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Short communication

Single-pulse subthalamic deep brain stimulation reduces premotor-motor facilitation in Parkinson's disease

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ABSTRACT

Introduction: Deep brain stimulation improves motor symptoms in Parkinson's disease and changes primary motor cortex excitability, but how subthalamic nucleus stimulation affects premotor-motor cortical connectivity remains unclear.

Methods: We investigated 10 Parkinson patients in whom single subthalamic nucleus stimulation was time-locked to transcranial magnetic dual-coil, paired-pulse stimulation of the dorsal premotor and primary motor cortex. Premotor-motor interaction with deep brain stimulation switched off was compared to 10 controls.

Results: Parkinson patients showed abnormally facilitated premotor-motor interaction with deep brain stimulation switched off compared to controls. This abnormal premotor-motor facilitation was abolished during subthalamic nucleus stimulation at 3 Hz.

Conclusions: In Parkinson's disease, aberrant signals from the basal ganglia leading to a loss of physiological premotor-motor inhibition can be normalized by subthalamic deep brain stimulation. This effect is likely mediated by activation of subthalamic-pallidal-thalamic projection to the premotor cortex.

1. Introduction

Parkinson's disease (PD) is characterized by decreased primary motor cortex (M1) inhibition and excessive facilitation at the cortical level as demonstrated in transcranial magnetic stimulation (TMS) studies [1]. Cortical abnormalities in PD also involve secondary motor areas [2]. The interactions between the dorsal premotor cortex (PMd) and M1 are of particular interest because the PMd plays a major role in movement preparation. PMd-M1 interaction is inhibitory in healthy subjects [3] and is altered in PD [4]. Subthalamic nucleus deep brain stimulation (STN DBS) is an established treatment in PD. Paired-associative stimulation studies have demonstrated that STN DBS restored intracortical M1 inhibition and normalized motor cortex plasticity [5]. Studies that paired DBS pulses with M1-TMS have shown time dependent facilitation of M1 excitability at specific interstimulus intervals (ISI) [5,6]. Pairing of stimulation of subcortical and cortical regions provides a unique opportunity to study the dynamics of basal ganglia-cortical interactions *in vivo*. However, this technique has not been applied to the PMd. In the present study, we investigated the time course of single-pulse STN DBS on PMd-M1 interaction in PD. We hypothesized that pathologic PMd-M1 facilitation could be abolished by preceding STN DBS at specific time intervals.

2. Material and methods

2.1. Participants

Ten PD patients (one female, mean age 62, range 54–71 years) with STN DBS were recruited from Toronto Western Hospital, Canada and the University Hospital Schleswig-Holstein Lübeck, Germany (Table 1) and gave written informed consent. The study was approved by the local ethics committees. All patients had undergone bilateral

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Table 1
Demographic and clinical data of all patients.

Patient number	Sex	AAE	AAO	DD	TSS	LED pre DBS	LED post DBS	UPDRSIII DBS Off	UPDRSIII DBS On	DBS parameters	STN-L
1	M	63	42	21	8	1750	1350	n. a.	33	3.6 V, 60 µs, 250 Hz*	7-, case +
2	M	61	42	19	11	2000	1075	34	22	4.8 V, 60 µs, 185 Hz*	5-, case +
3	M	62	49	13	3	3000	1225	42	33	5.7 V, 90 µs, 60 Hz*	11-, case +
4	M	55	41	14	6	2350	900	68	34	5.8 V, 60 µs, 60 Hz*	10-, case +
5	M	71	58	13	1	1767	1400	38	28	3 V, 60 µs, 80 Hz*	10-, case +
6	F	68	60	8	1	950	275	40	33	4 mA, 40 µs, 130 Hz^{X}	9-, case +
7	M	54	39	15	1	1717	200	67	29	2.5 V, 60 µs, 130 Hz*	10-, case +
8	M	65	34	31	7	1250	1225	64	49	4.2 V, 60 µs, 80 Hz*	7-, case +
9	M	56	43	13	3	1455	525	58	35	2.3 V, 90µs,150 Hz^{Y}	1-, case +
10	M	68	55	13	3	1384	975	22	12	2.8 V, 90 µs, 130 Hz^{Y}	1-, case +
Mean (+/- SD)		62 (6)	46 (9)	16 (6)	4 (3)	1762 (587)	915 (437)	48 (17)	31 (10)		

