Cortical somatosensory processing after botulinum toxin therapy in post-stroke spasticity

Tomáš Veverka, MD, PhD, Petr Hlušťík, MD, PhD, Pavel Otruba, MD, Pavel Hok, MD, PhD, Robert Opavský, MD, PhD, Jana Zapletalová, MSc, PhD, Petr Kaňovský, MD, PhD

Abstract
In dystonic and spastic movement disorders, abnormalities of motor control and somatosensory processing as well as cortical modulations associated with clinical improvement after botulinum toxin A (BoNT-A) treatment have been reported, but electrophysiological evidence remains controversial. In the present observational study, we aimed to uncover central correlates of post-stroke spasticity (PSS) and BoNT-A-related changes in the sensorimotor cortex by investigating the cortical components of somatosensory evoked potentials (SEPs). Thirty-one chronic stroke patients with PSS of the upper limb were treated with BoNT-A application into the affected muscles and physiotherapy. Clinical and electrophysiological evaluations were performed just before BoNT-A application (W0), then 4 weeks (W4) and 11 weeks (W11) later. PSS was evaluated with the modified Ashworth scale (MAS). Median nerve SEPs were examined in both upper limbs with subsequent statistical analysis of the peak-to-peak amplitudes of precentral P22/N30 and postcentral N20/P23 components. At baseline (W0), postcentral SEPs were significantly lower over the affected cortex. At follow up, cortical SEPs did not show any significant changes attributable to BoNT-A and/or physiotherapy, despite clear clinical improvement. Our results imply that conventional SEPs are of limited value in evaluating cortical changes after BoNT-A treatment and further studies are needed to elucidate its central actions.

Abbreviations: ADL = activities of daily living, BoNT-A = botulinum toxin A, CNS = central nervous system, fMRI = functional magnetic resonance imaging, IQR = interquartile range, MAS = modified Ashworth scale, PPC = posterior parietal cortex, PSS = post-stroke spasticity, SD = standard deviation, SEPs = somatosensory evoked potentials.

Keywords: botulinum toxin, somatosensory cortex, somatosensory evoked potentials, spasticity, stroke

1. Introduction
Post-stroke spasticity (PSS) is one of the main motor consequences of stroke.[11] Severe PSS lowers the patient’s quality of life and frequently causes significant limitations of gross and fine motor control, gait/falling, and activities of daily living (ADL).[12] Recommended treatment regimens to alleviate PSS combine physiotherapy procedures and botulinum toxin A (BoNT-A) applications.[3–5] BoNT-A has been proven to be safe and effective in relieving upper limb PSS and improving motor functions.[6,7] BoNT-A produces its therapeutic effects primarily by inhibiting acetylcholine release from the pre-synaptic terminals of the alpha motoneurons on muscle spindles.[8–10] Besides this peripheral site of action, central effects have been reported as well.[11,12] Effects of BoNT-A injected in the periphery likely spread through supraspinal mechanisms and may even cause reorganization of the cerebral cortex.[13] Various neurophysiological techniques have been applied to investigate BoNT-A-related modulation of the sensorimotor cortex.[14] Somatosensory evoked potentials (SEPs) have been established as an appropriate method for assessing the integrity of sensory-motor pathways and studying the effect of the afferent peripheral inputs on the sensorimotor cortex.[15] Several studies have shown that cortical components of SEPs are altered in stroke patients and they may even have a prognostic value in predicting recovery of the upper limb function.[16,17] More interestingly, there is evidence that BoNT-A application not only leads to improvement of spasticity but is also associated with the normalization of impaired cortical SEPs.[18–20] However, despite these results, it is still under debate whether cortical SEPs are sensitive enough to detect the central (remote) effects of BoNT-A treatment.[14]

The purpose of the present study was to uncover central correlates of PSS and BoNT-A-related changes in the sensorimotor cortex, investigating the cortical components of SEPs. We hypothesized that pathological SEPs would be recorded over the lesioned hemisphere and that they would partially normalize after BoNT-A application and physiotherapy. A longitudinal study protocol with three time-points was designed to separate the effects of BoNT-A application from the effects of physiotherapy.
2. Methods

