The effect of afferent training on long-term neuroplastic changes in the human cerebral cortex

R.L.J. Meesen[1,2], O. Levin[2] and S.P. Swinnen[2]

[1]REVAL - Rehabilitation and Health Care Research Center, Department of Health Care, University college of Limburg, Hasselt, Belgium
[2]Motor Control Laboratory, Department of Biomedical Kinesiology, Group Biomedical Sciences, K.U. Leuven, Belgium

Abstract- **In the present study we explored the effect of long-term intervention protocol (3 w, 1 h/day) with sensory stimulation on neuroplastic changes in the human motor cortex. Interventions consisted of repetitive activation of afferent pathways of the right abductor policies brevis (APB) muscle with tendon vibration (TV) and transcutaneous electrical nerve stimulation (TENS). The representations of the hand (APB, ADM) and forearm (FCR, ECR) muscles were mapped using transcranial magnetic stimulation (TMS) before and after the 3 weeks of sensory intervention (TV and TENS) groups or after similar periods of daily active training of the APB or rest (control). Our observations showed a significant increase in motor cortical representation of all the four muscles (as measured by changes in the map size) for the TENS group. No such effects were observed in the tendon vibration group, active training group or the control group.**

Keywords- **Afferent stimulation, neuroplasticity, transcranial magnetic stimulation (TMS)**

I. Introduction

Sensorimotor reorganization within the human cerebral cortex occurs during development, as a result of practice and experience, and following brain damage [1]. Studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) showed that repetitive proprioceptive stimulation activates large parts of motor networks both in the contralateral and ipsilateral hemispheres (in addition to the primary sensory area) [2]. This has recently been linked with the emergence of a delayed facilitation or depression in the excitability of cortical circuits during and/or immediately after the end of repetitive afferent stimulation [3-6]. Yet, the long-lasting effects of afferent stimulation on structural reorganization in the motor cortex remain largely unknown.

In humans, representational cortical plasticity can be assessed at a regional level by means of transcranial magnetic stimulation (TMS) mapping of corticomotor representations [7-9]. The TMS mapping technique has been used extensively to address dynamic changes in corticomotor representations following various experimental and pathological conditions [10]. Single TMS pulses are delivered via a focal figure-of-8 coil to scalp positions arranged in a coordinate system overlying the primary motor cortex (M1). By measuring the motor evoked potential (MEP) amplitude in the targeted muscle(s), 'maps' based upon spatial changes in MEP amplitude among multiple stimulation positions can be composed. In this way, a functional topographic map of the M1 projection to hand and forearm muscles can be obtained. Motor output maps can be quantified by a number of variables, such as the optimal stimulation position, the map area and volume [8-9].

In the present study we explored the effect of long-term intervention protocol (3 weeks, 1 hour/day) with sensory stimulation on neuroplasticity in the primary motor cortex of normal healthy volunteers. Previous studies have demonstrated that the TMS mapping technique is sensitive to detect changes in the motor representation following somatosensory stimulation paradigms. Consequently, we wondered whether a recently introduced type of interventional somatosensory stimulation, i.e., muscle tendon vibration, has the potential to drive changes in human motor cortex organization. This question could be possibly relevant in the search for interventional protocols that promote functional recovery after central nervous system injury [11].

II. Methodology

Subjects: A total of 48 neurologically healthy right-handed volunteers participated in the present study (20 males, 28 females mean age 27,6 SD14,2 range 18-53 years). The participants were naive about the purpose of the experiment, were screened for potential risk of adverse events during TMS (Wassermann et al. 1998), and provided written informed consent prior to participation. The experimental procedures were approved by the local Ethics Committee for Biomedical Research at the Katholieke Universiteit Leuven, according to the Declaration of Helsinki.

Intervention: Interventions consisted of repetitive activation of afferent pathways of the right abductor policies

T. Jarm, P. Kramar, A. Županič (Eds.): Medicon 2007, IFMBE Proceedings 16, pp. 643–646, 2007
www.springerlink.com

brevis (APB) muscle with tendon vibration (TV, n=12), transcutaneous electrical nerve stimulation (TENS, n=12), daily active training of the APB (n=12) or no intervention (control, n = 12). Tendon vibration (80 Hz, 1 mm) was applied at the muscle belly of the right APB muscle by a purpose-built shaker, structured from a DC motor (Maxon 34EBA201A). TENS (100 HZ) was applied via an electrical stimulator (Chattanooga Digitens).