AAE = age at examination in years; AAO = age at onset in years; DD = disease duration in years; TSS = time since surgery in years; UPDRS III = part three of the Unified Parkinson's Disease Rating Scale; LED pre DBS = L-Dopa equivalent dose before DBS implantation (mg/day); UPDRSIII DBS Off = UPDRS III with DBS switched off on both sides, but on dopaminergic medication; UPDRSIII DBS On = UPDRS III with DBS switched on with clinically optimal DBS parameters and on dopaminergic medication; LED was calculated using the following formula: LE = total dose of immediate release levodopa (with peripheral decarboxylase inhibitor) + (0.75 x dose of controlled-release levodopa) + (100 x dose of pramipexole) + (16.7 x dose of ropinirole); in the last row mean values (Mean) with standard deviations (SD) for each parameter are expressed; Deep brain stimulation was delivered by a quadripolar electrode: *Medtronic lead model 3387; ^{Y}Medtronic lead model 3389; ^{X}Boston Scientific lead model DB-2201 Standard; the Medtronic electrode contains 4 contacts from ventral to dorsal numbered 4–7 (patients 1, 2 and 8), 8–11 (patient 3 - 7) or 0 - 3 (patients 9 and 10) and for Boston Scientific electrode 8 contacts from ventral to dorsal numbered 9-16 (patient 6). The electrodes are 1.27 mm (model 3387 and 3389) or 1.3 mm (model DB-2201) in diameter. The contacts are 1.5 mm in length and are spaced 1.5 mm (model 3387), 0.5 mm (model 3389) or 2.0 mm (model DB-2201) apart; STN-L = the contact polarity information refer to the left STN electrode.

implantation of STN DBS with quadripolar electrodes (seven patients received model 3387 and two received model 3389; Medtronic, Minneapolis, MN and one patient received model DB-2201 Standard; Boston Scientific), and had been treated with DBS for > 6 months with stable improvement of PD symptoms (Table 1). All patients took their regular dopaminergic medications and participated in two experiments in random order. We excluded patients with severe rest tremor in the right hand which may interfere with TMS recordings.

In Experiment 1, STN DBS was switched off and PMd-M1 interaction was investigated. An established MRI-neuronavigated dual-coil, paired-pulse TMS paradigm at 6 ms ISI with two Magstim 200^{2} magnetic stimulators and two figure-of-eight coils (70 mm M1, 25 mm PMd) was used (Fig. 1a) [7]. The conditioning stimulus intensity over left PMd was 90% active motor threshold (AMT) or 110% resting motor threshold (RMT). The test stimulus intensity over left M1 was adjusted to produce motor evoked potentials (MEP) of ~1 mV. Surface EMG was recorded from the first dorsal interosseous muscle. Ten trials for each condition were applied. Paired *t*-test (Bonferroni corrected p value of ≤0.025) was used to compare the mean unconditioned and conditioned peak-to-peak MEP amplitudes of each conditioning pulse intensity. PMd-M1 interaction was expressed as ratio of conditioned to unconditioned MEP. PD patients were compared to a group of 10 age and sex matched controls (two females, mean age 62, range 49–72 years) using unpaired *t*-test.

