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Myths and Facts About the EARLYSTIM Study

W.M. Michael Schüpbach, MD,[1] Jörn Rau, MSc,[2] Jean-Luc Houeto, MD, PhD,[3] Paul Krack, MD, PhD,[4] Alfons Schnitzler, MD, PhD,[5] Carmen Schade-Brittinger, BSc,[2] Lars Timmermann, MD, PhD,[6] and Günther Deuschl, MD, PhD[7]*

[1]*Assistance-Publique Hôpitaux de Paris; Centre d'Investigation Clinique 9503, Institut du Cerveau et de la Moelle épinière; Département de Neurologie, Université Pierre et Marie Curie–Paris 6 et INSERM, CHU Pitié-Salpêtrière, Paris, France, and Movement Disorders Center, Department of Neurology, Bern University Hospital and University of Bern, Switzerland*
[2]*Coordinating Center for Clinical Trials, Philipps-University, Marburg, Germany*
[3]*Service de Neurologie, CIC INSERM-1402, CHU de Poitiers et Université de Poitiers, Poitiers, France*
[4]*Department of Neurology, University Hospital, INSERM U836, Grenoble, France*
[5]*Department of Neurology, Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University, Duesseldorf, Germany*
[6]*Department of Neurology, University of Cologne, Cologne, Germany*
[7]*Department of Neurology, University Hospital Schleswig-Holstein, Christian-Albrechts-University Kiel, Germany*

ABSTRACT: DBS of the STN improves quality of life (QoL) and motor function not only in advanced Parkinson's disease (PD), but also in PD with early motor complications, as shown in the recent EARLYSTIM study. In spite of the evidence in favor of STN-DBS, the findings of the EARLYSTIM study have recently been controversially debated. Here, we argue that a placebo or lessebo effect is unlikely to have relevantly contributed to the favorable outcome of STN-DBS in the EARLYSTIM study. The method of quantification of the placebo effect of DBS in a previous publication reveals flaws leading to implausible results, and therefore the placebo effect of DBS remains currently elusive, especially because blinding of PD patients with STN-DBS as a crucial preassumption for assessing a placebo effect is practically impossible. Moreover, we claim that the extent of such a placebo effect is most likely very small. Specific challenges of STN-DBS at an earlier stage of PD and inclusion criteria are the risk of inclusion of patients who later evolve to atypical parkinsonism, the risk of a floor effect for the benefit from DBS, the need for experienced multidisciplinary care including prevention of suicidal behavior, and the need for highly qualified long-term follow-up. The EARLYSTIM study has shown that STN-DBS may be proposed earlier on in the course of PD, as soon as motor complications start to cause relevant disability despite proper medical management. This can lead to a gain of several years of improved QoL.

Key Words: EARLYSTIM study; deep brain stimulation; placebo effect; subthalamic nucleus; Parkinson's disease

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***Correspondence to:** Prof. Dr. Günther Deuschl, Department of Neurology, University Hospital Schleswig-Holstein, Campus Kiel, Christian-Albrechts-University Kiel, Germany, Arnold-Heller-Strasse 3, D-24105 Kiel, Germany; g.deuschl@neurologie.uni-kiel.de

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DBS of the STN has been used since the 1990s in patients with advanced Parkinson's disease (PD) to treat severe motor fluctuations and dyskinesia, which could no longer be managed with medication. Initially, many uncontrolled studies and, finally, several large, randomized, controlled, multicenter studies have proven the powerful beneficial effect of STN-DBS on motor signs and quality of life (QoL).[1] It is partially sustained for at least 8 to 10 years according to open long-term studies. Meanwhile, many centers take care of patients who have been living with STN-DBS for more than 15 years. STN-DBS is an established therapy and part of the treatment guidelines for advanced PD worldwide.

Given the positive effect on QoL, many clinicians wondered whether DBS is also helpful in earlier stages of PD and might defer the stigmatizing effects of the disease and therefore psychosocial deterioration.[2] This

was the topic of the recently published EARLYSTIM study.[3]

