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Parieto-motor Cortical Dysfunction in Primary Cervical Dystonia

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ABSTRACT

Background: Dystonia is considered as a motor network disorder involving the dysfunction of the posterior parietal cortex, a region involved in preparing and executing reaching movements.
Objective/hypothesis: We used transcranial magnetic stimulation to test the hypothesis that cervical dystonic patients may have a disrupted parieto-motor connectivity.
Methods: We enrolled 14 patients with primary cervical dystonia and 14 controls. A paired-pulse transcranial magnetic stimulation protocol was applied over the right posterior parietal cortex and the right primary motor area. Changes in the amplitudes of motor evoked potential were analyzed as an index of parieto-motor effective connectivity. Patients and healthy subjects were also evaluated with a reaching task. Reaction and movement times were measured.
Results: In healthy subjects, but not in dystonic patients, there was a facilitation of motor evoked potential amplitudes when the conditioning parietal stimulus preceded the test stimulus applied over the primary motor area by 4 ms. Reaction and movement times were significantly slower in patients than in controls. In dystonic patients, the relative strength of parieto-motor connectivity correlated with movement times.
Conclusions: Parieto-motor cortical connectivity is impaired in cervical dystonic patients. This neurophysiological trait is associated with slower reaching movements.

Introduction

Dystonia is a movement disorder characterized by excessive involuntary muscle contraction. Primary focal dystonias are more common than primary generalized dystonias [1]. Cervical dystonia is the most common form of focal dystonia [2].

The pathophysiology of dystonia is not completely understood. Impaired inhibition at multiple levels of the central nervous system is present [3], with alterations of motor circuits involving the basal ganglia [4], the cerebellum [5,6] and the sensorimotor cortex [7,8]. Recent evidences seem to suggest that the dysfunction of the motor network involves other cortical areas such as the parietal cortex [9,10]. Neuropathological and neuroimaging evidences reviewed in a recent paper [11], suggest that the parietal region is implicated in different forms of dystonia, in terms of changes of regional blood flow or gray matter volume. A reduction of the parietal cortex activation was detected during imaging of movement in patients with cervical dystonia [12]. Moreover, after repetitive transcranial magnetic stimulation (TMS) over the parietal cortex, the activation of the parietal cortex during motor execution, measured by functional magnetic resonance imaging (fMRI), was reduced in patients with cervical dystonia [13].

In the current study we aim to explore, with a TMS technique, the connectivity among the posterior parietal cortex (PPC) and the ipsilateral primary motor area (M1) [14] in cervical dystonia. With this method a conditioning stimulus (CS) is first used to activate putative pathways, while a second test stimulus (TS), delivered over M1 a few milliseconds later, is used to explore changes in

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excitability produced by the input [14,15]. In healthy subjects, a conditioning TMS pulse applied over the right PPC is able to increase the excitability of the hand area of the right M1 [16].

The PPC-M1 interaction is crucial in preparation and planning of reaching and grasping movements toward visual targets [17–19], as well as in visuospatial mechanisms that affect temporal performance, accuracy and variability [18,20]. Reaching movements have been proved as a reliable behavioral correlate of the PPC-M1 interaction, because the excitability of this pathway varies during the task [17]. Dystonic patients may show behavioral motor task abnormalities; in fact reaction time task studies in patients with idiopathic torsion dystonia showed that initiation and execution responses were slower than in control subjects [21].

Hence our aim was to study PPC-M1 connectivity in cervical dystonic patients, at rest, using this paired-pulse TMS protocol. Moreover we hypothesize that the efficacy of PPC-M1 interaction could be directly related to the slowness in movement time that characterizes cervical dystonic patients.

Methods and materials

Subjects

Fourteen right-handed patients (5 men, 9 women, mean age 48 ± 14 years, disease duration 8 ± 5 years) affected by primary cervical dystonia (Table 1) were recruited from the Movement Disorders Outpatient Clinic at the Hospital Universitario Virgen del Rocío in Seville, Spain. Diagnosis of cervical dystonia was made by expert neurologists, based on clinical and anamnestic findings. The assessment included a complete Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS). The TMS experiments were performed at least 3 months after the last botulinum toxin injection. All other oral drugs were stopped 48 h before the TMS experiments.

