Sensorimotor network in cervical dystonia and the effect of botulinum toxin treatment: A functional MRI study

Robert Opavský *, Petr Hluštík, Pavel Otruba, Petr Kaňovský

Department of Neurology, Faculty of Medicine and Dentistry, Palacký University and University Hospital, Olomouc, Czech Republic

ABSTRACT

Background: The evidence suggests that the origin of primary dystonia is at least partly associated with widespread dysfunction of the basal ganglia and cortico–striato–thalamo–cortical circuits. The aim of the study was to assess the sensorimotor activation pattern outside the circuits controlling the affected body part in cervical dystonia, as well as to determine task-related activation changes induced by botulinum toxin type A (BoNT-A) treatment.

Methods: Seven patients suffering from cervical dystonia and nine healthy controls were examined with functional MRI during skilled hand motor task; the examination was repeated 4 weeks after BoNT-A application to dystonic neck muscles.

Results: Functional MRI data demonstrated overall reduced extent of hand movement-related cortical activation but greater magnitude of blood oxygenation level dependent signal change in the contralateral secondary somatosensory cortex in patients compared to controls. Effective BoNT-A treatment led to reduced activation of the ipsilateral supplementary motor area and dorsal premotor cortex in patients. The patients’ post-treatment sensorimotor maps showed significantly smaller basal ganglia activation compared to controls.

Conclusions: These results provide imaging evidence that abnormalities in sensorimotor activation extend beyond circuits controlling the affected body parts in cervical dystonia. The study also supports observations that BoNT-A effect has a correlate at central nervous system level, and such effect may not be limited to cortical and subcortical representations of the treated muscles.

1. Introduction

Cervical dystonia (CD) is the most common form of focal dystonia characterized by involuntary sustained contractions of the neck muscles resulting in abnormal rotation or tilt of the head into specific directions [1]. The pathophysiology of CD and other focal dystonias has not been fully elucidated so far.

Results from neurophysiological and morphological studies suggest a significant contribution of the basal ganglia and thalamus in the development of focal dystonias [2]. Recently, it has become clear that the role of the basal ganglia extends beyond motor control into cognitive and sensory functions as well as in sensorimotor integration [3].

Converging data from both functional imaging and electrophysiological experiments in dystonic patients also suggest functional abnormalities in premotor and primary sensorimotor cortical areas together with aberrant sensorimotor integration, which is considered to be a crucial factor for the development of focal dystonia [3–5]. However, the published studies differ in terms of observed hypo- and hyperactivation in these cortical areas. Differences among task conditions, including testing of dystonia-affected and unaffected body parts can partly explain this variance. It is also a matter of debate whether different types of primary dystonias share identical pathophysiological traits [6].

This evidence together indicates that primary dystonia is associated with sensorimotor dysfunction in the basal ganglia and cortico–striato–thalamo–cortical motor circuits [2,3] and several studies suggested that these abnormalities extend beyond the sensorimotor circuits controlling manifestly affected body parts [7–9].

Botulinum toxin type A (BoNT-A) is currently considered to be one of the most effective therapeutic options in the management of focal dystonias [10]. Clinical effect of BoNT-A on dystonia is assumed to be mediated by dynamic changes at multiple levels of the sensorimotor system, from the neuromuscular junction [11] up to the cerebral cortex, as documented by previous behavioral and electrophysiological studies [7,8]. To compare sensorimotor network beyond representation of affected body part in CD patients and normal controls and the possible cortical changes induced by BoNT-A treatment, we employed functional MRI (fMRI) and a skilled motor task performed with the unaffected hand.

2. Subjects and methods

Seven cervical dystonia patients (1 male and 6 females; aged 53.1 ± 8.2 years, range 36–58 years) were recruited from the Movement Disorders Center at the Department of Neurology, University Hospital,
Olomouc, Czech Republic. All suffered from cervical dystonia manifesting with rotational torticollis (3 left-sided and 4 right-sided) and were good responders to BoNT-A. Demographic and clinical characteristics of patient group are given in Table 1.

Nine healthy controls (2 males and 7 females, aged 55.2 ± 6 years, range 28–63 years) without history of neurological or psychiatric disease were recruited from the community to be sex- and age-matched to the patients. All patients and controls were right handed (Edinburgh Handedness Inventory, patients 93.6 ± 4.1 and controls 91.2 ± 5.7), and conventional brain MRI was normal in all subjects.

