THE EFFECTS OF MOTOR IMAGERY AND PAIRED ASSOCIATIVE STIMULATION ON CORTICAL EXCITABILITY

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ABSTRACT

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The plasticity of the brain is an increasingly important topic for physical therapists interested in (re)learning and repair following injury. A number of potential endogenous and exogenous protocols have been developed with the improved understanding of the mechanisms of synaptic plasticity. The purpose of this study was twofold: First, the effect of motor imagery of plantarflexion on motor cortex excitability was investigated since it has been shown that motor imagery may result in the same types of plastic changes in the motor system as actual physical practise. The second aim was to study the effect of facilitatory paired associative stimulation (PAS) on motor imagery. PAS is an exogenous protocol which has been used to induce bidirectional changes in the motor cortex excitability. Transcranial megnetic stimulation was used to measure changes in the motor evoked potentials (MEPs) of the soleus muscle with, and without, motor imagery and before, immediately after, and 15 min after the PAS intervention. During motor imagery of plantar flexion, a remarkable increases in the amplitude of the MEP of the soleus were observed with each time points 76 ± 62 %; 30 ± 33 % and 31 ± 50 %, respectively. The lack of background EMG assured that changes weren't associated with muscle activity. Interestingly, instead of facilitatory PAS, the protocol induced a remarkable inhibitory PAS. Inhibition was bigger with the motor imagery condition (38 ± 19 % and 31 ± 28 %) compared to the passive condition (16 ± 26 % and 5 ± 37 %), suggesting that the effect of PAS was more substantial during motor imagery. It can be concluded that the use of motor imagery in neurological rehabilitation may be defended on the basis of these results.

KEYWORDS: plasticity, paired associative stimulation, motor imagery, neurorehabilitation

INDEX

ABBREVIATIONS

ANOVA	analysis of variance
EMG	electromyography
EPSP	excitatory post-synaptic potential
fMRI	functional magnetic resonance imaging
ISI	interstimulus intervall
LTD	long-term depression
LTP	long-term potentiation
MEP	motor evoked potential
MVC	maximal voluntary contraction
PAS	paired associative stimulation
RMS	root-mean-square
SEP	somatosensory-evoked potential
SD	standard deviation
SOL	soleus
TA	tibialis anterior
TMS	transcranial magnetic stimulation

Chemistry abbreviations:

Ag	silver
AMPA	α-amino-5-hydroxy-3-methyl-4-isoxazole propionic
C	carboxyl
CaM	calmodulin
Ca++	calcium ion
Cl	chloride
Glu	glutamate
K+	potassium ion
Mg++	magnesium ion
N	amino
Na+	natrium ion
NMDA	N-methyl-D-aspar

1 INTRODUCTION

There are many neuromodulatory protocols developed to induce plasticity which facilitates motor learning and thus promotes recovery. Earlier studies (Pascular-Leone et al. 1994) have demonstrated an association between motor learning and increased corticomotor excitability and guided to exogenous modulation of motor cortex excitability during rehabilitation. A new and promising protocol is the paired associative stimulation (PAS) technique which combines peripheral electrical nerve stimulation with cortical transcranial magnetic stimulation (TMS). PAS is based on Hebb's law of coincident summation which means that paired peripheral and cortical stimulation synchronously activate common neurons within the motor cortex and can produce long lasting changes in cortical excitability. Depending on the interstimulus interval (ISI), PAS can produce either long-term potentiation (LTP) or long-term depression (LTD). PAS induced plasticity is rapidly evolving, long-lasting, reversible and topographically specific. (Stefan et al. 2000.)

Another, endogenous rehabilitation method which is used for motor learning and neurological rehabilitation is motor imagery. Although motor imagery is not associated with overt movements, it has comparable benefits on acquisition of motor skills. The rationale behind motor imagery is that it shares common neural substrates with the actual execution of a task. Earlier studies have proven the effectiveness of motor imagery, but clinical evidence is still modest. (Munzert et al. 2009.)

In a clinical domain, several aspects of movement disturbances are not only related to motor execution but also on motor planning. That is why motor imagery appears to be reasonable exercise during rehabilitation. Motor imagery can also be practised by people who are unable to move by themselves. To date, there is no clear evidence for the modulation of excitability of lower limb muscles during motor imagery. It has been proven that imagined foot dorsiflexion increases corticospinal excitability of the tibialis anterior muscle (Bakker et al. 2008). However, it is known that tibialis anterior is a special muscle with privileged cortical representation (Brooks and Stoney 1971; Drew 1991). In the present study, the effect of motor imagery of foot plantar flexion on the excitability of cortical representation of soleus (SOL) muscle was investigated. Another

aim of this study was to investigate the effect of PAS on motor imagery. PAS mainly affects the execution phase of movement. It was suggested that after the facilitative PAS protocol, motor imagery would further enhance the excitability of the passive muscle. TMS and H-reflex were used to measure the excitability changes of an anti-gravity soleus muscle. There are not other studies investigating PAS and motor imagery techniques together. Favorable results would indicate possible applications in rehabilitation settings, for example, with Parkinson's disease and stroke patients.

2 PLASTICITY OF THE HUMAN BRAIN

Human brains need to be adaptable. Cortical connections are continuously reorganized as a result of alterations in the peripheral and central inputs. This ability of sensory and motor cortices to dynamically reorganize is called plasticity. Plasticity of the brain is important for learning, memory (Sanes and Donoghue 2000), and recovery from brain injury (Nudo et al. 1996). The term plasticity refers to the capacity of the brain to change and to the intrinsic property of the human nervous system that lasts throughout a life span. An artificially induced plasticity may be defined as any functional change within the nervous system outlasting the experimental manipulation (Classen and Ziemann 2003). There are several mechanisms in the brain to induce plasticity. Rapid plastic changes can be achieved by the uncovering of latent or existing connections (Jacobs and Donoghue 1991), activation of existing but silent synapses (Nusser et al. 1998), activity-dependent synaptic plasticity (Bliss and Lomo 1973) and generalized excitability changes in postsynaptic neurons (Gomperts et al. 1998). Morphological changes like neurogenesis, synaptogenesis and synaptic remodelling are mechanisms which take more time to develop (Geinisman 2000; Kleim et al. 1996). Several mechanisms can operate simultaneously, or in some serial order. These mechanisms are in turn under constant control of plasticity-regulating mechanisms such as homeostatic signalling and meta-plasticity. (Abraham and Bear 1996; Turrigiano 1999.)

The theory of synaptic plasticity was first introduced by Canadian physiological psychologist Donald Hebb (1904-1985). His theory is known as Hebb's law and it can be paraphrased: “Neurons that fire together wire together.” Hebb's law still underlies the current thinking of the dynamics of synaptic plasticity. It is proposed that activity-dependent synaptic plasticity is the most probable mechanisms mediating motor learning. (Berlucchi and Buchtel 2009.) Activity-dependent synaptic plasticity means that alterations in cortical organization emerge through changes in synaptic efficacy within the cortex, and elsewhere in the nervous system. The change can be either long-term potentiation (LTP) or long-term depression (LTD). LTP means long lasting enhancement of synaptic transmission whereas LTD means weakening of synaptic transmission that lasts from hours to days. The activity-dependent LTP and LTD appears to be a universal property of excitatory synapses in the brain and a lot of

experimental work is done to explain the molecular mechanisms of these plasticity forms (figure 1). (Malenka and Bear 2004.)