2.1. Patients

The protocol of the observational study was approved by the Ethics committee of University Hospital Olomouc and was conducted in accordance with the tenets of the Declaration of Helsinki. All subjects provided their written consent before participating in this study. Thirty-one right-handed chronic stroke patients (20 males and 11 females) with clinically relevant PSS of the upper limb and at least three months since stroke were recruited from the Comprehensive Stroke Center at the Department of Neurology, University Hospital, Olomouc, Czechia. The mean age at study entry was 59 ± 14.9 (SD) years. The patients’ demographic characteristics are listed in Table 1. Enrolled subjects were required to be in the chronic stage of first-ever ischemic stroke; the time from stroke onset to the study entry ranged from 3 to 139 months, the median was 10 months. The ischemic lesions, confirmed by magnetic resonance imaging or computed tomography, were subcortical or cortico-subcortical within the middle cerebral artery territory. Hand spasticity was clinically relevant and exceeded 1 on the modified Ashworth scale (MAS).[21] Exclusion criteria were: history of BoNT-A application or drugs affecting muscle hypertonus intake; contraindications for BoNT-A application; and SEPs exclusion criteria (i.e., implanted electronic devices). All subjects underwent clinical and electrophysiological evaluation just before BoNT-A application (week 0, W0), 4 weeks later (W4), and 11 weeks later (W11). A longitudinal within-subject study design was used, in which each patient served as their own internal control.

2.2. Clinical evaluation

PSS was evaluated using the MAS at each visit. The MAS was scored separately for fingers and wrists and the values were averaged together (global MAS score). For statistical analysis, a grade of 1+ on the MAS was recorded as 1.5. Further clinical investigations included the following standardized scales performed at W0: the modified Medical Research Council scale[22] to test upper extremity strength and the Barthel Index[23] and the modified Rankin Scale[24] to assess disability. The clinical characteristics of the subjects are listed in Table 1.

2.3. Treatment

All subjects were treated with BoNT-A injections into the spastic muscles of the affected arm at W0 followed by a dedicated physiotherapy protocol.[25,26] The injections were performed using EMG guidance (Medtronic Keypoint, Alpine Biomed ApS, Denmark), preferably using electrical stimulation to localize the target. The following muscles were always injected: flexor carpi ulnaris, flexor carpi radialis, flexor digitorum superficialis, and flexor digitorum profundus. Each muscle was consistently

---

**Table 1**

Demographic and clinical characteristics.

