Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits

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Electrical stimulation of the subthalamic nucleus is an established treatment for patients with advanced Parkinson's disease with pharmacologically unresponsive fluctuations. Compared with pharmacological treatment, subthalamic neurostimulation significantly improves motor symptoms, particularly during the phases of poor response to drug treatment, and reduces the severity of dyskinesias. Importantly, it also significantly improves quality of life and other integral measures of disease severity. The treatment response can last for more than 10 years, although there is no evidence that levodopa-resistant symptoms are delayed by subthalamic neurostimulation. At present, the mean disease duration for patients at the time of implantation is 12 years. In a recent study (EARLYSTIM) in patients with a disease duration of 7·5 years and fluctuations for 1·5 years, similar improvements in clinical outcomes were reported. These findings suggest that neurostimulation of the subthalamic nucleus could be used earlier in the disease course for carefully selected patients if the benefits of the treatment are weighed against the surgical risks and the lifelong need for specialised care by an experienced team. As mobility is consistently improved during the times with poor mobility by reducing fluctuations and delaying levodopa-sensitive complications, we propose that this treatment changes the disease course.

Lancet Neurol 2013; 12: 1025–34

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Introduction

Parkinson's disease is a progressive disease that is characterised by tremor, rigidity, bradykinesia, and postural disturbances. These motor symptoms can initially be controlled with levodopa and other dopaminergic drugs, but motor fluctuations and dyskinesias develop after a few years leading to progressive motor dysfunction and deterioration in quality of life (QoL). The motor fluctuations, which are characterised by rapid changes between good response to dopaminergic drugs (the on state) and phases of immobility resulting from poor response to the drugs (the off state), lead to increasing disability as the disease progresses. Dyskinesias are mostly seen during the on state. High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for advanced Parkinson's disease with motor fluctuations.[1,2] At present, patients who undergo STN neurostimulation are a mean of 60 years old and have a mean disease duration of 12 years.[3–7] The outcomes of treatment are satisfying provided strict inclusion criteria are followed.[8–11] Findings from the recent EARLYSTIM trial have shown superiority of STN neurostimulation compared with medical treatment at a mean of 7·5 years after disease onset, when patients are just beginning to experience fluctuations.[12,13] At present, we calculate that STN neurostimulation is used in fewer than 2% of all patients with Parkinson's disease, mainly because of the possible risks of surgery.

In this Personal View, we aim to address the question of whether use of this intervention can be extended to improve the QoL of patients with early fluctuating disease. We therefore discuss three key issues: (1) the efficacy of STN neurostimulation for the treatment of Parkinson's disease; (2) whether patients with Parkinson's disease should receive STN neurostimulation at an earlier stage of disease; and (3) whether STN neurostimulation could delay or modify the course of the disease.

STN stimulation for Parkinson's disease

Effects on disease symptoms

The effects of STN neurostimulation on the symptoms of Parkinson's disease are summarised in figure 1, which shows in a schematic way the outcomes of the procedure on mobility. Compared with drug treatment, the most relevant effect of STN neurostimulation is the improvement of motor function during the off state, in particular the severity of motor symptoms in the off state and the duration of the off state. In effect, this improves the mobility of patients during the times of the day when it would otherwise be at its poorest and thereby enables them to return to a daily life that can be planned. The extent of improvement in motor symptoms during the off state is therefore the most relevant clinical outcome. Furthermore, STN neurostimulation results in a reduction in the subjectively measured off time and in the severity of dyskinesias during the on state.

There have been six appropriately powered randomised controlled studies[3–7,12] that compared STN neurostimulation with best medical treatment or stimulation of the internal segment of the globus pallidus as well as a meta-analysis of 22 case series and of small controlled trials (figure 2).[8] In these studies, the improvement of mobility during the off state (stimulation on and medication off; figure 1) ranged from about 35% to 50%,[3,4,6,7,12] with one exception of only 25%.[5,14] Possible reasons for the differences in efficacy of neurostimulation have been discussed elsewhere.[15] The improvement in mobility during the off state explains the improvement in activities of daily living during the off state (25–50%,[3,4,6,7,12] with one exception of about 10%).[5] The off time was reduced by between 25% and 68%. After STN neurostimulation the levodopa equivalent dose could be reduced by between 31% and 58% compared with baseline. The controlled studies have also shown that STN neurostimulation significantly improves the on state by an average of 15·5%,[3,4,6,11] with one exception[5] in which there