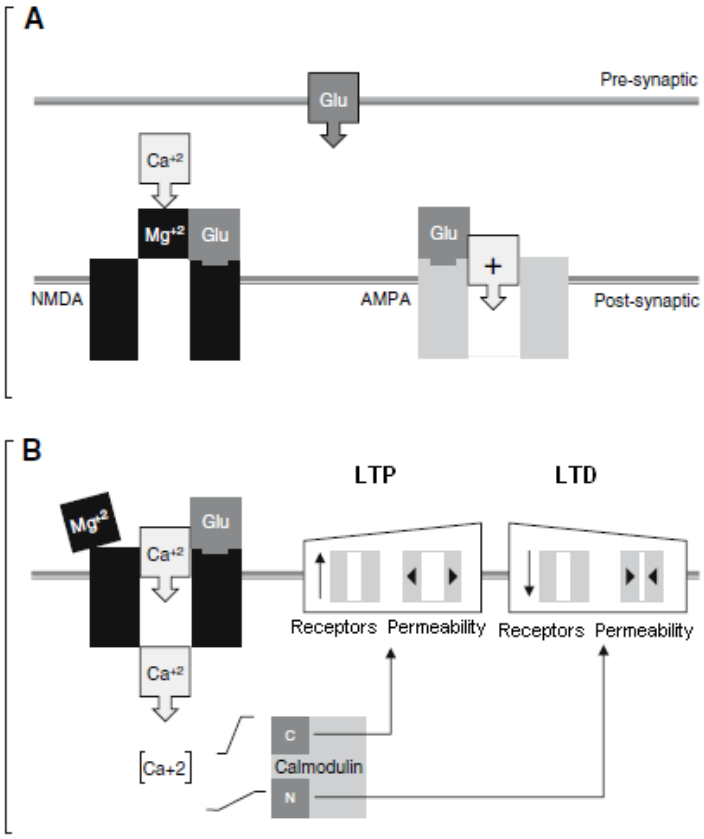

Figure 1. A model of activity dependent LTP and LTD mechanisms. A: Pre-synaptic glutamate release which then binds to post-synaptic NMDA and AMPA receptors. B: Sufficient EPSP releases the voltage-gated magnesium block and allows calsium influx. Calsium regulates if the LTP or LTD is induced. (modified from Thickbroom 2007.)

LTP and LTD plasticity are consequences of molecular changes in N-methyl-D-aspartic (NMDA) and α-amino-5-hydroxy-3-methyl-4-isoxazole propionic (AMPA) receptors and ionic changes with calcium (Ca++) and magnesium (Mg++) at excitatory glutamergic synapses (figure 1). First glutamate is released pre-synaptically and binds to AMPA receptors. AMPA receptors become permeable to cations natrium (NA+) and kalium (K+) and this influx generates an excitatory post-synaptic potential (EPSP). Glutamate also binds to and opens NMDA receptor channels but there is still a voltage-gated Mg++ block which prevents the cation influx. Sufficient post-synaptic depolarization caused by EPSPs can release the Mg++ block and allow Ca++ influx. Ca++ is the trigger for synaptic plasticity and regulates whether the LTP or LTD is

induced. Calmodulin (CaM) in the cell has two calcium-binding lobes. If there is a rapid increase in the Ca++ concentration, carboxyl (C) lobe binding occurs and leads to the LTP. C-lobe binding triggers a kinase pathway that results in exocytosis of AMPA receptors, and auto-phosforylation of surface receptors which leads to better permeability. A slower increase in Ca++ concentrations leads to amino (N) lobe binding and LTD. N-lobe binding triggers phosphatase pathways that endocytose AMPA receptors and decreases the permeability of the surface receptors. NMDA receptor activation depends on both pre-and post-synaptic events, and thus is consistent with the usual interpretation of Hebb's law, which present pre- and post-synaptic correlation. (Collingridge 2003; Thickbroom 2007.)

Studies of the motor cortex have proven that learning and practice influnence cortical organization and that learning operates through the LTP and LTD-mediatied mechanisms. This means that there is a therapeutic potential to restructure an impaired or damaged motor cortex via appropriate physical or other rehabilitation. (Butler and Wolf 2007.) Several non-invasive human brain stimulation techniques have been developed to induce plasticity changes that last for minutes to hours after the intervention. The intervention protocols may involve peripheral nerve stimulation, cortical stimulation or a combination of peripheral and cortical stimulation. (Thickbroom 2007.) The latter protocol is termed paired associative stimulation (PAS). PAS combines percutaneous electrical stimulation of a peripheral nerve and transcranial magnetic stimulation (TMS) over the contralateral motor cortex. This novel protocol is based on Hebb's law of coincident summation where the two stimuli are paired to activate brain networks at approximately the same time. PAS is compatible with the activity-dependent models of plasticity. (Stefan et al. 2000.)

3 PAIRED ASSOCIATIVE STIMULATION

PAS was first introduced by Stefan et al. (2000) (figure 2). PAS may produce a long-lasting change in cortical excitability which can then be easily quantified by TMS. PAS induces rapidly envolving (<30 min), longlasting (>60 min), yet reversible and input-specific changes in corticomotor excitability when the interval between the two associative stimuli is appropriate. In the hand area, motor cortex excitability increases if the interstimulus interval (ISI) is longer (25 ms) than the time needed for the afferent inputs to reach the motor cortex, and decreases if the interstimulus interval is shorter (10 ms) than the afferent time. Afferent time, travelling from the peripheral nerve to the primary somatosensory cortex, is about 20 ms for the hand. It can be measured by somatosensory-evoked potentials (SEP). Travelling from the somatosensory cortex to the motor cortex, the central processing time, takes about 3 ms. (Stefan et al. 2000; Wolters et al. 2003.) It has been demonstrated that the change in excitability is cortical in origin when the hand areas are stimulated. (Di Lazzaro et al. 2009a, 2009b.) It is proposed that plasticity mechanisms are similar to the LTP and LTD. The possible neural substrate might be the horizontal cortico-cortical connections within the motor cortex (Rioul-Pedotti et al. 2000).

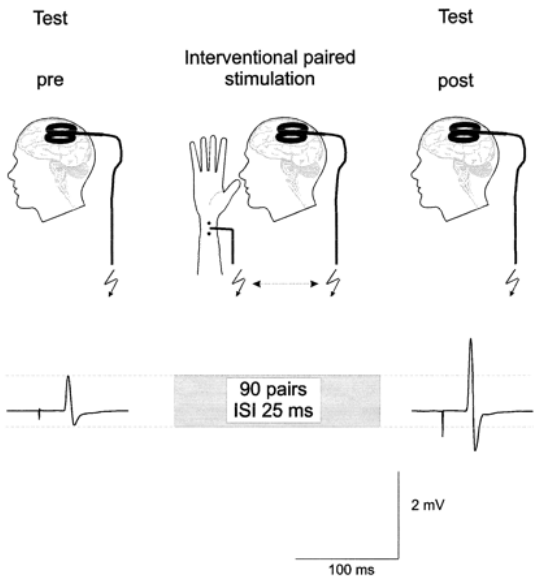

Figure 2. The experimental design by Stefan et al. in 2000. The test MEP amplitudes were elicited by single-pulse TMS before and after the intervention. There is increase in the MEP amplitude after the PAS of 90 pairs of stimuli with ISI of 25 ms.