| Patient | Age | Sex | Stroke to W0 (months) | Affected hand | mRS | BI | mMRC (WF/WE, FF/FE) | Global MAS W0 | Global MAS W4 | Global MAS W11 |
|---------|-----|-----|-----------------------|---------------|-----|----|---------------------|----------------|----------------|----------------|
| 1       | 64  | F   | 6                     | R             | 3   | 70 | 0/0/0               | 2              | 1.25           | 1.75           |
| 2       | 68  | M   | 7                     | L             | 2   | 90 | 4/4/4               | 2              | 1.25           | 2              |
| 3       | 51  | F   | 23                    | R             | 3   | 65 | 0/0/0               | 3              | 2              | 2              |
| 4       | 75  | F   | 10                    | R             | 3   | 85 | 1/1/2               | 2              | 1              | 2              |
| 5       | 22  | M   | 3                     | R             | 3   | 85 | 0/0/0               | 3              | 1              | 2.5            |
| 6       | 25  | F   | 11                    | L             | 3   | 80 | 1/0/0               | 2.5            | 1.5            | 2.5            |
| 7       | 60  | M   | 9                     | L             | 2   | 90 | 4/4/4               | 3              | 2              | 2.5            |
| 8       | 77  | M   | 18                    | R             | 2   | 70 | 4/3/3               | 3              | 1.75           | 3              |
| 9       | 74  | F   | 3                     | L             | 4   | 40 | 0/0/0               | 3              | 2              | 3              |
| 10      | 54  | M   | 15                    | R             | 2   | 85 | 4/3/3               | 1.5            | 2              | 2              |
| 11      | 62  | M   | 139                   | L             | 3   | 90 | 0/0/0               | 2.5            | 1.5            | 2.25           |
| 12      | 69  | F   | 9                     | R             | 3   | 85 | 0/0/0               | 2.5            | 1.5            | 2              |
| 13      | 69  | M   | 9                     | R             | 3   | 90 | 0/0/0               | 2.5            | 2              | 2.5            |
| 14      | 66  | M   | 4                     | L             | 3   | 80 | 2/3/2               | 3              | 1.75           | 2.5            |
| 15      | 71  | M   | 76                    | R             | 3   | 95 | 2/3/2               | 2.5            | 1.75           | 2.5            |
| 16      | 66  | M   | 14                    | R             | 3   | 85 | 2/1/2               | 2              | 2              | 2              |
| 17      | 51  | F   | 19                    | L             | 4   | 75 | 0/0/0               | 3              | 1.25           | 2              |
| 18      | 72  | M   | 23                    | R             | 3   | 100| 3/3/3               | 1.5            | 1              | 1              |
| 19      | 33  | M   | 32                    | L             | 3   | 70 | 2/1/3               | 2              | 1              | 2              |
| 20      | 44  | M   | 3                     | L             | 2   | 100| 4/3/3               | 1.5            | 0.5            | 0.5            |
| 21      | 31  | M   | 7                     | L             | 3   | 90 | 1+/0+/1+/1+        | 3              | 1.5            | 2.5            |
| 22      | 67  | F   | 5                     | R             | 4   | 60 | 0/0/0               | 3              | 2              | 3              |
| 23      | 63  | M   | 38                    | L             | 4   | 65 | 1/0/1               | 3              | 3              | 3              |
| 24      | 49  | M   | 43                    | L             | 2   | 100| 4/3/3               | 2              | 0.5            | 0.5            |
| 25      | 60  | M   | 21                    | R             | 3   | 75 | 0/0/0               | 3              | 2              | 2.5            |
| 26      | 72  | M   | 15                    | R             | 4   | 60 | 4/3/3               | 2              | 0.5            | 2              |
| 27      | 71  | F   | 18                    | L             | 2   | 90 | 4/3/3               | 2              | 0.5            | 2              |
| 28      | 55  | F   | 10                    | R             | 3   | 85 | 2/0/0               | 2.5            | 2              | 1.75           |
| 29      | 55  | M   | 9                     | L             | 3   | 90 | 3/2/3               | 2              | 1.25           | 2              |
| 30      | 69  | M   | 4                     | R             | 2   | 80 | 3/2/3               | 2              | 1.5            | 2              |
| 31      | 70  | F   | 8                     | R             | 3   | 95 | 0/0/0               | 2              | 1.75           | 2.5            |

Bi=Barthel Index, FE=finger extensors, FF=finger flexors, L=left, MAS=modified Ashworth scale, mMRC=modified Medical Research Council scale, mRS=modified Rankin Scale, R=right, WE=wrist extensors, WF=wrist flexors.
injected with BoNT-A in a fixed dose of 50 UA (BOTOX; Allergan, Inc., Irvine, CA, USA) in accordance with current recommendations.5,27 Physiotherapy started several days after the BoNT-A injection (W0). Initial inpatient physiotherapy lasting for 2–4 weeks was followed by outpatient physiotherapy until the third clinical evaluation (total of 11 weeks). Patients underwent daily physiotherapy sessions for 1 h on weekdays, that is, five times per week. Individual kinesiotherapy included posture-locomotion training towards restitution of bipedal posture and gait, motor recovery of the hips and trunk using elements of the Bobath concept, proprioceptive neuromuscular facilitation, respiratory physiotherapy, reflex and myofascial techniques, anti-spastic positioning, occupational therapy, and training of independence in ADL. Proper adherence to the physiotherapy protocol was checked at each examination throughout the study period.

