Subthalamic nucleus stimulation for Parkinson's disease preferentially improves akinesia of proximal arm movements compared to finger movements

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gests a role for abnormal rhythmicities in central movement mechanisms. This role has been proposed by Brown and colleagues, who also have suggested that these rhythmicities in myoclonus are exaggerations of normal rhythms.[2] Our combined results from time and frequency domain analysis suggest that myoclonus in PD occurs when neuronal populations in the sensorimotor area are driven to an extreme amount of synchronous activity with increased coupling between the sensorimotor cortex and motorneuron pools that manifests as increased corticomuscular coherence. In addition, our results from studying the time-locked coherence changes before myoclonus suggest that, in individuals with PD and small amplitude myoclonus, the corticomuscular coherence values are abnormally elevated even when the myoclonus is not occurring. Thus, the pathophysiological mechanism that causes the high baseline coherence does not appear by itself to be sufficient to generate the myoclonus. This finding suggests that another influence such as improper input into the sensorimotor cortex or an intrinsic neuronal circuitry defect is necessary to trigger the generation of the excessive activation from the sensorimotor cortex. Indeed, the neuronal circuitry defect that produces the abnormally high baseline coherence may or may not be the same as that which creates the sudden and irregular increase in corticomuscular coherence that correlates with the myoclonus cortical discharge.

The abnormally high corticomuscular coherence values without the presence of myoclonus and the tendency toward higher coherence values in the PD group compared to the control group suggest that corticomuscular coherence is more sensitive than either the detection of visually perceptible myoclonus movements or surface EMG abnormalities. In terms of sensorimotor neuron populations, this abnormality represents an abnormal degree of time-locked correlation between axodendritic pyramidal neuron activity arising from the sensorimotor cortex and EMG activation. This "decrease in chaos" or increase in synchronization may result from defective surround inhibition due to decreased inhibitory inputs or excessive excitatory input into the sensorimotor cortex.

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Subthalamic Nucleus Stimulation for Parkinson's Disease Preferentially Improves Akinesia of Proximal Arm Movements Compared to Finger Movements

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Abstract: **Deep brain stimulation of the subthalamic nucleus (STN-DBS) reduces akinesia in Parkinson's disease but its impact on fine motor functions was unknown. We assessed the effects of DBS and a levodopa (L-dopa) test on the timing of the precision grip in 18 patients. Improvement on UPDRS-items reflecting hand functions and the shortening of the first phases of the precision grip were more distinct in the L-dopa test than in the pure STN-DBS condition. Other**

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akinesia items and the time for build-up of lifting force were equally improved in both conditions. This suggests that routine STN-DBS might not be equally effective on all aspects of fine motor functions. © 2003 Movement Disorder Society

Key words: akinesia; subthalamic nucleus; deep brain stimulation; Parkinson's disease; grip force

Patients with Parkinson's disease (PD) suffer from progressive akinesia in the course of their disease. Akinesia improves with dopaminergic medication but motor fluctuations and levodopa (L-dopa)–induced dyskinesias (LID) often limit its use in advanced stage. Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a highly effective treatment for motor symptoms in L-dopa–responsive PD.[1,2] Its overall benefits on akinesia resemble that of L-dopa.[3,4] The undoubted and substantial anti-akinetic benefits of DBS, however, have been evaluated mainly in movements where axial and proximal muscles are the prime movers (proximal appendicular movements), i.e., walking, arm swing, or tapping movements.[3–7] A predominant effect of stimulation on axial akinesia compared to akinesia of the upper limb has been described with clinical scores,[7] but this differential effect has not been challenged by objective measures.

Our clinical experience suggested that anti-akinetic effect of STN-DBS on proximal ballistic movements of the limbs is more distinct than on fine motor functions. It was our aim to challenge this hypothesis by objective measures, and to assess akinesia of the precision grip in a functionally relevant context that requires co-ordination of both axial appendicular and distal muscles of the upper limb. Grasping to lift a small object seemed a suitable task, because it involves the parallel control of both grip force, exerted by distal muscles, and load (lifting) force, exerted mainly by axial muscles. This synergy of the precision grip has been studied extensively in healthy subjects[8,9] and in parkinsonian patients.[10–13] It seemed suitable to challenge a possible imbalance of the effect of STN-DBS on proximal compared to distal appendicular akinesia.

