

The effect of subthalamic nucleus deep brain stimulation on precision grip abnormalities in Parkinson's disease

Stuart J. Fellows^{a,*}, Martin Kronenbürger^a, Niels Allert^b, Volker A. Coenen^c,
Christoph Fromm^a, Johannes Noth^a, Peter H. Weiss^{a,d}

^a Neurologische Klinik, Universitätsklinikum der RWTH Aachen, Pauwelsstrasse 30, D-52074 Aachen, Germany

^b Neurologisches Rehasentrum Godeshöhe, Waldstrasse 2-10, D-53177 Bonn, Germany

^c Neurochirurgische Klinik, Universitätsklinikum der RWTH Aachen, Pauwelsstrasse 30, D-52074 Aachen, Germany

^d Institut für Medizin, Forschungszentrum Jülich, D-52425, Jülich, Germany

Received 7 July 2005; accepted 2 December 2005

Abstract

We have studied grip force performance in a group of 10 patients who were in a stable state after implantation of bilateral stimulating electrodes in the subthalamic nuclei (Stn) to counter drug-resistant or drug-induced symptoms of advanced Parkinson's disease. The patients were required to use a precision grip to lift an object which recorded grip force development and lift dynamics. Lifting was performed with stimulation on and with stimulation off under optimal medication. Post-operatively, dyskinesia was absent in all patients in both conditions, but in the 'off' state the patients showed the profound bradykinesia and excessive levels of grip force development associated with Parkinson's disease from its early stages. In the stimulation 'on' state both the rate of grip force development and the speed of the lifting phase were increased significantly. The excessive levels of grip force present in the stimulation 'off' state, and present from the early stages of the disease, however, were even more marked with Stn stimulation on. It is suggested that this results from a failure to modify stored motor programs developed over a long period under the influence of bradykinesia, leading to an inappropriately prolonged duration of grip force development when this influence is removed by Stn stimulation. Thus although Stn stimulation achieved a dramatic improvement in the mobility of the patients in general, and in the dynamics of hand movements specifically, by improving rates of force development and lifting dynamics, it does not restore, and may even worsen, the ability to match lifting parameters to actual conditions.

© 2006 Published by Elsevier Ltd.

Keywords: Grip force; Subthalamic nucleus; Deep brain stimulation; Parkinson's disease

1. Introduction

A significant percentage of patients with Parkinson's disease eventually become non-responsive to dopaminergic medication or develop severe side effects, such as wearing-off and fluctuations. These patients have, since the early 1990s, often been treated by pallidotomy [1]. Pet studies have shown that this procedure results in increases in movement-related blood flow in the supplementary motor area (SMA) [2]. These blood flow increases are correlated with improved motor scores on the United Parkinson's

disease rating scale (UPDRS) and faster movement times for the hand in simple and choice reaction tasks [3]. Subsequently deep brain stimulation (DBS) of the Globus pallidus interna (Gpi) using implanted electrodes replaced pallidotomy, as it was associated with less morbidity and more easily allowed bilateral application, while achieving comparable results [4,5]. Recently, DBS of the subthalamic nucleus (Stn) has become the preferred procedure [6], as it has been shown to yield greater improvements on the UPDRS motor scores [7–9], increases in movement-related blood flow in the SMA [10], and improved performance in a range of cognitive tests [11]. Furthermore Stn stimulation, in contrast to Gpi stimulation, is effective in the off-medication state, allowing a reduction in L-dopa dosage [12]. Dopamine treatment is thought to alleviate the motor deficits associated with Parkinson's disease by increasing

* Corresponding author. Tel.: +49 241 8080328; fax: +49 241 8082444.
E-mail address: sfellows@ukaachen.de (S.J. Fellows).

