and is longest in the small hand muscles (3, 4). Electrical stimulation of cutaneous nerves have been shown to shorten the CSP (3). CSPs can normally be elicited at a slightly lower TMS stimulation intensity than the MEP threshold.

Both spinal and cortical mechanisms are responsible for the CSP, with the initial 50-60 ms of the silent period attributed to spinal mechanisms such as recurrent Renshaw cell inhibition, post-excitatory motor neuron refractoriness, and afferent inhibition by Ia interneurons (10-12). The remainder of the CSP seems to be entirely caused by cortical inhibition, probably mediated by GABA receptors (13).

1.1.2.3 Long-lasting effects following TMS

Trains of repetitive TMS stimulation, rTMS, can induce modulations of cortical excitability that last beyond the immediate stimulation period (14, 15). The effect can be inhibitory or facilitatory on both motor and non-motor brain regions, depending on the stimulation frequency and other less important stimulation variables. Slow (below 1 Hz) rTMS has been shown to suppress cerebral blood flow and metabolism to the stimulated area, while rapid (above 5 Hz) rTMS was shown to increase blood flow (16-18). Furthermore, long-term depression or potentiation of cortical synapses, modulation of neurotransmitters, and gene induction have been put forth as other possible explanations for the effects of rTMS at various frequencies (19,20). TMS is currently widely used in treatment of psychiatric disorders and

several companies have yielded FDA clearance to use rTMS in treatment of depression (i.e. Smart Focus® TMS, Nexstim company, Finland).

1.1.3 Applied TMS

One of the important properties of TMS distinguishing it from transcranial electrical stimulation (TES) is its propensity to mainly activate axons within the cortical part of the cerebrum, even at high stimulation intensity (21). This makes TMS particularly useful in researching physiological functions and pathological abnormalities of both somatic and neuropsychological aspects of humans from the perspective of cortical excitability. These investigations sometimes overlap with possible diagnostic applications in clinical medicine. Furthermore, through its ability to induce long-lasting modulation of cortical excitability, TMS shows promising applications in assisting treatment of a wide spectrum of clinical conditions in the fields of neurosurgery, neurology, and psychiatry.

1.1.3.1 Research applications

1.1.3.1.1 Cognitive neuroscience

TMS can map brain function by investigating what information is processed in a given brain structure, and when such processing occurs (4). This has contributed to the understanding of perception, attention, awareness, learning, language, and plasticity (5). Since TMS causes only a brief, reversible disruption of cortical function, it enables the study of brain function in healthy subjects without the compensatory cognitive and neuroplastic changes seen in subjects with abnormal brains often used in such investigations. In the case of rTMS, there is greater disruption of activity in the targeted cortical region as rTMS frequency increases, with greater final behavioural effects (4). Most studies of cognitive function employ a figure-8 coil for its ability to induce a relatively concentrated and focused electric field (5). TMS activates many neurons at once, and induces disorder in the information processing system being studied, disrupting task performance in a random manner. At the point of maximal activation, the signal-to-noise ratio will be lowest. Thus, TMS stimulation of an area known to be involved in a given cognitive task is unlikely to produce the same coordinated pattern of neural activity that is seen when performing that task without TMS, yet the downstream effects of stimulation at the primary site corresponds well with the activation produced by self-induced behaviour. As with other TMS investigations, the applications in cognitive neuroscience are limited to superficial cortical regions, and trying to stimulate deeper cortical structures may also stimulate the more

superficial overlying cortex. Most superficial cortical regions of the brain can be studied using TMS, and a few examples will be included here to illustrate the the spectrum of possibilities the technology brings to the field of cognitive neuroscience.

When applying high-frequency repetitive TMS over the right parietal cortex, a transient neglect syndrome results (22). In relation to the visual system, TMS is helping to answer questions about the interactions between the primary visual area (V1) and the extrastriate visual areas (V2-V5) in producing awareness of specific visual attributes (23). When applying TMS over the V5 area, an illusory motion perception is experienced in normal individuals with an intact V1 area, but not in individuals with a defective V1 area. In speech function, TMS can induce speech arrest, dysarthria-like errors, as well as speech and language related errors (24-26). Stimulation of the left frontal cortex can also lead to impairments in verbal recall and picture-word matching (27,28).

1.1.3.1.2 Medical research

TMS is showing promise in the research and treatment of a diverse and expanding assortment of medical conditions, ranging from specific somatic diseases like movement disorders to neurologic, psychiatric, and cognitive ailments such as epilepsy, depression, schizophrenia, anxiety disorders, and stuttering (5). Diseases involving the nervous system often give rise to alterations in one or more of the TMS-associated neurophysiological measurments, for instance MEP threshold, amplitude, duration, or latency; cortical silent period; measures of cortical facilitation and inhibition; as well as other parameters (Table 1). Following is a non-exhaustive survey that illustrates some of the findings resulting from such use of TMS in medical research.

Table 1. Neurophysiological parameters for various disorders

Disorder	MEP[a] amplitude	CMCT[b]	MT[c]	CSP[d]
Multiple sclerosis	Reduced	Increased	Increased	Prolonged
Stroke	Reduced	Increased	Increased or reduced	Shortened or prolonged
Cervical myelopathy	Reduced	Increased	Increased	Shortened
ALS[e]	Reduced	Increased	Increased (late) or reduced (early)	Normal or shortened
Parkinson disease	Facilitated at rest	Normal	Normal	Shortened
Dystonia	Normal at rest, facilitated during activity	Normal	Normal	Shortened
Cerebellar ataxia	Normal or reduced	Increased	Increased	Prolonged
Epilepsy	Normal or reduced	Normal	Normal, reduced, or increased	Normal, shortened, or prolonged

Adapted from Rossini 2015 (4)
[a] Motor evoked potential
[b] Central motor conduction time
[c] Motor threshold
[d] Cortical silent period
[e] Amyotrophic lateral sclerosis

Several pathological conditions involve altered cortical excitability or defective interactions between cortical and subcortical structures (1). As mentioned earlier in the section about cortical facilitation and inhibition, there are complex mechanisms interacting to inhibit or facilitate excitation at the cortical level, and these are of interest to medical researchers since many pathological conditions have been found to affect them. The use of a paired-pulse technique is favorable when investigating these phenomena. It essentially involves delivering two cortical TMS impulses of variable intensity and separated by a specific ISI, then performing various measurments to determine the extent of facilitation or inhibition caused by the first impulse judging by the altered response of the organism to the second.

Altered paired-pulse curves compared to healthy individuals are found in several nervous system disorders (29-32). Certain distinct clinical entities share the same abnormalities upon paired-pulse investigation, such as dystonia and idiopathic Parkinson disease. Also disorders without obvious motor cortical pathology involve changes in the paired-pulse curve, including schizophrenia, depression, and obsessive-compulsive disorder (33-35).

A variant of paired-pulse stimulation involves delivering a single TMS pulse to anatomically distant areas of the cortex, which facilitates investigation into potential inter-

hemispheric interactions (1). Such interactions are absent in patients with cortical myoclonus, suggesting a transcallosal or cortical inhibitory interneuron defect (36). In contrast, recovering stroke patients and patients with mirror movements often show changes in these interactions (37).

Paired-pulse investigations have also been employed in studying effects of drugs targeting the human motor cortex, which might be clinically useful in selecting the optimal medications for patients with individually specific pathologic changes in the cortex (38).

Various movement disorders can cause abnormal durations in the CSP. In amyotrophic lateral sclerosis (ALS) there is impaired intracortical inhibition, which decreases the CSP (39,40). A subgroup of patients with hemiparesis following acute stroke may have prolonged CSP duration, but a normal central motor conduction time (CMCT) and MEP in the affected side, while their symptomatology resembles motor neglect (41). As their clinical condition improves, the CSP duration has been observed to decrease concomitantly. This has led some to suggest that for certain stroke patients with features of motor neglect, the cause of the motor disturbance is excessive motor cortical inhibition, rather than a direct corticospinal problem.

Similar to CSPs is the phenomenon whereby a TMS impulse to the motor cortex is able to suppress ongoing EMG activity in the ipsilateral hand muscles. This ipsilateral silent period is of significantly shorter duration than contralateral CSPs, and is thought to be mediated by transcallosal inhibition (42). Neurological diseases affecting the corpus callosum can be accompanied by delayed or absent ipsilateral silent periods. In multiple sclerosis (MS), such abnormalities — even if clinically silent — is thought to be associated with poor prognosis in the cognitive domain (43).

