Sensory Tricks and Brain Excitability in Cervical Dystonia: A Transcranial Magnetic Stimulation Study

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ABSTRACT

Background: Sensory tricks such as touching the face with fingertips often improve cervical dystonia [CD]. This study is to determine whether sensory tricks modulate motor cortex excitability, assessed by paired-pulse transcranial magnetic stimulation [p-pTMS].
Methods: Eight patients with rotational CD underwent p-pTMS, at rest and when the sensory trick was applied. To test intracortical inhibition [ICI] and facilitation [ICF], the amplitude ratio between conditioned and unconditioned cortical motor evoked potentials was measured at several interstimulus intervals (ISI 1, 3, 15, and 20 ms) and compared with controls mimicking patients' sensory tricks.
Results: At rest, a significant ICF enhancement was found at ISIs 15 through 20 in patients compared with controls, whereas no significant ICI changes were observed. Sensory tricks significantly reduced the abnormal ICF in patients and did not induce any change in controls.
Conclusions: In our CD patients, sensory tricks seem to improve dystonia through an inhibitory effect on motor cortex excitability.
Key Words: cervical dystonia; sensory trick; transcranial magnetic stimulation; intracortical inhibition; intracortical facilitation

Antagonistic gestures such as touching the face with fingertips ("sensory trick") may relieve dystonic symptoms in a percentage of patients with idiopathic cervical dystonia (CD) as high as 70%, although the exact mechanism of these tricks is still unknown.[1]

Several transcranial magnetic stimulation (TMS) studies, performed with paired stimuli to assess motor cortex excitability, provided conflicting evidence of decreased[2] rather than unchanged[3] intracortical inhibition (ICI) in patients with arm dystonia, sometimes depending on the performance of specific motor tasks.[4,5] In cervical dystonia, reduced inhibition at interstimulus interval [ISI] of 3 to 5 ms and enhanced intracortical facilitation [ICF] at ISI 10 to 20 were reported when both ipsilateral and contralateral hemispheres to the head turning were stimulated.[6] In this study, we hypothesized that sensory tricks might modulate the primary motor cortex excitability, as revealed by intracortical inhibition/facilitation.

Methods

Eight outpatients with primary CD (5 women; mean age, 48.3 y; standard error [SE], 3.4 y; range, 30-61 y), treated with botulinum toxin at our Institute, entered the study. Main inclusion criteria were: (1) clinical and instrumental diagnosis of idiopathic CD of rotational kind; (2) absence of fixed postures because of skeletal neck deformity; (3) presence of one or more sensory tricks significantly improving abnormal neck posture; (4) neither intake of drugs potentially affecting ICI/ICF for at least 3 weeks before test nor botulinum toxin injections in the previous 3 months; (5) signed informed consent to undergo the study. Cervical dystonia severity was evaluated by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[7] Eight healthy subjects (5 women; mean age, 46.9 y; SE, 3.3 y; range, 29-60 y) were recruited as controls.

All subjects sat in a comfortable chair, wearing a swimming cap with sites of magnetic stimulation marked with ink. For paired-pulse TMS (p-pTMS), 2 Magstim 200 magnetic stimulators (Magstim Ltd, Whitland, Dyfed, UK), connected by a Bi-stim module, delivered pulses through a figure-of-eight focal coil (70 mm external diameter) positioned over the hand area

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TABLE 1. Single and paired-pulse TMS data (mean ± SE)

	RMT	MEP_{amp}	MEP_{test}/MEP_{amp} [%] ISI 1 ms	ISI 3 ms	ISI 15 ms	ISI 20 ms
CD_{bsl}	63.7 ± 1.2	1.9 ± 0.2	44.9 ± 9.8	46.5 ± 11.3	166.2 ± 12.8[a,b]	207.4 ± 20.1[a,b]
CD_{ST}	62.5 ± 2.3	2.0 ± 0.3	50.0 ± 13.3	65.7 ± 20.2	103.6 ± 13.6	107.3 ± 14.9
$Ctrl_{bsl}$	56.1 ± 3.6	2.8 ± 0.6	37.1 ± 4.3	41.6 ± 6.6	112.4 ± 7.2	135.3 ± 10.8
$Ctrl_{ST}$	46.2 ± 2.5	2.6 ± 0.6	34.0 ± 11.9	46.4 ± 11.9	137.2 ± 16.1	123.6 ± 14.0

RMT, resting motor threshold (in % maximum stimulator output); MEP_{amp}, peak-to-peak amplitude of unconditioned MEP; MEP_{test}, peak-to-peak amplitude of conditioned MEP; ISI, interstimulus interval; bsl, baseline; ST, sensory trick; Ctrl, controls.
[a]$P < 0.01$ CD patients at baseline versus controls.
[b]$P \leq 0.001$ CD patients at baseline versus during sensory trick.

