Neuroscience Letters 628 (2016) 1–9

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

Single session intermittent theta-burst stimulation on the left premotor cortex does not alleviate freezing of gait in Parkinson's disease

Céline Tard[a,b,c,*], Hervé Devanne[c,d], Luc Defebvre[a,b], Arnaud Delval[a,c]

[a] Université de Lille, U1171 troubles cognitifs, dégénératifs et vasculaires, Lille, France
[b] Service de Neurologie et Pathologie du mouvement, Hôpital Roger Salengro, CHU de Lille, Lille, France
[c] Service de Neurophysiologie Clinique, Hôpital Roger Salengro, CHU de Lille, Lille, France
[d] Université du Littoral Côte d'Opale, Calais, France

HIGHLIGHTS

- rTMS over Pre-motor cortex could modify FoG in PD.
- FoG occurrence, gait initiation and continuous gait were recorded.
- iTBS of the left premotor cortex does not alleviate FoG in PD.

ARTICLE INFO

Article history:
Received 20 March 2016
Received in revised form 16 May 2016
Accepted 27 May 2016
Available online 3 June 2016

Keywords:
Transcranial magnetic stimulation
Non-invasive brain stimulation
Prefrontal cortex
Motor area

ABSTRACT

Objective: To investigate the efficiency of intermittent theta-burst stimulation (iTBS) to alleviate the symptoms of freezing of gait (FoG) in Parkinson's disease (PD).
Methods: We performed a cross-over, sham-controlled study of patients with severe PD, bilateral motor signs and debilitating, severe FoG, that was levodopa-sensitive but not controlled by optimal dopatherapy. We applied iTBS to the left premotor cortex and measured FoG, gait initiation and continuous gait, before and immediately after the iTBS session. All patients received sham and true iTBS with a one-week interval and in randomized order.
Results: 15 patients were included in the study. Recordings were performed under usual medication and all patients always showed unresponsive freezing. The pre- and post-stimulation gait trajectories did not differ in terms of the mean trajectory completion time or the percent time with FoG. The percent time with FoG was 6% greater after sham stimulation and 3% lower after iTBS ($p > 0.05$). Visual cueing modified gait initiation and continuous gait but these latter were not influenced by rTMS.
Conclusions: The present study provides Class I evidence that iTBS of the left premotor cortex does not alleviate FoG in PD.

1. Introduction

Freezing of gait (FoG) in Parkinson's disease (PD) is a very disabling symptom that is rarely completely alleviated by levodopa therapy [1]. This symptom affects about 77% of patients in PD [2] and increases the risk of falls and injuries [3]. Patients with FoG present gait abnormalities such as reduced step length, step time and length asymmetry and elevated variability (for a review, see [4]). However, FoG often occurs when gait is not stereotyped, e.g. during turns or when walking through a narrow passage [5]. Gait initiation is also a typical trigger for FoG in general and "akinetic freezing" in particular [6], i.e. the occurrence of a motor block (and thus delayed motor initiation) despite voluntary effort and the intention to initiate movement [7]. There are several possible explanations for this phenomenon, including both cognitive aspects (interference impairment and difficulty in selecting a motor program) and motor aspects (decoupling between the motor program and motor execution) [8]. Management of FoG is difficult and despite the use of optimal medical and non pharmacological interventions, most patients continue to experience FoG [9].

* Correspondence to: Neurologie et Pathologie du Mouvement, Neurologie A, Hôpital Salengro, Centre Hospitalier Universitaire, F-59037 Lille cedex, France.
E-mail address: arnaud.delval@chru-lille.fr (C. Tard).

http://dx.doi.org/10.1016/j.neulet.2016.05.061
0304-3940/

Clinical evaluation remains the gold standard to quantify FoG [10]. Gait initiation is also of particular interest when seeking to study all the aspects that lead to FoG [11]. Motor preparation can be monitored by measuring anticipated postural adjustments (APAs) that can be influenced by attentional or cognitive factors and are a hallmark of FoG. For example, FoG can features brief episodes of alternate leg trembling (corresponding to multiple APAs) and delayed step initiation [12]. Step initiation can be generated externally by visual stimuli (i.e. cues) that minimize dependency of the basal ganglia and help to recruit compensatory cortical networks [13]. The orientation processes induced by an instruction concerning the side of step initiation (left or right) have been relatively well characterized [14] and are related to APA errors [15,16]. Taken as a whole, these findings show that during a visually-cued step initiation task, APAs are relevant markers for motor selection, program and execution and the coupling between these processes. During cued step initiation, the patient has to commit to voluntary action and adjust the movement to suit the external circumstances (e.g. designation of the leg used for step initiation); this creates a potential conflict and reproduces the conditions of FoG (with jamming of the system) [8]. Even for continuous gait, it is well documented that PD patients rely more on visual feedback to control balance and locomotion than healthy subjects do [17]. Cueing gait on a treadmill (using strips) is then beneficial for patients with FoG [18]. As when the subject has to integrate external stimuli and adjust his/her step speed, duration or length accordingly (referred to as "modulated gait" [19]), the premotor cortex (PMc) [19] appears to be a key element in the coordination of the lower limb muscles [20,21].