The EARLYSTIM study was a trial on STN-DBS in PD with early motor complications. Patients were included up to 3 years after the appearance of motor fluctuations or dyskinesia, on average, 1.7 years after the end of the "honeymoon" phase. Patients with best medical treatment (BMT) according to published evidence were compared to STN-DBS in combination with BMT. The primary outcome measure in the EARLYSTIM trial, the summary index of the PDQ-39 (39-item Parkinson's Disease Questionnaire for QoL) differed, on average, by 26% in favor of STN-DBS, compared to the BMT group. This result is almost identical to the findings in a pilot study with early patients[2] and a large DBS trial in advanced patients,[4] both being models for the design of the EARLYSTIM study. For patients with STN-DBS, a significant advantage was found after 2 years not only for QoL, but also for motor parkinsonian signs ON and OFF medication, motor fluctuations and dyskinesia, activities of daily living (ADL) in the worst condition, overall psychiatric morbidity, mood, and social adjustment (as shown in Fig. 1A,B). No outcome measure showed a statistically significant advantage for patients in the medical control group. Moreover, BMT was confirmed in 96% of all patients by an expert panel who was not involved with patient care. The methodology[5] brought the author of the editorial to the publication of the EARLYSTIM article to commend the study as "one of the most rigorously conducted trials of neurostimulation."[6] The results of this study are even more consistent than controlled DBS studies in advanced patients. The effects are much stronger than in drug trials in advanced PD. This applies particularly to the improvement of QoL, which is unparalleled by any other intervention.[7] The results are stable not only over a 6-month, but also over a 2-year period. The slight worsening in the second year for QoL is similar for the BMT and DBS group.

In this comfortable situation of unambiguous outcomes, full transparency, and good methodological quality, the investigators of the EARLYSTIM study chose to let the data speak for themselves by cautiously concluding that STN-DBS "may be a therapeutic option for patients at an earlier stage than current recommendations suggest." However, recent discussions surprisingly brought up criticisms challenging the conclusions of the EARLYSTIM study. Many aspects of this critique are directed against STN-DBS in general and are not specific for EARLYSTIM. In view of these discussions, we would like to address several issues that have been raised, namely, (1) a potential placebo effect of STN-DBS as well as a lessebo effect of patients not undergoing STN-DBS, (2) the approach to ensure BMT, and (3) the specific risks to consider when STN-DBS is offered at a lower threshold. We also discuss the consequences of the EARLYSTIM trial for patient management.

The Placebo Effect and Lessebo Effect of DBS

To what extent could the findings of the EARLYSTIM study be explained by a placebo effect? It has been suggested that DBS has a high placebo effect because the dopaminergic system in PD has been related to a considerable placebo effect and because surgical procedures in general may have large placebo effects.[8] However, this has never been proven for DBS in PD, but has been inferred from a well-demonstrated placebo effect in trials on fetal cell transplantation[9] as well as trials using viral vectors for gene therapy.[10,11]

A placebo is defined as a "substance or procedure that is objectively without specific activity for the condition being treated," but nevertheless elicits a response in the patient as a result of expectation. The placebo effect is the intervention-related objective and subjective impact in a human subject not resulting from the specific efficacy of the intervention. A placebo effect is often not sustained. The prevalence of a placebo effect was stable at 8% to 9% in a therapeutic trial over 6 months in PD patients receiving placebo treatment. However, no patient showed placebo-associated improvement on all study visits, illustrating the ephemeral nature of the placebo effect in a given subject.[12]

Two aspects of STN-DBS that both could induce a placebo response must be distinguished. The first is the lesion effect of electrode implantation, and the second is the actual stimulation. To assess the respective contributions to a placebo effect, these two aspects are considered separately here. For both, only the acute effects can be measured, most commonly using the motor score of the UPDRS-III.

The Placebo Effect of Electrode Implantation in DBS Patients

DBS surgery involves microlesioning several structures along the implantation trajectory. Particularly, implanting an electrode of 1.3 mm in diameter into the $12 \times 5 \times 3$ millimeter small STN[13] induces a lesion effect. A positive clinical effect of a lesion was first demonstrated in the context of thermocoagulation of the basal ganglia.[14] With DBS electrodes alone, a microlesion effect[15] has convincingly been documented recently in a randomized, controlled study.[16] In 35 of 136 implanted patients, stimulation was not immediately begun, but deferred for 3 months. The comparison between the two groups showed a significant difference with an improvement for the adjusted 3-month mean change of 2.1 points on the UPDRS-III scale among operated, but not stimulated, patients, compared to 16.1 points among the 100 implanted patients receiving immediate stimulation. The intragroup effect of implantation without stimulation of

