RESEARCH PAPER

Movement kinematic after deep brain stimulation associated microlesions

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ABSTRACT

Backgrounds Deep brain stimulation is widely used for the treatment of movement disorders such as Parkinson's disease and dystonia. After the implantation of electrodes an immediate improvement of clinical symptoms has been described. It is unclear, whether movement kinematics are also changed by this 'microlesion effect'.

Methods To gain further insight into these mechanisms, we studied arm, hand and finger movements preoperatively and immediately after the implantation of deep brain stimulation electrodes in patients with Parkinson's disease and dystonia.

Results After implantation and without stimulation there was a clear reduction of clinical symptoms in both groups, as has been described previously. However, movement velocity was affected differently. Parkinsonian patients showed increased movement velocity postoperatively, whereas dystonic patients were significantly slower after electrode implantation.

Conclusions Lesioning and stimulation of these structures have the same beneficial clinical effects. Furthermore we suggest that globus pallidus internum lesions act by inhibiting a system which mainly acts upon muscular tone and limb posture whereas subthalamic stimulation or lesion causes a more unspecific disinhibition of movements.

INTRODUCTION

Deep brain stimulation (DBS) with multipolar electrodes connected to a subcutaneous pacemaker has evolved into a standard technique, targeting the subthalamic nucleus (STN) or the globus pallidus internum (GPi) in advanced idiopathic Parkinson's disease (PD)[1 2] or the GPi in severely impairing primary dystonia.[3 4]

After DBS lead implantation and even before the actual electrical stimulation is initiated, many patients show an improvement of symptoms due to a so-called microlesion effect (MLE). It seems most likely that the MLE is caused by an oedema, which surrounds the electrode and causes inactivation of neurons or fibres. Intraoperative microelectrode penetrations may also play a role. The MLE has been observed in both PD patients[5 6] and patients with dystonia in whom the MLE-induced symptom reduction was a good predictor of outcome after 6 months.[7] In STN electrode implantation this effect equals the clinical benefit 6 months postoperatively.[8] However, the positive MLE on clinical symptoms was not seen by all authors.[9]

The aforementioned studies on the MLE in PD as well as in dystonia used motor scales taken by expert neurologists to assess clinical improvements. However, kinematic data of specific movements have not been reported in these circumstances. The present study set out to investigate the impact of the MLE on specific parameters of proximal and distal arm and hand movements. Specifically, we were interested in whether a small lesion within the GPi in dystonic patients would cause the same movement changes as a STN lesion in Parkinsonism, as one might conclude from the above-cited studies. The answers to these questions are relevant for understanding the mechanisms by which DBS causes symptom relief and may explain certain adverse symptoms caused by stimulation.

METHODS

Subject selection and clinical assessment

Sixteen patients undergoing DBS were investigated. Seven had electrodes implanted bilaterally in the STN for advanced PD (mean age: 61 years; SD: 5) and nine bilaterally in the GPi for cervical dystonia (mean age: 50 years; SD: 13). None of the dystonic patients had any dystonic symptoms in the arms, hands or fingers. All preoperative and postoperative recordings were done while patients were in the off-drug state for at least 8 h. The regular preoperative levodopa equivalence of PD patients was calculated according to Krack (table 1).[10]

Clinical rating was performed before and after surgery without medication or stimulation, using the motor Unified Parkinson's Disease Rating Scale and the modified Hoehn and Yahr scale for PD and the Toronto Western Spasmodic Torticollis Rating Scale and the Global Dystonia Rating Scale for dystonic patients. The study was approved by the ethics committee of the medical faculty of the Ludwig-Maximilian University, Munich. All subjects gave their written informed consent prior to participation. Clinical information about patients is given in table 1.

