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# Transcranial magnetic stimulation improves cognition over time in Parkinson's disease

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ABSTRACT

*Introduction:* Cognitive impairment can occur in the early phase of Parkinson's disease and increases the risk of developing dementia. Cognitive deficits were shown to be associated with functional alterations in the dorsolateral prefrontal cortex (DLPFC) and caudate nucleus. Two previous transcranial magnetic stimulation studies over the left DLPFC showed short-term improvement in cognitive performance and focused on specific task.

*Methods:* 28 patients with idiopathic Parkinson's disease and mild cognitive impairment received intermittent "theta burst" stimulation (iTBS) (active, N = 14; or sham, N = 14) over the left DLPFC, twice a day for three days with 1–2 days in between. Detailed neuropsychological assessment of five cognitive domains was performed before iTBS and on days 1, 10, and 30 after the last iTBS session. Composite Z-scores were calculated for each domain and for overall cognition.

*Results:* Our results showed an increase in overall cognition up to one month in both groups but this effect was only significant in the active group. Improvements were seen in the attention domain for both groups and in the visuospatial domain in the active group only. No significant differences were found between the groups.

*Conclusion:* These preliminary findings suggest that active iTBS might improve overall cognitive performance in patients with Parkinson's disease with mild cognitive impairment and that this effect can last up to one month. This cognitive improvement, is likely mediated by improvement on visuospatial abilities. Further studies are needed to explore the potential of iTBS as a therapeutical tool to slow cognitive decline in patients with Parkinson's disease.

## 1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease [1]. Cardinal symptoms of PD consist of motor deficits caused by the loss of dopaminergic neurons in the substantia nigra pars compacta. It is now known that patients with PD have cognitive deficits, even in the early phase of the disease and mild cognitive impairment (MCI) in patients with PD has been shown to increase the incidence of dementia [2].

MCI can affect one or more cognitive domains. Previous studies reported an association between MCI and functional alterations in the dorsolateral prefrontal cortex (DLPFC) and in the caudate nucleus [3,4]. Indeed, during execution of a cognitive task, Monchi et al. (2012) showed reduced activation in the cognitive part of the cortico-striatal loop, which involves the DLPFC and the caudate nucleus, in patients with PD compared to healthy controls [5]. This decreased activation has also been reported to be stronger in PD patients with MCI (PD-MCI) compared to those with normal cognition at the same stage of the disease [6]. While dopaminergic medication may help stabilize motor symptoms in Parkinson's disease, very few therapies are currently

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available to improve cognitive deficits or stop their decline.

Transcranial magnetic stimulation (TMS) is a non-invasive method which generates an electromagnetic field around a coil, making it possible to temporarily stimulate or inhibit neurons in a brain region. Previous TMS studies in healthy controls analysed the cognitive cortico-striatal loops and showed that excitatory repetitive TMS over DLPFC increased dopamine release in the caudate nucleus [7], while continuous theta burst stimulation (TBS) over DLPFC decreased striatal dopamine release and impaired executive performance, as tested by the Montreal Card Sorting Task [8]. TMS has also been shown to improve cognitive performance. Indeed, several studies applied a TMS protocol over DLPFC and reported a significant increase in the scores of cognition in non-PD patients [9] and in healthy controls [10]. One previous study reported no significant changes in cognitive performance after applying rTMS over DLPFC in patients with PD [11]. This might be due to using only one stimulation session, which was shown to induce neuronal changes only up to a few hours [12]. One method to increase the effect's duration is to apply TMS in multiple sessions. After applying several sessions of rTMS over DLPFC, significant increase in cognition in depressed patients with Parkinson's disease has been reported by previous studies [13,14]. However, these studies concentrated only on the effect of specific cognitive tasks (associated with the depressive symptoms), and one did not use sham TMS [14].