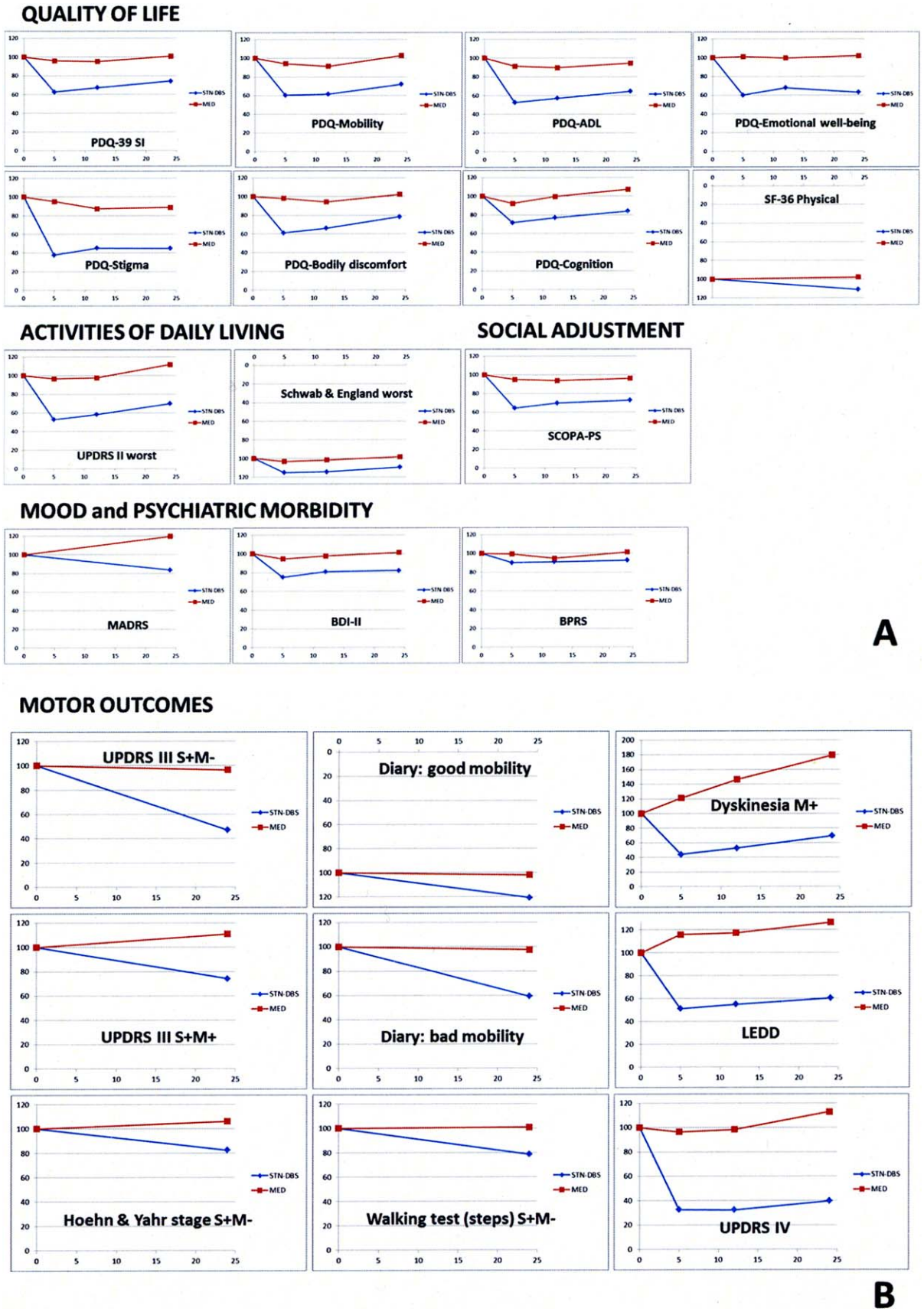

FIG. 1. Results of the EARLYSTIM study. Only changes are shown that are significantly different between the treatment groups. All significant changes are in favor of STN-DBS. All graphs are scaled to 100% (baseline).[3] The abscissa shows months after randomization. (A) Outcomes for QoL, activities of daily living, social adjustment, mood, and psychiatric morbidity. (B) Outcomes related to motor function and medication. SI, summary index; SF-36, Short Form 36 Health Survey; UPDRS part II = activities of daily living, part III = motor rating, part IV = complications of medical treatment (dyskinesia, motor fluctuations); SCOPA-PS, Scales for Outcomes in Parkinson's Disease–Psychosocial; MADRS, Montgomery-Åsberg Depression Rating Scale; BDI-II, Beck Depression Inventory II; BPRS, Brief Psychiatric Rating Scale; S+, with stimulation at follow-up for the STN-DBS group; M–, without medication; M+, with medication; LEDD, L-DOPA equivalent daily dose; walking test, number of steps over 2 × 7 meter distance.

