

# Motor learning elicited by voluntary drive

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## Summary

Motor training consisting of voluntary movements leads to performance improvements and results in characteristic reorganizational changes in the motor cortex. It has been proposed that repetition of passively elicited movements could also lead to improvements in motor performance. In this study, we compared behavioural gains, changes in functional MRI (fMRI) activation in the contralateral primary motor cortex (cM1) and in motor cortex excitability measured with transcranial magnetic stimulation (TMS) after a 30 min training period of either voluntarily (active) or passively (passive) induced wrist movements, when alertness and kinematic aspects of training were controlled. During active training, subjects were instructed to perform voluntary wrist flexion–extension movements of a specified duration (target window 174–186 ms) in an articulated splint. Passive training consisted of wrist flexion–extension movements elicited by a torque motor, of the

same amplitude and duration range as in the active task. fMRI activation and TMS parameters of motor cortex excitability were measured before and after each training type. Motor performance, measured as the number of movements that hit the target window duration, was significantly better after active than after passive training. Both active and passive movements performed during fMRI measurements activated cM1. Active training led to more prominent increases in (i) fMRI activation of cM1; (ii) recruitment curves (TMS); and (iii) intracortical facilitation (TMS) than passive training. Therefore, a short period of active motor training is more effective than passive motor training in eliciting performance improvements and cortical reorganization. This result is consistent with the concept of a pivotal role for voluntary drive in motor learning and neurorehabilitation.

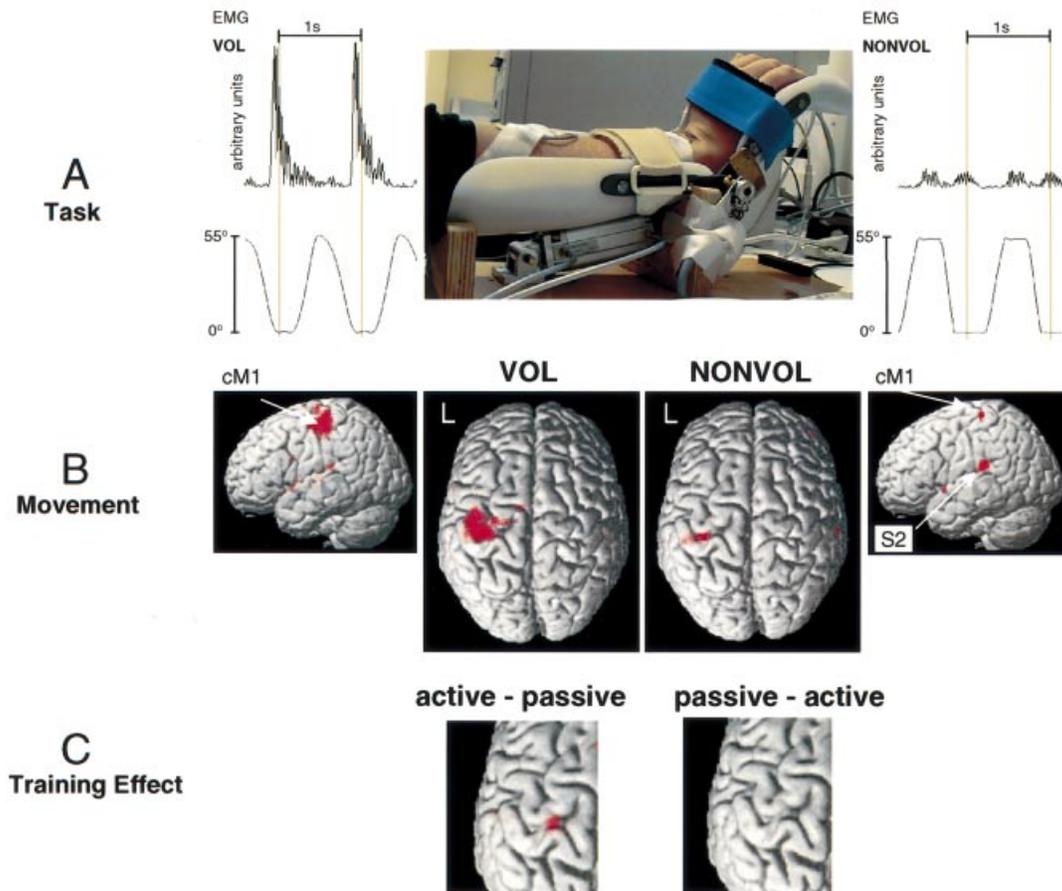
**Keywords:** motor performance; active and passive training; TMS; fMRI; motor learning