All patients and controls were well acquainted with the study contents and examination methods and provided written informed consent prior to enrollment. The study was conducted according to the Declaration of Helsinki 1975 (5th revision 2000, clarifications 2002 and 2004) and approved by the local ethics committee of our hospital.

2.1. Behavioral assessment

The severity of cervical dystonia was determined using the Tsui score [12] at two timepoints: week 0, when patients were screened, enrolled and treated with BoNT-A and at week 5, always on the day of the fMRI session.

2.2. Treatment

All patients were treated with botulinum toxin type A (Botox; Allergan, Inc, Irvine, CA, USA), which was injected at week 0 following the fMRI session into cervical muscles, based on the previous polysomnographic examination. BoNT-A was used at a concentration of 25 U/ml.

The details of the polysomnographic examination and BoNT-A application have been described in our previous work [8].

2.3. Functional MRI tasks

During the fMRI examination, subjects performed a skilled finger movement with their eyes closed: the thumb must in succession briefly touch the index finger twice, the middle finger once, the ring finger three times and the little finger twice, then the movement order is reversed. This task, originally employed by Roland et al., was used for its engagement of proprioception and a proven capacity to activate both primary and higher sensorimotor cortical areas [13]. Prior to the functional brain imaging session, the subjects practiced the task for approximately 10 min.

The tested extremity in all cervical dystonia patients was ipsilateral to the direction of the head deviation, in order to test hemisphere containing the primary sensorimotor cortical representations of the dystonic muscles.

During MR imaging, participants were lying supine and instructed to keep still and not to offer any resistance to dystonic head rotation. Pre-recorded voice instructions to initiate and terminate active finger movement, were presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA, U.S.A.) and provided in MR-compatible headphones. In a block paradigm, active finger movements (7.5 s) alternated with rest (7.5 s) for a total of 4 min. Each participant had 2 such runs with the same hand. Task performance was visually monitored.

In all cervical dystonia patients, the first fMRI session (at week 0) was scheduled at least 4 months after previous BoNT-A treatment. At this time, the absence of BoNT-A effect is expected [14]. The same day, after the fMRI session, BoNT-A was locally administered. The second fMRI examination followed after 4 weeks, when the maximal clinical effect is expected [14].

In a group of controls, a single fMRI examination was carried out, always testing the dominant right hand.

2.4. Data acquisition

MRI data were acquired on 1.5-Tesla scanners (Avanto and Symphony; Siemens, Erlangen, Germany) with a standard head coil. The MR imaging protocol covered the whole brain with 30 axial slices, 5-mm thick, including anatomical T1-weighted images to provide an immediate overlay with functional data, fluid attenuated inversion recovery (FLAIR) images to visualize brain lesions, functional T2-weighted blood oxygen level-dependent (BOLD) images during task performance and rest, and a high-resolution 3-dimensional anatomical scan (magnitization-prepared rapid acquisition gradient echo [MPRAGE]). BOLD images were acquired with repetition time/echo time = 2500/40 ms, field of view = 220 mm to provide 3.4-mm × 3.4-mm × 5.0-mm resolution. In total, 96 images were acquired per each 4-minute functional run, giving 192 images per session. Subject’s head was immobilized with cushions.

2.5. Analysis

Prior to fMRI analysis, the imaging data of 3 patients with tested left hand were flipped in the left–right direction to allow group analysis [15]. fMRI data pre-processing and analysis were carried out using FSL, the FMRIB’s software library ([16]; http://www.fmrib.ox.ac.uk/fsl). fMRI data analysis was performed with FEAT (FMRI Expert Analysis Tool), version 5.91. The following pre-statistics processing was applied: motion correction using FMRIB’s MCFLIRT; slice-timing correction using Fourier space time-series phase-shifting; nonbrain removal using FMRIB’s BET; spatial smoothing using a Gaussian kernel of 8-mm full width at half-maximum; grand-mean intensity normalization by a single multiplicative factor; and high-pass temporal filtering (Gaussian weighted least-squares straight-line fitting, with sigma = 15.0 s). Time-series statistical analysis was carried out using FMRIB’s FILM with local autocorrelation correction. Registration to high-resolution structural and/or standard space images was carried out using FMRIB’s FLIRT.