The MT is typically increased in diseases that might involve the corticospinal tract, like MS, stroke, and injury to the brain or spinal cord (44-47). In ALS, the MT evolves as the disease progresses, generally being decreased in the earlier stages, and increased later on (48-50). TMS can reveal early involvement of cranial nerves in ALS patients before the existence of clinical corticobulbar signs (39).

MEP amplitude can provide valuable information about the integrity of the corticospinal tract and the excitability of the motor cortex and synapses at lower levels (1). A reduced amplitude suggests the presence of a central conduction failure. Accordingly, a patient with preserved MEPs contralateral to an acute stroke lesion is expected to have a better prognosis than a patient with absent MEPs. As mentioned previously, the relationship between the TMS stimulation intensity and the resulting MEP amplitude is described by a sigmoid stimulus-response curve (4). This curve is subject to shifts in the context of a variety of neurophysiologic

states characterized by altered excitability, e.g. the effects of drugs like lorazepam and lamotrigine on the central nervous system (CNS); as well as disorders where corticomotor conduction is abnormal, like in motor stroke and ALS (51).

Knowledge from various research into disease-associated abnormalities of specific TMS-measurements allows identification of signature findings in some of the pathological conditions when considering multiple measurments (1). As an illustrative example, consider how integration of the CMCT with MEP amplitude can potentially permit differentiation between groups of diseases based on their distinctive signature changes those measurements. Demyelinating diseases such as MS or cervical spondylitic myelopathy show significant increase in CMCT (46,48,52,53). Conversely, conditions involving loss of neurons or axons, such as ALS, tend to have only mild or no decrease in CMCT, but instead show characteristically decreased MEP amplitudes.

Also some non-motor related phenomena can be explored using TMS, and have medical relevance. As an example, occipital lobe stimulation with single-pulse TMS evokes phosphenes in many individuals. Analogously to the MT for the motor cortex, a threshold stimulus intensity can be determined for phosphene elicitation. These thresholds have found to be significantly lower in patients with migraine, implying increased excitability in the visual cortex (54,55).

1.1.3.2 Clinical applications

Apart from the expanding number of use cases of TMS for research purposes, there are several areas of clinical medicine that are advancing thanks to the introduction of this technology. Diagnostic and prognostic applications derive from the ability of TMS to uncover information about motor cortical excitability; functional integrity of intracortical structures; corticospinal, corticonuclear, and callosal nerve fiber functional integrity; as well as nerve root and peripheral nerve integrity (1). For treatment purposes, rTMS in particular has shown promise for being a practical aid in the remedy of a spectrum of ailments due to the persistence of clinical effects beyond the immediate application (56).

1.1.3.2.1 TMS as diagnostic and prognostic tool

TMS can assist in localization of nervous system lesions, distinguishing whether they are predominantly demyelinating or axonal in nature, and predict functional outcome after injuries (1). Certain diseases allow for early diagnosis by TMS, such as MS, Bell's palsy, psychogenic paresis, and plexus neuropathy. In others like stroke and cervical spondylosis, TMS is useful also in prognostic prediction.

In the field of neurosurgery, nTMS helps plan interventions in the preoperative period by localizing and assessing the function of specific brain areas (1,4). Compared to functional magnetic resonance imaging (fMRI), mapping using nTMS provides better temporal resolution, is more practical to use in a clinical setting, and is not subject to ambiguities resulting from neurovascular coupling variation (57). Presurgical mapping of the motor homunculus has been shown to decrease risk of inducing postoperative motor deficits by helping surgeons more easily navigate the cortex in cases of lesions, such as tumors, distorting brain architecture. For surgical treatment of epilepsy, nTMS may help in planning the procedure, and reduce the number of invasive electroencephalography (EEG) electrodes necessary for intraoperative navigation. Presurgical language mapping with rTMS may help to indicate awake surgery and guide intraoperative language mapping (58). High-frequency rTMS delivered to the dominant hemisphere can induce speech arrest and therefore help to localize speech-related areas of cortex (59). Intraoperatively TMS is being used to optimize surgical procedures by monitoring corticospinal tract function, thereby decreasing unwanted neurological sequelae due to iatrogenic injuries (1). TMS is also advantageous as a less painful and more focal alternative to TES in brainstem and spinal surgeries, or for interventions using spinal anesthesia.

1.1.3.2.2 TMS for therapy and rehabilitation

Much of the use of TMS for therapeutic purposes rests on the idea that pathologically altered levels of cortical activity can be normalized, and thus result in clinical improvement (1). Long-lasting effects of rTMS are seen following application to the motor cortex, as well as to other cortical areas including visual, prefrontal, and parietal lobes; and the cerebellum. Currently, the strongest evidence favoring rTMS use in therapeutic settings exists for depression and pain (56).

rTMS for the treatment of depression is probably the most thoroughly investigated therapeutic application (1). In patients with medication-resistant major depression, 3-6 weeks of daily high-frequency rTMS directed at the left dorsolateral prefrontal cortex (DLPFC) results in significant improvement (1,4,56). Supported by somewhat weaker evidence is the low-frequency stimulation of the right DLPFC for improvement of depression (1,56). Researchers are still investigating optimal stimulation intensity, duration, and focus of application for maximizing clinical improvement (4). The positive effects of rTMS on depression likely develop over the course of several weeks, and it is speculated that after an initial protocol of daily application, one treatment per week might suffice as maintenance therapy. Ongoing

investigations are also looking into whether rTMS may be beneficial as maintenance therapy following electroconvulsive therapy.

Chronic neuropathic and non-neuropathic pain can be treated with TMS (56). Application of high-frequency rTMS to the primary motor cortex contralateral to the pain shows definite pain relief (4). After 5 days of such stimulation, long-lasting pain relief was induced in patients with post-stroke pain, trigeminal neuropathy, and phantom limb pain. Further study of rTMS directed at DLPFC has been encouraged in context of neuropathic pain investigation, due to the known relationship between chronic pain and depression. In fibromyalgia patients, levels of pain and quality of life improved up to several months following repeated high-frequency rTMS sessions to the left DLPFC. In migraine patients, high-frequency rTMS of the left primary motor cortex (M1) has been shown to decrease frequency and intensity of migraine attacks. Low-frequency rTMS over the right secondary somatosensory cortex can relieve the visceral pain experienced by patients suffering from chronic pancreatitis.

Apart from depression and pain control, several other disorders can probably also be improved using the technology, albeit currently supported by less evidence (56). High-frequency rTMS of the left DLPFC has shown to improve the negative symptoms of schizophrenia. Low-frequency rTMS to the contralesional M1 seems to be beneficial in patients with chronic motor stroke. The same stimulus applied over the left temporoparietal cortex might result in clinical improvement for patients with tinnitus and auditory hallucinations. In patients with Parkinson disease, improved hand function has been demonstrated following high-frequency rTMS to the contralateral motor cortex (1). Tic frequency is reduced following low-frequency rTMS to the motor cortex in patients with tic disorder. Other small-sample studies have shown promising use of rTMS for intractable seizures, cortical myoclonus and Broca aphasia.

1.2 Vibration and related sensory stimuli in humans

1.2.1 Physiology and anatomy of vibration sensation

Vibration sensation is initiated by activation of Meissner (20-50 Hz) and Pacinian (60-400 Hz) corpuscles, located superficially in the dermal papillae, and deeper in the dermis, respectively (60,61). Pacinian corpuscles adapt more rapidly and have a lower response threshold relative to Meissner corpuscles, which in turn cause them to have a larger receptive field. The vibration threshold for any area of skin is correlated to the density of these cutaneous mechanoreceptors (62). Fingertips are the most sensitive part of the hand in response to

vibrational stimuli due to a large density of Pacinian corpuscles. Moreover, hairy skin is less sensitive to vibration compared to glabrous skin, as Pacinian corpuscles seem to be absent in these locations.