**Abbreviations:** cM1 = contralateral primary motor cortex; ECR = extensor carpi radialis; EPI = echo planar imaging; fMRI = functional MRI; ICF = intracortical facilitation; ICI = intracortical inhibition; MEP = motor evoked potentials; MT = resting motor threshold; nonvol = non-voluntary; RC = recruitment curves; S2 = secondary somatosensory cortex; SPM = statistical parametric mapping; TMS = transcranial magnetic stimulation; vol = voluntary

## Introduction

Motor training results in performance improvements that are associated with cortical reorganization (Nudo *et al.*, 1996; Karni *et al.*, 1995; Pascual-Leone *et al.*, 1995; Shadmehr and Holcomb, 1997; Classen *et al.*, 1998; Muellbacher *et al.*, 2001). Recent studies demonstrated that somatosensory input in the form of peripheral nerve stimulation results in functional changes in corticomotor excitability (Ridding *et al.*, 2000; Stefan *et al.*, 2000; Kaelin-Lang *et al.*, 2003). The link between somatosensory input and motor output is emphasized further by reports demonstrating that somatosensory stimulation of peripheral nerves leads to improvement of motor functions mediated by the stimulated body part

in patients with brain lesions (Struppler *et al.*, 1996; Conforto *et al.*, 2002). Additionally, training consisting of performance of passive movements in functionally relevant contexts often is utilized in rehabilitative medicine, particularly when patients with brain lesions such as stroke are not able or are too weak to perform voluntary movements (e.g. Hummelsheim and Eickhof, 1999). It has been also reported that performance of passively elicited movements activates cortical regions similar to those activated by voluntary movements (Weiller *et al.*, 1996; Carel *et al.*, 2000; see also Mima *et al.*, 1999). These results led to the proposal that training consisting of performance of passive movements



**Fig. 1** (A) Forearm and hand of a healthy volunteer positioned on the splint and connected to a torque motor (centre). Subjects performed voluntary and passively elicited wrist extension movements during active and passive motor training, respectively. Averaged rectified EMG and wrist extension associated with representative voluntary (vol, left) and non-voluntary (nonvol, right) movements. After amplification (500 times) and highpass filtering (5 Hz), the EMG signal was digitized at 5 kHz. During the non-voluntary movement, EMG showed two peaks: one following the splint elevation and one following the lowering of the hand. Note the similar maximal displacement of the splint in both movement types. (B) Top and lateral left view of fMRI activation patterns of all subjects ( $n = 12$ ) during voluntary (vol) and non-voluntary (nonvol) movements projected on the SPM99 single subject segmented brain. Both vol and nonvol showed cM1 activation; nonvol additional activation was seen in the left secondary somatosensory cortex (S2; corrected for the whole brain volume with  $P < 0.05$ ). (C) Active training resulted in significantly higher activation in cM1 than passive training (post-pre;  $t = 8.45$ ;  $P_c < 0.05$ , left). Passive training showed no significant effect if compared with active training (right).

could be as effective as active movements in eliciting reorganization in the primary motor cortex and possibly result in similar behavioural gains (Alary *et al.*, 1998; Carel *et al.*, 2000).

This study was designed to compare the behavioural and functional neurophysiological changes associated with performance of a 30 min training period of passively induced or voluntary movements in a group of healthy volunteers when kinematic aspects of training and alertness were controlled.

## Methods

### Paradigm

During training, subjects ( $n = 25$ , 18 of them females, age  $27.08 \pm 8.22$  years) were seated. Their forearms and hands were immobilized with Velcro on an articulated splint that allowed comfortable wrist movements (Fig. 1). The elbow

position was kept stable during the experiments. The order of training sessions, active or passive, each lasting for 30 min, was counterbalanced across subjects. Eight subjects [six investigated with transcranial magnetic stimulation (TMS), one with functional MRI (fMRI), and one with fMRI for active training, and with TMS for passive training] participated in both active and passive training sessions with the order randomized and separated by 3 months or more. Prior to fMRI data acquisition, the participants signed an informed consent form. The study conformed with the Declaration of Helsinki and was approved by the local ethics committee of the Medical Faculty at The University of Tübingen.

