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Safety study of 50 Hz repetitive transcranial magnetic stimulation in patients with Parkinson's disease

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ABSTRACT

Objective: Repetitive transcranial magnetic stimulation (rTMS) has shown promising results in treating Parkinson's disease (PD), but the best values for rTMS parameters are not established. Fifty Hertz rTMS may be superior to $\leqslant$ 25 Hz rTMS investigated so far. The objective of this study was to determine if 50 Hz rTMS could be delivered safely in PD patients since current safety limits are exceeded.
Methods: Fifty Hertz rTMS was applied with a circular coil on the primary motor cortex (M1). Stimulation intensity was first tested at 60% rest motor threshold [RMT] and 0.5 s train duration and then increased in 0.5 s steps to 2 s, and by 10% steps to 90% RMT. Multi-channel electromyography (EMG) was recorded to control for signs of increasing time-locked EMG activity including correlates of the spread of excitation and after-discharges, or an increase of M1 excitability. Pre- and post-50 Hz rTMS assessments included EEG, Unified Parkinson Disease Rating Scale (UPDRS), Grooved Pegboard Test, Serial Reaction Time Task (SRTT), Folstein Mini-Mental Status Examination (MMSE) and Verbal Fluency to control for motor and cognitive side effects.
Results: Ten PD patients were investigated. Multi-channel EMG showed no signs of increased time-locked EMG activity including correlates of the spread of excitation and after-discharges, or increased M1 excitability in 9 patients. A PD patient with bi-temporal spikes in the pre-testing EEG had clinical and EMG correlates of spread of excitation at 90% RMT, but no seizure activity. Pre- and post-50 Hz assessment showed no changes. No adverse events were observed. Fifty Hertz rTMS was well tolerated except by 1 patient who wished to terminate the study due to facial muscle stimulation.
Conclusion: Fifty Hertz rTMS at an intensity of 90% RMT for 2 s appears safe in patients with PD, but caution should be taken for patients with paroxysmal EEG activity. For this reason, comprehensive screening should include EEG before higher-frequency rTMS is applied.
Significance: This is the first study to investigate safety of 50 Hz rTMS in humans.
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1. Introduction

High-frequency (>1 Hz) repetitive transcranial magnetic stimulation (rTMS) has been successfully applied as a potential therapy in Parkinson's disease (PD). A wide range of high-frequencies up to 25 Hz rTMS has been safely investigated in PD patients, and 25 Hz rTMS has shown improved gait which often only partially responds to dopaminergic therapy (Lomarev et al., 2006). Non-invasive brain stimulation using rTMS might represent a powerful addition to conventional therapy in PD. Twenty-five Hertz rTMS has been postulated to be superior to 10 Hz rTMS (Khedr et al., 2006), and, thus, higher-frequencies may yield a greater therapeutic effect. Before therapeutic effects of higher-frequencies up to 50 Hz rTMS, which are out of range of frequencies known to be safe (Wassermann, 1998), can be investigated, their safety must be established.

The purpose of this study was to test the safety of longer and higher-intensity 50 Hz rTMS of the motor cortex (M1) in PD patients which exceeds currently approved frequency and intensity limits for healthy subjects and to establish new safety guidelines for future higher-frequency rTMS therapeutic trials in PD.

The most serious side effect of high-frequency rTMS is the induction of a seizure. To minimize seizure risk, the study was

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designed to test the safety of 50 Hz rTMS by stepwise increasing intensity and duration while simultaneously monitoring for warning signs of an impending seizure. In addition, motor and cognitive tests were performed to exclude other potential adverse effects.

In establishing guidelines for the safe combination of rTMS frequency, intensity and train duration to stimulate the M1 in healthy subjects, we looked specifically for two phenomena suggestive for potentially dangerous increased cortical excitability: (a) brief EMG bursts (BEB) which persist after the rTMS train has ceased, and (b) spread of excitation (SE) to muscles not activated by single-pulse TMS during the 50 Hz rTMS train (Wassermann, 1998). BEB is considered an EMG correlate of an after-discharge in the EEG, which is a recognized sign of epileptic activity (Ajmone Marsan, 1972; Wassermann, 1998). SE has been observed preceding TMS-induced seizures (unpublished observation), but the mechanism is unknown. SE is postulated to indicate a breakdown of lateral inhibition in the cortex which might predispose to seizure generation (Pascual-Leone et al., 1993b, 1994). An alternative explanation is that "recruitment" of more proximal muscles with higher threshold than those of the hand occurs later when a certain "amount" of stimulation has been applied which could appear like a propagation of excitation. We also looked for increased MEP amplitudes in the target muscle to single pulse (supra-threshold) TMS between 50 Hz rTMS trains indicating increased M1 excitability which was previously documented after supra-threshold high-frequency rTMS (Pascual-Leone et al., 1994). At present, low-intensity 50 Hz rTMS by means of short bursts of 5–15 stimuli and triple-bursts repeated at 5 Hz (Theta-Burst Stimulation [TBS]) have only been investigated; these were safe in healthy subjects (Huang and Rothwell, 2004; Huang et al., 2005) and subsequently were applied in various disease conditions without reports of seizures or other adverse events.

