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ORIGINAL RESEARCH

Intermittent Theta-Burst Stimulation of the Right Dorsolateral Prefrontal Cortex to Promote Metaphor Comprehension in Parkinson Disease: A Case Study

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Abstract

This single-case research-designed study explored whether intermittent theta-burst stimulation (iTBS) of the right dorsolateral prefrontal cortex (DLPFC) could improve metaphor comprehension in people with Parkinson disease (PD) and language impairments. A right-handed participant with PD diagnosed 9 years ago, receiving long-term treatment with levodopa, and with metaphor comprehension impairment was recruited to undergo 10 sessions of sham stimulation (in 2wk), a washout period (6wk), and then 10 sessions of iTBS (in 2wk). Clinical scores of metaphor comprehension and motor evaluation (Unified Parkinson Disease Rating Scale part III) and transcranial magnetic stimulation to test the excitability of the primary motor cortex (M1) were used at baseline, postsham, post-iTBS, and at 3 follow-ups (8, 14, and 20wk post-iTBS). Metaphor comprehension was improved after iTBS, and the highest scores were obtained 8 weeks later ($P=.01$). This improvement was correlated with the increase of the right M1 excitability ($r=-.86$, $P=.03$) and with the decrease of transcallosal inhibition latency from the left to the right hemisphere ($r=-.88$, $P=.02$). Sham yielded no effect ($P>.05$). Administration of iTBS over the right DLPFC improved metaphor comprehension likely by a long-term influence on brain synaptic plasticity, including improvement of interhemispheric dialogue. More studies are warranted to confirm these findings in larger samples of participants with PD.

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The loss of nigrostriatal neurons in Parkinson disease (PD)[1] possibly disrupts the frontostriatal circuits that include structures engaged in motor and cognitive abilities, such as the premotor areas, the primary motor cortex (M1), and the dorsolateral prefrontal cortex (DLPFC).[2] Motor circuits dysfunction in PD induces motor symptoms such as tremors, rigidity, and postural instability, while the dysfunction of prefrontal cortex circuits is associated with cognitive issues including deficits of executive function (eg, working memory, mental flexibility, inhibition deficits)[2,3] and of metaphor comprehension.[4-7] Metaphor comprehension is often impaired in PD, likely because it requires high-level cognitive abilities.[8,9] Given that its impairment, even in the early stages of the disease, is associated with executive deficits[6,7,9] and that DLPFC is hypoactivated in PD,[10,11] it is suggested that metaphor processing relies on the integrity of executive functions and of DLPFC networks.[6,12,13]

Repetitive transcranial magnetic stimulation (TMS) is a noninvasive and painless approach used to influence brain excitability.[14] This rapid-rate repetition of transient magnetic pulses of very high intensity is capable of activating the cerebral tissue at high or low frequencies in order to increase or decrease, respectively, the excitability of cortical neurons, thus influencing synaptic conductance and favoring plastic mechanisms of adaptation in the brain.[15] Repetitive TMS of DLPFC or M1 can activate the frontostriatal circuits, thus triggering the release of dopamine within the striatum.[16,17] Given that dopamine release in PD may partially reactivate the frontostriatal function that is impaired, including the motor and DLPFC function, repetitive TMS presents a potential for improving cognitive and motor symptoms in PD.

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For example, high-frequency repetitive TMS of M1 in PD has been shown to reduce motor symptoms (particularly rigidity),[18] and repetitive TMS of DLPFC has been shown to enhance working memory, inhibition, and mental flexibility.[19,20] In the study by Srovnalova et al,[21] only repetitive TMS of the right DLPFC, not the left, improved planning in PD, likely because the right DLPFC is more involved in high-level cognitive processes. In line, neuroimaging studies showed that the comprehension of novel metaphors (involving high-level cognitive ability) specifically activated the right DLPFC.[22,23] However, whether repetitive TMS of the right DLPFC influences language abilities has never been addressed in PD.