2.1 points (95% confidence interval [CI]: −8.9; 5.2) on the UPDRS-III was not significant, and patients in this group knew that they were not stimulated. Moreover, the relative contribution of a microlesion and a placebo effect of surgery cannot be disentangled, and the microlesion may partly or fully abate over time. Therefore, it is reasonable to conclude that the potential placebo response to the surgical procedure of STN implantation itself, based on this study, is negligible. Moreover, most of an effect of implantation without stimulation is likely to be a true therapeutic effect as a result of the lesion. Such implantation effects that must not be mistaken as a neuroprotective effect are well known and can explain improvements of mobility as well as worsening of word fluency, as demonstrated in the very same study.[16] Taken together, there remains little room for a placebo effect.

The Stimulation-Associated Placebo Effect of DBS

DBS is a very potent treatment differing from medication or other surgical interventions such as transplantation by its immediate strong effect. Patients feel stimulation either directly with sensory phenomena when the stimulator is switched on or indirectly by their rapidly changing mobility. It is therefore practically impossible to blind PD patients to STN-DBS treatment in a research trial. This makes the quantification of a potential placebo effect of DBS a formidable challenge, if not impracticable.

The therapeutic effect of DBS is measured by comparing motor signs ON versus OFF stimulation. The stimulation-associated placebo effect is part of this therapeutic effect. The simplest way to assess it would be a two-arm study with patients after 12 hours OFF stimulation being blindly randomized either to stimulation OFF or stimulation ON. This is exemplified in Figure 2A, where the expectation-related improvement of motor function can be measured in the arm without stimulation. This study has never been done, but was constructed here to explain the principle. The stimulation-associated placebo effect would be 4 of 23 (i.e., 17.3%). The unavoidable disadvantage of this design is the lack of true blinding because the patients know their stimulation status (ON or OFF).

Another approach based on published data of the DBS study group trial[17] has previously been used to glean information about a placebo effect of DBS.[18] The expectation associated with switching the stimulator ON or OFF in subjects who most likely know whether or not they are stimulated has been studied (Fig. 2). Group 1 is first OFF and then ON stimulation, and group 2 is first ON and then OFF stimulation. The investigator claims that the expectation is higher in group 1 anticipating the relief to get switched on, compared to group 2 with low expectation because switching off is anticipated (Fig. 2B). In our example, the effect would be maximally (23-21)/23 corresponding to 8.7%. Given that patients were not blinded, this cannot be considered a placebo effect, but rather the open expectation in patients who are aware of the treatment they are about to receive. However, by using a different calculation with these data, the erroneous claim for a 39% placebo effect has been published.[18] The used formula did not describe the placebo effect, but quantified the residual effect of the first treatment condition remaining after switching to a second treatment condition in a crossover design. This effect is not a placebo effect, but reflects a carryover, which had been found to be not significantly different from zero in the original publication.[17] Moreover, the claimed 39% placebo effect of DBS results from pooling data of STN-DBS (placebo effect: 31%) and pallidal DBS with the implausible result of a placebo effect of 100% calculated separately.[18] We conclude that the true placebo effect of DBS remains unknown. Thus far, no design used in previous studies could realistically quantify the true placebo effect of DBS. We will deliberate in the next paragraph that it is either a negligibly small effect or an effect that is stable for years.

Estimating the Size of the Placebo Effect in STN-DBS

Clinicians fear the placebo effect because it will usually fade away over a short period. The patient could therefore undergo a futile and potentially risky invasive treatment with a small or absent long-term benefit. In return, the long-term course is helpful to estimate the extent of a possible placebo effect.

Controlled as well as long-term studies of STN-DBS show that the effect measured with the UPDRS-III is large and stable.[1] This overall effect contains the placebo effect; therefore, we label this here as therapy+placebo effect. This therapy+placebo effect of DBS shows a symptom-specific decline over years, which is more pronounced for some symptoms (e.g., axial symptoms) than for others (e.g., tremor), but the overall UPDRS-III is used as the standard measure.[1] Thus far, the decline over time of the UPDRS-III in patients with DBS has been related to disease progression, rather than to an abating placebo effect, but for the sake of rigorousness, we will debate this here: Patients with DBS are commonly assessed in the conditions ON and OFF stimulation as well as ON and OFF medication resulting in four assessments. The best condition is ON stimulation ON medication; the worst condition is OFF stimulation OFF medication. The former condition is the more reliable measure because of long-lasting carryover effects after withdrawal of stimulation and medication in the respective OFF conditions.[19,20] This is exemplified in Figure 3

