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a preliminary study**

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# **Transcranial magnetic stimulation transiently reverses funding in Parkinson's disease: a preliminary report**

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## ABSTRACT

*Background and Purpose:* Amongst the impulse control disorders (ICDs) associated with dopamine replacement therapy in patients with Parkinson's disease (PD) is a repetitive complex stereotyped behaviour called punding. Disruption of the reciprocal loops between the striatum and structures in the prefrontal cortex (PFC) following dopamine depletion may predispose to these behavioural disorders in PD. We aimed at assessing the effects of transcranial magnetic stimulation (rTMS) over the dorsolateral PFC (DLPFC) on punding in PD. *Methods:* We used low-frequency (LF) rTMS in four PD patients presenting punding. *Results:* Punding was transiently reversed by LF rTMS of DLPFC without enhancing motor impairment. The effect was more sustained after right DLPFC rTMS. *Conclusions:* LF rTMS produces a transient beneficial effect in PD patients with punding, similar to that reported in PD patients with levodopa-induced dyskinesias. RTMS might have therapeutic potential for the treatment of punding and perhaps other ICDs in PD.

**Key words:** Parkinson's disease, punding, impulse control disorders, repetitive transcranial magnetic stimulation

## Introduction

In Parkinson's disease (PD), there is increasing evidence for disorders in the impulsive-compulsive spectrum, related to the disease itself, to the pharmacological management of the disease or to both. These disorders include dopamine dysregulation syndrome, with addictive and stereotyped behaviour, and impulse control disorders, such as pathological gambling, compulsive shopping, binge eating and hypersexuality. A phenomenologically distinct compulsive behavior known as punding (a complex stereotypical behaviour characterized by intense fascination for repetitive meaningless movements that is recognized by the patient as disruptive but associated with feeling of calmness/relief) has also been reported in PD patients under dopaminergic therapy [1-3]. Although the pathophysiology of underlying mechanisms is not fully understood, disruption of the reciprocal loops between the striatum and structures in the prefrontal cortex (PFC) following dopamine depletion is thought to predispose to these behavioral disorders in PD. The inferior frontal gyrus/dorsolateral PFC is important in shifting attention, which contributes to the ability to resist intrusive information such as thinking about drugs/behaviors [4]; subjects with ventromedial PFC lesions show characteristic deficits in planning, and often make decisions that lead to negative consequences [5]. On the other hand, the medial PFC innervates the striatum (in particular the nucleus accumbens and anteromedial caudate-putamen), and participates in the regulation of subcortical dopaminergic mechanisms [6,7].

Another major complication of long-term dopaminergic treatment of PD are dyskinesias. Clinical and preclinical studies suggest that chronic intermittent dopamine receptor agonist treatment induces dyskinesias and punding [8].

Transcranial magnetic stimulation (TMS), a non-invasive means of electrically stimulating neurons in the human cerebral cortex, is able to modify neuronal activity locally and at distant sites when delivered in series or trains of pulses [9]. Repetitive TMS (rTMS) can be applied as continuous trains of low-frequency (1 Hz or less) or bursts of higher frequency ( $\times$  1 Hz) rTMS; in general, low-frequency (LF) rTMS is thought to reduce, and high-frequency rTMS to enhance excitability in the targeted cortical region. In particular, slow rTMS, where 1 magnetic pulse is applied every second (1 Hz), delivered to the motor cortex can give rise to a lasting decrease in corticospinal excitability [10,11]. LF rTMS to the supplementary motor area was found to reduce levodopa-induced dyskinesia but only for up to 30 minutes [12].

A small open study of LF rTMS over motor cortex showed reduction of peak dose dyskinesia, which was measurable and significant a day after the last session [13]. Filipovic and colleagues [14] demonstrated the existence of residual beneficial clinical aftereffects of consecutive daily applications of LF rTMS on dyskinesias in PD.

