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Bilateral low frequency rTMS of the primary motor cortex may not be a suitable treatment for levodopa-induced dyskinesias in late stage Parkinson's disease

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ABSTRACT

Background: In late stage Parkinson patients there is an unmet need for new treatments to adequately control motor complications, especially dyskinesias. In several preliminary studies, it has been suggested that applying unilateral low-frequency repetitive transcranial magnetic stimulation (LF rTMS), delivered at the primary motor cortex (MC) or the supplementary motor area (SMA), may reduce levodopa-induced dyskinesias (LID), either in a single or a multiple session stimulation protocol. In our current clinical research, we examined whether single or multiple (accelerated) sham-controlled bilateral LF rTMS session(s) applied to the primary motor cortices are able to reduce levodopa-induced dyskinesias in patients with advanced Parkinson's disease.

Methods: During a levodopa challenge test, we first investigated the effect of a single sham-controlled session of LF rTMS (1 Hz) to both left and right primary motor cortical areas on dyskinesias and motor function in nine late-stage Parkinson patients. In a second study, patients were assigned to a five day sham-controlled bilateral motor cortex cross-over accelerated LF rTMS protocol and effects on dyskinesias, motor and executive function and emotional status were assessed.

Results: We found no significant clinical change in levodopa-induced dyskinesias and motor function with either stimulation protocol.

Conclusions: One or multiple bilateral LF rTMS session(s) applied to the primary motor cortex were unable to reduce levodopa-induced dyskinesias in late-stage Parkinson patients.

1. Introduction

The management of levodopa-induced dyskinesias (LID) remains a huge challenge in late-stage Parkinson's disease (PD). Modifying dopaminergic treatment and/or adding anti-dyskinetic agents, such as amantadine or clozapine, can provide a relief in some cases, but this is mostly insufficient and treatment is limited due to the occurrence of intolerable side effects. Some patients with levodopa-induced dyskinesias can benefit from bilateral subthalamic deep brain stimulation (DBS) but the inclusion criteria are strict and a substantial amount of patients do not qualify [1].

The mechanisms underlying these dyskinesias are still not fully understood. A single photon emission tomography study measuring regional cerebral blood flow found a relationship between LID and hyperactivity of primary and associated motor cortices, which may be due to excessive disinhibition of thalamocortical neurons [2]. In normal control subjects, motor cortex excitability can be decreased by low-frequency repetitive transcranial magnetic stimulation (LF rTMS) when applied directly over the motor cortex [3], or indirectly when delivered to the cerebellum modulating cerebello-thalamocortical pathways [4].

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In PD patients, a single or multiple session(s) of LF rTMS applied to the supplementary motor area (SMA) through one central midsagittal coil, or multiple unilateral sessions to the primary motor cortex (MC) (for review see Table 1), and cerebellar continuous theta burst stimulation (cTBS), a novel TMS technique able to decrease excitability of the underlying cortex [5], all were reported to transiently reduce LID [6–11].

In spite of the beneficial outcomes the LF rTMS effect on LID seems rather moderate and transient. In addition since dyskinesias are seldom strictly unilateral, the aim of this current study was to determine whether one single or multiple bilateral accelerated sham-controlled LF rTMS session(s) applied to the primary motor cortex could potentiate this effect and reduce LID. Since some preliminary studies suggest a possible beneficial effect of LF rTMS on depression and executive functions in Parkinson's Disease [12,13], along with safety, we also assessed the effect of LF rTMS on executive function and mood as secondary outcome measures. We expected that the bilateral LF procedures would be safe and would not evoke cognitive or psychiatric problems. We hypothesized that accelerated real LF treatment and not the single sessions or sham treatment would result in meaningful clinical decreases in LID.

2. Methods

2.1. Study population

Fifteen patients with diagnosis of idiopathic Parkinson's disease according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria [14] were enrolled. Inclusion criteria were: (a) Hoehn and Yahr scale score of at least 2 in OFF; (b) treatment with levodopa for at least 1 year, add-on treatment with a dopamine agonist and/or entacapone and/or a MAO-B inhibitor is permitted; (c) the presence of bothersome LID (item 33 of Unified PD Rating Scale, UPDRS $\geq$ 2) during >25% of waking hours (item 32 of UPDRS $\geq$ 2); (d) an optimal and stable medication dose for at least 4 weeks preceding inclusion; (e) no evidence of dementia according to the DSM-IV criteria and (f) no contra-indication for rTMS. Nine late-stage PD patients were included in the single session and six in the multiple session study. One patient participated in both LF rTMS protocols. In order to avoid carry-over effects, a time window of at least 6 months was respected between the 2 stimulation protocols. Patient characteristics for both studies are listed in Table 2.