activation of the Sma and reducing or abolishing high frequency oscillations in the Stn [13]. These mechanisms would appear to be mimicked by Dbs of the Stn. Furthermore, the effects of stimulation are rapidly reversed when stimulation is switched off and, importantly for the patient's comfort, even more rapidly restored when the stimulation is switched on again. Thus it should be possible, by examining patients with Stn stimulation on and off, to directly assess its effects on a functional motor task, such as the precision grip paradigm, which represents a reliable quantitative assessment of motor performance. Wenzelburger et al. [14] have used this paradigm to examine parkinsonian patients with implanted Stn electrodes and reported that stimulation resolved the grip force overshoot associated with L-dopa-induced dyskinesia. This form of grip force overshoot, however, resembles the grip force abnormalities observed in Huntington's chorea [15] and shows important differences from the exaggerated and markedly slowed grip force profile characteristic of even the early stages of Parkinson's disease [16,17]. Accordingly we decided to investigate grip force performance in a group of patients with implanted Stn electrodes, but in whom L-dopa-induced dyskinesias were not present in either the stimulation 'on' or the 'off' condition.

2. Methods

The study involved 10 out-patients of our clinics who had undergone, at least 3 months previously, implantation of bilateral stimulating electrodes in the Stn to counter drug-resistant or drug-induced symptoms of advanced Parkinson's disease (see Table 1 for clinical details). They received their normal medication during the study. Their L-dopa-equivalent doses ranged from 100 to 650 mg/day. Patients gave their informed consent to all procedures, which had been approved by the local ethics committee. They were first assessed clinically using the motor section of the united Parkinson's disease rating scale (UPDRS).

They then performed the lifting protocol (see below) using their dominant hand (in all cases right), as determined by the Edinburgh Handedness Inventory [18]. The stimulator was then switched off and a 20–40 min pause was taken until the stimulation 'off' state was well established. The clinical assessment and the lifting protocol were then repeated, after which the stimulator was reactivated at the previous levels.

Details of the apparatus and methods employed have been fully described elsewhere [16], but there follows a brief summary. The investigation was performed in a quiet room with subdued lighting. The subject was seated in a stable chair which supported the back (but not the head) before a table on which was situated the lifting device. A curtain obscured the patients' view of their hand and the object. Subjects were positioned so that they were able to grip the object between their forefinger and thumb and lift and hold the object at the wrist while their elbow remained fully supported on a padded rest. The measuring instruments built into the device registered the grip force exerted on the object (9301b, Kistler, Winterhur, Switzerland) and its vertical position (T60500, Vac, München, Germany). These signals were amplified and then passed to the analogue-to-digital converter board (Ni-Pci-Mio-16xe, National Instruments, Austin, TX, USA) of a laboratory computer (Macintosh G3/400, Apple, Cupertino, CA, USA) sampling each channel at 2.5 kHz.

The subjects were required, without visual feedback concerning hand position, to grip and lift the object 4–6 cm above the table, then hold it steady for 4–6 s before replacing the object on the table and releasing it. The contact pads on the object for thumb and forefinger were covered with sandpaper (extra-fine, corn 400). A second laboratory computer (Macintosh Iivx, Apple) was used to control the load of the object via a servo-device. A torque motor attached via a non-elastic band to the object was used to alter object load between lifts without the subject's knowledge in a pseudo-random manner between two levels, namely 3.3 N (light) and 7.8 N (heavy), such that five lifts could be selected for each load where the load remained

Table 1
Clinical detail of the patients

Patient	Age	Sex	Time elapsed since operation (months)	UPDRS III pre-op medication off	UPDRS III pre-op medication on	UPDRS III post-op stimulation off	UPDRS III post-op stimulation on	L-dopa equivalent
UV	55	F	9	46	14	52	7	100
RP	46	M	13	52	21	16	5	400
HS	54	F	16	31	3	50	23	600
TP	67	M	18	–	–	47	13	650
AN	68	M	4	46	25	41	16	300
MF	71	F	17	38	14	33	13	150
HH	69	M	3	47	13	41	11	400
NB	65	M	3	38	10	51	5	300
TS	72	F	22	49	17	47	11	200
MH	49	F	15	43	9	31	3	300

UPDRS score is for the motor section only. Pre-operative values obtained off medication (pre-op off) and with L-dopa challenge (pre-op on). Post-operative values obtained on medication (see L-dopa equivalent), with stimulator on/off. All patients were free from dyskinesia post-operatively.

