

The Effect of Long-Term TENS on Persistent Neuroplastic Changes in the Human Cerebral Cortex

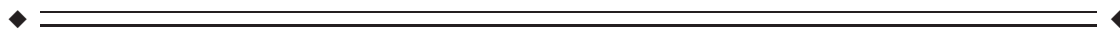
Raf L.J. Meesen,^{1,2,3*} Koen Cuypers,^{1,3} John C. Rothwell,⁴
Stephan P. Swinnen,² and Oron Levin²

¹REVAL-Rehabilitation and Health Care Research Center, Department of Healthcare,
University College of Limburg, Hasselt, Belgium

²Motor Control Laboratory, Research Center for Movement Control and Neuroplasticity,
Department of Biomedical Kinesiology, Group Biomedical Sciences, K.U. Leuven, Belgium

³Hasselt University, Biomedical Research Institute, Agoralaan, Diepenbeek 3590, Belgium

⁴Sobell Department of Neurophysiology, Institute of Neurology, Queen Square,
London, United Kingdom



Abstract: The long-term effect of daily somatosensory stimulation with transcutaneous electrical nerve stimulation (TENS) on reorganization of the motor cortex was investigated in a group of neurologically intact humans. The scalp representation of the corticospinal projection to the finger (APB, ADM) and forearm (FCR, ECR) muscles was mapped by means of transcranial magnetic stimulation (TMS) before and after a 3-week intervention period, using map area and volume, and topographical overlaps between the cortical motor representations of these muscles as primary dependent measures. Findings revealed a significant increase in cortical motor representation of all four muscles for the TENS group from pre to posttest (all, $P \leq 0.026$). No significant changes in cortical motor representations were observed in the control group. The present observations highlight the potential benefit of sensory training by means of TENS as a useful complementary therapy in neurorehabilitation. *Hum Brain Mapp* 32:872–882, 2011. © 2010 Wiley-Liss, Inc.

Key words: somatosensory stimulation; corticomotor representations; neuroplasticity; transcranial magnetic stimulation (TMS)



INTRODUCTION

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*Correspondence to: Raf L.J. Meesen, REVAL Research Group, Department of Healthcare, PHL University College, Guffenslaan 39, Hasselt 3500, Belgium. E-mail: raf.meesen@phl.be

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Somatosensory stimulation activates large parts of the motor and sensory networks, both in the contralateral and ipsilateral hemispheres [Deletis et al., 1992; Duclos et al., 2007; Matteis et al., 2003; Naito et al., 1999; Nelles et al., 1999; Nudo et al., 1996; Radovanovic et al., 2002]. For example, medical imaging techniques have shown activation in contralateral sensorimotor cortex, inferior parietal cortex (bilateral), ipsilateral cerebellum, and (medial) premotor areas [Carel et al., 2000; Naito et al., 1999; Nelles et al., 1999]. This activity reflects the anatomical connectivity of the stimulated M1/S1, known to possess

direct monosynaptic connections with all of the aforementioned areas [Classen et al., 1998; Nelles et al., 2001].

The effect of somatosensory stimulation on corticomotor excitability has been explored in humans by using transcranial magnetic stimulation (TMS) during and/or after the application of e.g., electrical nerve stimulation [Fraser et al., 2002; Hamdy et al., 1998; Ridding et al., 2001], muscle-tendon vibration [Rosenkranz and Rothwell, 2003; Steyvers et al., 2003a, b], cyclical passive movement [Lewis and Byblow, 2004; Mace et al., 2008], or temporary deafferentation [Ziemann et al., 1996]. These observations have recently been linked with the emergence of lasting facilitation or depression of excitability of neuronal populations in the primary motor cortex [Forner-Cordero et al., 2008; Mace et al., 2008; Rosenkranz and Rothwell, 2006; Rosenkranz et al., 2008; Steyvers et al., 2003a]. Yet, the long-lasting changes in corticomotor excitability induced by direct activation of Ia afferent pathways via passive movement or muscle vibration were somewhat more feeble and/or focal [Lewis and Byblow, 2004; Mace et al., 2008] as compared with those scenarios in which facilitation (or depression) in excitability of the corticospinal projections to targeted musculature were monitored following training with electrical nerve stimulation [Fraser et al., 2002; Hamdy et al., 1998; Ridding et al., 2001; Tinazzi et al., 2005].

Electrical nerve stimulation in general, and transcutaneous electrical nerve stimulation (TENS) in particular have been applied successfully in neurorehabilitation, such as in the treatment of stroke [Levin and Hui-Chan, 1992; Ng and Hui-Chan, 2007; Sonde et al., 1998], urinary symptoms [Skeil and Thorpe, 2001], spinal cord injury [Fung and Barbeau, 1994; Goulet et al., 1996], multiple sclerosis [Armutlu et al., 2003; Miller et al., 2007], writer's cramp [Tinazzi et al., 2006] and/or to reduce movement disorders caused by tremor, myoclonia, or dystonia [Bending and Cleves, 1990; Foley-Nolan et al., 1990; Toglia and Izzo, 1985]. This body of literature suggests that daily training with TENS may effectively activate larger parts of the underlying distributed sensorimotor networks of the brain. Studies that have evaluated the long-term effects of TENS on the reorganization of corticomotor representations are sparse. Nonetheless, a recent study revealed that multiple sessions of peripheral nerve stimulation can facilitate training effects on motor function after subacute stroke [Conforto et al., 2010].