2. Methodology

2.1. Study population

Ten patients (5 women and 5 men, mean age 62.6 ± 9.6 years, range 50–77 years, 9 right-handed and 1 ambidextrous) with mild to moderate PD (Hoehn and Yahr stage mean 2.3 ± 0.4 in "on" and 2.7 ± 0.3 in "off" medication state) were investigated (see Table 1). An eligible patient withdrew for personal reasons after signing the consent. Inclusion criteria were men and women aged 40–80 years with PD in a Hoehn and Yahr (HY) stage of 2–4 while "off" medication. The same inclusion criteria were used in a published 25 Hz rTMS trial (Lomarev et al., 2006) which would also be applied when selecting the target PD population for future rTMS trials. Baseline assessment included a detailed medical history, neurological examination and electroencephalography (EEG). Exclusion criteria were significant medical or psychiatric illness, dementia, pregnancy, history of seizures, epilepsy or epileptiform discharges in the EEG, concurrent use of tricyclic antidepressants, neuroleptics or other drugs with strong contraindications for rTMS because of their seizure threshold lowering potential. In contrast, drugs considered a relative contraindication according to a recent Consensus Conference and commonly used in PD such as selective serotonin re-uptake inhibitors ($n = 3$), anti-cholinergics ($n = 1$) or occasional antihistamines ($n = 1$) were not excluded.

We also excluded persons with pacemakers, brain stimulators, medication pumps or any type of metal object in the head including eyes except for dental appliances or fillings which might pose a physical hazard during rTMS.

The study was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board and the Food and Drug Administration (FDA) from whom an IDE was obtained. Written informed consent was obtained from all study patients.

2.2. Repetitive TMS procedures

Fifty Hertz rTMS of the left primary motor cortex (M1) was performed using a circular 90-mm coil connected to a Magstim Rapid magnetic stimulator (Whitland, Dyfed, UK). A coil holder (Magstim, Whitland, Dyfed, UK) kept the coil in a constant position with reference to the patient's head. The patient was seated in a comfortable chair in a reclined position; a head restraint was applied to prevent movements. The coil was placed at the optimal position ("hot spot") over the left motor cortex for eliciting motor-evoked potentials (MEPs) in the right abductor pollicis brevis (APB), the target muscle, while avoiding stimulation of proximal arm muscles as much as possible. The position of the stimulating coil was marked on a cap which was tightly fixed and monitored throughout the experiment. Patients were tested while on medication and asked to relax during the testing. We refrained from testing when patients experienced significant dyskinesias or tremor precluding fixed positioning or relaxation. Patients wore ear plugs during the testing.

Individual resting motor threshold (RMT) of the APB was determined to the nearest 1% of the maximum stimulator output and defined as the minimal stimulus intensity required to elicit MEPs of > 50 μV in at least 5 of 10 consecutive trials.

EMG activity was recorded from the target muscle APB, and also the extensor carpi radialis (ECR), biceps brachii (BB), and the deltoid (DEL) muscles of the right arm using silver–silver chloride surface EMG electrodes placed over these muscles in a belly-tendon montage. EMG amplitude was amplified using a conventional EMG machine (Nicolet Viking, Skovlunde, Denmark) and filtered with a bandpass between 100 and 2500 Hz. The signal was digitized at a frequency of 5 kHz and exported into a computer for further off-line analysis.

Table 1
Motor and cognitive tests before and after 50 Hz rTMS testing.

		Before (mean ± SD)	After (mean ± SD)	Change (median, range, in %)	*P*-value
MMSE		29 ± 1.1	29.4 ± 0.7	0, −3.5 to 7.1	0.26
Verbal Fluency	Letters	13.7 ± 4.2	14.4 ± 4.1	0.9, −15.2 to 41.4	0.41
	Category	19.5 ± 6	21.8 ± 6	−5.2, −21.2 to 114.3	0.86
SRTT	Visuomotor speed	691 ± 240 ms	645 ± 157 ms	2.5, −12.9 to 24.5	0.21
Grooved Pegboard	Right hand	117 ± 39.5 s	114.9 ± 38.7 s	−1.3, −22.2 to 32.8	0.96
	Left hand	127.9 ± 48.2 s	134 ± 63 s	−7.4, −26.1 to 19.7	0.44
Combined	Right hand	12.4 ± 5.2 s	11.7 ± 5.0 s	3.4, −13.9 to 19.3	0.09
Movement	Left hand	12.9 ± 5.6 s	12.4 ± 5.7 s	4.9, −30.9 to 13.7	0.09
10-m walk	Time	8.2 ± 1.7 s	7.7 ± 2 s	5.5, −6.7 to 23.3	0.11
	Steps	15 ± 2.7	14.7 ± 2.4	0, −7.7 to 12.5	0.33
UDPRS III	Motor score	21.1 ± 5.9	21.7 ± 7.4	−5.1, −16.7 to 27.8	0.48