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Theta burst stimulation over premotor cortex in Parkinson's disease: an explorative study on manual dexterity

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Abstract Dorsal pre-motor cortex (PMd) is thought to play a role in fine motor control. The aim of the present study was to investigate whether inhibitory or excitatory stimulation of PMd would have an impact on manual dexterity in Parkinson's disease (PD). Fifteen patients with PD participated in this study. High resolution structural MRI was used for neuro-navigated TBS. Participants were targeted with one train of TBS in three experimental sessions: sham stimulation over vertex, continuous TBS (cTBS) over PMd and intermittent TBS (iTBS) over PMd, respectively. Dexterity was measured by a coin rotation task (CRT), which is a valid measure to detect limb kinetic apraxia (LKA). Neither cTBS or iTBS significantly interfered with CRT. Post hoc sub-analysis in a group of PD patients ($n = 5$) with stronger baseline impairment, indicating LKA, revealed further deterioration of dexterous performance for the cTBS condition ($p = 0.04$). This sham controlled pilot study demonstrates that TBS over PMd does not significantly interfere with dexterity in PD. However, patients with dexterous impairment qualifying for LKA may be more susceptible to TBS.

Keywords Manual dexterity · Premotor cortex · Limb kinetic apraxia · Parkinson's disease · Coin rotation

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Introduction

Loss of manual dexterity, not explained by elementary motor deficits has been defined as limb kinetic apraxia (LKA). It is thought to be caused by the disruption of innervatory patterns, probably stored in the pre-motor cortex (Heilman et al. 2000). Recently, LKA has been suggested to explain dexterous disability in patients with Parkinson's disease (PD) (Quencer et al. 2007; Gebhardt et al. 2008; Foki et al. 2015; Vanbellingen et al. 2011). Furthermore, LKA is predictive for impaired activities of daily living (ADL), which require dexterity skills, even at early-to-moderate disease stages (Foki et al. 2016). The coin rotation task (CRT) was used as a surrogate marker of LKA, because CRT, in contrast to bradykinesia, shows little responsive to dopaminergic treatment (Gebhardt et al. 2008). Furthermore, the CRT was related mainly to apraxia and showed little association with bradykinesia (Vanbellingen et al. 2011).

There are only a few imaging studies which address the neural basis of innervatory patterns underlying fine motor skills. An early case series study in stroke patients reported that damage to the pre-motor cortex was associated with LKA (Freund and Hummelsheim 1985).

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Further support in favor of the pre-motor cortex comes from an fMRI study which demonstrated significant activations of secondary areas, including the pre-motor cortex, while sparing the primary sensorimotor cortex, when healthy subjects had to perform ipsi-lateral distal finger movements (Nirkko et al. 2001). Some neuro-imaging studies point to a pre-motor dys-balance of activation in PD, when complex movements were performed (Haslinger et al. 2001; Sabatini et al. 2000). A recent fMRI study in early PD suggested that the primary somatosensory cortex could be a marker of LKA (Foki et al. 2015). Underlying this was reduced activation of the primary sensory cortex, and hyper-activations of the primary motor, SMA, but also of the parietal and pre-motor cortical areas. However, the interpretation of fMRI activations is not always straightforward. Activation in fMRI indicates that a certain region supports the related task, but how crucial it is for the task performance remains ambiguous (de Graaf and Sack 2011; Logothetis 2008).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method that can transiently interfere with cortical activity. The advantage of a theta burst stimulation (TBS) protocol is that the application of one short single train produces behavioral effects outlasting stimulation up to 30 min (Nyffeler et al. 2006; Cazzoli et al. 2009a, b). Continuous theta burst stimulation (cTBS), has been shown to have inhibitory effects on motor cortex whereas intermittent theta burst stimulation (iTBS) is excitatory in nature (Goldsworthy et al. 2012). TBS over PMd in PD has only been applied in a few studies. For instance, cTBS stimulation over SMA showed mild positive effects on upper limb bradykinesia (Eggers et al. 2015). Furthermore, the application of iTBS over primary motor cortex improved mood (Benninger et al. 2012). Pre-motor dorsal areas have been targeted in PD by traditional rTMS protocols (Mir et al. 2005; Buhmann et al. 2004), not exploring behavioral effects, but the influence of PMd on motor cortex excitability.