Transcranial Magnetic Stimulation: The representation areas of the hand (APB, ADM) and forearm (FCR, ECR) muscles were mapped using transcranial magnetic stimulation (TMS) before and after the 3 weeks intervention. Representation areas were mapped with a protocol modified from Wilson et al [9]. Subjects wore a specifically-built tight-fitting cap with a 1×1-cm orthogonal coordinate system referenced to the vertex (Cz) on it. The cap was positioned using cranial landmarks (nasion-inion) and the external auricular meatus as references. Single TMS pulses (interstimulus interval: 6s) were applied in 1 cm-steps in a clockwise spiral course beginning at the optimal stimulation position for the FCR. Each stimulation position was stimulated 8 times before moving to the adjacent grid point, until the border of the motor maps of each target muscles had been defined. The total number of points in each mapping session covered between 100 (10 × 10) and 225 (15 × 15) positions.

Single-pulse transcranial magnetic stimuli were delivered by means of a Dantec MagLite r-25 stimulator (Medtronic, Skovlunde, Denmark) (maximal stimulator output: 1.5 Tesla) with a figure-of-eight coil (MC-B70 magnetic coil transducer, outer radius diameter: 50 mm). The magnetic stimulus had a biphasic pulse configuration with a pulse width of 280 μs. The coil was positioned tangentially to the scalp over the subjects' left hemisphere with the coil handle pointing backward and rotated 45º away from the midsagittal line. The optimal stimulation position (hot-spot) for eliciting MEP's in each of the four muscles was marked with a soft-tip pen. Stimulation intensity for mapping of the FCR- and ECR M1 representation was initially set at 120 % of the FCR rest motor threshold (rMT). rMT was determined at the optimal stimulation position as the lowest intensity needed to evoke MEP's in the relaxed FCR of at least 50 μV amplitude in five out of ten consecutive trials [12].

Data Analysis: The size of the APB, ADM, FCR and ECR MEPs was measured by calculating the peak-to-peak amplitude of the signal. The number of active positions in each map was determined as points whose stimulation evoked a mean MEP in the target muscle with peak-to-peak amplitude of at least 100 μV. Mean peak-to-peak amplitudes of MEP waveforms obtained at each scalp site were plotted against antero-posterior and mediolateral distance. 3D-representations of mean motor outputs for the four target muscles were composed by linear interpolation of the mean MEP-amplitudes between adjacent stimulation positions (Matlab 6.5, MathWorks, Inc.). Mean MEP at each position was then normalized by mean MEP score at the hot-spot. The *motor representation area* of each muscle was defined as the number of stimulus positions whose stimulation evoked a mean MEP in the target muscle with a magnitude of at least 10 % its respective normalized peak. *Map area* referred to the contour *Map volume* referred to the sum of the mean amplitudes at all active stimulation positions.

Advanced linear models applications (STATISTICA 6.0, StatSoft Inc.) were used for statistical analysis. Mapping variables were statistically compared by means of a 2 × 4 × 4 (TEST × GROUP × MUSCLE) analyses of variance (ANOVAs). The factor TEST consists of two levels, referring to the pre/post mapping sessions. The factor GROUP consists of four levels referring to TENS, TV, active and control groups and MUSCLE consists of four levels referring to four tested muscles (APB, ADM, FCR and ECR). When significant effects were found, post hoc testing (Bonferroni) was conducted to identify the source of the differences.

III. Results

Examples of individual maps are illustrated in Figure 1, while group results are shown in Figure 2. Overall, we found large differences in the motor cortical representation of the hand muscles (ABP and ADM) between pre- and post maps in the TENS and TV groups but not in the active training or control groups. This observation is confirmed largely by the significant TEST × GROUP × MUSCLE interaction with respect to both map area and volume ($F_{9,99}$ >3.43, $p < 0.01$). However, a significant enhancement in the motor representations of area and volume from Pre to Post mapping sessions was observed only in the TENS group [APB, ADM, FCR and ECR: all, $p < 0.01$] whereas no such effects were observed in subjects of the remaining groups.

IV. Discussion

The present experiment shows for the first time that changes in the cortical representation of the hand muscles can be generated by repetitive activation of sensory afferences in the targeted muscle, with the larger effects observed in the TENS group. TENS is routineously applied as a proprioceptive stimulation technique in neurorehabilitation that has shown to activate large parts of the sensori-

motor network as well as to induce facilitatory and/or inhibitory effects on the corticospinal motor representation of the targeted muscles when administered repeatedly [6]. The underlying mechanisms of those long-lasting effects are not yet completely understood.