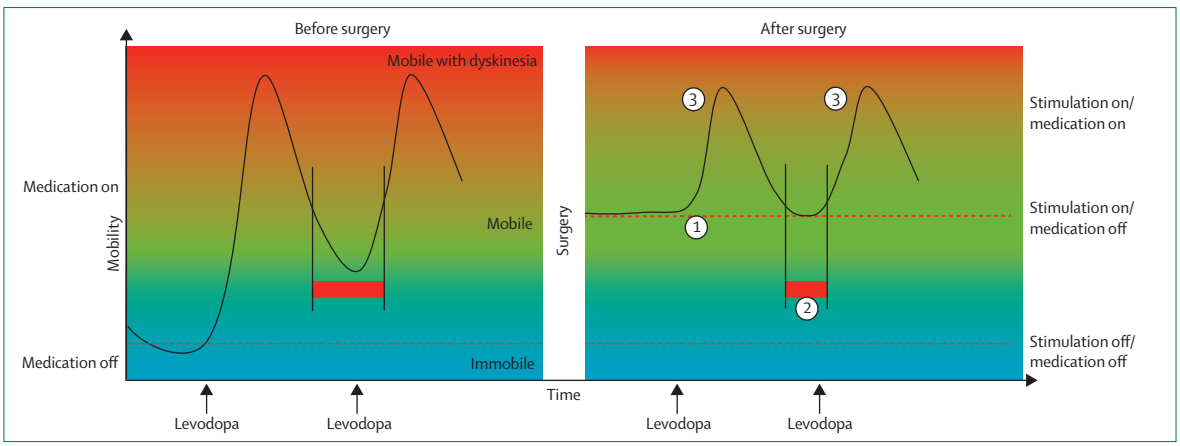

Figure 1: **Main effects of subthalamic neurostimulation in patients with Parkinson's disease**
Different states of mobility (black line) that might occur during day and night time and how they are measured in a standardised way in clinical studies. The immobile state (blue), the mobile state (green), and the mobile with troublesome dyskinesia state (red) are represented. Changes between these states can be measured using the unified Parkinson's disease rating scale (UPDRS) during the levodopa test; patients are assessed without any medication in the morning (medication off) and after a supramaximal dose of levodopa (medication on). After surgery patients can be assessed with the stimulator turned on (stimulation on) or off (stimulation off). Medication and stimulation changes can be combined after surgery. The most important clinical outcome is mobility during the stimulation on and medication off condition, when medication no longer works but stimulation is still effective because it is maintained for 24 h. During the stimulation on and medication on condition the optimum effect of medication and stimulation can be detected. During these conditions parkinsonian symptoms (UPDRS III, motor score) and activities of daily living (UPDRS II, ADL) can be assessed. Data on the severity of dyskinesias during the preceding week are measured by use of a questionnaire. The number of hours in the off state (red bars) or mobile state with or without dyskinesia are recorded in a patient diary, in which the patient records their level of mobility and dyskinesias every hour. The main effects of subthalamic neurostimulation are the improvements during the worst state (ie, stimulation on and medication off) because neurostimulation improves mobility even without medication (1), the shortening (and improvement) during the off states (2), and the reduction of dyskinesias (3). Mobility during the on state is only slightly improved (not shown).

was a worsening of symptoms (figure 2). As expected, the improvement seen in the on state in most studies is lower than that in the off state owing to a ceiling effect of levodopa plus neurostimulation. During the on state the reduction in dyskinesia by 40–60% contributes strongly to the overall improvement of the patients' mobility. Despite differences in the efficacy between studies, these data show that STN neurostimulation has a consistent effect on key parameters of mobility in Parkinson's disease.

The most robust score to assess the power of an intervention for Parkinson's disease is the Hoehn and Yahr scale,[16] which classifies patients into five stages according to unilateral or bilateral symptoms, postural stability, and need for help. Figure 3 shows the Hoehn and Yahr scores of patients during baseline and after STN neurostimulation from two controlled studies of STN neurostimulation for which original data were available: one in patients with advanced disease (mean disease duration 13·4 years [SD 5·7])[3] and the other in patients with early fluctuating disease (7·5 years [SD 2·9]) in the EARLYSTIM trial.[12] The improvement in score was substantial for both stimulation groups. The greatest improvements in scores were reported for patients with poor Hoehn and Yahr scores at baseline. On average, patients with advanced disease and scores of 4 or 5 at baseline improved to a disease stage close to 3 after stimulation. For the patients with early fluctuating disease and scores of 3 or 4, stimulation led to an improvement in scores to below 2·5. By contrast, in patients in the best medical treatment groups who had high Hoehn and Yahr scores at baseline there was only a slight improvement in scores of about 0·5, and for those with low scores at baseline there was even a slight worsening in scores. Owing to the floor effect of this scale, major improvements of patients with a Hoehn and Yahr score below 2·5 cannot be expected. Taken together, these findings show that in the off state of fluctuating Parkinson's disease STN neurostimulation profoundly improves the motor features of the disease measured with the Hoehn and Yahr scale to an extent that is unparalleled by medical treatment. Additionally, this conclusion can be applied to patients with early fluctuating disease, who seem to improve to a similar degree to patients with advanced disease.

Stability of symptomatic improvements

Several studies on the long-term responsiveness of Parkinson's disease symptoms to STN neurostimulation have been reported over the past decade. Figure 4 shows findings from eight studies with 5-year follow-up periods[17–24] and three studies with follow-up periods of 8–10 years[25–27] that assessed the effects of STN neurostimulation on symptomatic improvement. In these studies, the unified Parkinson's disease rating scale III (UPDRS III) motor and UPDRS II activities of daily living scores (both in the stimulation on and medication off state) progressively worsened over time but were still better than the scores in the medication off state before surgery. Although these studies are from different populations, they show surprising consistency. However, the different Parkinsonian symptoms do not respond uniformly: whereas improvements in tremor, rigidity, and dyskinesia were maintained over time, axial