Surgical intervention

DBS electrodes were implanted by MRI-guided stereotaxy in the STN for PD (model 3389, Medtronic Neurological Division, Minnesota, USA) and in the GPi for dystonia (model 3387, Medtronic). PD patients were operated on under local anaesthesia and patients with dystonia under general anaesthesia. Initial target coordinates were 20 mm lateral, 4 mm below and 3 mm anterior to the midpoint of the anterior and posterior commissures for dystonia, and 11 mm lateral,

Table 1 Clinical details of PD and dystonic patients

Parkinson's disease						Dystonia					
			Pre/post-op						Pre/post-op		
Case/ Gender	Age (yrs)	Disease duration (yrs)	Motor UPDRS scales	H&Y staging	Pre-op L-dopa equivalent (mg/day)	Case/ Gender	Age (yrs)	Disease duration (yrs)	TWSTRS scales	GDS scales	Pre-op medication (daily dose)
1/M	56	12	25/9	3.5/1.5	1050	1/M	66	6	20/12	35/24	No medication
2/M	59	8	26/10	3.5/1.5	1630	2/F	63	13	38/16	20/10	No medication
3/M	69	10	16/11	2/1.5	980	3/M	30	18	6/4	15/8	Diazepam 5 mg
4/M	67	8	40/29	4/3	1400	4/M	40	8	10/7	17/10	No medication
5/M	57	8	14/10	3.5/1.5	1000	5/F	52	11	23/11	10/4	No medication
6/M	63	18	25/18	3/2	1100	6/M	50	34	16/7	18/13	No medication
7/F*	57	20	36/24	5/4	1620	7/M*	57	7	25/16	21/8	No medication
						8/F*	30	15	18/13	35/30	Tetrabenazine 25 mg
						9/M*	59	8	24/20	12/9	No medication

All scalings were assessed during off-medication and off-DBS state.
*Subject executed motor tasks only with right hand while other subjects performed with both hands.
M, male; F, female; UPDRS, Unified Parkinsons's Disease Rating Scale; H & Y, Hoehn and Yahr staging; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; GDS, Global Dystonia Rating Scale.

3 mm posterior and 3 mm below for the STN. These standard target coordinates were then adjusted based on individual anatomical MRI-landmarks, if necessary. Microelectrode recordings (usually three tracks per side) were used to detect target-specific neuronal discharges. Correct electrode placement was verified for all cases by postoperative 1.5T MRI.

Experimental set-up

All tests were conducted preoperatively as well as on the first or second day after the implantation of DBS electrodes. We scaled clinical symptoms and applied a test battery of arm, hand and finger movements as specified below. Subjects were seated in a comfortable chair with a backrest for the tapping and pronation tasks and stood during the boxing task. Tasks were performed with both sides sequentially, if possible (see below). All tasks were first demonstrated by the investigator and a brief practice trial was performed to familiarise subjects with the tasks. No external pacing or starting cues were given. In the PD group one subject could not perform any motor task with the left hand because of severe tremor, before and after surgery. In three patients with dystonia, left-sided movements were not possible postoperatively due to intravenous catheters for antibiotics (table 1).

Distal movements: finger tapping (FT), pronation-supination movements (PSM)

Figure 1A,B illustrates the experimental setup for repetitive finger tapping (FT) and repetitive alternating forearm pronation and supination movements (PSM). FT was performed with the index finger against the thumb. Subjects were asked to fully open the index finger and the thumb, before tapping the thumb and to perform this movement repetitively as fast as possible. Two small ultrasound emitters (diameter: 10 mm, height 8 mm) were placed on the index finger and the thumb and their three-dimensional spatial positions were continuously recorded with an ultrasound-based system (sampling frequency: 50 Hz; resolution: 0.5 mm; CMS20S, Zebris, Isny, Germany). Forearm PSM were performed with the subjects holding a cardboard tube (4 cm diameter, 15 cm length) in their fist with one ultrasound marker mounted on each end of the tube. Repetitive PSM had to be as large and fast as possible. Subjects were allowed to hold their hands in the most comfortable position; the ultrasound sensor board was then adjusted to reliably record the movements in that comfortable position (see figure 1). FT and PSM tasks were each recorded for 25 s, starting 5 s after movement onset.

