Effect of Repetitive Arm Cycling Following Botulinum Toxin Injection for Poststroke Spasticity: Evidence From fMRI

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Abstract

Background and objective. Investigations were performed to establish if repetitive arm cycling training enhances the anti-spastic effect of intramuscular botulinum toxin (BTX) injections in postischemic spastic hemiparesis. Effects on cerebral activation were evaluated by functional magnetic resonance imaging (fMRI).

Methods. Eight chronic spastic hemisindrome patients (49 ± 10 years) after middle cerebral artery infarction (5.5 ± 2.7 years) were investigated. BTX was injected into the affected arm twice, 6 months apart. Spasticity was assessed using the Ashworth Scale and range of motion before and 3 months after BTX injections. Images were analyzed using Brain Voyager QX 1.8, and fMRI signal changes were corrected for multiple comparisons.

Results. During passive movements of affected and nonaffected hands, fMRI activity was increased bilaterally in the sensorimotor cortex (MISI), secondary somatosensory areas (SII), and supplementary motor area predominantly in the contralesional hemisphere, compared with the rest. Following repetitive arm cycling, fMRI activity increased further in MISI of the lesioned hemisphere and SII of the contralesional hemisphere. For patients with residual motor activity, treatment-related fMRI activity increases were associated with reduced spasticity; in completely plegic patients, there was no fMRI activity change in SII but increased spasticity after training.

Conclusion. Increased activity in SII of the contralesional hemisphere and in MISI of the lesioned hemisphere reflect a treatment-induced effect in the paretic arm. It is hypothesized that the increased BOLD activity results from increased afferent information related to the antispastic BTX effect reinforced by training.

Keywords
repetitive arm cycling, botulinum toxin, stroke, spasticity, neuronal plasticity, fMRI

Introduction

Spastic hemisindrome is a major sequel of stroke impairing recovery. Only 5% of adults regain full arm function after stroke, and 20% regain no functional use. Functional magnetic resonance imaging (fMRI) has been used to visualize brain regions activated in relation to stroke recovery. For example, Johansen-Berg and collaborators performed one of the first fMRI studies with 10 stroke patients in a 2-week home-based therapy program based on the principles of the constraint technique. The results showed a correlation between changes in sensorimotor brain activation and therapy-mediated improvement in motor function. Many factors may contribute to fMRI changes during the course of improving upper-extremity gains after stroke, including cortical plasticity, altered performance such as increased movement speed or abnormal deficit compensation strategies, and poststroke spasticity, which to our knowledge has not been addressed by fMRI studies.

Spasticity develops in the weeks after acute brain lesions, mainly in antigravity muscles (leg extensors and arm flexors).
Spasticity affects movement in terms of velocity and the movement path of limbs. It also requires an extra effort to move the afflicted limbs. One medical treatment option is to inject botulinum toxin (BTX) locally into the motor end plate regions of antigravity muscles. BTX has been shown to be a safe, effective treatment of upper-limb spasticity caused by stroke or traumatic brain injury, with improvement of upper-limb function. Several studies also showed that repetitive movement training after BTX injection enhances the effect on spasticity. Reduced spasticity may improve the range of motion (ROM) of affected joints, thereby augmenting the efficacy of rehabilitation. Because spasticity changes movement patterns and frees stiff limbs for voluntary movement, these therapy-related changes should alter motor and somatosensory representations in the brain relevant for recovery. To our knowledge, only 1 author has examined somatosensory cortex activity following selective dorsal rhizotomy for lower-extremity spasticity in cerebral palsy. However, despite widespread use, no study has examined neuroanatomical correlates in the human brain associated with changes in spasticity following BTX in poststroke rehabilitation.

We therefore investigated the following hypotheses: (1) Repetitive cycling training enhances the effect of BTX on spasticity, evaluated by improved ROM and Ashworth score; and (2) The combined treatment of BTX injection and cycling arm training changes the neuroanatomical representations.

**Patients and Methods**

**Patients**

Over a period of 1 year, 9 patients who had a severe spastic hemisindrome, with spasticity greater than or equal to 1+ on the Modified Ashworth Scale, as a result of a first hemiparetic stroke and a single brain lesion (Figure 1) were recruited from 3 neurological centers and the University Hospital of Lausanne (CHUV, Switzerland). They were stable from an ischemic stroke with onset 2 to 12 years earlier.

Entry criteria included being able to tolerate 30 minutes of arm training and having normal vision and language function (Table 1). Informed consent was given by all patients prior to the study in accordance with the Declaration of Helsinki after ethical approval was received from the independent institutional ethical committee.