The beneficial effects of LF rTMS on dyskinesias are thought to rely on the transient depression of synaptic excitability at cortical level or on the promotion of depotentiation at corticostriatal circuits. Based on this assumption, we hypothesized that inhibition of dorsolateral PFC (DLPFC) by LF rTMS may also modulate motor stereotyped behaviors in PD patients. DLPFC is a common target for rTMS experiments and therapeutic protocols; in this study we used DLPFC LF rTMS in four PD patients who showed funding.

## Methods

### Patients

We studied 4 patients with PD who develop funding. Demographic and clinical characteristics of the patients are shown in Table 1. The patients recognized that time spent on these activities was

excessive and inappropriate, but found it difficult to disengage from these activities, as he described them as ‘very soothing’, became irritated if they were interrupted and were sometimes frustrated by their inability to stop these behaviors.

All the patients were on dopaminergic medication, and were taking no other drugs that could affect cortical excitability.

Punding scale score [2,15] was carried out before (T0), 1 hour (T1), 12 hours (T2) and 24 hours (T3) after TMS examination. The self-report questionnaire survey [15] was adapted from Evans et al.'s [2] ‘Punding in Parkinson's Disease’. The adapted questionnaire was scored separately for each activity giving a value between 0 and 42, with higher scores indicative of punding.

At the same time the patients also completed the doubting and hoarding distress subscales of an obsessive-compulsive inventory (OCI) [16]. The psychopathological assessment also comprised the Hamilton Anxiety Scale [17] (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) [18].

The patients were also screened for other ICDs; all the patients only have punding behaviour.

The control group consisted of nine age-matched control subjects (mean years 65.2 years, range 59-71 years).

The patients and the control subjects provided informed consent before participation in the study, which was performed according to the recently updated safety and application guidelines [19] and approved by the Ethics Committee.

## **Transcranial magnetic stimulation**

Magnetic Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, UK) was used. The real rTMS was carried out using a standard Magstim figure-of-eight coil; the sham rTMS was carried out with a Placebo Coil System (Magstim Company). Three series of 600 stimuli at 1 Hz rate, with 1-minute breaks in between, were applied during each rTMS session (for a total of 1.800 stimuli, duration 32 minutes). The stimulator intensity was set to be just below the active motor threshold (AMT). AMT was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 200 V in 50% of 10 trials) during isometric contraction at about 20% maximum [20]. The DLPFC is a broad area; we used a site similar to that used by other research groups using TMS [21,22]. The coil was placed 5 cm anterior from the hand motor area on the left and right hemispheres and held parallel to the midsagittal line. The hand motor area was located by finding the lowest threshold spot for activating the contralateral FDI muscle.

The patients and the controls were blinded to the real vs sham therapy. Real rTMS with selected intensity did not induce muscle contractions in any of the patients. The patients and the controls were given real rTMS to the right DLPFC and the left DLPFC and a sham rTMS to the right DLPFC on separate days, with an intersession interval of 4 days.

The order of the rTMS treatments was randomly assigned and counterbalanced across subjects. The time of day for treatment visits was kept constant for each patient.

The primary outcome analyses were the changes of the Punding scale score and of the OCI distress rating scores induced by rTMS, while secondary outcome measures analysis included changes in HAM-A and HAM-D scores.

## **Statistical Analysis**

In order to assess whether the test scores of the patients were statistically different from those of the control group, we performed a two-samples t-test for the scores at time T0. As for the effect of

rTMS stimulation, for each time of examination, we used a two-samples t-test for the score differences with respect to time T0 of the 4 patients against the 9 controls. The mean score difference of the patients revealed in which direction (if any) the rTMS affected the patients' score (either by increasing or decreasing it). p-value < 0.05 was taken as the significant threshold for all individual and multiple comparisons. We computed also the effect sizes and power for all individual comparison.

This analysis was performed for each of the 6 test scores and is based on a normality assumption on the distribution of the scores. In order to control for non-normality, we replicated the analysis via the non-parametric Mann-Whitney tests.