The present case study investigated whether repetitive TMS of the right DLPFC could improve metaphor comprehension in PD that is often impaired because of the requirement of several high-level executive and language resources.[9,24,25] Intermittent theta-burst stimulation (iTBS) (a repetitive TMS protocol with theta-burst frequency) was used for its long-lasting excitatory effects on brain activity (ie, beyond the end of stimulation[26]) and its capacity to increase M1 excitability in individuals with PD.[27] iTBS has already been applied over the DLPFC in PD and was shown to be safe and to improve mood, but not motor performance.[28] Even if the effects of iTBS over the DLPFC on language and executive deficits in PD had never been specifically investigated, some exploratory studies[29,30] in patients with poststroke aphasia showed a beneficial effect of several iTBS sessions on semantic fluency. Improvement of discourse production, sentence comprehension, picture naming, and short-term verbal memory was also detected after iTBS.[30] Altogether, these studies suggest that the right DLPFC usually involved in metaphor comprehension is hypoactivated in PD and that iTBS may improve its function by increasing cerebral excitability. Our working hypothesis was that metaphor comprehension deficits could be improved after 10 sessions of right DLPFC iTBS, as compared with 10 sham sessions, and in association with changes of brain motor function, as tested by TMS of M1.

Case description

A 75-year-old right-handed man (French native speaker with idiopathic PD diagnosed 9y ago) with metaphor comprehension deficits participated in our study. The research protocol and tests were approved by the ethics committee of the Centre Hospitalier Universitaire of Québec and were administered according to ethical guidelines. The participant signed the informed written consent before the onset of experimental procedures. Table 1 presents the clinical characteristics at baseline: motor symptoms (Unified Parkinson Disease Rating Scale part III)[31]; motor disability (Hoehn & Yahr stage); general cognitive function (Montreal Cognitive Assessment)[32]; depressive symptom severity (Beck Depression Inventory Version IA)[33]; executive function (eg, working memory, mental flexibility, and inhibition, respectively assessed by letter-number sequencing test,[34] alternating verbal fluency task (naming, alternatively, as many musical instruments and fruits as possible in 90s), and Stroop Color-Word Test (inhibition time).[35] (For reliability and validity of each clinical test in people with PD, see appendix 1) Exclusion criteria were (1) neurologic disease other than PD; (2) any change in medication 1 month before enrollment and during the protocol; (3) depression and related medication (cutoff Beck Depression Inventory Version IA score, 13)[36]; and (4) dementia (cutoff Montreal Cognitive Assessment score, <16).[37] Exclusion criteria relative to TMS were as follows: (1) metal in eyes, skull, or jaw; (2) brain tumor, infection, or surgery; (3) seizures/epilepsy history; (4) medication lowering seizure threshold; (5) pacemaker; (6) medication pump or deep brain stimulator; and (7) heart disease.[38]

List of abbreviations:

AMT	**active motor threshold**
ANOVA	**analysis of variance**
DLPFC	**dorsolateral prefrontal cortex**
FDI	**first dorsal interosseous**
$GABA_A$	**gamma-aminobutyric acid type A**
IHI	**interhemispheric inhibition**
iSP	**ipsilateral silent period**
iTBS	**intermittent theta-burst stimulation**
M1	**primary motor cortex**
MEP	**motor-evoked potential**
PD	**Parkinson disease**
SICF	**short-interval intracortical facilitation**
SICI	**short-interval intracortical inhibition**
TMS	**transcranial magnetic stimulation**

Procedure

A single-case reversal design was adopted where 1 experimenter not involved in outcome measures and analyses applied sham and iTBS series to the participant who was naïve to what he was receiving. The experimenters analyzing data remained blind to files codification until completion of analyses. A 6-phase protocol was conducted over 58 weeks (fig 1): 2 preintervention baselines (20wk apart); 10 sessions of sham over the right DLPFC (in 2wk); postsham testing (immediately after last sham session); washout (6-wk break); 10 sessions of iTBS over the right DLPFC (in 2wk); post-iTBS testing (immediately after last iTBS session);

Table 1 Characteristics of PD case

Characteristics	Values
Age (y)	75
Education (y)	11
Sex	Male
Laterality	Right-handed
Disease duration (y)	9
Levadopa dose (mg/d)	750
Dominant motor symptom	Tremor
UPDRS-III (total) (max: 156)	18
UPDRS-III (rigidity) (max: 20)	2
UPDRS-III (tremor) (max: 28)	5.5
UPDRS-III (posture stability) (max: 8)	2
Hoehn and Yahr (stage)	2
Montreal Cognitive Assessment* (/30)	26
Alternating fluency (no. of words in 90s)	15
Letter-number sequencing (span) (max: 8)	5
Stroop (inhibition time) (s)	82
Beck Depression Inventory Version IA† (/63)	7

Abbreviations: max, maximum; UPDRS-III, Unified Parkinson Disease Rating Scale part III.

* Cutoff score for dementia[37]: <16.

† Cutoff score for depression[36]: 13.