### Active training

Subjects were instructed to perform 300 voluntary wrist flexion–extension movements of a specified duration (target

**Table 1** Psychophysical evaluations and movement duration during training

	TMS and fMRI	
	Active average (SD)	Passive average (SD)
Reward (Euro)	25.53 (11.83)	24.35 (13.02)
Concentration (VAS)	6.97 (1.68)	6.69 (1.80)
Motivation (VAS)	5.17 (1.98)	4.96 (1.42)
Frustration/satisfaction (VAS)	7.12 (1.26)	6.32 (2.00)
Movement duration (ms)	184.87 (8.86)	177.81 (9.34)
Movement range	55°	55°
Velocity (°/s)	297.51	309.32

VAS = visual analogue scale.

window 174–186 ms) in an articulated splint (Fig. 1A). Each training movement was performed in response to a go signal displayed on the screen, starting at a resting position and ending at the maximal excursion level of the splint (~55°). Preliminary experiments demonstrated that a target window of 174–186 ms led, over a 30 min training period, to a characteristic learning curve. Subjects received a feedback signal following each training movement. A red, blue or green bar displayed on a screen indicated that the movement duration for that specific trial was either too short (<174 ms), too long (>186 ms) or right on target (174–186 ms), respectively. The height of the bars indicated the distance from the target window. Hits within the target window relied on accurate control of movement duration and were rewarded with 0.15 Euro per hit. All feedback responses were recorded for playback during passive training.

### Passive training

A motor torque played back 300 passive wrist movements, with velocity, range and movement duration comparable with those in the active training (see Table 1). Each passive movement was followed by the presentation of a played back feedback signal (pre-recorded from the same subject if already tested with active training, or from another subject's active training session). The total number of feedback signals, the number of hits within the target window and the total payment received were similar to those in the active training. To maintain subjects' alertness, they were told that EEG activity induced during relaxation controlled the number of hits and therefore the financial reward (modified from Birbaumer *et al.*, 1999). For the EEG self-regulation task, two surface electrodes were positioned over Cz and over the right mastoid. The feedback signal had been pre-recorded and the subjects could not influence it. The procedure ensured maintenance of a constant attention level in the passive movement condition comparable with the active condition. After each experimental session, concentration, motivation and the subject's perception of success were assessed using visual analogue scales (0–10).

### Motor performance

After each training period, subjects were asked to perform 50 voluntary movements within the required target window. The end point measure of the study was the total number of hits after active and passive training.

### fMRI

Two fMRI determinations (~40 min duration each) were carried out before and immediately after training. Subjects lay supine in the scanner with their eyes closed. Their heads were immobilized in order to minimize movements, and the hand position on the non-magnetic splint was kept constant as described. Voluntary wrist movements (vol) were paced by an acoustic metronome, and passive wrist movements (nonvol) were elicited by a non-magnetic torque motor, both at 1 Hz. EMG was recorded during passive and active movements in the scanner immediately preceding the measurements using surface electrodes overlying the extensor carpi radialis (ECR) muscle ( $n = 11$ ; data from one individual were corrupted) and a specially designed EMG system appropriate for measurements in the fMRI environment (IED system, Hamburg; two channels; using superficial silver chloride electrodes). EMG data (digitized at 5 kHz) were filtered (high pass: 5 Hz), amplified (500 times), rectified and stored for off-line analysis. Average rectified EMG activity was calculated for each movement type, both voluntary and passively elicited (vol and nonvol).