An increase in volume and/or area of the motor representations of the hand muscles is argued to indicate recruitment of a greater number of descending motor pathways in response to cortical stimulation with TMS. In general, the size of MEP provides an indication of the level of excitability of the corticospinal pathways; the MEP peak-to-peak indicates the peak of simultaneous excitement of the descending pathways and map area reflects the total amount of excited motorneurons [13]. As stimulus intensity was kept at the same level in both the pre- and post-intervention sessions, we propose that the sustained increase in map area could signify a gradual increase in the number of active motor neuron as a result of the intervention.

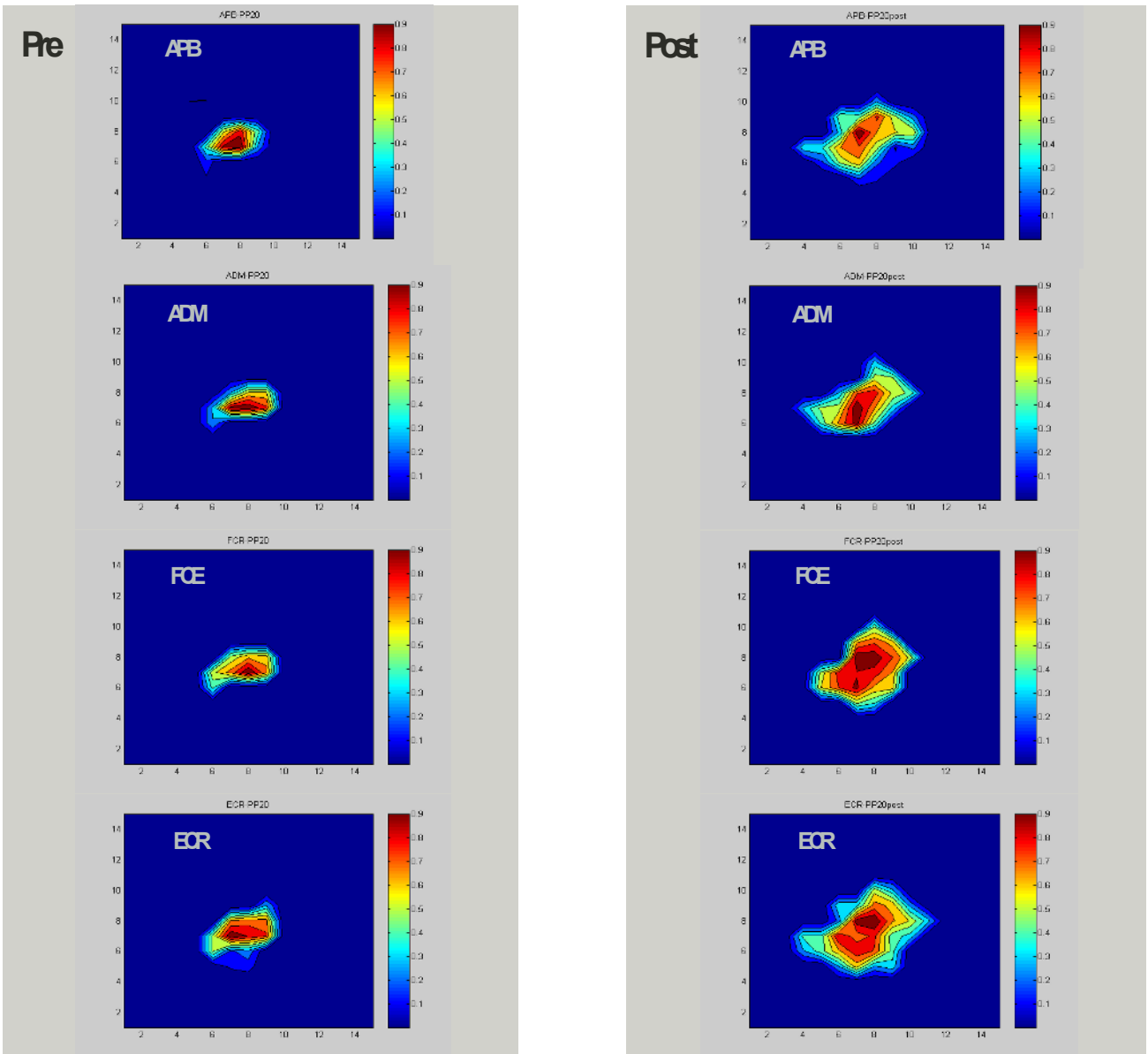

Fig. 1 Representative map areas of the ABP, ADM, FCR and ECR muscles before (Pre – left hand column) and after 3 weeks (Post – right hand column) period of sensory intervention with TENS.

