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Effects of cerebellar theta-burst stimulation on arm and neck movement kinematics in patients with focal dystonia ☆

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HIGHLIGHTS

- Cerebellar cTBS reduced the M1 excitability in cervical dystonia, but not in focal hand dystonia.
- Cerebellar cTBS had no effect on movement kinematics in either cervical dystonia or focal hand dystonia.
- The data indicate that the pathophysiological role of the cerebellum is not identical in all types of dystonia.

ABSTRACT

Objective: To investigate the cerebellar inhibitory influence on the primary motor cortex in patients with focal dystonia using a cerebellar continuous theta-burst stimulation protocol (cTBS) and to evaluate any relationship with movement abnormalities.
Methods: Thirteen patients with focal hand dystonia, 13 patients with cervical dystonia and 13 healthy subjects underwent two sessions: (i) cTBS over the cerebellar hemisphere (real cTBS) and (ii) cTBS over the neck muscles (sham cTBS). The effects of cerebellar cTBS were quantified as excitability changes in the contralateral primary motor cortex, as well as possible changes in arm and neck movements in patients.
Results: Real cerebellar cTBS reduced the excitability in the contralateral primary motor cortex in healthy subjects and in patients with cervical dystonia, though not in patients with focal hand dystonia. There was no correlation between changes in primary motor cortex excitability and arm and neck movement kinematics in patients. There were no changes in clinical scores or in kinematic measures, after either real or sham cerebellar cTBS in patients.
Conclusions: The reduced cerebellar inhibitory modulation of primary motor cortex excitability in focal dystonia may be related to the body areas affected by dystonia as opposed to being a widespread pathophysiological abnormality.
Significance: The present study yields information on the differential role played by the cerebellum in the pathophysiology of different focal dystonias.

1. Introduction

Adult-onset focal dystonia is clinically characterized by involuntary muscle contractions and abnormal postures that can affect different body regions, including the upper limb and neck (Defazio et al., 2007; Albanese et al., 2013; Jinnah et al., 2013).The pathophysiology of focal dystonia is still not entirely clear. Although dystonia is considered a basal ganglia disorder (Bhatia and Marsden 1994; DeLong and Wichmann 2007), recent studies indicate that

Abbreviations: AMT, active motor threshold; ANOVA, analysis of variance; CD, cervical dystonia; cTBS, continuous theta-burst stimulation; EMG, electromyographic; FDI, first dorsal interosseous; FHD, focal hand dystonia; HS, healthy subjects; IC, index of curvature; I/O, input–output; MSO, maximal stimulator output; MEP, motor-evoked potential; M1, primary motor cortex; RMT, resting motor threshold.

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the cerebellum may also be involved in this condition (Sadnicka et al., 2012; Prudente et al., 2014; Malone et al., 2014).

The results of animal studies show that abnormal cerebellar signalling may produce dystonia-like movements (Pizoli et al., 2002). Neuropathological examinations in post-mortem brain tissue of patients with cervical dystonia (CD) reveal Purkinje cell degeneration, areas of focal gliosis and torpedo bodies (Prudente et al., 2013). Clinical observations also indicate that focal dystonia may be associated with structural lesions of the cerebellum and its afferent pathways (LeDoux and Brady 2003; Batla et al., 2015). Moreover, neuroimaging studies using various techniques have provided evidence of cerebellar grey matter changes and altered cerebello-thalamo-cortical pathways in patients with focal hand dystonia (FHD) or CD (Draganski et al., 2003; Delmaire et al., 2007). Functional neuroimaging investigations have demonstrated abnormal resting state cerebello-thalamo-cortical connectivity in FHD patients (Dresel et al., 2014; Bharath et al., 2015).

Neurophysiological studies have also provided evidence of several cerebellar abnormalities in focal dystonia (Sadnicka et al., 2012). Eyeblink classical conditioning, a form of associative learning mediated by cerebellar circuits, is abnormally reduced in focal dystonia (Teo et al., 2009; Hoffland et al., 2013). Studies based on repetitive transcranial magnetic stimulation (TMS) techniques have shown that cerebellar stimulation in patients with FHD does not influence primary motor cortex (M1) excitability (Brighina et al., 2009; Hubsch et al., 2013).

Recent findings have raised a number of issues regarding the pathophysiological role of the cerebellum in focal dystonia that deserve further investigation. The abnormalities of the cerebellar influence on M1, as tested by repetitive TMS techniques, have been reported in FHD, whereas no data are available for CD. It is therefore unknown whether the abnormalities of the cerebellar inhibitory modulation of M1 are a common feature of the various forms of focal dystonia. In addition, no study has yet specifically addressed a possible relationship between abnormalities of the cerebellar inhibitory modulation of M1 and movement abnormalities in patients with focal dystonia. This information might provide further insight on the pathophysiological role of the cerebellum in focal dystonia.