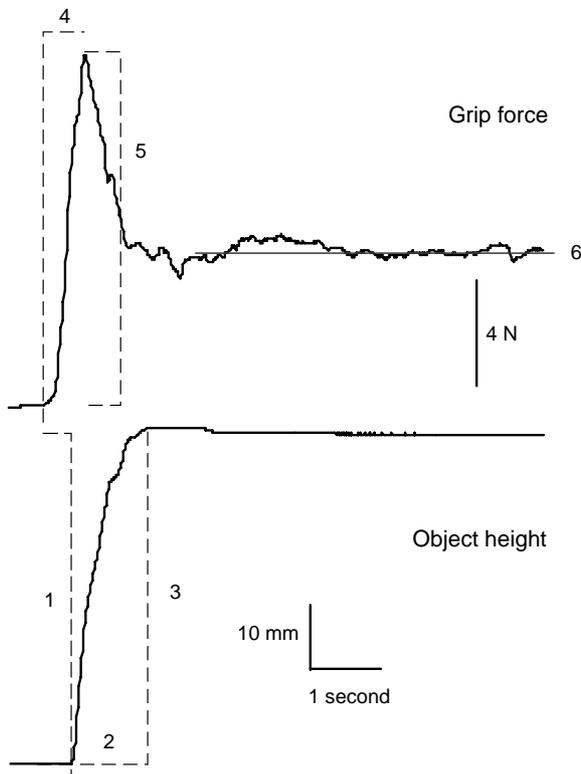


Fig. 1. Parameters measured from the grip force and object position curves. 1: Time from grip force onset to onset of object lifting (Igl, ms). 2: Duration of object lifting (ms). 3: Amplitude of object lifting (mm). 4: Time to reach peak grip force amplitude (tpgf, ms). 5: Peak grip force amplitude (Pgf, N). 6: Grip force used to hold object at a steady height (Sgf, N).

unaltered from the preceding lift. A 10–15 second pause was allowed between each lift.

The grip force curves obtained from each of the lifts performed was subsequently measured (see Fig. 1) to yield a series of parameters: Igl: time between the onset of grip force and the lift-off of the object (ms); tpgf: time taken to reach the peak grip force (ms); Pgf: peak grip force magnitude (N); and Sgf: the stable grip force adopted while holding the object steady above the table (N). The Igl may be considered to provide a measure of the co-ordination between the fingers gripping the object and more proximal arm muscles responsible for the actual horizontal lift of the object. tpgf provides information about the rate of grip force development at the fingers. Pgf provides information on the largely automatic processes of the selection from memory of motor sets matched to object properties [19], while the Sgf is the result of modification of these stored commands by actual sensory feedback concerning object properties obtained during the lift itself [20]. The height and duration of the lift were also measured and processed to yield the mean lifting velocity (mm/s) during the lifting phase. The mean rate of grip force development (N/s) was also obtained in order to correct for differences in peak force.

Statistical analysis was performed using the SPSS 11 package (SPSS, Inc., Chicago, IL, USA). For this purpose

the median value obtained from five lifts with a given load were obtained for each parameter and compared between the stimulation on and stimulation off conditions using an exact, one-tailed Wilcoxon signed ranks test.

3. Results

The patients were subjectively much more mobile in the stimulation 'on' condition, and, as can be seen in Fig. 2, this was confirmed by a significant improvement in the clinically assessed motor scores (mean 31 points \pm 3; $p=0.001$). This represents an average improvement of 75% (\pm 5), comparable with the improvement achieved during a pre-operative L-dopa challenge ($69\% \pm 4$; see Table 1).