Afferent signaling is mediated by a chain of three successive neurons with myelinated Aβ-type axons (61). The first-order neurons are pseudounipolar neurons entering the spinal cord through the dorsal roots and ascending ipsilaterally in either the fasciculus gracilis (lower body) or the fasciculus cuneatus (upper body) of the dorsal columns. The synapse with the second-order neurons occurs in the nucleus gracilis or nucleus cuneatus of the caudal medulla. These fibers then decussate as the internal arcuate fibers and ascend contralaterally forming the medial lemniscus until synapsing in the ventral posterior lateral nucleus of the thalamus. The third-order neurons ascend in the internal capsule before synapsing in the somatosensory cortex.

1.2.2 Reflexes and interactions originating from peripheral stimulation

The well-known spinal stretch reflex is mediated by afferent Ia neurons and efferent motorneurons (61). A similar reflex — the Hoffmann reflex (H-reflex) — involves the same axons, but is elicited by electrical stimulation of the afferent nerve rather than by mechanical activation of muscle spindles, and can therefore be utilized in assessing modulation of monosynaptic reflex activity in the spinal cord, thus serving as a proxy for alpha motorneuron excitability (63).

When electrically stimulating a peripheral nerve, the resulting action potential travels both in the orthodromic and antidromic directions (64). The former elicits a CMAP, also known as an M response. The latter causes "backfiring" in a small number of motor neurons, which then generate another orthodromic wave termed the F wave. This manifests as late potentials of low amplitude.

Upon application of vibration to a muscle, a monosynaptic phasic reflex is elicited (65). If the stimulus continues, a tonic vibration reflex (TVR) is seen (66). This reflex causes tonic contraction in the vibrated muscle and relaxation of its antagonist muscles. The effect is initiated by muscle spindles. Münte *et al.* found that somatosensory evoked potentials (SEPs) recorded following peripheral long-lasting vibration consisted of two components: one phasic, lateralized component during the first 100 ms; and a later negativity in a symmetrically distributed pattern beginning around 400 ms (67).

1.3 The motor system and descending pathways

Activation of skeletal muscles in humans is made voluntary by their connection to the cerebral cortex via upper- and lower motor neurons (UMNs and LMNs, respectively) (68). For this discussion, the lateral corticospinal tract is of particular interest. This descending motor pathway has its cell bodies located partly in the primary motor cortex, but also receives significant contributions from cell bodies located in the premotor- and supplementary motor cortex, as well as the primary sensory areas of the parietal cortex. These UMNs descend through the corona radiata and converge in the posterior limb of the internal capsule. After traveling through the cerebral peduncles and basal pons, the fibers thicken in the pyramids on the anterior medulla. Most of the fibers the decussate in the caudal medulla, and continue through the lateral column of the spinal cord which finally directs the UMNs to their destination synapses with the LMNs in the anterior horn. The LMNs form the peripheral nerves that innervate distal muscles.

1.4 Peripheral stimulation and TMS in combination

Since afferent signals from peripheral nerves are routed to the central nervous system (CNS), and TMS has the ability to interfere with CNS activity, a lot can be learned about the function of the nervous system in physiological and pathological states by measuring how certain parameters are affected by the interaction of peripheral stimulation by various modalities with central stimulation by TMS at different temporal intervals.

1.4.1 Cortical facilitation and inhibition

Paired-pulse TMS has enabled the study of complex facilitatory and inhibitory interactions within the cerebral cortex (4). By varying the strength of the conditioning and test stimuli as well as the ISI duration, several of these mechanisms have been discovered, but gaining a complete understanding of the interactions is still an area of active research. They involve a system of interconnected afferent and efferent neurons, modulated by inhibitory and facilitatory interneurons. Facilitation seems to often be mediated by glutamate or norepinephrine, while inhibition is generally mediated by GABA, although variations have been observed (Table 2).

Table 2. Overview of circuits involved in cortical facilitation and inhibition

	SICI[a]	LICI[b]	SICF[c]	ICF[d]	SIHI[e]	LIHI[f]	SAI[g]	LAI[h]	CBI[i]
Conditioning stimulus	Sub[j]	Supra[k]	Supra	Sub	Supra contra M1	Supra contra M1	Median n. ES[l]	Median n. ES	Sub contra cerebellum
Test stimulus to M1	Supra	Supra	Sub / threshold	Supra	Supra	Supra	Supra	Supra	Supra
ISI[m] (ms)	1-6	50-200	1.0-1.5, 2.3-3.0, 4.1-5.0	8-30	8-12	40-50	20-25	200	5-8
Proposed neurotransmitter/receptor	$GABA_A$, DA	$GABA_B$	GLU, $GABA_A$	GLU NE	Unknown	$GABA_B$	ACh, $GABA_A$	Unknown	Unknown

[a] short-interval intracortical inhibition; [b] long-interval intracortical inhibition; [c] short-interval intracortical facilitation; [d] intra-cortical facilitation; [e] short-latency interhemispheric inhibition; [f] long-latency interhemispheric inhibition; [g] short-latency afferent inhibition; [h] long-latency afferent inhibition; [i] cerebellar inhibition; [j] sub-threshold TMS; [k] supra-threshold TMS; [l] electric stimulation; [m] inter-stimulus interval

Of special note here are short-latency afferent inhibition (SAI), long-latency afferent inhibition (LAI), and afferent facilitation (AF), in which peripheral afferent stimulation with electrical stimuli serves as the conditioning stimulus (4,69). These inhibitory and facilitatory processes reflect sensorimotor integration at the cortical level.

1.4.2 Effects of peripheral stimulation on TMS-induced parameters

Much of the research involving peripheral stimulation combined with TMS has made use of the MEPs that can be recorded by EMG from distal muscles (70). A typical protocol includes some controlled manner of inducing afferent stimulation, followed by TMS stimulation to the motor cortex at a tightly controlled temporal delay, which in turn gives rise to MEPs in the distal somatotopically corresponding muscle. The methods that have been used to initiate afferent volleys include direct cutaneous electrical stimulation of the peripheral nerve (71,72); mechanical vibration of muscle tendons or muscle bellies (65,73-76); cutaneous vibration at locations distant to muscles, primarily fingers; (77-79) and voluntary activity such as muscle contraction (65).

Mechanical vibration applied to the *abductor digiti minimi* muscle (ADM) just before stimulation of the corresponding motor cortex with single-pulse TMS was shown by Claus *et al.* to affect the compound muscle action potential (CMAP) recorded from that muscle, depending on the duration and frequency of vibration and the temporal delay between onset of vibration and the TMS stimulus (65). Following a 170 Hz vibration stimulus of 100 ms duration, an enhanced muscle response to TMS was seen at ISIs of 9, 10, and 14 ms compared to resting conditions. This enhancement was absent at the 11 ms ISI. CMAP delay remained unchanged. In a different protocol using long-lasting vibration at 120 Hz of 6000 ms duration, they found

enhanced muscle responses for multiple ISIs in the interval 120-5000 ms, as well as shortened CMAP latencies.

Komori *et al.* found similarly increased MEP responses in the thenar muscles when TMS stimulation was delivered 50 to 80 ms after the onset of electrical stimulation of the median nerve at the wrist, or the recurrent thenar motor branch; whereas no change was observed when the electrical stimulation was applied to the digital nerves (77).

Using vibration at 80 Hz for a duration of 1500 ms, Rosenkranz *et al.* demonstrated increased MEP amplitude in each of three vibrated intrinsic hand muscles when a TMS stimulus was delivered 1000 ms following the onset of vibration (75). The non-vibrated muscles had depressed MEPs in the same trials.

When one minute of 80 Hz vibration was applied to the thenar eminence in hemiparetic subjects, De Andrade Melo *et al.* recorded MEP amplitude levels comparable to those of healthy subjects (80). This vibration also increased the maximal rate of force production in both the hemiparetic subjects and the healthy controls.

1.4.3 Location and mechanism of the interactions between peripheral stimulation and TMS

In studying effects of muscle vibration on MEPs, Kossev *et al.* showed that using TES for cortical stimulation did not alter MEP amplitude, area, and latency under conditions where TMS did result in such changes (73). They suggested that the interaction between TMS and vibration takes place upstream from where TES effects are exerted, i.e. above the proximal segments of the pyramidal axons in the cerebral cortex. Macefield *et al.* suggested that changes in cortical excitability is due to changes in synaptic transmission at the cuneate nucleus and thalamo-cortical levels (81). Schürmann *et al.* also demonstrated an enhancement of the P25 component of the SEP when TMS was delivered concurrent with electrical stimulation of the right median nerve at the wrist (82). The existence of local interaction between the SEP activity and the TMS-evoked activity at the cortical level was one interpretation offered by the authors.