2.4. Somatosensory evoked potentials (SEPs)

Median nerve SEPs were examined in both upper extremities using the Keypoint device (Medtronic, Dublin, Ireland). We used a previously published protocol for recording and stimulation.15,28 Both median nerves were consecutively stimulated at the wrist. Square-wave pulses lasting 0.1 ms were used at an intensity that was 1.5 times higher than the motor threshold that evoked thumb twitching. A 5-Hz stimulation frequency was used in all examinations. The cortical components of SEPs were recorded over the contralateral somatosensory cortex by using surface silver-silver chloride electrodes in C3+, C4+, C3, and C4’ electrode positions according to the International 10–20 system. C3+ and C4+ were placed 2 cm posterior to C3 and C4; C3’ and C4’ were placed 2 cm anterior to C3 and C4. Mutually connected earlobes were used as a reference. Skin resistance was maintained at 4 kΩ and was checked repeatedly during each recording session. The responses were filtered using a bandpass filter of 10–2000 Hz, and the time base was 50 ms. Analysis time was 5 ms/division. Two runs of 500 artefact-free sweeps were averaged in each recording session. The peaks were labelled according to the nomenclature published by Donchin et al.29 Peak-to-peak amplitudes of postcentral N20/P23 (at C3+ and C4+ electrodes) and precentral P22/N30 (at C3’ and C4’ electrodes) components were then measured in the superimposed runs and subsequently statistically analysed. To prevent the baseline shift bias, the absolute values of the N20, P23, P22, and N30 were not used. Side-to-side ratios of N20/P23 and P22/N30 amplitudes (affected/unaffected side) were then calculated. Additionally, absolute latencies for N20 (measured from the beginning of the stimulus to the maximal level of negative deflection) were recorded.

2.5. Statistics

All statistical analyses were carried out using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The Wilcoxon signed-rank test with Bonferroni correction was used to compare global MAS scores from W0, W4, and W11. Differences in SEPs of affected and unaffected side at W0 were analysed using the Wilcoxon signed-rank test. Changes in SEPs at W4 (BoNT-A-effect) and W11 (effect of physiotherapy), as compared to W0, were tested using the Friedman test. Normal distribution was verified by the Shapiro–Wilk test. A P-value less than .05 was considered statistically significant (P < .05).

3. Results

3.1. Clinical

Treatment with BoNT-A and subsequent physiotherapy significantly reduced PSS of the upper limb. Global MAS showed statistically significant decreases at W4 (P < .0001) with subsequent increases at W11 (P = .013), although the reduction against W0 remained significant (P < .0001). The median global MAS scores were 2.50 at W0 (interquartile range (IQR) = 2.0–3.0), 1.50 at W4 (IQR = 1.13–2.00), and 2.00 at W11 (IQR = 2.0–2.5). Individual MAS scores for each subject are listed in Table 1 and statistical data are illustratively presented in a box plot in Figure 1.

3.2. SSEP

At the baseline (W0), the peak-to-peak amplitude of postcentral N20/P23 during stimulation of the impaired limb was significantly lower in comparison to the unaffected side (P = .003). The peak-to-peak amplitude of precentral P22/N30 and the absolute latency for N20 did not significantly differ between the affected and unaffected sides (Table 2).

After the treatment, none of the assessed cortical SEP values (postcentral N20/P23, precentral P22/N30, side-to-side ratios of N20/P23 and P22/N30, and absolute latencies for N20) yielded statistically significant treatment-related changes despite clear clinical improvement (Table 3).

4. Discussion

In the present study we aimed to uncover central correlates of PSS and BoNT-A-related changes in the sensorimotor cortex by investigating the cortical components of SEPs. Our results revealed the expected decrease of SEP amplitude over the postcentral sites in the lesioned hemisphere; however, we did not find the hypothesized change of SEP parameters associated with BoNT-A therapy.