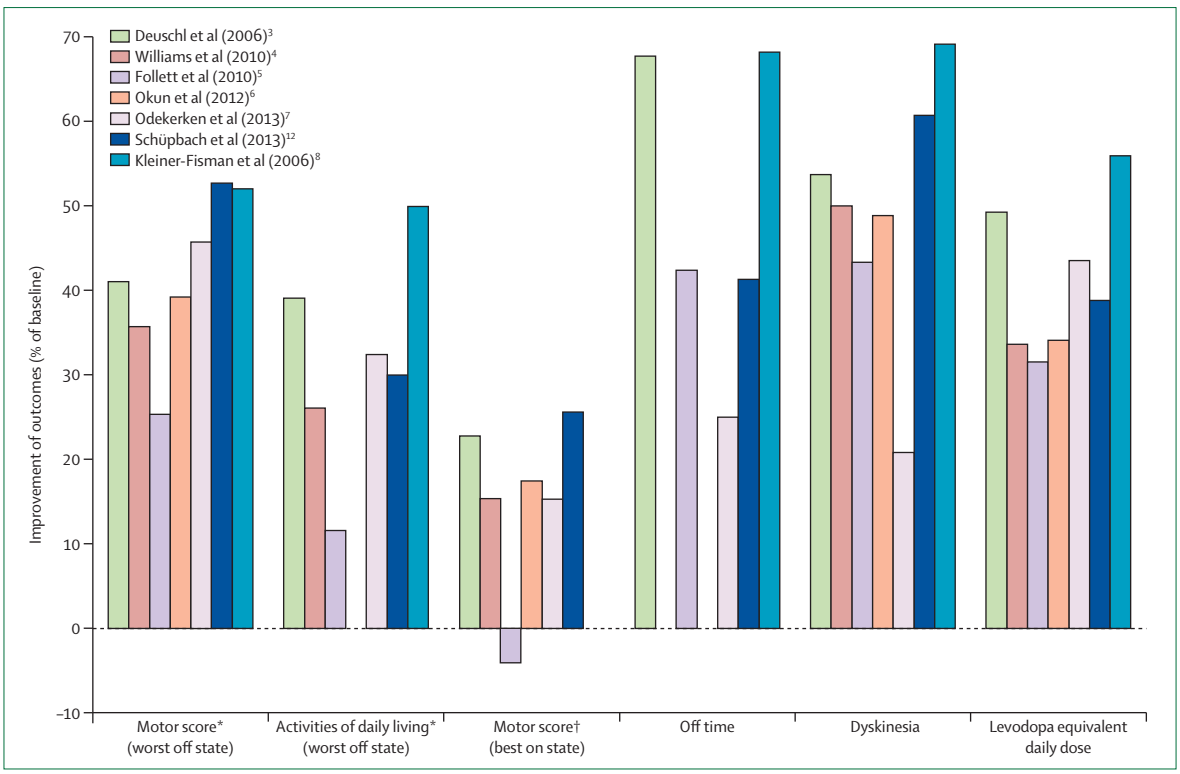

***Figure 2*: Effects of subthalamic neurostimulation on motor score, activities of daily living, off time, dyskinesia, and levodopa equivalent daily dose**
The results of six randomised controlled studies in patients with advanced disease (the neurostimulation group only)[3–7,12] and one meta-analysis[8] are shown. Only intragroup changes are reported, rather than a comparison with the appropriate control group. Improvements of the motor score and activities of daily living were measured after 6 months,[4] 1 year,[5,7,8] or 2 years.[2,6] All bars show percentage of the baseline values (100%). Missing bars indicate that the corresponding data were not available for that particular study. UPDRS=unified Parkinson's disease rating scale. *Mobility was measured during the stimulation on and medication off state with the UPDRS III (motor score) and UPDRS II (activities of daily living). †Mobility was measured during the stimulation on and medication on state with the UPDRS III (motor score).

symptoms, speech, and gait worsened over time (figure 4). Additionally, levodopa equivalent daily dose, measured according to established standards,[12,28] was maintained at low levels. Parkinson's disease seems to ultimately lead to dementia after decades.[29] So far, there is no evidence that STN neurostimulation can shorten or delay the occurrence of these late stages of Parkinson's disease.

The differences in responsiveness of parkinsonian symptoms to STN neurostimulation has led to new combinations of symptoms in patients after stimulation, which are not typically noted in patients with Parkinson's disease who have not had stimulation.[30] Although these long-term studies had large dropout rates, owing to death of the patients and loss to follow-up, and do not have control groups, they provide meaningful evidence for the very-long-term benefits of STN neurostimulation on symptoms of Parkinson's disease.

Effects on QoL

In Parkinson's disease, QoL[31] and related measures, namely activities of daily living (UPDRS II)[32] and psychosocial scales (scales for outcomes in Parkinson's disease–psychosocial [SCOPA-PS]),[33] progressively worsen in association with disease stage. QoL is an integral assessment, including motor, non-motor, cognitive, and emotional dimensions, and although summary scores on QoL scales worsen as disease progresses,[31,34] the different dimensions of QoL are not equally affected. QoL was the main outcome parameter for two studies in patients with advanced Parkinson's disease[3,4] and in the EARLYSTIM trial of patients with early fluctuating disease.[12,13] Figure 5 shows data for advanced disease[3] and early fluctuating disease.[12] In both studies the mean values of the Parkinson's disease questionnaire 39 (PDQ-39) at baseline were higher (ie, worse) for subscores that are strongly influenced by motor aspects of the disease (eg, mobility, activities of daily living, bodily discomfort, emotional wellbeing, and stigma) than for parameters that are less influenced by motor aspects (communication, cognition, and social support) (figure 5). Interestingly, although baseline values differed between the two studies,[3,12] the poorer scores on all PDQ subscales in patients with advanced disease[3] were proportional to those in patients with earlier disease,[12] suggesting that lower QoL in patients with advanced disease could be explained by disease progression.

