

Imagery-induced Cortical Excitability Changes in Stroke: A Transcranial Magnetic Stimulation Study

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Focal transcranial magnetic stimulation (TMS) was employed in a population of hemiparetic stroke patients in a post-acute stage to map out the abductor digiti minimi (ADM) muscle cortical representation of the affected (AH) and unaffected (UH) hemisphere at rest, during motor imagery and during voluntary contraction. Imagery induced an enhancement of the ADM map area and volume in both hemispheres in a way which partly corrected the abnormal asymmetry between AH and UH motor output seen in rest condition. The voluntary contraction was the task provoking maximal facilitation in the UH, whereas a similar degree of facilitation was obtained during voluntary contraction and motor imagery in the AH. We argued that motor imagery could induce a pronounced motor output enhancement in the hemisphere affected by stroke. Further, we demonstrated that imagery-induced excitability changes were specific for the muscle 'prime mover' for the imagined movement, while no differences were observed with respect to the stroke lesion locations. Present findings demonstrated that motor imagery significantly enhanced the cortical excitability of the hemisphere affected by stroke in a post-acute stage. Further studies are needed to correlate these cortical excitability changes with short-term plasticity therefore prompting motor imagery as a 'cortical reservoir' in post-stroke motor rehabilitation.

Keywords: functional recovery, motor imagery, motor mapping, TMS

Introduction

Motor imagery is a cognitive task which refers to the internal reproduction of a specific movement without any overt motor output. Converging evidence from cognitive, physiological and neuroimaging studies demonstrated that motor imagery shares features with actual movements such as common neural representations at cortical levels (Jeannerod, 1994; Decety, 1996; Roth *et al.*, 1996; Gerardin *et al.*, 2000; Sirigu and Duhamel, 2001; Stippich *et al.*, 2002; Hanakawa *et al.*, 2003; Dechent *et al.*, 2004; Rodriguez *et al.*, 2004), kinematic constraints (Parsons, 1994; Sirigu *et al.*, 1995), temporal properties (Decety *et al.*, 1989; Parsons, 1994), effects on motor performances (Feltz and Landers, 1983; Yue and Cole, 1992) and role in the acquisition of new motor skills (Pascual-Leone *et al.*, 1995; Mulder *et al.*, 2004). Transcranial magnetic stimulation (TMS) studies in healthy subjects reported a modulation of corticospinal excitability during motor imagery and demonstrated that the dynamic pattern of motor cortex excitability changes during imagined movements was similar to that observed when actual activities were performed (Abbruzzese *et al.*, 1996, 1999; Yahagi *et al.*, 1996; Kasai *et al.*, 1997; Kiers *et al.*, 1997; Rossi *et al.*, 1998; Yahagi and Kasai, 1998; Fadiga *et al.*, 1999; Hashimoto and Rothwell, 1999; Rossini *et al.*, 1999; Facchini *et al.*, 2002; Stinear and Byblow, 2003,

2004; Levin *et al.*, 2004; Li *et al.*, 2004; Vargas *et al.*, 2004). It was found that the excitability of cortical representation of a given muscle involved in a motor imagery task was transiently increased compared with a rest condition and that motor imagery specifically facilitated motor responses in the 'target' muscle similarly to the real movement (Rossi *et al.*, 1998; Fadiga *et al.*, 1999; Rossini *et al.*, 1999; Facchini *et al.*, 2002). Given the close relationship between mental simulation of movements and excitability changes in the motor system, together with the evidence that many patients with stroke retained the ability to mentally represent activities that they can no longer physically perform, motor imagery practice has been successfully employed as a possible rehabilitative strategy for motor recovery after brain damage (Weiss *et al.*, 1994a,b; Sirigu *et al.*, 1996; Johnson, 2000; Jackson *et al.*, 2001; Page *et al.*, 2001; Yoo *et al.*, 2001; Johnson *et al.*, 2002; Stevens and Stoykov, 2003; Dijkermann *et al.*, 2004; Johnson-Frey, 2004). However, little is known about the neurophysiological mechanisms underlying the motor imagery effects in stroke patients and to the best of our knowledge this is the first study evaluating imagery-induced cortical excitability changes of the motor cortex after stroke. The main goal of the present study was to assess whether motor imagery modulated the excitability of cortical representation of a hand muscle in the hemisphere affected by stroke. Focal TMS was applied to different scalp positions over the motor strip to map out the cortical representation of the abductor digiti minimi (ADM) muscle in a group of post-acute hemiparetic stroke patients. The ADM muscle cortical maps were obtained from affected (AH) and unaffected (UH) hemispheres, and the excitability changes during imagery of the little finger abduction (ADM-'think') were evaluated and compared with a rest condition ('rest') and with those induced by the voluntary contraction of the target muscle (ADM-'contr'). The specificity of motor imagery excitability changes on the ADM muscle cortical representation was evaluated by simultaneously mapping out responses from another upper limb muscle, well separated from the one 'target' of motor imagery as the extensor digitorum communis (EDC) muscle, which is not involved as 'prime mover' in the ADM-'think' task. Finally, the effects of imagery on motor cortex excitability were analyzed with respect to stroke lesion locations.

Materials and Methods

Patients

Seventeen first-ever stroke inpatients (6 women, 11 men; mean age, 63.6 ± 10.4 years) were recruited from a large stroke population in our rehabilitation hospital. They were in a post-acute stage (mean 73.2 ± 14.6 days) from mono-hemispheric stroke. Criteria for their inclusion were: (i) CT or MRI documenting a unilateral vascular

lesion; (ii) age below 81 years; (iii) mild to moderate motor deficits; and (iv) absence of cognitive or language impairment as assessed by standard neuropsychological examinations. Exclusion criteria were concomitant neuropathies, systemic vasculopathies and presence of cognitive deficits. All patients were right-handed as assessed by the Edinburgh Handedness Inventory Scale (Oldfield, 1971). Ten patients had an ischemic lesion on left and seven patients on right hemisphere.

