Functional MRI with motor imagery task show CNS effects and brain plasticity after botulinum toxin therapy in spastic hemiplegic stroke patients

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Aims and objectives

Spasticity, an increase in velocity-dependent resistance to stretching, is a movement disorder that manifests clinically as hyper-reactivity of the muscles [1]. It commonly occurs after ischemic lesion to the central nervous system, and 80% of stroke patients experience motor deficit due to damage to the pyramidal and/or extrapyramidal pathways [2]. These clinical features are defined as upper motor neuron syndrome, which is characterised by both positive (spasticity) and negative (hyposthenia) phenomena [3]. Spasticity in particular is a common phenomenon, and may strike roughly 38% of stroke patients a year after the ischemic event [4].

Stroke patients are spontaneously able to regain partial motor function through "brain recovery" processes linked to cortical plasticity. However, botulinum toxin A (BoNT-A) can be used to reduce involuntary muscle contraction in such patients, the rationale being that it does so by reducing cholinergic transmission at the neuromuscular junction, provoking paralysis. Local administration of BoNT-A has been shown to be more effective than systemic approaches, and is therefore a first-line treatment in muscle hyperactivity after stroke [5-7].

Although the peripheral effects of botulinum toxin are well known, only recently has evidence regarding its potential effects on the central nervous system, in particular the cerebral cortex, begun to emerge [8,9]. These effects may be explained by a reduction in the length/number/density/excitability of type 1a sensory nerve fibres, a phenomenon that has already been described in dystonia [10,11].

Thus the aim of a peripheric botulin toxin therapy is mainly to reduce spasticity, so allowing a more regular and ordinated pattern of movement that will work on cortical function, allowing eventual a better cortical organization of neuronal activation.

This primary afferent fibre reduction and cortical plasticity are both reflected in changes in cortical activation during the actual and imagined execution and of motor tasks. So-called "motor imagery" is the dynamic state during which the representation of a specific motor action is reactivated within the working memory, without any evident motor output, and it is governed by the principles of the central motor nervous system [12,13]. Motor imagery has potential applications in motor skills training in both healthy subjects (e.g., athletes and professional musicians) and patients with neurological damage. Nevertheless, thus far few studies have focussed on motor imagery training as a means of obtaining functional recovery after stroke [14,15].

We set out to evaluate the modulatory effects of botulinum toxin therapy on the central nervous system over time on stroke-derived spastic hemiplegia patients. The primary end-point was to confirm the existence of such an effect, using fMRI to record cerebral plasticity phenomena.
Methods and materials

Patients

Ten healthy volunteers (all with left hemisphere cerebral dominance) were recruited as a control group, and were subjected to the fMRI protocol to study the brain areas activated during real and imagined motor and listening tasks.

Seven patients affected by spastic hemiplegia following ischemic or haemorrhagic stroke were also recruited according to the following inclusion criteria [16]:

- Hemiplegia after acute ischemic or haemorrhagic stroke, as documented by CT scan;
- At least 6 months’ time elapsed after stroke;
- Upper limb spasticity of at least 1+ on the Modified Ashworth Scale (MAS) [17];
- Complete distal spastic plegia of the upper limb (residual force of finger and thumb flexors and extensors M=0 on the Medical Research Council Scale [18]
- Final BoNT-A treatment and no rehabilitation therapy in the three months before enrolment.
- The exclusion criteria were as follows [16]:

<table>
<thead>
<tr>
<th>wN° Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Side of lesion</th>
<th>Site of Lesion</th>
<th>Side of Dominance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>43</td>
<td>Right</td>
<td>Basal Ganglia</td>
<td>Right</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>48</td>
<td>Left</td>
<td>Fronto-parietal</td>
<td>Right</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>50</td>
<td>Right</td>
<td>Basal Ganglia</td>
<td>Right</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>61</td>
<td>Left</td>
<td>Fronto-parietal</td>
<td>Right</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>45</td>
<td>Right</td>
<td>Fronto-Temporo-Parietal</td>
<td>Right</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>47</td>
<td>Left</td>
<td>Basal Ganglia / Insula</td>
<td>Right</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>42</td>
<td>Left</td>
<td>Basal Ganglia</td>
<td>Right</td>
</tr>
<tr>
<td>Overall</td>
<td>3F 4M</td>
<td>48</td>
<td>3 R and 4 L</td>
<td>Heterogeneous</td>
<td>Right</td>
</tr>
</tbody>
</table>
• Fixed contracture and/or bone deformity of upper limb;
• Cognitive impairment limiting comprehension of motor tasks during treatment;
• Concomitant progressive central nervous system disease;
• Peripheral nervous system disease/myopathy;
• Previous surgery to upper limb extensor or flexor muscles, or arthrodesis to the compromised side.

**Study protocol**

All subjects were informed as to the nature of the fMRI test before undergoing a total of three sessions, one at T0 (before commencing BoNT-A therapy), the second at T1 (4 weeks after the treatment), and the last at T2 (8 weeks after treatment).