The Ethics Committee of UZ Brussel approved the study, and written informed consent was obtained from all patients. Treatment remained unchanged throughout the study period.

2.2. Single session stimulation protocol

2.2.1. Clinical assessment

To determine patient's motor symptoms and dyskinesia scores, we used a levodopa challenge test. After a 12-h overnight food and medication withdrawal, patients received 125% of their morning levodopa equivalent dose as a soluble immediate release levodopa/benzeraside formulation. UPDRS motor scores were obtained by a blinded rater prior to and 30, 60, 90 and 120 min after levodopa intake (T_0, T_{30}, T_{60}, T_{90} and T_{120}). Patients were seated in a chair and were videotaped.

Two independent raters, blinded to the LF rTMS procedure, video-rated dyskinesias using the Modified Abnormal Involuntary Movement Scale (mAIMS) at the same above mentioned time points [15]. After complete relaxation and during a mental activation task (counting backwards from 100 skipping two digits), the worst observed dyskinesias were scored in seven body parts (each limb, face, neck, trunk) on a 5-point scale (0 = absence to 4 = severe). Consensus scores were generated comparing both raters' individual scores.

This levodopa challenge test protocol was repeated twice in each patient with at least one week interval between sessions. Bilateral sham and motor cortex LF rTMS were applied in a randomized order in each individual patient.

2.2.2. Single session rTMS stimulation protocol

In order to avoid dyskinesia-induced head movements potentially compromising correct MC targeting during pulse delivery, we decided upon a simultaneous sham-controlled bilateral LF rTMS stimulation protocol lasting 16 min, starting immediately after

Table 1
Overview of inhibitory rTMS/cTBS on frontal cortical area's for the treatment of LID in Parkinson's disease.

Number of patients	Uni- or bilateral	rTMS	Design	Target	Number of sessions	Dyskinesia scale	Testing condition	Outcome on dyskinesias	Reference
8	Bilateral 1 central coil	1 Hz	Cross-over Sham controlled	SMA	Single	AIMS	Apomorphine infusion	Improvement	Koch et al. 2005 [8]
10 10	Bilateral 1 central coil	1 Hz	Cross-over Sham controlled	SMA	Single Multiple (5)	AIMS Diary	Levodopa challenge test Levodopa challenge test	Improvement No change	Brusa et al. 2006 [6]
6	Unilateral	1 Hz	No sham	MC	Multiple (10)	CAPSIT-PD LF-ADLS Diary	Levodopa challenge test	Improvement	Wagle-Shukla et al. 2007 [11]
10	Unilateral	1 Hz	Cross-over Sham controlled	MC	Multiple (4)	CDRS Diary	Usual treatment	Improvement	Filipovic et al. 2009 [7]
17	Bilateral 1 central coil	1 Hz	Parallel group Sham controlled	SMA	Multiple (10)	AIMS VAS	Levodopa challenge test	Improvement	Sayin et al. 2014 [10]
8 8	Unilateral	cTBS	Cross-over Sham controlled	IFC MC	Single	AIMS	Levodopa challenge test	Improvement No change	Cerasa et al. 2015 [20]
9 6	Bilateral 2 seperate coils	1 Hz	Cross-over Sham controlled	MC	Single Mutiple (10) Accelerated	AIMS UPDRSIV PDYS-26	Levodopa challenge test Usual treatment	No change No change	Current study

AIMS [15]; CAPSIT-PD dyskinesia scale [28]; LF-ADLS: Lang-Fahn Activities of Daily Living Scale [29]; CDRS: Clinical Dyskinesia Rating Scale [30]; PDYS-26 [16]; VAS Visual Analog Scale.
cTBS continuous Theta Burst Stimulation; MC Motor Cortex; SMA Supplementary Motor Area; IFC Inferior Frontal Cortex.