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Reduced parietal activation in cervical dystonia after parietal TMS interleaved with fMRI

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ABSTRACT

Objective: Clinically normal hand movement with altered cerebral activation patterns in cervical dystonia (CD) may imply cerebral adaptation. Since impaired sensorimotor integration appears to play a role in dystonia, left superior parietal cortex modulation with repetitive transcranial magnetic stimulation (TMS) was employed to further challenge adaptation mechanisms reflected by changes in cerebral activation.
Methods: Seven CD patients and ten healthy controls were scanned on a 3T magnetic resonance imaging (MRI) scanner with 1 Hz inhibitory interleaved TMS. They executed and imagined right wrist flexion/extension movements. Each task was preceded by a 10-s period with or without TMS.
Results: The activations of both tasks after TMS in controls showed a similar pattern as found in CD without TMS, i.e. activation increases in bilateral prefrontal and posterior parietal regions during both tasks and decreases in right anterior parietal cortex during imagery ($P < 0.001$). the activations of both tasks after TMS in CD were weaker but with a similar trend in activation changes. Only in the right angular gyrus, TMS significantly failed to induce an activation increase in CD as was seen in the controls ($P < 0.001$).
Conclusion: The similarity between TMS effects on the distribution of cerebral activations in controls and the pattern seen in CD may support the concept that CD make use of compensatory circuitry enabling clinically normal hand movement. The fact that a similar but weaker TMS effect occurred in CD could suggest that the capacity of compensation is reduced. Particularly for the right angular gyrus, this reduction was statistically significant.

1. Introduction

Cervical dystonia (CD) is defined as a movement disorder with abnormal involuntary muscle contractions and postures of head and neck. The execution of hand movement seems clinically normal. However, we have recently demonstrated with functional magnetic resonance imaging (fMRI) that the cerebral organization underlying hand movements in CD differs from normal [1], while subtle changes in muscle contraction were also found by electromyography [2]. The association of apparent normal hand function and deviant distribution of cerebral activation might suggest a flexibility of the brain to adapt to impaired cortical function by recruiting other cortical areas to perform the desired task. This issue was further addressed in the present study.

The cause of CD is unknown, although, neuroimaging studies have reported abnormal function of brain areas during task performance in dystonic body parts. Basal ganglia and prefrontal cortex were overactivated in a positron emission tomography (PET) study with joystick movement in patients with idiopathic torsion dystonia [3] and in a review of PET studies with hand movement in focal hand dystonia [4]. Two fMRI studies employing finger tapping in focal hand dystonia [5] and movement and imagery of wrist flexion/extension movements in dystonia associated with complex regional pain syndrome [6] showed underactivation in the primary sensorimotor cortex and adjacent sensorimotor-related areas. In contrast, in other fMRI and PET studies performing hand

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movements in task-specific dystonia these regions were overactivated [7,8].

The parietal cortex plays an important role in the higher-order sensory processing by integrating information on (visuo)spatial perception, body scheme and proprioception in order to prepare (spatial) movement [9,10]. Changes in activation may reflect deficits in processing and integration of this sensory information. This concept is supported by various observations. A sudden deficit in sensory signaling is reflected in 5–21% of CD who had an injury in the neck prior to the onset of dystonic symptoms [11]. Changing sensory or proprioceptive feedback is demonstrated in the use of sensory tricks in CD. Performance of these maneuvers can temporarily alleviate dystonic symptoms. Interestingly, imagery of sensory tricks alone can be sufficient to modulate these sensorimotor networks and improve symptoms [12]. One might thus infer that there is a lack of sufficient sensory information processing in CD. Naumann et al. argued that adding sensory information by applying a sensory trick particularly enables antero-ventral parts of the parietal cortex, containing the secondary sensory areas, to temporarily switch of the dystonic drive [13]. Interestingly, in CD voxel-based morphometric structural changes have also been reported in the specific parts of the parietal cortex containing the integration of sensory information [14]. Thus, impaired sensorimotor function seems to play an important role in the aetiology of dystonia [1,15].