The present study aimed to reveal the effects of a daily somatosensory stimulation with TENS over the right abductor pollicis brevis (APB) muscle on cortical representations of hand and forearm muscles in healthy volunteers (see Fig. 1). On the basis of the known connectivity between primary sensory and motor cortical areas [Quartarone et al., 2003; Zarzecki et al., 1978], we hypothesized positive effects of the sensory intervention on the motor map representation(s) after 3 weeks of daily training. More specifically, as a result of the existence of (1) widespread connectivity between, e.g., the median and ulnar

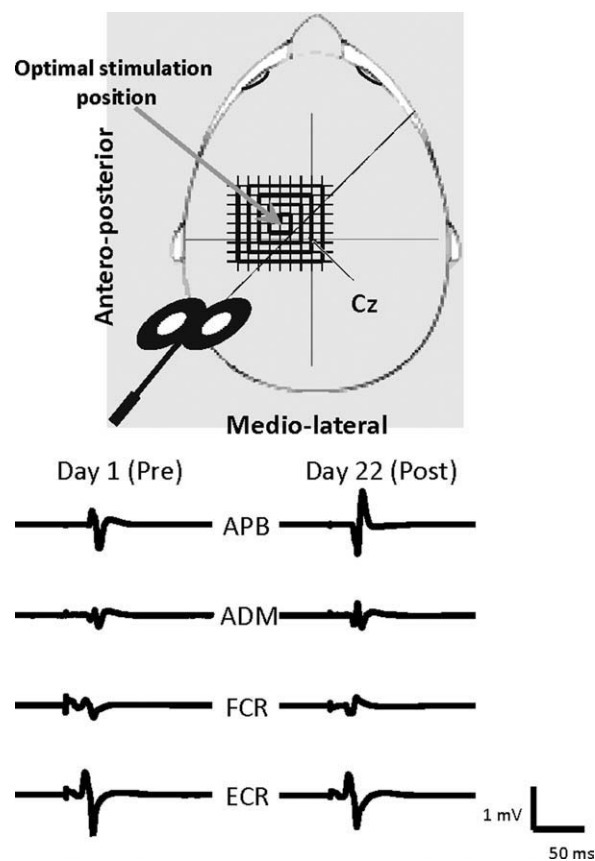


Figure 1.
Illustration of the TMS mapping procedure.

nerves [Kimura et al., 1983] and/or (2) simultaneous activation of primary and secondary afferent networks [Quartarone et al., 2006], we hypothesized that TENS applied to the APB would induce a global effect on hand (APB, ADM) and forearm (FCR, ECR) representations. Changes in motor cortex representations were assessed by means of a TMS mapping protocol, examining differences in loci and size of the cortical motor maps of the hand and forearm musculature [Thickbroom et al., 1999; Wassermann et al., 1992; Wilson et al., 1996]. This technique has been used previously to assess changes in corticomotor representations of upper/lower limb musculature following limb amputation [Cohen et al., 1991; Fuhr et al., 1992] or specific skill learning [Pascual-Leone et al., 1993, 1994].

MATERIALS AND METHODS

Subjects

Participants were 24 healthy and neurologically intact right-handed volunteers (10 males, 14 females, mean age 27.4, SD 14.8, range 18–54 years). They were naive about

the purpose of the experiment, were screened for potential risk of adverse events during TMS [Wassermann, 1998], and provided written informed consent prior to participation. Handedness was determined by the Edinburgh Handedness Inventory [Oldfield, 1971]. The experimental procedures were approved by the local Ethics Committee for Biomedical Research at Katholieke Universiteit Leuven, according to the Declaration of Helsinki.

Experimental Procedures

Participants were randomly assigned to two groups ($n = 12$ each): TENS and control (CONTROL). All subjects underwent two TMS mapping sessions, i.e., prior to the start of (at day 1) and following the intervention (at day 22). The intervention consisted of daily sessions over a period of 21 days. Participants in the control group preserved their normal daily activities without any intervention.

TENS (biphasic symmetrical rectangular pulse-wave at 100 Hz, 250 μ s pulse width) was delivered for a total duration of 60 min per day to the right APB muscle, using a constant current stimulator (Intellect Digitens, Chattanooga Group, Hixson, TN). Self-adhesive electrodes (dura Stick II, 1.5 cm \times 4 cm) were placed on the belly of the right APB and their locations were marked over the skin with a surgical pen to preserve locations across the daily sessions. Stimulus intensity was set at a sensory threshold just below motor threshold, producing a continuous tingling sensation in the stimulated area without any visible muscle twitch or pain.