The aim of the present study was to investigate the role of the dorsal pre-motor cortex (PMd) in manual dexterity in PD. For this purpose we conducted an MRI-based neuronavigated TBS study. Due to the proof of concept nature of this study we applied only one train of TBS. Based on previously described effects of TBS on synaptic plasticity (Huang et al. 2005; Goldsworthy et al. 2012; Zamir et al. 2012), we hypothesized that manual dexterity in PD may transiently deteriorate with cTBS over PMd, due to its inhibitory nature. We further conjectured that dexterity may improve with iTBS, which is excitatory per se.

Materials and methods

Patients

Fifteen PD patients (4 women, aged between 53 and 81, mean = 66.4, SD = 9.4), all right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield 1971), participated in this study. Nine patients had mild wearing off fluctuations (one patient with peak dose dyskinesias), the other six patients were stable responders to L-DOPA. The diagnosis was achieved according to the criteria of the United Kingdom Brain Bank by expert neurologists (Hughes et al. 1992). A further inclusion criterion was the score above 23/30 on the Montreal Cognitive Assessment (MoCA), to exclude severe cognitive impairment (Hoops et al. 2009). Informed written consent according to the latest version of the Declaration of Helsinki was obtained from each subject prior to the experiment. The local ethics committee of the state of Bern approved the study. All subjects had normal or corrected-to-normal vision and hearing, and were screened for exclusion criteria for TMS application, such as current pregnancy, personal or family history of epilepsy or epileptic fits, and any psychiatric, neurologic, or medical history. Furthermore, subjects with any contra-indications for MRI (such as metallic foreign bodies and pacemakers) were not included in this study. Clinical and demographic variables are presented in Table 1.

Based on our previous studies in PD using CRT as an outcome (Bohlhalter et al. 2011; Vanbellingen et al. 2011) a power analysis yielded a sample size of 14 patients providing 80 % power, with a 2-sided alpha-level of 0.05, to detect a 10 % difference in the coin rotation task (baseline mean values = 11.50, SD = 1.1) between real stimulation and sham.

Experimental Protocol

First, all subjects underwent structural MRI acquisition to be used for the imaging-guided neuro-navigation. Second, a repeated measures design was employed with three experimental sessions conducted in weekly intervals: sham stimulation, cTBS and iTBS. The exact target stimulations site for the PMd is specified in the next section. The order of stimulations was counterbalanced across patients. Consequently, five patients received sham, cTBS or iTBS as a first stimulation. The behavioral tasks immediately followed the stimulation application. For the patients with wearing OFF fluctuations the experimental sessions were scheduled based on medication intake times. Accordingly, stimulation was applied during their best ON state, which was approximately 1.5–2 h after last L-DOPA intake.

Table 1 Clinical characteristics of PD patients ($n = 15$)

Pat	Sex	Age	MoCa	Dis dur. (y)	H&Y (ON)	LD equiv.	Lapsed time dop.	CRT baseline	Mod. MDS-UPDRS	Less Symp S	Jamar	Prop
1	F	62	25	7	2	1152	1.5	13.33	4	Left	13.00	6
2	M	64	28	10	2	1083	2	17.83	3	Left	7.67	6
3	M	74	30	1	1	134	2	12.67	2	Left	11.67	6
4	M	53	28	9	2	401	1	14.00	4	Right	18.33	6
5	M	65	30	17	3	1464	1.5	9.67[a]	13	Right	16.00	6
6	M	63	27	2	1	284	2	13.83	4	Right	14.67	5
7	M	73	30	3	2	1200	1.5	9.33[a]	10	Left	14.67	6
8	M	71	30	8	2	512	1.5	10.00	8	Left	15.67	6
9	M	69	30	5	2	302	2	14.67	7	Right	21.00	6
10	F	57	30	2	1	267	2	9.33[a]	6	Right	10.33	6
11	M	81	26	14	3	946	2	9.67[a]	15	Left	14.67	6
12	M	80	28	13	3	938	2	10.33	12	Right	16.67	5
13	F	54	29	3	1	588	1	10.00	3	Left	11.67	6
14	M	54	29	13	3	588	1	7.00[a]	10	Left	12.00	5
15	F	55	28	5	2	446	1.5	10.33	5	Right	12.00	6

Pat patient number, *m* male, *f* female, *MoCA* montreal cognitive assessment, *y* year, *H&Y (ON)* Hoehn und Yahr stage in ON, *LDequiv* Levodopa equivalent, *Lapsed Time Dop.* actual lapsed time from dopamine intake, *CRT* coin rotation test, *MDS-UPDRS* modified MDS-UPDRS upper limb score in ON, *Less Symp. Side* less symptomatic side with regard to motor parkinsonian symptoms, *Prop* Proprioception score

