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Slow (1 Hz) repetitive transcranial magnetic stimulation (rTMS) induces a sustained change in cortical excitability in patients with Parkinson's disease

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ABSTRACT

Objective: Low-frequency (⩽1 Hz) rTMS (LF-rTMS) can reduce excitability in the underlying cortex and/or promote inhibition. In patients with Parkinson's disease (PD) several TMS elicited features of motor corticospinal physiology suggest presence of impaired inhibitory mechanisms. These include shortened silent period (SP) and slightly steeper input–output (I–O) curve of motor evoked potential (MEP) size than in normal controls. However, studies of LF-rTMS effects on inhibitory mechanisms in PD are scarce.

Objective: In this companion paper to the clinical paper describing effects of four consecutive days of LF-rTMS on dyskinesia in PD (Filipović et al., 2009), we evaluate the delayed (24 h) effects of the LF-rTMS treatment on physiological measures of excitability of the motor cortex in the same patients. There are very few studies of physiological follow up of daily rTMS treatments.

Methods: Nine patients with PD in Hoehn and Yahr stages 2 or 3 and prominent medication-induced dyskinesia were studied. This was a placebo-controlled, crossover study, with two treatment arms, "real" rTMS and "sham" rTMS (placebo). In each of the treatment arms, rTMS (1800 pulses; 1 Hz rate; intensity of the real stimuli just-below the active motor threshold) was delivered over the motor cortex for four consecutive days. Motor cortex excitability was evaluated at the beginning of the study and the next day following each of the four-day rTMS series (real and sham) with patients first in the practically defined "off" state, following 12 h withdrawal of medication, and subsequently in a typical "on" state following usual morning medication dose.

Results: The SP was significantly longer following real rTMS in comparison to both baseline and sham rTMS. The effect was independent from the effects of dopaminergic treatment. There was no difference in MEP size, rest and active motor threshold. The I–O curve, recorded from the relaxed muscle, showed a trend towards diminished slope in comparison to baseline, but the difference was not significant. There was no consistent correlation between prolongation of SP and concomitant reduction in dyskinesia following real rTMS.

Conclusions: Low-frequency rTMS delivered over several consecutive days changes the excitability of motor cortex by increasing the excitability of inhibitory circuits. The effects persist for at least a day after rTMS.

Significance: The results confirm the existence of a residual after-effect of consecutive daily applications of rTMS that might be relevant to the clinical effect that was observed in this group of patients and could be further exploited for potential therapeutic uses.

1. Introduction

A number of studies have shown that rTMS can modulate the excitability of the motor cortex beyond the period of stimulation. Increased excitability usually occurs if higher frequencies (above 5 Hz) are used (Pascual-Leone et al., 1994), while decreases in excitability have been shown not only in the motor cortex, but also in the visual cortex, if low-frequency (⩽1 Hz) trains are given for 5 min or more (Chen et al., 1997; Boroojerdi et al., 2000; Cantello et al., 1991; Maeda et al., 2000; Muellbacher et al., 2000). The mechanism involved is not known, but the stimulation rate is similar to that producing long-term depression in animal studies (reviewed in Post et al., 1999; and Ziemann, 2004). In addition, the

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effects of rTMS are not restricted only to the point of stimulation, but can be also detected at distant though connected sites within the same functional circuit both at cortical and subcortical levels (Fox et al., 1997; Gerschlager et al., 2001; Siebner et al., 2003).

There are reports of a beneficial clinical effect of low-frequency rTMS (LF-rTMS) on diseases with increased cortical excitability such as focal hand dystonia (Siebner et al., 1999, 2003) and epilepsy (Tergau et al., 1999; Fregni et al., 2006). There is also evidence that the physiological effect in patients may even be stronger than that seen in healthy subjects (Siebner et al., 1999, 2003). In patients with Parkinson's disease (PD) several TMS elicited features of motor corticospinal physiology suggest that inhibitory mechanisms are impaired. These include shortened silent period (SP) and slightly steeper input–output (IO) curves of motor evoked potential (MEP) size than in normal controls – changes that are typically ameliorated by levodopa/dopaminergic medication in concert with relief of clinical symptoms (reviewed in Cantello et al., 2002; and Lefaucheur, 2005).

We have recently reported a beneficial clinical effect of LF-rTMS on medication-induced dyskinesia in PD (Filipović et al., 2009). As a part of that study we also recorded neurophysiological parameters of cortical excitability. This provided an opportunity to test whether in a group of patients with a condition characterized by reduced cortical inhibition, LF-rTMS applied over motor cortex for several consecutive days is able to induce a sustained and measurable change in the excitability of the motor cortex and in particular increase the excitability of inhibitory mechanisms.