Transcranial Magnetic Stimulation

TMS mapping of the right APB, abductor digiti minimi (ADM), flexor carpi radialis (FCR), and extensor carpi radialis longus (ECR) was done by means of a magnetic stimulator (Dantec MagLite r-25, Medtronic, Skovlunde, Denmark). Single-pulse magnetic stimuli were delivered with a figure-of-eight coil (MC-B70 magnetic coil transducer; outer radius diameter: 50 mm; maximal output: 1.5 Tesla). For each subject a customized cap was made out of thermoplastic material (Aquaplast-T Solid, 20 cm \times 15 cm \times 0.24 cm, Sammons Preston Polyon, Cedarburg) with references to anatomical landmarks (left and right external auditory meatus and occiput) to ensure reproducibility of measurements across the experiment. An orthogonal coordinate system referenced to the vertex was marked on each cap. The coil was positioned tangentially to the scalp over the subjects' left hemisphere with the coil handle pointing backward and rotated 45° away from the midsagittal line (see Fig. 2).

The optimal location (hotspot) for eliciting motor evoked potentials (MEPs) from the right APB, i.e., the target muscle, was identified and marked with a soft-tip pen to ensure reproducibility of coil positioning in each participant. In all cases, a response of the ADM, FCR, and ECR

was also evoked in this position. Next, the rest motor threshold (rMT) was determined at the optimal scalp positions of the APB, ADM, FCR, and ECR. For all muscles, the rMT was defined as the lowest intensity of magnetic stimulation required to evoke MEPs larger than 50 μ V amplitude in at least 5 of 10 trials in the relaxed muscle. The stimulation intensity for mapping was then set at 120% of the APB rMT. This intensity was preserved during both the pre and postmapping sessions. A grid of 225 (15 \times 15) positions, spaced 1 cm along both the medio-lateral and antero-posterior axes, was marked on each cap. In producing maps, single TMS pulses were applied in 1 cm-steps in a clockwise spiral course, beginning at the hotspot of the APB muscle (see Fig. 1). Each position was stimulated 8 times (interstimulus interval: 5–8 s, at random) before moving to the adjacent grid point, until the border of the motor maps of all four muscles was defined.

EMG Recordings

Electromyographic (EMG) signals from the APB, ADM, FCR, and ECR of the right upper limb were collected by means of disposable, self-adhesive disc electrodes (Nutrode, Ag-AgCl sensor with Hydrogel, 35 mm diameter, GE Medical Systems Accessories Europe, Nanterre Cedex, France). For each subject, specific electrode placement for each of the four muscles was photographed and saved in a database. Skin surface was carefully shaved and degreased prior to electrode placement to achieve optimal conduction. The electrodes were additionally fixed to the skin with tape to ensure maximal contact (Leukopor, skin-friendly, nonwoven tape, 1.25 cm, BSN Medical GmbH and Co, Hamburg, Germany). After amplification (gain = 1,000) and bandpass filtering (4–1,500 Hz) (MEGA MESPEC 8000, Finland), the recorded EMG signals were digitized at 5,000 Hz (CED Signal Version 3.03, Cambridge Electronic Design, Cambridge, UK) and were stored on a laboratory computer for offline analysis. Data collection was initiated 50 ms prior to the delivery of TMS and lasted 150 ms. EMG activity from all four muscles was continuously monitored online during the mapping session. Background EMG activity was minimized by continuous online EMG monitoring during the experiment, as well as by offline analysis of the trials.

Data Analysis

The size of the APB, ADM, FCR, and ECR MEPs were measured offline by calculating the peak-to-peak amplitude of each waveform in a time window from 10 to 40 ms after the TMS stimulation pulse onset. The number of active positions in each map was determined as points whose stimulation evoked a mean MEP in the target muscles with a peak-to-peak amplitude of at least 100 μ V. Three-dimension representations of mean motor outputs