STN neurostimulation improves QoL substantially, as shown consistently in controlled and uncontrolled studies. Figure 5 shows this improvement for patients who underwent STN neurostimulation with advanced disease[3] after 6 months and with early fluctuating disease[12] after

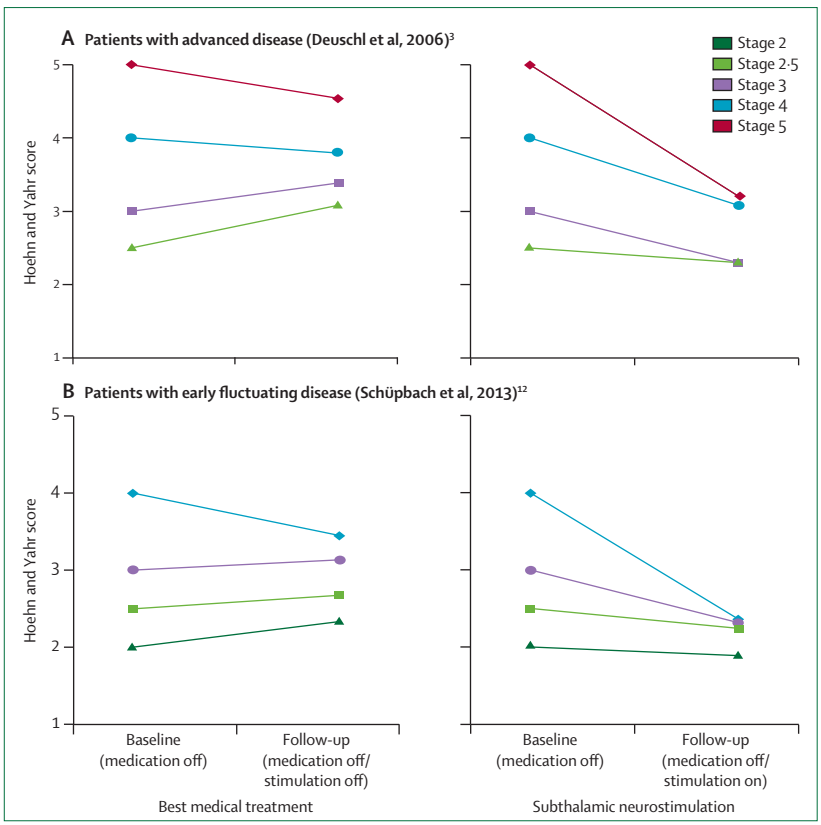

Figure 3: **Hoehn and Yahr scores of patients at baseline (medication off) and follow-up (stimulation on and medication off)**

Data from two studies were analysed: (A) a trial in patients with advanced disease with 6 months' follow-up[3] and (B) the EARLYSTIM trial in patients with early fluctuating disease with 2 years' follow-up.[12] Patients were grouped according to their Hoehn and Yahr stage during the off state at study entry (left-hand side of each graph). At follow-up (right-hand side of each graph), the outcome for each group is displayed as the mean value. In both studies, there were only minor improvements in Hoehn and Yahr score in the best medical treatment group, whereas the neurostimulation groups improved substantially. Patients with higher Hoehn and Yahr scores had a more pronounced improvement in their score than those with lower scores owing to the floor effect of the scale. Hoehn and Yahr stages are as follows: stage 1, unilateral disease; stage 2, mild bilateral disease without balance problems; stage 2·5, mild bilateral disease with balance problems; stage 3, mild-to-moderate bilateral disease, balance problems, independent in daily activities; stage 4, severe disability, able to walk and stand with some assistance; and stage 5, wheelchair bound or bedridden.

24 months. Most QoL dimensions were improved to a similar percentage in both studies after stimulation despite different baseline values (figure 5). The control populations in both studies, who received best medical treatment, showed slight worsening in QoL between baseline and follow-up (data not shown).[3,12]

We conclude that STN neurostimulation improves QoL both in early fluctuating disease and in advanced stages of the disease even if medical treatment no longer does. The extent and profile of improvement is similar for both groups of patients. No other treatment for Parkinson's disease improves QoL to a similar extent as does STN neurostimulation.[36]

Adverse events: weighing the risks

For DBS studies, adverse events are grouped into those related to surgery, to the implanted device, and to the stimulation or drug treatment. Surgical complications of STN stimulation are well studied, with several large documented cohort studies and reviews,[37–41] including controlled and uncontrolled studies. Overall mortality was 0·4% at 30 days after surgery in a study of 1183 consecutive patients treated with DBS[41] and 0·1% in a recent meta-analysis of 109 studies with 6237 patients.[38] The risk for intracerebral haemorrhage ranges from 1·6%[40] to 5% after DBS,[38] and the risk of asymptomatic haemorrhage is 0·9–1·9%.[38–41] However, not all studies routinely had post-operative imaging to enable detection of asymptomatic haemorrhages. The percentages of any serious adverse events with permanent sequelae in these studies were 1·0%[38,41] and 1·1%.[40] The number of penetrations with an electrode is a risk factor for intracerebral haemorrhage and is estimated to be 1·57% per penetration (95% CI 1·26–1·95%).[38] There is no relation between intracranial haemorrhage and age, sex, or duration of disease, but there is a significant positive relation with the number of microelectrodes used.[38]

Patients treated with DBS experience other surgically related adverse events including neurological symptoms (eg, effects on cognition and speech, hemiparesis, dysesthesia, and hemiplegia) in 0·72% and psychiatric symptoms (eg, depression, cognitive impairment, and major psychosis) in 0·31%.[38] Overall, there is no neuropsychological decline after DBS,[4,6,14,42] but frontal cognitive functions, namely verbal fluency[43] and performance on the Stroop test,[4] are worse than those of control individuals. This effect on frontal cognitive functions is unlikely to be related to stimulation but rather to small surgical lesions along the trajectory of the electrode.[6] Witt and colleagues[44] have shown that electrode trajectories intersecting particularly with the caudate nuclei significantly increased the risk for a decline in global cognition and working memory performance. The most common long-term hardware-related side-effect is infection associated with the system, mainly skin infections, which account for 4·5% to 15% of all infections over 5 years of follow-up.[37,45] By contrast, intracerebral infections seem to be rare.[39] Other complications include electrode migration[46] and lead fracture.[47] Up to 5·7% of patients receiving DBS need lead revision,[46] and the stimulator has to be surgically replaced after 4–7 years.[48,49] Overall, surgical complication rates differ widely among different centres.