Although no stroke type was actively excluded on anatomical grounds, there were possible sources of bias in our patient selection: (i) all patients had regained at least some ability to perform fractionated finger movements (ADM muscle contraction) with the affected hand; (ii) in all patients motor evoked potentials (MEPs) could be elicited from the paretic hand by magnetic stimulation of the affected motor area and patients in whom hand MEPs were absent using 100% TMS intensity of the stimulator's output were discarded from the study. As a result, our cohort consisted of five patients with infarcts to the internal capsule, eight patients with cortical lesions involving the parieto-temporal regions in which the primary motor cortex was spared and four patients with fronto-parieto-temporal lesions. In this latter group, direct cortico-motoneuronal projections to the spinal cord were partially spared, as suggested by the recovery of hand motor control to a level of producing fractionated finger movements. According to brain CT or MRI findings, the lesion was cortical in eight patients (three right, five left), cortical/subcortical in four (two right, two left) and capsular in five (two right, three left) (lesion locations were detailed in Table 1).

All patients were scored on the following outcome measures: Barthel Index (Mahoney and Barthel, 1965); Canadian Neurological Scale (Coté *et al.*, 1989), from which sub-scoring for hand functionality was extrapolated; Medical Research Council (MRC) Scale (1976); and Motricity Index (MI) for Upper Limbs (UL), where function was estimated on a scale from 0 to 100, with 0 being no function and 100 full function (Demeurisse *et al.*, 1980). Patients showed mild to moderate upper limb motor deficit and the strength of the paretic ADM muscle ranged from 2 and 5 on the MRC Scale (see Table 1). The Local Ethical Committee approved the experimental procedure in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

Transcranial Magnetic Stimulation

Motor maps were gathered through a 'figure-of-eight' coil (double 70 mm coil) connected with a magnetic stimulator (MagStim Co., Withland, Dyfed, UK). Patients were seated in a comfortable reclining armchair with both hands pronated on a pillow; they looked at a fixed point on the front

wall and did not have visual access either to the equipment display or to their hands. A tightly adherent and inelastic cap was modeled on the subject's head, with reference to anatomic landmarks (nasion-inion line, interaural line, meatal profiles). A grid of 19 positions, spaced 1 cm on the interaural and 1.5 cm on the sagittal line, was then tested on each hemisphere. Grids with more positions were tested, but they did not add significant information and were discarded as the total length of the session was excessive to allow sufficient compliance and collaboration by the patients. In producing maps, the center of the grid was positioned over the 'hot spot' site for the ADM muscle, preliminarily identified after TMS of several positions with suprathreshold pulses. The 'hot spot' was defined as the site whose stimulation elicited MEPs of the lowest threshold, highest amplitude and shortest latency. As a first step, the excitability threshold for MEPs elicitation was defined as the minimal TMS intensity able to determine MEPs of at least 50 μ V in 50% of 10–20 consecutive stimuli (Rossini *et al.*, 1994). TMS intensity was then increased by 10% of the threshold value to obtain a greater probability of eliciting MEPs at rest and was maintained constant along the three experimental sessions ('rest', ADM-'think' and ADM-'contr'). Three magnetic stimuli, separated by an interval of at least 10 s, were applied on each mapping position, with the coil maintained tangential to the scalp and the handle perpendicular to the supposed direction of the central sulcus. Averaged MEPs were stored on disk and measured off-line according with standardized parameters (Rossini *et al.*, 1994). A site was defined as excitable when TMS elicited at least two reproducible MEPs of at least 50 μ V of amplitude.

EMG Recordings

Motor responses (MEPs) were recorded from the ADM (17 patients) and EDC (seven patients) muscles contralateral to the stimulated hemisphere with a pair of 12 mm diameter surface Ag-AgCl electrodes taped in a belly-tendon montage. The amplified (100 μ V to 1 mV/div) and bandpass-filtered (0.1 Hz to 2 kHz) electromyographic (EMG) raw signal was digitized at a 20 kHz sampling rate and fed into a laboratory computer.

Experimental Procedures

'Rest' versus ADM-'Think'

In 17 patients, ADM motor maps were recorded successively during two experimental conditions: (i) complete mental and muscular relaxation ('rest'); and (ii) imagery of little finger abduction (ADM-'think'), in which patients were instructed to feel from inside rather than view from the outside the imagined movement and were asked to imagine doing movement with the same force, speed and repetition rate (\sim 0.3 c/s) as the actual performance. Before testing was initiated, subjects practiced until they were confident of appropriately performing the tasks. During this training stage, in order to check for the reliability of the ADM-'think' experimental condition, subjects were required to perform with the unaffected hand exactly what they were imagining. Only when the type of thought movement was correspondent to the required task, then subjects were asked to retain that imagery pattern and to perform it mentally for the affected hand. Magnetic stimuli were delivered 2–3 s after the appropriate verbal command (ADM-'think') given by one of the experimenters and therefore well outside the limits for a reaction time; in the interval between two successive stimuli, the subject was asked not to think about movement. The order of the experimental conditions was 'rest' and ADM-'think'. Randomization was not undertaken to avoid motor imagery continuing to operate during the rest condition. EMG monitoring and audio-feedback were used to make sure that patients did not contract their muscles at 'rest' and during ADM-'think'. Trials with unwanted EMG activity were off-line discarded from the analysis.

ADM-'think' versus ADM-'contr'

In seven patients, the ADM motor maps were also recorded during the voluntary contraction of the target muscle (ADM-'contr'). Patients were asked to perform active voluntary abduction of the little finger monitored by an EMG audio-feedback in order to check the level of EMG activity during the task. The order of the experimental conditions was 'rest', ADM-'think' and ADM-'contr' and the procedure was the same as in 'Rest' versus ADM-'Think'.