Rosenkrantz *et al.* has also shown a cortical interaction by providing evidence that intrinsic hand muscle vibration caused a decrease in SICI for that muscle, while increasing SICI for the non-vibrated neighbouring muscles (75). The opposite was seen for LICI, which increased in the vibrated muscle and decreased in the non-vibrated muscles. No alterations in ICF were seen in that study. Effects on the aforementioned intracortical parameters from cutaneous stimulation of the index finger could not be demonstrated consistently.

After vibrating the flexor carpi radialis (FCR) muscle at 80 Hz for 60 min, Forner-Cordero *et al.* recorded significantly increased MEP amplitude, motor output area, and map volume for the ECR muscle upon TMS application (76). They suggest that the antagonist vibratory response (AVR), which is of cortical origin, is responsible for this effect through a delayed facilitatory influence on the muscles antagonistic to the vibration-activated Ia afferents.

Tarlaci *et al.* demonstrated interactions between afferent vibratory stimuli and TMS at both spinal and cortical levels, and that these are subject to progressive alterations in the wake of acute stroke (79).

Modulation of Ia afferent input by prolonged vibration was shown by Lapole *et al.* to result in changes in motor cortical excitability (83). The same author later demonstrated increased sensorimotor integration at the cortical level, manifested by a combination of decreased SAI and LAI, and increased AF (69). The latter findings were not universal among test subjects however, suggesting that other factors also play a role.

ISI duration is important in determining the particular inhibition or facilitation mechanism that is enacted (4). Maximal inhibition in the SAI protocol occurs at an ISI of N20 plus 2 ms, which translates to 20-22 ms in the context of median nerve electrical stimulation at the wrist, and 25 ms for digit stimulation. To elicit LAI, the ISI between median nerve stimulation and TMS application needs to be about 200 ms. For ISIs in between those for SAI and LAI, motor cortical excitability can be seen to increase (69). This could be due to facilitation, or disinhibition.

1.4.4 The role of vibration frequency and duration

When applying vibration to the *extensor carpi radialis* muscle (ECR), Siggelkow *et al.* found increased MEPs and decreased MEP latencies in the same muscle following TMS when the vibration frequency (VF) was 80 Hz or 120 Hz (74). A simultaneous depression of MEPs in the antagonist muscle, *flexor carpi radialis* (FCR), was seen at all VFs tested. This phenomenon of opposite effect of vibration in the antagonist muscle was not observed for MEP latency, which shortened in both the ECR and FCR at VFs of 80 Hz and 120 Hz.

Krbot *et al.* found that a VF of 128 Hz with duration less than 300 ms was most useful in producing SEPs among the frequencies they examined, which ranged from 30 Hz to 256 Hz (84).

In a study by Smith *et al.* investigating the effect of prolonged muscle vibration on cortical excitability, an increase in MEP size and an enlarged cortical area of excitability resulted from 15 min vibration of the ECRL muscle, but not 30 min (85). This effect lasted 5

min after the end of vibration. Interestingly, vibration beyond 15 min duration entailed highly variable MEP modulation. Lapole *et al.* examined the H-reflex, F-waves, and MEP amplitudes in the tibialis anterior (TA) and soleus (SOL) muscles following 1 hour of 50 Hz vibration to the achilles tendon (83). H-reflex amplitude was reduced for the SOL muscle, but not the TA. Both muscles showed an increased MEP amplitude 1 hour after, but not immediately following, the end of vibration. No significant F-wave changes were observed.

The reponse to different VFs is also affected by pathological changes in tissues (79). Tarlaci *et al.* demonstrated that both low (30 Hz) and high (130 Hz) frequency peripheral vibration shortens MEP latency in normal subjects, but in patients having recently suffered acute stroke, the latency reduction was only seen for low frequency vibration. The MEP amplitude was also enhanced in the early stages of stroke, but normalized over the course of four to eight weeks.

2. OBJECTIVES

2.1 Aim

Much effort has previously been put towards investigating motor cortical excitability by applying peripheral afferent stimuli in the form of electrical stimulation to the nerves or vibration of the hand muscles. Therefore, the aim of the present study was to investigate cortical motor excitability in the presence of peripheral vibratory input to the hand digit.

2.2 Hypothesis

1. Afferent sensory stimulation in the form of peripheral vibration will lead to changes in the amplitude of MEPs.

2. Alterations in MEP amplitude will be dependent upon the specific ISI separating the conditioning stimulus (peripheral vibration) and the test stimulus (TMS to the motor cortex).

3. SUBJECTS AND METHODS

3.1 Subjects

11 healthy volunteer subjects were recruited (5 females and 6 males; age 40.18 ± 11.92 years; height 178 ± 7.1 cm; body mass 71.9 ± 12.6 kg; BMI 22.6 ± 3.2 kg/m^2), all of whom showed right-dominant handedness on the Edinburgh handedness inventory (86). None had any contraindications to TMS (87). Subjects were asked to abstain from ingestion of nicotine, alcohol, and caffeine-containing products; as well as not engage in strenuous physical activity for twelve hours prior to the experimental sessions.

Written informed consent were obtained from all subjects prior to participation. All procedures performed in the study were approved by the ethics committee at the University of Split School of Medicine.

3.2 MRI and nTMS

Head MRI in accordance with TMS requirements was performed for each subject at the Department of Diagnostic and Interventional Radiology (Clinical Hospital Split, Croatia) using a 1.5 T field strength Siemens Magnetom Avanto. The resulting images were integrated with a Nexstim NBS System 4 nTMS module to provide 3D reconstructions of the subjects' brains. A stereotactic navigation camera allows for computerized coordination of relative physical positioning of a subject's head and the TMS coil by attachment of several optical navigation markers on both objects. This setup allows for accurate positional calibration of the nTMS system to the individual MRI images.

The TMS coil used was of the figure-8 type with inner and outer winding diameters of 50 mm and 70 mm, respectively. The maximal electrical field according to the specification for the device is 172 V/m below the coil.

During the experiments, TMS pulses were triggered externally by a script that coordinated the delays between vibratory stimuli and TMS. The NBS system recorded coil orientation, location, and induced electric field for each pulse delivered.

3.3 Digit vibration

The device used to generate vibratory sensation was a Tactor (Dancer Design, St. Helens WA10 1LX, UK) which consists of an electromagnetic solenoid that repeatedly drives the tip of a nylon probe into contact with the underlying skin at a frequency proportional to the voltage delivered. The tactor measures 18 mm diameter, 12 mm height, with a mass of 5.4 grams. Using adhesive tape, the tactor was attached to the volar tip of the index finger (Figure 2). The tactor

was triggered by a custom made vibration stimulator prototype device, which in turned was controlled by a computer script for purposes of time coordination with TMS pulses (Figure 2). Vibration frequency was 120 Hz and lasted 500 ms for each trial.

3.4 MEP recording

A pair of self-adhesive surface EMG electrodes (Ambu Blue Sensor) in a belly-tendon montage were applied to the abraded and cleaned skin over the right *abductor pollicis brevis* muscle (APB) (Figure 2). These were connected using Nexstim EMG electrode cables to a 6-channel EMG and one common ground EMG amplifier with TMS-artefact rejection circuitry. The EMG module automatically calculated and recorded all MEP amplitudes and latencies during the experiments.