Finally, we investigated the effect of rTMS stimulation on the Punding scale score via a repeated measures ANOVA. We study the effect on the score difference  $y$  for the 13 subjects of the predictors SITE (factor  $\beta_j^S$  with categories Sham ( $j=1$ ), right DLPFC ( $j=2$ ) and left DLPFC ( $j=3$ ) and TIME (factor  $\beta_k^T$  with categories T1 ( $k=1$ ), T2 ( $k=2$ ) and T3 ( $k=3$ )) controlling for the GROUP (indicator variable  $\beta_l^G$  for the patients' group). We estimate the model with two-way and three-way interactions by adding a random intercept for each individual ( $i=1,\dots,13$ ):

$$y_{ijkl} = \mu + \alpha_i + \beta_j^S + \beta_k^T + \beta_l^G + \beta_{jk}^{ST} + \beta_{jl}^{SG} + \beta_{kl}^{TG} + \beta_{jkl}^{STG} + \varepsilon \quad (1)$$

(the superscripts are labels and do not represent power). The effects associated with TIME=1 SITE=1 and GROUP=0 are set to zero (reference levels),  $\alpha_i$  are i.i.d. gaussian with mean zero and  $\varepsilon$  is the error term.

## Results

### Punding scale

The Punding Scale score at T0 was significantly higher in the patient group ( $24.50 \pm 3.42$ ) than in the control group ( $10.44 \pm 4.10$ ;  $p < 0.0001$ ). After rTMS over the right DLPFC the Punding Scale score showed a significant decrease at T1 ( $p < 0.0001$ ) and at T2 ( $p < 0.0001$ ), while the effect disappeared at T3. After rTMS over the left DLPFC, we observed a significant decrease at T1 ( $p < 0.0001$ ), while at T2 and T3 there was a tendency toward a reduction but the difference did not reach a statistical significance. No effects were observed after sham stimulation.

Estimation of model (1) shows statistically significant interaction effects for  $\beta_{21}^{SG}$ ,  $\beta_{31}^{SG}$  (both negative with p-value  $< 0.0001$ ),  $\beta_{221}^{STG}$ ,  $\beta_{231}^{STG}$ ,  $\beta_{321}^{STG}$  and  $\beta_{331}^{STG}$  (all positive with  $p=0.008, 0.0075, <0.0001$  and  $0.0185$ , respectively); moreover all main effects and the intercept  $\alpha$  were not significantly different from zero (likelihood ratio test  $p=0.0134$ ). It confirmed that rTMS had no overall effect on the control group and, moreover, that no effects were observed after sham stimulation on the patients' group. The negative sign of  $\beta_{21}^{SG}$  and  $\beta_{31}^{SG}$  also confirms that both right and left DLPFC stimulations induced a lower score at T1, while the positive sign of  $\beta_{221}^{STG}$ ,  $\beta_{231}^{STG}$ ,  $\beta_{321}^{STG}$  and  $\beta_{331}^{STG}$  indicating that the effect disappeared at T2 and at T3.

## **Doubting and Hoarding distress rating scores of the OCI**

The Doubting Distress Rating score at T0 was significantly higher in the patient group ( $3.75 \pm 0.50$ ) than in the control group ( $0.22 \pm 0.44$ ;  $p < 0.0001$ ). After rTMS over the right DLPFC the Doubting Distress Rating score of the patients showed a significant decrease at T1 ( $p < 0.0001$ ), and at T2, while the effect disappeared at T3. After rTMS over the left DLPFC we observed a decrease only at T1. No effects were observed after sham stimulation. Similar results were obtained for the Hoarding distress rating score.

## **HAM-A, HAM-D**

The HAM-A score at time T0 was significantly higher in the patient group ( $18.25 \pm 3.50$ ) than in the control group ( $1.22 \pm 1.09$ ;  $p < 0.0001$ ). RTMS had no overall effect on the patient group. Similar conclusions apply for HAM-D and UPDRS.

No side effects and no adverse effects on motor function were noted in the patients, as evaluated according to the motor section of UPDRS [23].

The raw data are displayed in Figure 1. Mean scores are reported in Table 2, together with test results.

## **Discussion**

We found in this study that LF rTMS may suppress punding, as it does levodopa-induced dyskinesias in PD. Normal goal-directed behaviour is orchestrated by the striatum, through parallel circuits that interconnect [24]. The striatum is a mosaic of two compartments, a ventral  $\beta$ limbic part and a dorsal  $\beta$ sensorimotor part. The ventral part receives input from the prelimbic cortex, whereas the dorsal part (the matrix) from sensory and motor cortex areas.