Table 1
Stroke patients characteristics

Patient	Age	Lesion side and location	Outcome measures			
			Barth	MRC	Canadian	MI (UL)
1	67	Left P-T (cort)	55	4	9.5 (1)	84
2	55	Right F-P-T (cort/subcort)	50	3	8.5 (0.5)	34
3	65	Left IC	55	3	8 (0.5)	60
4	45	Right F-P-T (cort)	55	4	9.5 (1)	60
5	59	Right IC	80	3	8 (0.5)	91
6	72	Left P-T (cort)	70	4	9.5 (1)	84
7	62	Left IC	85	4	9 (1)	66
8	72	Left P-T (cort/subcort)	55	3	8 (0.5)	55
9	52	Left P-T (cort)	65	4	8.5 (1)	76
10	78	Left P-T (cort/subcort)	40	2	8 (0.5)	39
11	60	Right F-P-T (cort)	65	3	7.5 (0.5)	76
12	45	Left P-T (cort)	80	5	10 (1.5)	100
13	65	Right IC	80	3	7 (0.5)	100
14	74	Right P-T (cort)	85	4	9 (0.5)	76
15	61	Left IC	85	3	7 (0.5)	84
16	80	Right F-P-T (cort/subcort)	40	2	8 (0.5)	38
17	70	Left P-T (cort)	85	4	8.5 (1)	100
Mean	63.6		66.5	3.4	8.4 (0.7)	71.9
SD	10.4		16.0	0.8	0.9 (0.3)	21.6

Barth = Barthel Index; MRC = Medical Research Council scale; Canadian = Canadian Neurological scale (hand sub-score); MI (UL) = Motricity Index (Upper Limbs); P-T = parieto-temporal; F-P-T = fronto-parieto-temporal; IC = internal capsule.

ADM-‘think’ in Target (ADM) versus Control (EDC) Muscles

In the same subgroup of seven patients, motor maps were simultaneously recorded from the ADM and EDC muscles at ‘rest’ and during motor imagery of the target muscle (ADM-‘think’). The experimental procedure was the same as in ‘Rest’ versus ADM-‘Think’.

Data Analysis

The following neurophysiological parameters were measured: (i) excitability threshold; (ii) MEPs amplitude and latency from the ‘hot spot’ site (‘hot spot’-MEPs); (iii) motor maps area, defined as the number of scalp positions from which MEPs were elicited; and (iv) motor maps volume, which was the sum of the averaged MEPs amplitude from each excitable scalp positions; a logarithmic transformation ($\log \mu\text{V}$) was applied to amplitudes values in order to normalize data distribution.

For better data interpretation a parametric statistical analysis was used, taking into account all sources of variations. We applied analysis of variance (ANOVA) for repeated measures as the main statistical procedure, in which factors were always considered as within-subject, except when motor imagery effects were compared in right versus left cortical and in cortical versus capsular lesion patients; in these latter analyses we used Group as the between-subjects factor. To study the effect of motor imagery on ADM muscle maps area and volume, we employed Hemisphere (AH versus UH) and Condition (‘rest’ versus ADM-‘think’) as the main factors, while to analyze the specificity of this effect on target muscle, the factors Muscle (ADM versus EDC) and Condition were used, and the ANOVA was performed separately for each hemisphere. We also compared the effects of motor imagery to those of the voluntary contraction of the same muscle involved in the imagery task (ADM-‘contr’), using Hemisphere (AH versus UH) and Condition (‘rest’, ADM-‘think’ and ADM-‘contr’) as factors. Finally, statistical comparison between right versus left cortical and cortical versus capsular lesion patients was performed to evaluate if motor imagery effects on motor map area and volume were different with respect to the stroke locations. For all ANOVA, the main factors and their interaction were calculated. We performed *post hoc* comparisons (Tukey’s test) when the interaction was statistically significant. The assumption of sphericity was checked using Mauchly’s test, which did not result significant; no correction to degrees of freedom was applied. When just two means were compared Student’s *t*-test was used. Throughout all the statistical analysis, *P* value of 0.05 was set as level of significance.

Results

Motor Thresholds, ADM Muscle ‘Hot Spot’-MEPs Amplitude and Latency

At rest, mean values of threshold intensities were higher ($P < 0.001$), MEP amplitudes were smaller ($P < 0.05$) and latencies longer ($P < 0.001$) in the AH compared with UH. ‘Hot spot’-MEP amplitudes significantly increased in both the AH and UH during the ADM-‘think’ ($P < 0.05$) and ADM-‘contr’ conditions ($P < 0.001$) compared with ‘rest’. ‘Hot spot’-MEP latencies significantly shortened in both hemispheres ($P < 0.001$) only during ADM-‘contr’ and did not change during ADM-‘think’ (Table 2).

Table 2

Mean values (\pm SD) of excitability thresholds, MEPs amplitude and latency from the ‘hot spot’ in the affected (AH) and unaffected (UH) hemispheres at rest (‘rest’), during voluntary contraction (‘contr’) and during motor imagery (‘think’) of the ADM muscle

	Threshold		MEPs amplitude		MEPs latency	
	AH	UH	AH	UH	AH	UH
‘rest’	60.5 \pm 16.4	47.5 \pm 11.4	248 \pm 220	556 \pm 349	25.3 \pm 2.3	22.0 \pm 0.7
‘contr’			2179 \pm 2329	4621 \pm 2663	23.2 \pm 0.9	19.8 \pm 0.3
‘think’			532 \pm 496	1118 \pm 812	25.2 \pm 2.9	21.8 \pm 0.9

