Repetitive transcranial magnetic stimulation in patients with progressive supranuclear palsy: a pilot study

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Abstract

Progressive supranuclear palsy is a progressive neurodegenerative disorder for which no specific treatment is known at present. In this report we treated a small group of clinically diagnosed patients with rapid-rate repetitive transcranial magnetic stimulation of the motor cortex for five days. This resulted in modest and transient improvements, especially of the axial symptomatology. Side-effects were not reported.

Introduction

Progressive supranuclear palsy (PSP) is one of the atypical parkinsonian disorders. The clinical presentation is extremely variable (Lang, 2005), but supranuclear gaze palsy, axial rigidity and prominent and early falls stand out as the most characteristic features of classical PSP. In addition dysarthria and dysphagia, as well as cognitive and behavioral changes may occur early in the course of the disorder (Steele *et al.*, 1964; Maher and Lees, 1986; Collins *et al.*, 1995; Daniel *et al.*, 1995; Litvan *et al.*, 1996). In view of clinical heterogeneity, a diagnosis of PSP remains bothersome in many cases. A recent study reported an incorrect diagnosis of PSP in 43/180 clinically diagnosed patients (Josephs and Dickson, 2003). Another report suggested that the diagnostic accuracy for PSP at the time of death was relatively high, with a sensitivity of 84.2% and a specificity of 96.8% (Hughes *et al.*, 2002). To improve diagnostic accuracy, several sets of clinical and pathological diagnostic criteria were proposed (Collins *et al.*, 1995; Litvan *et al.*, 1996; Golbe *et al.*, 1988; Hauw *et al.*, 1994). At present, no specific therapy exists for PSP, but some patients will modestly and transiently respond to dopaminergic treatment (Lang, 2005; Constantinescu *et al.*, 2007).

In recent years, transcranial magnetic stimulation (TMS) has been used to investigate physiological alterations of the neural circuitry in parkinsonian disorders. In Parkinson's disease (PD), the motor cortex has shown excess excitability or reduced inhibition when tested at rest and defective or inadequately modulated activation during a voluntary output (Cantello *et al.*, 2002; Bares *et al.*, 2003). Likewise, motor cortex disinhibition was shown to be predominant in PSP patients (Kühn *et al.*, 2004). A recent TMS study, comparing PD with PSP and Multiple System Atrophy, suggested longer central motor conduction times and cortical silent period in PSP than in PD (Morita *et al.*, 2008). The authors attributed this difference to the histopathologically demonstrated degeneration and synapse loss in the motor cortex in PSP (Bigio *et al.*, 2001; Halliday *et al.*, 2005). Moreover, in contrast to PD patients, PSP patients fail to show an effect of TMS on reaction time, suggesting a problem in facilitation of reaction time, perhaps parallelling the reticular involvement in PSP (Molinuevo *et al.*, 2008). In addition, using TMS, an impairment of callosal integrity was suggested in PSP (Wolters *et al.*, 2004).

Repetitive TMS (rTMS) has been investigated as a potential treatment for a number of central nervous system disorders, including parkinsonism. The physiological background of rTMS is complex and the outcome is highly dependent upon the parameters used. A large variety of stimulation protocols was used for rTMS in PD, and both single session studies as well as multiple session studies were reported. Although in most studies high-frequency stimulation was used, a number of studies with low-rate stimulation have been published. Different outcome parameters were studied in all these reports. Consequently, the clinical outcome of these studies on the effects of rTMS in PD is variable (Cantello *et*

Table 1

Clinical and demographic data of patients

Pt nr/sex	Age (y)	Time since diagnosis (y)	supranuclear gaze palsy	frequent falls	dysarthria	dysphagia
1 F	60	3	+	+	+	+
2 M	77	2	+	+	+	+
3 M	75	2	+	+	+	-
4 M	70	5	+	+	+	-
5 M	66	2	+	+	+	+
6 M	72	7	+	+	+	+

Legend:
+ = present
- = absent
F = female
M = male

al., 2002; Khedr *et al.*, 2003; Edwards *et al.*, 2008). Moreover, concerns on potential placebo effects that further cloud the interpretation of previous studies have been raised (Strafella *et al.*, 2006; Kim *et al.*, 2008). At present, the therapeutic potential of rTMS in movement disorders and parkinsonism remains to be further explored.

The aim of the present pilot study is to explore the feasibility and clinical outcome of rTMS in a small group of PSP patients, using a rapid-rate stimulation protocol.

Patients and methods

Six patients fulfilling the NINDS-SPSP criteria for a clinical diagnosis of PSP (Litvan *et al.*, 1996) were included. All patients could be subtyped as the Richardson's syndrome subtype of PSP. Their clinical and demographic data are summarized in table 1.

