ARTICLE IN PRESS

Brain Stimulation ■■ (2016) ■■–■■

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

# Priming Hand Motor Training with Repetitive Stimulation of the Fingertips; Performance Gain and Functional Imaging of Training Effects

Martin Lotze [a,*], Aija Marie Ladda [a], Sybille Roschka [b], Thomas Platz [b], Hubert R. Dinse [c,d]

[a] Functional Imaging Unit, Center for Diagnostic Radiology, University of Greifswald, Germany
[b] BDH-Klinik Greifswald, Neurorehabilitation centre and Spinal Cord Injury Unit, University of Greifswald, Germany
[c] Neural Plasticity Lab, Institute for Neuroinformatics, Ruhr-University Bochum, Germany
[d] Department of Neurology, BG University Hospital Bergmannsheil, Ruhr University Bochum, Germany

ARTICLE INFO

*Article history:*
Received 27 April 2016
Received in revised form 1 October 2016
Accepted 5 October 2016
Available online

*Keywords:*
Motor training
Stimulation
Tactile priming
fMRI
Arm ability training

ABSTRACT

*Background:* Application of repetitive electrical stimulation (rES) of the fingers has been shown to improve tactile perception and sensorimotor performance in healthy individuals.
*Objective:* To increase motor performance by priming the effects of active motor training (arm ability training; AAT) using rES.
*Methods:* We compared the performance gain for the training increase of the averaged AAT tasks of both hands in two groups of strongly right-handed healthy volunteers. Functional Magnetic Resonance Imaging (fMRI) before and after AAT was assessed using three tasks for each hand separately: finger sequence tapping, visually guided grip force modulation, and writing. Performance during fMRI was controlled for preciseness and frequency. A total of 30 participants underwent a two-week unilateral left hand AAT, 15 participants with 20 minutes of rES priming of all fingertips of the trained hand, and 15 participants without rES priming.
*Results:* rES-primed AAT improved the trained left-hand performance across all training tasks on average by 32.9%, non-primed AAT improved by 29.5%. This gain in AAT performance with rES priming was predominantly driven by an increased finger tapping velocity. Functional imaging showed comparable changes for both training groups over time. Across all participants, improved AAT performance was associated with a higher contralateral primary somatosensory cortex (S1) fMRI activation magnitude during the grip force modulation task.
*Conclusions:* This study highlights the importance of S1 for hand motor training gain. In addition, it suggests the usage of rES of the fingertips for priming active hand motor training.
© 2016 Elsevier Inc. All rights reserved.

## Introduction

Repetitive somatosensory stimulation (rSS) of the fingers, either tactile or electrical, has been demonstrated to drive plasticity processes and to improve tactile perceptual abilities [1]. rSS is capable to reset the age-related decline of tactile discrimination in elderly individuals [2] and has also an impact on motor function [3]. The effectiveness of this method has been demonstrated in patients with chronic cerebral lesions during long (weeks to months) stimulation periods [4], and recently also in patients suffering from neuropathic pain [5]. Both stimulations of two and three hand nerves are comparably capable to improve motor function in healthy young participants [6]. However, somatosensory electrical stimulation was not capable to increase short term motor training effects in healthy volunteers in an earlier study [7].

Besides improvement of somatosensory abilities, application of rSS also improved motor performance in both healthy adults and elderly individuals [3,8] and patients [4]. However, how rSS affects the motor system remains largely speculative. It is generally believed that the transfer of beneficial effects to sensorimotor behavior elicited by sensory stimulation is based on interconnections between the somatosensory and motor cortices [9–11]. These interconnections are assumed to elicit a cortical reorganization in the primary motor cortex after stimulation, resulting in increased excitability of the motor cortical representations [12], in intracortical facilitation [13], and in a decrease in intracortical inhibition [14]. On the other hand, accurate sensory perception requires recurrent SI activation from the secondary motor cortex [15].

* Corresponding author. Fax: +49 3834 866898.
*E-mail address:* martin.lotze@uni-greifswald.de (M. Lotze).

1935-861X/© 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2016.10.004

Based on these interactions, motor training of hand and finger performance might well profit from somatosensory priming. We therefore explored the efficacy of a combination of rES of the fingertips before 2 weeks of motor training (arm ability training (AAT) [16]) of the left arm in healthy right handed participants. With the current study, we intended to investigate changes of neural representation after rES-primed motor training within the sensorimotor system. AAT is a comprehensive and repetitive motor training that has originally been developed for stroke patients.

In previous studies, we have demonstrated that AAT is capable of increasing motor performance of the non-dominant hand in strongly right-handed healthy participants [17]. In addition, we showed that both tactile resolution and motor performance increased during rES-primed AAT [18]. In the current study, we balanced two groups with and without rES before AAT for performance (AAT scores before training) and demographic data (age and gender) in order to quantify possible additional effects of rES priming.

Using fMRI, we aimed to investigate whether neural substrates underlying performance gain for the rES-primed training were different from those already reported for AAT training alone [17]. We therefore evaluated changes in fMRI activation over training in regions of interest (ROI) preselected on the basis of other studies on long-term motor training [19,20] to evaluate the impact of somatosensory stimulation priming on motor learning. We hypothesized that training should result in an activation decrease of cortical (secondary motor and somatosensory representation) areas, and an activation increase in subcortical (anterior cerebellar hemisphere, basal ganglia) areas.

## Materials and methods

### *Participants*

For the rES-primed arm ability training we included 15 healthy, right-handed participants aged 22–28 [25 (mean) ± 2.2 years (standard deviation); 7 women]. Handedness was determined using the Edinburgh Handedness Inventory with the laterality quotient (LQ), indicating strong dexterity (mean = 98.6 ± 3.7, range: 89–100). For the non-primed training we recruited 15 participants (24 ± 3.7 years; 6 women) who were also all strongly right-handed (LQ: 93.5 ± 5.5; range: 88–100). Both groups were balanced for comparable AAT-performance at the start of training.