Proximal movements: ballistic arm movements (boxing with touch; BT)

The experimental set-up is illustrated in figure 1C. The subjects performed repetitive fast ballistic boxing movements against a punching bag. The fist reached the bag before the arm was

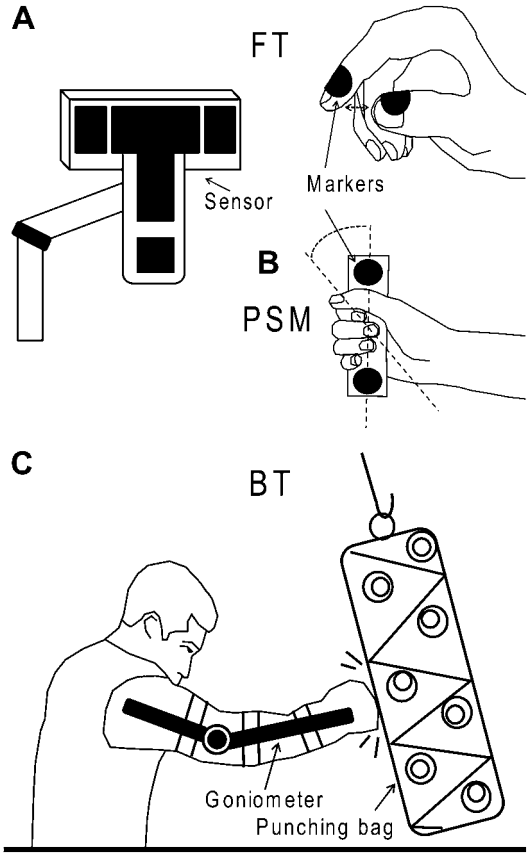

Figure 1 Schematic representation of experimental setup (A) FT: finger tapping; (B) PSM: forearm pronation and supination; (C) BT: ballistic movement (boxing with touch).

fully extended. Before surgery, some PD patients had to be seated in front of the bag. Patients performed 30–45 strokes with pauses after every 10–15 actions to prevent fatigue. A calibrated goniometer was used to record elbow joint position.

Data analysis and statistics

Data were analysed offline with MATLAB R2008b (The Mathworks, Lowell, Massachusetts, USA). From the three-dimensional datasets of the FT movements the distance between the two markers was calculated, and amplitude, frequency and peak velocity of each individual movement were determined. We evaluated peak velocity only, since an earlier study had shown that amplitude and velocity in this task are linearly correlated and frequency does not reflect bradykinesia.[11] For PSM, the three-dimensional data were transformed so that the variance was maximised in the plane of rotation (main axis transformation after eigenvector-determination). Thereafter, the angle between a line connecting the two markers and the horizontal was determined, and the angular amplitude, frequency and peak angular velocity were calculated for each cycle. Peak angular velocity of the movements was used as the criterion for evaluation. In the boxing task, peak angular velocity was computed for movements, which exceeded a minimum angular velocity of 20 deg/s. Kinematic data were pooled for both arms of an individual (see table 1) after the exclusion of differences between the dominant versus non-dominant hand with the t-test (see Results).

For preoperative and postoperative velocity comparison, only the fastest 30% of all trials were taken. The mean was calculated from these data, resulting in one value per test for each subject and test session. For the analysis of fatigue, all single strokes (or movements) of the FT and PSM task were evaluated and a quotient of fatigue was calculated from the mean velocities of the last 30% versus the first 30% of all trials. Fatigue effects were not analysed for the boxing task, since in this task small pause between movements prevented fatigue.

Statistical analyses were carried out with SPSS V.18. The differences between preoperative and postoperative values were determined with an analysis of variance for repeated measures and a general linear model of a two-factor mixed design for each of the four motor tasks. Between-group factors were 'PD' and 'dystonia'; within-subject factors were 'preoperative' and 'post-operative'. Non-spherical data was corrected for by the Green-house-Geisser method. A post-hoc paired t-test identified within-group differences between 'preoperative' and 'post-operative'. A percentage change in mean (angular) velocities was calculated separately. An α error <0.05 was taken for statistically significant differences; error bars in the figures show the SE of the mean.

RESULTS

Clinical ratings preoperatively and during MLE

Clinical improvement (without stimulation or medication) was significant after the operation in both groups. PD patients showed a mean reduction of the UPDRS III of 39.0% ($p<0.001$, paired t-test) as well as Hoehn and Yahr scale (38.8%, $p<0.001$). Dystonia patients improved in both the Toronto Western Spasmodic Torticollis Rating Scale (−41.1%, $p<0.004$, paired t-test) and the Global Dystonia Rating Scale (−36.6%, $p<0.001$).