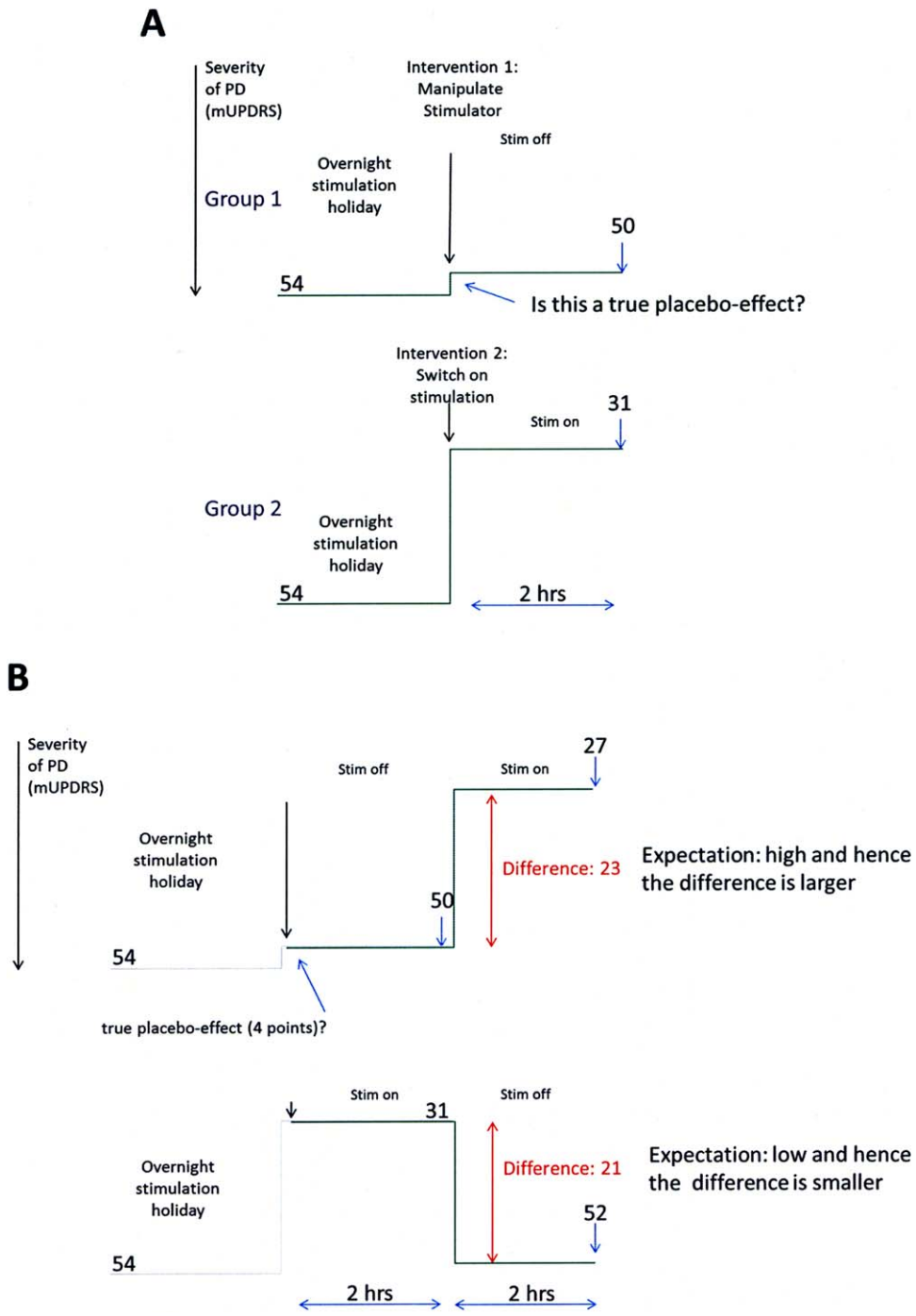

FIG. 2. (A) Hypothetical study design. The (open) expectation effect is not the (blinded) placebo effect of DBS. In a design where the patient does not know whether or not he or she will be stimulated, there may be a small positive or negative expectation effect. The limitation is that the patients cannot be blinded to the intervention. (B) A design previously used to estimate the placebo effect of DBS.[18] Here, the 2 × 2 design of an experiment ON versus OFF stimulation was used. However, this design does not measure the placebo effect, but the carryover effect. For details, see the text.

using the data by Krack et al. (2003).[21] There is a worsening of the UPDRS-III ON medication ON stimulation (Fig. 3, red line). This worsening of the therapy+placebo effect from the first to the fifth year after neurosurgery corresponds to 9.7 UPDRS-III points or 2.4 points annually in this cohort. According to our hypothesis, this may be explained either by a vanishing placebo effect or by disease progression. An annual worsening of 2.4 UPDRS-III points is, however, close to the natural progression of PD reported by Maetzler et al.,[22] who calculated an annual decline of 2.6 UPDRS-III points from placebo groups of large, randomized studies. Thus, the rate of disease progression does not leave room for a relevant long-lasting