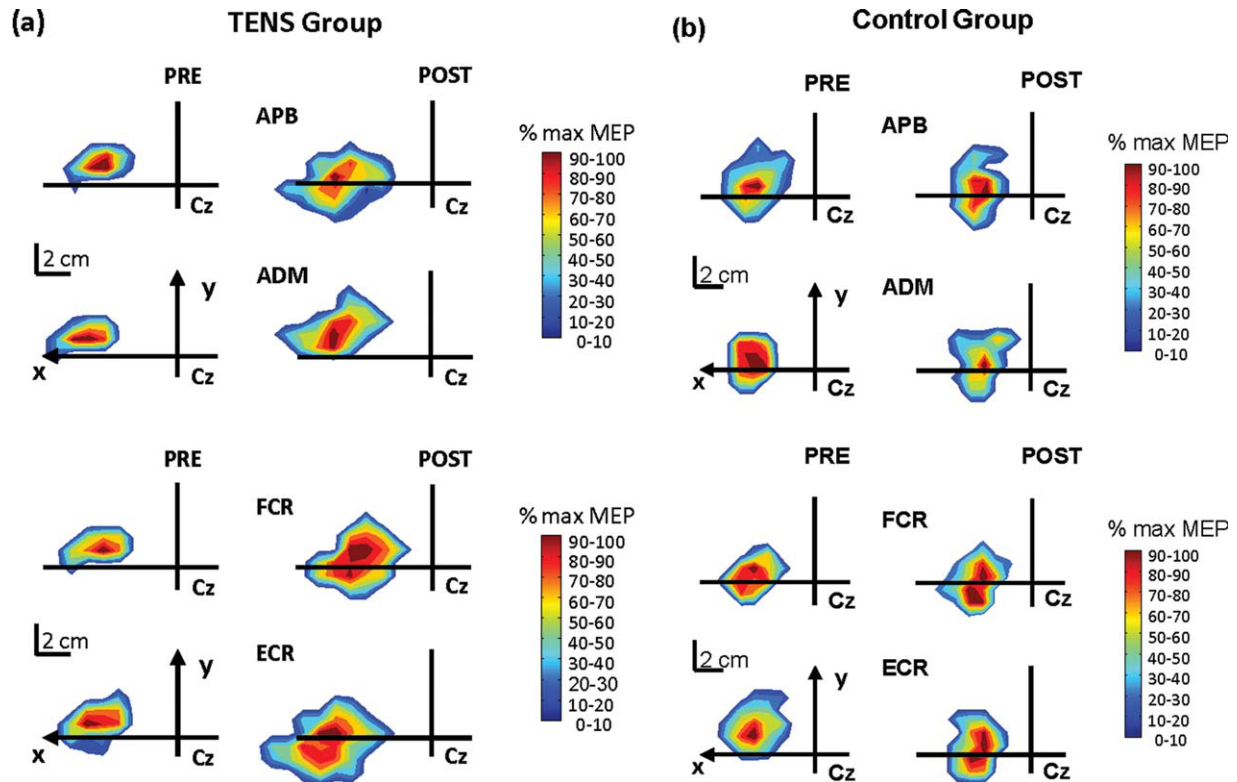


Figure 2.

Representative map areas of the APB, ADM, FCR, and ECR muscles before (Pre—left hand column) and after 3 weeks (Post—right hand column) of sensory intervention with TENS (a) as compared to control (b). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

for the four muscles were then composed by linear interpolation of the mean MEP amplitudes between adjacent stimulation positions (Matlab 6.5, MathWorks, Inc.).

For both pre and postmapping sessions, the cortical motor representation of the APB, ADM, FCR, and ECR was defined as the number of stimulus positions whose stimulation evoked a mean MEP in the target muscle with a peak-to-peak amplitude of at least 100 μV (= “active” stimulation positions). The peak-to-peak amplitudes obtained at the same stimulation site were averaged and normalized by their respective mean MEP amplitudes at the hotspot. 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% of its respective normalized peak. Map area referred to the contour, whereas Map volume referred to the sum of the mean amplitudes at all active stimulation positions. The center of gravity (CoG) was computed separately for each muscle as a measure of the amplitude-weighted centre of the motor representational map [Wassermann et al., 1992]. It is expressed as a bivariate measurement with a mediolateral (x) and antero-posterior coordinate (y), using the following formula: $\text{CoG} = [\sum a_i x_i / \sum a_i, \sum a_i y_i / \sum a_i]$, for stimulation position coordi-

nates x_i, y_i and amplitudes a_i . The magnitude of the CoG displacement vector, i.e., the Euclidean distance between the CoG locations at day 1 (preintervention mapping session) and day 22 (postintervention mapping session) was calculated.

Statistics

Advanced linear models applications (STATISTICA 6.0, StatSoft Inc.) were used for statistical analysis. Effects of interventions on corticospinal excitability and corticomotor representation were studied using the following dependent measures: mean MEP amplitude at optimal stimulation position (hotspot), location of hotspot, mean map area and mean map volume, map overlaps and the displacement of the map CoG. A $2 \times 2 \times 4$ (GROUP \times TIME \times MUSCLE) repeated measures analysis of variance (ANOVA) was used with GROUP (TENS, CONTROL) as between-subjects factor, and TIME (PRE-POST mapping session) and MUSCLE (APB, ADM, FCR, ECR) as within-subjects factors. Differences in topographical overlaps between cortical representations of the target (APB) and nontarget (ADM, FCR, and ECR) muscles in the pre and postmapping sessions were tested using a $2 \times 2 \times 6$

TABLE I. Mean (\pm SD) magnitudes of the MEPs (mV) in the pre and postintervention mapping sessions for the TENS and Control groups

	TENS		Control	
	Pre	Post	Pre	Post
APB	1.81 \pm 0.39	1.83 \pm 0.40	2.10 \pm 0.39	2.14 \pm 0.40
ADM	1.13 \pm 0.24	1.51 \pm 0.30	0.96 \pm 0.24	0.71 \pm 0.30
FCR	0.73 \pm 0.10	0.69 \pm 0.12	0.39 \pm 0.10	0.40 \pm 0.12
ECR	1.26 \pm 0.25	1.15 \pm 0.23	0.74 \pm 0.25	0.60 \pm 0.23

ANOVA with the factors GROUP (two levels), TIME (two levels) and MAP OVERLAP (six levels: APB-ADM, APB-FCR, APB-ECR, ADM-FCR, ADM-ECR, and FCR-ECR). T-tests were used to estimate whether potential changes in map area, volume or map overlaps differed significantly from zero. The magnitude of displacement of the estimated CoG positions along the anteroposterior and mediolateral axes were statistically compared using a 2 \times 4 (GROUP \times MUSCLE) ANOVA, to determine CoG stability between pre and postmapping sessions. The level of significance was set at $P < 0.05$.