Motor Imagery Effects on the ADM Muscle Motor Maps

An enhancement of motor cortex excitability was observed in the AH and UH during motor imagery task compared with ‘rest’. The two-way ANOVA performed on the ADM map area showed a significant difference in the factor Condition [$F(1,18) = 45.34$; $P < 0.001$] as in the interaction Hemisphere \times Condition [$F(1,18) = 25.80$; $P < 0.001$]. Post-hoc comparisons revealed that motor imagery significantly enlarged the ADM map area in both AH ($P < 0.001$) and UH ($P < 0.05$). The number of excitable scalp sites at ‘rest’ was smaller in AH (5.8 ± 3.2) than UH (8.7 ± 3.2 , $P < 0.001$) whereas it became almost identical in the two hemispheres (AH = 11.2 ± 4.1 ; UH = 10.5 ± 3.7), and the interhemispheric difference of this parameter was no longer observed during ADM-‘think’. Data analysis of the ADM map volume revealed that both main factors Hemisphere [$F(1,17) = 15.21$; $P < 0.001$] and Condition [$F(1,17) = 50.51$; $P < 0.001$] and the interaction Hemisphere \times Condition were significant [$F(1,17) = 6.86$; $P < 0.05$]. At post-hoc comparisons, motor imagery significantly increased the ADM map volume of the AH ($P < 0.001$) and UH ($P < 0.05$). The ADM map volume was smaller in AH compared with UH at ‘rest’ (AH = $2.8 \log \mu\text{V} \pm 0.8$; UH = $3.4 \log \mu\text{V} \pm 0.6$, $P < 0.001$) as well as during ADM-‘think’ (AH = $3.4 \log \mu\text{V} \pm 0.5$; UH = $3.7 \log \mu\text{V} \pm 0.6$, $P < 0.05$). Histograms of the ADM map area and volume of the AH and UH at ‘rest’ and during ADM-‘think’ are reported in Figure 1A and B respectively. In Figure 2 the two-dimensional flattened maps of the ADM muscle in the affected (AH) and unaffected (UH) hemisphere of a representative stroke patient are shown. In this patient (no. 6 in Table 1), the motor cortical output was reduced in the AH compared with UH at ‘rest’, and it significantly increased during ADM-‘think’ in a way which partly corrected the abnormal interhemispheric asymmetry of cortical excitability observed at rest condition; this finding suggested that, in this patient, motor imagery induced a greater amount of facilitation in the AH than UH.

Voluntary Contraction Effects on the ADM Muscle Motor Maps

An enhancement of the ADM motor maps area ($P < 0.001$) and volume ($P < 0.001$) was observed in the AH and UH during voluntary contraction of the target muscle compared with rest condition. When the effects of the voluntary contraction were compared with those induced by motor imagery, we found that ADM-‘contr’ induced a greater amount of excitability changes on maps area ($P < 0.05$) and volume ($P < 0.001$) than ADM-‘think’ in the UH, whereas the motor output facilitation induced by ADM-‘contr’ was very similar to that of ADM-‘think’ in the AH.

Motor Imagery Effects on ADM (Target) versus EDC (Control) Muscles Motor Maps

During ADM-‘think’, excitability changes were demonstrated on cortical representation of the ADM muscle whereas no significant facilitatory effects were observed on motor maps area and volume of the EDC muscle not involved in the imagery task. At ‘rest’, the EDC map area was 6.3 ± 2.4 (AH) and 6.8 ± 1.5 (UH), and the map volume was $2.9 \log \mu\text{V} \pm 0.4$ (AH) and $3.1 \log \mu\text{V} \pm 0.4$ (UH); only a slight increase of the EDC muscle maps area (AH = 7.6 ± 2.3 ; UH = 8.1 ± 2.1) and volume (AH = $3.0 \log \mu\text{V} \pm 0.3$; UH = $3.3 \log \mu\text{V} \pm 0.4$) was observed during ADM-‘think’ compared with ‘rest’. Figure 3 shows the

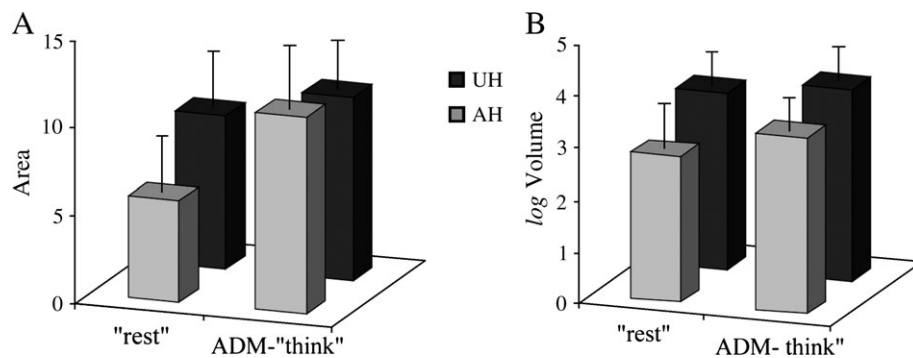


Figure 1. Histograms (mean values and error bars) of the ADM muscle map area (A) and volume (B) of AH and UH at 'rest' and during motor imagery (ADM-'think'). Area was expressed as the number of the excitable scalp sites. Volume was expressed as the sum of averaged MEPs amplitude (after log transformation = $\log \mu\text{V}$) from each excitable scalp positions. Motor imagery significantly enlarged the ADM map area and volume of both hemispheres (AH, $P < 0.001$; UH, $P < 0.05$). The ADM map area was significantly smaller in AH compared with UH ($P < 0.001$) at 'rest', and the number of the excitable scalp sites became similar in the two hemispheres during ADM-'think'.

