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Primary somatosensory cortical plasticity and tactile temporal discrimination in focal hand dystonia

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HIGHLIGHTS

- Theta-burst stimulation (TBS) changed the altered somatosensory temporal discrimination in patients.
- TBS elicited normal homotopic cortical plasticity in S1 in patients with dystonia.
- TBS over S1 failed to improve writing performances in patients with dystonia.

ABSTRACT

Objective: To investigate whether theta burst stimulation (TBS) applied over primary somatosensory cortex (S1) modulates somatosensory temporal discrimination threshold (STDT) and writing performances in patients with focal hand dystonia (FHD).
Methods: Twelve patients with FHD underwent STDT testing and writing tasks before and after intermittent, continuous, or sham TBS (iTBS, cTBS, sham TBS) over S1 contralateral to the affected hand. Twelve healthy subjects underwent iTBS and cTBS over S1 and STDT values were tested on the right hand before and after TBS.
Results: Baseline STDT values were higher in patients than in healthy subjects on both the affected and unaffected hand. In patients and healthy subjects iTBS decreased, whereas cTBS increased STDT values and did so to a similar extent in both groups. In patients, although STDT values decreased after iTBS, they did not normalize. S1 modulation did not improve the writing performance.
Conclusions: In patients, S1 responds normally to protocols inducing homotopic synaptic plasticity. The inhibitory interneuron activity responsible for STDT is altered.
Significance: The pathophysiological mechanisms underlying abnormal temporal discrimination differ from those responsible for motor symptoms in FHD.

1. Introduction

Focal hand dystonia (FHD) is characterized by prolonged and simultaneous forearm agonist and antagonist muscle co-contractions, which result in abnormal, twisting posturing (Hallett, 2006) leading to impaired task performance (Schabrun et al., 2009). Although the pathophysiology of FHD is still unclear, ample evidence shows loss of inhibition at multiple motor system levels (Berardelli et al., 1998; Berardelli, 2006; Defazio et al., 2007). The observation that primary motor cortex (M1) plasticity investigated using the paired associative stimulation (PAS) protocol, which entails coupling a somatosensory afferent volley and a transcranial magnetic stimulation (TMS) pulse on M1 at a specific interstimulus interval (ISI) (Quartarone et al., 2006) is altered in patients with FHD suggested a role for altered somatosensory processing in this condition (Abbruzzese and Berardelli, 2011; Nava and Röder, 2011; Belvisi et al., 2013). In line with previous experimental evidence of altered somatosensory processing, several studies in patients with FHD reported abnormalities in the organization of the finger representation in the primary somatosensory cortex (S1) (Bara-Jimenez et al., 1998; Meunier et al., 2001).

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Somatosensory temporal discrimination threshold (STDT) testing is a useful neurophysiological tool for investigating central somatosensory information processing in the temporal domain. The STDT is defined as the shortest interval that allows two temporally separate tactile stimuli to be perceived as clearly distinct (Lacruz et al., 1991). Extensive evidence showed that STDT values are higher in patients with various forms of focal dystonia, including FHD (Scontrini et al., 2009), as well as in patients with generalized dystonia (Aglioti et al., 2003) than in healthy subjects.

In healthy subjects, the STDT requires the integrity of multiple cortical and subcortical structures involved in somatosensory information processing (Ivry, 1996; Conte et al., 2012b). Evidence from studies using transcranial magnetic stimulation (TMS) in healthy subjects shows that theta-burst stimulation (TBS) – a repetitive transcranial magnetic stimulation (rTMS) technique that induces long-lasting homotopic changes in cortical activity (Huang et al., 2005; Iezzi et al., 2008; Conte et al., 2012a) – delivered over S1 modulates STDT values (Conte et al., 2012b). Continuous theta-burst stimulation (cTBS), eliciting inhibitory changes in cortical excitability resembling long-term depression-like (LTD-like) plasticity mechanisms, degrades STDT values, whereas intermittent TBS (iTBS), eliciting facilitatory effects resembling long-term potentiation-like (LTP-like) plasticity mechanisms, improves STDT values (Conte et al., 2012b).