None of the participants suffered from any neurological disorder or vascular disease (screening by questionnaire), nor were they on any regular medication (contraceptives excluded). Participants were recruited via notice boards at the university campus. Any previous or current regular activity in playing musical instruments was considered an exclusion criterion for study participation. All participants gave their written and informed consent according to the Declaration of Helsinki, and the study was approved by the ethics committee of the Medical Faculty of the University of Greifswald (BB 126/11).

### *Experimental schedule*

The training period extended over two weeks and comprised ten days of arm training. On days 1, 2 and 5, training took place in the laboratory in the presence of the instructor. On all other days, the participants practiced at home. A custom-made software was used (for details, see below) to document the performance times of each task during the training sessions, including graphical feedback to check for plausibility. Motor performance was assessed immediately prior to the first training session and after the second MRI scan. Whenever training or assessment was conducted, the participants were instructed to perform as fast as they could while keeping the number of errors low, unless the task design included externally paced movements (fist clenching in the scanning session with 1 Hz visually paced).

### *Training method*

Both the rES-group and the non-priming group were enrolled in the active upper limb training. We used a comprehensive finger-hand training developed for stroke patients with moderate upper limb motor impairment (arm ability training; AAT [16]). The AAT targets different sensorimotor abilities such as aiming (i.e. ability to perform quick goal-orientated movements: aiming), arm-hand steadiness (i.e. ability to keep the hand or arm steady; labyrinth, aiming and other trials), wrist-finger speed (i.e. ability to make fast isolated alternating movements of wrist and fingers: tapping), finger dexterity (i.e. ability to manipulate small objects: turning coins; small objects), manual dexterity (i.e. ability to grip and manipulate large objects with hands and arms: bolts and nuts; heavy objects) and visuomotor tracking (i.e. ability to move precisely under continuous visual control: crossing circles; labyrinth) [17,18].

Participants received detailed instructions on the AAT method and the documentation software that was used (AFT 1.2, Platz, Greifswald; Programming by OLIOID GmbH, Berlin, Germany). The time needed for the execution of each of the eight trained tasks was recorded and fed back graphically. Improved performance was indicated by reduced performance time, while the accuracy demands of the tasks were kept constant. All participants performed the training in the same standardized manner with two runs of task performance in a fixed sequence twice a day. The individual improvement was checked for plausibility by the instructor during the assessment sessions. After completion, the whole set was performed a second time, resulting in a total number of four repetitions per task. The duration of the daily training session was approximately 60 minutes.

### *rES protocol*

The participants of the rES-group were stimulated on their left fingertips for 20 minutes/day before they started motor training. The time between stimulation end and training was always less than 20 minutes. No stimulation was used in the non-rES group. The rES sequence consisted of stimulus trains of 1 s (single pulse-duration: 0.2 ms (square), frequency: 20 Hz) and inter-train intervals of 5 s. The sequence was played back from a digital storage device that triggered a standard two-channel TENS device (SM2-AKS, Pierenkemper, Germany) via a custom-made input-channel. The pulses were transmitted via adhesive surface electrodes (1 cm × 4 cm, Pierenkemper, Germany) fixed on the first and third finger-segments (cathode proximal; see Fig. 1). Stimulation intensity was adjusted to the twofold sensory threshold separately for median and ulnar nerve innervated fingers, resulting in an average initial stimulation intensity of 10.8 ± 1.5 mA on d1–d3 and 7.8 ± 0.9 mA on d4 and d5. The adjustment of stimulation current was set according to a previous study exploring the effect of stimulation intensity [1].

### *Motor performance testing*

The performance gain for the left hand was used as an outcome parameter. As a primary outcome variable, we assessed AAT performance as measured by trained doctoral students before and after AAT training separately for the left and right hands. Evaluation of performance was not blinded. The time needed to complete four repetitions of each of the eight training tasks was assessed (Fig. 1B) and changes were averaged as a percentage gain for the complete AAT. As a secondary outcome variable maximum grip force [bar]

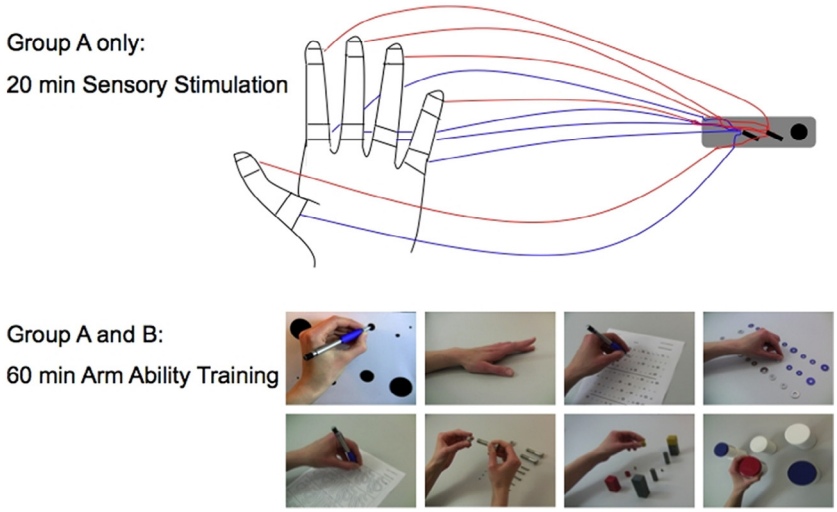


**Figure 1.** Top (A): The rES-primed participant group was treated with a 20 minute repetitive unattended electric stimulation of the fingertips before one hour of arm ability training. The non-primed group had only arm ability training. Bottom (B): Eight different tasks were applied during the arm ability training (from top left: aiming, tapping, crossing circles, turning coins, labyrinth, nuts and bolts, placing small objects, placing large objects).

was assessed by an experimenter using a vigorimeter (Gebrueder Martin GmbH & Co. KG, Tuttlingen, Germany). Grip force was assessed three times and the average value was calculated before and after training. For "writing", the number of letters copied was counted in 4 blocks, each lasting 20 seconds, and averaged.