No rehabilitation therapy, except for passive muscle stretching, was performed between sessions held at T0, T1 and T2. Healthy controls were also tested at the same three time intervals, T0, T1 and T2.

**Treatment**

Patients were given local injections of BoNT-A (incobotulinumtoxinA) at a dilution 100:2 cc 0.9% NaCl solution. The mean dose administered was 235 ± 138 U (Units), range 90-400, and muscles treated were: flexor digitorum superficialis (7 patients), flexor digitorum profundus (5 patients), flexor pollicis longus (7 patients), flexor carpi ulnaris (3 patients), flexor carpi radialis (2 patients), adductor pollicis (1 patient), opponens pollicis (1 patient), flexor pollicis brevis (1 patient), and pronator teres (1 patient). The mean interval between the stroke and the treatment was well over 6 months (47.2 ± 43 months, range 12-129 months).

**Experimental paradigm & fMRI technique**

Before each session, subjects were asked to practice the finger-tapping task with their good hand (real finger tapping, RFT) and subsequently to imagine performing the same task with their plegic hand (imagined finger tapping, IFT), or the contralateral in the case of healthy controls. The motor imagery task consists of performing a mental simulation of the movement associated with a kinaesthetic sensation (imagining oneself performing the task).

The experimental paradigm involved the alternation of two tasks (A and B) in which the first, A, was the target (real or imagined motor task) and the second, B, involved passively listening to musical tones to clear their mind. Three of these task sequences were performed by each subject in each fMRI session, as shown in table below. Audio and visual stimuli for task execution were delivered to subjects by means of NordikAktiva software (NordikNeuroLab, Bergen, Norway), and the hardware setup therefore comprised MRI goggles and headphones synchronized with the scanner, and
an MRI-compatible joystick for giving subjects task execution feedback. MR images were recorded using a Philips Achieva (version 2.5.3) 1.5 Tesla (Philips Healthcare, Best, The Netherlands), using an 8-channel phased-array synergy coil.

<table>
<thead>
<tr>
<th>TASK A</th>
<th>TASK B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Real finger tapping, FTR</td>
<td>Tonal Auditory Stimulus</td>
</tr>
<tr>
<td>2 Imagery finger tapping, FTI-1</td>
<td>Tonal Auditory Stimulus</td>
</tr>
<tr>
<td>3 Imagery finger tapping, FTI-2</td>
<td>Tonal Auditory Stimulus</td>
</tr>
</tbody>
</table>

A sequence of 3D T1-weighted images (TR: 25 ms; TE 4.6 ms; acquisition matrix: 240x240; voxel size: 1x1x1 mm³) was acquired before each session and used as a template for localization of functional activations. Each of three functional runs was acquired using axial echo-planar (EPI) scans (TE=50 ms, TR=3000 ms, matrix 128x128, FOV=230x230 mm, slice thickness=4 mm, 26 slices, 1NEX) comprising 90 volumes divided into 9 blocks corresponding to alternating tasks (A-B-A-B-A-B-A-B-A), each block made up of 10 volumes of duration 30s (total run duration 270s).

The paradigm was the same for healthy controls and patients and therefore comprised

- An activation phase in which the subject was asked to press the button on the joystick repeatedly with their good hand (or to imagine doing it with their plegic/contralateral hand) upon the command "MOVE HAND" projected into the MRI goggles (task A).
- A resting phase ("Rest") in which the subject was fed musical tones comprising a kind of melody through the headphones (task B).

**Statistical analysis**

Functional data was analysed by means of SPM software v.8b. Functional images were corrected for movement, co-recorded with the corresponding morphological images, normalized for Talairach space, and passed through a spatial smoothing filter (FWHM 8mm). The voxels activated during each task (A or B) were detected using level 1 analysis, identifying those activated during the task (FTR or FTI1/FTI2) as ON. Group analysis was then performed (level 2 analysis, p<0.001, without correction) for each task, and the SPM tool xjView was used to determine the maximum intensity and number of voxels in each functional area (cluster), and the Brodmann area involved (quantitative analysis).

The functional map renderings were saved, and examined independently by two neuroradiologist fMRI experts, who provided semi-quantitative scores. The inter-operator agreement was calculated using Cohen's k test.
Results

Controls

Both "first level" and "second level" group analysis showed that cerebral cortex in the primary and supplementary motor areas, the dorsolateral prefrontal area (DLPF), were activated during the motor imagery task. Group analysis of the three tests performed at T0, T1 and T2, showed no alteration over time.