The TBS protocol proposed by Huang et al. uses 50 Hz of stimulation frequency and confers a more durable stimulation effect [15]. In fact, Cheng et al. reported that intermittent theta burst stimulation (iTBS) over left DLPFC is best suited for enhancing executive function in patients with medication-resistant depression [16]. Since previous studies reported that cumulative sessions of rTMS or iTBS are needed in order to induce long-term therapeutic effects [17,18] even in cognitive functions [16], our current study aimed to determine whether repeated sessions of iTBS over DLPFC could lead to long-term improvement in cognitive performance in PD-MCI patients.

## 2. Materials and methods

### 2.1. Patients

We recruited 28 patients with PD at stages I to III of the Hoehn and Yahr scale from the Movement Disorders Unit of the McGill University Health Center, and the Quebec Parkinson Network. Patients were diagnosed by movement disorders neurologists and met the UK brain bank criteria for idiopathic Parkinson's disease. Subjects were ON medication at all times during the experiment. None of the participants ever received TMS prior to this study. All participants provided informed written consent and the study protocol was approved by the Research Ethics Committee of the Regroupement Neuroimagerie Québec.

Each patient underwent an assessment of their cognitive status using a comprehensive neuropsychological battery performed by a licensed neuropsychologist (Dr. MCB). The neuropsychological assessment measured five cognitive domains with at least two tests for each domain, as suggested by the Movement Disorders Society Task Force: (1) attention and working memory; (2) executive function; (3) language; (4) memory and verbal learning (5) visuospatial abilities (Supplementary Table 1). Only PD patients with MCI were included. MCI was defined by Level II criteria of the Movement Disorders Society Task Force and included: 1); a performance level of 1 standard deviation below population mean of the normative data sets in the same age range on at least two tests, either within a single cognitive domain or across different domains; 2) subjective complaint of cognitive decline from the patient or accompanying person; 3) absence of significant decline in daily living activities [based on clinical observations of the referring neurologists and neuropsychologist]; 4) absence of dementia as diagnosed by the evaluating neuropsychologist [based on the Movement Disorder Society Task Force guidelines (Level II) for the diagnosis of dementia in PD [19]], which include significant impairment in at least two domains and an impact on daily living resulting from cognitive deficits, over and above those imposed by motor and autonomic problems; (5) evidence of cognitive abnormalities that cannot be attributed to age.

**Table 1**
Demographic, clinical and neuropsychological data at baseline.

| Characteristics | active iTBS group (N = 14) | sham iTBS group (N = 14) | *p* value |
|---|---|---|---|
| Age | 71.3 ± 7.3 | 67.3 ± 5.2 | 0.212 |
| Sex, male/female | 8/6 | 11/3 | 0.225 |
| Disease duration | 10.39 ± 6.7 | 6.25 ± 3.0 | **0.047*** |
| Education | 16.0 ± 3.4 | 15.4 ± 2.9 | 0.705 |
| MoCA | 24.9 ± 2.5 | 24.8 ± 2.5 | 0.882 |
| UPDRS-III | 33.9 ± 15.7 | 30.2 ± 14.5 | 0.52 |
| BDI | 11.2 ± 4.3 | 11.5 ± 6.6 | 0.893 |
| BAI | 13.5 ± 5.4 | 9.1 ± 6.3 | 0.061 |
| AES | 5.1 ± 3.7 | 5.4 ± 4.1 | 0.885 |
| PDQ-39 | 24.5 ± 10.2 (N = 10) | 27.2 ± 12.5 | 0.587 |
| LED | 934 mg ± 593 | 911 mg ± 699 | 0.924 |
| SETS (expectations) | 4.3 ± 0.86 | 4.7 ± 0.77 | 0.234 |
| Overall cognition | −0.46 ± 0.32 | −0.45 ± 0.43 | 0.48 |
| Attention | −0.52 ± 0.28 | −0.41 ± 0.46 | 0.26 |
| Executive function | −0.25 ± 0.25 | −0.42 ± 0.48 | 0.17 |
| Memory | −0.19 ± 0.62 | −0.5 ± 0.65 | 0.15 |
| Language | −0.84 ± 0.51 | −0.69 ± 0.4 | 0.25 |
| Visuospatial abilities | −0.49 ± 0.68 | −0.25 ± 0.96 | 0.26 |

Mean ± SD is presented. AES, Apathy Evaluation Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; LED, Levodopa Equivalent Dosage; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson Daily Questionnaire-39; SD, standard deviation; SETS, Stanford Expectations of Treatment Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale-III.