RESULTS

MEP Amplitude at Hotspot

Three weeks of TENS did not affect the size of MEPs at the hotspots, suggesting that levels of corticospinal excitability at hotspot remained unchanged (Table I). Specifically, the 2 \times 2 \times 4 (GROUP \times TIME \times MUSCLE) ANOVA revealed a significant main effect for MUSCLE ($P < 0.01$) but the remaining main effects and the two and three factor interactions were not significant (all: $P > 0.2$).

Location of the Hotspot

The location of the hotspots did not change significantly between pre and postmapping sessions (all muscles: $P > 0.08$).

Map Area and Map Volume

Examples of individual maps are illustrated in Figure 2a (TENS) and 2b (CONTROL). Changes in mean map area and volume of the representations of the target (APB) and nontarget muscles (i.e., ADM, FCR, and ECR) from pre to posttest are demonstrated in Figure 3. Overall, changes in the group mean areas (Fig. 3a) and volumes (Fig. 3b) between pre and postmapping sessions were observed for all four muscles in the TENS group. The control group did not reveal any changes. The aforementioned observations were largely confirmed by the 2 \times 2 \times 4 (GROUP \times TIME \times MUSCLE) ANOVA, as discussed next.

With respect to map area, the main effects for TIME ($P < 0.01$) and GROUP ($P < 0.05$) and the GROUP \times TIME interaction ($P < 0.01$) were significant. The main effect

for MUSCLE ($P = 0.079$) and the remaining two and three factor interactions (all: $P > 0.5$) were not significant, suggesting that all four muscles present a similar increase in the representation of their map areas after the intervention. This finding enabled us to explore the significant GROUP \times TIME interaction in detail. Specifically, pairwise post hoc tests (Tukey HSD) revealed a significant increase of map area size in POST ($M = 25.0 \text{ cm}^2$) relative to PRE ($M = 14.9 \text{ cm}^2$) mapping session in the TENS group ($P = 0.0003$) while map area sizes in the CONTROL group were statistically identical: $M = 14.5 \text{ cm}^2$ (PRE) vs. $M = 15.2 \text{ cm}^2$ (POST) ($P > 0.9$). Across group effects were also significant: TENS-POST vs. CONTROL-PRE/POST (both, $P < 0.005$). Finally, t -tests for single means (TENS group: POST-PRE comparison to zero) showed that the map area of the target (APB) and the three nontarget muscles (ADM, FCR, and ECR) was significantly increased: APB ($69 \pm 15\%$ increase POST vs. PRE, $P = 0.001$), FCR ($73 \pm 21\%$ increase, $P = 0.007$), ECR ($89 \pm 27\%$ increase, $P = 0.008$), and ADM ($54 \pm 21\%$, $P = 0.026$). As expected, no consistent change in map areas between pre and postmapping sessions were observed in the CONTROL group (all muscles, $P > 0.3$).

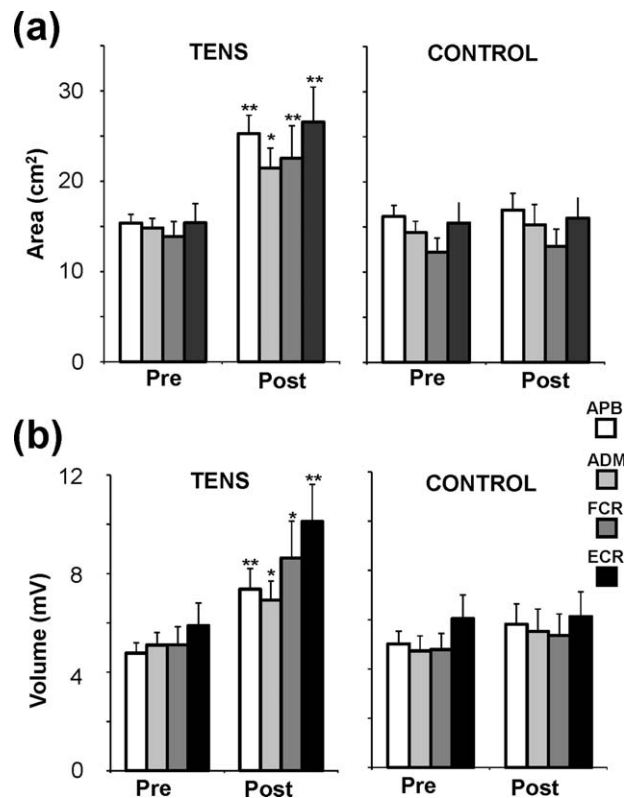


Figure 3.

Group data showing motor representation area and volume of the four muscles at pre and postmapping sessions; * $P < 0.05$ and ** $P < 0.01$ compared to the Prevalues.

