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Programming parameters of subthalamic deep brain stimulators in Parkinson's disease from a controlled trial

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A B S T R A C T

Background: Programming algorithms have never been tested for outcome. The EARLYSTIM study showed superior outcomes of deep brain stimulation of the subthalamic nucleus (STN-DBS) over best medical treatment in early Parkinson's disease (PD). Patients were programmed according to common guidelines but customized for each patient.

Methods: Stimulation parameters were systematically documented at 1, 5, 12, and 24 month in the cohort of 114 patients who had bilateral STN-DBS at 24 month. We investigated the influence of atypical programming, changes of stimulated electrode contacts and stimulation energy delivered. Outcomes were the Unified Parkinson's Disease Rating Scale (UPDRS) motor and ADL-subscores, health-related quality of life (PDQ-39) summary index and mobility- and ADL-subscores.

Results: At 1/5/12/24 months follow up, mean amplitude (1.8/2.5/2.6/2.8 V), impedance (1107/1286/1229/1189 Ω) and TEED (33.7/69.0/84.4/93.0 V2*µs*Hz/Ω) mainly increased in the first 5 months, while mean pulse width (60.0/62.5/65.1/65.8 µs), frequency (130/137.7/139.1/142.7 Hz) remained relatively stable. Typical programming (single monopolar electrode contact) was used in 80.7% of electrodes. Double monopolar (11/114) and bipolar (2/114) stimulation was only rarely required. There was no significant difference in clinical outcomes between the patient groups requiring contact changes (n = 32/28.1%) nor between typical

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(n = 83/72.8%) versus non-typical programming. Energy used for STN-DBS was higher for the dominant side of PD.
Conclusion: In the first 5 months an increase in amplitude is required to compensate for various factors. Monopolar stimulation is sufficient in 80% of patients at 24 months. Homogeneous stimulation strategies can account for the favorable outcomes reported in the Earlystim study.

Glossary

ADL	Activities of daily living
BMT	best medical treatment
DBS	deep brain stimulation
PD	Parkinson's disease
PDQ-39-SI	Parkinson's Disease Questionnaire summary index
STN	subthalamic nucleus
TEED	Total Electrical Energy Delivered
UPDRS	Unified Parkinson's disease rating scale

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for Parkinson's disease. The EARLYSTIM-study [1] has shown a superior effect of STN stimulation in PD-patients at an early stage of the disease compared to medical therapy only. The study centers in Germany and France are specialized in the management of patients with implanted DBS electrodes including programming. For the study common guidelines for programming [2–4] were standardized and used in all centers [1,5] and then adapted to the specific needs of each patient's disease.

DBS-programming studies are rare. Programming is based on a few rules which have been developed based on experience only and common sense has been expressed in some landmark publications and is otherwise an experience-dominated art. Updated programming recommendations [6] are now available but not in 2006 when this study was planned. Except for new electrode technology the old and new recommendations do not differ substantially. New programming methods [7–11] are currently studied but not yet ready for routine clinical use.

By investigation of programming of the EARYLSTIM patients we aim at testing the currently used programming algorithms and to find hints to improve programming of DBS PD patients especially for less specialized centers or outpatient clinicians. We looked for factors which could influence programming, especially mean amplitude, pulse width, frequency, changes in impedance and of total energy used over time, contact changes, atypical stimulation including non-monopolar, frequency other than 130 Hz and impulse duration larger than 60 μs. Correlation with adverse events will be separately analyzed with the topographical lead location with respect to the individual anatomy and thus was not examined in the current study.

2. Methods

In all patients quadripolar electrodes were implanted bilaterally in the STN (Model 3389, Medtronic Inc) and connected to either one dual channel Kinetra® (Medtronic Inc.) or two single channel Soletra® neurostimulators subcutaneously implanted. Both stimulators allow for identical use in stimulation parameters. DBS-programming parameters and impedance of electrodes was systematically documented in the main study covering a follow-up period of 2 years at 1 month (i.e. initial postoperative parameters) 5 months, 12 months and 24 months [5].

Monopolar stimulation was defined as typical stimulation, whereas bipolar or double monopolar stimulation, higher than 60 μs impulse duration and other than 130 Hz frequency was labeled as atypical stimulation. We looked which contact was used mostly and how often a contact was changed with the aim of clinical improvement due to better effectiveness or reduction of side effects. As Earlystim patients were implanted with Kinetra® or Soletra® systems more recently developed tools such as interleaving pulsing or current steering was not yet available in the present cohort.

Stimulation parameter setting was defined according to expert consensus as follows [5]: all stimulation contacts were assessed in the off-medication-condition and each of the 4 contacts of each lead was tested separately as monopolar cathode. Stimulation was initially set at 60 microseconds (μs) pulse duration (lowest available) and frequency of 130 Hertz (Hz); then voltage was gradually increased. The contact to choose for treatment was defined as the one with the largest therapeutic window the lowest threshold for maximal improvement of Parkinsonian signs and the highest threshold for side effects. If the result was not satisfactory, further modification of stimulation parameters was then left to the expert's discretion and could have included an increase of impulse duration > 60 μs, frequencies other than 130 Hz, double monopolar or bipolar settings. If special problems like festination, freezing, postural instability, speech disturbances or stimulation-induced dyskinesia appeared, they were handled according to standards [2,3]. As a measure of stimulation intensity, we used the Total Electrical Energy Delivered in 1 s ($TEED_{1sec}$), integrating voltage, frequency and pulse width, based on the equation: $TEED_{1\ sec}$ = [voltage^2 * pulse width * frequency]/impedance) ((V^2 * μs * Hz/Ohm) [12]. Stimulation parameters and impedance were systematically recorded at 1, 5, 12, and 24 months follow up visits. 4000 Ω is the maximal impedance reported in the study. In 9 cases we had missing data for impedance which were replaced by the standard impedance of 1000 Ω [12].