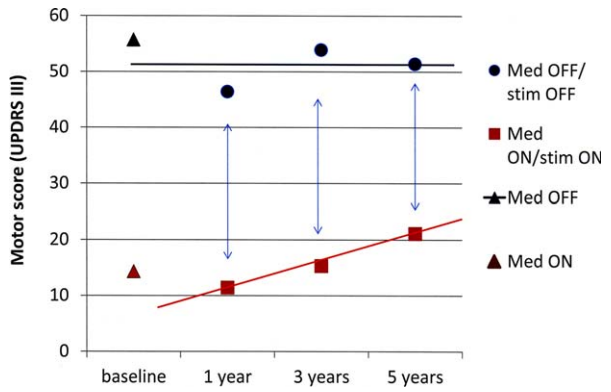

FIG. 3. The course of the worst (OFF stimulation, OFF medication) and best (ON stimulation, ON medication) motor status after STN-DBS displayed over a 5-year course in a large cohort of closely followed patients.[21] The effect of STN stimulation and dopaminergic medication is decreasing with a rate of 2.4 UPDRS-III points annually. This is in line with the 2.6-point annual disease progression calculated by Maetzler at al.[22] and does not leave room for a relevant placebo effect gradually disappearing over 5 years. The condition OFF stimulation OFF medication cannot be reliably evaluated because of residual effects outlasting the withdrawal period. UPDRS-III = motor part of the UPDRS.

placebo effect of DBS. Therefore, the true extent of the placebo effect of STN-DBS remains elusive, but it is very unlikely to be large according to these data from rigorous clinical long-term observation.

In addition to arguments against a large placebo effect in STN-DBS independent of disease stage or a specific study, there are additional arguments that are specific for the EARLYSTIM study: First, all relevant motor, cognitive, and life quality outcome measures are in favor of STN-DBS. There are no conflicting outcomes against STN-DBS. The time course of the changes is the same for all measures with improvement from the first assessment on and lasting to the final assessment. Second, the duration of the follow-up was long. A putative placebo effect would thus have to be extremely long lasting. This is unlikely given that disease progression leaves no room for a long-term placebo effect in STN-DBS as shown here. Third, quality of life, the main outcome parameter, cannot be assessed blindly. However, EARLYSTIM motor assessments were videotaped and evaluated by two blinded raters. No bias could be identified for the motor ratings, which may serve as a surrogate for the other assessments that could not be done in a blinded design. Fourth, the difference of most outcomes between the groups was very large. The 95% CIs did not overlap at all three follow-up assessments for QoL, the primary outcome measure, which is typically less prone to change than motor outcomes.

The Lessebo Effect and DBS Studies

The so-called lessebo effect, which is also known as negative placebo effect,[23,24] has been recently introduced for PD.[25] This effect describes the worsening of outcome (usually the UPDRS-III) in a randomized open trial resulting from the frustration caused in participants who know that they will not receive active treatment in contrast to those who know that they will receive active treatment. This is based only on studies on dopamine agonists, but not on surgical treatments of any kind. The investigators analyzed the difference in effect on the UPDRS-III in the arm with the active substance in studies, which had an active comparator or an inactive control.[25] Improvements of the UPDRS-III were 1.6 points lower, on average, in placebo-controlled trials than in those with an active control; this difference was termed the lessebo effect.

Although we cannot exclude that disappointment about being randomized to the medical control group may have influenced the outcome in some EARLYSTIM patients, all patients could receive STN-DBS after their participation in the trial, and many patients in the medical control group were relieved to have more time for psychological preparation. Moreover, toward the end of the trial, patients in the medical control group who were awaiting STN-DBS soon after the final study visit, became optimistic and hopeful because a powerful treatment came within near reach. This state of positive expectation in patients of the control group at the end of participation in a randomized trial may positively bias the final assessments similarly as the negative expectation in the beginning. One might call this effect the "sperabo effect" because it reflects the hope patients have for imminent relief through a promising treatment applied immediately after their participation in the study. However, both these effects are somewhat speculative and cannot be substantiated based on the data.