**Clinical Assessment**

Clinical assessment was performed with the following tests:

- **Modified Ashworth Scale** evaluated spasticity according to the study protocol, in the seated position: ordinal scale of tone intensity 0 to 4 as described by Bohannon and Andrews.

  0: no increase in muscle tone;
  1: slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the ROM when the affected part is moved in flexion or extension;
  1+: slight increase in muscle tone, manifested by a catch followed by minimal resistance through the remainder of the ROM, but the affected part is easily moved;
  2: more marked increase in muscle tone through most of the range of movement but affected part easily moved;
  3: considerable increase in muscle tone, passive movement is difficult; and
  4: affected part is rigid in flexion or extension.

- The Rivermead Motor Stroke Assessment interval scale of motor performance in poststroke patients assessed motor, leg, trunk, and arm movement.
- Range of motion (ROM) was used in which maximum active and passive flexion and extension of the elbow were evaluated with a goniometer.
- The Motricity Index (MI) was used for which the force of elbow flexors and extensors was determined manually and quantified according to the Medical Research Council Scale.

**Experimental Protocol**

The patients were injected with BTX at the beginning of the study and then a second time after 6 months (Table 2). Training started 2 weeks after the injections. To compensate for possible serial effects, the patients were randomly assigned to 2 treatment groups: one group was trained on a commercial motorized arm ergometer (MOTOmed viva, RECK, Betzenweiler, Germany) 3 times per week for 3 months (BTBC group; phase 1), whereas the other group was subjected to a control intervention and only played cards (BCBT group). After a 3-month period free of treatment, the protocol was crossed over, reversing the interventions (phase 2). Each patient underwent 6 clinical assessments. Therefore, patients were engaged for 9 months each. Test sessions were conducted 1 day before the BTX injection (time T1, time T3) and after 3 months of training or the control task (time T2, time T4). In addition, patients were examined clinically 2 weeks after BTX injection (time T1’, time T3’). At times T1, T2, T3, and T4, the patients underwent fMRI. During training, there was no clinical assessment.
Botulinum Toxin Injection

BTX (Allergan, Pfäffikon, Switzerland) was injected into the motor points of the biceps brachii, brachioradialis, flexor digitorum superficialis and profundus, and the flexor carpi ulnaris and radialis muscles (time 1 and time 3). Patients 2, 3, 4, 5, 6, and 8 received injections in the amounts of 50 U into the biceps brachii and 50 U into the brachioradialis muscles. In patients 1 and 7, 100 U was injected into the biceps brachii and 100 U into the brachioradialis muscles. The other 4 muscles received 25 U each, but patients 5 and 7 did not receive injections in these muscles.

Training

During the training phase, patients exercised 3 times a week for 30 minutes on the motorized arm ergometer. They rotated 15 minutes in one direction and 15 minutes in the other and were instructed to maintain a cycling speed of between 25 and 30 cycles per minute. Because the handles were connected,
the healthy arm was able to assist the hemiplegic arm. Resistance was added for patients who were able to rotate at 0.5 Hz only with the paretic hand. The affected arm was attached to the wing of the ergometer. One patient (patient 7) did not need any attachment and, furthermore, was able to rotate with some resistance added to the ergometer.

**Neurophysiological Measurements**

All neurophysiological measurements were made 6 times (T1, T1’, T2, T3, T3’, T4), independently of training (Table 2). Recordings were made with an ergometer constructed by the Fachhochschule für Technik und Architektur in Freiburg, Switzerland. This machine allowed the measurement of (1) the position of the handles with an angle encoder at 12-bit resolution and (2) the force applied to the handles, with strain gauges glued onto the cranks. The data were transferred by gliding contacts to the frame of the ergometer. The cranks could be adapted to the patients’ size. A variable mechanical resistance could also be added.

**Evaluation of Motor Activity**

Data of the passive ROM and MI of biceps flexion and triceps extension of all 6 evaluations were pooled because they both concern elbow movement. Because the distribution of their values was unequal, they were normalized (z score) prior to pooling. The mean of pooled data was therefore 0, and the variance was 1.

**Evaluation of Spasticity**

The ROM values for passive biceps extension and for the passive triceps flexion of the elbow, and the Ashworth Scale reflected the level of spasticity (Modified Ashworth Spasticity score). As with the motricity, the data were first normalized and then pooled.