The effects of L-dopa and STN-DBS on the motor score of the UPDRS are very similar.[1,4] More complex finger movements, however, might be underrated in the overall motor score and thus subtle differences in efficacy of either treatment on different motor programs might escape to the clinical evaluation. If a deficiency of the anti-akinetic effect of STN stimulation exists, it may be rather subtle compared to its great overall motor benefit. Nevertheless knowledge of such effects could give further insights into the mechanisms of stimulation.

SUBJECTS AND METHODS

Subjects and Experimental Conditions

We studied a consecutive series of 35 patients with idiopathic PD treated by chronic bilateral high frequency stimulation of the STN. The STN was visualized with stereotaxic MRI, allowing for direct anatomic targeting. Microrecording and microstimulation were used for electrophysiological control of the target. A quadripolar macroelectrode (DBS type 3389, Medtronic, Minneapolis, MI) was implanted bilaterally, and connected to a stimulator (Itrel II or Kinetra; Medtronic). The study was approved by the local ethics committee. Written informed consent was given by all patients. DBS amplitudes (mean 3.1 $\pm$ 0.8 V) were titrated for optimal control of akinesia and rigidity without evoking dyskinesias. We did not explore the thresholds for different aspects of akinesia. The L-dopa equivalent daily dose (LEDD) was calculated as described elsewhere.[12,13] LEDD was reduced after surgery by 47% to a mean equivalent dose of 710 mg.

Patients were assessed 3 months after surgery in 3 conditions. The assessments began with the baseline condition in the morning (*off*-drug/off-stim) after a 12-hour overnight withdrawal of dopaminergic treatment, 30 minutes after switching off the stimulation. Thereafter the patients were assessed in *on*-drug condition without DBS after a challenge with a suprathreshold dose of L-dopa.[4] The *on*-drug state (drug) was assessed at its peak motor effect. Tapping and the precision grip task were carried out immediately after the assessment of the UPDRS to avoid waning of the anti-akinetic effect. The overall time for those examinations was $<$20 minutes. A repetition of the same assessment was carried out the next day in the morning after a 12-hour overnight withdrawal of medication with both stimulators on (stim = *off*-drug/on-stim). Patients were videotaped during the entire L-dopa test.

The motor score (UPDRS III)[14] was rated in the baseline, drug, and stim conditions by the same rater (FK). Subscores of the akinesia of arms and legs (Items 25 + 26), and of the hands (Items 23 + 24) were derived from the UPDRS. They loaded on the same akinesia factors according to a factor analysis published recently.[15] The bilateral sum of each subscore ranged from 0 to 16. To rule out interference of hand tremor with the grip–lift task,[16] postural/action tremor of the upper limb (Item 21) was analyzed separately, with a bilateral sum of 0 to 8. The first 18 patients were selected for a more detailed analysis including rating of L-dopa–induced dyskinesias, hand tapping, and grip force coordination. Peak-dose dyskinesias were rated from the videotape by indepen-

dent, experienced raters.[17,18] Tapping was assessed using two counters set 20 cm apart, the patient alternatively hitting the button of either counter with the index by moving the arm from one button to the other and mean values of both sides were analyzed.[4] This kind of tapping movement required mainly a flexion and extension of the elbow joint, and a minor contribution of movements of hand and fingers.