Additionally, each participant underwent clinical evaluations that included: the Unified Parkinson's Disease Rating Scale Part III to quantify the motor severity of the disease, the Beck Anxiety Inventory, the Beck Depression Inventory and the Apathy Evaluation Scale in order to assess the level of anxiety, depressive and apathy symptoms, in addition to the Parkinson Daily Questionnaire to assess changes in quality of life. The Stanford Expectations of Treatment Scale was administered to assess the expectations regarding the iTBS protocol as it has been shown that placebo effects were linked to dopamine release [20].

Subjects were divided in two groups and received either active iTBS (n = 14, 6 women and 8 men, 71 ± 9.2 years of age) or sham stimulation (n = 14, 3 women and 11 men, 67 ± 7.3 years of age) using a randomization protocol of ASA-ASS-SAS-SAA, where S is sham and A is active iTBS. Participants were blinded to the type of stimulation received, study team members were not. Table 1 portrays the demographic, clinical and neuropsychological characteristics of the groups.

### 2.2. Experimental design

Participants underwent an MRI acquisition with a 3T Siemens TIM TRIO MRI scanner (Erlanger, Germany) at the Functional Neuroimaging Unit of the Centre de Recherche de l'Institut de Gériatrie de Montréal (CRIUGM). A high-resolution three-dimensional T1-weighted imaging MPRAGE sequence was acquired with a 12-channel coil (voxel size $1 \times 1 \times 1 mm^3$; field of view 256 mm (256 × 240 matrix); repetition time 2300 msec; echo time 2.91 msec; inversion time 900 msec; flip angle 9°; 160 slices).

After that participants were administered a neuropsychological battery and clinical tests (pre-TMS assessment). On the 2nd, 4th and 7th day we applied two iTBS sessions per day, separated by a 1-h break between sessions. After the TMS we administered alternative versions of the neuropsychological tests and clinical tests on the 1st, 10th and 30$^{th}$ day (post-TMS assessment). Alternative versions were used to reduce the practice effects. Fig. 1A illustrates the experimental design of this study.