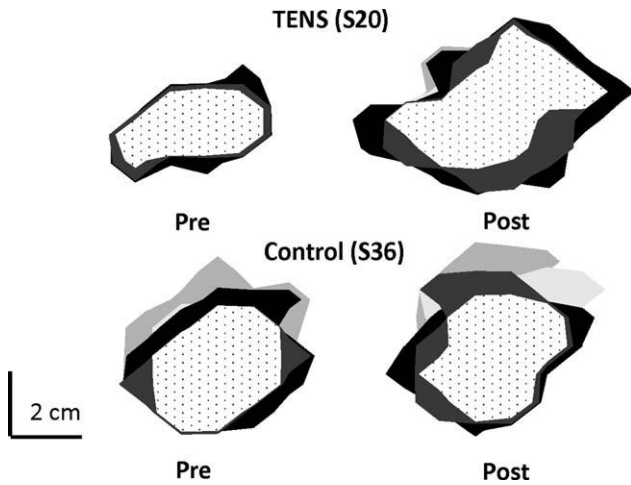


Figure 4.

Representative map areas of the APB (light-gray), ADM (intermediate gray), FCR (dark gray) and ECR (black) and their overlaps (dotted area) before (Pre—left hand column) and after 3 weeks (Post—right hand column) of sensory intervention with TENS versus control.

With respect to map volume, effects were largely similar but the main effect for GROUP ($P > 0.1$) was not significant. Again, *t*-tests for single means showed that the map volume in the TENS group was significantly increased in all four muscles: APB ($55 \pm 12\%$, $P = 0.001$), ADM ($46 \pm 18\%$, $P = 0.026$), FCR ($91 \pm 29\%$, $P = 0.010$), and ECR ($97 \pm 26\%$, $P = 0.004$).

In summary, participants in the TENS group showed a markedly increased map area and volume in all four muscles

Overlaps Between Muscle Cortical Representations

Representative examples of topographical overlaps between cortical representations of the target (APB) and nontarget (ADM, FCR, and ECR) muscles in the pre and

postmapping sessions are illustrated for two individuals (TENS and CONTROL) in Figure 4. The $2 \times 2 \times 6$ ANOVA revealed significant main effects for TIME ($P < 0.01$) and GROUP ($P < 0.05$) and a significant GROUP \times TIME interaction ($P < 0.01$). The main effect for MAP OVERLAP ($P > 0.1$) and the remaining two and three-factor interactions were not significant (all: $P > 0.3$). Pairwise post hoc test (Tukey HSD) on the significant GROUP \times TIME interaction revealed a significant increase of map overlap size in the POST ($M = 19.5 \text{ cm}^2$) relative to PRE ($M = 12.6 \text{ cm}^2$) mapping session in the TENS group ($P = 0.0008$) while no enlargements in map overlaps were noticed for the CONTROL group: $M = 11.3 \text{ cm}^2$ (PRE) vs. $M = 11.7 \text{ cm}^2$ (POST) ($P > 0.9$). Across group effects were also significant: TENS-POST vs. CONTROL-PRE/POST (both, $P < 0.01$). Yet, further inspection of our data showed that changes in topographical overlaps of the hand (i.e., APB and ADM) and forearm (i.e., FCR and ECR) musculature after 3 weeks intervention with TENS were more pronounced for some muscles than others. Specifically, significant enlargements in map overlaps were noticed for the representations of the APB, ADM, and ECR (TENS Group, contrast analyses for TIME (Tukey HSD); all, $P \leq 0.034$) but not for the aforementioned three muscles with FCR (all, $P > 0.06$). Group means (\pm SD) are shown in Table II.

Further, *t*-tests for single means (TENS group: POST-PRE comparison to 0) indicated that TENS intervention significantly increased the overlaps among cortical maps in the post as compared with the premapping session between the representations of the APB and ADM (PRE vs. POST, 52% increase; $P = 0.024$), APB and ECR (PRE vs. POST, 70% increase; $P = 0.002$) and ADM and ECR (PRE vs. POST, 73% increase; $P = 0.015$). Changes in size of overlaps between the FCR and the two finger muscles or FCR and ECR were either marginally significant or did not reach significance (all, $P > 0.05$). An increase in the size of the topographical overlap of the four cortical maps was also visible and reached marginal significance ($P = 0.052$).

TABLE II. The effect of training with TENS on overlaps between cortical representations of the target muscle (APB) and the three nontarget muscles (ADM, FCR, and ECR)

Cortical representations	Innervation	Pre (cm ²)	Post (cm ²)
APB \cap ADM	median/deep branch of ulnar (APB) and ulnar (ADM)	12.0 (1.9)	18.3 (4.8)*
APB \cap FCR	median (APB and FCR) and deep branch of the ulnar (APB)	11.7 (4.2)	17.5 (8.7) ^{NS}
APB \cap ECR	median/deep branch of ulnar (APB) and radial (ECR)	13.0 (3.8)	22.0 (8.0)**
ADM \cap FCR	ulnar (ADM) and median (FCR)	11.8 (4.1)	17.1 (8.6) ^{NS}
ADM \cap ECR	ulnar (ADM) and radial (FCR)	13.1 (3.7)	22.6 (11.2)**
FCR \cap ECR	median (FCR) and radial (ECR)	13.9 (3.7)	19.3 (11.2) ^{NS}
APB \cap ADM \cap FCR \cap ECR	median (APB and FCR), ulnar (APB and ADM) and radial (ECR)	9.8 (3.6)	12.8 (7.8) ^{NS}

Data are expressed as group mean \pm standard deviation (SD) for pre (baseline) and postintervention mapping sessions.