2. Methods

2.1. Design of study

This was a placebo-controlled, single-blinded, crossover study, with each treatment arm lasting 1 week, and each period of treatment separated by a minimum of 2 weeks (Fig. 1). The two treatment arms consisted of four successive daily visits (from Monday to Thursday) each, when either "real" rTMS or "sham" rTMS (placebo) were delivered. The same type of rTMS was used throughout successive 4 days and the order of the treatments was randomly assigned. The time of day for treatment visits was kept constant for each patient.

The baseline evaluation session (*e0*) was during a week preceding the first treatment session. The treatment evaluation sessions (*e1* and *e2*) were on the first Friday after the end of the each rTMS series (i.e. next day after the last rTMS session of each series), respectively. At each evaluation session, a set of clinical and neurophysiological tests was carried out with patients in so called practically defined 'off' state, following at least 12 h (overnight) refrain from anti-parkinsonian medication. Following this, a second set of tests was carried out once patients achieved a stable "on" state, after taking their usual morning medication dose. Since the study was designed to test the effect of rTMS on medication-induced dyskinesia in Parkinson's disease, each evaluation visit also included a clinical assessment. Patients were examined using Unified PD Rating Scale (UPDRS) Motor Section (Part 3). In addition, in the "on" state, dyskinesias were rated off-line from videotapes using the Clinical Dyskinesia Rating Scale (CDRS) developed by Hagell and Widner (1999). The most severe involuntary movements observed are scored from 0 (none) to 4 (extreme), in each of the seven body areas: face, neck, trunk, and four extremities, separately for hyperkinesias (i.e., choreic movements) and dystonia. The clinical results have been already published (Filipović et al., 2009). Sessions were always organised in the morning hours at the earliest convenience to the patient.

2.2. Patients

Nine right-handed, non-demented patients with idiopathic PD, satisfying United Kingdom Parkinson's Disease Society Brain Bank criteria (Gibb and Lees, 1988), manifesting obvious dyskinesias present most of the day were studied. They were recruited through the outpatient department of the Frenchay Hospital (Bristol, UK). All patients were on the fixed dose of their usual anti-parkinsonian medication for at least 1 month prior to starting the study until the end of the study. Informed consent was obtained from each patient according to the Declaration of Helsinki, and study protocol was approved by the Frenchay Local Research Ethics Committee. The details of patients' characteristic are presented on Table 1. They were essentially the same patients as in Filipović et al. (2009) paper, but without one patient whose neurophysiological data had to be discarded because inability to relax adequately due to excessive dyskinesias in the "on" phase.

2.3. Transcranial magnetic stimulation (TMS)

All transcranial magnetic stimulations, either single or repetitive, were performed with Magstim Rapid Transcranial Magnetic Stimulator (Magstim Company, Dyfed, UK). For "real" TMS a standard Magstim's 70 mm figure-of-eight coil was used. The "sham" rTMS was carried out with Placebo Coil (Magstim Company) that

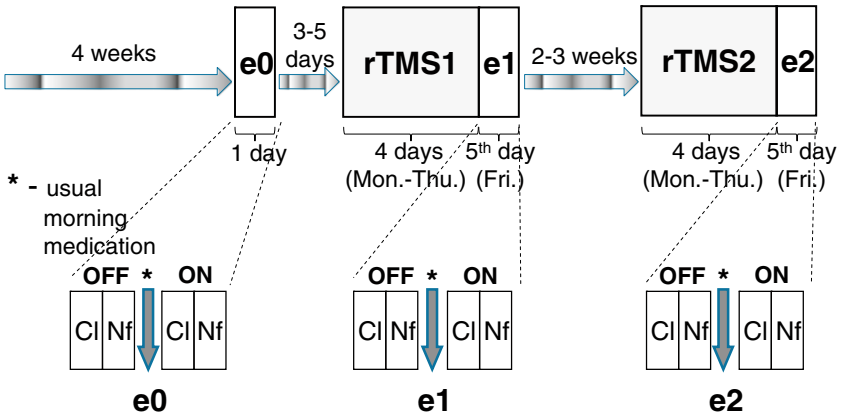

Fig. 1. Design of the study. The rTMS, either real of sham (placebo), was delivered in two four-day (from Monday to Thursday) long series (rTMS1 and rTMS2). Within a week before the first rTMS treatment series, the first/baseline evaluation session (*e0*) was scheduled. Subsequent evaluation sessions (*e1* and *e2*) were on the next day after the last rTMS session (i.e. Friday) of the each rTMS series, respectively. At each evaluation session, two identical sets of clinical (Cl) and neurophysiological (Nf) tests were carried out, first with patients in practically defined 'OFF' state, and then once patients achieved a stable "on" state, after taking their usual morning medication dose.