[a] Patients with CRT performance below the cut-off of 10 half turns per 10 s

Neuro-navigation

High-resolution T1-weighted structural images with a 3D-modified driven equilibrium Fourier transform (MDEFT) sequence (176 contiguous slices with 1 mm thickness, 256 mm × 256 mm FOV, TR = 7.92 ms, TE = 2.84 ms, flip angle 16°, matrix size = 256 × 256) were obtained from each subject using a 3T Siemens Trio whole-body MR scanner (Erlangen, Germany). A 12-channel head matrix coil was used for individual coil positioning.

A 3D reconstruction of the scalp and brain surfaces was produced based on the individual MRI scans, using the LOCALITE software (LOCALITE GmbH, Sankt Augustin, Germany). The LOCALITE software was combined with an infra-red tracking system which was used to co-register the 3D scalp reconstruction with the actual subjects' head, based on facial/cranial landmarks. Consequently, the target points (vertex, PMd) could be located on the real head for rTMS application. The PMd stimulation target (Brodmann area 6) was defined based on an overlapping PMd fMRI activity, during the coin rotation task, which we evaluated in a pilot study ($N = 5$). We found an fMRI peak at MNI: x −37, y −12, z 55 (see Fig. 1). According to SPM Anatomy Toolbox (Cytoarchitectonic probabilities) (Eickhoff et al. 2005), the coordinates probabilities are: for Area 6: 70 %, for Area 4a: 30 %, for Area 3b: 10 %. To minimize confounding effects of the motor parkinsonian symptoms, the PMd region contra-lateral to the less parkinsonian side, was targeted. In contrast to the parkinsonian symptoms LKA is not expected to be asymmetric. For LKA we assume that underlying neurodegenerative process in cortical areas is largely symmetric, therefore, affecting both upper limbs (hands) similarly.

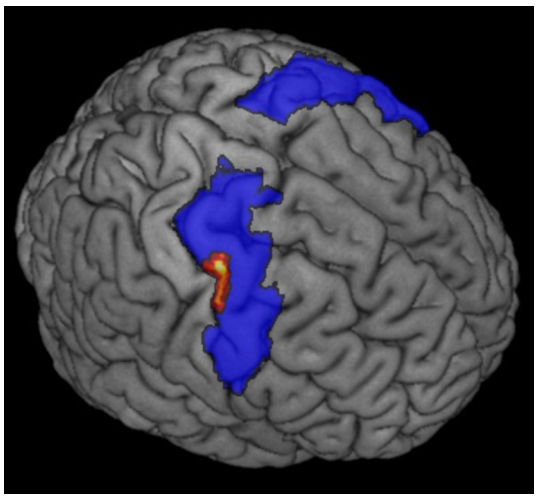

Fig. 1 Overlapping PMd fMRI activity. *Blue* PM from the WFU PickAtlas, *Red-Yellow* overlapping group fMRI activation. All images are superimposed on a normalized image (ch2better template) using the MRIcron software

Theta-burst stimulation

TBS was applied using a MagPro R30 stimulator (Medtronic Functional Diagnostics, Skovlunde, Denmark),

connected to a figure-of-eight coil (Magnetic Coil Transducer MC-B70, Medtronic) with an outer radius of 50 mm or to a similar looking sham coil (Magnetic Coil Transducer MC-P-B70, Medtronic). A cTBS protocol was used as described previously (Nyffeler et al. 2006, 2008; Cazzoli et al. 2009a, b; Cazzoli et al. 2013; Vanbellingen et al. 2014). In brief, a continuous train of 801 pulses was delivered in 267 bursts. Each burst consisted of 3 pulses at 30 Hz, with an interburst interval of 100 ms. The total duration of a single cTBS train was 44 s. For the iTBS protocol a 2 s train of TBS was repeated every 10 s for a total of 190 s. These protocols differ from the original protocol reported by Huang and colleagues, which used a higher burst frequency of 50 Hz (Huang et al. 2005). Recently, it has been shown that the 30 Hz protocol had similar neurophysiologic effects over primary motor cortex, such as decreased motor evoked potentials (MEPs) amplitudes (Wu et al. 2012 and Goldsworthy et al. 2012).