of the motor cortex. A subthreshold conditioning stimulus (threshold - 10% of maximum stimulator output) was followed by a suprathreshold test pulse (threshold + 20%) at various ISIs applied randomly (ISI 1, 3, 15, and 20 ms) to evaluate both ICI and ICF. Motor evoked potentials (MEPs) were recorded from first dorsal interosseous muscle (FDI) of the hand not performing the sensory trick, with a standard belly–tendon montage. The coil was placed on the contralateral hemisphere, approximately 3 cm lateral to the vertex, with the handle placed posteriorly and tangentially at 45 degrees. After a few suprathreshold stimuli were given to identify the optimum scalp position to elicit FDI motor responses, resting motor threshold (the lowest intensity producing MEPs ≥ 50 μV in 50% of 10 consecutive stimulations) was determined starting below the expected threshold, with 5% stimulator output increments. To reconstruct the ICI/ICF curves, mean peak-to-peak amplitude of at least five consecutive conditioned MEPs, expressed as the percentage ratio of unconditioned MEPs (5 stimuli), was measured for each ISI. The p-pTMS was randomly applied in two conditions: (1) at baseline, with the patient's head rotated according to dystonic symptoms; and (2) during the performance of the sensory trick, which consisted of placing one patient's hand on his or her chin to gently rotate the head back to the primary position. Coil position, MEP amplitude, and shape were carefully checked after each posture change. Controls were instructed to closely reproduce the specific posture and trick pattern of the patient they matched.

The ICI and ICF were compared among groups and conditions using a two-way analysis of variance, with the main factors group/position (4 levels: patients/baseline, patients/sensory trick, controls/baseline, and controls/sensory trick) and ISI (4 levels: 1, 3, 15, and 20). Post hoc analyses were performed using *t* tests with Bonferroni correction for multiple comparisons. The Kolmogorov-Smirnov test was used to check the normality of data distribution. Analyses were performed using the SPSS/PC+ 13.0 (SPSS Inc, Chicago, IL, USA).

Results

The CD mean duration was 5.5 (SE, 1.0) years, and mean TWSTRS score was 33.2 (SE, 2.3). Sensory tricks' inhibitory effects on dystonic electromyography involuntary activity[8] were first studied in two of eight patients. Such recordings were then stopped, because they were beyond the experimental design and deeply influenced patients' compliance, mainly during p-pTMS. Sensory tricks almost reversed head rotation to primary position in all patients, for a time lasting enough to perform TMS, as long as the fingers touched the face. The trick was applied against the direction of head rotation in four of eight patients, whereas the others performed their sensory trick following the direction of head turning (e.g., touching right cheek with ipsilateral hand to control a left rotational torticollis), realizing a sort of "agonistic," rather than "antagonistic," gesture. Because we recorded MEPs only from the hand not performing the trick, we stimulated the hemisphere contralateral to the rotation as frequently as the ipsilateral one, that is, in four of eight patients.

The TMS results (Table 1; Fig. 1) were first analyzed separately between CD subgroups with "agonistic" and "antagonistic" gestures, then they were pooled together because no significant differences were found between them. Given the normality of data distribution ($P > 0.15$ for all groups and ISI, Kolmogorov-Smirnov test), parametric statistics were suitable even for small sample dimension. The analysis of variance indicated significant effects of the main factors group/position ($F_{3,\ 112} = 6.983$, $P < 0.001$), and ISI ($F_{3,\ 112} = 69.205$, $P < 0.001$) on ICF and a significant interaction between the two main factors ($F_{9,\ 112} = 3.677$, $P < 0.001$). Post hoc analyses showed that, in the baseline condition, ICF was significantly increased in the CD group compared with controls (ISI 15: $P = 0.002$; ISI 20: $P = 0.007$). When patients performed their sensory trick, ICF was significantly reduced compared with baseline (ISI 15: $P < 0.001$; ISI 20: $P = 0.001$) and returned to values comparable to controls (ISI 15: $P = 0.29$; ISI 20: $P = 0.44$). No significant ICI changes