Performance gain of the left hand was calculated as percentage changes from the pre-measurement using the following formula: $((\text{post} - \text{pre})/\text{pre}) \times 100$. These were compared between training groups using independent t-tests after testing for relevant difference from normal distribution using the Kolmogorov–Smirnov-Test. We did not use an rmANOVA here because AAT-tasks had to be normalized with percentual improvement before averaging. fMRI-task performance (grip force modulation, finger sequence, writing) was monitored for offline analysis. Repeated measures ANOVAs were conducted with the within-factors group (rES-primed AAT versus non-primed AAT), time (pre, post) and hand (right, left).

*fMRI experimental design*

MRI-scanning was performed 3–4 days prior to the first day of motor training (pre measurement) and one day after the last block of training had been completed (post measurement). As participants lay on the patient table inside the scanner in a supine position, brain activity was measured during the performance of three different motor tasks with each hand. Two of the tasks were comparable to the trained movements of the AAT, containing the key elements of visually guided movements and repetitive single-digit tapping. The third task was a target force fist-clenching condition for evaluation of transfer effects. Each task was practiced for two minutes prior to scanning in order to achieve a stable performance. A block design was used for each task, alternating five blocks of rest with four blocks of activity. Each block lasted 20 seconds and visual cues indicated either activity (green screen) or rest (blue screen). These cues were transmitted via video projections and a mirror, using Presentation software (version 13.0; Neurobehavioral Systems; Albany, NY, USA 2009), which was triggered by the scanner. Using a pseudorandomized order we assessed each of the following tasks.

*Grip force modulation task*

A pneumatic rubber ball was squeezed with 1/3 of the maximum grip strength at 1 Hz frequency; visual feedback indicated force amplitude as well as a signal for pacing. Both amplitude and frequency of fist clenching were monitored and recorded using a Varioport system that converted pressure levels of the rubber ball into electric signals. Prior to each scanning session the maximum grip strength of either hand was assessed. The participant was asked to squeeze the rubber ball in a maximum voluntary contraction 8–10 times. The participant was then trained for 2 minutes to reach the target force (1/3 of maximum) and frequency (1 Hz).

*Tapping of a finger sequence*

Twelve numbers were presented visually, and corresponding buttons on a keypad (four-finger-keypads by LUMItouch, Harvard, USA, adapted for each hand) were pressed at 1 Hz frequency. The numbers 2, 3, 4 and 5 corresponded to index, middle, ring and little finger, respectively. An optic fiber system transferred information on key presses to a computer, where it was recorded by Presentation software. The finger sequence was trained outside the scanner room prior to each scanning session.

*Writing*

The participants were instructed to copy 12 single terms that were arranged in two columns on a horizontally oriented sheet of paper ($210 \times 297$ mm) using a pencil and cursive handwriting. The participants were asked to begin with the column next to the currently writing hand. A line underneath each term provided space for writing. Four sheets of paper with different terms but the same number of letters were used in a pseudorandomized order. All participants of both groups copied the same letters. The sheets were placed on a small desk with an angled board, positioned above the participant's abdomen. Small sandbags supported the upper arm to avoid additional movement, and a double-mirror attached to the head coil allowed for visualization during writing. Between blocks, an assistant standing next to the scanner changed the paper sheets. Performance measure was the number of letters copied, averaged over the four trials.

*fMRI measurements*

Data acquisition was performed with a Siemens Magnetom Verio 3T-scanner (Siemens; Erlangen, Germany), using a 32-channel head-coil. Field homogeneity was optimized prior to each session using

a shimming sequence. For anatomical images, 176 T1-weighted slices in sagittal orientation were acquired (magnetization prepared rapid gradient echo (MPRAGE); TR = 1.69 s; TE = 2.52 ms; voxel size = $1 \times 1 \times 1$ mm$^3$, two times GRAPPA acceleration). Functional images were gathered during motor task performance using T2*-weighted echo planar imaging (EPI) in transversal orientation, parallel to the AC-PC-line (TR = 2.00 s; TE = 30 ms, flip angle = 90°; FoV $192 \times 192$ mm$^2$; matrix size = $64 \times 64$, voxel size = $3 \times 3 \times 3$ mm$^3$). In total, 90 volumes were obtained, consisting of 34 slices each (thickness of 3 mm, with a 1 mm gap in between slices). To allow for T1 equilibration effects, the first two volumes of each session were discarded. 34 phase and magnitude images were acquired in the same FoV by a gradient echo (flip angle 60°; FoV $192 \times 192$ mm$^2$; slice thickness 3 mm; TR = 488 ms; $TE_1$ = 4.92 ms; $TE_2$ = 7.38 ms) to calculate a field map in order to correct geometric distortions in EPI images (unwarping [13]).

*fMRI data evaluation*

Data were analyzed using SPM8 (The Wellcome Trust Centre for NeuroImaging, London, UK) running on Matlab version 7.4 (The MathWorks, Inc.; Natick, MA, USA). The FieldMap toolbox was used to unwarp EPIs that were geometrically distorted due to magnetic field inhomogeneities [21]. To correct for movement artifacts, scans were realigned onto the first scan of each series. The EPIs were then coregistered to the T1-weighted anatomical image and resliced at $3 \times 3 \times 3$ mm$^3$. The T1-image was segmented and normalized to the Montreal Neurological Institute (MNI) image. To increase the signal-to-noise ratio, smoothing was performed using a $9 \times 9 \times 9$mm$^3$ full width half maximum (FWHM) Gaussian Kernel filter. Using the general linear model (GLM) we evaluated statistical maps of the main conditions and the comparisons between pre and post measurement for each individual. To perform group analysis, corresponding contrast images were compared in a full-factorial GLM random effects analysis. Within-subjects factors were 'session' (pre and post) and 'task' (grip force modulation, finger sequence, writing).