During stimulation, the examiner placed the coil over the target area. The figure-eight coil consists of two circular windings in which currents flow in opposite directions. This design results in a high eddy current density under the middle of the coil, enabling a highly localized stimulation compared with the circular coil. The subjects were asked to keep their eyes closed. Just before the experiment, the individual resting motor threshold (rMT) was defined as the lowest stimulation intensity applied over the left or right primary motor cortex capable of evoking a visible contraction of the contralateral small hand muscles in at least 5 out of 10 consecutive stimuli. The stimulation intensity was set at 80 % of the subjects' individual rMT.

Behavioral tasks

After stimulation, subjects were asked to perform behavioral tasks "offline", including the Coin rotation task (CRT) (Gebhardt et al. 2008; Vanbellingen et al. 2011), which was the primary behavioral outcome measure. To explore the specific effect of TBS on CRT, we controlled for motor parkinsonian symptoms, measured by a modified version of the MDS-UPDRS III (Goetz et al. 2008), strength using the Jamar, and a specific distal finger proprioceptive task (Gilman 2002). All tasks were performed by the less parkinsonian side.

The CRT is a screening test for impaired finger dexterity, well validated in PD (Quencer et al. 2007; Gebhardt et al. 2008; Vanbellingen et al. 2011; Foki et al. 2015). Patients were instructed to rotate a Swiss 20-Rappen coin (size, diameter = 20.9 mm; thickness = 1.6. mm; weight = 4.05 g) between their thumb, index and middle finger as rapidly as possible. Each trial consisted of three periods lasting 10 s. There was one practice trial. The CRT scores were calculated in accordance to previously published papers: CRT score = half turns − [(coin drops × 0.1) × half turns] (Gebhardt et al. 2008; Vanbellingen et al. 2011). Patients were instructed to pick up dropped coins immediately and were helped by the experimenter when needed. Test–retest reliability of the CRT is high in PD ($r = 0.91$, own unpublished data).

The severity of parkinsonian upper limb motor deficits was measured using a modified version of motor examination part III from the MDS-UPDRS (Goetz et al. 2008). This modified version consisted of the upper limb items, of which sum scores were calculated: 3.3 (rigidity), 3.4 (index finger tapping on the thumb 10 times as quickly and as wide as possible), 3.5 (tight fist and opening the hand 10 times as fully open and as quickly as possible), 3.6 (pronation-supination of the hand 10 times as fast and completely as possible), 3.15 (postural tremor), 3.16 (kinetic tremor), 3.17 (rest tremor amplitude) and 3.18 (constancy of rest tremor).

Pinch gauge was measured using the Jamar pinch gauge dynamometer (Sammons Preston Rolyan, 1000 Remington Blvd, Bolingbrook, IL, 60440). This measurement is a reliable and valid test to measures isometric pinch gauge strength (Peters et al. 2011). It was performed in an upright seating position with 90° flexion of the elbow next to the body. Three maximum voluntary pinch gauge strength movements were taken for the hand and mean values in kilograms force were taken.

Proprioception can be impaired in PD (Konczak et al. 2009) and was, therefore, measured in accordance with Gilman (2002). Using a goniometer, 6 movements of 15° of the distal phalange of the index finger were performed. The starting position was always 15° flexion of the distal phalange of the index. The investigator changed the position of the phalange in a pseudo-randomized order (flexion or extension). The patient (eyes closed) had to indicate whether flexion or extension ("up or down") was performed. A correct answer gave one point, resulting in a maximum of 6 points. A score <6 may indicate impaired proprioception (Foki et al. 2016).

The total administration time of the behavioral tasks was 30 min. The performance was scored based on the video recordings by two independent raters (T.V. and M.B.).

Data analysis

A repeated-measures analysis of variance (ANOVA) was performed to explore the effects of TBS over PMd. Since the primary interest of this study was to investigate the effect of TBS on CRT the statistical design consisted of the within-subject factors 'stimulation' (sham, cTBS, iTBS) and 'task' (Coin Rotation). To explore whether the other behavioral measurements (Mod-UPDRS, Jamar, Proprioception) were stable over the three stimulation conditions

several repeated-measures analyses of variance (ANOVA) were performed.

Sphericity was assessed by the Mauchly's test. If the sphericity assumption was violated, the degrees of freedom were adjusted according to the Greenhouse-Geisser method. The Bonferroni correction was used if post hoc comparisons were performed. The level of significance was set at $p = 0.05$ (two-tailed). All values are expressed as mean ± standard error of the mean (SEM). Statistical analyses were performed using PASW for Windows (version 23.0; SPSS, Inc. Chicago, IL, USA).