As expected, BoNT-A and physiotherapy effectively improved PSS. There was a significant decrease in the global MAS score at W4 and W11, with the maximal effect at W4, when the pharmaco logical peripheral effect of BoNT-A is assumed to be highest. This finding is in line with other studies evaluating BoNT-A efficacy in PSS.30 At W11, the global MAS score significantly increased but remained lower than at the baseline. Similarly, as in our recent functional magnetic resonance imaging (fMRI) study in an almost identical cohort of patients, some improvement of PSS persisted at the follow-up visits, even though the local BoNT-A effect should have waned.31 This observation could be explained by ongoing physiotherapy, but the theory of persistent central reorganization after BoNT-A should also be considered.12 A prolonged clinical effect of BoNT-A application, exceeding the average duration of the neuromuscular blockade, has been observed in clinical routine in a number of patients with spastic or dystonic disorders.32,33 Most of the neuropsychological evidence for distant effects of BoNT-A comes from studies with dystonic patients. Unlike PSS, with its well-defined lesion of descending tracts, dystonic disorders have different pathophysiology with no morphological impairment of the central nervous system (CNS). The putative mechanism by which BoNT-A injected in the periphery may induce dynamic changes at several hierarchical levels of the sensorimotor system, presumably including the cerebral cortex.
first postulated in cervical dystonia.\[15\] Despite substantial differences, the same plasticity mechanism is also presumed in spasticity. Besides its effect on extrafusal muscle spindles, BoNT-A alters pathological proprioceptive flow from intrafusal fibres through the Ia afferents to the CNS and indirectly modulates the sensorimotor cortex.\[10,34\] Kaňovský et al reported a higher amplitude of precentral P22/N30 and the normalization of this SEP component after BoNT-A treatment in cervical dystonia.\[15\] The authors concluded that the increased P22/N30 amplitude likely reflects abnormally enhanced cortical excitability and that BoNT-related change in amplitude might be a consequence of the normalization of this excitability. It should be noted that no significant abnormality in the postcentral component (N20/P23) was found in that study. Further studies reported impairment of both cortical excitability and intracortical inhibition in focal dystonia, as well as normalization following BoNT-A injection.\[35,36\] However, subsequent studies did not confirm normalized cortical excitability following BoNT-A therapy.\[37,38\] Similarly, no changes in SEPs before and after BoNT-A were reported by Contarino et al in patients with writer’s cramp.\[39\] Moreover, SEP amplitudes and latencies in patients with writer’s cramp did not differ from those of healthy controls.

In focal spasticity, several earlier studies focused on cortical SEPs and electrophysiology changes with BoNT-A treatment. Park et al and Frascarelli et al reported flat or abnormal SEPs in children with spastic cerebral palsy and improvement in SEPs after BoNT-A application.\[18,19\] They concluded that spasticity itself affects cortical SEPs and improvement in SEP parameters associated with reduced spasticity is likely related to a central reorganization. Another study by Basaran et al investigating patients with PSS showed longer N20 latency and lower N20-P25 in the affected limb compared to the unaffected side. However, even though BoNT-A led to improvement in SEPs, the difference did not reach statistical significance, likely due to small sample size.\[20\]

**Table 2**

|                          | Mean  | SD   | Median | Min  | Max  | Wilcoxon test | P  |
|--------------------------|-------|------|--------|------|------|---------------|----|
| N20 latency, unaffected limb (ms) | 20.85 | 1.68 | 20.90  | 17.40| 24.10| .729          |    |
| N20 latency, affected limb (ms)   | 20.93 | 1.53 | 21.00  | 18.40| 25.70| .308          |    |
| P22/N20, unaffected limb (μV)     | 1.74  | 1.40 | 1.43   | 0.04 | 5.78 | .003          |    |
| P22/N20, affected limb (μV)      | 1.49  | 1.17 | 1.34   | 0.15 | 5.24 | .003          |    |
| N20/P23, unaffected limb (μV)    | 2.95  | 2.33 | 2.44   | 0.47 | 9.67 | .003          |    |
| N20/P23, affected limb (μV)     | 1.73  | 1.94 | 1.10   | 0.17 | 8.75 | .003          |    |

*SD = standard deviation.*

*Statistically significant difference (P < .05).*
In our present study, prior to treatment the peak-to-peak amplitude of N20/P23 during the stimulation of the impaired limb was significantly lower than on the unaffected side, which agrees with the aforementioned studies. Abnormal or absent cortical SEP responses evoked from the affected limb are common in most stroke patients,[16] therefore, SEP abnormalities after stroke cannot be attributed to spasticity alone.