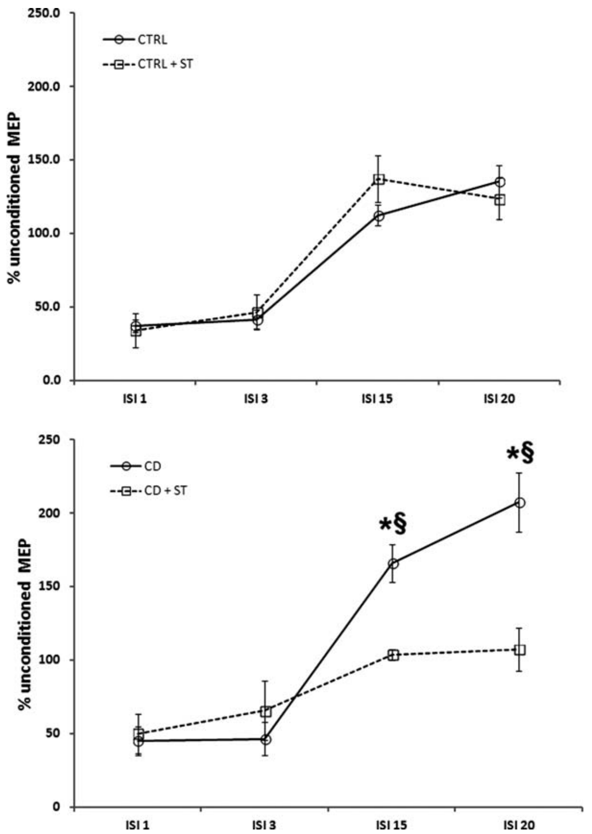

FIG. 1. Comparison of ICI/ICF plotting between controls (upper panel) and CD patients (lower panel). No significant differences were found between baseline and sensory trick (ST) curves in controls. The baseline ICF enhancement (ISI 15-20) observed in CD, which was statistically significant in comparison with controls, significantly recovered toward normal values with ST (*$P < 0.01$, CD patients without sensory trick versus controls; $^{\S}P < 0.01$, CD patients with and without sensory trick).

were observed between controls and CD patients at baseline or during the sensory trick ($P > 0.05$). Notably, mimicking the sensory trick did not significantly modulate ICI/ICF in controls.

Discussion

Our study demonstrated that CD patients treated with botulinum toxin present abnormally enhanced ICF values, promptly reversed by the sensory trick, in parallel with clinical dystonia relief. To our knowledge, this is the first evidence that trick-mediated dystonia improvement is related to changes of motor cortex excitability in CD; even though we lack any direct evidence, we can hypothesize that postural improvement is achieved through the inhibition of neck muscles' spasmodic activity.[8] The previously described ICI decrease was not observed in our patients; this was rather unexpected even in muscles not displaying overt dystonic behavior, because ICI decrease with FDI recordings was reported not only in arm[2] but also in neck[6] dystonia. This discrepancy may be better explained by different patients' characteristics, because the previous studies included patients with kinesigenic arm dystonia (some of which had been already injected), as well as CD patients who never received botulinum toxin. As a matter of fact, botulinum toxin treatment produces a significant, though transient, ICI increase in patients with arm dystonia, recovering toward pretreatment values after a few weeks.[9] Thus, to overcome this potential study drawback, we tried to perform p-pTMS in two naïve CD patients, but data could not be properly interpreted because of extensive head movements during recordings. Unlike Kanovsky et al.,[6] who reported reduced ICI in the hemisphere contralateral to head turning, we did not find any significant ICI interhemispheric change, either in "agonist" or in "antagonist" group. This might actually be the consequence of our small group size; other studies reported no abnormal ICI in focal arm dystonia.[3,10] The finding of enhanced ICF, on the other side, agrees well with the aforementioned study,[6] which reported similar features regardless of the side of the stimulated hemisphere. The evaluation of interhemispheric differences of ICI/ICF exceeded the purposes of this study; our feeling, however, is that the rotational posture does not necessarily mean that dystonia is a pure lateralized phenomenon, as demonstrated by findings of bilateral spasms of dystonic neck muscles in current electromyography practice.

Although either decreased ICI or enhanced ICF may somehow result in motor cortex hyperexcitability, they reflect different neurophysiological mechanisms,[11] which were related to γ-aminobutyric acid and glutamate neurotransmitters, respectively.[12-14] This could explain why ICI and ICF showed contrasting behaviors in our CD patients; moreover, ICF mechanisms are still not fully understood.[15]

Because of the small number of patients, these results should be taken cautiously, but they demonstrate that changes occur within the motor cortex excitability when sensory tricks are being performed. One could raise the question of whether this is a primary cortical mechanism or just an epiphenomenon of dystonic muscle activity fluctuations, either spontaneous or induced by botulinum therapy. The inhibitory effect of the sensory tricks on the overactivity of the motor cortex was already supported by an $H_2{}^{15}O$ positron emission tomography study, reporting decreased activity of the supplementary motor area and primary motor cortex contralateral to the head turn, as well as increased activity of the ipsilateral parietal cortex.[16] These new insights on the exteroceptive inhibition of dystonic spasms could have positive therapeutic outcomes in lower cranial as well as cervical dystonia.[17,18]

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