Dominant versus non-dominant arm

There was no significant difference in mean (angular) velocity between dominant and non-dominant arms across all four motor tasks (each $p>0.05$), in accordance with previous reports.[12] Therefore, data from both arms were pooled for further analysis.

Finger tapping (FT)

When both groups were analysed together, the speed of FT before and after surgery was not changed significantly (factor 'pre-post-op': ($F_{1,26}=0.028$; $p=0.87$). This was due to the opposite effect of the operation on tapping speed in the two groups (significant interaction of group and pre/post surgical performance—$F_{1,26}=7.36$; $p=0.012$). Specifically, dystonic patients slowed down their FT speed whereas PD patients exhibited faster movements after surgery. Paired t-tests revealed a significant postoperative decrease of velocity by 31% in the dystonic group ($t_{14}=3.08$; $p=0.008$). FT velocity in PD increased postoperatively by 51%, but this was not significant (paired t-test: $t_{12}=-1.5$; $p=0.16$; figure 2A).

Pronation-supination movement (PSM)

Concerning the velocity of the PSM task, both groups behaved differently with the dystonic patients showing slower and the PD patients showing faster movements compared to the

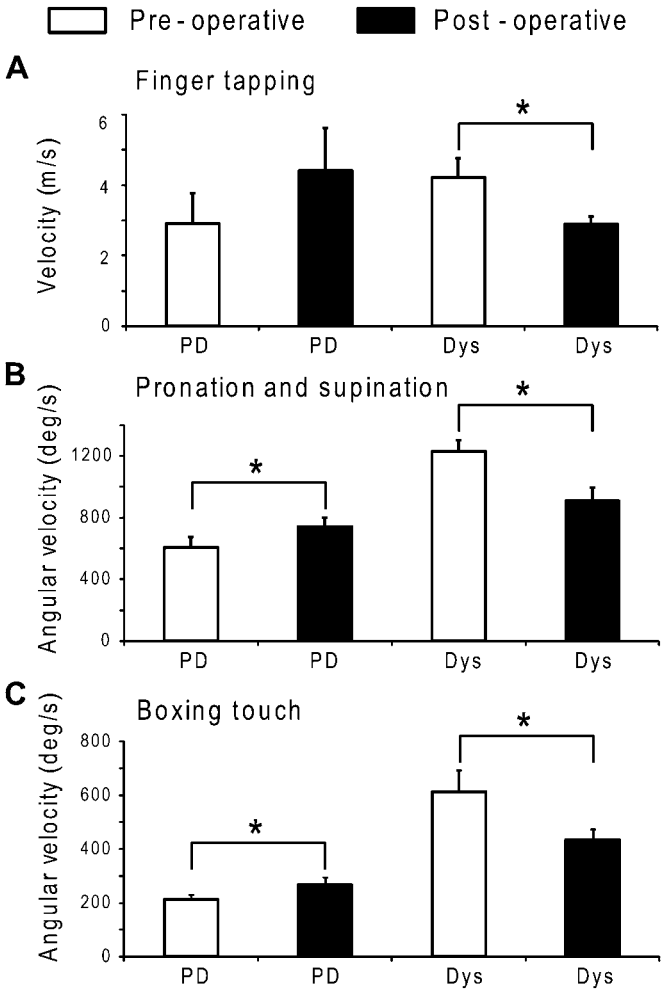

Figure 2 Illustration of preoperative and postoperative mean (angular) velocity of (A) finger tapping, (B) pronation and supination movements and (C) ballistic movements before and after the insertion of electrodes. PD: Parkinson's disease; Dys: dystonia. Note the significant effect (paired t-test, *$p<0.05$) between preoperative and postoperative motor performance.

preoperative tests (factor group: $F_{1,26}$=21.56; p=0.001; interaction between 'group' and 'within-group': $F_{1,26}$=17.20; p=0.001). This was confirmed by post-hoc paired t-tests revealing a significant increase in angular velocity in PD patients (t_{12}=−2.45; p=0.03, 22.78%) and a significant decrease in dystonia (t_{14}=3.54; p=0.003, −26.07%) (figure 2B).