Fourteen age-matched (6 men and 8 women, 48 ± 15 years), healthy, right-handed volunteers served as control subjects. They were recruited from the hospital and research staff. The study was approved by the local ethics committee and all the subjects gave written informed consent.

Experimental procedure

PPC-M1 connectivity

Subjects were seated comfortably and we followed the same design, electromyography (EMG) recordings and off-line peak-to-peak amplitude analysis that were used in a previous study [16,22]. The paired-pulse stimulation technique was used with two different high-power Magstim 200^2 machines (Magstim Co., Whitland, Dyfed, UK). The hand motor area of the right M1 was found at the point where the largest motor evoked potential (MEP) from the contralateral FDI muscle was elicited and the optimal position was marked on the scalp, to ensure the minimum displacement during the experiment. The intensity of the TS was adjusted to elicit 1 mV MEP amplitude in the relaxed FDI. The test stimulator was connected to a figure-of-eight coil with a 55 mm external diameter. The coil was positioned at a 45° angle from the midline to induce a posterior-anterior current flow. The conditioning stimulator was connected to a standard figure-of-eight shaped coil with a 70 mm external diameter, positioned over the P4 position (10-20 EEG system) (Fig. 1A). This site is situated in the inferior parietal lobule [18,23–26], that is part of the posterior parietal cortex, and it is defined by the following Tailarach coordinates: 38.4 ± 6.1, −67.2 ± 4.4, and 46.3 ± 5.8 mm [27]. The center of the coil was positioned over P4 tangentially to the skull and with the handle pointing downward and slightly medial (10°). MRI-guided frameless stereotaxy (Brainsight Frameless; Rogue Research, Montreal, Quebec, Canada) was used in all subjects to ensure the minimum displacement during PPC stimulation (Fig. 1B). We performed three blocks with different intensities of the CS set at 70%, 90% and 110% of the resting motor threshold (RMT). RMT was tested according to international standards [28], with the figure-of-eight shaped coil (70 mm diameter). Inter-stimulus intervals (ISI) between CS and TS were 2, 4, 6, 8, 10, 15, and 20 ms (Fig. 1A). Each block consisted of 20 trials only with TS and 10 trials with CS + TS for each ISI (total 90 trials per block). In each block the trials were randomly intermingled with an inter-trial time of 5 s. The order of presentation of the blocks of trials varied randomly in control and patients.

Reaction time task

We used a choice reaction time task similar to that adopted previously [17,22]. All subjects sat comfortably in a 45-cm-high straight-back chair facing a table, 120 cm wide and 60 cm deep. On the opposite edge of the table an upright, home-made flat wooden panel was fixed, 80 cm wide and 50 cm high, placed at 60 cm distance from the subject. Subjects placed the index finger of their left hand on an upraised bump (2.5 cm-diameter coin), that acted as starting point, on the table surface. Peripheral targets comprised 2 cm-diameter upraised bumps, positioned 20 cm left or right of a fixation cross at a viewing distance of 60 cm (Fig. 1C). The starting point

Table 1
Clinical characteristics of patients with primary cervical dystonia.

No.	Sex	Age (years)	Disease duration (years)	TWSTRS	BFMDRS	Dominant hand/ head deviation	Treatment (mg/day)
1	M	39	3	26.7	13.5	R/L	BT
2	F	34	15	16	12	R/R	BT
3	M	34	9	40.75	17.5	R/R	BT
4	M	32	15	32.25	8	R/R	BT
5	M	32	5	55.75	22	R/R	BT, clonazepam (2)
6	F	44	3	44	25	R/L	BT, clonazepam (10)
7	F	48	8	22.5	7.5	R/L	BT
8	F	68	10	32	6	R/L	BT
9	M	64	16	36	26	R/R	BT, trihexyphenidyl (6)
10	F	66	9	9.75	21	R/L	Trihexyphenidyl (6)
11	F	55	2	12	1.5	R/R	BT
12	F	68	4	30.75	23.5	R/L	BT
13	F	40	2	31	38.2	R/R	BT
14	F	48	8	25	39.5	R/L	BT

M = male; F = female; R = right; L = left; BT = botulinum toxin; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; BFMDRS = Burke–Fahn–Marsden Dystonia Rating Scale.