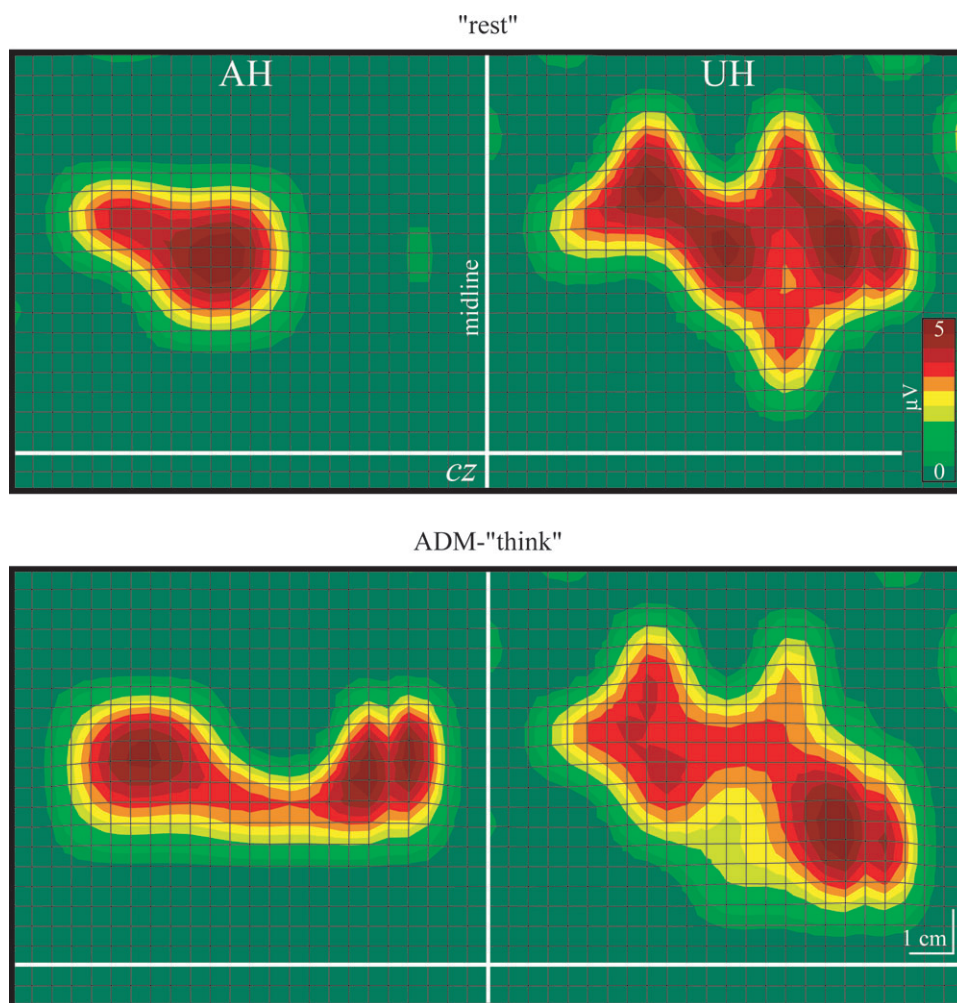


Figure 2. Two-dimensional flattened reconstruction of the ADM muscle cortical maps of AH and UH in a representative stroke patient (no. 6 in Table 1) at 'rest' and during motor imagery (ADM-'think'). The color code palette of each maps ranged from dark green (0 $\log \mu\text{V}$) to dark red (5 $\log \mu\text{V}$). The scale bar used was 1 cm for both x- and y-axes. The motor cortical facilitation induced by ADM-'think' was greater in the AH than UH, and the interhemispheric asymmetry of motor cortical output between AH and UH observed at 'rest' was corrected during the ADM-'think' task.

original MEPs recorded from the ADM and EDC muscles in the affected (AH) and unaffected (UH) hemisphere of a stroke patient. This patient (no. 13 in Table 1) suffered from an ischemic right capsular lesion. The ADM map area and volume

clearly increased from 'rest' to ADM-'think' in both hemispheres. On the other hand, no changes were observed in the map area and volume of the ECD muscle, not involved in the imagery task.