Postoperative and long-term management of patients receiving DBS needs special expertise. Neuropsychiatric problems such as postoperative confusion, depression, apathy,[50] suicides,[51,52] and impulse control disorders[50] can occur, particularly shortly after the operation. Findings from EARLYSTIM suggest that the patient group seeking this treatment, rather than the stimulation itself, is the reason for the higher risk for suicidality in surgically treated patients[12] (see later). Apathy, anxiety, and depression are closely related to postoperative drug management and can be controlled by adequate modulation of levodopa treatment.[50,53] Impulsive behaviours are a complication of DBS,[54–56] but DBS can

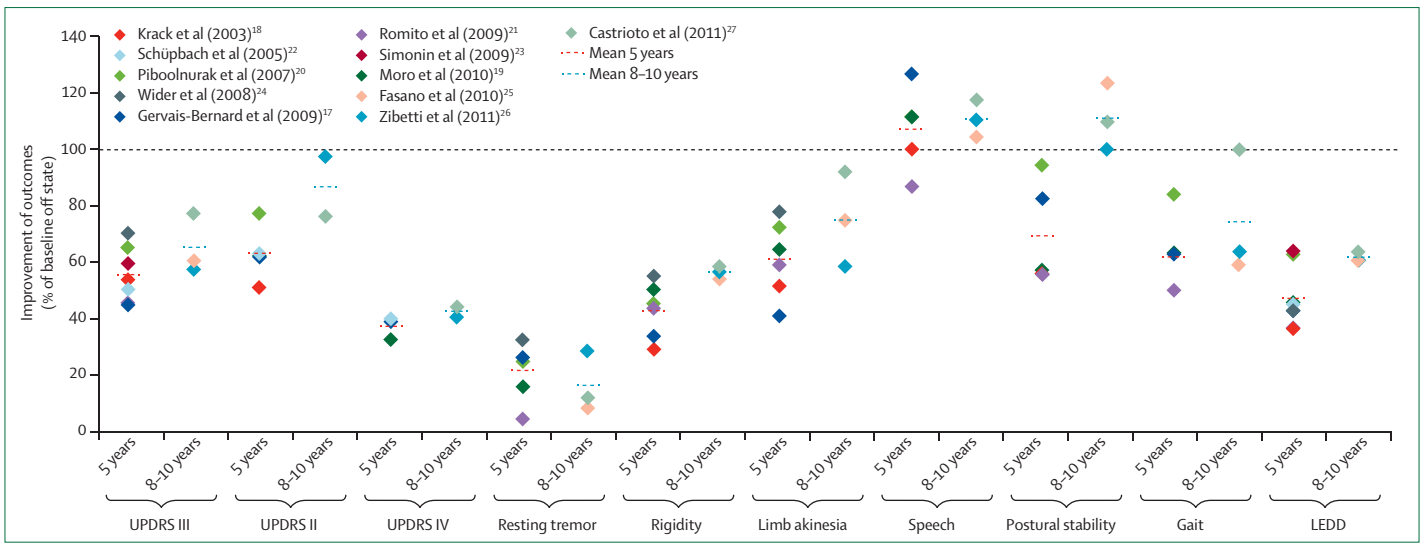

Figure 4: **Long-term responsiveness of Parkinson's disease symptoms to subthalamic neurostimulation**
Improvement in clinical outcomes after neurostimulation from eight long-term studies over a 5-year period[17–24] and three studies with 8–10 years' follow-up[25–27] are shown. Symptom severity is shown as a percentage of the preoperative worst state (medication off) indicated by the 100% line. The results of each study are represented by dots and the bar shows the mean value of the studies. Although several outcomes are improved over the observation period, symptoms such as speech, gait, and postural stability were closer to the baseline off state values or even worse. UPDRS III motor and UPDRS II activities of daily living scores were measured in the stimulation on and medication off state. UPDRS IV complications were measured for the preceding week. All subscores were compared in the stimulation on and medication off state: resting tremor, rigidity, limb akinesia, speech, postural stability, and gait. LEDD=levodopa equivalent daily dose. UPDRS=unified Parkinson's disease rating scale.

also improve impulse control disorders when drug treatment is managed appropriately.[57,58]

Among the motor symptoms, gait problems, speech problems, and eyelid opening apraxia might need special adaptation of stimulation and drug treatment. Weight gain[59] and sleep disorders[60] can occur. Special expertise of a multidisciplinary team is needed for management of patients with a stimulation implant to avoid the risk of suboptimum treatment of motor symptoms[61–63] and even social maladaptation.[64,65]

Treatment at an earlier stage of disease

If STN neurostimulation is efficacious at a mean of 12 years after the disease onset and shows enduring effects for at least 10 years (figure 4), why should this not be true at an earlier stage of the disease and why should implantation not be done earlier? There are two reasons not to undertake STN neurostimulation earlier in the disease course. First, dopamine-replacement treatments with levodopa and dopamine agonists are effective in patients with a favourable response to those treatments—ie, those with a selective lesion of the nigrostriatal dopaminergic pathway. Second, diagnostic accuracy is limited during the first years of the disease because atypical parkinsonism can mimic Parkinson's disease for a long period of time during the early stages of the disease.[66,67] Nevertheless, intervention with STN neurostimulation earlier in the disease course could prevent the development of motor complications at a much earlier timepoint and before long-term sequelae occur, such as psychosocial limitations and deterioration of QoL. Parkinson's disease is progressive, starts with a honeymoon period during which the drugs work well, but is then followed by a long period of fluctuating disease. Neurostimulation is particularly beneficial during this period of fluctuating disease. Late-stage disease is characterised by levodopa-resistant symptoms such as dementia, hallucinations, and falls,[29] which are unlikely to be improved by neurostimulation. Therefore, patients could have a longer favourable course of their disease, by delaying motor fluctuations, if they receive STN neurostimulation earlier.