In respect to the EARLYSTIM study, a relevant lessebo effect is unlikely. First, this effect is very small (1.6 UPDRS-III points) and thus below clinical relevance, especially with respect to the large clinical effects of DBS.[26] Second, the effect was specific for patients with early PD and was not found in patients with fluctuating disease. Fluctuations, however, were an inclusion criterion for the EARLYSTIM study. Third, a lessebo effect was found only in studies with a short duration (<3 months) and was absent in studies with a longer duration (≥ 3 months). The EARLYSTIM study had an observation period of 24 months. Fourth, the control group of EARLYSTIM was not a placebo group, but an active treatment group receiving BMT. The claim for a relevant lessebo effect in DBS studies is refuted by the investigators' own findings.[25] Fifth, a possible lessebo effect may have been counterbalanced by a sperabo effect in the final study assessment.

In summary, we conclude that (1) the surgery-induced placebo effect is small and most likely below 2 UPDRS III points, on average, (2) the frequently

quoted large placebo effect of STN-DBS relies on an erroneous calculation,[18] (3) a lessebo effect is not to be expected based on the available scientific literature, and, (4) most important, short- and long-term cohorts show only a small deterioration rate of the clinical effect of STN-DBS, which is compatible with disease progression. A relevant placebo or lessebo effect in addition to disease progression would result in more pronounced deterioration in the long-term course. Therefore, we conclude that the claim for major placebo effects is not substantiated both for DBS-cohorts with advanced disease as well as for the EARLYSTIM population.

Risk for Suboptimal Treatment of the Medical Control Group in EARLYSTIM

A reliable strategy to ensure BMT is of utmost importance in controlled trials on DBS because BMT in PD is highly individual and complex and therefore difficult to document. Furthermore, "add-on BMT" must also be applied to patients with STN-DBS. Two issues arise: (1) the remaining therapeutic potential of medical treatment when patients are recruited and (2) the question of whether the applied BMT strategy was indeed the best choice for the patients.

How much room for improvement with BMT was there in PD patients already treated in specialized centers and recruited for EARLYSTIM? The medical control group showed no change over 2 years in UPDRS-III ratings OFF medication, motor function assessed with the patient diary, or in QoL. This stabilization over 2 years is unexpected in a chronic progressive neurodegenerative disorder such as PD. However, the medical group worsened by 1.3 UPDRS-III points ON medication. Indeed, at the stage of beginning motor complications, progressive substantial worsening of motor function and QoL would be expected.[22] Jankovic et al.[27] found an annual progression of 1.34 points on the total UPDRS in the ON and 1.58 points in the OFF state, mainly driven by a worsening of the UPDRS-III. Similar findings were described in community based U.S.[28] and European studies.[29] Taken together, the extent of progression of motor signs ON medication in medically treated patients in the EARLYSTIM study corresponds to the expected disease progression, and the stabilization of QoL and motor diaries over the study period is better than expected and argues against suboptimal use of medical treatment.

EARLYSTIM has, for the first time, developed an explicit rational algorithm for BMT in a DBS study. This was based on the European guidelines for the treatment of PD.[30] An expert panel not involved with patient care monitored every single patient and confirmed BMT in 95% of all patients in EARLYSTIM. Therefore, BMT was better controlled than in any other large clinical PD trial published thus far. The enforced application of the BMT algorithm resulted in a 21% increase of the daily levodopa equivalent dose (LED) within 2 years needed to maintain the motor ON and QoL.

Specific Challenges to Consider When Earlier STN-DBS Is Envisaged

Inclusion of Patients With Atypical Parkinsonism

If DBS is offered earlier after diagnosis, some patients who will later develop atypical parkinsonian syndromes may be operated on. The benefits of DBS in these patients will be small and last shorter. Thus far, 3 cases had been rediagnosed as nonidiopathic PD in the EARLYSTIM cohort (0.8%) 8 years after the first randomization and approximately 15 years after diagnosis, which is lower than expected.[31]

Does DBS at a Lower Threshold Have Less Potential for Improvement (Floor Effect)?

Patients with worse motor impairment have a higher potential for improvement. However, EARLYSTIM has shown that the percentage improvement of the UPDRS-III with STN-DBS in the condition OFF medication is similar to that in patients with advanced PD. Less-severe signs of disease may result in less-subjective suffering. However, as soon as motor complications are present, QoL was considerably impaired with relatively high baseline scores of the PDQ-39 summary index in the EARLYSTIM trial (30 of 100 points). The almost identical relative improvement of QoL in patients with STN-DBS for earlier[2] and for advanced[4] PD (25% and 26%) suggests that there is already room for considerable improvement as soon as motor complications occur. In addition, a pilot trial with earlier STN-DBS[2] found an improvement of QoL of 24% predicting the main outcome of EARLYSTIM almost to the digit precisely.