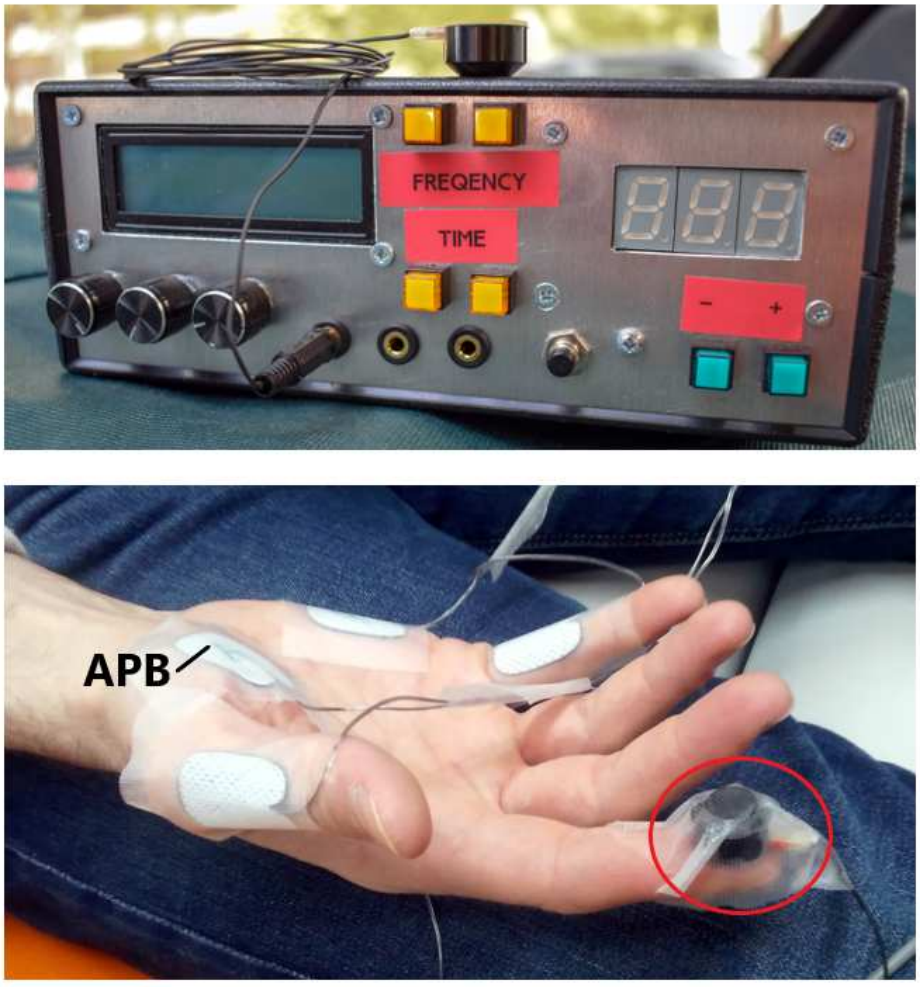

Figure 2. Upper: vibration controller; Lower: Vibrotactile stimulator (circled) and the EMG electrodes in the configuration used.
Source: Laboratory for Human and Experimental Neurophysiology, School of Medicine, Split.

3.5 Experimental protocol

Subjects participated in two experimental sessions where TMS was applied to the M1 area for hand muscle representation following peripheral vibration with a solenoid-type vibrotactile stimulator.

Before each session, the RMT was determined for every subject as the minimal TMS stimulus strength required to elicit at least 5 MEPs of 50 μV or more out of 10 trials (4). Mapping over the left M1 for APB was determined by the "omega knob" on axial MRI images or "hook structure" on sagittal MRI images (88). The central sulcus was also used as a landmark while moving the TMS coil tangentially to the central sulcus in the anterioposterior direction in order to find the M1 hot spot for APB (Figure 3).

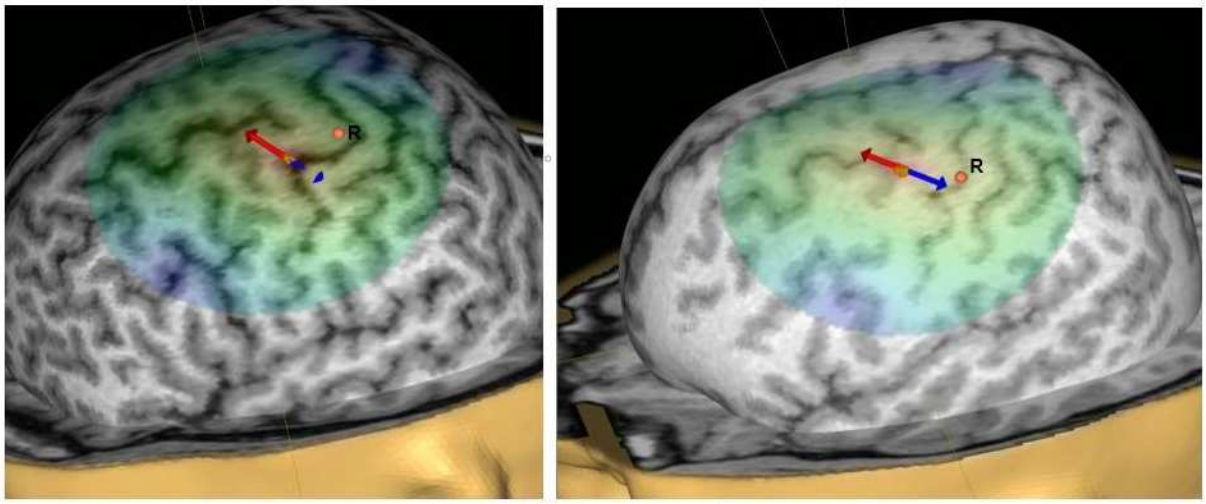

Figure 3. MRI navigation in one subject showing position of the stimulating points over the M1 for the APB muscle representation (88).
Source: Laboratory for Human and Experimental Neurophysiology, School of Medicine, Split.

The ISIs between the conditioning stimulus (digit vibration) and the test stimulus (TMS to the M1) were varied throughout each respective experimental session, and given in random order. For the first experimental session, hereby referred to as the short-interval session, the ISIs were 5, 6, 7, 8, 9, 10, 11, 12, and 14 ms; while in the second experimental session, hereby referred to as the long-interval session, they were 18, 20, 25, 30, 40, 50, 100, 200, 300 400, and 500 ms. For each subject, the two experimental sessions were separated by minimum 2 days. A control condition was established at the beginning each experimental session, and consisted of TMS stimulation of the M1 without any peripheral vibration input. During the experiments,

subjects were instructed to close their eyes and relax while reclining in a comfortable position with shoulder, elbow, and wrist joint angles at 25, 120, and 180 degrees, respectively.

TMS pulses were delivered to the M1 APB hotspot at 120% of maximal stimulator output during the experimental sessions. Each ISI in the two sessions had 10 trials, separated by an inter-trial interval of 5.5 s. All such trials for a given ISI will from here on be referred to as a session block. A schematic representation of the experimental workflow is shown in Figure 4.

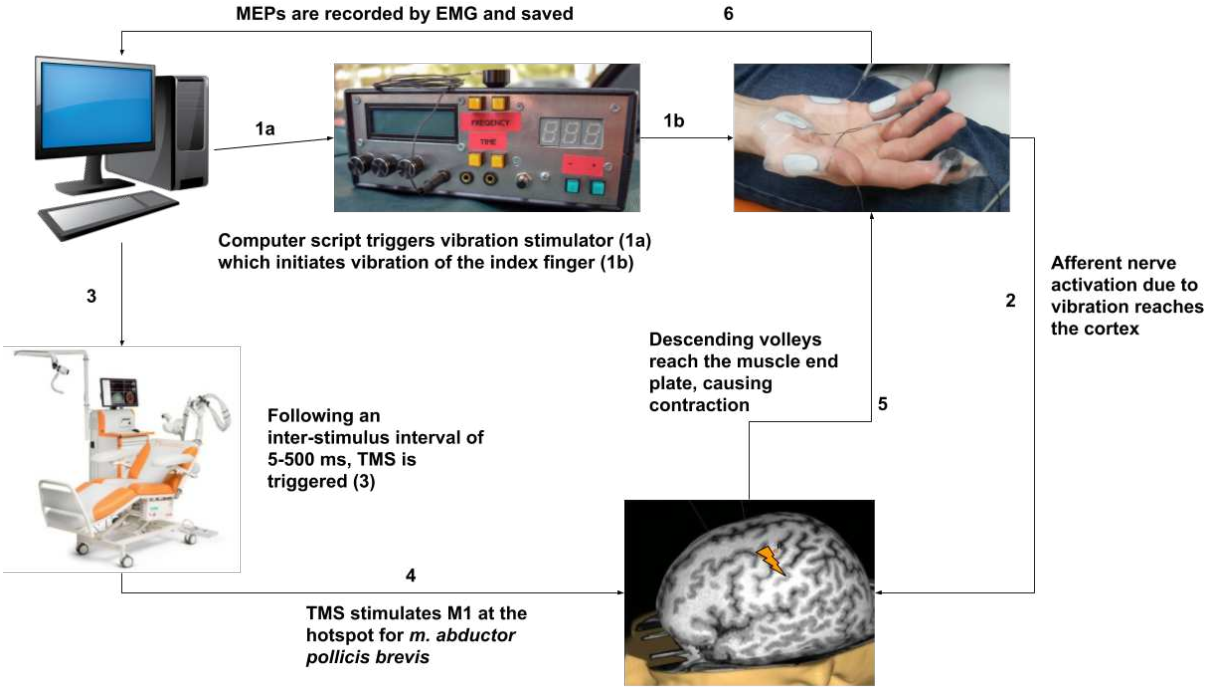

Figure 4. Experimental protocol.
Source of component images: Laboratory for Human and Experimental Neurophysiology, School of Medicine, Split; and Nexstim company.