3.1 PAS of the leg area

There are similar PAS experiments done in the leg areas, but with variable and diverse results. The optimal ISIs are not known for leg stimulation. Also, the origin of the change in excitability is partly different with legs compared to hands. Roy et al. (2007) reported that unlike PAS in the hand, the resting tibialis anterior (TA) was facilitated when the sensory inputs were estimated to arrive at the motor cortex 15 to 90 ms after cortical stimulation, which correspond to ISIs of (-40) to 35ms. Estimated afferent time for TA is from 28 to 47 ms, and the central processing time is about 4-10 ms. (Cruse et al. 1982; Jayaram and Stinear 2008; Roy et al. 2007). In the study the authors suggested that this broad range of facilitation occurred as a result of prolonged subthreshold excitability of the motor cortex after the suprathreshold pulse. Roy et al. (2007) didn't find the decrease in the excitability at an ISI of 40ms which Mrachacz-Kersting et al. (2007) found. Mrachacz-Kersting et al. (2007) also found an increase in excitability at ISIs of 45, 50 and 55 ms. They found a bigger increase when PAS was applied with the TA dorsi-flexing (ISI of 55 ms). This was in line with previous studies showing that stimulation is more efficient with voluntary activation of the target muscle (Khaslaskaia and Sinkjaer 2005). PAS-effects after interventions of different ISIs are compiled in the table 1.

PAS has also been delivered during walking because it could be a valuable rehabilitation tool in walking re-training programs. Stinear and Hornby (2005) paired TMS of the lower limb cortex with electrical stimulation of the common peroneal nerve and delivered it during the swing phase of walking. The authors found the bidirectional effects in the motor cortex excitability. Excitability increased when the ISI was longer (35 ms) than the estimated arrival time of the afferent volley in the somatosensory cortex, and decreased when the ISI was shorter (20 ms) than the afferent time. More recently, Jayaram and Stinear (2008) studied the effects of inhibitory PAS on stroke patients. After stroke there is an incresed inhibitory drive from the contralesional to the ipsilesional primary motor cortex which is called transcallosal inhibition. That is why the inhibitory PAS applied to the contralesional motor cortex can increase the excitability of the ipsilesional motor cortex. Jayaram and Stinear found that inhibitory PAS with ISI of 24 ms during walking increased the excitability of the ipsilesional motor cortex and decrased the excitability of the contralesional motor cortex. They

concluded that inhibitory PAS could be a useful rehabilitation tool for patients with neurological impairments. Roy et al. (2007) didn't find the inhibition close to the ISI used in Jayaram and Stinear's study. These two studies may not be comparable because the tasks; rest and walking, were different (Jayaram and Stinear 2008).

Table 1. PAS-effects in the leg area after interventios of different ISIs. F refers to facilitation (LTP) and I refers to inhibition (LTD).

		ISI (ms)											
STUDY	**AUTHOR**	**-40**	**-25**	**0**	**5**	**10**	**20**	**35**	**40**	**45**	**50**	**55**	**60**
PAS (passive)	Mrachacz-Kersting et al.2007								I	F	F	F	
PAS (active)	Mrachacz-Kersting et al.2007										F		
PAS (passive)	Roy et al. 2007	F	F	F			F	F					
paired stimulus (passive)	Poon et al. 2008										F	F	F
paired stimulus (active)	Poon et al. 2008				F	I	I	I	I				
paired stimulus (passive)	Roy and Gorassini 2008							I	I	F	F		
PAS+walking	Stinear and Hornby 2005						I	F					
PAS+walking	Jayaram and Stinear 2008						I						

Poon et al. (2008) investigated interaction of one pair of cortical and peripheral nerve stimulation in the soleus (SOL) muscle to study the time-course of facilitation and depression in different synaptic pathways. The authors found tri-modal patterns in the change of excitability. Excitability increased with ISIs of 0-5 ms, decreased with ISIs of 10-40 ms and increased again with ISIs of 50-60 ms. SOL was activated by 15-20% of the MVC during the stimulations. Poon et al. (2008) suggested that the early facilitation was spinal in origin because the ISI was optimal for summation of the two pathways at the spinal level. The authors suggested that the depression was also at the spinal level and resulted from post-synaptic afterhyperpolarization of motor neurons. The late facilitation was cortical in origin because the ISI was enough for the sensory afferent input to reach the motor cortex. Also, Roy and Gorassini (2008) studied interaction of one paired stimulation on TA and SOL muscles. The authors found that excitability increased with ISIs of 45-50 ms and decreased with ISIs of 33-38 ms. They proved that in contrast to the hand, the inhibition was subcortical in origin because the cervicomedullary induced responses decreased to a similar degree. There are no other studies, measuring the origin of paired stimulus inhibition in the leg area. The facilitation was cortical in origin resulting from reduced short interval intracortical

inhibition and increased intracortical facilitation. Also, the recruitment of early, middle and late descending corticospinal volleys increased.

3.2 PAS in rehabilitation

PAS intervention is most effective in rehabilitation when combined with functional therapy. Achieved benefits might last well after the intervention effects have settled or been homeostatically eliminated. The main purpose of the PAS intervention is to up-regulate plasticity mechanisms. Functional therapies could include a recruitment phase and a training phase. The recruitment phase is the intra-intervention period when a task could be performed before the intervention, or during the intervention, to prime the functional networks. After the intervention, when plasticity mechanisms might be up-regulated or when there are persisting changes in the excitability, the training phase in which further therapies could be implemented should be held. (Thickbroom 2007.)

The advantage of the PAS compared to pure TMS interventions is that it strengthens corticospinal connections providing a specific increase or decrease of excitability to the target muscles (Mrachacz-Kersting et al 2007). Previous studies have shown that the connectivity of corticospinal neurons is crucial for recovery after subcortical insult (Thomas and Gorassini 2005). There is a slight possibility of epileptiform seizures with TMS but not with the PAS (Anand and Hotson 2002). Such risks are not reported with repetitive electrical stimulation, but it requires higher amounts of stimuli to induce plasticity (Khaslaskaia and Sinkjaer 2005). PAS is efficient already after a 15 minute's intervention. Considering these benefits of PAS, it seems to be an attractive rehabilitation tool. (Jayaram and Stinear 2008; Mrachacz-Kersting et al 2007.) However, several PAS studies from different groups are now reported in the literature, and they show quite variable results. There are big inter-individual and even intra-individual variabilities of the after-effects of PAS interventions. When others have responded with LTP-like plasticity, others may have responded with LTD- like plasticity after same PAS protocol. (Fratello et al. 2006; Müller-Dahlhaus et al. 2008; Sale et al. 2007.)

The number of protocol parameters may influence PAS-induced changes like frequency, intensity, number and interstimulus interval of the two associative stimuli, attention, activation level of the target muscle, individual afferent times and the time of the day. Naturally, the anatomical differences in the orientation of sulci and gyri, and differences with the orientation of motor cortical interneurons, may affect the results. Older age decreases the magnitude of the plasticity effects. One more possible explanation for the variability might be genetic polymorphisms of neural signals involved with synaptic plasticity. PAS-effects critically depend on the recent history of neuronal activity, and this could be the reason for intra-individual variability. (Fratello et al. 2006; Müller-Dahlhaus et al. 2008; Sale et al. 2007.) Sale et al. (2007) proved that the time of the day affected PAS results. The authors found that the PAS intervention was more reliable when done during the afternoon when compared to the morning. The reason could be the circadian rhythms in hormones and neuromodulators which are known to influence neuroplasticity. Sale et al. (2007) suggested that PAS interventions should be done at a fixed time of day, preferably in the afternoon, to maximise neuroplasticity and minimize variability. There is also a need to define clearly the stimulation parameters for specific brain areas and specific patient populations before the PAS should be applied in the clinical settings.