We used echo planar imaging [EPI, matrix  $96 \times 128$ , FOV (field of view) 250 mm, TE (echo time) 59 ms, scan time 6 s, TR (repetition time) 8 s; 1.5 T scanner; Siemens Sonata] of the whole brain with 36 axially oriented slices of 3 mm slice thickness with a 1 mm gap. A total of 96 scans were obtained during each movement type (vol and nonvol; block design of six rest and six movement scans alternating 16 times). The order of vol and nonvol conditions during scans was counterbalanced. Data were analysed using the Statistical Parametric Mapping program (SPM99, Wellcome Department of Cognitive Neurology). Each individual scan was realigned to the first one of each scanning condition to correct for movement artefacts. Normalization was performed using the SPM template image ( $2 \times 2 \times 2$  mm). The EPI data were smoothed with a Gaussian filter of 6 mm. This high spatial resolution was chosen to differentiate activation within the pre- and postcentral gyrus. The coordinates of activation centres were transformed from the SPM-MNI space to the Talairach coordinates (Talairach and Tournoux, 1988) with the matlab program 'mni2tal' of Matthew Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging>). Twelve subjects (six of them females; age  $31.42 \pm 10.18$  years) participated in this part of the study.

### TMS

TMS measurements were obtained before and immediately after each training session. Subjects were seated comfortably in a reclining chair. Motor evoked potentials (MEPs) were recorded from silver chloride surface electrodes overlying the

**Table 2** fMRI data

Group statistics	Voluntary <i>t</i> values (coordinates)	Non-voluntary <i>t</i> values (coordinates)
CM1c	19.52 (-38, -20, 58)	10.54 (-36, -24, 60)
CS1	12.01 (-44, -23, 53)	7.21 (-30, -27, 49)
S2	NS	12.36 (-46, -28, 16)
Thalamus	12.81 (-14, -17, 6)	6.89 (-14, -21, 7)
Cerebellum	7.08 (20, -48, -19)	6.34 (32, -56, -22)

cS1 = contralateral primary somatosensory cortex.

right ECR muscle. Voluntary relaxation was monitored by continuous visual feedback of the EMG signal amplified to 500 $\times$ . After amplification and bandpass filtering (5–1000 Hz; notch filter: 50 Hz; Neuroscan, Herndon, USA), the EMG signal was digitized at 5 kHz. Focal TMS was delivered to the optimal scalp position for activation of ECR using a figure-of-eight coil connected to two Magstim 200 magnetic stimulators through a BiStim module (Magstim, Whitland, Dyfed, UK). The coil was placed tangentially to the scalp, with the handle pointing backward and rotated away from the midline by  $\sim 45^\circ$ . The current induced in the brain was therefore directed approximately perpendicular to the line of the central sulcus (Werhahn *et al.*, 1994). This position was marked on the scalp to ensure identical coil placement throughout the experiment. Measures of corticomotor excitability included resting motor thresholds (MTs), recruitment curves (RCs), and intracortical inhibition (ICI) and facilitation (ICF). The MT was the minimum stimulus intensity that produced MEPs  $>50 \mu\text{V}$  in at least three of five consecutive trials (Rossini *et al.*, 1994). RCs of increasing intensities of 10% steps were obtained in 10 trials per step starting at MT intensity and increasing up to 190% of the MT. MEP size provides information on neuronal excitability along the corticospinal system, which includes output cells in the motor cortex and motor neurons in the spinal cord (Devanne *et al.*, 1997; Chen *et al.*, 1998). MEP amplitudes were measured peak-to-peak from single trials, and later averaged off-line. A paired conditioning–test stimulus technique (Kujirai *et al.*, 1993; Ziemann *et al.*, 1996b) was used to study ICF and ICI in the ECR. The test stimulus intensity was adjusted to elicit an MEP of  $\sim 500$ – $1000 \mu\text{V}$  in peak-to-peak amplitude. The conditioning stimulus was set to 80% of the resting MT of the ECR. This low intensity stimulus does not produce changes in the excitability of spinal motoneurons (Kujirai *et al.*, 1993), so that any changes in the size of the control MEP elicited by the conditioning stimuli are attributable to intracortical mechanisms (Di Lazzaro *et al.*, 1998). Interstimulus intervals of 1, 2, 3, 8, 10 and 15 ms, and a test stimulus alone were presented intermixed in a pseudorandomized order and were applied 10 times each according to techniques previously described to measure corticomotor excitability. MEP amplitudes obtained at the different time intervals were expressed relative to the MEP amplitudes elicited by the test stimulus

alone (for details see Di Lazzaro *et al.*, 1998). Fourteen subjects (11 of them females; age  $23.93 \pm 3.73$  years) participated in this part of the study.