3.6 Data recording and statistical analysis

The experimental recordings of MEP latencies and amplitudes for each trial were processed by a custom MATLAB script for digital filtering and graphic representation of MEP responses. Statistical tests were conducted using Statistica 12 (StatSoft, Inc., Tulsa, USA), and visualized using the ‘matplotlib' package in the Python programming environment (89).

A z-sample test was performed for MEP amplitudes and latencies to exclude possible inter-individual differences (± 1.96 SD). MEP responses whose calculated z-scores placed them greater than 2 standard deviations from the mean were excluded from further analysis. These outliers constituted 2.5% of the raw data points from all trials. Normal distribution of the data

was confirmed by Kolmogorov-Smirnov and Shapiro Wilk tests. No violation of sphericity was detected by the Mauchly sphericity test.

Based on the preceding assumptions, repeated-measures analysis of variance (rANOVA) was performed to test whether peripheral vibration preceding TMS by various time intervals had a significant influence on MEP responses. The values recorded in the initial test during sessions served as control. When a significant relationship was proven with rANOVA, the Dunnett test of multiple comparisons was used *post-hoc* to pinpoint the ISIs that chiefly contributed to the effect using $P<0.05$ as the cut-off for significance.

4. RESULTS

MEP responses were not significantly different (did not exceed ± 1.96 SD) between subjects while using RMT 100% intensity. The RMT values determined from mapping the APB location in M1 did not differ significantly between subjects at 100% or 120% intensity (95% CI). Table 3 shows average RMTs at 100% and 120% intensity for both the short-interval and long-interval experiment, as well as the average MEP amplitudes and latencies recorded under those conditions (Table 3).

Table 3. Parameters measured at baseline conditions

Parameter	Short-interval sessions (N=11)	Long-interval sessions (N=11)
RMT[a] 100%	34.82±5.02	35.18±4.92
RMT 120%	41.45±6.02	41.82±5.91
MEP[b] amplitude (μV)	114.94±28.03	167.15±65.44
MEP latency (ms)	23.28±2.53	23.83±1.95

Data given as mean±standard deviation.
[a] Resting motor threshold (equals MT)
[b] Motor evoked potential

Descriptive statistical summaries of MEP latency and amplitude recordings from the short-interval and long-interval experiments are presented below (Table 4 and Table 5, respectively). Table 6 shows rANOVA findings from both sessions (Table 6).

Table 4. Short-interval session results

Session block	MEP latency (ms)	MEP amplitude (μV)
Control	24.41±1.40	470.31±152.48
5 ms	24.65±1.37	337.04±186.54
6 ms	24.68±1.39	376.38±200.91
7 ms	24.65±1.56	430.01±285.41
8 ms	24.82±1.57	412.03±221.58
9 ms	24.89±1.65	418.71±218.42
10 ms	24.56±1.29	483.96±221.50
11 ms	24.67±1.68	508.61±283.48
12 ms	24.59±1.48	535.76±230.48
14 ms	24.72±1.62	434.16±250.38

Data is presented as mean±standard deviation.

Table 5. Long-interval session results

Session block	MEP latency (ms)	MEP amplitude (μV)
Control	24.76±2.01	429.84±131.69
18 ms	24.47±1.80	422.45±154.57
20 ms	24.74±1.88	483.70±281.59
25 ms	24.63±1.93	409.13±100.09
30 ms	24.78±1.87	392.04±115.35
40 ms	24.98±1.87	315.32±156.86
50 ms	24.87±1.66	398.26±227.56
100 ms	25.02±1.79	279.23±178.19
200 ms	25.26±1.95	211.45±130.29
300 ms	25.23±1.86	256.91±121.72
400 ms	25.04±1.86	261.51±84.02
500 ms	25.04±1.84	293.36±149.40

Data is presented as mean±standard deviation.

Table 6. Analysis of variance in both short- and long-interval sessions

Session	Factor	Measurement	d.f.[a]	*F**	*P**	Dunnett *post hoc* test
Short	Session block: Control, 5, 6, 7, 8, 9, 10, 11, 12, 14 (ms)	MEP latency	9	1.039	0.415	*P*>0.05
		MEP amplitude	9	2.145	0.038	*P*>0.05
Long	Session block: Control, 18, 20, 25, 30, 40, 50, 100, 200, 300, 400, 500 (ms)	MEP latency	11	3.375	<0.001	*P*>0.05
		MEP amplitude	11	4.678	<0.001	Control vs 200 ms: *P*=0.001 Control vs 300 ms: *P*=0.023 Control vs 400 ms: *P*=0.029

* Repeated-measures ANOVA
[a] Degrees of freedom

4.1 Effects of digit vibration on MEP latency

MEP latencies were not significantly different across the ISIs in the short-interval experiment when compared to the control condition using ANOVA (F=1.039, P=0.415) (Figure 5).

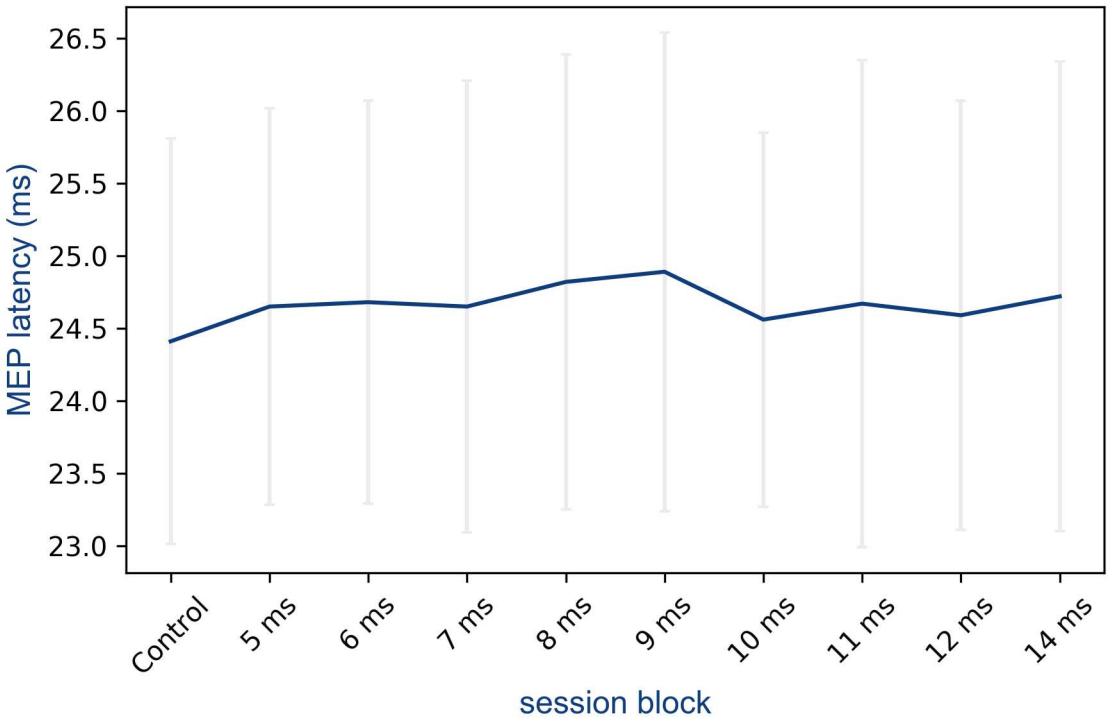

Figure 5. Mean MEP latencies in short-interval sessions.
Data presented as mean with standard deviation.