4 IMAGERY

Imagery has become an important technique in exercise psychology and rehabilitation with both athletes and patients. The rationale behind imagery is the hypothesis that actual movements and imagery involve the same cognitive functions. In this sense, it is possible to learn and achieve activity-dependent plasticity changes through mental training. This hypothesis is supported by behavioural and anatomical studies with fMRI and TMS measurements. (Munzert et al. 2009.) It has been reported that brain regions used during imagery are similar with those used during movements. There are two commonly used imagery forms; motor imagery and visual imagery of motor actions. Motor imagery is a broader phenomenon related to intending and preparing actions from first-person perspective. It involves both kinaesthetic and visual representations. Visual imagery, in contrast, refers to a third-person process involving only the visual representation of an action. (Jeannerod 1994.) Brain activation differs remarkably for different kinds of imagery. In this context, the focus will be on motor imagery because of the fact that it's functionally more equivalent with motor execution. (Lorey et al. 2009.)

Motor imagery is defined as a cognitive process in which a subject imagines performing a movement without actually executing it and without even tensing the muscles. It requires the conscious activation of brain regions that are also involved in movement preparation and execution, accompanied by a voluntary inhibition of the actual movement. Motor imagery uses a pre-existing body model which is processed from long-term memory to a working memory. This process of image generation constitutes a perception-like experience. At present, motor imagery is considered as a profound body-based simulation process that uses the motor system as a substrate. (Jaennerod 2001.) Recent computational models show similar conceptions of action control for both imagery and execution. In these models, the inverse model, the planner, maps the information between the movement goal and the motor command. A predictive forward-model estimates the anticipated sensory outcome. Although there is no movement-related sensory feedback during the imagery, the forward-model estimates still predict the sensory outcome in action simulation. (Wolpert and Miall 1996; Wolpert and Flanagan 2001.) This indicates that somatosensory processes are also an integral part of

motor imagery. Several studies have demonstrated that proprioceptive information is involved when simulating oneself by observing the influence of actual and imagined hand posture on motor imagery. (De lange et al 2006; Fourkas et al. 2006; Vargas et al. 2004.) Depending on the actual hand position, the afferent signal is either compatible or incompatible with the predicted outcome. Congruency between hand position and the imagined movement facilitates higher amounts of sensory input coming from the periphery (Lorey et al 2009; Shimura and Kasai 2002). This has been shown directly in TMS studies demonstrating higher excitability of the primary motor cortex when hand position matches the imagined movement (Fourkas et al. 2006; Vargas et al. 2004). Activation of the inferior parietal lobe during imagery demostrates integration of proprioceptive information when simulating oneself (Lorey et al. 2009). The inferior parietal lobe is related to higher order somatosensory functions and integration of somatosensory information (Cipolloni and Bandya 1999; Servos et al. 2001).

The mental simulation theory provides convincing arguments for processes that underlie mental training. It explains neural activation during motor imagery as well as behavioural outcomes. Also, autonomic nervous system responses have been reported to be similar with imagery and execution (Decety et al. 1993; Wuyam et al. 1995). Mental simulation theory involves two hypotheses: First, common neural representations can be activated during imagery and execution along with similar motor-relevant physiological responses. Second, differences can be assumed between imagery and execution reflecting the fact that imagery is a covert stage of action, whereas the execution also implies the overt behavioral stage. (Munzert et al. 2009.) In conclusion, correspondences, as well as differences, should be found on both a neural and behavioural level when studying motor imagery and motor execution. These correspondences and differences will be discussed in the next chapter.

4.1 The neurology of imagery

Motor imagery has measurable effects on the motor system and motor performance. TMS studies show that motor imagery increases focal cortical and corticospinal excitability (Facchini et al. 2002; Fadiga et al. 1999; Filippi et al. 2001; Fourkas et al. 2006; Jaennerod 1995; Kasai et al. 1997; Li 2007; Li et al. 2004; Li et al. 2009; Patuzzo et al. 2003; Sohn et al. 2003; Stinear and Byblow 2004; Yahagi and Kasai 1999). Incresed excitability is demonstrated by decreased motor threshold and facilitatory effects on the motor evoked potentials of the target muscles. Motor imagery-induced enhancement has two special features: first, it is highly muscle-specific. For example, a person is able to imagine individual finger movements despite the fact that multiple finger representations are highly interconnected in the motor cortex (Fadiga et al. 1999; Li 2007; Li et al. 2004). Second, the enhanced excitability is movement-specific (Hashimoto and Rothwell 1999; Stinear and Byblow 2003). This means that there is phase dependent modulation of MEPs during wrist flexion and extension movements. MEPs are larger in the wrist flexion muscles when the person is imagining flexion, and smaller when imagining extension (Hashimoto and Rothwell 1999). The opposite is true with the extensor muscles.

FMRI studies have reported that the same motor areas are activated during movements and motor imagery (Decety et al. 1994; Deiber et al. 1991; Lorey et al. 2009; Porro et al. 1996; Stephan et al. 1995; Munzert et al. 2008; Wolfensteller et al 2007). The activation coincidence is found in the primary motor cortex, primary somatosensory cortex, premotor cortex, pre-supplementary and supplementary motor corteces, the inferior and superior parietal lobe and also in the subcortical areas like the cerebellum and the basal ganglia (figure 3). The cortical areas are linked closely to the cerebellum and the basal ganglia thereby creating feedback loops together. The cerebellum is traditionally associated with coordination, sensorimotor integration, movement correction and feedback control. Brain research has shown that the motor cortex receives afferent information through the cerebello-thalamo-loop. Via this loop, the cerebellum modulates the motor cortex and its functions. (Nakano 2000.) The supplementary motor cortex plays a major role during movement execution and imagery. Neurons in the supplementary motor cortex are involved in the preparation of movements and the pre-supplementary motor cortex is also involved in movement

selection. However, studies show that activation of the supplementary motor cortex overlaps only partially indicating that some parts of it are activated during motor imagery only. A recent study by Kasses et al. (2008) suggests that during imagery, some of the neurons of the supplementary motor cortex inhibit the primary motor cortex and prevent motor execution. There are also some inconsistencies with the activation of the premotor cortex showing that the ventral premotor cortex is activated more during imagery. The premotor cortex is involved in planning of movement. (Gerardin et al. 2000).

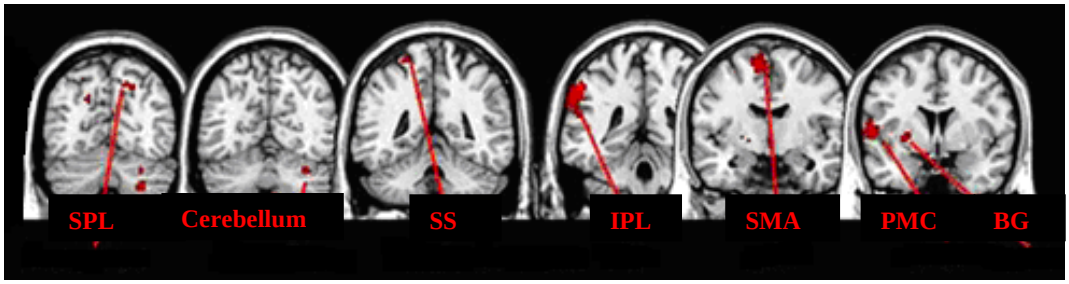

Figure 3. Anatomical regions of the brain activated during motor imagery. SPL refers to superior parietal lobe, SS refers to somatosensory cortex, IPL refers to inferior parietal lobe, SMA refers to supplementary motor cortex, PMC refers to premotor cortex and BG to basal ganglia. Also primary motor cortex was activated in this study. (modified from Lorey et al. 2009.)