### Statistical comparisons

Motor performance and analogue scales were compared using *t* statistics for independent samples with Bonferroni correction for multiple comparisons. fMRI data were analysed using: (i) SPM 99 one-sample random effects *t* tests to identify activation elicited by voluntary (vol) and passive (nonvol) movements in the absence of training, and an SPM99 two-sample random effect *t* test to compare differential activation in contralateral primary motor cortex (cM1) across training type for both the vol and nonvol movements together (post–pre). Significant activation was corrected for the left precentral gyrus (Tzourio-Mazoyer *et al.*, 2002). TMS measures of corticomotor excitability (MT, RC and ICI–ICF) were compared using three separate ANOVAs (analyses of variance) with factors training (active/passive) and time (pre-/post-training) followed by *post hoc t* tests corrected for multiple comparisons (Bonferroni correction). The normal distribution of the data was tested by Kolmogorov–Smirnov tests in advance. All statistical tests except those for fMRI data were performed with the Statistical Package for the Social Sciences (SPSS 10.05).

## Results

### Motor training

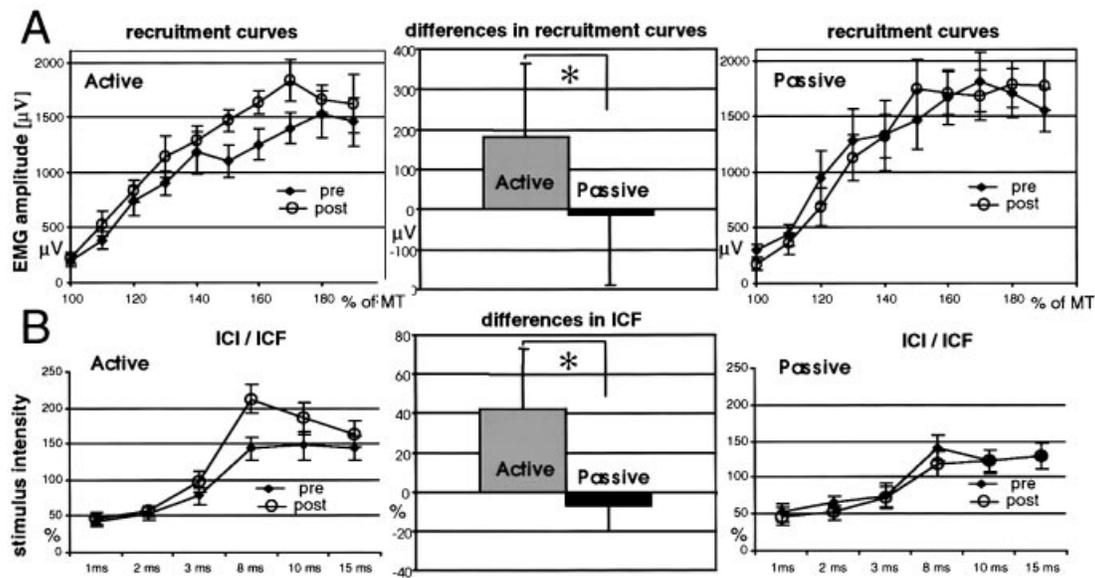
Subjects' self-assessment of concentration, motivation and satisfaction/frustration during training, as well as movement velocity, range and duration were comparable across training conditions (Table 1 and Fig. 1A).

### Motor performance

Motor performance was significantly better after active training ( $10.37 \pm 4.81$  hits per 50 trials) than after passive training [ $6.25 \pm 2.08$  hits per 50 trials;  $t(30) = 3.15$ ;  $P < 0.005$ ]. In a subgroup of subjects ( $n = 4$ ) in whom performance was tested before and after training, the active condition led to significant increases in the number of hits [from  $4.75 \pm 2.98$  to  $14.00 \pm 5.22$ ;  $t(3) = 3.07$ ;  $P < 0.05$ ], while the passive condition [from  $4.75 \pm 2.98$  to  $6.00 \pm 1.41$ ;  $t(3) = 0.76$ ; NS] did not.