In the long-interval experiment, significant prolongation of MEP latency was detected (F=3.375, P<0.001). However, *post-hoc* testing did not reveal any ISIs with significantly different MEP latency compared to the control condition (Figure 6).

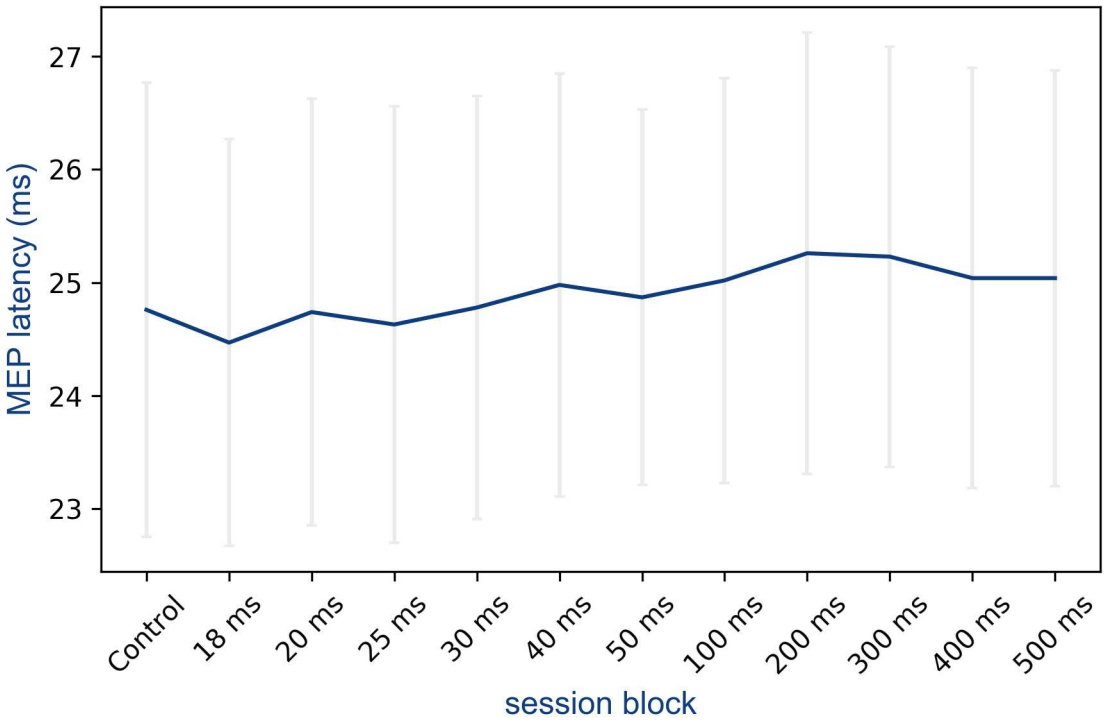

Figure 6. Mean MEP latencies in long-interval sessions.
Data presented as mean with standard deviation.

4.2 Effects of digit vibration on MEP amplitude

Analysis of variance revealed significant effects for MEP amplitude in both the short-interval and long-interval experiments (respectively, F=2.145, P=0.038; and F=4.678, P<0.001).

The short-interval experiment did not have any significant ISIs revealed by *post-hoc* testing (Figure 7).

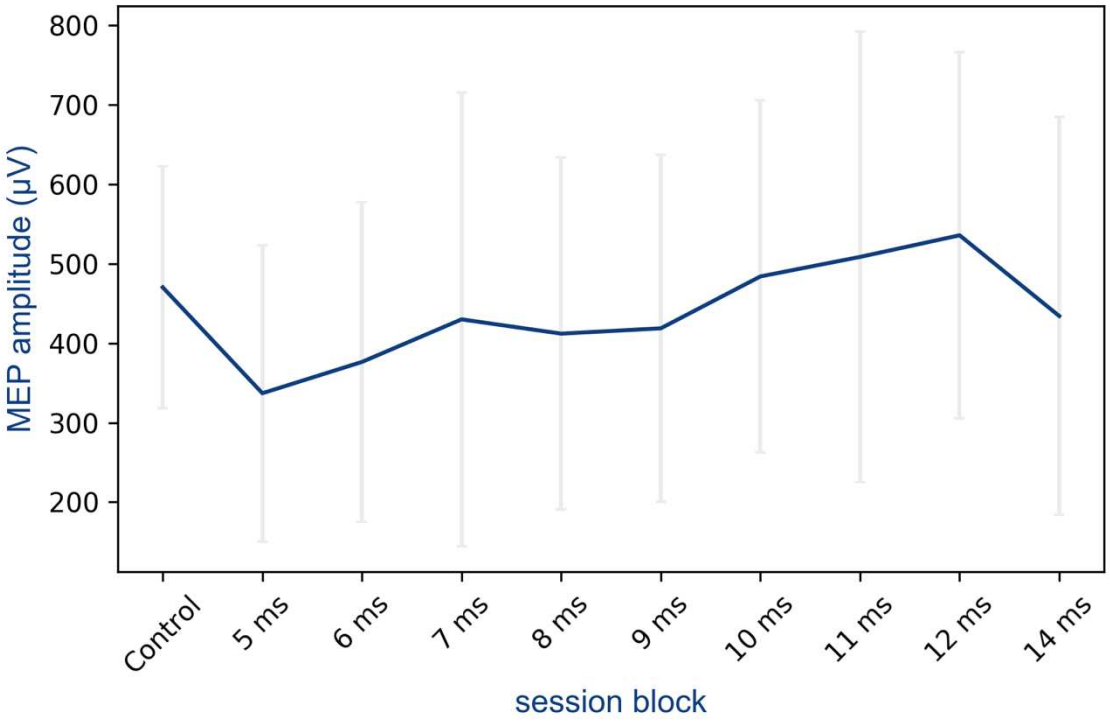

Figure 7. Mean MEP amplitudes in short-interval sessions.
Data presented as mean with standard deviation.

Significant decrease of MEP amplitudes in the long-interval experiment was confirmed by the Dunnett *post-hoc* test to occur at ISIs of 200 ms, 300 ms, and 400 ms compared to the control condition (Figure 8).

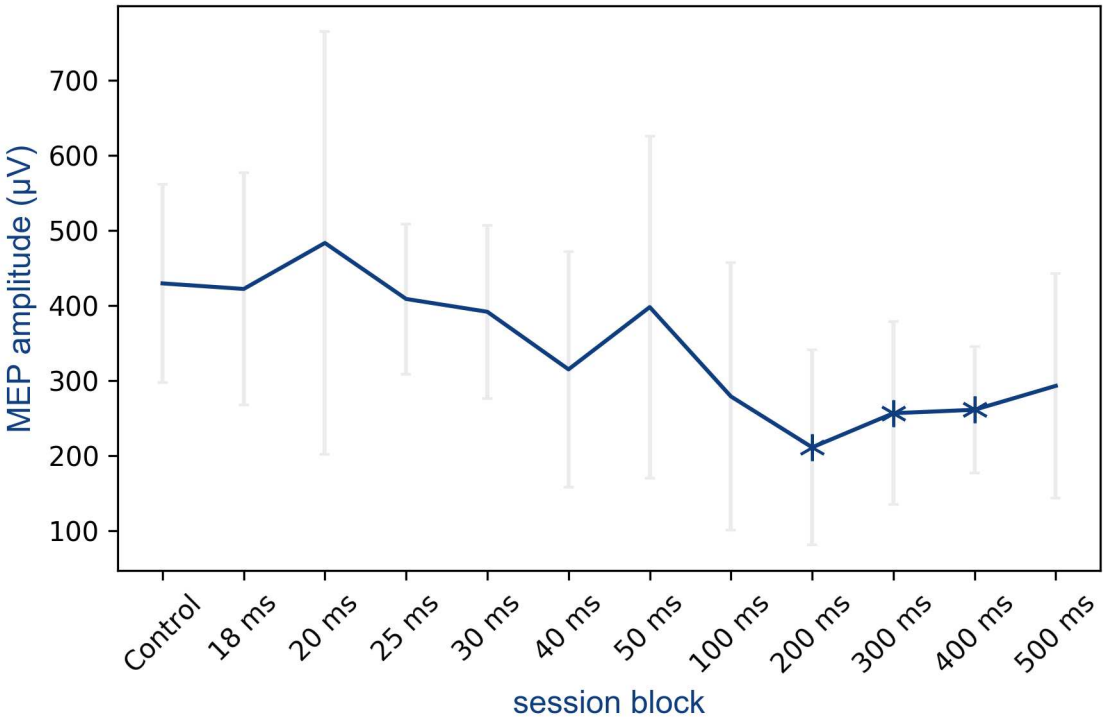

Figure 8. Mean MEP amplitudes in long-interval sessions.
Data presented as mean with standard deviation.
* Dunnett *post-hoc* test significance with *P*=0.001 (200 ms vs control); *P*=0.023 (300 ms vs control); *P*=0.029 (400 ms vs control)