The coordination between grip force development at the fingers and lifting force at the wrist, as expressed by the Igl values, was affected variably by Stn stimulation. On average the coordination improved slightly, as reflected by shorter Igl timing, but this reached significance only while lifting the light load (light 'off' 456 ± 50 , light 'on' 361 ± 25 , $p=0.023$; heavy 'off' 655 ± 72 , heavy 'on' 576 ± 64 , $p=NS$).

The effect of Stn stimulation on mean lifting velocity, in contrast, was consistent and clear. Fig. 3a and b shows the group mean values (\pm SEM). It may be seen that the patients achieved significantly higher velocities with stimulation 'on' than with stimulation 'off' both for the

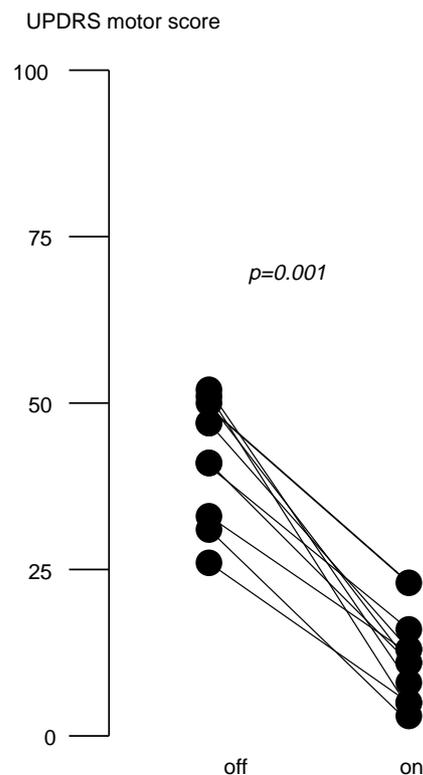


Fig. 2. Clinical effects of Stn stimulation.