**Statistical Analysis**

Clinically, the patients presented with either a completely paralyzed arm or with residual force. Because there were
patients with residual movement activity of the affected arm, whereas other patients were completely paralyzed, the patients were subdivided into 2 groups based on their MI (Table 1). Patients with residual motor activity in the spastic arm (MI = 2-5) were assigned to group M (patients 1-4). Patients who were completely paralyzed (MI = 0-1) were assigned to group NM (patients 5-8). Motor activity and spasticity scores were analyzed with ANOVA using as factors (1) the group (with and without motricity), (2) the muscle (biceps or triceps), (3) the time (T1, T2, T3, and T4), and (4) the training group (BTBC and BCBT groups).

**fMRI Scanning and Data Acquisition**

fMRI was performed in all patients on the same 3 T Trio MR scanner (Siemens, Erlangen, Germany) during passive extension–flexion movements of the affected and nonaffected arms at the elbow joint. Imaging parameters were as follows: TR = 4 s; TE = 30 ms; flip angle = 90°; and voxel size = 3 × 3 × 4.4 mm³. A total of 28 consecutive slices oriented parallel to the AC–PC plane were acquired, covering the whole brain. Patients were placed in a supine position onto the bed of the fMRI scanner. Patients were studied during passive movements of their left or right arm in randomized order, alternating the order of left–right flexion–extension of the elbow joint during 5 volume acquisitions (20 s), followed by 20 s of rest. Fixed springs attached to the hands allowed the experimenter to execute passive movements by pulling on strings. The movements executed according to a randomized list of affected and nonaffected sides were executed as short cascades of 1 extension or flexion movement per second each. The arms were returned to their initial positions by the force of the attached springs.

**fMRI Data Analysis**

Image analysis was performed with the fMRI analysis software package Brain Voyager QX 1.8 (Brain Innovation, Maastricht, The Netherlands). The images of each session were realigned to correct for head movements between scans. Preprocessing of the volume time courses involved Gaussian spatial smoothing (FWHM = 4 mm), removal of linear trends, and temporal high-pass filtering with a 3-minute cutoff to remove slow periodic drifts. All images were coregistered to each participant’s T1-weighted high-resolution anatomical scan. The volumes were normalized into Talairach space. In this normalization procedure, the images of the patients with right hemispheric lesions were flipped so that all lesions were in the “left” cerebral hemisphere, which is on the right-hand side in the fMRI images. A Gaussian model of the hemodynamic response function corrected for serial correlations was used to generate idealized response functions. These were used as regressors in a multiple fixed-effects regression model to contrast epochs of passive movements of the affected and nonaffected hand versus the rest condition, at each of the 4 time points. Given the potentially dynamic changes of BOLD activity during the different scanning sessions related to the therapeutic intervention and the limited number of patients, we restricted our analysis to those brain areas that were commonly activated at each time point. Therefore, we calculated the mean activity for all 4 sessions. The t contrast map for the entire group of 8 patients was corrected for multiple comparisons with q (FDR) < 0.05. Clusters surviving an extent threshold of 50 voxel are reported, a procedure that compensates for false positives arising from the correlation of adjacent voxels. The significantly activated areas were assigned to anatomical structures by locating the activation peaks (centers of gravity) in stereotactic space as previously described in detail. For the 5 significant areas, all voxels exceeding the threshold \( P < .05 \) both in passive movements of the affected and nonaffected hands were used to determine the BOLD activity (Table 3).

Thereafter, the BOLD activity was determined from the estimated \( \beta \) values (effect size) in the significantly activated areas. They were obtained for each time point (T1, T2, T3, T4) and compared statistically using an ANOVA and post hoc testing. Furthermore, the magnitude of the BOLD activity was related to the measures of movements of the affected and nonaffected hands.

**Results**

**Clinical Treatment Effects**

BTX and cycling arm training showed a trend \( (P = .062) \) toward less spasticity and ROM when the measurements at the final time point of investigation were compared with those at baseline. However, subgroup analysis revealed significant treatment effects as follows.

According to their motor capacity, the patients were subdivided into a subgroup with residual motor activity in the affected arm (M) and a subgroup of patients with no residual motor activity (NM). This difference in motor activity was significant \( (P < .001) \). Notably, however, evaluation by the Rivermead Motor Test did not pick up the difference in the degree of spastic hemiparesis. Anatomically, the motor output system was severely damaged in each patient. However, in group M (MI = 2-5), most parts of the motor cortex and corticospinal tract were spared (Figure 1). In contrast, in the severely plegic group NM (MI = 0-1), the brain lesions were in general larger and involved large parts of the motor cortex and the underlying white matter, including the location of the corticospinal tract.
Spasticity was reduced after 2 weeks by BTX injection in both patient groups in the injected biceps muscle but remained unchanged in the triceps muscle (Figure 2). The ANOVA results of the spasticity score with the factors motor activity groups (NM and M), session (1 and 2), treatment group (BTBC, BCBT), and muscle (biceps and triceps) showed that the session was the only significant factor ($F = 4.659; P < .033$).