In a regions-of-interest approach (ROIs) we analyzed the following areas (corrected for multiple comparisons within ROIs, $p < 0.05$, FWE-corrected; additional cluster threshold: > 5 voxel): primary motor cortex (M1), primary somatosensory cortex (S1), secondary motor cortex (supplementary motor area (SMA), premotor cortex (PMC), superior parietal lobe (sensorimotor integration), basal ganglia (putamen, pallidum, caudate), and anterior cerebellar hemisphere (feedforward loops; Larsell lobule IV–VII). Within BA 6 the border between SMA and PMC was defined at the superior frontal sulcus of the MNI-template ($-30 < x < 30$) marking $z = 50$ as the inferior border of the PMC. Significant brain areas were spatially assigned using SPM Anatomy Toolbox Version 1.7 [22] and, if areas were not defined by Anatomy, using Automated Anatomic Labeling [23]. ROI for S1 was restricted to the finger area (for somatotopic range of the S1 mask see Reference 24). The S1 mask has also been applied in previous investigations on S1 representations of the fingertips [25].

In order to explore associations of changes in neural representation with changes in motor performance of the trained task (arm ability training), we calculated a linear regression across all 30 participants restricted on the ROIs. We expected specific fMRI-associations with performance gain in the ROIs contralateral to the trained hand.

## Results

*Group homogeneity at training onset*

Participant groups were comparable with respect to age (non-rES: 23.53 ± 3.70 years, rES: 24.87 ± 2.23 years; n.s.) and left hand AAT-performance (aiming: non-rES: 71.69 ± 6.72 s, rES: 80.39 ± 10.10 s (n.s.); tapping: non-rES: 65.55 ± 8.62 s, rES: 70.22 ± 15.05 s (n.s.); crossing circles: non-rES: 68.40 ± 16.50 s, rES: 61.10 ± 12.51 s (n.s.); turning coins: non-rES: 50.74 ± 7.30 s, rES: 51.60 ± 9.51 s (n.s.); labyrinth: non-rES: 54.65 ± 9.41 s, rES: 50.27 ± 7.86 s (n.s.); bolts and nuts: non-rES: 49.21 ± 8.78 s, rES: 61.89 ± 11.64 s (n.s.); small objects: non-rES: 49.59 ± 11.18 s, rES: 50.97 ± 7.42 s (n.s.); heavy objects: non-rES: 59.49 ± 6.67 s, rES: 62.21 ± 9.52 s (n.s.)) at training onset. However, both training groups differed with respect to their handedness score (Oldfield handedness inventory: non-rES: 93.53 ± 5.50, rES: 98.6 ± 3.7; $t(28) = 2.96$; $p < 0.01$).

*Performance gain during training*

Primary outcome variable: For the non-primed group, motor performance averaged across all trained AAT tasks improved by 29.5 ± 3.5% for the trained left hand. AAT-tasks for the non-trained right hand of this group improved by 20.7 ± 5.1%. For the rES-primed group, motor performance averaged across all trained tasks improved by 32.9 ± 5.1% for the trained left hand. AAT-tasks for the non-trained right hand of this group improved by 22.0 ± 4.4%. For the trained left hand, the effect of rES-primed AAT was larger than those of the non-rES group (averaged AAT-tasks; $t(28) = 2.11$; Cohen's delta: 0.77; $p = 0.044$; two-sided; see Fig. 2) and was predominantly driven by finger tapping velocity increase (Cohen's delta: 0.85; the other seven tasks improved with an average effect size of Cohen's delta: 0.27).

As for the secondary, non-trained outcome variable, maximal grip strength for the trained left hand of the non-primed group increased by 1.9%, but by 10.0% for the rES-primed group ($t(28) = 2.02$; $p = 0.027$; one-tailed). Writing with the left hand showed a performance increase of 11.0% for the non-primed group, but an 18.6% increase for the rES-primed group (Fig. 3). The difference between training groups was not significant for left hand writing performance ($t(28) = 1.45$; n.s.), although it showed a moderate effect size (Cohen's delta: 0.53).

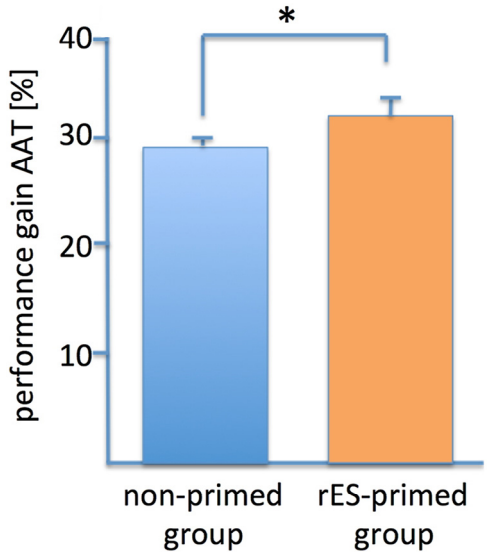


**Figure 2.** Primary outcome variable: The increase in the primary performance outcome (averaged the arm ability training (AAT) score) in the rES-group (orange bar; n = 15) for the trained left hand was higher (* $p < 0.05$) than that of the non-primed group (blue bar; n = 15; lines indicate standard error). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

