Parkinsonism and Related Disorders 21 (2015) 789–792

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Does the cerebellum intervene in the abnormal somatosensory temporal discrimination in Parkinson's disease?

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ARTICLE INFO

Article history:
Received 23 November 2014
Received in revised form
6 April 2015
Accepted 7 April 2015

Keywords:
Somatosensory temporal discrimination
Parkinson's disease
Cerebellum
Theta burst stimulation

ABSTRACT

Introduction: somatosensory temporal discrimination threshold (STDT) measures the ability to perceive two stimuli as being sequential. Altered STDT has been reported in Parkinson's disease (PD). The cerebellum seems to play a role in the pathophysiology of PD, and may consequently be involved in the pathophysiology of STDT abnormalities.

Methods: STDT was investigated in fifteen PD patients who underwent real and sham cerebellar continuous theta burst stimulation (cTBS) in the OFF condition. Eight patients underwent a further real cTBS session in ON condition. STDT was measured on both hands before, 5 and 25 min after real and sham cTBS delivered over the cerebellar hemisphere ipsilateral to the more affected side. We controlled the efficacy of our protocol by monitoring primary motor cortex (M1) excitability. Ten healthy subjects acted as control group.

Results: STDT values were increased in PD patients in the OFF condition compared with healthy subjects and PD patients in the ON condition. In PD patients OFF condition, real but not sham cerebellar cTBS, significantly reduced STDT values only in the hand ipsilateral to the stimulated cerebellar hemisphere. Cerebellar cTBS also decreased motor evoked potentials (MEP) size in the contralateral M1. When PD patients were tested in the ON condition, cerebellar cTBS failed to modify STDT values.

Conclusion: cerebellar cTBS improved STDT values in PD patients exclusively in OFF condition. We hypothesize that cerebellar stimulation partially compensates for increased STDT values only when patients are OFF dopaminergic therapy. This suggests that the cerebellum may act as compensatory system in PD.

1. Introduction

The somatosensory temporal discrimination threshold (STDT) measures the ability to perceive two stimuli as being sequential [1] and is considered a useful measure of sensory integration in normal subjects [2] and in patients with movement disorders [3]. In Parkinson's disease (PD), a number of papers have reported higher than normal STDT values [3–5], with changes in STDT being attributed to basal ganglia abnormalities [6]. In addition STDT abnormalities are improved by dopaminergic therapy [3,5]. A recent paper suggested that, besides the basal ganglia, the cerebellum also contributes to the pathophysiology of PD [7]. In PD cerebellum may be primarily involved in the pathophysiology or may intervene in compensatory mechanisms [7]. It is therefore possible that the physiological mechanisms underlying the STDT abnormalities described in PD also involve the cerebellum through its reciprocal connections with basal ganglia.

It has been demonstrated that it is possible to stimulate the cerebellum by means of transcranial magnetic stimulation (TMS) technique [8] with continuous theta burst stimulation (cTBS) protocol and investigate the effects of cerebellar stimulation on the STDT in healthy subjects [2]. Knowing more about the contribution of the cerebellum in the STDT abnormalities may shed light on the pathophysiological mechanisms of STDT in PD.

The aim of this paper was to see whether cerebellar stimulation in PD patients can modify abnormal STDT. Cerebellar cTBS may leave STDT values unchanged, suggesting that the cerebellum has no role in STDT abnormalities, or alternatively may modulate STDT

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http://dx.doi.org/10.1016/j.parkreldis.2015.04.004
1353-8020/

values, proposing its possible role in STDT processing. To do so we investigated possible effects of cTBS of the cerebellum on the STDT values in PD patients in OFF and ON therapy. In healthy subjects, cTBS is able to induce inhibitory effects in the stimulated brain area lasting about 30 min and resembling long-term depression (LTD)-like mechanisms [8]. Since cTBS of the cerebellum in normal subjects modulates the effect of cerebellar output to the contralateral primary motor cortex (M1) [8], to control the efficacy of the cerebellar-cTBS, we also monitored changes in M1 excitability by measuring the amplitude of motor evoked potentials before and after cerebellar cTBS.

2. Materials and methods

Fifteen PD patients (11 M/4 F; age: 62.4 ± 6.3 years; disease duration: 5.2 ± 4.3 years) and ten age-matched healthy subjects (5 M/5 F; age: 61.3 ± 7.7 years) were enrolled in the study. Patients were recruited from the movement disorders outpatient clinic at the 'Neuromed Institute', Pozzilli (Italy). Written informed consent was obtained from all the subjects. The experimental procedures were approved by the local institutional review board and were carried out in accordance with the Declaration of Helsinki.

2.1. Clinical evaluation

PD patients were enrolled according to the United Kingdom Parkinson's Disease Society Brain Bank criteria, recently reviewed by the EFNS/MDS-ES task force [9]. Motor symptoms were assessed using the Hoehn and Yahr Scale (H&Y: 1.4 ± 0.5) and Unified Parkinson's Disease Rating Scale (UPDRS: 11.53 ± 5.9). All the patients had resting tremor (tables in Supplementary data). Cognitive functions were assessed using the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) (table in Supplementary data). Exclusion criteria were an MMSE score lower than 27, and the presence of peripheral neuropathy or clinical signs of sensory deficit. None of the patients had mood disorders or took antipsychotic drugs. We performed MRI scan in all the patients to exclude major vascular and/or intracranial lesions. In 4 of the patients there were mild signs of chronic vascular encephalopathy. All fifteen patients were studied without pharmacological treatment (OFF therapy). Eight of them were also studied under medication (ON therapy). In the 8 selected patients studied under medication the severity of clinical features was similar to the 7 patients who did not take part in the experiment. Data obtained in PD patients were compared with those from healthy controls.