Higher-level analysis was carried out using FMRIB’s local analysis of mixed effects (FLAME) stage 1 + 2.Z (Gaussianized T/F) statistic images were thresholded using clusters determined by Z > 2.8 and a (corrected) cluster significance threshold of P = 0.05. For between-group contrasts (CD patients vs. controls), a two-sample t-test was used. For within-group contrasts (pre-BoNT-A vs. post-BoNT-A effect in patients), a paired t-test was employed.

<table>
<thead>
<tr>
<th>Patient nr.</th>
<th>Sex (M/F)</th>
<th>Age at exam (years)</th>
<th>Age at dystonia onset (years)</th>
<th>Type of dystonia</th>
<th>Injected muscles</th>
<th>Tsui score (1st examination)</th>
<th>Tsui score (2nd examination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>58</td>
<td>53</td>
<td>Torticollis left</td>
<td>SPL left, TRP right</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>58</td>
<td>42</td>
<td>Torticollis right</td>
<td>SCM left, TRP left, SPL right</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>36</td>
<td>28</td>
<td>Torticollis right</td>
<td>SPL right, SCM left</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>60</td>
<td>44</td>
<td>Torticollis left</td>
<td>SPL left, TRP right</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>56</td>
<td>45</td>
<td>Torticollis right</td>
<td>SPL right, SCM left</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>58</td>
<td>34</td>
<td>Torticollis right</td>
<td>SCM left, SPL right</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>46</td>
<td>42</td>
<td>Torticollis left</td>
<td>SPL left, SCM right</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

SPL = splenius capitis muscle; TRP = trapezoid muscle; SCM = sternocleidomastoid muscle.
Registration of each subject’s BOLD MRI data to standard space images (MNI152) was carried out using FLIRT and the results visually checked for alignment accuracy. Spatial coordinates are reported in the Montreal Neurological Institute (MNI) format.

3. Results

3.1. Behavioral and clinical

The performance of task was correct in all subjects. Duration of one cycle of skilled finger movement assessed during fMRI sessions did not significantly differ among subject groups (mean values: controls 7.1 s, pre-BoNT-A patients 7.3 s, and post-BoNT-A patients 7.1 s, P > 0.05, ANOVA).

All patients were injected into the muscles identified by polymyography; the mean total dose of BoNT-A was 107.0 (SD=18.9)U, the mean dose for one cervical muscle was 50.0 U.

Significant clinical effect of BoNT-A evidenced by the decrease of Tsui score (mean Tsui score change 2.8, paired t-test, p < 0.05) was observed. The mean Tsui score before BoNT-A treatment was 10.9 (SD=1.25), and the mean Tsui score after treatment was 8.0 (SD=1.20).

3.2. Imaging

3.2.1. Group mean activation

3.2.1.1. Control group. In the controls, skilled finger movement activated an extensive network of brain areas including the following: contralateral primary motor and somatosensory cortex, bilateral premotor cortex, bilateral supplementary motor area (SMA) (predominantly contralaterally), bilateral secondary somatosensory cortex (SII), bilateral insular cortex, bilateral superior parietal cortex, right inferior parietal cortex, bilateral cerebellum, bilateral thalamus, bilateral pallidum and left caudate (Fig. 1A).

3.2.1.2. Patients pre-BoNT-A treatment. In patients before BoNT-A treatment, skilled finger movement activated a similar, but less extensive network involving similar areas of the sensorimotor network (as in control group), except for bilateral thalamus, bilateral pallidum and left caudate. The bilateral SMA activation was lateralized more ipsilaterally, (Fig. 1B).

3.2.1.3. Patients post-BoNT-A treatment. The activation map of patients after BoNT-A therapy was even more reduced than before BoNT-A therapy. It comprised the same areas except for right SII and left superior parietal cortex. The bilateral activation of SMA was lateralized more contralaterally (Fig. 1C).

3.2.2. Between-group comparisons

3.2.2.1. Patients pre-BoNT-A vs. controls. Before BoNT-A, patients showed overactivity in the contralateral parietal operculum (MNI coordinates −42, −18, 22) compared to controls. No significant difference was detected in controls−pre-BoNT-A contrast (Fig. 2A and Table 2).