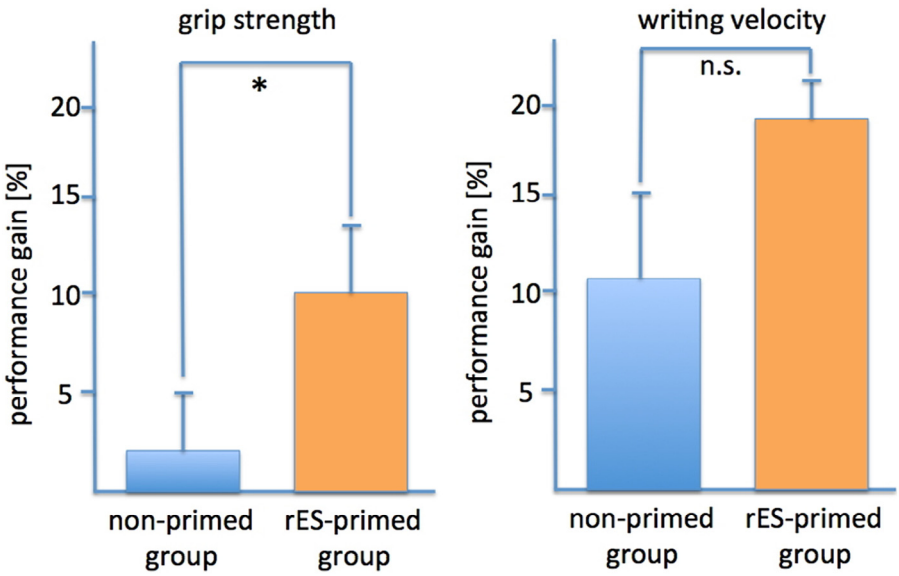


**Figure 3.** Secondary outcome variables. Left: For grip strength with the left hand the increase in performance in the rES-group was slightly higher (* $p < 0.05$, one-tailed) compared to the non-primed group. Right: For writing with the left hand, the difference between training groups did not reach significance. Lines indicate standard error.

*Performance control in the MRI*

Repeated-measures ANOVAs did not reveal significant differences between groups for the frequency or amplitude of grip force modulation, finger sequence errors, or number of written words. For the number of written letters, rmANOVA showed a significant effect for both time ($F(14,1) = 37.73$; $p < 0.001$) and hand ($F(14,1) = 180.85$; $p < 0.001$). The number of written letters improved for the trained left hand (rES-primed group: $t(14) = 6.93$; $p \leq 0.001$).

*FMRI results*

*Decrease of fMRI-activation after training (pre minus post)*

For the rES-primed group a relevant economization of activation in ROIs was observed only during the finger sequence task with the trained left hand. Significant ROIs comprised bilateral primary sensorimotor cortex, SMA, and superior parietal lobe (see Table 1). These results were not significantly different from those observed for the non-primed AAT group before [17]. Here left finger sequence performance showed an activation decrease in the dorsolateral prefrontal cortex, ipsilateral S1, ipsilateral parietal lobe, and bilateral SMA. All other tasks performed with either left or right hand showed no significant change over time.

*Increase of fMRI-activation after training (post minus pre)*

For the rES-primed group a relevant increase of MRI-activation was observed for the grip force modulation task performed with the trained left hand, consisting of an increase of activation in the ipsilateral putamen and pallidum (Table 2). This was a comparable effect as those reported for the non-primed AAT group before [17]. For the writing task with the left hand, an increased activation after training was observed in the right putamen and left anterior cerebellum (Table 2, Fig. 4). Except for the putamen effect, again, the results were the same as those reported for the non-primed AAT group. The finger sequence task showed only an

**Table 1**
Pre minus post (economization of fMRI-activation).

| Task | Area | T-value | p(FWE) | Cluster | x | y | z |
|---|---|---|---|---|---|---|---|
| Sequence left | M1S1 left | 3.86 | 0.034 | 19 | –12 | –36 | 69 |
| | | 3.77 | 0.045 | 32 | –39 | –27 | 42 |
| | M1S1 right | 3.82 | 0.039 | 77 | 48 | 9 | 33 |
| | | 3.77 | 0.044 | | 48 | 6 | 42 |
| | SMA | 4.52 | 0.002 | 90 | 6 | 24 | 45 |
| | | 3.98 | 0.014 | | 6 | 21 | 60 |
| | Superior parietal left | 3.71 | 0.04 | 11 | –42 | –45 | 57 |

M1S1: primary sensorimotor cortex; SMA: supplementary motor area.

**Table 2**
Post minus pre (increase of fMRI-activation).

| Task | Area | T-value | p(FWE) | Cluster | x | y | z |
|---|---|---|---|---|---|---|---|
| Fist clenching left | Putamen left (le) | 4.60 | 0.001 | 59 | –27 | 0 | 3 |
| | Pallidum le | 4.33 | 0.001 | 22 | –24 | 3 | 0 |
| Writing left | Ant. cerebellum le Larsell lobule 4–7 | 3.78 | 0.037 | 19 | –9 | –69 | –24 |
| | Putamen right (ri) | 3.69 | 0.023 | 6 | 27 | –3 | 12 |
| Sequence right | Caudate nucleus ri | 3.67 | 0.026 | 16 | 15 | 15 | 6 |
| | Putamen right ri | 3.52 | 0.039 | 17 | 18 | 15 | 3 |

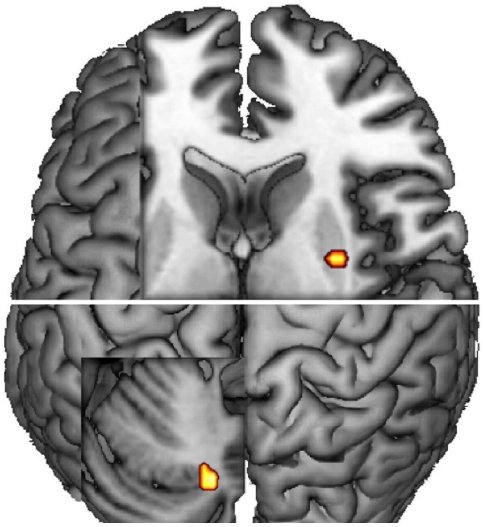

**Figure 4.** Increase in functional activation in the right putamen and left anterior cerebellum in the rES-primed group for the task "writing with left (trained) hand". Group analysis for 15 participants with rES-primed AAT over two weeks; post-measurement minus pre-measurement; $p < 0.05$; FWE-corrected for a region of interest analysis.