NS, not significant.

* $P < 0.05$ and

** $P < 0.01$, Post compared to Prevalues.

In summary, in addition to a noticeably increased map area in all four muscles, the TENS intervention was also shown to increase the topographical overlaps between cortical representations of the finger and forearm muscles. However, this effect was more prominent for the APB, ADM, and ECR than FCR.

Displacement of the Center of Gravity

The CoGs of the motor maps did not change between pre and postmapping sessions (all muscles: $P > 0.1$).

DISCUSSION

In this study, we investigated the effect of a somatosensory stimulation intervention with TENS across a 3 week period on the cortical motor representations in the intact human brain. Our observations demonstrate for the first time that the size of motor map representations of APB, ADM, FCR, and ECR muscles increased after TENS applied to the median nerve territory over the APB muscle.

The absolute size and spatial location of the map representation depend on factors such as coil orientation [Wilson et al., 1993, 1996], current spread [Roth et al., 1991], coil distance [Thickbroom et al., 1998], and the excitability of the underlying corticospinal projection [Ridding and Rothwell, 1997]. All these parameters were held constant in the present study. Even so, all muscles underwent a considerable increase ($> 50\%$) in the area of their cortical motor representation in the absence of changes in excitability of the most excitable zone ("hotspot") or the CoG of the motor maps. This suggests that TENS led to a change in the distribution of excitability in the motor output zones to each muscle, with the largest effects in the least excitable peripheral areas. This led to marked changes in the topographical overlaps between cortical representations of the target (APB) muscle and two of the three remaining muscles (i.e., ADM and ECR).

Modulation of Cortical Motor Representation

Our data, showing enlargement of the borders of cortical maps of the hand and forearm muscles, are in agreement with the findings of previous studies regarding the immediate poststimulation effects with electrical nerve stimulation [Hamdy et al., 1998; Ridding and Rothwell, 1997; Ridding et al., 2001] or muscle vibration [Forner-Cordero et al., 2008], as well as with the long-term effects induced by specific skill learning [Pascual-Leone et al., 1995] or constraint-induced movement therapy in stroke patients [Liepert et al., 2000]. Such changes are usually considered to reflect an expansion of the cortical motor representation of the muscles being investigated [Pascual-Leone et al., 1993, 1995; Ridding et al., 2001; Thickbroom et al., 1999]; for review see [Siebner and Rothwell, 2003]. However,

increased motor map expansion does not necessarily signify a true expansion of the underlying cortical projection zone [Ridding et al., 2001]. For example, it has been demonstrated that an increase in the excitability of corticospinal tracts at the original projection would equally lead to an increase in motor map area (e.g., Ridding and Rothwell, 1997). Nevertheless, further inspection of our data qualifies this possibility. First, the primary increase of the cortical motor map representations of the APB, ADM, FCR, and ECR in the postintervention mapping session was not accompanied by underlying changes in the excitability of corticospinal projections to those muscles. Specifically, we found neither significant enlargements nor reductions in the amplitudes of MEP at the hotspot between the pre and postmapping sessions. This finding contrasts with the increases in excitability of cortico-cortical and corticospinal circuitry, such as seen after electrical nerve stimulation [Fraser et al., 2002; Hamdy et al., 1998; Ridding and Rothwell, 1997]. However, these rarely last more than 2 h after the end of the intervention and often show a slight depression 24 h postintervention [Ridding et al., 2001]. Second, we observed no enlargement of the hotspots, neither in the target (APB) muscle nor in the remaining muscles tested. Specifically, we found no significant changes in the motor representation areas of all muscles at those active sites where the mean amplitude of MEPs, recorded at the pre/postmapping sessions, was larger than 40% of the mean MEP recorded at the hotspots. In other words, enlargement of cortical motor representations following 3 weeks of TENS occurred around the borders of the cortical motor maps, as established at the premapping session.

The mechanism responsible for the expansion of the maps cannot be determined from the present data. It could be caused by true reorganization of the connectivity patterns in the cortex; alternatively, it could simply result from an increase in the excitability of connections that were already present but not detected by the TMS method. However, the fact that the maps expanded in muscles distant from the site of stimulation is interesting. In this respect, it is plausible that the observed expansion of the output zones to all muscles may have been partially due to high overlaps in topographic and/or neuronal representations between the APB and the remaining muscles.