Results

The analyses reported are based on the behavioral task scores averaged across the two blinded raters, which showed high inter-rater reliability (for the CRT and Jamar: intraclass coefficient = 0.86–0.92, for MDS-UPDRS and proprioception: weighted kappa = 0.85–0.89). TBS was well tolerated and the patients did not complain of any side effect.

The within subject ANOVA revealed that both cTBS and iTBS did not significantly interfere with CRT as no interaction effect in the repeated measures ANOVA was found, $F_{[2,28]} = 0.65$, $p = 0.53$, $\eta^2 = 0.04$ (Fig. 2).

A post hoc sub-analysis, in a group of PD patients ($n = 5$) with stronger baseline impairment of dexterity (CRT sham performance <10 half turns per 10 s), revealed a significant deterioration of dexterous performance after cTBS compared to the sham condition ($t = 2.82$, $p = 0.04$) (Fig. 3). The cut-off of <10 half turns defines LKA (Hill et al. 2010).

With regard to the other behavioral tasks (Mod. UPDRS, Jamar, Proprioception) no significant differences were found indicating that upper limb motor parkinsonian symptoms, strength and proprioception were comparable over the three stimulation sessions (Table 2).

Discussion

This study aimed to investigate whether PMd plays a role in manual dexterity in PD using neuro-navigated sham controlled TBS protocol. A standardized, sensitive fine motor task, the CRT, was used to assess dexterity. Upper limb motor parkinsonian, strength, and proprioception were assessed across all stimulation procedures to control for primary sensory-motor functions. We found that cTBS and iTBS over PMd did not have a significant impact on manual dexterity in PD. However, in a subgroup of patients with dextrous impairment that qualifies for LKA, a significant effect to further deterioration was found for cTBS. In contrast, iTBS had no significant influence in more affected patients.

Several reasons may have contributed to the overall lack of effect of TBS over PMd. First, it is well accepted that PMd is primary active when fine coordinated finger movements are required (Freund and Hummelsheim 1985; Nirkko et al. 2001). However, other regions, such as the primary, somatosensory and SMA, representing parts of the sensorimotor network (Damoiseaux et al. 2006), also contribute to manual dexterity. In the earlier stages of PD this redundancy of network function may well be able to compensate for TBS interference on dexterity. By

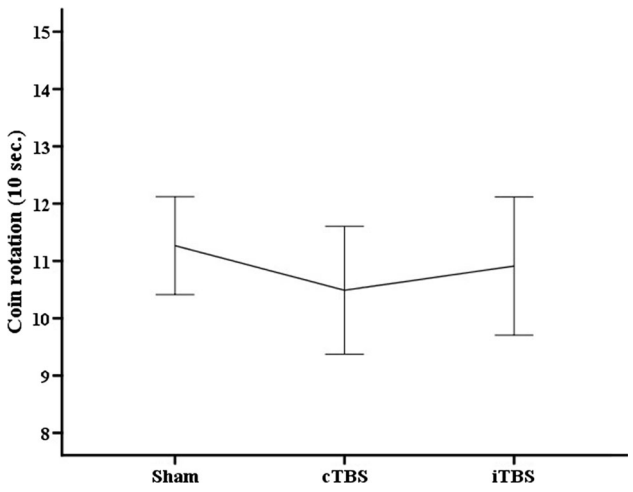

Fig. 2 Effect of TBS on Coin Rotation for the whole group ($n = 15$). Demonstrates no significant interaction effect of TBS over PMd for the Coin Rotation performances. The values reported in the graph are the mean ± standard errors

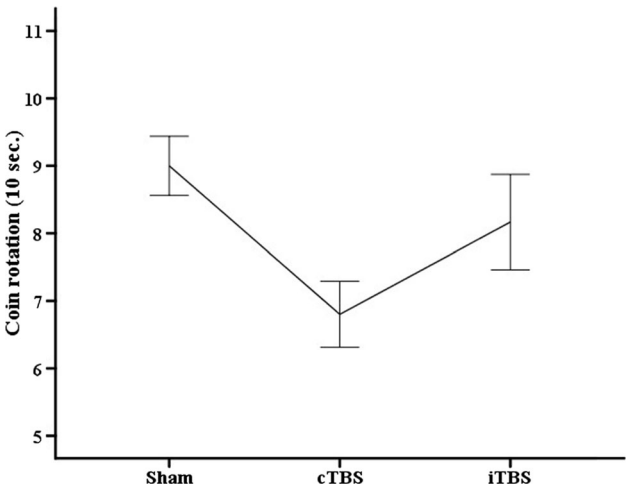

Fig. 3 Effect of TBS on coin rotation for subgroup ($n = 5$). Demonstrates a significant effect ($p = 0.04$) of cTBS versus Sham stimulation of Coin Rotation in 5 PD patients with more severe dextrous impairment (cut-off below 10 rotations). The values reported in the graph are the mean ± standard errors