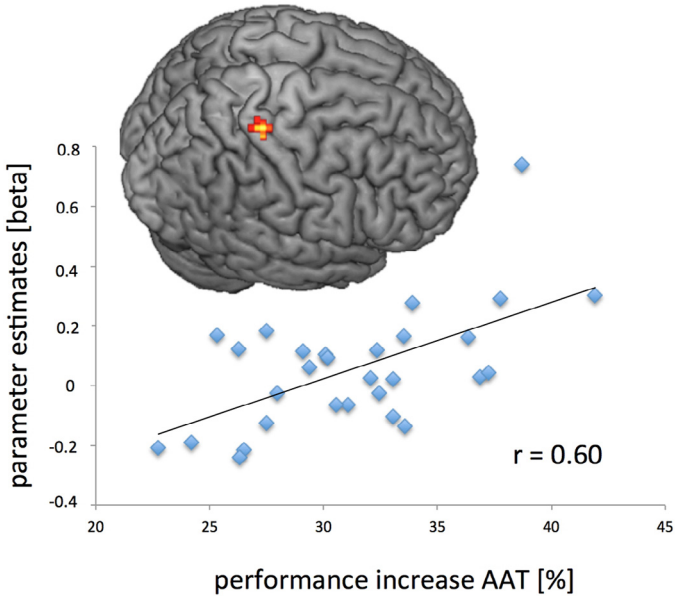


**Figure 5.** Linear regression analysis between fMRI activation magnitude [beta] increase after training in the contralateral S1 finger area ($t = 3.85$; MNI-coordinates: 21, –33, 48; projection on the rendered MNI-reference brain on top) during grip force modulation and performance increase of the AAT task for both training groups combined. Bottom: plot of linear regression and the corresponding correlation coefficient r.

economization of fMRI-activation for the trained hand. However, finger sequence performed with the non-trained right hand showed increased right caudate and putamen activation (Table 2). For the non-primed group, the differences post minus pre for the finger sequence were centered on the ipsilateral anterior cerebellar hemisphere, the cerebellar vermis and the SPL (BA 5).

*Direct comparisons of fMRI-activation maps between groups with and without rES*

There were no significant differences between both training groups when comparing changes of functional representation for the trained left hand over time (pre minus post or post minus pre, all three conditions).

*Associations between behavioral gain and fMRI activation magnitude*

After obtaining negative results from group comparisons, we asked what neural resources drive the performance gain in the AAT task. We hypothesized that an increased activation of the contralateral (right) primary somatosensory cortex (S1) is associated with improved motor performance [26]. We calculated the association of the increase in fMRI-activation for the grip task over time with changes in behavior (AAT-performance increase) and used data of both training groups. Linear regression revealed a positive association of fMRI-activation increase in the right S1 and the performance increase across all AAT-tasks ($t = 3.85$; $p_{FWE} = 0.039$; MNI-coordinates: 21, –33, 48; see Fig. 5).

## Discussion

Repetitive electric stimulation of the fingertips applied before daily arm ability training (AAT) increased performance gain for the trained tasks in the left upper limb. In addition, training effects were also observed for tasks not explicitly trained, indicating transfer and generalization of motor learning. This transfer was substantially larger in the rES group as compared to the non-primed group, indicating a beneficial effect of priming. In the rES group, fMRI showed an increase of basal ganglia and anterior cerebellar representation after training. Performance increase across all trained tasks for all participants (rES-primed and non-primed groups) was associated with an increase of contralateral S1 activation.

*Increase of performance gain by rES priming*

The arm ability training (AAT) is a comprehensive training, which is capable of increasing non-dominant hand motor performance in healthy participants [17]. Our study demonstrates that this performance gain can be further enhanced by rES priming of the fingertips. In addition, the healthy young individuals in our study profited not only for the trained tasks, but also even more for non-trained maximal grip strength of the left hand. In contrast, maximal grip strength was unchanged for non-primed AAT (increase of only 1.9%). This indicates that rES priming might be particularly efficient in driving generalization effects of motor training. It is also conceivable that ceiling effects limited a further improvement in the trained AAT tasks.

It has been demonstrated before that writing with the left or the right hand recruits common neural substrates in the dominant hemisphere [27,28]. Therefore it could be expected that rES priming of the left hand might not relevantly affect motor training of this task, since it should affect excitability of the right hemisphere [29]. However, we observed a quite remarkable effect size for improved velocity of left hand writing over time suggesting that in participants with lower initial performance or in patients with brain damage, rES may lead to significantly increased training outcomes.

The effect of rES amounted to about 3% in addition to the AAT effect in our healthy young group. The effect size observed here (between 0.77 and 0.53) is comparable to strategies increasing cortical excitability in the primary motor cortex directly using anodal TDCS (about 0.59 [30]). This suggests that unattended rES of the fingertips might be an alternative to the more often used anodal TDCS-priming.

*Possible mechanism of rES priming*

Repeated electrical stimulation of the fingers has been described to result in an increased cortical excitability of the somatosensory cortex as measured by paired pulse median nerve

evoked somatosensory potentials [29], increased fMRI-activation [31,32], parallel to an increase in spatial tactile acuity [6–8]. Typically, the individual gain in discrimination performance was positively correlated with an increase in cortical excitability [29], BOLD signal [31], or EEG-based dipole changes [33].

Somatosensory function and motor function are tightly linked together. Increasing S1-excitability has a direct effect on primary motor cortex excitability (for a recent review see Reference 34). Somatosensory deficits after stroke impair the recovery of voluntary movements [35]. It has been suggested that top-down control of the premotor cortex affects primary somatosensory processing and that the premotor cortex in rodents directly activates layer 5 dendrites in S1 in the absence of temporal coincidence with a bottom-up input [15]. In addition, higher BOLD amplitudes and synchronicity at rest, as measures of cortical activity and synchronicity, are related to better tactile discrimination abilities of the contralateral hand [36]. In humans, increased functional connectivity between SI and MI has been observed following rES [37]. Moreover, an increase in motor excitability after repetitive tactile training has been demonstrated [38].