As discussed earlier, the EARLYSTIM study[12,13] has attempted to answer the question of whether STN neurostimulation earlier in the disease course leads to better outcomes than medical treatment alone.[68] Patients were included when the diagnosis of Parkinson's disease was deemed established (ie, at least 4 years after disease onset), if the patient had a levodopa response of at least 50%, and fluctuations and dyskinesias for no longer than 3 years. 251 patients with a mean disease duration of 7·5 years and mean age of 52·5 years were randomly assigned to receive STN neurostimulation plus best medical treatment or best medical treatment alone and were followed up for 2 years. Compared with the medical treatment group, the primary outcome of QoL (PDQ-39) was significantly improved by 27% in the stimulation group ($p<0·001$). All major secondary outcomes were also significantly improved in the stimulation group compared with the medical treatment group: the motor score of the UPDRS III in the off medication state was 49% lower, the UPDRS II in the off medication state was 42% lower, the severity of levodopa-induced complications (UPDRS IV in the stimulation on and medication on state) was 74% lower, and the on time was 18% longer. Psychosocial functioning

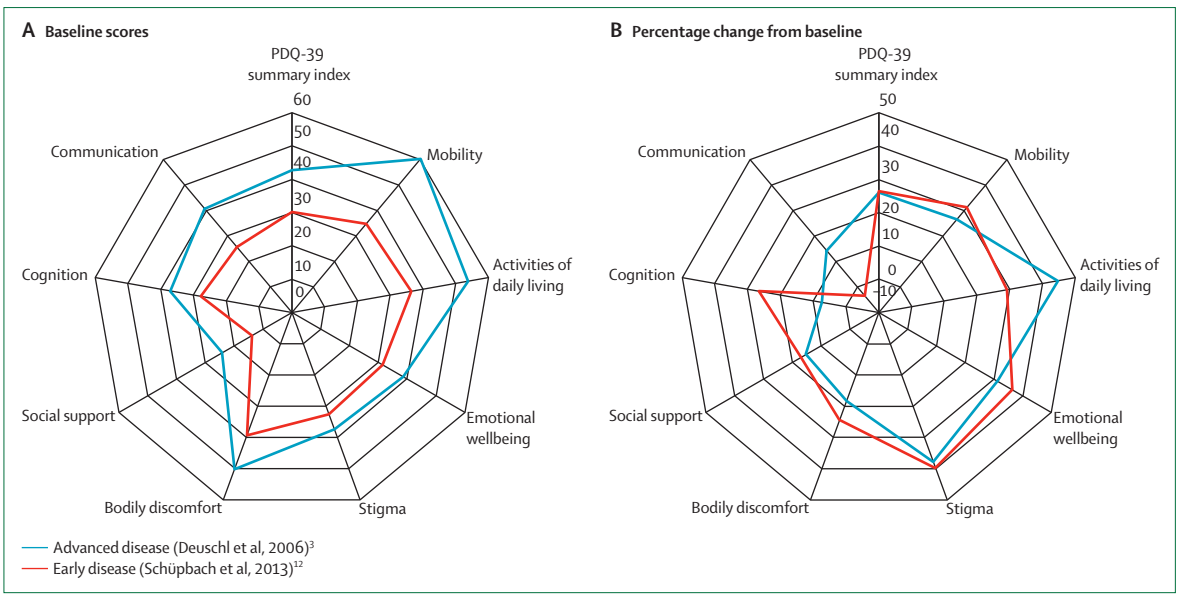

Figure 5: **Quality of life in patients with Parkinson's disease before and after subthalamic neurostimulation**
The spider diagrams show the results of the PDQ-39[35] (summary index and subscores) at baseline (A) and the percentage improvement after neurostimulation (B) in patients with advanced Parkinson's disease with a mean disease duration of 13·4 years[3] and in patients with early Parkinson's disease with a mean disease duration of 7·5 years at baseline.[12] Results are presented as absolute scores at baseline (A) and as the percentage change between baseline and follow-up (B). Most of the scores in the two cohorts differ by a third or more at baseline (A) suggesting that worsening of the scores is related to disease progression (higher scores indicate worse quality of life). Compared with baseline, quality of life was improved to a similar percentage after neurostimulation (B) in both patient groups for most of the dimensions, although there were differences for communication, cognition, and activities of daily living. PDQ-39=Parkinson's disease questionnaire 39.

was improved by 25% in the stimulation group compared with the medical treatment group. Similar differences were noted for depression and anxiety. Cognitive decline was not significantly different between the treatment groups. The levodopa equivalent daily dose was reduced by 39% in the stimulation group and increased by 21% in the medication group compared with baseline. Patients in the best medical treatment group showed no improvement from baseline in their mobility or QoL during the 2-year study period, which is disappointing with respect to the potential of medical treatment at this disease stage. This finding occurred despite the levodopa equivalent daily dose being increased from 950·3 mg to 1196·1 mg in the group who received best medical treatment alone.[12]

In the EARLYSTIM study,[12] adverse events were more common in patients who received STN neurostimulation than in those in the medical treatment group, mainly because of an increased incidence of mild adverse events related to the surgery. Serious adverse events unrelated to surgery were more common in the best medical treatment group (n=52) than in the stimulation group (n=24), with worsening of mobility, fluctuations, psychosis, impulse control disorders, and anxiety being the most common. In the stimulation group, depression and injuries were more common. 26 surgical complications occurred in 22 patients (17·7%), which all resolved after 2 years except for mild scarring in one patient. Surgical complication rates have been inconsistently reported in other studies but seem to be higher in patients with advanced disease: 18%,[5] 23%,[3] and 23·4%.[4] The low incidence of surgical sequelae in the EARLYSTIM study[12] is possibly because of the younger age of the patients at operation. Unscheduled visits, which were offered for all health problems, were more common in the best medical treatment group (n=343 visits) than in the stimulation group (n=277).