Timing of the Grip–Lift Movement

The experimental procedure for the analysis of grip–lift coordination was similar to that described previously.[10–13] The patients carried out the task in each condition with the arm moving freely, i.e., elbow flexion and shoulder abduction were required to lift the object. Its weight was 220 g and the sandpaper covered grip surfaces (granulation #320, diameter 17 mm) were 5.5 cm apart. Subjects were instructed to perform the task at a normal pace, i.e., no instructions were given regarding speed, accuracy, or force. The hand was held open at the level of the object and the subject grasped and lifted the object at a beep. After 5 seconds of holding it they were told to replace it at the table. Fifteen repetitions were recorded with a 5- to 10-second pause in between. The first five trials were regarded as practice trials and were not considered for data analysis, to minimize the influence of learning effects. Horizontal grip forces and vertical load forces were measured from thumb and index finger using 3-D sensors (Assurance F/T, USA), and were digitized at 400 Hz using *SC/ZOOM* software (Umea, Sweden). Temporal parameters were derived from the two early latencies, related with grasping (duration of grip preparation = DUR_{GPREP} and duration of preload phase = DUR_{PLOAD}; see Fig. 1)[12] and from the late phase, where the vertical lifting force increases (duration of load phase = DUR_{LOAD}). The sum of all three phases was depicted as total duration of the isometric phase (DUR_{ISO}). Mean values of both sides were entered into statistics to account for the bilateral effects of stimulation.

Statistics

Analysis of variance for repeated measurements (GLM procedure of *SPSS v. 10*, SPSS, Chicago, IL) was used to compare the temporal parameters between conditions, with TREAT as three-step factor (baseline, drug, stim); $P < 0.05$ after Bonferroni correction was assumed as significant. Friedman ANOVA and Wilcoxon test were computed to test the influence of treatment on the scores, and the level of significance was set to $P < 0.05$.

RESULTS

Clinical Scores

The UPDRS motor score was equally improved by both drug and stim, compared to baseline ($P < 0.01$ in both, see Table 1). The effects of drug and stim on the akinesia score of arm & leg compared to baseline were likewise equal ($P < 0.01$ in both). A reduction of the hand akinesia score also occurred by stim ($P < 0.05$) and by drug ($P < 0.01$).

We calculated the change of scores in relation to baseline (*off*-drug/off-stim) to compare between the therapeutic effects of *drug* and *stim* (Fig. 2). These therapeutic effects on hand akinesia, however, were stronger in *drug*, compared to *stim* condition (relative reduction of the score by −52% vs. 27%, $P < 0.05$). Such differential effects were not seen for the akinesia of arm & leg (relative reduction of the score by −51% vs. −47%, NS) and for the motor score (−50% vs. −46%, NS). The same was true for the tapping rate, which was enhanced by both *drug* and *stim* ($P < 0.01$), without differences between the therapeutic effects (+25% and +27%, NS; see Table 1). Both *drug* and *stim* induced mild on-state dyskinesias (scores 2.3 vs. 2.9, NS) although a clear reduction was seen compared to the pre-surgical test (7.1, $P < 0.01$ compared to examination after surgery, pre-surgical variables not shown in the table).

Effect of Treatment on Duration of Grip Phases

The duration of the total isometric phase (DUR_{ISO}) was shortened by both *drug* and *stim* ($P < 0.01$ compared to baseline, see Table 2). If DUR_{ISO} was examined in detail, however, *stim* did not shorten its early phases (DUR_{GPEP} and DUR_{PLOAD}, NS), but only its late phase (DUR_{LOAD}, $P < 0.01$ compared to baseline). *Drug*, on the other hand, shortened all phases consistently (DUR_{GPEP} and DUR_{PLOAD}, $P < 0.05$; DUR_{LOAD}, $P < 0.01$ compared to baseline). Therefore, the shortening of DUR_{ISO} by *stim* was based mainly on an enhanced performance in the late phase, whereas *drug* acted similarly on all parts of DUR_{ISO} (Table 2).

We then calculated the therapeutic effect of *drug* and *stim* on phase durations with reference to the baseline condition (*off*-drug/off-stim). This analysis showed that the differences of therapeutic effects of *stim* and *drug* on the early phases were significant (Fig. 3). Although the impact of *drug* and *stim* on DUR_{LOAD} were equivalent (−24% vs. −27%, NS), the shortening effect of *drug* on $DURG_{PREP}$ prevailed that of *stim* (−26% vs. −7%, $P < 0.05$) and the same was true for DUR_{PLOAD} (−29% vs. −12%, $P < 0.05$).