DBS May Be Unnecessary in Patients With a Mild Course of PD

Early DBS prevents patients from developing severe motor complications. Not all patients would have developed severe motor complications, and some might have remained relatively stable with medically manageable motor complications. DBS must always be justified by signs and symptoms that can be expected to respond to DBS and that are present at a severity that leads to subjectively sufficient impairment of QoL to request surgical treatment. The relation of risk versus benefit must be acceptable for the

TABLE 1. Suggested criteria for STN-DBS of PD with early motor complications

- Diagnosis of PD without conflicting evidence after disease duration ≥4 years[a]
- Excellent response to L-DOPA (≥50%)[a]
- Presence of motor complications (motor fluctuations and/or dyskinesia) of any severity but disturbing for the patient[a]
- No relevant cognitive deficits (Mattis Dementia Rating Scale score ≥130)[a]
- No major comorbidities jeopardizing surgery or DBS programming[a]
- No ongoing major depression (Beck Depression Inventory II score <25)[a] or other psychiatric contraindications[a]
- No neurosurgical contraindications[a]
- Stable social situation and realistic expectations from surgery
- Access to an experienced multidisciplinary team for patient selection, surgery, programming, and long-term care[a]

[a]Inclusion criteria for EARLYSTIM.

individual patient. Relatively mildly affected patients have been included, but they have been randomized to either treatment group. Given the considerable improvement of QoL in patients with STN-DBS, we do not consider DBS unnecessary in this cohort. This is different for STN-DBS applied in the honeymoon phase before the appearance of motor complications. A recent pilot study[32] showed neither motor nor QoL advantages among operated patients, compared with the patients with medical treatment.

Multidisciplinary Care, Especially Measures to Prevent Suicidal Behavior, May Not Be Sufficiently Available at all Centers

STN-DBS is a complex treatment and must be combined with excellent medical treatment of PD. Unless the necessary resources and expertise to optimally treat patients are available, STN-DBS cannot be expected to yield the results as found in the EARLYSTIM trial. Close monitoring of psychiatric status is essential in patients after STN-DBS. However, suicidal behavior has been observed also among patients in the medical control group to a similar degree. This risk profile is probably a trait of patients who qualify for DBS and opt for an invasive treatment, rather than a direct adverse consequence of DBS itself. During the recruitment for the EARLYSTIM study, more-conservative patients who were reluctant to undergo surgery and participate in a trial with randomization to one of two treatment options turned down participation in the trial. Although inclusion criteria were meticulously adhered to, there was an inherent recruitment bias because rather the "adventurers" among patients approached for participation eventually accepted to be included. This may have contributed to the selection of a study population with higher risk-taking behavior and may have contributed to the risk for suicidal behavior of the study cohort overall.

Early surgery will result in more years lived with an implanted device

This will result in more adverse events related to the stimulation material, including battery replacements. However, at least over the 2 years of randomized, controlled follow-up, adverse events related to the implanted material did not have an impact on QoL that would have precluded a significant advantage for operated patients as a group. Long-term follow-up of patients with DBS may be challenging and requires the appropriate resources. Long-term studies showing benefits of DBS even after 10 years in patients who underwent surgery at an advanced stage of PD corroborate the long-term usefulness of DBS in spite of potential device-related problems. The next years will see strong technological developments of the hardware for DBS not only in terms of more elaborated stimulating devices, but also in terms of battery lifetime with projected lifetimes of 25 years. Earlier operation may then turn into an advantage also from the safety point of view.

Conclusion

Convinced to have refuted the criticism uttered against EARLYSTIM, we nevertheless reflect on the surprising reluctance to accept the consequences of the EARLYSTIM trial. We are reminded of an old truth that the perception of important new and genuine findings evolves in three stages: First, the matter is ridiculed, then it is heavily opposed to, and finally it is accepted as self-evident. STN-DBS at an earlier stage seems now to be at the second stage. Most opposing arguments could be identified here as not scientifically sound. The EARLYSTIM study provides level A evidence in favor of STN-DBS over BMT in PD patients under 61 years with recent onset of motor complications. STN-DBS is a powerful tool to improve our patients, and particularly their QoL, and should at least be carefully discussed with all patients who can potentially benefit from it. Refusal of this thoroughly evidence-based conclusion may have other than scientific reasons. Our conclusion for clinical practice is to discuss the possibility of DBS when the selection criteria of Table 1 are fulfilled.

The EARLYSTIM study has shown that STN-DBS is superior to best medical treatment for patients with PD and early motor complications who fulfill the inclusion criteria (Table 1). The arguments for a strong placebo effect and a lessebo effect of STN-DBS are scientifically not sound. ■

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