5. DISCUSSION

In the present study we were interested in how afferent volleys interact with the motor cortex. This investigation measured MEPs elicited with TMS at various delay intervals following high frequency vibration of the index finger. It was found that MEP amplitude was significantly decreased when the vibration preceded TMS by ISIs of 200-400 ms.

Sensorimotor integration is known to take place at different levels along the brain-peripheral receptor axis, including in the spinal cord and both cortical and subcortical areas of the brain (90). Paired-pulse TMS protocols allow the application of conditioning stimulation of cutaneous nerves and muscle afferents at the peripheral end of this axis, which can have both facilitatory or suppressive effect on subsequent MEPs. In protocols measuring intracortical inhibition and facilitation by having both the conditioning stimulus and the test stimulus be applied in the form of TMS to the cortex, an important methodological step is to determine the proper intensity of the conditioning stimulus and proper magnitude of the ISI (91-94). Therefore, we know more about suppressive and facilitatory effects on MEPs in those paired pulse protocol measuring intracortical inhibition and facilitation compared to paired pulse protocols using different modalities. One common way of applying such peripheral conditioning has been through electrical stimulation of the median or digital cutaneous nerves, which results in suppressed MEPs for ISIs of 19–50 ms (SAI) and for ISIs of 200-1000 ms (LAI) (70). Less has been described about the phenomena occuring in the context of vibration as the peripheral conditioning modality. Previous work has highlighted that facilitation (not suppression) of MEPs result when vibration is applied to muscle, suggesting that the specific type and location of receptors activated by vibration is of importance for the resulting effect of afferent signaling on sensorimotor integration (65,73,75,80,83). It is known that peripheral vibration can generate SEPs in the somato-motor areas of the cortex, and that they occur around 200-400 ms following the initial stimulation, which lends support to the idea that peripheral vibration might indeed have some cortical effect (84,95).

The present investigation also employed a type of vibrotactile device that uses a solenoid mechanism to induce sensory input to the finger. In addition to the vibration effect generated, it is possible that the various skin receptors have a somewhat different manner of activation as a result of the repeated direct contact that the nylon rod makes with the cutaneous surface of the digit, and that such an effect is wholly or partly additional to, and separate from that of more conventional vibration. This is an interesting thought when considering that the results here were more similar to Tamburin 2001 which also found MEP inhibition of similar magnitude following conditioning stimuli to the fingers, but using electric modality instead of vibration

(78). At this point it is difficult to make any conclusions from the comparative MEP changes caused by different conditioning modalities like vibration versus electric stimulation.

Strengths of this investigation include the high number of pooled trials resulting from a decent number of subjects participating in the experiments; and the fact that ISIs spanning a wide range were tested against the control condition. One possible point to be raised is whether it would have been better to combine the short- and long interval experiments (ISIs) into one session for each participant to control for inter-day variations, but it could be argued that in such a setting the procedure would take up too much time and make the test subjects uncomfortable. Furthermore, although subjects were asked about use of the three most common drugs (caffeine, nicotine and alcohol) and vigorous physical activity on the day of the experiments, the screening could possibly have been extended to include a wider questionnaire able to detect partcipiants at risk for having altered cortical excitability stemming from influence of other relatively common pharmacological agents or states known to affect such parameters (96-100).

Peripheral application of vibratory stimulation can have clinical implications for the treatment of various pathological conditions. In cases of insults to regions associated with UMNs such as spastic conditions, cerebral palsy, or stroke, the modulatory effects that peripheral vibration has on central cortical excitability can be beneficial for level of functioning and healing in patients, and has been recommended as part of a rehabilitation regime along side other treatment modalities (101,102). Any such beneficial clinical effects must be balanced against potential negative implications of peripheral vibration, since it is known that too much stimulation may have detrimental effects over time, such as causing a progressively dysfunctional thermal sensation (103). The use of TMS protocols like the paired-pulse technique ultimately helps us test the effects of peripheral vibration input on motor cortical excitability.

6. CONCLUSIONS

1. In a conditioning-test paradigm, peripheral vibration applied to the index finger at various random ISIs in the range 5-500 ms before TMS to M1 had an effect on resulting MEP amplitude.

2. The effect of peripheral vibration on MEP amplitude was dependent on the ISI, and was found to be suppressive at long ISIs of 200, 300, and 400 ms.

These findings of suppression at long ISIs are consistent with cortical excitability alterations suggested to be due to result of arrival of the antidromic sensory volley to the motor cortices.

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8. SUMMARY

Objectives: Much effort has previously been put towards investigating motor cortical excitability by applying peripheral afferent stimuli in the form of electrical stimulation to the nerves or vibration of the hand muscles. The aim of the present study was to investigate cortical motor excitability in the context of peripheral cutaneous vibration input to the finger.

Materials and methods: 11 healthy subjects underwent a conditioning-test (CT) protocol with peripheral vibration of the index finger serving as conditioning, and TMS to M1 serving as test stimulus. Vibration and TMS were separated by randomized inter-stimulus intervals (ISIs) in the range 5-500 ms. Resulting motor evoked potentials (MEPs) were recorded with EMG from the abductor pollicis brevis (APB) muscle, and statistical analysis was performed for its amplitude and latency.

Results: Statistically significant suppression of MEP amplitudes in the upper extremity muscle were proven for the ISIs 200, 300, and 400 ms.

Conclusion: These findings of suppression of the MEP response at long ISIs are consistent with cortical excitability alterations suggested to result from sensorimotor integration processes following arrival of the afferent sensory volley to the motor cortices.

9. CROATIAN SUMMARY

Naslov: Utjecaj periferne elektromagnetske vibracije na motoričku podražljivost kore mozga: navigacijska transkranijalna magnetska stimulacija

Ciljevi: Dosadašnja istraživanja su bila usmjerena na ispitivanje podražljivosti motoričke kore mozga tijekom apliciranja aferentne električne stimulacije živca ili podraživanjem mišića perkutano. Cilj naše studije je bio istražiti podražljivost motoričke kore vibracijskom stimulacijom prsta.

Materijali i metode: 11 zdravih ispitanika sudjelovalo je u protokolu u kojemu periferni stimulus (vibracija elektromagnetskog tipa na vrh prsta) prethodi magnetskoj stimulaciji motoričke kore mozga. Interstimulus interval između vibracijske i magnetske stimulacije bio je između 5-500 milisekundi. Motorički evocirani potencijali (MEP) su snimani površinskim elektrodama postavljenim na abductor pollicis brevis mišić ruke. Provedena je statistička analiza u kojoj se evaluirala latencija i amplitude MEP odgovora.

Rezultati: Statistička analiza je pokazala značajno smanjenje amplitude MEP odgovora na interstimulus intervalima od 200, 300 i 400 ms.

Zaključak: Supresivni učinak MEP odgovora pronađen na specifičnim interstimulus intervalima ide u prilog objašnjenju da je došlo do promjena u podražljivosti kore mozga koje vrlo vjerojatno postoje zbog procesa somatosenzorne integracije koji se događa nakon dolaska afferentnog signala prema motoričkoj kori mozga.

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