In the present study, we first investigated the effects of cerebellar cTBS in patients with FHD and CD, as indexed by M1 excitability changes in the contralateral hemisphere. We then explored the relationships between individual M1 excitability changes following cerebellar cTBS with arm and neck movements as evaluated by a clinical assessment and kinematic analysis. Data from FHD and CD patients were compared with those observed in healthy controls.

2. Methods

2.1. Participants

Thirteen patients with FHD (2 women; mean age ±1 standard deviation: 48.5 ± 15.0) and 13 patients with CD (8 women; mean age ±1 standard deviation: 46.7 ± 14.5) were enrolled in the study (Table 1). A control group of thirteen healthy subjects (HS) (6 women; mean age ±1 standard deviation: 49.9 ± 11.3; Table 1) was also included in the study. The diagnosis of FHD and CD was based on clinical criteria (Albanese et al., 2013). The clinical assessment included the Wissel scale for FHD patients (Wissel et al., 1996) and the Toronto Western Spasmodic Torticollis Rating Scale-TWSTRS for CD patients (Comella et al., 1997). All the patients were right-handed and all patients with FHD had right arm dystonia. None of the patients exhibited upper limb tremor or neck pain that might interfere with the kinematic recordings. All the patients were studied three months after their last botulinum toxin injection and none of them were taking other medications active at the central nervous system level at the time of the experiments. The experimental procedures were approved by the local institutional review board and all the subjects gave their written informed consent to participation in the study. The experiments adhered to Declaration of Helsinki regulations.

Table 1
Demographic and clinical data.

	FHD patients	CD patients	HS
Gender	11M/2F	5M/8F	9M/6F
Age (years)	48.5 ± 15.0	46.7 ± 14.5	49.9 ± 11.3
Disease duration (years)	6.2 ± 6.6	6.4 ± 6.5	–
Clinical Score	11.6 ± 5.3	20.5 ± 9.8	–

Gender (M = male; F = female). FHD = focal hand dystonia; CD = cervical dystonia, HS = healthy subjects. The clinical score (at baseline) in FHD patients refers to the Wissel Scale writing movement score (ranging from 0 to 28). The clinical score (at baseline) in CD patients refers to the Toronto Western Spasmodic Torticollis Rating Scale-TWSTRS (ranging from 0 to 85). Plus and minus values are means ±1 standard deviation.

2.2. TMS and electromyographic techniques

TMS was delivered through two Magstim magnetic stimulators (Magstim Company, Withland, UK) connected with a figure-eight coil placed tangentially to the scalp with the handle pointing towards the back and approximately 45° away from the midline.

We assessed M1 excitability using single pulse TMS. For this purpose we first measured the resting motor threshold (RMT), i.e., the intensity of M1 stimulation able to elicit motor-evoked potential (MEP) of ∼50 μV peak-to-peak amplitude in the resting first dorsal interosseous (FDI) muscle, as shown by surface electromyography (EMG). After the RMT assessment we collected the MEP input–output (I/O) curve using stimulation intensities of 100%, 110%, 120%, 130%, 140% and 150% of the RMT in random order. Traces with background EMG activity ⩾50 μV were rejected online (less than 1% of trials).

We delivered cerebellar cTBS (ipsilateral to the affected side of the body in FHD patients) at intensities of 80% of the active motor threshold (AMT), i.e., the intensity of M1 stimulation able to elicit motor-evoked potential (MEP) of ∼200 μV peak-to-peak amplitude in the tonically active FDI muscle, using a biphasic magnetic stimulator. The cTBS protocol consists of high frequency (50 Hz) burst of three stimuli, repeated at 5 Hz for an overall duration of 40 s. Cerebellar real cTBS was delivered with the coil positioned over the cerebellar hemisphere, i.e., 3 cm laterally to and 1 cm below the inion, while cerebellar sham cTBS consisted of the stimulation of neck muscles. Sham cTBS does not stimulate the cerebellum but does induce slight twitches in the neck muscle similar to those induced by real cTBS (Koch et al., 2008; Hoffland et al., 2012, 2013; Li Voti et al., 2014; Schirinzi et al., 2016).

Surface EMG was recorded from the FDI muscle ipsilateral to cerebellar cTBS using silver chloride electrode. EMG signals were amplified and band-pass filtered (20 Hz-1 kHz) using Digitimer D 360 (Digitimer, UK). EMG recordings were sampled at 5 kHz and stored on a PC using an analog–digital converter (AD 1401 plus Cambridge Electronic Design, UK). Off-line analysis was then performed using dedicated software (Signal® version 4.00, Cambridge Electronic Design, UK).

2.3. Kinematic recordings and analysis of arm and neck movements

During the experiments, FHD, CD patients and HS were seated in a chair with their limbs resting on a table. The arm and neck movements were assessed using a dedicated optoelectronic device (SMART, BTS, Milan, Italy) consisting of three infrared cameras