These wide-spread cerebral network changes seen in parietal, prefrontal cortices and basal ganglia in CD may seem at odds with the fact that dystonic symptoms are usually only localized in one body part, particularly in the neck, while movements in other body parts seem clinically normal. However, investigation of CD with fMRI during movement of a non-dystonic body part resulted in similar abnormal cerebral activations as during dystonic movement [1]. It was hypothesized that this association between reduced activation in movement-associated brain regions and clinically normal movement performance may imply effective compensation mechanisms in CD. The brain's ability to adapt to new situations can be observed in clinical neurological conditions [16,17]. Another way to explore these adaptation mechanisms is to modulate neural networks with transcranial magnetic stimulation (TMS). TMS is produced by a magnetic pulse that can induce an electric current in the brain. It creates an action potential in the cells that can have either a stimulatory or inhibitory effect on neural networks depending on the stimulation parameters. By applying a 1 Hz inhibitory train of pulses TMS can disrupt cerebral activity (e.g. creating a temporary virtual lesion) in order to explore the functional relevance of the targeted area and reorganization of its connected neural networks [18]. Compensational activation to TMS applied virtual lesions has been demonstrated in target areas as primary motor cortex [19], dorsal premotor regions [20] and dorsolateral prefrontal cortex [21]. Compensation also appears to occur after TMS induced modulation of the superior parietal cortex in healthy controls (HC); 'compensatory' increases were seen in posterior parietal and prefrontal networks during hand movement execution and imagery [22].

As similar patterns of changed activation were observed in CD and HC after TMS, a mechanism of compensation is suggested indeed. The present study aimed to investigate whether such compensation can be further challenged by TMS in CD. We expected increased activation with maintained ability to perform clinically normal movement in a non-dystonic body part. We therefore introduced movement execution and imagery tasks. Movement imagery is in the same class of neural processing as movement preparation, neural circuits required prior to movement execution are expected to be activated during movement imagery. These circuits contain precentral sulcus, prefrontal, posterior superior parietal, subcortical and cerebellar regions, while little imagery-related activity is expected in primary motor and sensory areas [1,23]. The advantage of a movement imagery task is that it enables the study of these circuits without the blurring effect of sensory feedback, as seen during movement execution [24]. In order to challenge possible compensatory networks, we chose to induce virtual TMS lesions on the superior parietal cortex. Effects of changes in activation during the motor tasks were measured directly with fMRI (interleaved TMS/fMRI [25]). The choice of the superior parietal cortex was based on fMRI studies which show underactivation in this specific area [1,5]. Further inhibition of this region with TMS might stress compensatory networks even more. These compensatory networks are assumed to contain (i) the prefrontal cortex, previously seen overactivated in CD, presumably as adaptation to impaired parietal function, and (ii) posterior parietal regions, showing adaptive increases in HC after superior parietal cortex modulation.

2. Materials and methods

2.1. Subjects

Seven CD patients (mean age 57 ± 16 (SD), 6 females) and ten age-matched HC (mean age 53 ± 11 (SD); 8 females) were studied. Six patients had CD (one with concurrent spasmodic dysphonia), one had generalized dystonia (DYT1 mutation carrier negative). All patients presented with CD as leading symptom (Table 1). Subjects signed informed consent approved by the Medical University of South Carolina institutional review board. All were right-handed (Annett Handedness Scale [26]). No subject had a medical history of neurological disorders except primary dystonia. Each subject underwent one 15-min session during which the effect of interleaved TMS/fMRI was assessed.

Table 1
Subject characteristics.

	Gender	Age	Predominant dystonic movement	Additional symptoms	Treatment for dystonia
Cervical dystonia					
1	F	48	Left laterocollis	Upper extremity tremor	Botulinum toxin (18 days[a])
2	F	79	Right laterocollis	None	None
3	F	65	Left laterocollis	Generalized dystonia	Botulinum toxin (91 days[a])
4	F	71	Left laterocollis	Upper extremity tremor	Botulinum toxin (24 days[a])
5	F	25	Right laterocollis	None	Botulinum toxin (48 days[a]), trihexyphenidyl, tizanidine, clonazepam
6	M	54	Anterocollis	Spasmodic dysphonia	Trihexyphenydil
7	F	66	Right laterocollis	None	Clonazepam
Mean ± SD			57 ± 16		
Healthy controls					
1–10	8F, 2M				
Mean ± SD			53 ± 11		

[a]The time between botulinum toxin injections and MRI scan.