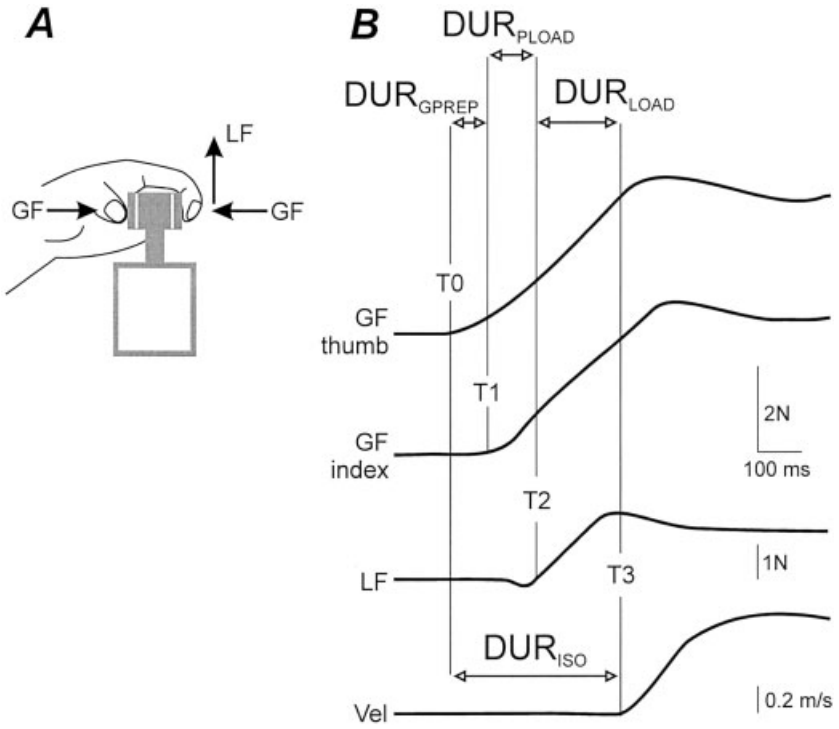

FIG. 1. Illustration of the grip–lift paradigm (**A**) and its temporal parameters (**B**). The object was contacted typically first by the thumb (T0) and then by the index finger (T1). The grip force and load force increased in parallel during the loading phase until lift-off (T2, Vel = positive velocity in vertical direction). Temporal parameters were calculated as follows: duration of grip preparation (DUR_{GPREP} = T1 − T0), preload phase duration (DUR_{PLOAD} = T2 − T1), and load phase duration (DUR_{LOAD} = T3 − T2).

Spearman correlation between the durations of all grip phases and the on-state dyskinesia score was weak ($R < 0.4$, NS). The same applied for correlations of the phase durations with both the L-dopa equivalent dose and the tremor score ($R < 0.51$, NS).

DISCUSSION

This study demonstrates a differential effect of STN-DBS compared to a L-dopa challenge in a relatively large group of patients. Benefits for distal appendicular akinesia were more pronounced after L-dopa than after pure DBS. This was reflected by a slightly smaller reduction of akinesia of hand and fingers by DBS, compared to a more pronounced effect of L-dopa. An equal effect of DBS and drug was observed on the akinesia of proximal appendicular movements as scored in the UPDRS. Similarly, the benefits of stimulation almost spared both early (grasping) phases of the precision-grip task, whereas a clear shortening of the late (loading) phase by STN-DBS was observed. The faster build-up of lifting force in the late phase by DBS was sufficient to speed up the

TABLE 1. *Effect of STN-DBS and of L-dopa on UPDRS subscores, timed tapping, and* on-*state dyskinesias*

	Hand akinesia	Arm and leg akinesia	Motor	Tremor	Taps/min	Dyskinesia
Baseline	6 ± 3.9	7.2 ± 3.2	39.3 ± 16.7	1.6 ± 1.8	208 ± 57	—
L-Dopa challenge	2.9 ± 3[a]	3.5 ± 1.8[a]	19.6 ± 11[a]	0.8 ± 1.5	253 ± 60[a]	2.3 ± 2.8
STN-DBS	3.8 ± 3.4[b]	3.8 ± 1.8[a]	21.2 ± 12.4[a]	0.7 ± 1.5	255 ± 59[a]	2.9 ± 1.9

Values are expressed as mean ± SD of the score.