In Experiment 2, the left STN DBS frequency was set to 3 Hz, which was the lowest possible frequency of the stimulator, at clinically used pulse width (60 µs) and voltage (2.3–5.8 V). At this frequency, we paired DBS pulses of the left STN with dual-pulses given to PMd-M1 TMS. Therefore, DBS used monopolar stimulation with the clinically used contact as the cathode and the case of the pulse generator as the anode. The right STN DBS was switched off. DBS artefacts registered by surface electrodes over the chest were used to trigger the TMS pulses. The PMd-M1 setup was identical to Experiment 1. By adding STN conditioning, we created six triple-pulse stimulation conditions of STN-PMd-M1 with STN-PMd ISIs of 3, 4, 10, 18, 23, and 161 ms. We also tested six dual-pulse stimulation conditions of STN-M1 pulses without PMd conditioning with STN-M1 ISIs of 9, 10, 16, 24, 29, and 167 ms. Since the PMd-M1 ISI was fixed to 6 ms, the ISIs between STN and M1 stimulation were identical in the triple and dual-pulse conditions. The different conditions were tested in random order with 10 trials per condition. PMd-M1 interactions during STN stimulation at specific intervals were expressed by the MEP amplitude ratios of STN-PMd-M1 conditions to those of STN-M1 conditions without PMd stimulation at the corresponding ISI.

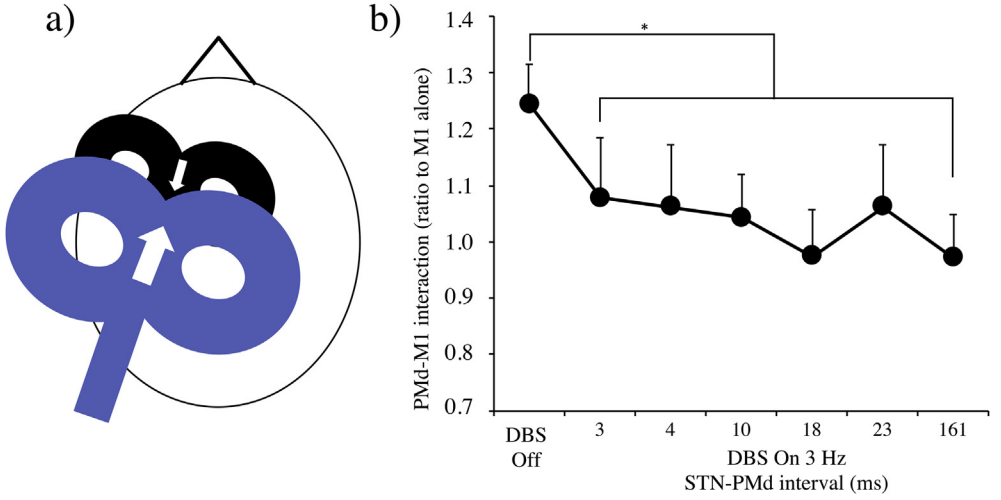

Fig. 1. A) Neuronavigated dual-coil PMd-M1 TMS paradigm; Black coil = PMd coil. White arrow = anterior-to-posterior current flow. Blue coil = M1 coil. Larger white arrow = posterior-to-anterior current flow. B) Comparison of PMd-M1 interaction with DBS off (Experiment 1) and with STN DBS on 3 Hz at different STN-PMd intervals (Experiment 2). For DBS off, PMd-M1 interaction is the ratio of MEP amplitude from PMd-M1 stimulation to M1 stimulation alone. PMd-M1 interaction in the presence of STN DBS is represented by the MEP amplitude ratios of STN-PMd-M1 to STN-M1. Asterixis: p = 0.044, paired *t*-test, mean of all triple-pulse conditions against PMd-M1 DBS off.

To investigate the net effect of STN conditioning on PMd-M1 interaction, paired *t*-test of the mean of all six triple-pulse STN-PMd-M1 conditions (Experiment 2) and the mean of the dual-pulse PMd-M1 condition with DBS switched off (Experiment 1) was used. Paired *t*-test was used due to the asymmetrical data distribution in both experiments. In addition, the individual triple-pulse conditions at each ISI were compared separately with the PMd-M1 interaction when DBS was switched off with Bonferroni correction for multiple comparisons (p value < 0.008).