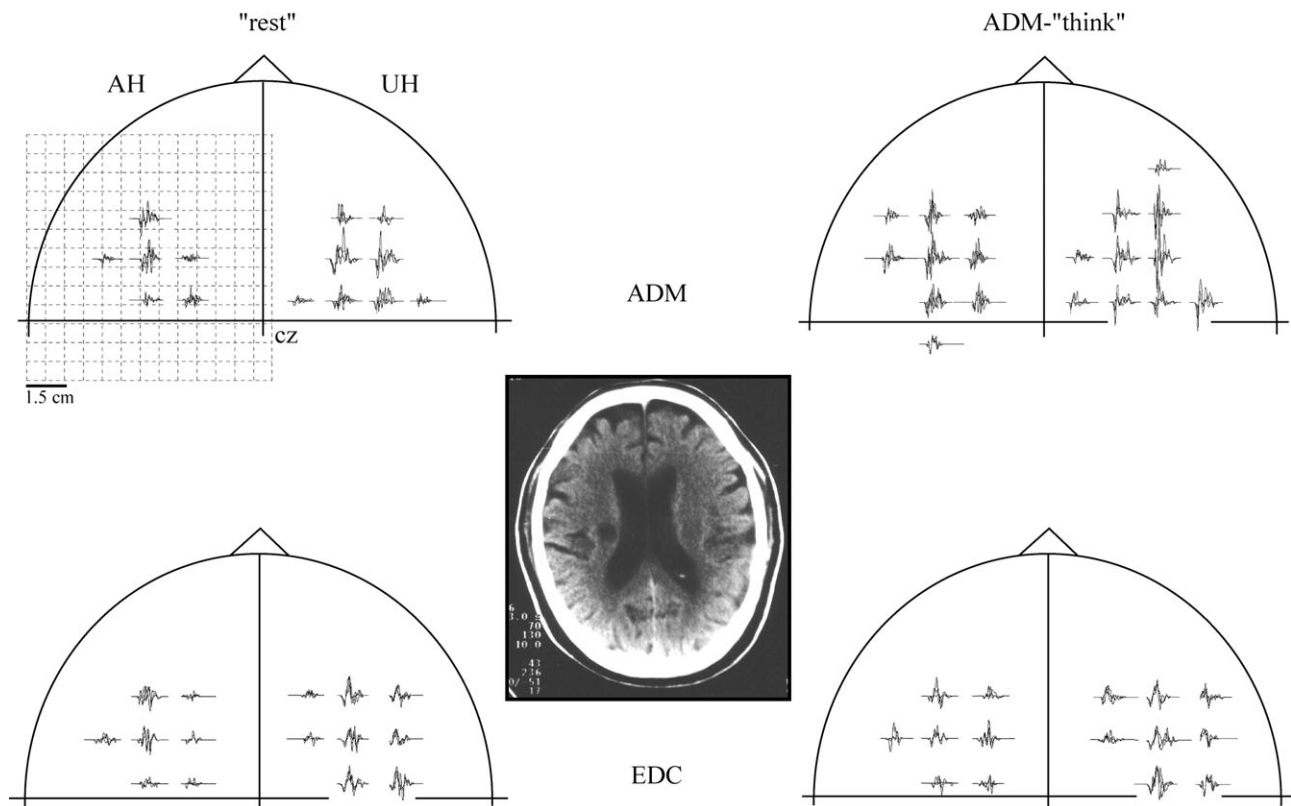


Figure 3. Cortical maps showing the original MEPs of the ADM (upper) and EDC (lower) muscles of AH and UH in a stroke patient (no. 13 in Table 1) with an ischemic capsular lesion on the right hemisphere. A real grid (light grey dotted line) was superimposed on the schematic head to show the stimulated scalp sites. The number of excitable sites (ADM map area) and MEPs amplitude (ADM map volume) clearly increased from 'rest' to ADM-'think' in both the AH and UH. Conversely, no changes were observed in the map area and volume of the EDC muscle.

Motor Imagery Effects in Respect to the Stroke Lesion Locations

The imagery-induced cortical excitability changes were not different in right (five patients) versus left cortical (seven patients) or in cortical (12 patients) versus capsular (five patients) lesion patients, as shown by the lack of significant results for main factors and their interactions (three-way ANOVA: Group \times Hemisphere \times Condition). However, because of the small patients sample size in each subgroup, these results should be confirmed in a larger population of patients.

Discussion

In the present study we found that motor imagery significantly enhances the cortical representation of a hand muscle in a population of hemiparetic post-acute stroke patients. This motor output facilitation is more marked in the stroke than in the unaffected hemisphere, in a way which partly corrects the reduced cortical excitability of the affected motor cortex observed in rest condition. Motor imagery appears to induce a good synchronization of the corticospinal output of the affected hemisphere, and the cortical excitability changes induced by the imagery task are very similar to those observed during voluntary contraction of the paretic hand. The motor imagery effects on stroke hemisphere are found to be selective on the synaptic efficacy at the map periphery, as shown by the recruitment of additional scalp sites (map area) rather than enhancement of the amplitude of motor responses (map

volume). Additionally, the excitability changes are specific for the cortical representation of the muscle involved as 'prime mover' in the imagery task, confirming that, as previously reported in healthy subjects, the imagery facilitation is strictly related to the motor strategy planned by the subject (Rossi *et al.*, 1998; Fadiga *et al.*, 1999, 2002; Rossini *et al.*, 1999). This focal and specific imagery-induced motor output facilitation is observed in both hemispheres of patients, suggesting that the ability to imagine movements is preserved for both non-paretic as well paretic hand. Some authors (Sirigu *et al.*, 1996; Johnson, 2000) reported that patients with parietal lesions lose their ability to perform several motor imagery tasks. In the present study, no differences were observed when the imagery-induced motor output facilitation was evaluated with respect to the stroke lesion locations, allowing us to speculate that also patients with parietal lesions do not have difficulty to mentally represent a simple finger abduction task.

The pattern of imagery-induced facilitation is different in the affected compared with unaffected hemisphere, probably for a different excitatory state of the motor cortex in the damaged hemisphere, which could be due to a decrease of the inhibitory inputs to the M1. This finding is well supported by several TMS studies investigating the excitability of the M1 inhibitory interneurons by the paired-pulse technique, that reported a reduced amount of intracortical inhibition in the affected hemisphere of stroke patients (Liepert *et al.*, 2000; Cicinelli *et al.*, 2003). Meanwhile, in healthy subjects, the imagery-induced cortical excitability changes occur as a result of

decreased activity in the inhibitory circuits within the motor cortex (Abbruzzese *et al.*, 1999; Stinear and Byblow, 2004). Furthermore, in animal models of focal infarct, a down-regulation of GABA_A receptors is shown in the ipsilesional and contralesional hemisphere for a long period after the brain damage (Nudo and Duncan, 2004). These functional changes could explain the M1 hyperexcitability.

Why M1 Should Be more Excitable Following Stroke?

Converging studies support the notion that the motor system reacts to a damage in a way that attempts to generate the best functional motor output given the anatomical constraints (Johansen-Berg *et al.*, 2002; Miyai *et al.*, 2003). Motor cortex hyperexcitability has been described following stroke and its role in cortical reorganization has also been suggested. (Nudo, 1999; Liepert *et al.*, 2000; Manganotti, 2002). Several explanations can account for this M1 hyperexcitability. First, in cortical lesions affecting a portion of M1 and in subcortical lesions affecting a contingent of corticospinal fibers, one possible reason arises from a mismatch between the dispatched motor program and the sensory feedback; in other words, the 'target' muscles are less energized by the usual gradation of output stemming from M1. Consequently, the motor system needs to be settled at a different output 'gain', in order to achieve the same performance (strength, speed etc.). Another possibility is that lesions partially affecting the M1 and/or the corticospinal pathway may lead to the enrolment of the secondary motor areas with their own projections, which are known to be less numerous and less excitatory at the spinal level than those from M1 (Maier *et al.*, 2002). Thus, the motor cortex hyperexcitability could be necessary to generate an output to the spinal motoneurons in the most efficient way. Finally, in cortical lesions that spared the primary motor system, the M1 hyperexcitability might be the result of a deregulation of the excitatory/inhibitory circuits, due to the breakdown of the reciprocal connections within the parieto-frontal network. The functional consequences of this M1 hyperexcitability could be a facilitation of the activity-dependent plastic changes.

What Will Be the Benefit of the Motor Imagery in the Post-stroke Rehabilitation?