Although TBS could in theory influence the STDT by modulating S1 plasticity, no studies have investigated whether S1-iTBS and cTBS changes these patients' abnormal STDT values. Given that the STDT is abnormal also in unaffected relatives of patients with dystonia (Bradley et al., 2009) changes in the STDT are unlikely to explain motor disorders in patients with dystonia. It is, however, unknown whether abnormal sensory integration favors the development of motor disturbances caused by the lack of inhibition in the motor system. If abnormal sensory integration favors motor disturbances then possible S1 TBS-induced modulation of STDT abnormalities might in turn ameliorate motor performances. No studies have investigated whether S1 TBS influences writing performance in patients with FHD. Besides extending current knowledge on S1 cortical plasticity in FHD, this information might suggest new strategies for improving motor disturbances in patients with FHD.

We therefore designed this study to investigate whether TBS-induced homotopic synaptic plasticity in S1 – as tested using inhibitory and facilitatory protocols – modulates STDT abnormalities in patients with FHD, and whether possible TBS-induced changes in the psychophysical variable STDT parallel clinically evident changes in motor disturbances as measured with a writing task. To investigate whether TBS-induced changes in patients with FHD resemble those in healthy subjects, we also compared changes in STDT values after iTBS and cTBS over S1 in patients with FHD and age-matched healthy volunteers.

2. Methods

2.1. Subjects

We enrolled 12 right-handed patients with FHD (mean age: 43 ± 3 years) and 12 right-handed age-matched healthy volunteers (mean age 42 ± 4 years). All the FHD patients were recruited from the movement disorders outpatient clinic at the "Sapienza" University of Rome. Five of the 12 patients had dystonia only during the writing task (simple writer's cramp-WC) and 7 patients had dystonia also in other motor tasks (dystonic WC) (Sheehy and Marsden, 1982). Clinical and demographic data are shown in Table 1. The 10 patients who were receiving treatment with botulinum toxin injections were studied at least four months after the last treatment. None of the patients had a history of other neurological or psychiatric disorders and none of the patients was receiving central nervous system-acting medication when studied. The severity of dystonia was assessed with the Arm Dystonia Disability Scale (ADDS) (Fahn, 1989). Written informed consent was obtained from all the subjects. The experimental procedures were approved by the local institutional review board and conducted in accordance with the Declaration of Helsinki. The diagnosis was based on examination by neurologists experienced in movement disorders. Patients with peripheral sensory neuropathy documented on clinical and conventional nerve conduction studies were excluded.

2.2. Stimuli and STDT procedure

The STDT was investigated by delivering paired stimuli starting with an ISI of 0 ms (simultaneous pair), and progressively increasing the ISI in 10 ms steps, according to the experimental procedures used in previous studies (Scontrini et al., 2009, 2011; Conte et al., 2010, 2012b; Rocchi et al., 2013; Tinazzi et al., 2013). Paired tactile stimuli consisted of square-wave electrical pulses delivered with a constant current stimulator (Digitimer DS7AH) through surface skin electrodes with the anode located 0.5 cm distally to the cathode applied on the volar surface of the index finger of the left and right hand. The stimulation intensity was defined for each subject by delivering a series of stimuli at an increasing intensity from 2 mA in 0.5 mA steps; the intensity used for the STDT was the minimal intensity perceived by the subject in 10 of 10 consecutive stimuli. The first of three consecutive ISIs at which participants recognized the stimuli as temporally

Table 1
Clinical features of patients with focal hand dystonia.

Patient	Sex	Age (years)	Disease duration (years)	ADDS	Type of FHD	BoNT therapy duration (years)
1	M	65	50	26	Dystonic WC	9
2	M	55	17	51	Simple WC	11
3	M	51	17	64	Simple WC	1
4	F	40	32	56	Dystonic WC	–
5	M	39	4	64	Dystonic WC	1
6	M	38	4	47	Dystonic WC	1
7	M	31	14	73	Simple WC	3
8	F	38	28	54	Simple WC	4
9	M	49	16	64	Simple WC	5
10	M	43	3	51	Dystonic WC	–
11	M	47	24	60	Dystonic WC	10
12	M	27	5	73	Dystonic WC	1
Mean ± SE		43 ± 3	17 ± 4	57 ± 3		4.6 ± 1

ADDS = Arm Dystonia Disability Scale; FHD = Focal Hand Dystonia; WC = writer's cramp; BoNT = Botulinum Toxin.