3.2.2.2. Patients post-BoNT-A vs. controls. Post-treatment activation map showed significant reduction in globus pallidum internum (GPi) bilaterally, more expressed ipsilaterally (MNI coordinates 16, 0, 4; −18, −2, 0) (Fig. 2C and Table 2). There was no significant difference in the post-BoNT-A−controls contrast.

3.2.3. Within-group comparison

3.2.3.1. Patients pre-BoNT-A vs. post-BoNT-A treatment. Significant decrease of activation after BoNT-A treatment was detected within the hand representation area in the right SMA and dorsal premotor cortex (PMd) (MNI coordinates 26, −10, 70; 0, 0, 64) (Fig. 2B and Table 2). No significant difference was found in post-BoNT-A−pre-BoNT-A contrast.

No major movement artifacts were observed during fMRI examinations.

4. Discussion

The presented study brought three main findings: first, we report reduced overall extent of hand movement-related cortical activation but greater focal magnitude BOLD signal change in the left (contralateral) SII in CD patients compared to controls. Secondly, we have observed reduction of SMA and PMd activations in CD patients following BoNT treatment of dystonic muscles. Thirdly, the post-treatment motor maps of CD patients show significantly weaker basal ganglia activation compared to controls.

We are aware of the methodological limitation presented by the inability to directly investigate cortical and subcortical representation of the neck muscles involved in cervical dystonia using fMRI, as this would cause severe head movement artifacts. Nevertheless, at least two lines of
arguments support the use of the hand as a probe into sensorimotor function in cervical dystonia. First, cortical representations of neck and hand muscles are in close proximity to each other in normal subjects [17,18] and may be enlarged and overlap in patients with CD [7]. Second, this model has been repeatedly used in electrophysiological studies which documented cortical and subcortical abnormalities, as well as the effect of BoNT in CD [8,19,20].

Previous electrophysiological and imaging evidence suggests disorders of both motor and sensory cortical processing in cervical dystonia, perhaps at the level of sensorimotor integration [21]. Abnormal cortical excitability [22] and activation [23] have been observed when contrasting CD patients and normal controls. Several behavioral studies also documented diffuse cortical abnormality extending beyond the clinically affected body part in CD [7,9]. This observation further supports the use of hand movement as the active task in our study.

Sensorimotor network activation in our age-matched healthy controls is in agreement with recent fMR imaging studies of sequential finger movement [24].

In contrast to healthy controls, the extent of cortical activation in CD patients showed diffuse reduction. This finding agrees with results of another functional imaging study on cervical dystonia patients and could be explained by higher inter-individual variability in the spatial pattern of recruited compensatory circuits resulting in a low group mean activation [23]. Alternatively, the reduced activation extent may relate to the reported generalized kinematic deficits [9].

The pre-BoNT→ controls contrast revealed significant cortical hyperactivity in the parietal opercular cortex in CD patients, contralaterally to the tested hand. Abnormal activation in this area was reported in previous dystonia imaging studies testing sensorimotor tasks with both the affected and unaffected body parts [23].

The parietal operculum contains the human SII, which is presumed to play a role in higher-order functions in somatosensory processing, but is also believed to perform integration of information from the two sides of the body, and participate in visuospatial attention, learning and memory. Furthermore, SII appears significantly involved in motor processing and integration as it is active not only during passive and active finger movements but also during movement imagery [25].

Taken together, these data suggest that the documented excessive activity in non-primary somatosensory cortex may represent aberrant sensorimotor processing, which is considered to be a key factor for the development of focal dystonias [26]. This idea is supported by the latest work of Obermann et al., who demonstrated disinhibition in SII, primary somatosensory and other cortical areas following pure kinesthetic somatosensory stimulation [27]. We can speculate that the overactivation of SII could also be an imaging correlate of deficient cortical inhibition detected recently in neurophysiological studies [28]. The abnormal cortical activation detected during skilled motor task performed with non-dystonic body part confirms previous electrophysiological observations that sensorimotor abnormalities in the dystonic brain extend beyond directly clinically affected sensorimotor representations [8,9].