### fMRI

Duration of movements and range of movements were similar in the vol and nonvol tasks (see example in Fig. 1A), while EMG activity in ECR was substantially higher in the vol than in the nonvol task (Wilcoxon test:  $z = 2.40$ ;  $P < 0.05$ ). In the initial analysis, SPM99 showed activation of contralateral primary somatosensory cortex and cM1 associated with



**Fig. 2** (A) Recruitment curves increased significantly after active (left; pre- and post-) but not after passive (right; pre- and post-) training. Differences between RC before and after training were significantly larger for active than for passive training (centre,  $*P < 0.05$ ). Bars indicate standard errors. (B) Intracortical facilitation (ICF; interstimulus interval of 8–15 ms) increased significantly after active training (left; pre- and post-) but did not change after passive training (right; pre- and post-). Differences in ICF were significantly larger for active than for passive training (centre;  $*P < 0.05$ ). Bars indicate standard errors.

**Table 3** TMS data

	Active		Passive	
	Pre-average (SD)	Post-average (SD)	Pre-average (SD)	Post-average (SD)
RMT* (%)	41.17 (6.91)	41.47 (6.92)	40.92 (4.44)	41.62 (5.50)
RC <sup>2</sup> ( $\mu\text{V}$ )	937.89 (594.68)	1145.48 (627.11)	1249.68 (860.66)	1238.45 (828.86)
ICI <sup>+</sup> (%)	54.05 (55.54)	63.77 (76.77)	64.73 (52.36)	57.00 (442.14)
ICF <sup>†</sup> (%)	143.05 (101.93)	186.40 (184.79)	131.81 (99.96)	123.48 (69.73)

\*rMT = resting motor threshold in % of the total stimulator output; RC = average recruitments 100–190% of RMT; <sup>+</sup>ICI = all values of intracortical inhibition in relation to the reference stimulus; <sup>†</sup>ICF = all values of intracortical facilitation in relation to the reference stimulus.

performance of vol and nonvol movements. Additionally, the secondary somatosensory cortex (S2), at the inferior border of the postcentral gyrus, was active only with nonvol movements (Fig. 1B; Table 2).

Active training resulted in significantly higher activation in cM1 than passive training ( $t = 8.45$ ,  $P_c < 0.05$ ; coordinates:  $-28$ ,  $-25$ ,  $53$ ; Fig. 1C).

### TMS measurements

MT (Table 3) did not change significantly across training or time. For RC, there was a significant effect of training [ $F(79) = 6.91$ ;  $P < 0.01$ ], time [ $F(79) = 5.74$ ;  $P < 0.05$ ] and training  $\times$  time interaction [ $F(79) = 5.41$ ;  $P < 0.05$ ]. RC increased after active [pre-, 937.89  $\mu\text{V}$ ; post-, 1145.48  $\mu\text{V}$ ;  $t(87) = 3.93$ ;  $P < 0.001$ ] but not after passive [pre-, 1249.68  $\mu\text{V}$ ; post-, 1238.45  $\mu\text{V}$ ;  $t(99) = 0.23$ ; NS; see Fig. 2A] training. The increase in RC was more prominent in the active than in the passive condition [ $t(198) = 2.56$ ;

$P < 0.05$ ]. For ICF, there was a significant effect of training [ $F(276) = 21.96$ ;  $P < 0.001$ ], time [ $F(276) = 6.26$ ;  $P < 0.05$ ] and training  $\times$  time interaction [ $F(276) = 13.82$ ;  $P < 0.001$ ]. ICF increased with active [ $t(279) = 3.43$ ;  $P < 0.001$ ] but not with passive training [ $t(296) = 1.33$ ; NS; see Fig. 2B]. The increase in ICF was larger in the active than in the passive condition [ $t(58) = 2.50$ ;  $P < 0.05$ ]. ICI showed no significant effect for training and time, but did for the training  $\times$  time interaction [ $F(276) = 9.24$ ;  $P < 0.005$ ]. *Post hoc t* tests did not show significance across time with either active [ $t(292) = 2.01$ ; NS] or passive [ $t(296) = 2.23$ ; NS] training.

### Discussion

The results from this study demonstrate that active training led to significant improvements in motor performance while passive training did not when movement kinematics (range, duration and velocity) and subjects' alertness over a 30 min training period were controlled.