Boxing with touch (BT)

Analysis of variance for repeated measures results revealed significant differences between groups and significant effects of interaction (group: $F_{1,26}$=22.36; p=0.001; group*within-group interaction: $F_{1,26}$=9.74; p=0.004). PD patients were significantly faster after DBS surgery (t_{12}=−2.20; p=0.04, 25.82%), while dystonic subjects performed this task with significantly lower angular speed after surgery (t_{14}=2.70; p=0.017, −28.97%) (figure 2C).

Fatigue effects

The quotient of fatigue was slightly less after surgery in both PD and dystonia in FT and PSM, although this change was not statistically significant (p >0.05) (figure 3).

DISCUSSION

In this study, we investigated the consequences of the MLE on clinical scores and kinematic movement parameters in patients with two different complex movement disorders. This makes it debatable whether the results can be generalised to gain knowledge about the function of the basal ganglia in the normal state. This will be discussed below. The main finding of our study was that movement velocity as investigated in our tests was unexpectedly reduced postoperatively in all three tasks in dystonia. In contrast, our PD patients performed proximal and distal movements faster after STN implantation, which we attribute to the bilateral MLE imposed on the STN.[8] This is comparable to iatrogenic lesions of the STN that have been applied sporadically as a therapy for PD.[13] A manifold of studies on the kinematics of movements have shown that STN stimulation reliably reduces parkinsonian bradykinesia.[14 15] Proximal arm movements seem to benefit slightly more than distal movements, especially when grasping movements are considered.[12 16] However, distal movements such as handwriting[17] and muscle force control seem to normalise under STN stimulation.[16] With regard to these studies and our results it seems that the MLE affects kinematic parameters similarly to stimulation.

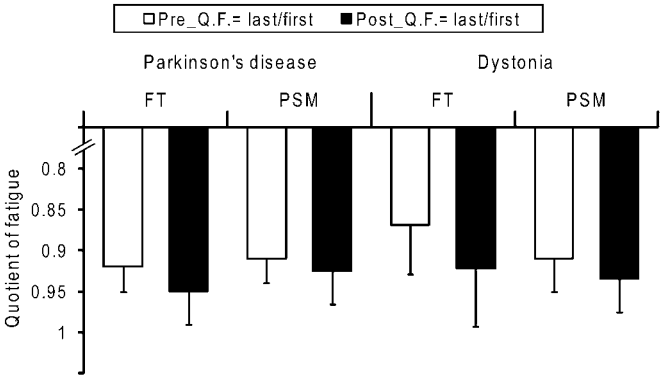

Figure 3 Quotient of fatigue (QF) in PD and dystonia preoperatively and postoperatively during finger tapping (FT) and pronation and supination movements. Mean value of QF shows reduction of the fatigue score (not significant) after the electrode implantation.

This would be in favour of the 'silencing' hypothesis as opposed to the 'entrainment' hypothesis, which holds that specific stimulation frequencies may actively influence basal ganglia networks.[18]