Interestingly, the observed increase in TENS-induced representational reorganization of cortical maps is neither restricted to the motor areas nor to common innervation pathways (Table II). For example, prolonged (3 weeks) TENS treatment over the median nerve in MS patients has revealed that increases in tactile sensitivity were not restricted to thumb and index finger areas but also expanded to the fifth finger area [Cuypers et al., in press]. The fact that TENS-induced enlargements in the hand motor and/or sensory representations occur at multiple sites, suggests that somatosensory stimulation of peripheral afferent pathways with TENS might spread to nonstimulated parts of the somatosensory network. Electrophysiological and/or neuroimaging mapping

suggests that this phenomenon may occur both at the peripheral and supraspinal (cortical) levels [Kimura et al., 1983; Krause et al., 2001; Kurth et al., 2000; Sato et al., 2005].

The present findings provide indirect support for a strong connectivity between the somatosensory and motor areas. Electrophysiological animal research has revealed topographically and functionally specific corticocortical excitatory connections between somatosensory areas and primary motor cortex (M1) [Caria et al., 1997; Ghosh and Porter, 1988; Huerta and Pons, 1990; Lucier et al., 1975; Murphy et al., 1975].

The Mechanisms Underlying Motor Reorganization

We can only speculate on the mechanisms involved in the changes we observed here. Long-lasting changes in cortical motor excitability produced by repetitive central or peripheral stimulation have been shown to depend on long-term potentiation (LTP) or long-term depression (LTD). For example, it has been demonstrated that layer II/III horizontal connections in rat primary motor cortex, which are capable of LTP and LTD, are strengthened during acquisition of a new motor skill [Rioult-Pedotti et al., 2007]. Furthermore, animal studies suggest that LTP-like processes in motor cortex transiently increase synaptic strength, by insertion of glutamate receptors to existing synapses [Harms et al., 2008; Rioult-Pedotti et al., 2007]. In humans, learning of new motor skills is also shown to be associated with LTP-like changes in activity of cortical synapses which are most likely mediated by down-regulation of GABAergic inhibition [Rosenkranz et al., 2007]. Our observations indicated that (1) the 3 weeks intervention with TENS expanded the overlaps between output zones of neighboring muscles without inducing discernible changes in the level of corticospinal excitability around the hotspots, and that (2) enlargement of cortical motor maps occurred around the borders of their preintervention regions. In line with the aforementioned observations, it is reasonable to assume that long stimulation periods may result in the formation of new connections. Studies using pharmacological interventions may help to further unravel these mechanisms.

It is also meaningful to address how the present data can be reconciled with previous reports on the effect of single sessions of TENS on cortical excitability. Tinazzi et al. [2005] have shown that prolonged somatosensory stimulation with TENS induces long-lasting depression in MEPs from the target muscle while having the opposite effect (i.e., long-lasting facilitation) on the nontarget muscles, however, this was not confirmed by others [Fernandez-del-Olmo et al., 2008]. Nevertheless, the suggestion of simultaneous changes in excitatory and inhibitory pathways made by Tinazzi et al. [2005] may be one way in which it is possible to account for the simultaneous

enlargement of cortical motor representations in the stimulated (APB) and nonstimulated muscles in the absence of a change in global excitability (e.g., rMT) of the descending motor pathways to these muscles. In this respect, the contribution of the GABAergic inhibitory system to the emergence of TENS-induced plasticity may remain a viable but not exclusive means for inducing cortical map changes, as observed in the present study. In the absence of direct recordings of synaptic dynamics or pharmacological manipulation, any inference about the physiological basis of the present findings must be made with caution.

Even though the present findings are encouraging, some limitations need to be recognized. First, no follow-up measurements were conducted beyond the postintervention test to examine the lasting effects of the intervention. Second, no sham TENS group beyond our current control group was included to examine placebo effects. However, as participants were healthy and naïve about the purpose of the study, it is unlikely that our observations were biased by placebo effects. Finally, changes in the motor representation of the hand may be caused by unspecific reasons such as attentional drift away from the zone of stimulation. However, observations from the present and other studies [e.g., Cuypers et al., in press; Ridding et al., 2001] suggest that TENS-induced modulations in cortical motor representations (or tactile sensitivity) extended beyond the boundaries of the stimulated zone, indicating spread of activation from stimulated to nonstimulated parts of the somatosensory network.

Clinical Applications

The present observations highlight the potential of somatosensory stimulation to serve as a useful complementary therapy in neurorehabilitation. We have shown that TENS-induced enlargements in cortical motor maps were not restricted to the stimulated muscle but also extended to other hand and forearm muscles. However, therapeutic choices for global versus local effects will have to be made according to the specific disorder under treatment. In any case, it is clear that interventions that are first and foremost sensory in nature, do impact upon motor representations that persist for more than 20 h following the intervention. More research will be necessary to differentially “tune” M1 reorganization by further manipulation of the type of somatosensory stimulation and its parameters.

Since only healthy volunteers were included in this study, generalization of the results to patient populations should be made with caution. However, a recent study using exactly the same intervention protocol (i.e. TENS to the right APB muscle, 1 h a day for 3 weeks) in patients with MS, showed long-lasting improvements in tactile sensitivity. MS patients reached the same level of sensitivity as healthy subjects immediately after the intervention, and significant long-term effects were reported up to 3 weeks

following the last intervention [Cuypers et al., in press]. Overall, this suggests that TENS may be particularly useful as a complementary therapeutic tool in neurorehabilitation.

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