Regarding the main aim of our study, cortical SEPs did not show any significant changes attributable to BoNT-A and/or physiotherapy. After the treatment, although there was clear clinical improvement, none of the assessed cortical SEP values yielded statistically significant treatment-related changes. These findings are in line with our previous study, which had a similar design and a smaller number of patients.[24] The only study that reported improvement in SEPs after BoNT-A application in PSS was preliminary and conducted in a small cohort of spastic patients, which limits its overall impact.[20]

Our results, in a large group of patients with PSS, may be explained by several considerations. First, the central effects of BoNT-A may not involve primary somatosensory cortical responses as recorded by our SEP protocol. In our recent neuroimaging study using fMRI, we demonstrated that BoNT-A treatment and physiotherapy applied for more than 5 weeks yield statistically significant changes attributable to BoNT-A and/or physiotherapy. These findings are in line with our previous study, which had a similar design and a smaller number of patients.[24] The only study that reported improvement in SEPs after BoNT-A application in PSS was preliminary and conducted in a small cohort of spastic patients, which limits its overall impact.[20]

Table 3

| Changes in somatosensory evoked potential values at W4 (BoNT-A-effect) and W11 (effect of physiotherapy), against W0. | Mean | SD | Median | Min | Max | Friedman test P |
|---|---|---|---|---|---|---|
| Affected limb | | | | | | |
| N20 latency W0 (ms) | 20.93 | 1.53 | 21.00 | 18.40 | 25.70 | .215 |
| N20 latency W4 (ms) | 21.27 | 2.09 | 21.00 | 17.60 | 26.20 | |
| N20 latency W11 (ms) | 20.96 | 1.90 | 21.00 | 18.20 | 25.60 | |
| P22/N30 W0 (µV) | 1.49 | 1.17 | 1.34 | 0.15 | 5.24 | .241 |
| P22/N30 W4 (µV) | 1.06 | 0.62 | 0.95 | 0.19 | 3.03 | |
| P22/N30 W11 (µV) | 1.36 | 1.16 | 0.97 | 0.10 | 6.05 | |
| N20/P23 W0 (µV) | 1.73 | 1.94 | 1.10 | 0.17 | 8.75 | .857 |
| N20/P23 W4 (µV) | 1.51 | 1.46 | 0.86 | 0.23 | 7.49 | |
| N20/P23 W11 (µV) | 1.78 | 1.85 | 0.79 | 0.11 | 6.95 | |
| Unaffected limb | | | | | | |
| N20 latency W0 (ms) | 20.85 | 1.68 | 20.90 | 17.40 | 24.10 | .512 |
| N20 latency W4 (ms) | 21.00 | 1.76 | 20.30 | 17.10 | 24.10 | |
| N20 latency W11 (ms) | 20.66 | 1.49 | 20.40 | 17.90 | 24.10 | |
| P22/N30 W0 (µV) | 1.74 | 1.40 | 1.43 | 0.04 | 5.78 | .879 |
| P22/N30 W4 (µV) | 1.71 | 1.27 | 1.11 | 0.13 | 5.23 | |
| P22/N30 W11 (µV) | 1.65 | 1.25 | 1.30 | 0.35 | 6.02 | |
| N20/P23 W0 (µV) | 2.95 | 2.35 | 2.44 | 0.47 | 9.67 | |
| N20/P23 W4 (µV) | 3.75 | 2.89 | 2.78 | 0.74 | 14.23 | |
| N20/P23 W11 (µV) | 3.12 | 2.16 | 2.63 | 0.51 | 9.96 | |

SD = standard deviation.
Statistically significant difference (P < .05).

5. Conclusions

In PSS, median nerve SEPs manifest the expected decrease of SEP amplitude over the lesioned hemisphere. In contrast to recent fMRI findings, there were no significant changes associated with BoNT-A treatment and physiotherapy applied for more than three months. Future studies with altered methodology may be needed to detect electrophysiological correlates of spasticity therapy.
References

[1] Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers. Neurology 2013;80:45–52.

[2] Sommerfeld DK, Eck EU-B, Svensson A-K, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. Stroke 2004;35:134–9.

[3] Hesse S, Werner C. Poststroke motor dysfunction and spasticity: novel pharmacological and physical treatment strategies. CNS Drugs 2003;17:1093–107.

[4] Ward AB, Aguilar M, De Beyl Z, et al. Use of botulinum toxin type A in management of adult spasticity—a European consensus statement. J Rehabil Med 2003;35:98–9.