With regard to our dystonic patients, the first question arising is whether stimulation and lesion exert the same effect on the motor system, as implied by our clinical results because these show an amelioration of symptoms which is also achieved by subsequent activation of the electrodes. Partial relief of dystonic symptoms caused by the MLE has been reported before.[19 20] These observations indicate that the implantation-induced MLE, stimulation and surgical ablation (ie, thermo-coagulation), which has been used in the last century for the treatment of dystonia,[21] all produce a beneficial reduction of the pathophysiological processes causing dystonia. The beneficial effects of GPi lesion/stimulation are contrasted with unwanted effects which, in our study, appeared as reduced movement velocity after electrode implantation in dystonic patients. Proximal (boxing) and distal movements (FT and pronation/supination) were equally affected. Several recent reports show that bradykinesia can also be induced by GPi stimulation and has a serious clinical impact.[22] The latter authors reported the results of a questionnaire aimed at detecting symptoms of bradykinesia and found that handwriting was the most frequently affected motor function. Furthermore, they found a tendency for higher ratings of the bradykinesia questionnaire score to be associated with more benefit from the treatment. Micrographia was also reported as a sequel of GPi-DBS in another patient.[23] Slowing of gait and even freezing of gait were seen in 8.5% of patients after GPi-DBS for different types of dystonia[24] and could not be attributed to electrode misplacement or abnormal stimulation parameters. In their series, two patients experienced falls due to freezing of gait with subsequent hip fractures. Parkinsonism was induced in a patient with craniocervical dystonia by GPi-DBS during stimulation of the most ventral GPi electrode contact.[25] Stimulation of more dorsal contacts reduced Parkinsonism at the price of returning dystonia. Thus it seems that the level of bradykinesia in these circumstances is directly correlated with the relief of dystonia. In this regard, some parallels emerge between dystonia and levodopa-induced dyskinesias (LID) in PD. Both are dyskinetic movements which mainly affect proximal muscles and are enhanced during voluntary movement and reduced during rest. Both can be treated by lesioning or stimulation of the GPi. The functional role of the GPi in this regard has also been studied in primates: tonic inhibitory output from the GPi is important for the maintenance of postural stability,[26 27] and inactivation resulted in dysmetric arm movements. On the contrary, inactivation of the globus pallidus externum can cause dystonic posturing.[27] Also local field potentials (LFPs) recorded from DBS electrodes point to a similar pathophysiology of dystonic cramps and LID. Low frequency synchronisation of LFPs (<10 Hz) was seen in the STN and GPi during a dyskinetic state in a patient suffering from PD (simultaneous recordings from GPi and STN).[28] In dystonia, 4–10 Hz synchronisation of LFPs was shown in the GPi,[29 30] and temporal coupling between dystonic muscle activity and pallidal oscillation in the range of 3–20 Hz has been reported.[31] Single cell recordings from humans suggest that the discharge rate of GPi neurons is reduced in dystonia while oscillatory activity in the 2–10-Hz band is increased.[32] Thus it seems that lower frequency synchronisation (below 10 Hz) is a typical and possibly causal feature during dystonic cramps as well as LID.

Considering these findings and our results the question arises whether the reduction of movement velocity caused by the MLE

and also reported for GPi stimulation is somehow selective or not. In this regard, one point merits discussion: GPi stimulation in PD can have prokinetic effects.[33] This, however, is possibly due to stimulation of more dorsal contacts which reduce bradykinesia whereas ventral contacts reduce LID and may increase Parkinsonian bradykinesia.[34 35] Interestingly, while stimulating ventral GPi contacts in PD patients, Krack and colleagues[36] not only noted increased bradykinesia but also a reduction in rigidity which might therefore be considered to belong to the dystonia/LID-complex mentioned above.

On the basis of our clinical findings (reduction of dystonia by MLE) and the cited papers, the system which is influenced by ventral GPi stimulation seems to be mainly involved in regulating muscle tone and automated limb posturing. These movements can be pathologically enhanced in dystonia, Parkinsonian LID or Parkinsonian rigidity, and are subsequently reduced by ventral GPi stimulation. The mechanism by which bradykinesia emerges in these instances is not clear but it may be speculated that it is the consequence of a specific reduction of muscle tone and automated movements. In the other system, which can be influenced by STN stimulation, a reduction of subthalamic activity (by stimulation or lesion) causes exaggerated fast limb movements (hemiballism) or 'normalisation' of pathological slowness in PD.[37] Overstimulation may also increase 'automated' movements as in LID. Therefore a rather unselective disinhibition of movements may be caused by STN stimulation or lesion. In the normal state these two systems allow for the smooth performance of limb movements and concurrent equilibration of body and limb posture.

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Contributors KB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AS, SK, JHM and KB participated in the conception and design of the study. AS and KB analysed and interpreted the data. AS provided methodological and statistical expertise and critically reviewed the paper. AS and KB wrote the manuscript and provided important intellectual content.

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Competing interests JHM and KB have received speaker honoraria from Medtronic, Inc.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethics committee of the medical faculty of the Ludwig-Maximilian University, Munich.

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