L-Dopa challenge and stimulation (STN-DBS) both improved akinesia, but the improvement of hand akinesia by STN-DBS was less than by L-dopa challenge (see Figure 2). Akinesia of arm and leg was equally improved by L-dopa challenge and STN-DBS.

Score ranges were 0–16 for akinesia of the hands and of arms and legs (n = 35), 0–108 for the motor score of the UPDRS (n = 35), 0–8 for tremor of the hands (postural/action tremor, n = 35), and 0–28 for dyskinesias (peak dose dyskinesias, n = 18).

[a]$P < 0.01$; [b]$P < 0.05$, compared to baseline (*off*-drug/off-stim).

STN-DBS, subthalamic nucleus-deep brain stimulation.

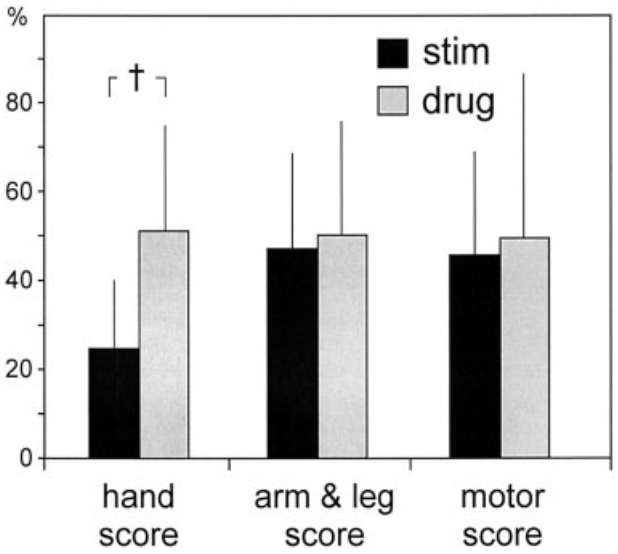

FIG. 2. Differential effect of STN-DBS (*stim*) and L-dopa (*drug*) on clinical akinesia and the motor score. The impact of *stim* on the hand akinesia score was less than that of *drug*. All other measures were improved similarly by drug and DBS. Bars represent mean therapeutic effect in relation to baseline condition (*off*-drug/off-stim), error bars show SD, n = 35. $^{\dagger}P < 0.05$ effect of stim compared to drug.

grip-lift synergy. Early and late phases of the grip-lift task, however, were equally shortened by drug.

The grip–lift synergy studied here allows a separation of two early phases, until a stable grasp is achieved, and a late phase in which the vertical load force increases until the object is lifted off.[8] Although several muscles of hand, arm and shoulder act concerted, the focus of motor control undergoes substantial changes throughout grasping to lift an inertial object according to studies using transcranial magnetic stimulation of the corticospinal tract.[19–21] The intrinsic hand muscles receive their strongest cortical drive as the digits close around the object, matching the early phases of the task used in the present study.[20] The powerful boosting of the drive to hand muscles is mediated by cutaneous afferent input from the gripping digits.[19] As soon as a stable grasp is achieved the facilitation of the distal hand muscles decreases rapidly[20] and control moves over to proximal muscles exerting the lifting force. In the late (loading) phase the corticospinal drive to muscles of arm and shoulder increases rapidly while lifting and holding the object.[19–21] In summary, the early phases of the grip-lift task could reflect mainly the efficiency and speed of force development by distal appendicular hand muscles, whereas the late phase may represents more of the speed by proximal appendicular arm muscles. Therefore, the differential speed of force development in the late compared to the early phases may be due to a predominant effect of STN-DBS on proximal appendicular akinesia. Alternatively, the threshold for an optimal effect of DBS on distal akinesia could have been different from that used in the present study.