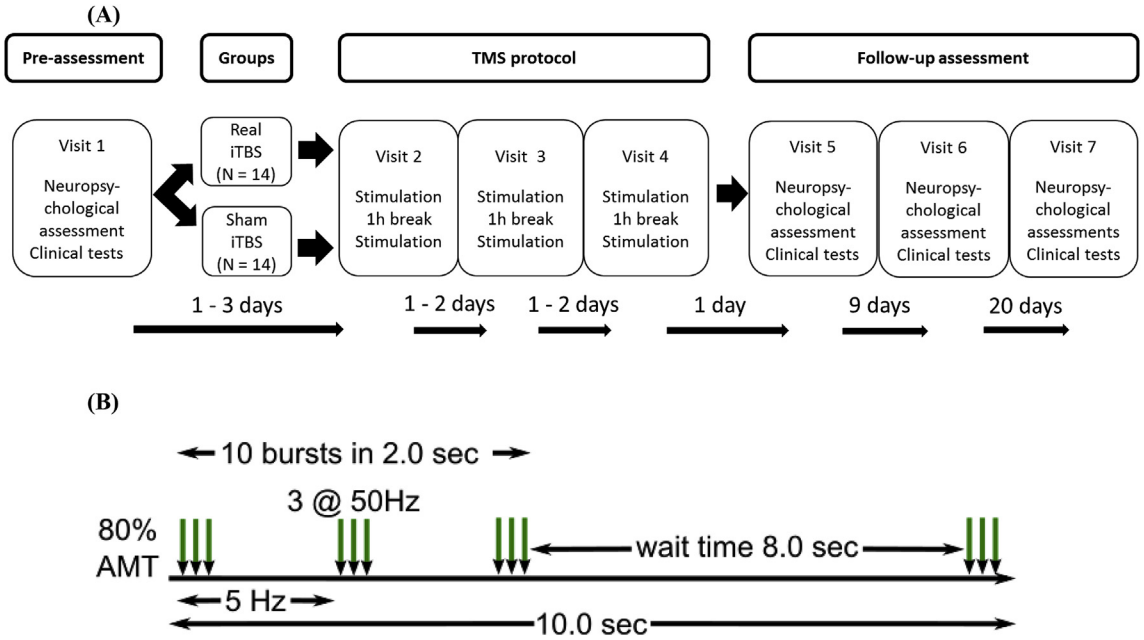


**Fig. 1. Experimental design of the study.** (A) Schedule: Participants were first screened during their pre-assessment visit, before receiving a TMS protocol (active iTBS or sham iTBS) lasting 3 visits. They were later followed up at 1, 10 and 30 days after the TMS protocol. iTBS = intermittent theta burst stimulation; TMS = transcranial magnetic stimulation; (B) iTBS protocol.

The TMS procedures are described in details in the supplementary information. Briefly, we first determined the active motor threshold used a Magstim Super Rapid2 (Magstim, UK) stimulator connected to a figure-of-eight cooled air-film coil. The active motor threshold was determined by applying single TMS pulses over the left motor hand area and increasing the stimulating levels until a motor evoked potential was reliably elicited for at least 50% of 10 consecutive stimulations and lesser levels of stimulation failed to elicit consistent muscle contractions. To find the left DLPFC, we used the MNI coordinates (x = −48; y = 36; z = 26) defined in the standardized stereotaxic space based on our previous data that showed decreased activity in the DLFPC and caudate nucleus during a set-shifting task in PD-MCI patients [6] using the Brainsight infrared optical tracking and frameless stereotaxic system (Brainsight 2.2.10, Rogue Research, Canada) based on the individual patient's anatomical MRI. The iTBS protocol was applied at an intensity of 80% active motor threshold, 2 s TBS train (3 pulses of stimulation at 50 Hz repeated every 200 ms) repeated every 10 s for a total of 190 s (or 600 pulses) (Fig. 1B). Sham condition followed the same procedures, except that a Magstim sham coil was used. Both coils were identical in appearance and produced similar auditory stimuli but the sham coil did not elicit any magnetic stimulation.

### 2.3. Statistical analysis

Neuropsychological data were converted to Z-scores [Z-score formula: (individual score – normative data mean score)/normative data mean standard deviation]. The normative data took into account age and education. For each cognitive domain, calculations were performed by averaging all z-scores tests per domain. The global cognitive score was calculated by averaging all domain Z-scores (Supplementary Table 1). Repeated measures ANCOVA was performed using the statistical software package (SPSS 22), with a 4 × 2 factorial design that used Time (pre, post-1day, post-10days and post-30days) and Group (active iTBS and sham iTBS) as factors. ANCOVA was performed for the average neuropsychological data Z-scores as continuous variables corrected for disease duration, and a second ANCOVA for the average Z-scores of clinical data as continuous variables (Supplementary Table 3).

Pairwise comparisons using two-tailed paired t-tests were performed when ANCOVA showed a significant main effect. Mauchly's sphericity test did not show significant effects. All data followed normal distribution as determined using the Shapiro-Wilk normality test ($p < 0.05$) Bonferroni-corrected $p$-values < 0.05 are reported.

## 3. Results

Comparisons of initial demographic characteristics between groups revealed a significantly longer disease duration in the active iTBS group at baseline (p = 0.047), which was used as covariate. Comparison between baseline domain Z-scores did not show any significant differences between the groups.