[5] Wissel J, Ward AB, Ertinggaard P, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. J Rehabil Med 2009;41:13–25.

[6] Sheean G, Lannin NA, Turner-Stokes L, Rawicki B, Snow BJ. Cerebral Palsy InstituteBotulinum toxin assessment, intervention and after-care for upper limb hyperreflexia in adults: international consensus statement. Eur J Neurol 2010;17:74–93.

[7] Sumnerhagen KS, Oliver J, Francisco GE. Assessing and treating functional impairment in poststroke spasticity. Neurology 2013;80:35–44.

[8] Simpson LL. The binary toxin produced by Clostridium botulinum enters cells by receptor-mediated endocytosis to exert its pharmacologic effects. J Pharmacol Exp Ther 1999;251:1223–8.

[9] Dressler D, Saleri FA, Barbosa ER. Botulinum toxin: mechanisms of action. Arq Neuropsiquiatr 2005;63:180–5.

[10] Rosales RL, Dressler D. On muscle spindles, dystonia and botulinum toxin. Eur J Neurol 2010;17:71–80.

[11] Giladi N. The mechanism of action of botulinum toxin type A in focal dystonia is most probably through its dual effect on efferent (motor) and afferent pathways at the injected site. J Neurol Sci 1997;152:132–5.

[12] Currà A, Trompetto C, Abbruzzese G, Berardelli A. Central effects of botulinum toxin. Eur J Neurol 2010;17:74–54.

[13] Palomar FJ, Mir P. Neurophysiological changes after intramuscular injection of botulinum toxin. Clin Neurophysiol 2012;123:54–60.

[14] Kaňovský P, Streitová H, Dufek J, Znojil V, Daniel P, Rektor I. Change in lateralization of the P22/N30 cortical component of median nerve somatosensory-evoked potentials in patients with cerebral dystonia after successful treatment with botulinum toxin A. Mov Disord 1998;13:108–17.

[15] Fays H, Van Hees J, Bruyninckx F, Mericis R, De Weerdt W. Value of somatosensory and motor evoked potentials in predicting arm recovery after a stroke. J Neurol Neurosurg Psychiatry 2000;68:323–31.

[16] Al-Rawi MAW, Hamdan FB, Abdal-Muttalib AK. Somatosensory evoked potentials as a predictor for functional recovery of the upper limb in patients with stroke. J Stroke Cerebrovasc Dis 2009;18:262–8.

[17] Park ES, Park CE, Kim DY, Kim YR. The effect of spasticity on cortical somatosensory-evoked potentials: changes of cortical somatosensory-evoked potentials after botulinum toxin type A injection. Arch Phys Med Rehabil 2002;83:1592–6.

[18] Frascarelli F, Di Rosa G, Bisozi E, Castelli E, Santilli V. Neurophysiological changes induced by the botulinum toxin type A injection in children with cerebral palsy. Eur J Paediatr Neurol 2011;15:59–64.

[19] Basaran A, Emre U, Karadavut KI, Bulmus N. Somatosensory evoked potentials of hand muscles in stroke and their modification by botulinum toxin: a preliminary study. J Rehabil Med 2012;44:541–6.

[20] Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67:206–7.

[21] Paternostro-Sluha T, Grim-Stieger M, Posch M, et al. Reliability and validity of the Medical Research Council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. J Rehabil Med 2008;40:665–71.

[22] Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J 1965;14:61–5.

[23] Otruba P, Vysloužil M, et al. Specific protocol of physiotherapy in stroke patients. Cesk Slov Neurol N 2008;71:74.

[24] Veverka T, Hluštík P, Hok P, et al. Sensorimotor modulation by botulinum toxin A in post-stroke arm spasticity: passive hand movement. J Neurol Sci 2016;362:14–20.

[25] Quinn TJ, Dawson J, Walters MR, Lees KR. Variability in modified ranking scoring across a large cohort of international observers. Stroke 2008;39:2975–9.

[26] Kroboth A, Schusterová B, Tomsová J, et al. Progression of post-stroke spasticity—a European consensus statement. J Neurolog Sci 2016;362:14–20.