The results from the analysis of grip forces are in line with our clinical findings in a larger group of post-surgical patients. Although STN-DBS reduced global akinesia, this effect was stronger on the UPDRS-items estimating akinesia of proximal compared to distal appendicular muscles.

An analysis of proximal and distal appendicular akinesia in STN-DBS has not been reported to our knowledge. A moderate effect of pallidotomy on parkinsonian akinesia has been observed for proximal ballistic movements whereas only minor improvements were seen for distal or complex fine movements.[22–24] Siebner and colleagues[25] found that handwriting improved by STN-DBS, but they reported no comparison with the effect of L-dopa. In the current study, tapping speed and the UPDRS motor score improved to a similar extent as reported previously.[1,4,5,26–29] The lack of a differential effect of drug and stim on tapping speed in those studies may be due to an involvement of both proximal and

TABLE 2. *Effect of L-dopa and STN-DBS on the temporal variables of the grip–lift synergy*

	Early		Late	Total
	DUR_{GPREP}	DUR_{PLOAD}	DUR_{LOAD}	DUR_{ISO}
Baseline	75 ± 57	140 ± 84	177 ± 80	344 ± 125
L-Dopa challenge	55 ± 52[b]	99 ± 78[b]	127 ± 57[a]	243 ± 106[a]
STN-DBS	65 ± 39	121 ± 79	119 ± 41[a]	265 ± 83[a]

Mean durations of the phases are shown in msec ± SD.

The total duration of the isometric phase (DUR_{ISO}) was subdivided into two early phases (DUR_{GPREP} and DUR_{PLOAD}) and a late phase (DUR_{LOAD}). The shortening of DUR_{ISO} was mainly caused by a faster execution of DUR_{LOAD}, while L-dopa shortened all phases consistently.

$^{b}P < 0.05$, $^{a}P < 0.01$, compared to baseline (*off*-drug/off-stim condition).

STN-DBS, subthalamic nucleus-deep brain stimulation.

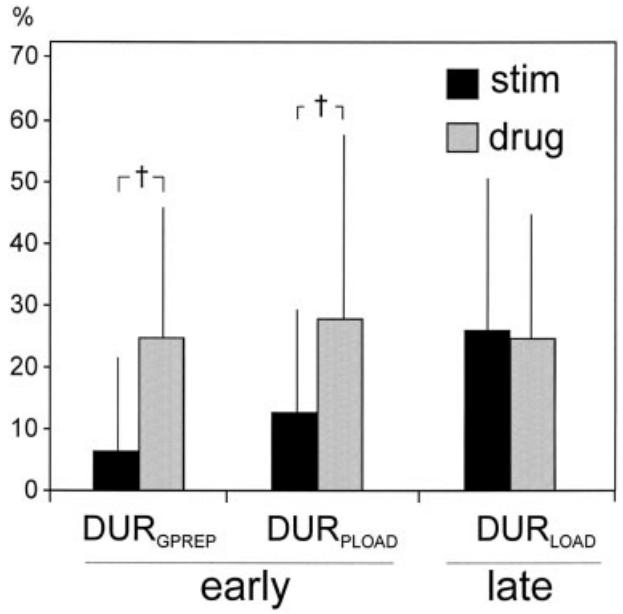

FIG. 3. Differential effect of STN-DBS (stim) and L-dopa (drug) on the timing of the grip–lift synergy. Note that stim shortened the early phases of DUR_{GPREP} and DUR_{PLOAD} less than drug, whereas the late phase DUR_{LOAD} was equally shortened by stim and drug. Bars represent mean therapeutic effect with reference to baseline condition (*off*-drug/off-stim), error bars show SD, n = 18. $^{\dagger}P < 0.05$ effect of stim compared to drug.

distal appendicular muscles or to the repetitive nature of this task. Repetitive movements are presumably governed by the supplementary motor area (SMA),[30,31] which is depressed in PD,[32] but can be strongly activated both by STN-DBS[33,34] and by dopamine agonists.[35] Although in the present study the total movement time was shortened equally by stim and drug, a detailed analysis of the movement phases exhibited differential effects. Such attempts were not made in previous studies on the effect of DBS on fine motor functions. A moderate effect of pallidotomy on parkinsonian akinesia has been observed for proximal (ballistic) movements only whereas distal or complex (fine) movements were not improved.[22–24]

No differential effects were seen in the preparation and execution of aiming movements, with an equal impact of levodopa and DBS.[3,36] This might relate to the minor involvement of distal appendicular muscles in aiming.