The duration of motor training was 30 min, long enough to elicit measurable behavioural gains as well as neurophysiological changes in motor training paradigms (Classen *et al.*, 1998; Liepert *et al.*, 1999; Stefan *et al.*, 2000). Training strategies that do not involve performance of voluntary movements can elicit performance improvements and motor learning. For example, movement imagination can improve motor performance in healthy volunteers (Pascual-Leone *et al.*, 1995; Yáñez *et al.*, 1998). Somatosensory input originating in electrical or magnetic stimulation delivered to peripheral nerves can lead to improvements in muscle strength in the stimulated body parts in patients with brain lesions (Struppler *et al.*, 1996; Conforto *et al.*, 2002). These findings led to the proposal that training consisting of performance of passive movements could be as effective as training of voluntary movements in eliciting behavioural gains (Alary *et al.*, 1998; Carel *et al.*, 2000). The finding that training periods of passively elicited movements performed over several weeks resulted in changes in fMRI activation patterns in the M1 of healthy volunteers was interpreted as evidence of the ability of passive training to elicit cortical reorganization (Carel *et al.*, 2000). Behavioural correlates of these changes or data on the kinematic details of the practised movements have not been reported (Carel *et al.*, 2000).

This study provides evidence that training periods consisting of active and passively elicited movements comparable in terms of kinematics led to differential changes in motor performance and cortical reorganization. At a behavioural level, our results are consistent with the view that active training is more effective than passive training in eliciting performance improvements. This conclusion does not rule out the possibility that more intensive or longer lasting passive training sessions could elicit some behavioural gains.

Both voluntary and passively elicited movements (before any training intervention) led to activation of M1, consistent with previous reports (Weiller *et al.*, 1996; Alary *et al.*, 1998; Carel *et al.*, 2000; but see also Mima *et al.*, 1999). However, the magnitude of activation and the size of the activated area within cM1 before training were larger with voluntary than with passively elicited movements. Motor training led to differential effects on activation patterns within cM1 characterized by significantly higher fMRI activation with active than with passive training. The fMRI blood oxygen level-dependent (BOLD) signal conveys information on the extent of neuronal activity within a specific region, and reflects the magnitude of inputs converging onto a cortical region and of intracortical processing within that given region (Logothetis *et al.*, 2001). The fMRI results indicate that active motor training enhanced processing within the M1 more than passive training. The neurophysiological findings using TMS complement this notion. TMS is a non-invasive technique that allows the evaluation of corticomotor neuronal excitability levels in humans (Hallett, 2000). When applied to the motor cortex, TMS activates predominantly cortico-cortical connections projecting to pyramidal tract neurons within the motor cortex (Amassian *et al.*, 1987; Day *et al.*, 1987).

Therefore, the increase in the recruitment curve is consistent with an active training-dependent increase in corticomotor neuronal excitability (Devanne *et al.*, 1997). The enhancement of intracortical facilitation using the paired pulse technique may reflect an increase in activity in excitatory intracortical circuits (Rothwell, 1996; Ziemann *et al.*, 1996a).

In summary, our results demonstrate that active motor training is more effective than passive training in eliciting performance improvements, local increases in fMRI BOLD activation and in intracortical excitability in the cM1. These differences are consistent with a more prominent increase in the strength of inputs converging onto pyramidal tract neurons and enhanced intracortical processing within the primary motor cortex with active than with passive training.