The mixed-design repeated measures ANCOVA of average Z-scores between assessments (Fig. 2) showed a main effect of Time in *Overall Cognition* ($F_{3,72} = 4.2$, $p = 0.008$, $\eta_p^2 = 0.146$), *Attention* ($F_{3,72} = 6.27$, $p = 0.001$, $\eta_p^2 = 0.201$) and *Visuospatial* domain ($F_{3,72} = 4.23$, $p = 0.008$, $\eta_p^2 = 0.145$), but not in *Executive Function* ($F_{3,72} = 0.65$, $p = 0.585$), *Language* ($F_{3,72} = 0.633$, $p = 0.596$) or *Memory* ($F_{3,72} = 0.777$, $p = 0.511$). Time × Group interaction did not show any significant changes and main effects of Group were not observed.

Pairwise comparisons showed significant differences in *Overall Cognition* in the active group only (active pre vs. post-30days p = 0.011, post-1day vs. post-30days p = 0.009), in *Attention* for both groups (sham pre vs. post-30days p = 0.011, post-1day vs. post-30days p = 0.03; active pre vs. post-10days p = 0.026, pre vs. post-30days p = 0.009) and in the *Visuospatial domain* for the active group only (active pre vs. post-1day p = 0.003, pre vs. post-30days p = 0.008).

The mixed-design repeated measures ANCOVA of average Z-scores of other clinical data (Supplementary Table 3) did not show any significant differences.

## 4. Discussion

Our study revealed a potential positive impact of iTBS on the overall cognitive performance in patients with Parkinson's disease who have cognitive deficits. Increased cognitive performance was mainly mediated by attention and visuospatial abilities. Our protocol was able to maintain the increased cognitive performance for up to one month. The