To test for possible differences between STN-PMd-M1 triple-pulse and STN-M1 dual-pulse conditioning in Experiment 2, we performed a repeated measure analysis (ANOVA) using the factors PMd (PMd present in triple-pulse conditions vs. PMd absent in dual-pulse conditions) and ISI (STN-PMd ISIs: 3, 4, 10, 18, 23, and 161 ms and STN-M1 ISIs: 9, 10, 16, 24, 29, and 167 ms).

Due to our small sample size and the data may not be normally distributed, we performed additional non-parametric test (Wilcoxon signed-rank test, Mann-Whitney test and Friedman analysis) to confirm our results.

3. Results

3.1. Premotor-motor interaction with STN DBS switched off

When DBS was switched off in Experiment 1, comparison of the unconditioned peak-to-peak MEP amplitudes with PMd-conditioned MEPs using paired *t*-test showed significantly larger PMd-conditioned MEP amplitudes at 110% RMT (unconditioned mean MEP ± standard error (SEM) = 1.3 ± 0.22 mV; conditioned mean MEP 1.61 ± 0.26 mV; paired *t*-test p = 0.005; Wilcoxon signed-rank test p = 0.013), but not at 90% AMT (unconditioned mean MEP = 1.03 ± 0.23 mV; conditioned mean MEP = 1.25 ± 0.40 mV; paired *t*-test p = 0.315; Wilcoxon signed-rank test p = 0.799) in PD patients. This PMd-M1 interaction was facilitatory in PD patients but inhibitory in healthy controls at conditioning intensity of 110% RMT (PD mean MEP ratio = 124 ± 7%, controls = 95 ± 7%). The group difference was significant (unpaired *t*-test p = 0.007; Mann-Whitney test p = 0.015). There was no difference between PD patients and controls at 90% AMT (PD = 111 ± 11%, controls = 108 ± 22%; unpaired *t*-test p = 0.894; Mann-Whitney test p = 0.353).

3.2. Effects of STN conditioning on PMd-M1 interaction

Mean PMd-M1 amplitudes with preceding DBS at 3 Hz and a PMd pulse intensity of 110% RMT significantly differed from those without DBS (paired *t*-test p = 0.044; Wilcoxon signed-rank test p = 0.037). Abnormal PMd-M1 facilitation in the off state (Experiment 1; 124 ± 7%) was reduced with DBS switched on 3 Hz (Experiment 2; mean of all triple-pulse conditions = 102 ± 3%; Fig. 1b). However, there was no specific ISI effect when comparing the individual triple-pulse conditions with the DBS off dual-pulse condition after Bonferroni correction with a corrected p value of < 0.008 (Fig. 1b). No significant difference between DBS switched off (111 ± 11%) and on 3 Hz (mean of all triple-pulse conditions = 102 ± 5%, paired *t*-test p = 0.44; Wilcoxon signed-rank test p = 0.646) was seen for the PMd conditioning intensity of 90% AMT.

Repeated-measure ANOVA (and Friedman analysis) of Experiment 2 did not show a significant effect of the factor PMd and ISI, and no significant interaction of factors. During the 3 Hz STN stimulation abnormal PMd activity was reduced, resulting in no significant difference between STN-PMd-M1 triple-pulse and STN-M1 dual-pulse condition of Experiment 2. The clinical parameters (age at onset, disease duration, UPDRS III score, L-Dopa equivalent dose) did not correlate with TMS findings.

4. Discussion

To our knowledge, this is the first study that investigated the effects of single STN stimulation on PMd-M1 interactions in PD. In our advanced PD patients, aberrant signals from STN and other basal ganglia nuclei likely affected PMd-M1 interactions causing abnormal PMd-M1 facilitation. Such facilitation was reduced by preceding STN stimulation at all ISIs tested. Contrary to our hypothesis, we did not observe effects at specific intervals.