PD patients may develop plastic changes in the striatal matrix leading to hyperkinesias, caused by extracellular striatal dopaminergic fluctuations due to pulsatile dopamine replacement therapy. As soon as these changes are also seen in the striatal striosomes, a stereotyped, non adaptive, rigide, behaviour (punding) may occur.

Indeed, dopaminergic treatment primes the dorsal striatal system to respond to a subsequent dopaminergic challenge both with hyperkinesias and repetitive, stereotyped behaviour in an animal

model for PD [25]. In the monkeys, repeated exposure to cocaine (an animal model of punding) leads to stereotyped behaviour linked to dorsal striatal activation [26]. A glutamate receptor antagonist was able to reduce the dorsal striatal overactivation and the associated behaviour abnormalities in the animal PD-model [25]. The dorsal striatal overactivation supposedly results from a disruption of the normal and controlled flow of information from ventral to dorsal striatal structures, probably caused by glutamatergic hypersensitivity.

Both the dorsal striosomes and the matrix are regulated by glutamatergic neurons via N-methyl-D-aspartate (NMDA) receptors [27]. Combined activation of sensitized dopamine and NMDA receptors may be required to evoke both levodopa-induced dyskinesias and punding in patients with PD, even if the involved neuronal networks may differ. Glutamatergic projections from the cerebral cortex are known to modulate signal transduction of basal ganglia-thalamocortical circuits and the sensitized glutamate NMDA receptors also may be required to express levodopa-induced dyskinesias and stereotypies [28]. The rationale for trying LF rTMS is based on the evidence that it induces a long-lasting decrease of motor cortex excitability that could antagonize glutamatergic hypersensitivity by reducing the response of the striatum to glutamatergic excitatory inputs.

Interestingly, the NMDA receptor antagonist amantadine suppresses the expression of levodopa-induced dyskinesias [29] and was also found to be effective in reducing punding in a PD patient [30]. Moreover, punding is associated with ICDs, according to a recent cross-sectional study [31]. Punding treatment is usually based on the reduction of dopamine replacement therapy, which frequently results in increased motor disability. Our patient's punding was reversed by rTMS, which did not aggravate motor function.

The fact that PD patients often become anxious, stressed or frustrated when stopped in their compulsive behaviours, suggests that emotional/motivational factors are also involved in punding to

a certain degree. It should be noted that all the patients present mild to moderate anxiety; however, TMS failed to modify significantly the HAM-A score in these patients.

We found significant changes in the Doubting and Hoarding Distress Scales of the OCI after rTMS. This finding is in agreement with several lesion, neuroimaging and neuropsychological studies indicating that the cortico-striatal circuitry may have a key role in the pathogenesis of obsessive-compulsive disorders [32,33]. Therefore, another possible interpretation of our results is that TMS of the DLPFC affects the compulsive aspects of punding (the sense of needing to engage in a behavior and the relief that arises from engaging in it), and this is the reason why the significant results on the punding scale are associated with change in OCD subscale measures.

The fact that PD patients often become anxious, stressed or frustrated when stopped in their compulsive behaviours, suggests that emotional/motivational factors are also involved in punding to a certain degree. It should be noted that all the patients present mild to moderate anxiety; however, TMS failed to modify significantly the HAM-A score in these patients.

A limitation of this study is the small patient sample. Although further studies on a large group of patients are warranted, the present report suggests that rTMS might have therapeutic potential for the treatment of punding in PD patients. Our preliminary findings might open up a new therapeutic perspective in impulse-compulsive disorders in PD based on neuromodulation.

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## **Figure legend**

Figure 1:

Primary and secondary outcome measures before (T0), 1 hour (T1), 12 hours (T2) and 24 hours (T3) after TMS examination to the right DPLFC (black), the left DPLFC (dark gray) and after sham stimulation (light gray). Lines show mean scores among controls (solid lines) and patients (dashed lines).