Which other factors might hamper the performance in the precision grip task? Hypothetically, L-dopa-induced dyskinesias may induce a compensatory slowness of grasping. In this case, however, slowness should be more pronounced in *on*-drug/on-stim condition where dyskinesias are at their worst, which was not the case. No correlation was observed between the phase durations and the severity of on-state dyskinesias. Furthermore, a selective interference of involuntary movements with grasping, but not with lifting, rendered a major contribution of LID to the slowness very unlikely. The consistent findings from clinical scores and the precision grip measures render this possibility unlikely.

Tremor has also been considered a source of slowness in PD[37–39] but tremor scores were the same on DBS or drug alone in the present study. Therefore tremor reduction does not explain differential effects of both conditions.

Mechanisms of the Differential Effects

What could be the pathophysiology underlying differential effects of STN-DBS and levodopa? Discrete finger movements by distal appendicular muscles and the precision grip depend on the primary motor cortex,[21,40–43] which is activated by dopaminergic treatment,[44] but not by STN-DBS.[33,34] In proximal appendicular movements, in contrast, muscles of the limb girdle and the upper arm are the prime movers. These proximal and axial muscles are controlled by a widely distributed network involving the premotor cortex and basal ganglia,[45,46] and the upper brainstem.[47–49] Particularly the pedunculopontine nucleus (PPN) has a role in preparation and execution of axial and proximal appendicular movements.[50,51] STN-DBS is expected to release the activity of the PPN,[50–53] and activates the premotor cortex.[33,34] This may explain the outstanding effects of STN-DBS on proximal appendicular and axial akinesia.

CONCLUSION

This study confirms overall similarities between the anti-akinetic effect of L-dopa and STN-DBS. There is one noticeable discrepancy, however, as STN stimulation does not improve distal appendicular akinesia and the precision grip to the same extent than proximal appendicular movements whereas L-dopa does. The close connectivity between STN and motor areas of the brainstem or the premotor cortex could underlie a more direct effect of DBS on proximal akinesia. We could not exclude the possibility that akinesia of proximal and distal muscles resolves at different thresholds because the parameters of DBS were not varied in this study. Further research in DBS should address the role of thresholds for proximal and distal aspects of akinesia.

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Is the Target for Thalamic Deep Brain Stimulation the Same as for Thalamotomy?

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Abstract: **Deep brain stimulation (DBS) has virtually replaced thalamotomy for the treatment of essential tremor. It is thought that the site for DBS is the same as the optimal lesion site; however, this match has not been investigated previously. We sought to determine whether the location of thalamic DBS matched the site at which thalamotomy would be performed. Eleven patients who had detailed microelectrode recording and stimulation for placement of DBS electrodes and subsequent successful tremor control were analysed. An experienced surgeon, blinded to outcome and final electrode position, selected the ideal thalamotomy site based on the reconstructed maps obtained intraoperatively. When the site of long-term clinically used DBS and theoretical thalamotomy location was calculated in three-dimensional space and compared for each of the *x*, *y*, and *z* axes in stereotactic space, there was no significant difference in the mediolateral location of DBS and theoretical lesion site. There was also no difference between the theoretical lesion site and the placement of the tip of the electrode; however, the active electrodes used for chronic stimulation were significantly more anterior ($P = 0.005$) and dorsal ($P = 0.034$) to the ideal thalamotomy target. This mismatch may reflect the compromise required between adverse and beneficial effects with chronic stimulation, but it also suggests different mechanisms of effect of DBS and thalamotomy.**

Key words: thalamus; microelectrode recording; deep brain stimulation; tremor

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