The recovery from stroke is likely to be a function of neuronal reorganization within the remaining motor-related areas and it is widely recognized that this reorganization is correlated to the degree of damage in the motor system. It is reported that, when M1 is damaged, the dorsal part of the premotor cortex seems to behave as an 'executive' motor region, becoming a crucial node for the motor command (for a review, see Ward, 2004). On the other hand, the recovery would be optimal when M1 is not only preserved structurally, as after subcortical — as opposed to cortical — strokes, but is also capable of enhanced workload, i.e. it is not completely disconnected. In this case, the unmasking of previously silent synapses, as well as enhanced input from neighbouring premotor and supplementary motor areas, would implement this over recruitment of the affected-side M1. Within this theoretical framework, it is conceivable that mental imagery of movements, which shares features with the actual motor performance, when combined with rehabilitation procedure, would concur in driving the reorganization of the new functional motor architecture, that critically depend on the surviving elements of the network and on their efficacy.

To the best of our knowledge, this is the first study demonstrating that motor imagery induces a motor output facilitation in a hemisphere affected by a vascular lesion. However, this observation is strictly true for a patients population in whom the motor system is partially spared. At present, we still do not know if imagery-induced excitability changes correlate with short-term brain plasticity and further studies are needed to evaluate if the use of mental practice will give benefits in the rehabilitation of post-stroke motor disorders.

Notes

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References

- Abbruzzese G, Trompetto C, Schieppati M (1996) The excitability of the human motor cortex increases during execution and mental imagination of sequential but not repetitive finger movements. *Exp Brain Res* 111:465–472.
- Abbruzzese G, Assini A, Buccolieri A, Marchese R, Trompetto C (1999) Changes of intracortical inhibition during motor imagery in human subjects. *Neurosci Lett* 263:113–116.
- Cicinelli P, Pasqualetti P, Zaccagnini M, Traversa R, Oliveri M, Rossini PM (2003) Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. *Stroke* 34:2653–2658.
- Cotè R, Battista RN, Wolfson C, Boucher J, Adam J, Hachinski V (1989) The Canadian Neurological Scale: validation and reliability assessment. *Neurology* 39:638–643.
- Decety J (1996) The neurophysiological basis of motor imagery. *Behav Brain Res* 77:45–52.
- Decety J, Jeannerod M, Prablanc C (1989) The timing of mentally represented actions. *Behav Brain Res* 34:35–42.
- Dechent P, Merboldt KD, Frahm J (2004) Is the human primary motor cortex involved in motor imagery? *Brain Res Cogn Brain Res* 19:138–144.
- Demeurisse G, Demol O, Robaye E (1980) Motor evaluation in vascular hemiplegia. *Stroke* 11:382–389.
- Dijkerman HC, Letswaart M, Johnston M, MacWalter RS (2004) Does motor imagery training improve hand function in chronic stroke patients? A pilot study. *Clin Rehabil* 18:538–549.
- Facchini S, Muellbacher W, Battaglia F, Boroojerdi B, Hallett M (2002) Focal enhancement of motor cortex excitability during motor imagery: a transcranial magnetic stimulation study. *Acta Neurol Scand* 105:146–151.
- Fadiga L, Buccino G, Craighero L, Fogassi L, Gallese V, Pavesi G (1999) Corticospinal excitability is specifically modulated by motor imagery: a magnetic stimulation study. *Neuropsychologia* 37:147–158.
- Fadiga L, Craighero L, Buccino G, Rizzolatti G (2002) Speech listening specifically modulates the excitability of tongue muscles: a TMS study. *Eur J Neurosci* 15:399–402.
- Feltz DL, Landers DM (1983) The effects of mental practice on motor skill learning and performance: a meta-analysis. *J Sport Psychol* 5:25–27.
- Gerardin E, Sirigu A, Lehericy S, Poline JB, Gaymard B, Marsault C, Agid Y, Le Bihan D (2000) Partially overlapping neural networks for real and imagined hand movements. *Cereb Cortex* 10:1093–1104.
- Hanakawa T, Immisch I, Toma K, Dimyan MA, Van Gelderen P, Hallett M (2003) Functional properties of brain areas associated with motor execution and imagery. *J Neurophysiol* 89:989–1002.
- Hashimoto R, Rothwell JC (1999) Dynamic changes in corticospinal excitability during motor imagery. *Exp Brain Res* 125:75–81.
- Jackson PL, Laffeur MF, Malouin F, Richards C, Doyon J (2001) Potential role of mental practice using motor imagery in neurologic rehabilitation. *Arch Phys Med Rehabil* 82:1133–1141.
- Jeannerod M (1994) The representing brain: neural correlates of motor intention and imagery. *Behav Brain Sci* 17:187–245.
- Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM (2002) Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Neurology* 58:2731–2742.