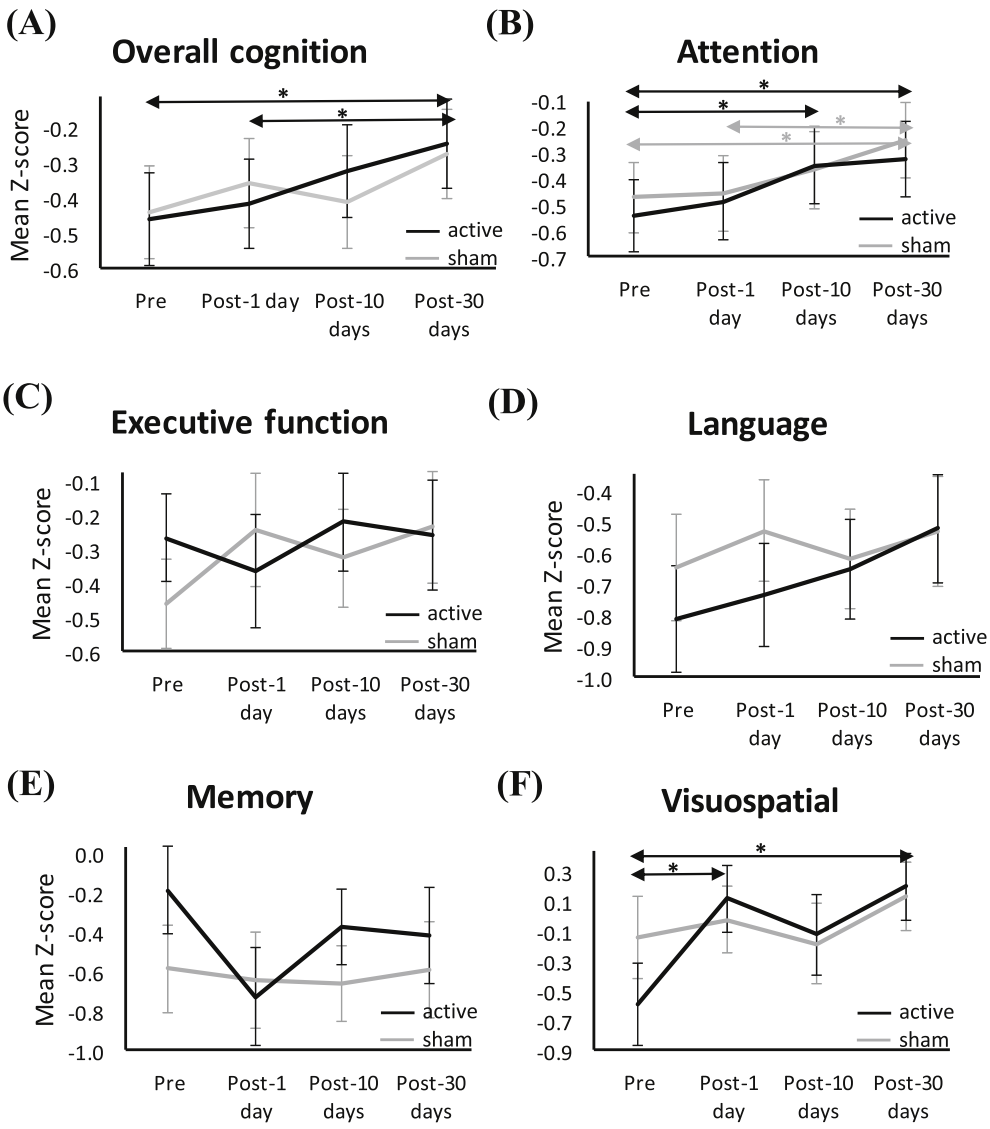


**Fig. 2. Average Z-scores throughout all four neuropsychological assessments corrected for the disease duration.** Average composite Z-scores in **(A)** overall cognition, **(B)** attention, **(C)** executive function, **(D)** language, **(E)** memory and **(F)** visuospatial function during each assessment. Lines represent the sham (grey) and the active iTBS (black) group. Significant differences are illustrated by asterisks: *Bonferroni-corrected $p < 0.05$.

current protocol showed significant improvement in *Overall Cognition*, *Attention* and *Visuospatial* domains, but the changes were also depicted in the sham group for attention.

Our current results are in line with previously published reports. A 10 day protocol of rTMS applied in patients with Parkinson's disease showed improved performance in attention, executive function (as measured by Stroop Color and Word test and Wisconsin Card Sorting Task) [13] and memory (measured with Hooper visual organization test [13] or memory subscore of the Dementia Rating Scale [14]). The measured improvement was present for up to two [14] or eight [13] weeks after the stimulation. However, these studies did not use comprehensive neuropsychological assessment nor a sham protocol and were specifically targeting depressed patients with Parkinson's disease. These important limitations strongly increase the conclusion bias regarding the true potential of rTMS since depression was reported to have a negative influence on cognitive performance [21] and the absence of a sham protocol did not allow the avoidance of potential learning effects. We aimed to assess an improved protocol that was applied in patients without depression (as measured by the Beck Depression Inventory score, Table 1) and added a sham group.

Our results of improved *Overall Cognition* seem to be associated with improved *Attention* in the sham and active groups and improved *Visuospatial function* only in the active group.

The improved performance in the *Attention* domain could be explained by the fact that we stimulated the DLPFC. This region was reported to harbor preferential associations with caudate nucleus, since an increase in dopamine release was induced after applying rTMS over DLPFC [8,22]. Specifically, the DLPFC-striatal link has been shown to be significantly activated during attention [23] reflected in the set-shifting tasks. Furthermore, patients with Parkinson's disease and MCI have significantly reduced activity in these regions when compared to Parkinson's disease patients with normal cognition [6], reflecting DLPFC-striatal link's importance for cognitive performance. Thus, our results might suggest that iTBS over DLPFC reinforces activation of the 'cognitive' cortico-striatal loop and improves attention.