4.1. BoNT-A treatment effect

The mean group activation map following BoNT-A therapy comprised the same key elements of movement-related circuits as in controls and patients before treatment, but the activation was even more spatially reduced. We may speculate that such hypoactivation is caused by more pronounced individual variability of circuits involved in amelioration of dystonia following therapy.

In our patient group, a significant reduction of task-related activation within the ipsilateral SMA and dorsal premotor cortex was observed following successful BoNT-A treatment. There was also a trend in SMA activation in patients to change lateralization from predominantly ipsilateral to contralateral after BoNT-A, whereas the activation of controls was predominantly contralateral.

Since the definition of SMA as a separate motor area, its function remains incompletely characterized. In general, activation in the SMA is considered to be tightly associated with movement generation and control: posture regulation, internal generation of movement, bimanual coordination and movement sequencing [29]. In dystonia, primate models demonstrated SMA hyperexcitability, as well as abnormal increase of

---

**Table 2**

Local maxima of differential activation: between- and within-group contrasts.

<table>
<thead>
<tr>
<th>MNI</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Contrast:</strong></td>
<td></td>
</tr>
<tr>
<td>pre-BoNT→ controls</td>
<td></td>
</tr>
<tr>
<td>Left secondary somatosensory cortex</td>
<td>−42</td>
</tr>
<tr>
<td>Right dorsal premotor cortex</td>
<td>26</td>
</tr>
<tr>
<td>Right supplementary motor cortex</td>
<td>0</td>
</tr>
<tr>
<td>Contrast: controls→ patients post-BoNT→</td>
<td></td>
</tr>
<tr>
<td>Right pallidum</td>
<td>16</td>
</tr>
<tr>
<td>Left pallidum</td>
<td>−18</td>
</tr>
</tbody>
</table>

MNI = Montreal Neurological Institute.
proprceptive inputs to SMA together with wider sensory receptive fields and a mismatch between sensory inputs and motor outputs [30]. These observations may suggest that abnormal sensory inputs coming to SMA neurons participate in the development of dystonia.

Like SMA, the dorsal premotor cortex (PMd) is a part of motor cortex generally considered to be relevant to the planning, selection and execution of motor actions [31] as well as to sensorimotor integration in normals [6]. In generalized and focal dystonia patients, PET studies have reported hyperactive PMd and hypoactive M1 during movement compared to normals [32]. Based on these observations, a few studies successfully employed inhibitory effect of repetitive transcranial magnetic stimulation (rTMS) over PMd to alleviate symptoms of focal dystonia [31]. The decreased activation of PMd ipsilateral to the tested hand observed in our study following successful therapy could be considered an effect analogous to the transient inhibition induced by rTMS, but here induced by BoNT-A.

Our third major result involves lower basal ganglia activation in BoNT-A-treated patients compared to normals. In cervical dystonia, the study of Obermann et al. [34] demonstrated increased bilateral activation of the basal ganglia and thalamus during non-dystonia associated task. This abnormal activation in the basal ganglia could represent a compensatory mechanism of the ineffective compression of multiple motor and sensory inputs before their transition for further cortical processing. Internal pallidum serves as a target for effective modulation of cervical dystonia and other forms of primary dystonias using deep brain stimulation, with not exactly characterized mode of action. The post-treatment hypoa- ctivation of GPI more expressed in physiologically relevant ipsilateral side, which was demonstrated in the study thus may correspond to functional “normalization” presumably mediated by recruitment of neuronal circuits comprising the BC.

Reduced SMA, PMd and GPI activations detected in our small study following successful treatment of CD may suggest amelioration of abnormal processes in these structures with subsequent correction of defective sensorimotor integration. The fact that these changes were detected during a skilled motor task performed with a clinically normal limb may further endorse observations of remote effects of BoNT-A [7,8]. The study reinforces the role of abnormal somatosensory processing in the development of cervical dystonia, as well as the fact that these abnormalities extend beyond the circuits directly controlling affected body part.

From the data above we may suggest that the clinical benefit of BoNT-A in focal dystonia patients is mediated not only by its peripheral effects but also by the central ones.

Acknowledgement

This study was supported by the grant No. NS9920-4/1998 from the Internal Grant Agency, Ministry of Health, Czech Republic.

References