Volunteer

Cluster 1  
Voxel n 5  
peak intensity 5,8315  
Site Fusiform R

Cluster 13  
Voxel n 127  
peak intensity 14,2253  
Site Parietal inf R

Cluster 15  
Voxel n 7  
peak intensity 7,5103  
Site Parietal inf L

Cluster 16  
Voxel n 34  
peak intensity 9,8075  
Site supr  

Patients

All patients managed to complete the three fMRI sessions at T0, T1 and T2, and none reported any difficulty in performing the tasks. Fig. 1 on page 9 show the motor areas activated in one patient who had suffered stroke to the right basal ganglia during
the motor imagery tasks at T2 (8 weeks after botulinum toxin therapy). Fig. 2 on page 9 shows the cerebral activation upon motor imagery stimulation, subjected to level2 analysis, at T0 (A); 4 weeks after the treatment, T1 (B); and 8 weeks after treatment, T2 (C). As we have previously noted that repeating the motor imagery task improves results and provides better statistical significance, we performed statistical analysis on the data from the second of the two tests.

Findings from one of the 7 stroke patients (14.3%) were not significant after SPM post-processing; the patient in question had extensive ischemic damage to the parietal lobe and the test was not found to be diagnostic. Post-processing images were assessed by two radiologists, who scored the activation of the various cortical areas as follows: 0 = no activation, 1 = possible activation, and 2 = certain activation. There was very good agreement between the two sets of qualitative scores (K=0.92).

Some of our patients were left-handed, and so in order to obtain a homogeneous group for level 2 analysis, some images were inverted (flipped) so that all lesions were pictured on the right. Level 2 analysis of the patients revealed the following:

![Graph A: Extension of Cerebral Activation](image)

![Graph B: Intensity of Cerebral Activation](image)

**Fig. 3:** Charter 1 a-b: Activation of relevant brain areas showing number and intensity of voxels

**References:** Radiology, Università del Piemonte Orientale - Novara/IT
Fig. 4: Charter 2 a-b: Level 2 analysis of motor area activation showing voxel numbers and intensity

References: Radiology, Università del Piemonte Orientale - Novara/IT

- At T0, activation was mainly seen in the secondary visual cortex (Brodmann area 18) and secondary motor areas (SMA and Brodmann 6); activation was bilateral but greater voxel numbers and intensity were seen in the hemisphere contralateral to the lesion.

- At T1, the activation of the supplementary motor area was reduced bilaterally, in terms of both voxel number and intensity; this was most evident in the lesioned hemisphere, at the SMA, in which voxel numbers were reduced by roughly 73.2% with respect to T0 was observed, and Brodmann area 6, in which a reduction in voxel number of roughly 79.8% with respect to T0 was observed.

- At T2, the main finding was a further reduction in bilateral secondary motor area activation, once again most evident in the SMA of the lesioned hemisphere, and Brodmann area 6 displayed a reduction in the number of voxels and an increase in the activation intensity of the same.
Images for this section:

**Fig. 1:** Post-processed image (SPM software) of right basal ganglia stroke patient performing motor imagery task at T2. Note the activation of areas M1, SMA, DPLF and cerebellum

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Fig. 2: A-C: Level 2 analysis of Brodmann area 6 in patient group showing mean activations at T0 (A), T1 (B) and T2 (C), respectively before BoNT-A therapy and 4 and 8 weeks after. Note the progressive reduction in size and improved definition of the activation cluster.

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**Fig. 3:** Charter 1 a-b: Activation of relevant brain areas showing number and intensity of voxels

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**Fig. 4:** Charter 2 a-b: Level 2 analysis of motor area activation showing voxel numbers and intensity

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Conclusion

To conclude, through fMRI we were able to confirm our initial hypothesis, namely that as well as exerting peripheral effects and therefore representing a useful physiotherapy tool, peripheral administration of the antispastic BoNT-A also affects the CNS, causing changes in cerebral activation.

In fact it provokes the same effects on cortical and subcortical reorganization described after "recovery" through physiotherapy, i.e., a loss of the initial chaotic pattern of multiple random activations, and the progressive establishment, especially between T1 and T2, of an ordered activation network including cerebellar regions, and greater activation of the SMA, as well as a greater focalization (reduction) in such activation in terms of voxel numbers and intensity.

The possible explanation of this phenomenon can be related to a central effect by reduction in the length/number/density/excitability of type 1a sensory nerve fibres, as previously said [6,7]; this phenomenon affects the pattern of cortical activation after months, acting as a "trainer" in inducing progressively a better cortical reorganization. This is confirmed by our and also previous papers fMRI data.

In our sample this occurred in correspondence to the brain plasticity phenomena induced by the locoregional treatment, which was administered so long after the stroke that the influence of spontaneous recovery phenomena can be ruled out. As these modulation and brain plasticity changes were observed late after stroke, it would be interesting to study them in more depth.

Surely, this pilot study highlights the role of Motor Imagery as a potential interesting tool to study motor function and recovery plegic patients.

It would also be useful to repeat our investigation on a larger patient sample, as the small sample size and inclusion of left- and right-handed patients within it are its major limitations. That being said, other studies in the literature have been based on similar, or even smaller, samples [5,15,36], and, like us, other authors have made use of the image flipping technique to overcome the handedness issue in level 2 analysis [5,36].