In order to perform the rTMS procedure, first the site for motor cortex stimulation for both lower limbs was identified by defining the stimulation site resulting in a maximal motor evoked potential in the anterior tibial muscle. For this purpose a vertex coil was used. The motor threshold was defined as the minimal stimulator output current resulting in a motor evoked potential of at least 50μV in at least 5 of 10 trials. The rTMS procedure was performed using 10Hz stimulation at a stimulator output current of 80% of the motor threshold for 5 seconds, followed by 55 seconds of rest. This cycle was repeated 20 times in one single session, resulting in a total of 1000 pulses/session. The trial consisted of daily sessions for five consecutive days.

All patients were evaluated before the first session and directly following the final session by means of the subsections of the clinical rating scale for PSP (Golbe *et al.*, 2007) for bulbar exam, supranuclear ocular motor exam, limb exam and gait/midline exam.

One patient underwent the entire procedure 3 times with 4-week intervals, which allows to estimate reproducibility of the results.

As the number of patients is small only rough data will be presented. No formal statistical analysis was done.

Results

In 5/6 patients, the total score of the subsections improved after our rTMS procedure. The scores for the individual subsections are presented in fig. 1. It is clearly visible that the most prominent improvements were found on the gait/midline symptoms. Except for the discomfort of the stimulation no specific side-effects were found in the six patients of this study.

In addition to the measured improvements, patients also reported a subjective improvement of overall function and mobility, which was however short-lived. Reportedly, the improvements lasted for a period of only 2-3 days.

Repetition of the entire trial in one patient (pt 1) resulted in similar improvements at three different occasions (Fig. 2).

Discussion

Our preliminary findings suggest a potential benefit of rapid-rate rTMS in patients with PSP. Especially gait and midline symptoms, which are a major burden in this disorder, seemed to be potential targets for this therapeutic intervention.
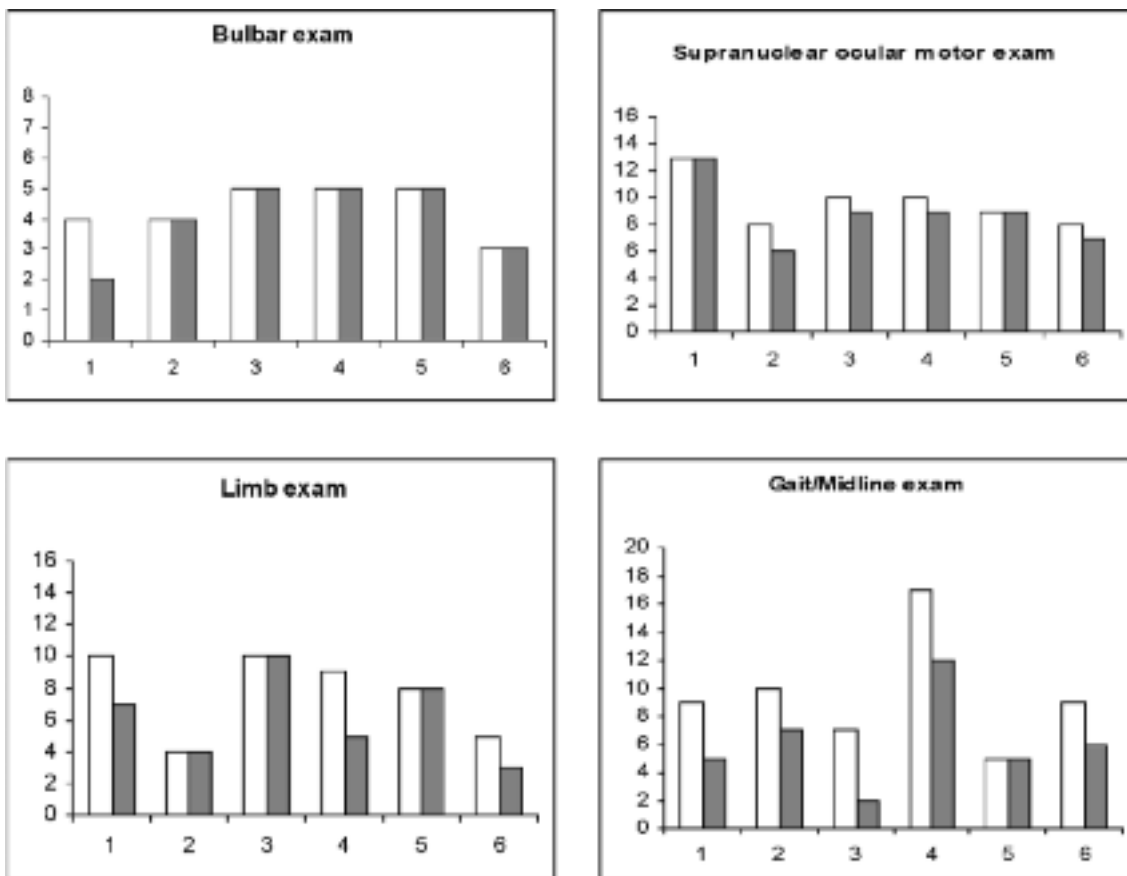
FIG. 1. — Individual scores for sections of the PSP clinical rating scale. White bars indicate scores before the trial, gray bars post-trial scores. The Y-axis indicates the maximum score per section.
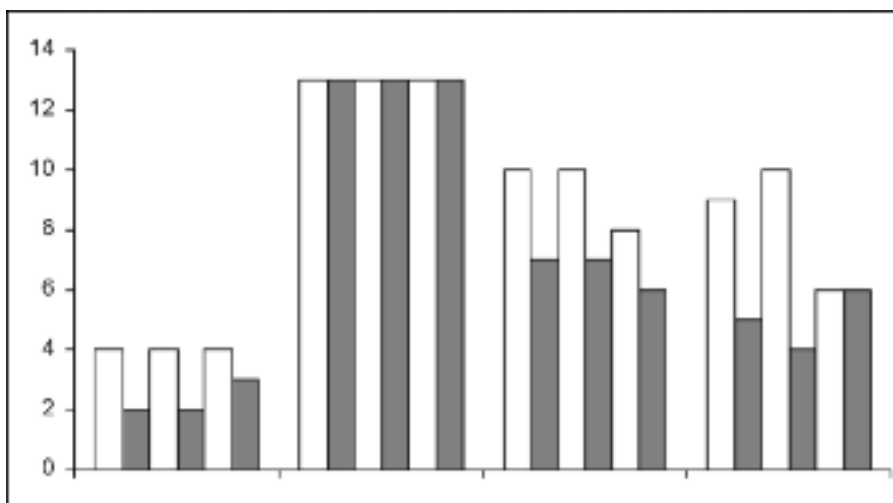