The PMc is known to be hypoactive in PD patients with FoG [22,23]. The frontal cortex appears to be involved in the integration of external stimuli and the adaptation of step parameters [24] and the PMc particularly is important for stimulus-driven action. The left PMc [25–28] may be strongly involved in motor selection as a function of attention orientation [29]. Overlap with the frontal eye field also explains the left PMc's particular role in perception-action coupling via the frontoparietal network [21,27,30,31]. Lastly, the frontoparietal network's role and the PMc's involvement in visually guided motor selection in humans have been evidenced by studies of reaching tasks with upper limb movements [32–38].

Repetitive transcranial magnetic stimulation (rTMS) is a useful tool for inducing temporary changes in brain cortical excitability [39] The rTMS train affects cortical networks during stimulation and for about one hour afterwards [40]. Moreover, rTMS is able to modify the excitability of local interneurons (a local effect) and induce changes in the excitability of spatially distant but functionally interconnected cortical areas (a network effect) [41]. For instance, high-frequency rTMS over the PMc was able to increase the excitability of the ipsilateral primary motor cortex [36]. The striatum may also be involved downstream [42]. In a paradigm of motor execution or selection with the upper limb, low-frequency rTMS (decreasing cortical excitability) of the left PMc was associated with a deterioration in performance [43].

The primary objective of the present study was to establish whether or not the modulation of left PMc excitability by rTMS would alleviate FoG.

The secondary objectives were: (i) to determine whether or not intermittent theta burst stimulation (iTBS, a type of rTMS, which reportedly increases neuronal excitability [44,45]) over the left PMc could influence APAs for visually driven step initiation. (ii) to determine whether iTBS could influence standard (non-cued) locomotion and/or visually cued locomotion.

In view of the above observations, we hypothesized that rTMS on the PMc could alleviate FoG and modulate visually cued gait initiation in parkinsonian freezers by reducing abnormal APAs. Moreover, iTBS over the left PMc could influence standard (non-cued) locomotion and/or visually cued locomotion. In fact, patients with FoG present gait abnormalities such as reduced step length, step parameter asymmetry and elevated step parameter variability. Hence, we expected to see (i) an improvement in kinematic spatiotemporal parameters in freezers during visually cued gait (vs. non-cued gait) and (ii) an improvement in these parameters after iTBS (vs. pre-iTBS gait) under cued conditions.

2. Methods

2.1. Subjects

Patients with PD diagnosed according to Gibb's criteria [46] were enrolled from the active case file of the Movement Disorders Department at Lille University Hospital (Lille, France) (Table 1). The patients were selected on the basis of their answer to item 3 of the FoG questionnaire [47]. To ensure that FoG episodes were levodopa-sensitive, we looked at the levodopa acute administration test in each patient's medical records and confirmed these data by the observation of motor fluctuations. To ensure that FoG was not controlled by medication, we asked patients to perform 540° turns to the left and to the right (at normal and maximum speeds) when they were in the "on" state (i.e. while taking their usual medications). Only patients with clinically confirmed, treatment-refractory "off" FoG (despite having a stable medication regimen for at least the previous 3 months) were eligible for inclusion.

The exclusion criteria included the inability to walk alone, the use of deep brain stimulation, the presence of neurological disorders other than PD, ongoing major depression, epilepsy, intracranial (cochlear) or cardiac metallic implants [48].

The study was approved by the local independent ethics committee (*CPP Nord-Ouest IV*, Lille, France; reference 13/41, n°2013-A00737-38) and promoted by Lille University Hospital.

2.2. Experimental design

All participants were evaluated before the iTBS session (the "pre" measurement) and immediately after the session (the "post" measurement). For each patient, the active and sham sessions were performed in a random order, at the same time of day and at a one-week interval. The participant was blinded to the active vs. sham nature of the session. In order to accentuate intracortical facilitation, we applied the iTBS with biphasic, normal current (anteroposterior) [44,45].

2.2.1. FoG evaluation

The main efficacy criterion was the percent time with FoG during a standardized FoG trajectory comprising gait initiation, turning (360- and 540-degree turns at the preferred speed and at maximum speed), walking through a narrow passage and dual-tasking (walking while counting backwards in threes) [5]. The trajectories were filmed with a video camera. Offline, two raters (AD and CT) determined the completion time and the time with FoG for each part of the trajectory. The raters were blinded to the stimulation condition (sham vs. iTBS) and the sequence ("pre" vs. "post" measurement).

2.2.2. The step initiation task

The patient stood on a force platform (the OR6 from AMTI, Watertown, MA, USA) and had to initiate a step as soon as he/she saw a visual stimulus on a screen placed 2 m in front of him/her. A vertical arrow indicated that the patient could freely choose the starting foot (referred to as the execution condition or simple reaction time (RT) task), whereas an horizontal arrow pointing to the left or the right indicated the starting foot (referred to as the selection condition or choice RT task). Thirty trials were performed for each condition at each session, with 10 trials for the execution con-