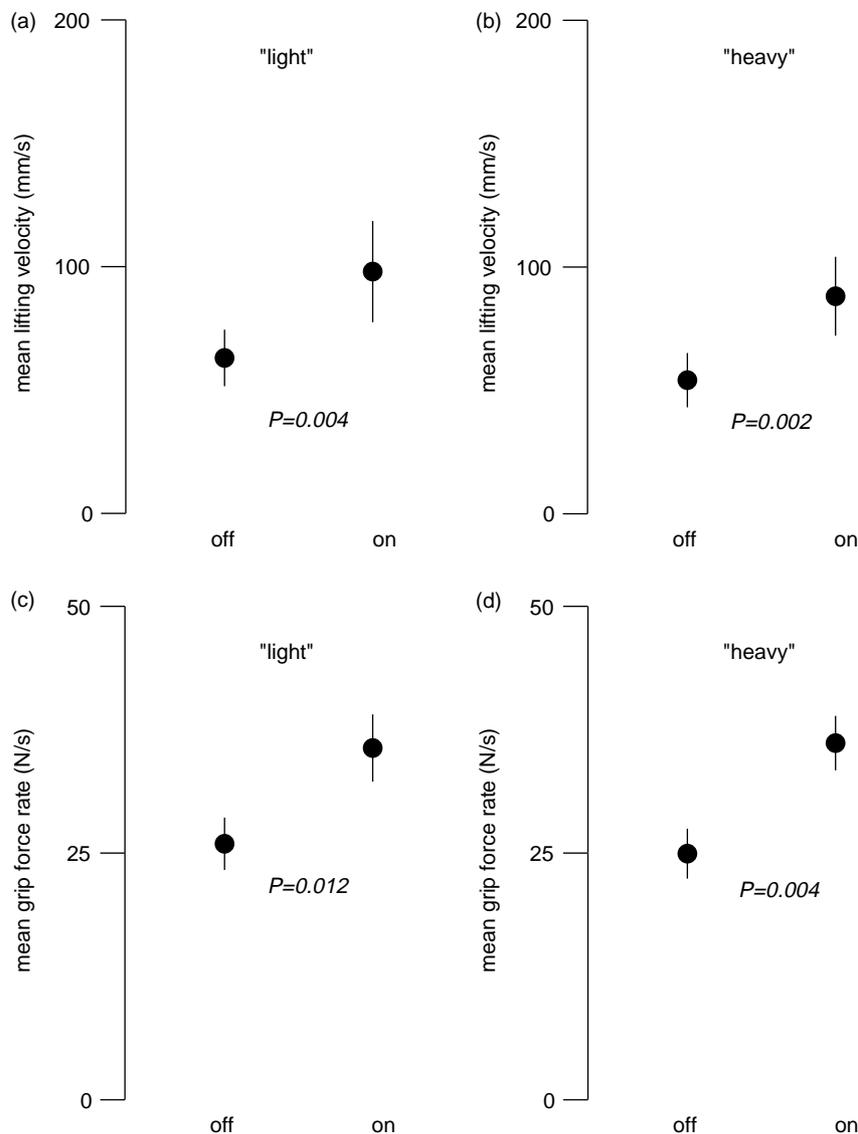


Fig. 3. group means (\pm SEM) for lifting velocity for a light (a) and heavy (b) load, and mean rate of grip force development (light (c), heavy (d)) with and without Stn stimulation. It may be seen that in all cases a significant improvement in both lifting velocity and the rate of grip force development was associated with Stn stimulation.

light and for the heavy load ($p=0.004$ and 0.002 , respectively).

This increase in speed of movement at the wrist, was matched by clear differences in the rate of grip force development seen at the fingers. The lower two panels of Fig. 3 display the group mean values (Fig. 3c, 'light' load; Fig. 3d, 'heavy' load). Stimulation resulted in a marked and statistically significant increase in the rate of grip force development (light $p=0.012$; heavy $p=0.004$).

With stimulation 'off' the patients showed pathologically exaggerated grip force values for both Pgf and Sgf. The extent of these abnormalities was comparable to those seen in both medicated [16] and de novo Parkinson's disease [17] without dyskinesia.

Perhaps surprisingly, given the clear clinically-assessed improvement seen when the stimulator was activated, the

extent of these grip force abnormalities increased significantly under the stimulation on condition for both Pgf (light $p=0.005$; heavy $p=0.007$) and Sgf (light $p=0.024$; heavy $p=0.032$). Group mean values (\pm SEM) are shown in Fig. 4a and d. In contrast, the time taken to reach peak grip force, which is normally scaled with variation in grip force amplitude [21], remained largely unchanged between the 'off' and 'on' conditions (Fig. 4e and f), particularly with the light load, despite the significant differences in Pgf amplitude.

4. Discussion

In line with the marked improvement in the clinical rating score, Stn stimulation resulted in significant