Table 2 Results of behavioral task (Mod-MDS-UPDRS, Jamar, Proprioception) across the three stimulation conditions

	Sham	*cTBS*	*iTBS*	*p* value
MDS-UPDRS III	7.07 ± 4.08 (2–15)[a]	6.67 ± 4.30 (2–15)[a]	8.27 ± 4.42 (3–17)[a]	0.10
Jamar (Strength)	14.07 ± 3.34 (7.7–21)[a]	14.02 ± 4.33 (9–20)[a]	14.07 ± 3.35 (8.7–19.3)[a]	0.99
Proprioception	5.80 ± 0.41 (5–6)[a]	5.73 ± 0.46 (5–6)[a]	5.60 ± 0.63 (5–6)[a]	0.51

[a] Mean ± SD = Standard deviation (range)

contrast, in more advanced stages of PD, extended involvement of network sites may overwhelm compensatory mechanism. This may explain the adverse effect of cTBS on dexterity in the more severely affected patients. This interpretation is in line with earlier neuro-imaging studies pointing to an overactive pre-motor area, particularly in more advanced PD (Sabatini et al. 2000; Haslinger et al. 2001), corroborating a possible compensatory role of PMd.

Second, the TBS protocols used may be responsible for the lack of significant findings in this explorative study. It has been suggested that iTBS in PD may induce long-term potentiation (LTP) like plasticity, and cTBS may elicit depression (LTD) like effects (Huang et al. 2005; Goldsworthy et al. 2012; Zamir et al. 2012). However, the effects of different TBS protocols may vary in early and more advanced PD patients. For instance, Kishore et al. (2014) found that fluctuating patients without dyskinesia had LTP but no LTD while fluctuating patients with dyskinesia lost both types of plasticity. These data suggest that the TBS response of PD patients are not fixed but may vary with the disease progression and with the onset of motor complications. Interestingly, the different TBS responses also depended on the actual motor state. For instance, fluctuating non-dyskinetic patients in ON state demonstrated both LTP and LTD, indicating a positive dopaminergic effect on both mechanisms of neuroplasticity. However, in our subgroup of PD patients with LKA, most patients were non-dyskinetic and always in ON when stimulated. Therefore, effects of both stimulation protocols would have been expected, although we only found a significant cTBS effect. Further studies need to explore the relevance of dopaminergic neuroplasticity for behavioral effects of the two TBS protocols.

Third, it remains to be explored whether several cTBS trains instead of only one stimulation session could have been more effective as shown for stimulation of SMA (Eggers et al. 2015). However, based on previous findings on praxis movements (Vanbellingen et al. 2014) the power analysis suggested that 14 patients would be sufficient to reach a significant result. Indeed, between TBS and sham an expected difference of 10 % in the CRT performance was found, although only in the more affected patient subgroup. Our findings suggest that subsequent studies should focus on PD patients with LKA. In addition, to further validate the effect of TBS on dexterity, exact dose–response relationships may be of interest.

Fourth, in this study we used the figure-of-eight coil allowing more focal stimulation, possibly at cost to the effect strength. Therefore, based on the negative results presented here, we suggest that for future studies round coils are used which target larger cortical areas with potentially stronger influence on motor performance.

To conclude, this is to our knowledge the first sham controlled neuro-navigated rTMS study exploring manual dexterity in PD. Although the overall effect of this study was negative we could demonstrate that in PD with LKA, cTBS over PMd may further interfere with manual dexterity. Future studies should take into account the inter-individual variability of cortical plasticity observed in fluctuating PD patients (Kishore et al. 2014) allowing to stratify (cTBS or iTBS) according to the different profile of LTP-like and LTD-like alterations. This may ultimately allow identifying eventual responders or non-responders using a specific TBS protocol. Subsequent TBS studies may benefit from targeting additional cortical areas, such as the S1 or SMA.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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