There has been some debate concerning the role of the primary motor cortex during imagery. It has been argued that the primary motor cortex is the executor of motor commands and that this stage should be suppressed to avoid overt movement. Recent studies prove the activation of the primary motor cortex during imaginary. (Porro et al. 1996; Lorey et al. 2009; Munzert et al 2008; Sharon et al. 2008; Wriessnegger et al. 2008.) Naturally, the activation is smaller compared to that of execution. It is suggested that rather than just being the executor, the primary motor cortex also supports more cognitive functions (Sanes and Donoghue 2000). The primary motor cortex shows anticipatory activity for movement sequences (Bremmer et al. 2005), it receives input from the muscle spindels (Naito et al. 2002) and its posterior part is modulated by attentional processes (Binkofski et al 2002). The contribution of imagery is not known but it is suggested that especially preparation for motor imagery contributes to the activation of the primary motor cortex (Johnson et al. 2002). The efferent command of

motor imagery is not necessarily completely suppressed. Studies have proven that motor imagery influences spinal excitability (Li et al. 2004). Thus, during motor imagery, a subthreshold signal may be generated by the primary motor cortex producing the changes in the excitability at the spinal level. In conclusion, a complete coincidence is not found in all cases with some areas being activated only during imagery and some areas being more activated during movements.

Similarities between imagined and executed actions have also been found with behavioural studies (Feltz and Landers 1983; Rodriguez et al. 2009; Yágüez et al. 1998; Yue and Cole 1993). The time to execute a motor pattern is the same for real and imagined movements (Abbruzzese et al. 1996). In both cases, the time increases when the difficulty of the task increases, and when the demand of accuracy increases (Decety and Lindgren 1991; Jeannerod and Frak 1999). This virtual-real congruency has been found in healthy subjects and in patients (Sabate et al. 2004; Sabate et al. 2007). Mental durations of movements can be taken as an indirect measure for the control of imagery process and most behavioural studies are based on these execution-time studies. A recent study by Rodriguez et al. (2009) studied the kinematics of the virtual and real movements. The authors found strong similarity between virtual and real movements in complex motor patterns needing attention, but not in simple movements which can be partly performed in an automatic way.

After discussing the details in this chapter concerning the mental simulation theory, there are strong arguments for both of the hypotheses previously mentioned. Both correspondences and differences are found between motor imagery and execution. Furthermore, it seems like motor imagery and execution establish same basic neuronal processes.

4.2 Imagery in rehabilitation

Motor imagery is a covert stage of motor action which includes the goal and the plan of the action, as well as the prediction of their effects on the musculoskeletal system and external world. This internal simulation of motor action may provide the neurobiological basis for motor learning, and thus, for the use of imagery in rehabilitation. Adult brains are highly dynamic, meaning that cortical connections are reorganized continuously as a result of alterations in peripheral and central inputs. The purpose of motor imagery is to teach patients strategies that facilitate the reorganization of the affected brain areas and loops by activating intact neurons and strengthening activity in other neural loops. (Gueugneau et al. 2009; Lorey et al. 2009; Mulder 2007; Munzert et al. 2009) Previous studies show that motor imagery training has resulted in behavioral improvements with both athletes and patients (Christacou et al 2007; Crosbie et al. 2004; Fansler et al. 1985; Lotze and Cohen 2006). Improvements are associated with changes in the functional reorganization of the brain. It has been reported that motor imagery and physical training induce similar neuronal changes in the cortical area and in the cerebellum.

Mental training has also been applied to overcome strength losses and to produce force gains (Christacou et al 2007; Crosbie et al. 2004; Fansler et al. 1985; Sidaway and Trzaska 2005 Zijdewind et al 2003). Isometric training by motor imagery has been reported to increase force in the trained muscle and also in the contralateral untrained muscle (Yue and Cole 1993). Motor imagery reduces strength losses after immobilization. Newsome et al. (2003) reported significantly larger strength losses in a control group when compared to a motor imagery group after 10 days of forearm immobilization. These studies are consistent with the present theory of the force increase stating that strength increase does not only depend on the changes in muscle mass and muscle composition, but also on neuronal adaptations. According the theory; the early strength increase following training within the first weeks precedes increases in muscle mass, training of one limb produces strength increases also in the contralateral limb and training of a specific muscle does not transfer to all motor tasks that are integrated in the trained muscle. (Enoka 1997.) Positive effects of motor imagery provide strong arguments for the mental simulation theory. It seems that mental simulation also alters the recruitment and firing frequency of motor neurons, which is

one way to obtain strength increases. The presented experiments are too short to cause muscle hypertrophy, and therefore they can be taken as a proof of the effects of repeated motor programming during the imagery.

Efficiency of mental training depends on the practitioner's ability to generate mental motor images. Elite athletes have better imaginary skills than less successful athletes (Calmels et al. 2003). Elderly people have slightly worse imaginary capacity than younger ones (Mulder et al. 2007). Patients have different imaginary skills depending on their injury. Some stroke patients have demonstrated impairment of motor imagery skills (Stinear et al. 2007). Parkinson's disease induces deficits in the working memory which is needed during imaginary and therefore these patients' imagery ability might be affected (Dominey et al. 1995). The variability of skills within different groups is probably the reason for the rarity of group studies on the clinical effects of motor imagery. It is not yet possible to say what type of patients would profit most from the imagery. (Mulder et al. 2007.) In addition, the time of the day effects the ability to train mentally. Gueugneau et al. (2009) demonstrated that circadian fluctuation of motor imagery occurs and that optimal training time is in the afternoon. However, imagery offers considerable advantages in the therapeutic settings; first, it provides an opportunity to get additional training effects. Second, it does not cost a lot, needs no institutional context and involves no safety risks. Third it is possible to start imagery at an early stage of rehabilitation when moving might be impossible. (Munzert et al. 2009.)

5 THE PURPOSE OF THE STUDY

There were two aims for this study. First, the effect of motor imagery of plantarflexion on the excitability of cortical projections to the SOL was investigated employing a single pulse TMS. The second aim was to explore the effect of facilitatory PAS on motor imagery. Also, the effect of PAS on spinal excitability and the sustainability of PAS were examined.

The questions include: can motor imagery influence on the SOL, which is a lower leg anti-gravity muscle? and is motor imagery more efficient after the PAS? The hypothesis is that motor imagery will increase the corticospinal excitability of SOL but less than measured in the TA (57%), which have bigger cortical representations (Bakker et al. 2008). It is also expected that motor imagery could still increase cortical excitability after the PAS-induced facilitation. According to previous studies PAS is long-lasting and the increase in excitability is cortical in origin (Mrachacz-Kersting et al. 2006; Roy et al. 2007)

6 METHODS

6.1 Subjects

Eleven healthy volunteers participated in the study (9 women, 24 ± 3 years, 61 ± 6 kg, 165 ± 7 cm). None of the subjects had any history of neuromuscular or orthopedic disease. Before testing, all subjects were informed about the procedures and they signed informed consent. The study was approved by the University ethics board in conformity with the Declaration of Helsinki.