On the other hand, the significant improvement in *Attention* was also shown in the sham group. One potential explanation is that sham rTMS has been shown to elicit a placebo effect and striatal dopamine release in patients with PD [22]. Furthermore, even though we used alternative neuropsychological tests, when available (Supplementary Table 2) and there were no differences between the groups regarding the expectation as measured with the Stanford Expectations of

Treatment Scale (Table 1, Supplementary Table 3) – our protocol still cannot exclude that improved *Attention* is due to a learning effect. To address this inconsistency, we have to outline that there are familiarity and practice effects in serial neuropsychological evaluations. Considering that we used different tests for different time points, when available – the potential learning effect seems to be associated with the practice effect and not the familiarity one. Furthermore, the involvement of the stress is also an important factor that might have biased the results, since the effect of stress has been shown to affect performance in elderly populations [24]. Finally, *Attention* is known to improve after certain visits and because participants will learn how to stay more attentive knowing the context of the formal evaluation [25–27]. All these factor together outline that the improved *Attention* in our protocol can have different explanations, and none of them at the moment can be excluded.

A distinct result was reported for the *Visuospatial* domain. Significant improvements were depicted only in the active group. These results can be explained by iTBS capacity to modulate posterior parietal cortex activity, which was reported in healthy controls during an executive planning task [28]. Posterior parietal cortex has been shown to be involved in spatial representation [29], visual attention [30] and executive function [31]. This region receives projections from the visual system and integrates them with signals from the auditory, vestibular and somato-sensorial systems [29] This integration process is a component of visuospatial abilities and is crucial for the localization of multiple stimuli in an environment. Therefore, our protocol seems to modulate specifically the visuospatial performance and spatial representation.

The results of this study should be considered in light of several limitations. First, the number of tests used for each domain is different and this might have induced domain alteration bias due to unbalanced number of tests. Considering that up to date there are no reliable measurements to establish weights for tests that are being used, we have chosen the path of diminishing the bias by increasing the number of tests aiming to increase the reliability of the quantified measurements. Secondly, we cannot exclude completely the potential effect of the sham coil. Previous studies reported that sham rTMS induces increased dopamine release in the ‘cognitive’ cortico-striatal loop in patients with Parkinson's disease [22] which has an effect similar to iTBS [20]. Nevertheless, a potential sham effect cannot explain the improved visuo-spatial performance in the active group only.

In conclusion, to the best of our knowledge this is the first sham controlled multiple session TMS study that extensively investigates the effect of iTBS on cognitive performance in patients with Parkinson's disease. This preliminary study suggests that active iTBS improves global cognitive performance significantly in patients with Parkinson's disease who have mild cognitive impairment and the positive effect is maintained for up to one month after the stimulation. This global improvement was not significantly different between the two groups (active and sham) and seems to be mediated primarily by better performance over time in *Attention* in both groups while *Visuospatial function* enhanced performance was reported in the active group only. Future large-scales studies are warranted to confirm and investigate more precisely these findings in order to determine whether TMS is a viable treatment complement for cognitive deficits in PD.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.006.

## Contributors

Project concept and design by OM, AS; Project organization and execution by JT, AH, BMC, SJ, OM, MAB, ALL, CD; Data analysis and statistical analysis by JT, SJ, AH, OM; Manuscript first draft by JT, AH; Manuscript review and critique by OM, AS, AH, MAB, ALL, BMC, CD, JT, SJ. All authors have approved the final article.

## Conflicts of interest

Trung Jessica, Hanganu Alexandru, Jobert Stevan, Degroot Clotilde, Mejia-Constain Béatriz, Bruneau Marie-Andrée – none; Lafontaine Anne-Louise – Advisory Boards and Honoraria from UCB Pharma, Novartis, AbbVie, Teva; Strafella Antonio – received research funding from Canadian Institute of Health Research, Canada Research Chair Program, National Parkinson Foundation, Parkinson's Disease Foundation, Parkinson Society Canada and Weston Brain Institute; Monchi Oury – Grants from Canadian Institutes of Health Research, Parkinson Society Canada, Natural Sciences and Engineering Research Council of Canada, Fonds de la Recherche Québec (Santé).

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