Accordingly, there are ongoing direct interactions between motor and somatosensory cortex that might be crucial for mediating the beneficial effects of sensory priming of motor behavior. We therefore suggest that an increase in S1 excitability results in a widespread facilitation of primary sensorimotor plasticity and of training effects on both somatosensory and motor performances. This increase in somatosensory performance might especially improve finger tapping rates, an ability that showed the highest effect size of all AAT tasks in the rES-primed group.

### *Overall changes in functional activation after rES-primed repetitive motor training*

We found an economization of ipsi- and contralateral primary and secondary sensorimotor areas (M1, S1, SMA, superior parietal cortex) after training for the finger sequence task. For long term motor training, an economization of cortical representation sites has been previously described especially for motor sequence training [39,40]. Furthermore, expert instrumentalists, in comparison to non-musicians [41] or amateurs [42], show decreased motor activations within the SMA, the PMC, and the ipsilateral M1 during movement performances of varying complexities. Increased activity of the putamen and the ipsilateral cerebellum was found during fist clenching and in the contralateral putamen during writing with the left hand after rES-primed AAT. This finding supports data on changes in functional motor representation after long term training [40]. The cerebellar activations included both anterior and posterior regions, and also anterior parts of the vermis. For the latter, we assume an involvement in the generation of a rhythmic writing component [43].

### *Limitations of the study*

We were not able to observe relevant differences between the rES-primed and the non-primed AAT groups with regard to changes in fMRI-representation of the motor tasks tested. This might be caused by a lack of statistical power, but also by the fact that the fMRI tasks tested were not completely identical to the tasks trained. Changes due to different training procedures might therefore remain unrecognized for the tested conditions. In addition, long-term training procedures show less prominent changes than those present shortly after short-term training [26,40], which might well decrease the effect between training groups, too. In addition we followed the rES protocol developed by the group of Schlieper and Dinse [1]. There might well be developments from other groups which might be even more advantageous for modulating sensorimotor interaction and for priming upper limb motor training as suggested by other groups [38,44]. Furthermore, the lack of a non-trained control group excludes further conclusions differentiating between habituation and training effects. It is also well possible that the effects of the AAT protocol when applied in healthy young adults show severe ceiling effects, thereby masking possible differences evoked by the addition of priming. An additional limitation is the lack of blinding during data analysis. Blinding should be added in a future study comparing additional effects of somatosensory priming on active motor training.

## Conclusions

Repetitive electrical stimulation of the fingertips might be a useful strategy to further enhance motor training gain induced by active motor training. The average improvement of only 3% for the trained tasks makes it possible that the small effects in young healthy adults are due to ceiling. Testing elderly participants or patients is therefore necessary to obtain more information about the beneficial role of rES-based priming. Given the finding of associated primary somatosensory cortex activation increase over all trained participants with training gain, the upper limb motor training should be more focused on somatosensory aspects.

## Acknowledgements

We would like to thank Andrea Daniela Walz and Karla Doppl for measurement and data evaluation of the non-primed group. We would also like to thank Evangelia Kaza for help on the development of fMRI-data evaluation scripting, and Nicola Neumann for helpful comments on the manuscript. The study was partially supported by a grant for Martin Lotze from the DFG (LO-795-1).

## References

[1] Schlieper S, Dinse HR. Perceptual improvement following repetitive sensory stimulation depends monotonically on stimulation intensity. Brain Stimul 2012;5(4):647–51.
[2] Dinse HR, Kleibel N, Kalisch T, Ragert P, Wilimzig C, Tegenthoff M. Tactile coactivation resets age-related decline of human tactile discrimination. Ann Neurol 2006;60:88–94.
[3] Kalisch T, Tegenthoff M, Dinse HR. Repetitive electric stimulation elicits enduring improvement of sensorimotor performance in seniors. Neural Plast 2010;690531.
[4] Kattenstroth J-C, Kalisch T, Peters S, Tegenthoff M, Dinse HR. Long-term sensory stimulation therapy improves hand function and restores cortical responsiveness in patients with chronic cerebral lesions. Three single case studies. Front Hum Neurosci 2012;6:224.
[5] David M, Dinse HR, Mainka T, Tegenthoff M, Maier C. High-Frequency repetitive sensory stimulation as intervention to improve sensory loss in Patients with complex regional Pain syndrome I. Front Neurol 2015;6:242.
[6] Sorinola IO, Bateman RW, Mamy K. Effect of somatosensory stimulation of two and three nerves on upper limb function in healthy individuals. Physiother Res Int 2012;17(2):74–9.
[7] Veldman MP, Zijdewind I, Solnik S, Maffiuletti NA, Berghuis KM, Javet M, et al. Direct and crossed effects of somatosensory electrical stimulation on motor learning and neuronal plasticity in humans. Eur J Appl Physiol 2015;115(12):2505–19.
[8] Kowalewski R, Kattenstroth JC, Kalisch T, Dinse HR. Improved acuity and dexterity but unchanged touch and pain thresholds following repetitive sensory stimulation of the fingers. Neural Plast 2012;2012:974504.
[9] Jones EG, Coulter JD, Hendry SH. Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. J Comp Neurol 1978;181:291–347.
[10] Stepniewska I, Preuss TM, Kaas JH. Architectonics, somatotopic organization, and ipsilateral cortical connections of the primary motor area (M1) of owl monkeys. J Comp Neurol 1993;330(2):238–71.
[11] Wu CW, Kaas JH. Somatosensory cortex of prosimian Galagos: physiological recording, cytoarchitecture, and corticocortical connections of anterior parietal cortex and cortex of the lateral sulcus. J Comp Neurol 2003;457(3):263–92.