6.2 Experimental design

Subjects were seated on a custom built ankle dynamometer (University of Jyväskylä) with the right leg extended (ankle 90°, knee 180° and hip 120°) and left leg resting on a footplate. The right foot, right knee and hip were tighly secured with bands and the hands were resting in the lap during the measurements. As a short warm-up, subjects trained using the right isometric plantarflexion movement. Then they performed three maximal voluntary contractions (MVCs) where the highest peak value was considered as the MVC. The TMS coil was placed on the head with rubber straps. MEPs were recorded before, immediatly after (post 1), and 15 min after (post 2) PAS intervention from the SOL muscle in passive condition and during motor imagery. H-reflex responses were also measured before and after the PAS.

6.3 Procedures

TMS. Transcranial magnetic stimulation was delivered using two mono-pulse Magstim 200^2 stimulators connected by a BiStim^2 system with a 9-cm double batwing coil (Magstim, Whitland, UK). The coil was placed over the leg area of the left motor cortex and it was oriented to induce posterior-anterior currents in the brain. The optimal stimulus site for the SOL was usually located 1 cm lateral and 1 cm posterior to the

vertex. Threshold was defined as the lowest stimulus intensity needed to elicit visible MEP in 3 out of 5 trials while the subject was sitting still. Stimulus intensity was set to 120% of the threshold, and this intensity was used throughout the experiment. A custom made coil holder and rubber straps were used to fix the coil firmly on the head. The position of the coil was marked on a closely fitting cap worn by the subjects. The cap also protected hair from cold spray (PRF101, Taerosol, Finland) if the coil needed cooling down during the measurements.

Electrical stimulation. An electrical rectangular pulse with duration of 0,1 ms was delivered to the common tibial nerve using a constant-current stimulator (DS7A, Digitimer, Hertfordshire, UK). A circular cathode with a pickup area of 77 mm^2 (Unilect short-term ECG Electrodes, Ag/AgCl, Unomedical Ltd., UK) was placed over the tibial nerve on the popliteal fossa and an oval shaped, 5,08 cm x 10,16 cm, anode (V-trodes neurostimulation electrodes, Mattler Electronics corp., USA) was placed above the patella. While measuring the H-reflex, current intensity corresponded to 20 % ± 0,025 % of the maximal M-wave. H-reflex response from the SOL was measured 10 times in passive condition before and after the PAS.

PAS. Paired associative stimulation consisted of a single electrical stimulation of the tibialis nerve delivered at 150 % of motor threshold, followed by a single TMS pulse with interstimulus interval of 20 ms. The ISI of 20 ms was chosen to induce LTP based on the previous study of Roy et al. (2007). A total of 200 pairs of stimuli were applied at rate of 0,2 Hz. To optimize the LTP effect, subjects produced isometric plantarflexion of 5 % of the MVC during the whole PAS intervention (Mrachacz-Kersting et al. 2006). There was a computer screen in front of the subject to show the level of force.

6.4 Data collection

A bipolar Ag/AgCl electrode was used to measure EMG from the SOL. An electrode pair was placed longitudinally between the muscle mid belly and tendon. Interelectrode distance was 2 cm, electrode shape was circular and diameter 5 mm. A reference electrode (Unilect) was placed on the head of the tibia. In addition, one monopolar electrode (Unilect) was placed next to the SOL bipolar electrode to measure MEP responses. The reference for the monopolar electrode was placed on the opposite tibia bone. The skin under the electrodes was shaved, abraded and cleaned with alcohol to reduce the interelectrode resistance below 5 kΩ.

The EMG activity from the SOL, rate of current in the coil and reaction forces from the force platform of the footplate were stored simultaneously on a personal computer. EMG was amplified (gain = 1000) and band-pass filtered (10-1000 Hz) (Cambridge Electronics Design Limited, UK). Data was collected into the computer via 16-bit AD converter (CED Power 1401, Cambridge Electronics Design Limited, UK) with a sampling frequency of 1 kHz for force, 2 kHz for bipolar electrode, 5 kHz for monopolar electrode and 15 kHz for the coil current.

6.5 Tasks

In the passive condition, subjects were instructed to keep all muscles relaxed and not to imagine any movement or be engaged in other cognitive activities. Ten stimulations were delivered at approximately 10 s intervals

During motor imagery, subjects were asked to imagine a single maximal plantar flexion movement after a verbal command, and to sustain this condition until the TMS was delivered. The following procedures were applied to achieve as constant imagery as possible for all subjects. A good description of the image and training of imagery were provided before stimulation. This training included the actual execution of the movement for performing the kinesthetic task, and an avoidance of actual execution during motor imagery. The level of force was instructed to be maximal since the mental effort for motor imagery is force dependent (Cowley et al. 2008). Subjects were

instructed to imagine in a first person perspective, as if they were performing the plantarflexion, but without making any actual movements. Imagery was done with the eyes closed to optimize the performance (Hashimoto & Rothwell 1999; Fourkas et al. 2006b). It is also suggested that the motor cortex excitability is greater with the eyes closed (Leon-Sarmiento 2005). Five successful imagery trials were measured by TMS. After each imagery trial, subjects were asked if they succeeded with the task. A specific requirement was that SOL remained electrically silent before and during the imagery.

6.6 Data analysis

Spike 2 software (CED, Cambridge, UK) was used to analyze peak to peak amplitudes of SOL MEPs. The values of each set (10 for passive and 5 for imagery) were averaged and then the averaged MEPs were normalized to passive pre-intervention MEPs. Results were compared with repeated measures of ANOVA. Background EMG was calculated for each TMS trial with the root-mean-square (RMS) of 1 s before the MEP. H-reflex responses were analyzed using two-tailed t-test. The significance level was set at $P < 0,05$. If not stated otherwise, all data are given as mean ± standard deviation (SD).

7 RESULTS

Pre-PAS results showed significant increase (76 ± 62 %) in the peak-to-peak amplitudes of the imagery SOL MEPs compared to passive MEPs (figure 4). Also during post 1 and post 2 the MEPs were significantly elevated (30 ± 33 and 31 ± 50) when comparing with the passive condition. However, the elevation was much smaller after the PAS. There was no background EMG activity in the muscles.

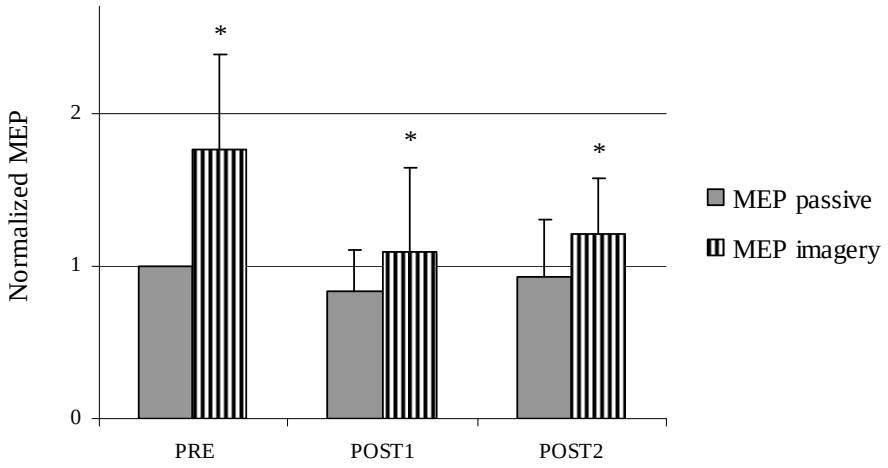

Figure 4. Normalized SOL MEP results when comparing passive and imagery conditions. Imagery MEPs are expressed as percentige of the pre-passive MEPs.