2.2. Stimuli and STDT procedure

Paired tactile stimuli consisted of square-wave electrical pulses delivered using a constant current stimulator (Digitimer DS7AH) through surface skin electrodes with the anode located 0.5 cm distally of a cathode applied to the index finger of the left and right hands. The STDT was investigated by delivering paired stimuli, starting with an inter-stimulus interval (ISI) of 0 msec (simultaneous pair) and progressively increasing the ISI in 10 msec steps, according to the experimental procedures used in previous studies [2,3] (Supplementary data).

2.3. Transcranial magnetic stimulation

cTBS was delivered by means of a Super Rapid Magstim 200 stimulator (The Magstim Company Ltd, Whitland, Dyfed, UK) with the coil positioned tangentially to the scalp. The handle was pointed upwards for the real stimulation and over the neck muscles for the sham stimulation [10]. We stimulated the cerebellar hemisphere ipsilateral to the more affected side (table in supplemental data). cTBS was delivered over the cerebellar hemisphere with the coil placed 1 cm below and 3 cm laterally from the inion. Bursts of three pulses at 80% of AMT were delivered at 50 Hz and repeated every 200 ms in a continuous train lasting 40 s, yielding a total of 600 pulses according to the method used in previous studies [8].

A monophasic Magstim stimulator (The Magstim Company Ltd, Whitland, South West Wales, UK) connected to a figure-of-eight coil was used to deliver single transcranial magnetic stimulation (TMS) pulses over the FDI motor hot-spot to probe M1 excitability after cerebellar-cTBS. Twenty MEPs at 120% RMT intensities were collected before (T0), 5 min (T1) and 25 min (T2) after cerebellar cTBS (Supplementary data).

2.4. Electromyographic recordings

Electromyographic (EMG) and MEP recordings were performed through a pair of Ag/AgCl electrodes placed over the FDI muscle ipsilateral to the stimulated cerebellar hemisphere – to test AMT – and the FDI muscle contralateral to the stimulated cerebellar hemisphere – to test M1 excitability before and after cTBS – in a belly-tendon fashion. (See Supplementary data)

2.5. Statistical analysis

One-way ANOVA was run to evaluate differences in baseline STDT (absolute values) between PD patients OFF therapy, PD patients ON therapy and healthy subjects.

A repeated measures ANOVA with factors STIMULATION (two levels: real vs. sham), HAND (two levels: target hand vs. non-target hand) and TIME (two levels: T1 and T2) was used to analyze changes in STDT values (expressed as a percentage of the STDT values at T0) in patients with PD in the OFF therapy assessment. Further repeated measures ANOVA with factors THERAPY (two levels: ON vs. OFF), HAND (two levels: target hand vs. non-target hand) and TIME (two levels: T1 and T2) was used to analyze changes in STDT values (expressed as a percentage of the STDT values at T0) in the 8 patients who underwent the ON and OFF therapy assessment. Between group repeated measures ANOVA with factors HAND (two levels: target hand vs. non-target hand) and TIME (two levels: T1 and T2) was used to evaluate changes in STDT values (expressed as a percentage of the STDT values at T0) in PD patients and healthy subjects. Paired sample T test was used for the post-hoc analysis.

Between-group repeated measures ANOVA with factor TIME (two levels: T1 and T2) was performed to analyze percentage changes in MEP size induced by cerebellar cTBS in PD patients OFF therapy and in healthy subjects. Holm's correction for multiple comparisons was applied to disclose false significance. $P < 0.05$ indicated statistical significance.

3. Results

One-way ANOVA, used to compare baseline absolute STDT values in PD patients OFF and ON therapy and in healthy subjects, revealed a significant effect of factor group ($F = 6.12$, $p = 0.006$). Post-hoc showed that STDT values were higher when patients were compared with healthy subjects ($p = 0.006$) as well as were slightly higher when patients were OFF therapy than ON therapy ($p = 0.08$) (Fig. 1).

3.1. Effects of cerebellar real and sham cTBS on STDT values at baseline in OFF patients

Repeated measures ANOVA showed a significant STIMULATION and HAND interaction ($F = 11.16$, $p = 0.004$) and HAND and TIME interaction ($F = 6.35$, $p = 0.02$). In PD patients in the OFF state, real but not sham cerebellar cTBS reduced STDT values only in the hand ipsilateral to the stimulated cerebellar hemisphere (Table 1 and supplementary data).

3.2. Effects of cerebellar real cTBS on STDT values in patients ON and OFF therapy and in healthy subjects

Repeated measures ANOVA showed a significant THERAPY and HAND interaction ($F = 6.67$, $p = 0.03$). Post-hoc showed that in the PD patients who underwent both ON and OFF therapy

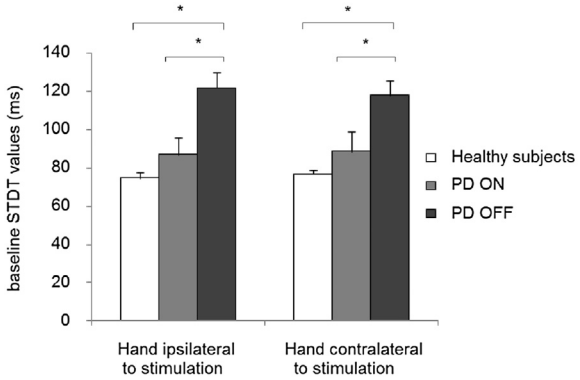

Fig. 1. Somatosensory temporal discrimination threshold (STDT) expressed in milliseconds tested on the hand ipsilateral and contralateral to the stimulated cerebellar hemisphere in patients with Parkinson's disease on medication (PD ON), off medication (PD OFF) and healthy subjects.