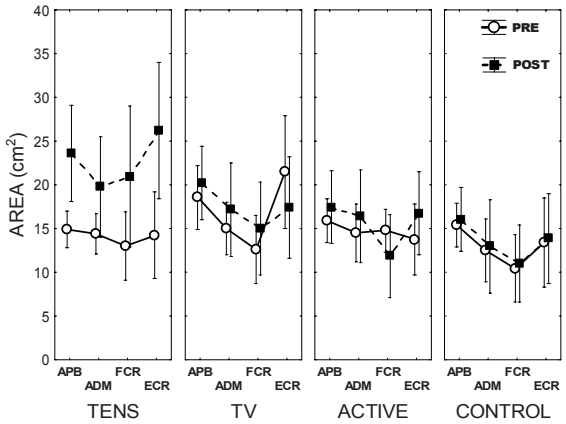

Fig. 2 Group data showing motor representation area of the four muscles at Pre and Post mapping sessions.

This phenomenon may have been mediated either by affecting the excitability of pre-synaptic axonal elements or changing the efficiency of trans-synaptic interactions [7]. However, the most recent findings point to the involvement of a perceptual-to-motor transformation of the afferent-induced proprioceptive information, most likely occur at the cortical level rather than being a purely spinal reflex mechanism [14]. Besides the critical importance of obtaining fundamental insights into the mechanisms that drive plasticity in the human brain, the current state of knowledge also highlights the potential advantage of sensory training (transcutaneous electrical nerve stimulation) to serve as a useful complementary therapy in neurorehabilitation.

Acknowledgment

Support for this study was provided through a grant from the Flanders Fund for Scientific Research (FWO Project G.0292.05).

References

1. Donoghue JP (1995) Plasticity of adult sensorimotor representations. Curr Opin Neurobiol 5:749-754.
2. Nelles G, Jentzen W, Jueptner M et al. (2001) Arm training induced brain plasticity in stroke studied with serial positron emission tomography. NeuroImage 13:1146-1154.
3. McKay D, Brooker R, Giacomin P et al. (2002) Time course of induction of increased human motor cortex excitability by nerve stimulation. NeuroReport 13:1271-1273.
4. Steyvers M, Levin O, Van Baelen M et al. (2003) Corticospinal excitability changes following prolonged muscle tendon vibration. NeuroReport 14:1901-1905.
5. Steyvers M, Levin O, Verschueren SMP et al. (2003) Frequency-dependent effects of muscle tendon vibration on corticospinal excitability: a TMS study. Exp Brain Res 151: 9-14.
6. Tinazzi M, Zarattini S, Valeriani M et al. (2005) Long-lasting modulation of homan motor cortex following prolonged transcutaneous electrical nerve stimulation (TENS) of forearm muscles: evidence of reciprocal inhibition and facilitation. Exp Brain Res 161:457-464.
7. Siebner HR, Rothwell J (2003) Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 148:1-16.
8. Wassermann EM, McShane LM, Hallett M et al. (1992) Noninvasive mapping of muscle representations in human motor cortex. Electroencephalogr Clin Neurophysiol 85:1-8.
9. Wilson SA, Day BL, Thickbroom GW et al. (1996) Spatial differences in the sites of direct and indirect activation of corticospinal neurones by magnetic stimulation. Electroencephalogr Clin Neurophysiol 101:255-261.
10. Pascual-Leone A, Grafman J, Hallett M (1994) Modulation of cortical motor output maps during development of implicit and explicit knowledge. Science 263:1287-1289.
11. Fraser C, Power M, Hamdy S, et al. (2002) Driving plasticity in human adult motor cortex is associated with improved motor function after brain injury. Neuron 34:831-840.
12. Rossini PM, Barker AT, Berardelli et al. (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.
13. Ikoma K, Samii A, Mercuri B et al. (1996) Abnormal cortical motor excitability in dystonia. Neurology 46:1371-1376
14. Swayne O., Rothwell J., Rozenkranz K (2006) Transcallosal sensorimotor integration: Effects of sensory input on cortical projections to the contralateral hand. Clin Neurophysiol 117: 855-863

Author:	Prof. dr. Raf L.J. Meesen
Institute:	REVAL - Rehabilitation and Health Care Research Center
Street:	Guffenslaan 39
City:	B-3500, Hasselt
Country:	Belgium
Email:	raf.meesen@phl.be