FIG. 2. — Results for three trials in pt 1. The interval between trials was at least two weeks. White and gray bars indicate pre- and post-trial evaluations. The four blocks demonstrate respectively bulbar exam, supranuclear oculor motor exam, limb exam and gait/midline exam.

The rTMS methodology used in the present study might have influenced or biased our findings. We deliberately targeted the lower limb motor area, as was done by Khedr *et al.* in their study on rTMS in PD (Khedr *et al.*, 2003), who also found improvements in gait in their patients. The use of a rapid-rate stimulation protocol was similar to the majority of other studies in PD, although the exact protocol used was adopted from a study on the effects of rTMS in neuropathic pain (Khedr *et al.*, 2005). From a physiopathological point of view, rapid-rate stimulation is believed to facilitate or disinhibit cortical activity. The interpretation of positive findings in our patients, as well as in the majority of studies with PD, is therefore not straightforward in view of the already decreased cortical inhibition in parkinsonian disorders. This remains a topic of debate (Cantello *et al.*, 2002).

In view of the small number of patients studied, and considering the absence of a sham-stimulation control, we cannot be entirely confident of the validity of our findings. Therefore, it would be worthwhile to conduct a new trial in a larger group and perhaps using a sham-stimulation controlled cross-over design.

Unfortunately, the benefits found seemed to be short-lived, which obscures the relevance in terms of long-term treatment. However, if our results could be confirmed, this would possibly open new therapeutic windows for patients with PSP. Hypothetically, the aim could be to translate transient positive results of rTMS trials to a more lasting result with chronic cortical stimulation. Although this remains speculative, the response to rTMS in chronic pain is already suggested to be predictive of the effect of chronic motor cortex stimulation (Cioni and Meglio, 2007). Chronic cortical stimulation has indeed been studied in patients with PD, and although the results were not entirely equivocal, there seems to be a consensus for a potential effect of chronic high-frequency extradural motor cortex stimulation on all cardinal signs of PD, including axial signs (Pagni *et al.*, 2005; Cioni, 2007; Cilia *et al.*, 2007). At present, these results are still awaiting further confirmation and elaboration. However, in view of the concerns on the effects of deep brain stimulation on mental functions in patients with PD, a recent study confirming the stability of neuropsychological function and an improved quality of life during chronic cortical stimulation is encouraging (Munno *et al.*, 2007). It remains to be established if PSP patients would also be potential candidates for such an invasive treatment.

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