Suicides or suicidal attempts occurred in three patients in the medical treatment control group and in four patients in the stimulation group.[12] Hence, the two groups had a similar suicidal risk, which was also reported in a recent post-hoc analysis[69] of another controlled trial;[5] however, the risk in most of the neurostimulation studies is higher than that for patients with Parkinson's disease in general.[52] These findings suggest that patients who are interested in undergoing surgery have a higher risk for suicidality, rather than this being a specific effect of neurostimulation. This is an important finding of EARLYSTIM and needs to be addressed during selection and follow-up of patients who are treated with STN stimulation.

We conclude that EARLYSTIM has provided coherent evidence in favour of STN neurostimulation with regard to the important motor, non-motor, and holistic outcome parameters for Parkinson's disease and has shown limited long-term sequelae except for risk of suicidal behaviour. However, despite the promising outcomes of this study, the results should be interpreted with caution in clinical practice: patients were carefully selected for inclusion in the trial according to strict criteria (panel) and in the absence of contraindications, and the study was done at highly experienced centres with multidisciplinary teams.[13]

Modification of disease course

The mechanisms of nerve cell death in Parkinson's disease have been studied for more than 30 years, but as yet there is no coherent explanation for the progressive degeneration of brain dopaminergic neurons.[70] Several types of molecular abnormalities have been identified, such as high production of free radicals in the substantia nigra,[71] decreased production of trophic factors by glial cells (astrocytes),[72] a deficit in mitochondrial function,[73] proteasomal dysfunction,[73] an exacerbated inflammatory process,[73] and the spreading and accumulation of α-synuclein.[74] These processes are probably not affected by neurostimulation, but subsequent network changes due to nigral degeneration could be involved in the disease process; in particular, an excess of glutamate could contribute to the mechanisms of nerve cell death. Intact nigral dopaminergic neurons are controlled directly by a glutamatergic projection from the STN to the substantia nigra. Thus, an excess of glutamate could accelerate dopaminergic nerve cell death because glutamate becomes toxic in various pathological situations.[75] Additionally, overactivity of the STN occurs in Parkinson's disease,[76,77] leading to excessive production of glutamate in the vulnerable substantia nigra.

If the notion of overactive production of glutamate contributing to dopaminergic nerve cell death is correct, one way to reduce the rate of dopaminergic degeneration would be to reduce the overactivity of the STN. Pretreatment of the STN with lesions, high-frequency stimulation, or near-infrared light treatment led to a significant reduction in dopaminergic cell death in the substantia nigra in 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine rat[78–81] and monkey[82–84] models of Parkinson's disease. These findings suggest that use of prolonged continuous high-frequency stimulation of the STN might not only improve motor symptoms, but might also decrease the rate of dopaminergic cell death, thereby reducing disease progression.

However, clinical data supporting this hypothesis are sparse. Hilker and colleagues[85] found that the rate of loss of dopaminergic terminals in patients treated with STN neurostimulation was similar to that in medically treated patients, which was interpreted as a strong argument against any neuroprotective role of STN neurostimulation. Moreover, there is no evidence that neurosurgery can improve some major non-motor symptoms, such as dementia and falls, that occur late in the disease. Also, preliminary data do not suggest a delay of mortality after STN neurostimulation.[86]

Another difficulty is the design of a clinical study to test whether STN neurostimulation causes neuroprotection. Such a study would need full randomisation against a large cohort of patients receiving best medical treatment and a very long observation period, which is neither ethically nor logistically feasible. However, very large registries, which can control for the different confounders, could be of use. Also, future clinical studies will need to address the issue of an improved disease course over a patient's lifetime in a more holistic manner. Major disease-related effects such as severe on–off fluctuations, which limit patients' abilities to plan their day, inability to manage daily living because of daytime sleepiness, or pain and other non-motor disabilities are important factors for patients.[87] These outcomes are best measured with non-motor,[88] QoL,[89] and activities of daily living scales,[90] or even rough measures such as the Hoehn and Yahr staging for Parkinson's disease. Additionally, these studies must assess late-stage outcomes,[91,92] such as hallucinations, dementia, nursing-home placement, and death.[93]

***Panel:* Suggested criteria for neurostimulation of Parkinson's disease at an early disease stage**

- Definite diagnosis of Parkinson's disease (>4 years, without conflicting evidence)*
- Excellent response to levodopa (≥50%)*
- Fluctuating disease, even if only mild*
- No cognitive disturbances (Mattis score ≥130)*
- No major comorbidities*
- No major depression (Beck depression score II <25)* or other psychiatric contraindications*
- No neurosurgical contraindications*
- Brain MRI without significant lesions*
- Stable social situation
- Realistic expectations from surgery
- Access to an experienced multidisciplinary team for patient selection, surgery, programming, and long-term care*

*Inclusion criteria for EARLYSTIM.[12]

Conclusions

Although the evidence for neuroprotection in Parkinson's disease with stimulation is poor, STN neurostimulation seems to be superior to medical treatment, even when more holistic treatment outcomes are taken into account. The available data show that STN neurostimulation improves the overall disease burden to a greater extent than does medical treatment. In six large, methodologically sound studies of STN neurostimulation in advanced disease and in early fluctuating disease,[3–7,12] the most relevant outcome parameters were improved for an assessment period of 6 months to 2 years compared with best medical treatment. Even Hoehn and Yahr scores in the medication off state and QoL were significantly improved. The uncontrolled long-term studies (over 5–10 years) of patients with advanced Parkinson's disease suggest that the effect of STN neurostimulation is maintained, because the patients have better outcomes in the medication off state than at baseline up to 10 years after the operation, although signs of disease progression, particularly axial symptoms, bradykinesia, and deterioration in general mobility did occur.