Unexpectedly, there was remarkable reduction in peak-to-peak amplitudes in both conditions immediately after the PAS (figure 5). Normalized MEP values were 1,0; 0,84 ± 0,26 and 0,95 ± 0,37 for the passive and 1,76 ± 0,62; 1,09 ± 0,34 and 1,21 ± 0,50 for the imagery in pre, post 1 and post 2. Thus, MEP declined 16 ± 26 % and 5 ± 37 % with passive and 38 ± 19 % and 31 ± 28 % with imagery in post 1 and post 2, respectively. Average SOL MEP responses are presented in the figure 6. PAS effect was significant in the imagery condition ($p < 0,01$) and almost significant ($p = 0,067$) in the passive condition in post 1. There was a trend of returning excitability in post 2. The absolute values of the MEPs for each subject are presented in the table 2. H-reflex values were 9,25 ± 3,1 mV in pre and 9,25 ± 3,0 mV in post 1. Corresponding maximal M-waves were 15,7 ± 5,1 mV and 15,6 ± 4,8 mV, which makes SOL H-reflex 59 % of M – max in both post 1 and post 2. Thus, PAS intervention did not affect the H/M ratio in passive condition. Raw M-wave and H-reflex sweeps are presented in the figure 7.

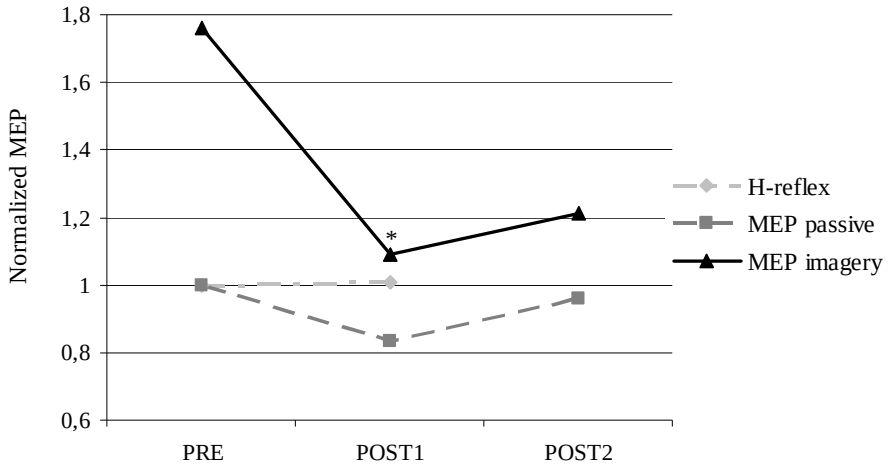

Figure 5. Normalized SOL MEP and H-reflex results after the PAS intrvention. H-responses are normalized to pre-values.

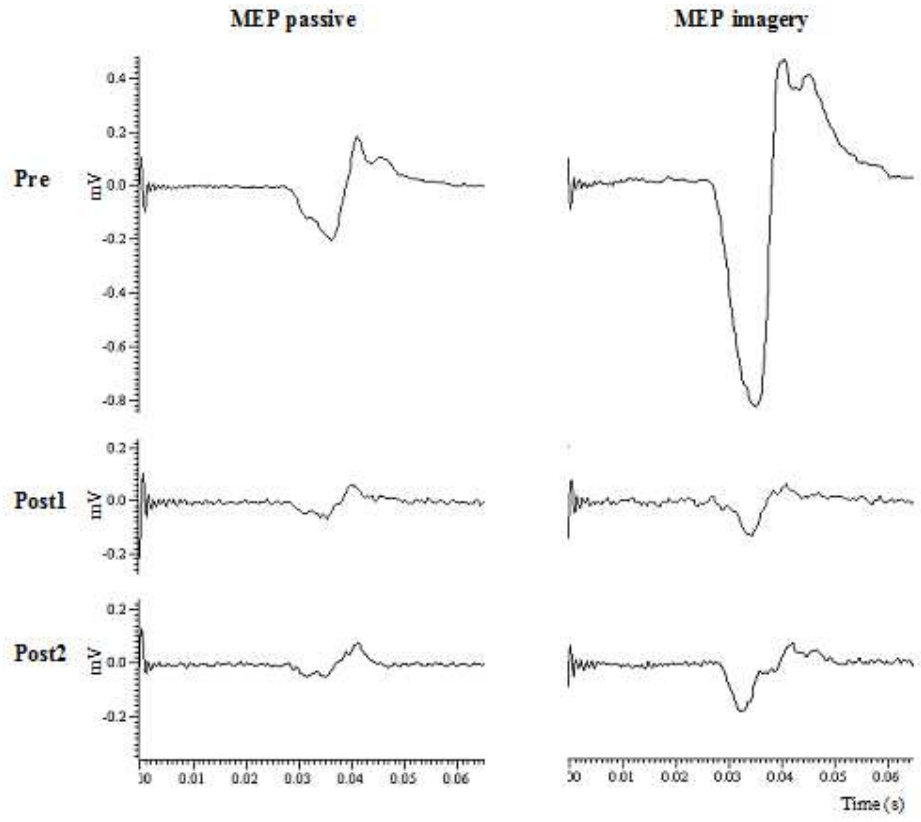

Figure 6. Average SOL MEP response collected in passive and imagery conditions in one representative subject in pre, post 1 and post 2 measurements. Passive data is average of 10 trials and imagery data is average of 5 trials.

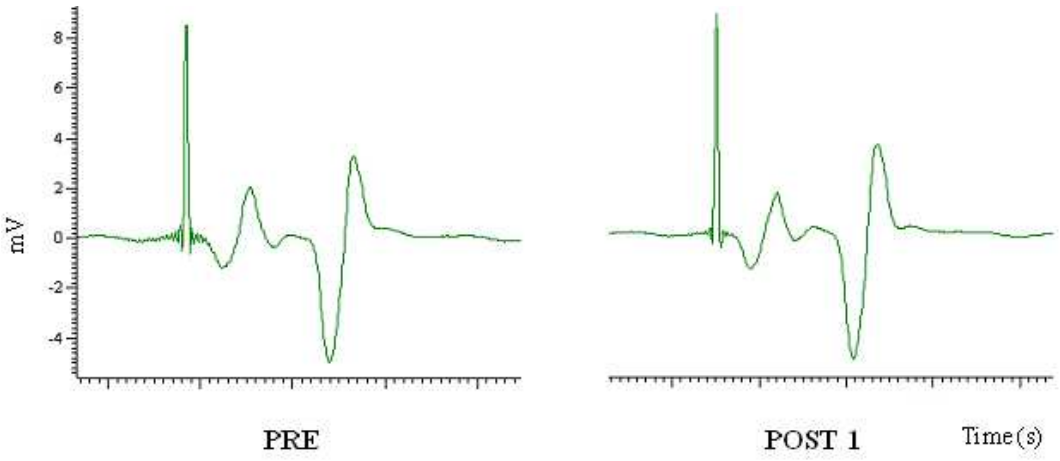

Figure 7. Raw H-reflex sweeps in one representative subject in the SOL muscle in pre and post 1 measurements. There was no change in the peak-to-peak amplitude of the H-reflex.

