fMRI of rehabilitation in chronic stroke using MR-compatible robots

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Introduction– Brain imaging studies in chronic stroke patients have shown evidence for plastic changes co-localization of areas showing structural and functional plasticity after a stroke [1]. Training-induced reorganization of the motor system has been consistently reported, leading to improvements in function commonly seen over weeks, months, sometimes years after stroke [2, 3]. Robot-assisted therapy has been shown to result in significant gains in motor coordination and muscle strength of the exercised shoulder and elbow, sustained in a three-year period following discharge from the hospital [4]. Here, we present results combining motor fMRI with a novel MR-compatible hand-induced robotic device (MR_CHIROD) [5-8] to monitor rehabilitation after chronic stroke.

Materials and Methods– Patients had first-ever left-sided ischemic subcortical middle cerebral artery (MCA) stroke ≥ 6 months prior, with no spasticity or joint stiffness. Patients trained at home and underwent serial MR evaluation at baseline (before training), 4 weeks after baseline, (halfway through the training period), 8 weeks after baseline (at the end of the training period), and twelve weeks after baseline (4 weeks after training ended) to assess permanence of the effects. Training at home consisted of squeezing a gel exercise ball with the paretic hand at approximately 75% of maximum strength for 1 hour/day, 3 days/week. For each patient, reference (100%) was own maximum force, defined as the force at which subjects could just completely squeeze the MR_CHIROD [group max force: 128 N ± 13 N (n = 5, male)]. All studies were performed on a Siemens Tim Trio (3T). BOLD fMRI was performed using GRAPPA gradient-echo EPI (TR/TE=3000ms/30ms, 1.56 mm×1.56 mm×3 mm). T1-MPRAGE and FLAIR served as anatomical reference and to localize hyperintense regions and stroke lesions. A block design paradigm was used for fMRI. During the action period, subjects squeezed the MR_CHIROD and released continuously. Squeezing rate was guided by a visual 'metronome' cue circle oscillating radially at 0.5 Hz. A fixation cross was projected during rest. Each volunteer performed the paradigm at 45%, 60%, and 75% of their maximum grip strength and could fully squeeze the device at all levels. The percent levels compensate for performance confounds. Care was taken to minimize elbow flexion and/or reflexive motion, and head motion (typically 0.1 to 0.4 mm). Images were normalized to MNI152 space and smoothed with a 4×(voxel dimension) Gaussian kernel. Significant voxels were $P<0.05$, corrected. Clusters of statistically significant voxels were further selected for BOLD ≥ 2.0% [9]. While the numerical value of 2.0% is in itself arbitrary, only cortical motor areas are consistently activated at such BOLD values. The 2.0% threshold thus served as a filter, selecting regions of interest without enforcing their boundaries *a priori.* Number counts of activated voxels were averaged across subjects. Comparisons between effort levels (B-A, C-A, Fig. 2) were done using t-test (two-tailed; normality of variances: $P = 0.94$, Shapiro-Wilks); $P<0.05$ was considered significant.

Results– Increased force of squeezing resulted in increased activation in the SMC and recruitment of other cortical areas, especially the SMA (representative patient images, Fig. 1; and Fig. 2) and areas in the cerebellum (data not shown). Figure 2 shows that at three different performance levels (45%, 60%, and 75% of maximum effort level) and at three different time points (halfway through training, curve [A], at the end of training [B], and follow-up after training [C]) significant changes in the numbers of activated voxels were observed. During the training period the number of activated voxels increased with force of squeezing; at the end of the first training period the curve of activated voxels versus force started from the final level achieved in the previous assessment and increased further from that point; and, four weeks later the fMRI data indicated persistence of effects: changes that occurred during training were sustained after training (curve C). At the 45% level, A (mean number of activated voxels ± SD, 35 ± 15) differed from B (236 ± 32), $P = 0.0022$, and from C (246 ± 30), $P = 0.0016$. At the 60% level, A (116 ± 31) differed significantly from B (271 ± 33), $P < 0.05$, and from C (271 ± 26), $P < 0.05$. At the 75% level A (180 ± 22) differed significantly from B (295 ± 38), $P < 0.05$, and from C (246 ± 20 voxels) $P < 0.05$. However, at no effort level did the number of activated voxels in C significantly differ from that at B.

Discussion– We find that even in chronic stroke patients, increased squeezing force results in increased contralateral SMC and SMA activation (Fig. 4), previously demonstrated in healthy volunteers [9, 10]. The major finding of our study is that training-induced functional cortical plasticity persists even in chronic stroke patients. This finding supports previous reports [11, 12] that showed sustained improvement in motor abilities four months after discharge. We conclude that rehabilitation of stroke patients can be induced by motor training, resulting in functional cortical plasticity. We suggest that online brain fMRI using novel hand devices provides accurate monitoring and can be used in rehabilitation.

Figure 1. fMRI with MR_CHIROD revealed functional cortical plasticity in chronic stroke patients. A: 63yo, right-handed male with subcortical MCA stroke, 4 years post-stroke, halfway through training. **B:** Patient performance after training. The patient squeezed the MR_CHIROD at 45%, 60%, and 75% of maximum grip force. Activation threshold $P < 0.05$, corrected. SMC activation, larger arrow; SMA activation, smaller arrow.

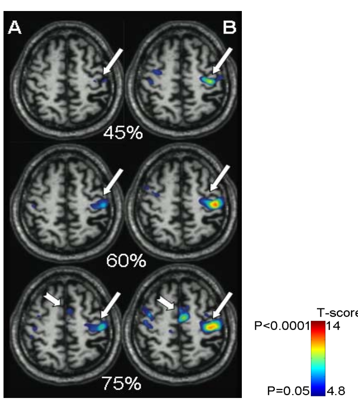
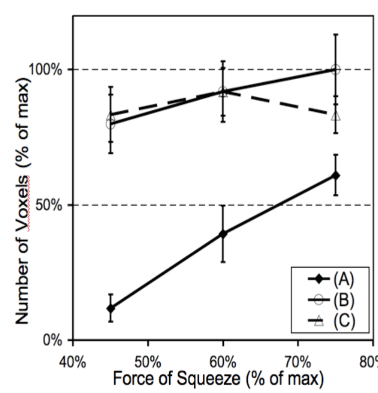


Figure 2. Number of activated voxels in the left (contralateral) SMC as a function of squeezing force in chronic stroke patients. The lower line (A) depicts patient performance halfway through training. The upper, solid line with circles (B) depicts patient performance at the end of training; and the upper broken line with triangles (C) depicts patient performance at the follow-up exam after training. Note the persistence of increased cortical activation observed during and after the training period.



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