[27] Simpson DM, Hallet M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Neurology 2016;86:1818–26.

[28] Opavský R, Otruba P, Vysloužil M, et al. Post-stroke upper limb spasticity—modulation with botulinum toxin type A: a therapy and reflection in somatosensory cortical activation. Ceska a Slovenska Neurologie a Neurochirurgie 2011;74:54–59.

[29] Donchin E, Callaway E, Cooper E, Desmedt R. Publication criteria for studies of evoked potentials (EP) in man. Report of the Methodology Committee. Progress in clinical neurophysiology: Vol 1 Attention, voluntary contraction and event-related cerebral potentials; Basel: Karger. Published online January 1, 1977:11–1.

[30] Baker JA, Pereira G. The efficacy of Botulinum Toxin A for spasticity and pain in adults: a systematic review and meta-analysis using the grades of recommendation, assessment, development and evaluation approach. Clin Rehabil 2013;27:1084–96.

[31] Veverka T, Hok P, Otruba P, et al. Botulinum toxin modulates posterior parietal cortex activation in post-stroke spasticity of the upper limb. Front Neurol 2019;10:495.

[32] Hallett M. Mechanism of action of botulinum neurotoxin: unexpected consequences, Toxicon 2018;147:73–6.

[33] Weise D, Weise CM, Naumann M. Central effects of botulinum neurotoxin evidence from human studies. Toxins 2019;11:21.

[34] Trompetto C, Bove M, Avanzino L, Francavilla G, Berardelli A, Abbruzzese G. Intrafusal effects of botulinum toxin in post-stroke upper limb spasticity. Eur J Neurol 2008;15:367–70.

[35] Gilo F, Currà A, Lorenzano C, Modugno N, Manfredi M, Berardelli A. Effects of botulinum toxin type A on intracortical inhibition in patients with dystonia. Ann Neurol 2000;48:20–6.

[36] Kaňovský P, Bares M, Streitová H, Klabajová H, Daniel P, Rektor I. Abnormalities of cortical excitability and cortical inhibition in cervical dystonia evidence from somatosensory evoked potentials and paired transcranial magnetic stimulation recordings. J Neurol 2003;250:42–50.

[37] Boroojerdi B, Cohen LG, Hallett M. Effects of botulinum toxin on motor system excitability in patients with writer’s cramp. Neurology 2003;63:1546–50.

[38] Allam N, Fonte-Boa PM, Tomaz CA, Brasil-Neto JP. Lack of effect of botulinum toxin on cortical excitability in patients with cranial dystonia. Clin Pharmacol 2016;52:281–5.

[39] Contarino MF, Kruisdijk JJM, Koster L, et al. Sensory integration in writer’s cramp: comparison with controls and evaluation of botulinum toxin effect. Clin Neurophysiol 2007;118:2195–206.

[40] Münte TF, Jobges EM, Wieringa BM, et al. Human evoked potentials to long duration vibratory stimulus: role of muscle afferents. Neurosci Lett 1996;216:163–6.

[41] Kagigi R, Shibasaki H. Effects of age, gender, and stimulus side on scalp topography of somatosensory evoked potentials following median nerve stimulation. J Clin Neurophysiol 1991;8:320–30.

[42] Jung P, Baumgartner U, Bauermann T, et al. Asymmetry in the human primary somatosensory cortex and handedness. Neuroimage 2003;19:913–23.
[43] Mas MF, Li S, Francisco GE. Centrally mediated late motor recovery after botulinum toxin injection: case reports and a review of current evidence. J Rehabil Med 2017;49:609–19.

[44] Nevrýl M, Hluštík P, Hok P, Otruba P, Tüdös Z, Kařovský P. Changes in sensorimotor network activation after botulinum toxin type A injections in patients with cervical dystonia: a functional MRI study. Exp Brain Res 2018;236:2627–37.

[45] Hamalainen H, Kekoni J, Sams M, Reinikainen K, Näätänen R. Human somatosensory evoked potentials to mechanical pulses and vibration: contributions of SI and SII somatosensory cortices to P30 and P100 components. Electroencephalogr Clin Neurophysiol 1990;75:13–21.