Table 2. Absolute values of the SOL MEPs in passive and imagery conditions. MEP amplitudes for the subject 2 were averaged already in signal form because of noise and thus, there is no SD values.

ID	PRE (mV)		POST 1 (mV)		POST 2 (mV)	
	Passive	**Imagery**	**Passive**	**Imagery**	**Passive**	**Imagery**
1	0,67 ± 0,21	1,05 ± 0,27	0,55 ± 0,15	0,94 ± 0,18	0,86 ± 0,23	
2	0,22	0,3	0,25	0,34	0,25	0,25
3	0,47 ± 0,18	0,74 ± 0,19	0,31 ± 0,10	0,43 ± 0,10	0,63 ± 0,25	0,70 ± 0,18
4	1,35 ± 0,46	2,30 ± 0,35	1,11 ± 0,23	1,05 ± 0.30	0,57 ± 0,32	0,50 ± 0,43
5	0,69 ± 0,27	1,16 ± 0,18	0,59 ± 0,17	0,68 ± 0,16	0,37 ± 0,11	0,66 ± 0,29
6	0,50 ± 0,22	1,12 ± 0,35	0,30 ± 0,19	0,51 ± 0,25	0,53 ± 0,32	1,02 ± 0,53
7	0,84 ± 0,21	0,82 ± 0,16	0,87 ± 0,35	0,93 ± 0,24	1,20 ± 0,35	1,46 ± 0,34
8	2,75 ± 0,92	4,28 ± 0,50	3,81 ± 1,02	2,94 ± 0,74	3,32 ± 0,67	3,54 ± 0,43
9	0,50 ± 0,53	1,21 ± 0,53	0,30 ± 0,15	0,83 ± 0,21	0,50 ± 0,62	0,78 ± 0,30
10	2,78 ± 0,21	3,22 ± 0,41	2,22 ± 0,48	2,48 ± 0,48	1,70 ± 0,33	2,25 ± 0,34
11	0,45 ± 0,27	1,44 ± 0,43	0,22 ± 0,08	0,25 ± 0,05	0,23 ± 0,12	0,35 ± 0,23
Mean ± SD	**1,02 ± 0,23**	**1,60 ± 0,13**	**0,96 ± 0,28**	**1,04 ± 0,20**	**0,93 ± 0,18**	**1,15 ± 0,11**

8 CONCLUSIONS

From the hypothesis it was expected that motor imagery of plantarflexion would increase the excitability of the soleus muscle and that motor imagery would still increase cortical excitability after the PAS-induced facilitation. The first expectation was met, but the second one was not. During motor imagery, the excitability of SOL increased 76,4 % compared to passive conditions which was even more than Bakker et al. (2008) found with tibialis anterior muscle (57 %). Motor imagery of plantar flexion reduced relatively the trial-to-trial variability of resting MEPs which can be seen from the SD values in table 2. Reduced variability reveals stable imagery skills of subjects. There were no differences between background EMG values during passive and imagery conditions indicating that cerebral activity differences were not due to muscle activity. Since the H-reflex was not measured during imagery, it can not be ruled out that changes in the spinal excitability might have also contributed to the results. The reason for the bigger facilitation of SOL compared to Bakker et al.'s (2008) TA facilitation might be methodological since in this study MEP amplitudes were measured with monopolar electrode and Bakker et al. measured MEP areas with bipolar electrode. Obtained TA MEPs had been polyphasic while SOL MEPs were clear one-wave responses, from which it was reasonable to measure amplitudes. The results for the SOL are consisted with previous studies with upper limb movements (Facchini et al. 2002; Stinear and Byblow 2004; Fourkas et al. 2006), upper leg movements (Tremblay et al. 2001) and TA movement, and thus provide further evidence regarding the effect of motor imagery of lower limb movements on corticospinal excitability.

The problem with the second hypotheses was that the PAS protocol did not induce the expected facilitation. Contrary to Roy et al. (2007) results, this study induced remarkable inhibition with the ISI of 20 ms. MEP decline was 16 % and 5 % in the passive condition, and even more (39 % and 31 %) in the imagery condition in post 1 and post 2, respectively. However, results are in line with the walking studies where ISI of around 20 ms have resulted in inhibition of motor cortex excitability (Stinear and Hornby 2005; Jayaram and Stinear 2008). As stated before, the optimal ISI for the leg area is not known. However, Roy et al. (2007) found the most significant facilitation with the ISI of 20 ms in the TA muscle. A possible explanation for the reversed results

is the differences in the PAS protocols. In this study there were more stimuli, higher frequency and active SOL while Roy et al. (2007) had resting TA during the PAS intervention. The reason for PAS inhibition is said to be the refractoriness of neurons produced by their postsynaptic afterhyperpolarization (Roy et al. 2007). The afterhyperpolarization might be stronger and longer with active muscle and therefore the inhibition could be produced with the ISI of 20 ms in the active but not in the passive muscle. Poon et al. (2008) found longer inhibition period when stimulating active muscle compared to passive muscle, where they did not find a significant inhibition at all (table 1). Previous studies have demonstrated the importance of the PAS protocol and task when assessing the modulation of the lower limb motor system (Petersen et al. 1998; 2001). The origin of the inhibitory PAS is speculated in many studies where it is suggested to be cortical. There is only one previous study which has actually measured it, and found the spinal origin of the inhibition (Roy and Gorassini 2008). On the contrary, in this study there were not any changes with H-reflex responses after the PAS, indicating the cortical origin of inhibitory PAS. However, Roy and Gorassini studied only one pair of stimuli and not the whole PAS protocol which probably explains the different results. The present study did not manage to show the sustainability of PAS effects because 15 minutes after the intervention inhibition was not significant anymore. Despite the trend of returning excitability, the inhibition was still evident.

Since the PAS induced inhibition, it was interesting that imagery MEPs were more suppressed compared to passive MEPs after both post-intervention measurements. Thus, the inhibition was stronger during motor imagery than during passive conditions. During motor imagery there are many neurons involved in the task and therefore there are more neurons to get inhibited and to reduce the excitability when comparing to passive condition. The subjects also reported difficulty to perform motor imagery after the PAS. It could be speculated that facilitation would also be stronger during motor imagery after facilitatory PAS. Herein it still is remaining unsolved. This was first study to show PAS inhibition in SOL and in a sitting position with ISI of 20 ms. Inhibitory PAS has been used to reduce increased transcallosal inhibition from the contralesional hemisphere after stroke. It has been demonstrated that decrease in the transcallosal inhibition unmasks preexisting neural networks and contributes to cortical reorganization in the ipsilesional hemisphere (Jayaram and Stinear 2007; 2009). Since

after PAS, motor imagery is also inhibited in the contralesional hemisphere, it might enable the ipsilesional hemisphere to produce more powerful motor imagery.

The results of this study have potential applications in rehabilitation settings as they provide evidence that motor imagery can be used to facilitate motor responses in the lower extremity when real movement is impaired or not possible. Furthermore, these results suggest the possibility of combined PAS and motor imagery to be integrated to rehabilitation protocol to facilitate motor recovery.

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