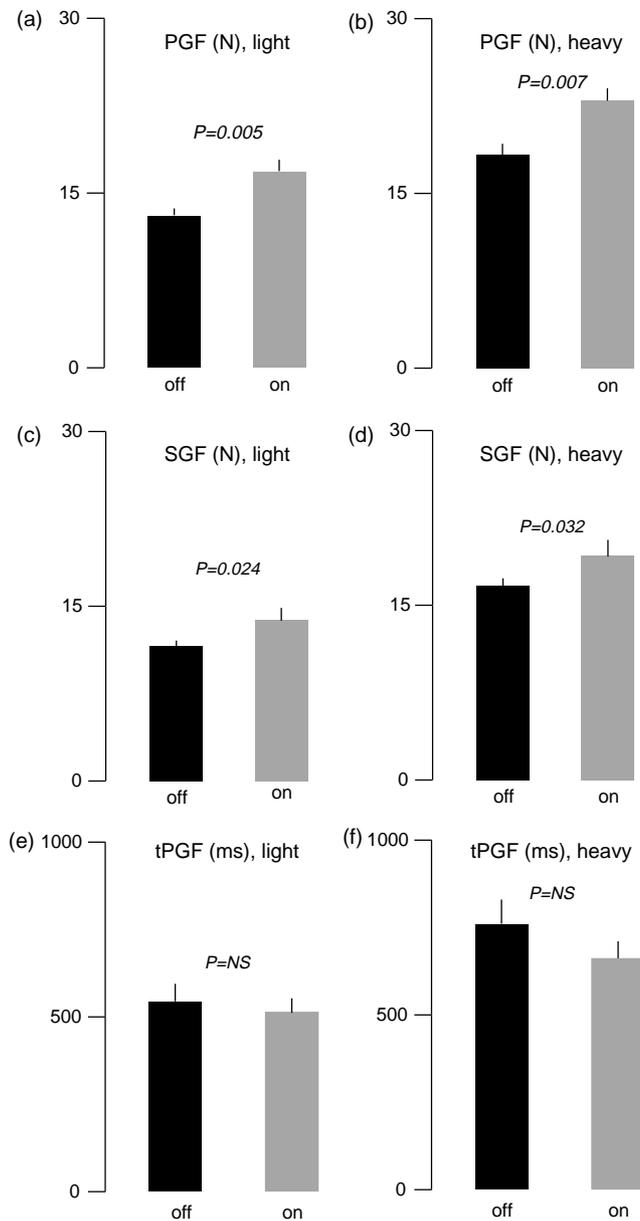


Fig. 4. effect of STN stimulation on the PGF ((a) light, (b) heavy) and SGF ((c) light, (d) heavy). It may be seen that the excessive grip force levels characteristic of Parkinson's disease are significantly worsened during STN stimulation. (e) and (f) show the time taken to reach peak grip force (tPGF) with and without STN stimulation for the light and heavy load, respectively. Note that little or no change in the tPGF occurs, especially with the light load, although the rate of grip force development is significantly higher with STN stimulation.

improvement in the slowed grip force development characteristic of Parkinson's disease from its early stages [17]. This was associated with higher velocities during object lifting, presumably due to a similar increase in the rate of force development in the wrist muscles, as the minor improvement observed in finger/wrist coordination (Igl) does not seem sufficient to explain the magnitude of the velocity changes. Thus a major effect of Stn stimulation would seem to be a reduction in bradykinesia, a result

supported by earlier studies both in the monkey [22] and in man [4,13,14,23].

In addition to the marked slowing in grip force development, another characteristic of Parkinson's disease from the early stages onwards is an exaggeration in the grip forces employed in lifting and holding an object [16,17]. In contrast to the positive effects of Stn stimulation on the rate of grip force development, Stn stimulation does not improve the grip force overflow: indeed the grip force became even more markedly exaggerated in this condition. This effect was not found in a recently published study from Nowak et al. [23]. Indeed, Nowak's group found a slight improvement in grip force exaggeration with stimulation on. However, there exist important methodological differences between our study and that of Nowak et al. The latter used a predictable load and allowed visual control of the lift. Under these conditions it has been shown that grip force exaggeration is almost eliminated in parkinsonian patients [16], presumably by removing the need for on-line processing of sensory information required by unpredictable loading. Thus it seems likely that the extra exaggeration in grip force we found with STN stimulation is associated with the mechanisms responsible for adaptation to unpredictable motor requirements.

Another possible contradiction to our findings comes from Wenzelburger et al. [14], who reported that Stn Dbs resolved the grip force overshoot associated with L-dopa-induced dyskinesia. However, as has been pointed out in an earlier paper [17], grip force overshoot associated with dyskinesia would seem to be a different phenomenon to the grip force overshoot seen in Parkinson's disease in the absence of dyskinesia. It is, therefore, not so surprising to discover that the two forms of exaggerated grip force are differentially affected by Stn Dbs. It must also be borne in mind that none of our patients showed dyskinesia in either the stimulation 'on' or 'off' state. Furthermore, there was no correlation between the extent of the increase in grip force exaggeration seen under stimulation 'on' conditions and the patients' L-dopa dosage ($r^2 = -0.005$; $p = 0.358$). Thus this effect would seem to arise as the result of STN stimulation, rather than the effects of medication.