Training decreased spasticity in group M ($P < .05$) but tended to increase spasticity in group NM ($P = .091$). In contrast, in the treatment group, we could not detect any effect on the motor activity of the biceps and triceps muscles, possibly because of the small number of patients.

### Treatment Effects and fMRI

In all 4 fMRI sessions, BOLD activity was increased in the whole group of patients with passive movements of both the affected and the nonaffected arms (Figure 3). When the unaffected arm was moved, BOLD activity increased bilaterally in the sensorimotor cortex (MISI), the secondary somatosensory area (SII), and contralesionally in the supplementary motor area. The activated area in MISI of the contralesional hemisphere extended into the premotor cortex and the superior parietal lobule. Passive movements of the affected hand also activated MISI bilaterally; the activated area was, however, smaller, and the activation was less pronounced (Figure 3, Table 3). No activation was detected in either ipsilateral or contralesional SII. Activation in MISI was dorsal and medial to the normal sensorimotor hand area, corresponding to the normal representation of proximal arm and trunk areas. Regional analysis showed that there were 2 areas with a significant increase in mean activity, related to the combined effect of BTX and training over the observation period.

BOLD activity in SII of the contralesional hemisphere changed similarly with passive movement of the healthy arm in group NM (Figure 4A) and group M patients (Figure 4B). It increased steadily during the study. This result was expected from the training effect because of the direct afferent sensory connections from the healthy arm to the contralesional, nonaffected SII. The ANOVA performed on the BOLD activity in the contralesional SII with the factors motor activity groups (NM and M), session (1 to 4), and arm (affected and healthy)
Diserens et al revealed the significance of the group NM/M factor ($F = 21.831; P < .001$) and of the arm factor ($F = 29.081; P < .0001$). However, BOLD activity with passive movements of the affected arm tended to differ between groups M and NM ($P = .055$). Whereas in group M it increased similarly to the healthy arm, it decreased in group NM.

The second area in which BOLD activity changed significantly over the study was the MISI of the lesioned hemisphere dorsomedial to the sensorimotor hand area. The ANOVA performed on the BOLD activity with the factors motor activity groups (NM and M), treatment group (BTBC, BCBT), session (1 to 4), and arm (affected and healthy) showed that NM/M group ($F = 15.207; P < .0001$) and session ($F = 4.170; P < .013$) were all significant factors. In fact, passive movement of the affected arm led to increased activity in both group M and NM patients (Figure 5A). Similarly, BOLD activity in relation to passive movements of the unaffected arm increased in group M patients. In contrast,
the changes in BOLD activity remained unchanged throughout the study with movement of the healthy arm in group NM (Figure 5B). Also, we did not detect any effect in the treatment group, possibly because of the small number of patients.

These results suggest that the combined effect of BTX and arm training induced changes in the dorsomedial portion of the sensorimotor arm representation.

Discussion

Our findings partially confirm the hypothesis that repetitive cycling training prolongs the effect of BTX injection on spasticity but only for patients with residual motor function (group M). Reduction of spasticity improved the ROM of passive arm movements. As repetitive cycling training also affects the antagonistic muscle (in our case, the triceps muscle), the reinforced antagonistic function could have contributed to prolong the effect of BTX and improve ROM. Second, the increase in BOLD activity in relation to passive arm movements in the dorsomedial portion of the sensorimotor cortex (MISI) in the lesioned hemisphere and in the secondary somatosensory area (SII) of the contralesional hemisphere can be explained by a combined effect of BTX and repetitive arm cycling training. Because there was neither improvement in spasticity nor training-induced increase in BOLD activity with passive arm movements in completely paralyzed patients (group NM), some residual motor activity seems to be mandatory for this effect. Most important, these data suggest that the combined BTX treatment and cycling arm training results in representational changes of sensorimotor cortical areas.