STN neurostimulation might cause a change in the disease course in the sense that levodopa-sensitive complications of the disease are postponed. In the short and medium term, STN neurostimulation is treating and

Search strategy and selection criteria

We did a Medline search to identify controlled studies that compared neurostimulation of the subthalamic nucleus with best medical treatment or stimulation of the internal segment of the globus pallidus in more than 50 patients with Parkinson's disease. Reports published in English before June 2013 were included. The search terms were "deep brain stimulation", "Parkinson", and "controlled". The search revealed six studies that met the criteria, of which two compared stimulation of the subthalamic nucleus with stimulation of the internal segment of the globus pallidus. We undertook another search for long-term studies of cohorts that received subthalamic neurostimulation for Parkinson's disease. Seven studies were identified that followed up patients for 5 years and three studies for 8–10 years. Findings from case series and small controlled studies are covered by other reviews on the topic. Predefined outcome parameters were collected from these studies and compared. Group statistics were not applied. Data from a German study on quality of life in patients with advanced disease and data from the EARLYSTIM trial were compared for specific outcomes.

preventing motor and non-motor fluctuations, and it improves dyskinesia and socially disabling tremor. The improvement of the symptoms of the off state, which limit normal life, is unparalleled by medical treatment. Patients can plan daily activities instead of retreating from social life and becoming dependent on carers. Problems due to high drug doses occur less frequently after STN neurostimulation because drug treatment can be reduced and simplified. In particular, impulse control disorders and dopaminergic-induced psychoses, which are dramatic life events that change social relations and interpersonal relations within families, are less common. Findings from the controlled studies discussed in this Personal View provide the background for the hypothesis of a modification of the disease course after STN neurostimulation.

In the late stage of Parkinson's disease, when levodopa-resistant symptoms start to dominate the clinical features, STN neurostimulation provides only limited benefit and has led to new combinations of symptoms.[30] Akinesia and gait problems are no longer well treated but, unlike patients under medical treatment alone, patients treated with STN neurostimulation at this stage do not have motor fluctuations, tremor, and rigidity. There is no evidence that dementia, autonomic disturbances, and nursing-home placement can be postponed, and the late stage of the disease remains a serious challenge for patients, carers, and physicians.

Thus, the Parkinson's disease course seems only to be modified substantially by STN neurostimulation during the intermediate period, after patients have started to experience fluctuations and before they develop severe levodopa-resistant and stimulation-resistant symptoms. Because this intermediate period can last for decades, particularly in young patients, the option of earlier stimulation might be of interest to more patients than are treated at present. Results of the EARLYSTIM study[12] suggest that STN neurostimulation is more effective than best medical treatment even at earlier stages of the disease (7·5 years of disease duration) when fluctuations and dyskinesias start to affect patient wellbeing. If undertaken earlier during the disease course, STN neurostimulation might therefore induce a "second honeymoon for Parkinson's disease".[94] Findings from EARLYSTIM[12] show a non-converging difference in QoL between stimulation and best medical therapy over a 2-year period in a population of patients with early Parkinson's disease. Whether patients with early fluctuating disease who received stimulation will still have a better disease course when they reach the disease duration of the patient groups with advanced disease (11–14 years disease duration) is unknown. This question will be answered with follow-up data from the EARLYSTIM study. Future studies will also need to address the issue of prolongation of patients' lifetime and the differences in disease course over the lifetime. Methodologically, these factors will be challenging to assess because the outcomes for such studies would need to include late-stage milestones such as dementia, hallucinations, nursing-home placement, and death.[93]

At present, STN neurostimulation for patients with Parkinson's disease with early fluctuations seems scientifically justified and could change our treatment approach to Parkinson's disease. The benefits of STN neurostimulation for patients with early fluctuations need to be weighed against the risks of surgery. Severe surgical side-effects can limit the use of STN neurostimulation, but the findings from EARLYSTIM suggest that earlier surgery might be associated with fewer surgical sequelae.[12] At present, STN neurostimulation has regulatory approval in Europe for Parkinson's disease with no restrictions for early fluctuating disease, whereas in the USA it is not approved for early fluctuating disease. Choosing STN neurostimulation or maintaining medical treatment alone should remain an individual decision between the patient and the neurologist, within current regulatory guidelines. The most important predictors for good outcomes are levodopa sensitivity of the symptoms, the scarcity of cognitive disturbances, and several conditions outlined in the panel. We believe this treatment should be reserved for carefully selected patients and should be managed by experienced multidisciplinary teams.

Contributors

Both authors contributed equally to all parts of this work.

Conflicts of interest

GD has received lecture fees from Orion, Lundbeck, Medtronic, Desitin, Teva, and Pfizer and has served as a consultant for Teva, Novartis, Sapiens, and Medtronic. He has received royalties from Thieme publishers. He is a German government employee and receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health, and Medtronic. YA has received lecture fees and travel stipend from Medtronic and Servier. He is a French government employee and has received grants from the French Ministry of Health and Medtronic.

Acknowledgments

GD is supported by the German Research Council (SFB 855).

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