But why, then, does Stn Dbs result in even greater exaggeration of pathological non-dyskinetic grip force levels? An explanation for this phenomenon may lie in the largely unaltered duration of grip force development in the initial lifting phase (tpgf). Coupled to a significant improvement in the rate at which grip force is developed, an increase in grip force amplitude is inevitable. But why are the patients unable to shorten the duration of grip force development and thus reduce (or even maintain) the grip force levels seen in the stimulation 'off' state? It is known from fmri studies in normal subjects that the basal ganglia and the supplementary motor area play a role in duration perception [24], and thus the disruption of function in these areas in Parkinson's disease might lead to problems in controlling the duration of motor sequences [25]. It has also

been shown that the basal ganglia are heavily involved in learned movements, taking over from the cerebellar activity seen during early learning as responses become automated [26]. It is well established that the initial phase of grip force development is a pre-programmed event, selected from motor memory on the basis of object characteristics and previous experience [21]. Although the patients in the study were tested months after implementation of Stn Dbs, it must be borne in mind that they had many years of experience in using a hand severely affected by bradykinesia. Modification of motor programs established under the influence of bradykinesia would seem to be impaired in the patients. An explanation for this may lie in the findings of Jahanshahi et al. [11], that while Stn Dbs improves response times in simple sorting tasks, it is actually detrimental to the performance of tasks requiring ‘changing behavior in novel contexts’: in the case of the present study the selection and modification of grip force profiles to reflect actual conditions. It would seem that Stn Dbs ensures that, for our patients, ‘old habits die hard’.

Acknowledgements

We would like to thank Professor Klaus Willmes for statistical advice and Luisa Metten and Ruth Freyaldenhoven for help in data acquisition. This work was supported by a grant from the Deutsche Forschungsgemeinschaft (Dfg We2857/2-1).