STN DBS has previously been shown to restore decreased intracortical inhibition and plasticity of M1 in PD. Pairing STN DBS with M1-TMS at specific ISIs found increased M1 excitability at short (~3 ms) and medium ISI (~23 ms) [5], which coincided with latencies of cortical evoked potentials recorded with EEG [6]. Repeated pairing of STN DBS and M1-TMS at these two intervals induced M1 plasticity [5]. M1 activation at short ISI is likely due to antidromic activation of the hyperdirect cortical-STN pathway, which was also demonstrated in animal studies [8]. Facilitation at medium ISI likely represents orthodromic conduction through the indirect basal ganglia pathway [6].

We here show that the abnormal PMd-M1 facilitation with DBS switched off was not present when single-pulse STN DBS was followed by PMd stimulation regardless of the timing of PMd stimulation. Our results suggest that, although 3 Hz STN stimulation does not show a clinical benefit in PD patients, it restores physiological PMd-M1 interaction. Presumably, 3 Hz STN stimulation alters activity in subthalamic-pallidal-thalamic projections to the cortex including the premotor area. This effect was also shown during STN microelectrode stimulation at 5–10 Hz, that resulted in evoked potentials over the premotor cortex recorded with high-resolution electroencephalography [9]. During 3 Hz STN DBS, the abnormal PMd activity on M1 was reduced, resulting in comparable activity during STN-PMd-M1 triple-pulse and STN-M1 dual-pulse stimulation in Experiment 2. However, it is also possible that STN DBS lowers the M1 MEP threshold by other mechanisms, such as reducing pathological cross-frequency coupling between STN and M1 that would otherwise lead to a reduction of M1 output in PD.

Although 3 Hz STN stimulation abolished PMd-M1 facilitation, there was no clinical benefit. Clinical effects may require further PMd-M1 excitability changes with restoration of physiological inhibitory interactions and changes in other cortical areas [10]. In a similar vein, repetitive TMS of the PMd in PD patients increased the duration of the silent period, as a measure of corticospinal excitability, but also had no clinical effect [11].

A previous dual-pulse TMS study in PD patients showed PMd-M1 facilitation in the off medication state, which changed to inhibitory interaction while on dopaminergic medication [10]. A similar effect was seen in heterozygous *Parkin* and *PINK1* mutation carriers showing PMd-M1 facilitation which changed to inhibitory interactions after the first L-Dopa intake [7]. We found that PMd-M1 interactions were facilitatory with STN DBS switched off while patients were still on dopaminergic medication. This difference compared to previous studies can be explained by the fact that the patients studied here had more advanced PD and were taking lower L-Dopa dosages due to STN DBS than those in previous studies (Table 1). When DBS was switched off, dopaminergic medication was not sufficient to restore normal PMd-M1 inhibitory interaction. This is consistent with the finding that patients had significant worsening of motor symptoms when DBS was switched off (mean increase of 17 points in UPDRS III, Table 1). Our patients were heterogeneous in terms of clinical and demographic parameters, which might have influenced our neurophysiological results.

Abnormal neuronal activity of the premotor and parietal areas in PD was also evident in previous imaging studies [12]. This overactivity of premotor–parietal circuits may represent a neural correlate of adaptive plasticity as a compensatory mechanism for deficient activation of impaired striatal-mesial–frontal projections [12]. Given the intense functional connectivity between PMd and M1 and between basal ganglia and M1 in humans [5,9], it is conceivable that abnormal STN

activity in PD drives some of the changes in premotor-motor cortical excitability and interaction found in our PD patients. This may explain our finding that modulating STN excitability by changing STN DBS from off to 3 Hz was able to reduce abnormal PMd-M1 facilitation to more physiological inhibitory connection, independent of the time intervals between STN DBS and PMd stimulation tested [9]. This finding is potentially relevant for management of PD patients. PMd-M1 interactions can be further investigated as a potential neurophysiological marker for DBS response. Future studies can examine whether higher frequencies of STN stimulation lead to further restoration of PMd-M1 inhibition and associated clinical improvement.

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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.2019.08.003.

Declaration of interest

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Authors‘ roles

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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