The possible benefit of cycling arm training for patients with residual force was based on the following considerations: (1) Arm cycling increases the antagonistic force of the triceps, increasing this antagonist function to the biceps maintaining an increased ROM after BTX injection and (2) rhythmic training, such as arm cycling or treadmill training, induces phasic flexor and extensor movements involving rhythmic muscle and tendon stretching, gamma activation, and sensory input on the spinal level. The repetitive character could entrain supraspinal spasticity control through long-term potentiation.8 We, therefore, expected increased BOLD activity related to arm movements after training in the sensorimotor cortex and the secondary somatosensory area.22 Unfortunately, involuntary head movements associated with voluntary movements of the affected arm were of such a magnitude that an fMRI study of active arm movements was not possible. Therefore, in this fMRI study, which to the best of our knowledge is the first to evaluate the indirect effect of BTX on spasticity after training, we used passive movements to explore the effect of antispastic treatment in hemiparetic stroke patients. Thus, the direct effect of spasticity was not assessed. Nevertheless, we were able to probe the effect of a combined antispastic treatment, which involved the use of BTX injections and cyclic arm training. In fact, the BOLD activity changes in MISI and in SII in our study suggest that the modified motor pattern, with increased ROM in patients with residual strength after training on an arm ergometer, increased afferent information and thus the size of cortical responses to somatosensory input in the representation area of the trained upper-arm muscles. A recent review23 underlines the importance of the relationship between spasticity and functional deficit. An activation of SII in the lesioned hemisphere, however, was not found in each patient because SII was damaged by the infarct in the majority of severely affected patients. An increase in BOLD activity in the intact hemisphere was also present with movements of the affected arm.
in group M patients. The lack of activation in group NM was presumably a result of the large infarct lesion, which probably interrupted the transcallosal connections between SI and SII in the lesioned hemisphere as well as between SII in either hemisphere. The second area showing significant changes of BOLD activity was MISI in the affected hemisphere. This activity occurred in a dorsal and medial portion of the precentral and postcentral gyrus where the proximal part of the arm is known to be represented. Thus, BOLD activity changes were presumably generated in a partially functional cortical area adjacent to the infarct. When the affected arm was moved passively, BOLD activity increased in both M and NM patients. However, when the ipsilateral healthy arm was moved, a BOLD increase was observed only in group M patients. Presumably, activity in MISI was mediated via connections through the corpus callosum, which are therefore at least in part functional.

The observations in this fMRI study support the notion of a learning effect in cortical sensorimotor representations resulting from arm cycling training in patients treated with BTX in their paretic arm. The lack of changes in BOLD activity in contralesional SII in completely paralyzed patients (group NM) in relation to passive movements of the affected (ipsilateral) arm contrasts with the increase in BOLD activity in contralesional SII in patients with residual motor activity (group M). Conversely, the increase in BOLD activity in MISI in the lesioned hemisphere in group M patients in relation to passive movements of the nonaffected hand can be explained by transcallosal transmission. Accordingly, there may be an increased afferent input from the nonaffected hand from the contralesional MISI area via interhemispheric callosal connections as was hypothesized for somatosensory reorganization. We, therefore, suggest that arm cycling following BTX injection into the biceps and triceps muscles is suited to induce functional changes in sensorimotor cortical areas, which may contribute to posts ischemic cerebral plasticity. However, the BOLD changes were actually recorded in response to passive arm movements. The interesting question is how this experimental finding translates into the clinical motor capabilities of the patients studied.

This study has limitations. First, the sample of patients was small, and there was heterogeneity among the patients regarding the severity of the motor deficit. Such limitations are frequent in any study of BTX-associated therapy of upper-limb spasticity in ambulatory chronic patients. For these reasons, we chose a cross-over design for the training protocol.

In conclusion, bilateral arm cycling training following BTX treatment of the biceps and triceps muscle of the affected arm resulted in a passive movement–related increase of BOLD activity in SII of the contralesional hemisphere and in MISI of the lesioned hemisphere in chronic stroke patients with spastic hemiparesis and residual motor function. The greater BOLD activity at the final scan in group M compared with NM patients suggests increased afferent information processing from direct afferents and interhemispheric callosal connections as a result of training-induced plasticity in group M patients. In contrast, the lack of SII response in NM patients could be explained by an absence of posts ischemic plastic changes in accordance with previous functional imaging studies of learned nonuse. Accordingly, spasticity is an important determining element of movement-related BOLD changes, which appear to differentially affect the bihemispheric sensorimotor relay nodes engaged in poststroke recovery. The functional imaging data of this study are suited to demonstrate the antispastic benefit of repetitive cycling training for patients with residual force in poststroke upper-limb spasticity.

Acknowledgments

This work was aided by Allergan (Switzerland), the Centre d’Imagerie Biomédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL, and the Leenaards Jeantet Foundations, and the MOTOmed viva was generously provided by RECK-Technik GmbH & Co KG. The study was made possible thanks to the work of the interdisciplinary staff of the Foundation Plein Soleil. The authors are grateful to Prof R. Frackowiak for his constructive comments on this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received funding supported by NEURAXO Biotec GmbH, Erkrath, Germany.

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