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### References

- Alary F, Doyon B, Loubinoux I, Carel C, Boulanouar K, Ranjeva JP, et al. Event-related potentials elicited by passive movements in humans: characterization, source analysis, and comparison to fMRI. *Neuroimage* 1998; 8: 377–90.
- Amassian VE, Quirk GJ, Stewart M. Magnetic coil versus electrical stimulation of monkey motor cortex (abstract). *J Physiol* 1987; 394: 119P.
- Birbaumer N, Ghanayim N, Hinterberger T, Iversen I, Kotchoubey B, Kübler A, et al. A spelling device for the paralysed. *Nature* 1999; 398: 297–8.
- Carel C, Loubinoux I, Boulanouar K, Manelfe C, Rascol O, Celsis P, et al. Neural substrate for the effects of passive training on sensorimotor cortical representation: a study with functional magnetic resonance imaging in healthy subjects. *J Cereb Blood Flow Metab* 2000; 20: 478–84.
- Chen R, Tam A, Buetefisch C, Corwell B, Ziemann U, Rothwell J, et al. Intracortical inhibition and facilitation in different representations of the human motor cortex. *J Neurophysiol* 1998; 80: 2870–81.
- Classen J, Liepert A, Wise SP, Hallett M, Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. *J Neurophysiol* 1998; 79: 1117–23.
- Conforto AB, Kaelin-Lang A, Cohen LG. Increase in hand muscle strength of stroke patients after somatosensory stimulation. *Ann Neurol* 2002; 51: 122–5.
- Day BL, Thompson PD, Dick JP, Nakashima K, Marsden CD. Different sites of action of electrical and magnetic stimulation of the human brain. *Neurosci Lett* 1987; 75: 101–6.
- Devanne H, Lavoie BA, Capaday C. Input–output properties and

- gain changes in the human corticospinal pathway. *Exp Brain Res* 1997; 114: 329–38.
- Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. *Exp Brain Res* 1998; 119: 265–8.
- Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000; 406: 147–50.
- Hummelsheim H, Eickhof C. Repetitive sensorimotor training for arm and hand in a patient with locked-in syndrome. [Review]. *Scand J Rehabil Med* 1999; 31: 250–6.
- Kaelin-Lang A, Luft AR, Sawaki L, Burstein A, Sohn YH, Cohen LG. Modulation of human corticomotor excitability by somatosensory input. *J Physiol* 2002; 15: 623–33.
- Karni A, Meyer G, Jezzard P, Adams MM, Turner R, Ungerleider LG. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 1995; 377: 155–8.
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. *J Physiol* 1993; 471: 501–19.
- Liepert J, Terborg C, Weiller C. Motor plasticity induced by synchronized thumb and foot movements. *Exp Brain Res* 1999; 125: 435–9.
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 2001; 412: 150–7.
- Mima T, Sadato N, Yazawa S, Hanakawa T, Fukuyama H, Yonekura Y, et al. Brain structures related to active and passive finger movements in man. *Brain* 1999; 122: 1989–97.
- Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M. Role of the human motor cortex in rapid motor learning. *Exp Brain Res* 2001; 136: 431–8.
- Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci* 1996; 16: 785–807.
- Pascual-Leone A, Dang N, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J Neurophysiol* 1995; 74: 1037–45.
- Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. *Exp Brain Res* 2000; 131: 135–43.
- Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. 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* 1994; 91: 79–92.
- Rothwell JC. The use of paired pulse stimulation to investigate the intrinsic circuitry of human motor cortex. In: Nilsson J, Panizza M, Grandori F, editors. *Advances in magnetic stimulation. Mathematical modelling and clinical applications*. Pavia: PI-ME Press; 1996. p. 99–104.
- Shadmehr R, Holcomb HH. Neural correlates of motor memory consolidation. *Science* 1997; 277: 821–5.
- Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 2000; 123: 572–84.
- Struppler A, Jakob C, Muller-Barna P, Schmid M, Lorenzen H-W, Paulig M, et al. Eine neue Methode zur Fruherehabilitation zentralbedingter Laehmungen von Arm und Hand mittels Magnetstimulation. *Z EEG EMG* 1996; 27: 151–7.
- Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. 3-D proportional system: an approach to cerebral imaging. Stuttgart: Thieme; 1988.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; 15: 273–89.
- Weiller C, Jueptner M, Fellows S, Rijntjes M, Leonhardt G, Kiebel S, et al. Brain representation of active and passive movements. *Neuroimage* 1996; 4: 105–10.
- Werhahn KJ, Fong JK, Meyer BU, Priori A, Rothwell JC, Day BL, et al. The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. *Electroencephalogr Clin Neurophysiol* 1994; 93: 138–46.
- Yágüez L, Nagel D, Hoffman H, Canavan AGM, Wist E, Hoemberg V. A mental route to motor learning: improving trajectorial kinematics through imagery training. *Behav Brain Res* 1998; 90: 95–106.
- Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. *J Physiol* 1996a; 496: 873–81.
- Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Ann Neurol* 1996b; 40: 367–78.

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