References

- [1] Brooks DJ, Samuels M. The effects of surgical treatment of Parkinson’s disease on brain function: PET findings. *Neurology* 2000;55(Suppl. 6):S52–S9.
- [2] Grafton ST, Waters C, Sutton J, Lew MF, Couldwell W. Pallidotomy increases activity of motor association cortex in Parkinson’s disease: a positron emission tomographic study. *Ann Neurol* 1995;37:776–83.
- [3] Limousin P, Brown RG, Jahanshahi M, Asselman P, Quinn NP, Thomas D, Obeso JA, Rothwell JC. The effects of posteroventral pallidotomy on the preparation and execution of voluntary hand and arm movements in Parkinson’s disease. *Brain* 1999;122:315–27.
- [4] Brown RG, Dowsey Limousin P, Brown P, Jahanshahi M, Pollack P, Benabid A-L, Rodriguez-Oroz MC, Obeso JA, Rothwell JC. Impact of deep brain stimulation on upper limb akinesia in Parkinson’s disease. *Ann Neurol* 1999;45:473–8.
- [5] Krack P, Pollack P, Limousin P, Hoffmann DS, Benazzouz A, Le Bas JF, Koudsie A, Benabid A-L. Opposite motor effects of pallidal stimulation in Parkinson’s disease. *Ann Neurol* 1998;43:180–92.
- [6] Limousin P, Pollak P, Benazzouz A, Hoffman DS, Le Bas JF, Broussolle E, Perret JE, Benabid AL. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995;345:91–5.
- [7] Krack P, Pollak P, Limousin P, Hoffmann DS, Xie J, Benazzouz A, Benabid A-L. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson’s disease. *Brain* 1998;121:451–7.
- [8] Volkmann J, Sturm V, Weiss PH, Kappler J, Voges J, Koulousakis A, Lehrke R, Hefter H, Freund H-J. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson’s disease. *Ann Neurol* 1998;44:953–61.
- [9] Volkmann J, Allert N, Voges J, Weiss PH, Freund H-J, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. *Neurology* 2001;56:548–51.
- [10] Limousin P, Greene J, Pollak P, Rothwell JC, Benabid A-L, Frackowiak RJS. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson’s disease. *Ann Neurol* 1997;42:283–91.
- [11] Jahanshahi M, Ardouin CMA, Brown RG, Rothwell JC, Obeso JA, Albanese A, Rodriguez-Oroz MC, Moro E, Benabid A-L, Pollack P, Limousin-Dowsey P. The impact of deep brain stimulation on executive function in Parkinson’s disease. *Brain* 2000;123:1142–54.
- [12] Rodriguez-Oroz MC, Rodriguez M, Guridi J, Mewes K, Chockman V, Vitek J, DeLong MR, Obeso JA. The subthalamic nucleus in Parkinson’s disease: somatotopic organization and physiological characteristics. *Brain* 2001;124:1777–90.
- [13] Levy R, Lang AE, Hutchinson WD, Lozano AM, Dostrovsky JO. Simultaneous repetitive movements following pallidotomy or subthalamic deep brain stimulation in patients with Parkinson’s disease. *Exp Brain Res* 2002;147:322–31.
- [14] Wenzelburger R, Zhang B-R, Poepping M, Schrader B, Müller D, Kopper F, Mehdorn HM, Deuschl G, Krack P. Dyskinesias and grip control in Parkinson’s disease are normalized by chronic stimulation of the subthalamic nucleus. *Ann Neurol* 2002;52:240–3.
- [15] Schwarz M, Fellows SJ, Schaffrath C, Noth J. Deficits in sensorimotor control during precise hand movements in Huntington’s disease. *Clin Neurophysiol* 2001;112:95–106.
- [16] Fellows SJ, Noth J, Schwarz M. Precision grip and Parkinson’s disease. *Brain* 1998;121:1771–84.
- [17] Fellows SJ, Noth J. Grip force abnormalities in de novo Parkinson’s disease. *Mov Disord* 2004;19:560–4.
- [18] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97–113.
- [19] Gordon AM, Westling G, Cole KJ, Johanson RS. Memory representations underlying motor commands used during manipulation of common and novel objects. *J Neurophysiol* 1993;69:1789–96.
- [20] Westling G, Johansson RS. Factors influencing the force control during precision grip. *Exp Brain Res* 1984;53:277–84.
- [21] Johansson RS. How is grasping modified by somatosensory input? In: Humphrey D, Freund H-J, editors. *Motor control concepts and issues*. Dahlem konferenzen. Chichester: Wiley; 1991. p. 331–55.
- [22] Baron MS, Wichmann T, Ma D, DeLong MR. Effects of transient focal inactivation of the basal ganglia in parkinsonian primates. *J Neurosci* 2002;22:592–9.
- [23] Nowak DA, Topka H, Tisch S, Hariz M, Limousin P, Rothwell JC. The beneficial effects of subthalamic nucleus stimulation on manipulative finger force control in Parkinson’s disease. *Exp Neurol* 2005;193:427–36.
- [24] Ferrandez AM, Hugueville L, Lehericy S, Poline JB, Marsault C, Pouthas V. Basal ganglia and supplementary motor area sub-tend duration perception: an fMRI study. *Neuroimage* 2003;19:1532–44.
- [25] Weiss PH, Stelmach GE, Hefter H. Programming of a movement sequence in Parkinson’s disease. *Brain* 1997;120:91–107.
- [26] Penhune VB, Doyon J. Dynamic cortical and subcortical networks in learning and delayed recall of timed motor sequences. *J Neurosci* 2002;22:1397–406.