[12] Ridding MC, McKay DR, Thompson PD, Miles TS. Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. Clin Neurophysiol 2001;112(8):1461–9.
[13] Kobayashi M, Ng J, Théoret H, Pascual-Leone A. Modulation of intracortical neuronal circuits in human hand motor area by digit stimulation. Exp Brain Res 2003;149(1):1–8.
[14] Classen J, Steinfelder B, Liepert J, Stefan K, Celnik P, Cohen LG, et al. Cutaneomotor integration in humans is somatotopically organized at various levels of the nervous system and is task dependent. Exp Brain Res 2000;130(1):48–59.
[15] Manita S, Suzuki T, Homma C, Matsumoto T, Odagawa M, Yamada K, et al. A top-down cortical circuit for accurate sensory perception. Neuron 2015;86(5):1304–16.
[16] Platz T, Winter T, Müller N, Pinkowski C, Eickhof C, Mauritz KH. Arm ability training for stroke and traumatic brain injury patients with mild arm paresis: a single-blind, randomized, controlled trial. Arch Phys Med Rehabil 2001;82:961–8.
[17] Walz A, Doppl K, Kaza E, Roschka S, Platz T, Lotze M. Changes in cortical, cerebellar and basal ganglia representation after comprehensive long term unilateral hand motor training. Behav Brain Res 2015;278C:393–403.
[18] Ladda AM, Pfannmöller JP, Kalisch T, Roschka S, Platz T, Dinse HR, et al. Effects of combining 2 weeks of passive sensory stimulation with active hand motor training in healthy adults. PLoS ONE 2014;9(1):e84402.
[19] Doyon J, Penhune V, Ungerleider LG. Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. Neuropsychologia 2003;41:252–62.
[20] Hardwick RM, Rottschy C, Miall RC, Eickhoff SB. A quantitative meta-analysis and review of motor learning in the human brain. Neuroimage 2013;67:283–97.
[21] Hutton C, Bork A, Josephs O, Deichmann R, Ashburner J, Turner R. Image distortion correction in fMRI: a quantitative evaluation. Neuroimage 2002;16:217–40.
[22] Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 2005;25:1325–35.
[23] 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.
[24] Weibull A, Bjorkman A, Hall H, Rosen B, Lundborg G, Svensson J. Optimizing the mapping of finger areas in primary somatosensory cortex using functional MRI. Magn Reson Imaging 2008;26(10):1342–51.
[25] Pfannmöller JP, Schweitzer R, Lotze M. An automated analysis protocol for high resolution BOLD-fMRI mapping of the fingertip somatotopy in Brodmann area 3b. Magn Reson Imaging 2015;43(2):479–86.
[26] Lotze M, Braun C, Birbaumer N, Anders S, Cohen LG. Motor learning elicited by voluntary drive. Brain 2003;126(4):866–72.
[27] Rijntjes M, Dettmers C, Büchel C, Kiebel S, Frackowiak RS, Weiller C. A blueprint for movement: functional and anatomical representations in the human motor system. J Neurosci 1999;19(18):8043–8.
[28] Planton S, Jucla M, Roux F-E, De Monet J-F. The “handwriting brain”: a meta-analysis of neuroimaging studies of motor versus orthographic processes. Cortex 2013;49:2772–87.
[29] Höffken O, Veit M, Knossalla F, Lissek S, Bliem B, Ragert P, et al. Sustained increase of somatosensory cortex excitability by tactile coactivation studied by paired median nerve stimulation in humans correlates with perceptual gain. J Physiol 2007;584(Pt 2):463–71.
[30] Kang N, Summers JJ, Cauraugh JH. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2016;87(4):345–55.
[31] Pleger B, Foerster AF, Ragert P, Dinse HR, Schwenkreis P, Malin JP, et al. Functional imaging of perceptual learning in human primary and secondary somatosensory cortex. Neuron 2003;40(3):643–53.
[32] Hodzic A, Veit R, Karim AA, Erb M, Godde B. Improvement and decline in tactile discrimination behavior after cortical plasticity induced by passive tactile coactivation. J Neurosci 2004;24(2):442–6.
[33] Pleger B, Dinse HR, Ragert P, Schwenkreis P, Malin JP, Tegenthoff M. Shifts in cortical representations predict human discrimination improvement. Proc Natl Acad Sci USA 2001;98(21):12255–60.
[34] Veldman MP, Maffiuletti NA, Hallett M, Zijdewind I, Hortobágyi T. Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans. Neurosci Biobehav Rev 2014;47:22–35.
[35] Nudo RJ, Friel KM, Delia SW. Role of sensory deficits in motor impairments after injury to primary motor cortex. Neuropharmacology 2000;39(5):733–42.
[36] Haag LM, Heba S, Lenz M, Glaubitz B, Höffken O, Kalisch T, et al. Resting BOLD fluctuations in the primary somatosensory cortex correlate with tactile acuity. Cortex 2015;64:20–8.
[37] Freyer F, Reinacher M, Nolte G, Dinse HR, Ritter P. Repetitive tactile stimulation changes resting-state functional connectivity-implications for treatment of sensorimotor decline. Front Hum Neurosci 2012;6:144.
[38] Schabrun SM, Ridding MC, Galea MP, Hodges PW, Chipchase LS. Primary sensory and motor cortex excitability are co-modulated in response to peripheral electrical nerve stimulation. PLoS ONE 2012;7(12):e51298.
[39] Shadmehr R, Krakauer JW. A computational neuroanatomy for motor control. Exp Brain Res 2008;185(3):359–81.
[40] Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. Neuron 2011;72(3):443–54.
[41] Lotze M, Scheler G, Tan HRM, Braun C, Birbaumer N. The musician’s brain: functional imaging of amateurs and professionals during performance and imagery. Neuroimage 2003;20:1817–29.
[42] Pau S, Jahn G, Sakreida K, Domin M, Lotze M. Encoding and recall of finger sequences in experienced pianists compared to musically naives: a combined behavioural and functional imaging study. Neuroimage 2013;64:379–87.
[43] Penhune VB, Zattore RJ, Evans AC. Cerebellar contributions to motor timing: a PET study of auditory and visual rhythm reproduction. J Cogn Neurosci 1998;10(6):752–65.
[44] Chipchase LS, Schabrun SM, Hodges PW. Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters. Clin Neurophysiol 2011;122(3):456–63.