- Johnson SH (2000) Imagining the impossible: intact motor representations in hemiplegics. *Neuroreport* 11:729-732.
- Johnson SH, Sprehn G, Saykin AJ (2002) Intact motor imagery in chronic upper limb hemiplegics: evidence for activity-independent action representations. *J Cogn Neurosci* 14:841-852.
- Johnson-Frey SH (2004) Stimulation through simulation? Motor imagery and functional reorganization in hemiplegic stroke patients. *Brain Cogn* 55:328-331.
- Kasai T, Kawai S, Kawanishi M, Yahagi S (1997) Evidence for facilitation of motor evoked potentials (MEPs) induced by motor imagery. *Brain Res* 744:147-150.
- Kiers L, Fernando B, Tomkins D (1997) Facilitatory effect of thinking about movement on magnetic motor-evoked potentials. *Electroencephalogr Clin Neurophysiol* 105:262-268.
- Levin O, Steyvers M, Wenderoth N, Li Y, Swinnen SP (2004) Dynamical changes in corticospinal excitability during imagery of unimanual and bimanual wrist movements in humans: a transcranial magnetic stimulation study. *Neurosci Lett* 359:185-189.
- Li S, Latash ML, Zatsiorsky VM (2004) Effects of motor imagery on finger force responses to transcranial magnetic stimulation. *Brain Res Cogn Brain Res* 20:273-280.
- Liepert J, Storch P, Fritsch A, Weiller C (2000) Motor cortex disinhibition in acute stroke. *Clin Neurophysiol* 111:671-676.
- Mahoney FI, Barthel DW (1965) Functional evaluation: the Barthel Index. *Md State Med J* 14:61-65.
- Maier MA, Armand J, Kirkwood PA, Yang HW, Davis JN, Lemon RN (2002) Differences in the corticospinal projection from primary motor cortex and supplementary motor area to macaque upper limb motoneurons: an anatomical and electrophysiological study. *Cereb Cortex* 12:281-296.
- Manganotti P, Patuzzo S, Cortese F, Palermo A, Smania N, Fiaschi A (2002) Motor disinhibition in affected and unaffected hemisphere in the early period of recovery after stroke. *Clin Neurophysiol* 113:936-943.
- Medical Research Council Scale (1976) Aids to the examination of the peripheral nervous system. Memorandum no. 45. London: Her Majesty's Stationery Office.
- Miyai I, Yagura H, Hatakenaka M, Oda I, Konishi I, Kubota K (2003) Longitudinal optical imaging study for locomotor recovery after stroke. *Stroke* 34:2866-2870.
- Mulder T, Zijlstra S, Zijlstra W, Hochstenbach J (2004) The role of motor imagery in learning a totally novel movement. *Exp Brain Res* 154:211-217.
- Nudo RJ (1999) Recovery after damage to motor cortical areas. *Curr Opin Neurobiol* 9:740-747.
- Nudo RJ, Duncan PW (2004) Recovery and rehabilitation in stroke: introduction. *Stroke* 35(11 Suppl 1):2690.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97-113.
- Page SJ, Levine P, Sisto SA, Johnston MV (2001) Mental practice combined with physical practice for upper-limb motor deficit in subacute stroke. *Phys Ther* 81:1455-1462.
- Parsons LM (1994) Temporal and kinematic properties of motor behavior reflected in mentally simulated action. *J Exp Psychol Hum Percept Perform* 20:709-730.
- Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M (1995) Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J Neurophysiol* 74:1037-1045.
- Rodriguez M, Muniz R, Gonzalez B, Sabate M (2004) Hand movement distribution in the motor cortex: the influence of a concurrent task and motor imagery. *Neuroimage* 22:1480-1491.
- Rossi S, Pasqualetti P, Tecchio F, Pauri F, Rossini PM (1998) Corticospinal excitability modulation during mental simulation of wrist movements in human subjects. *Neurosci Lett* 243:1-5.
- Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 91:79-92.
- Rossini PM, Rossi S, Pasqualetti P, Tecchio F (1999) Corticospinal excitability modulation to hand muscles during movement imagery. *Cereb Cortex* 9:161-167.
- Roth M, Decety J, Raybaudi M, Massarelli R, Delon-Martin C, Segebarth C, Morand S, Gemignani A, Decorps M, Jeannerod M (1996) Possible involvement of primary motor cortex in mentally simulated movement: a functional magnetic resonance imaging study. *Neuroreport* 7:1280-1284.
- Sirigu A, Duhamel JR (2001) Motor and visual imagery as two complementary but neurally dissociable mental processes. *J Cogn Neurosci* 13:910-919.
- Sirigu A, Cohen L, Duhamel JR, Pillon B, Dubois B, Agid Y, Pierrat-Deseilligny C (1995) Congruent unilateral impairments for real and imagined hand movements. *Neuroreport* 6:997-1001.
- Sirigu A, Duhamel JR, Cohen L, Pillon B, Dubois B, Agid Y (1996) The mental representation of hand movements after parietal cortex damage. *Science* 273:1564-1568.
- Stevens JA, Stoykov ME (2003) Using motor imagery in the rehabilitation of hemiparesis. *Arch Phys Med Rehabil* 84:1090-1092.
- Stinear CM, Byblow WD (2003) Motor imagery of phasic thumb abduction temporally and spatially modulates corticospinal excitability. *Clin Neurophysiol* 114:909-914.
- Stinear CM, Byblow WD (2004) Modulation of corticospinal excitability and intracortical inhibition during motor imagery is task-dependent. *Exp Brain Res* 157:351-358.
- Stippich C, Ochmann H, Sartor K (2002) Somatotopic mapping of the human primary sensorimotor cortex during motor imagery and motor execution by functional magnetic resonance imaging. *Neurosci Lett* 331:50-54.
- Vargas CD, Olivier E, Craighero L, Fadiga L, Duhamel JR, Sirigu A (2004) The influence of hand posture on corticospinal excitability during motor imagery: a transcranial magnetic stimulation study. *Cereb Cortex* 14:1200-1206.
- Ward NS (2004) Functional reorganization of the cerebral motor system after stroke. *Curr Opin Neurol* 17:725-730.
- Weiss T, Hansen E, Beyer L, Conradi ML, Merten F, Nichelmann C, Rost R, Zippel C (1994a) Activation processes during mental practice in stroke patients. *Int J Psychophysiol* 17:91-100.
- Weiss T, Hansen E, Rost R, Beyer L, Merten F, Nichelmann C, Zippel C (1994b) Mental practice of motor skills used in poststroke rehabilitation has own effects on central nervous activation. *Int J Neurosci* 78:157-166.
- Yahagi S, Kasai T (1998) Facilitation of motor evoked potentials (MEPs) in first dorsal interosseous (FDI) muscle is dependent on different motor images. *Electroencephalogr Clin Neurophysiol* 109:409-417.
- Yahagi S, Shimura K, Kasai T (1996) An increase in cortical excitability with no change in spinal excitability during motor imagery. *Percept Mot Skills* 83:288-290.
- Yoo E, Park E, Chung B (2001) Mental practice effect on line-tracing accuracy in persons with hemiparetic stroke: a preliminary study. *Arch Phys Med Rehabil* 82:1213-1218.
- Yue G, Cole KJ (1992) Strength increases from the motor program: comparison of training with maximal voluntary and imagined muscle contractions. *J Neurophysiol* 67:1114-1123.