Outcome measures were the Unified Parkinson's Disease Rating Scale (UPDRS III), subscores for the lateralized motor function (questions 20–26 of the UPDRS III, separate for each side) and the activities of daily living subscore (UPDRS II). Furthermore the PDQ-39 summary index and the PDQ-39 subscores, PDQ-39 mobility and PDQ-39 ADL [13] were analyzed. Differences were compared between baseline in the medication-off condition and the stimulation-on and medication off-state at 24 months.

Those analyses involving one group used a mixed model repeated measures analyses with normality assumptions, time as a repeated factor, a generalized covariance matrix, and site as a random effect. For those analyses with comparison groups, the factors of group and group*time interaction were added to the model. Reported are the generalized least squares estimations with standard errors (SE). *P*-values $p \leq 0.05$ were considered statistically significant and no multiplicity adjustment was used.

2.1. Ethics, funding and sponsor

This study was registered at ClinicalTrials.gov (NCT00354133). The sponsors were the Universitätsklinikum Schleswig-Holstein, Germany, and the Hospital Pitié-Salpêtrière, Paris, France. The study protocol and statistical plan is available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1205158/suppl_file/nejmoa1205158_protocol.pdf. The study has been approved by the Kiel and Paris University ethics committees and by all local ethical committees.

3. Results

Fig. 1 shows the consort flow diagram for this study. All patients with bilateral programming at the 12- and 24-month visits were

included in the analysis. 114 patients met this criterion. There were 83 patients at 24 months with bilateral single monopolar stimulation. Polarity configuration was not the same at all three visits (5, 12, and 24 months) explaining the different sample size for the visits (see Fig. 1).

3.1. Programming parameters

At the 24-month visit, 83 of 114 patients received typical bilateral single monopolar stimulation and 31 patients atypical stimulation. The following atypical stimulation was applied: bilateral bipolar (2/31), bilateral double monopolar (11/31), bipolar on one side and single monopolar on the other side (5/31), or double monopolar on one side and single monopolar on the opposite side (13/31). A total of 228 leads was analyzed among which 184 had typical single monopolar stimulation (Table 1). Changes in stimulation amplitude, pulse width, frequency and in impedance over the course of the two year follow-up period are shown in Table 2.

The first question was how stimulation parameters were adapted during the study period. The mean $TEED_{1\ sec}$ at the first programming of the neurostimulator was 34.2 $TEED_{1\ sec}$ and increased at 24 months to 100.1 $TEED_{1\ sec}$ ($p < 0{,}0001$, Fig. 2A). Hence the steepest increase of stimulation energy is between the first programming and 5 months. Between 5 and 24 months stimulation energy was less but still significantly increased over the whole 2-years period. Changes in amplitude, pulse width and frequency over the 2 years follow up period are shown in Table 2. Mean impedance changed from baseline (1107 Ohm) to 5 months (1286 Ohm), 12 months (1229 Ohm) and at 24 months (1189 Ohm) (Table 2).

The stimulated contact is selected by the programming physician as the one with the best effect and minimal side-effect. In more than 50% of the implanted leads the second most proximal out of the four contacts of the quadripolar leads was used (contacts 2 and 6, n.b. proximal and distal contact are used by some groups synonymously as dorsal and ventral contacts.) Single monopolar programming was used in more than 80% of leads (184/228) (Table 1) and more than 70% of patients (83/114). Adaptation of frequency and pulse width are other means to possibly improve the clinical result. The pulse width was only slightly increased from 60 μs to 65 μs. In four cases the frequency was reduced to 83.8 (± 13.8) Hz and in 32 patients the frequency was increased to a mean of 175 (± 23.0) Hz.

Table 1
Patient characteristics (n = 114 patients, 228 electrodes).

Cohort (at 24 months, left and right leads)	No of patients (% of patients)	No of electrodes	% of electrodes
Programming cohort (patients)	114	228	100%
Typical stimulation (single monopolar)	83/114 (72.8%)	184/228	80.7%
Atypical Stimulation	31/114 (27.2%)	44/228	19.3%
Bipolar	2/31 (6.5%)	9/228	3.9%
Double monopolar	11/31 (35.5%)	35/228	15.4%
Non-60 μs pulse width	25/114 (21.9%)	50/228	21.9%
Non-130 Hz frequency	43/114 (37.7%)	86/228	37.7%
Change of contact	32/114 (28.1%)	74/228	32.5%
Energy changes of TEED ≥ 20	39/83[a] (47.0%)	78/184[a]	42.4%

[a] TEED was calculated from the electrodes with monopolar stimulation.

There were no systematic differences between stimulation energy on the right and left side ($p > 0.15$ for all measures and visits) and for this reason stimulation parameters are averaged across sides (Table 2). Asymmetry of the disease is a typical feature of Parkinson's disease and such asymmetry remains stable throughout the evolution of the disease. We defined the body side of initial affection with PD as the dominant side of PD. The TEED was found to be statistically significantly higher for electrodes contralateral to the dominant side (44% left first, 57% right first, p's < 0.05, Fig. 2). No significant differences were found for left-right comparison.

The precision of lead placement may affect the TEED as the second side placement may be less precise due to brain shift or other perioperative factors. The surgery sequence was therefore included in the analysis. Of the 83 monopolar subjects at 24 months, this variable was missing in 5 patients. A mixed model repeated measures analysis was conducted on the difference in TEED between initially implanted side

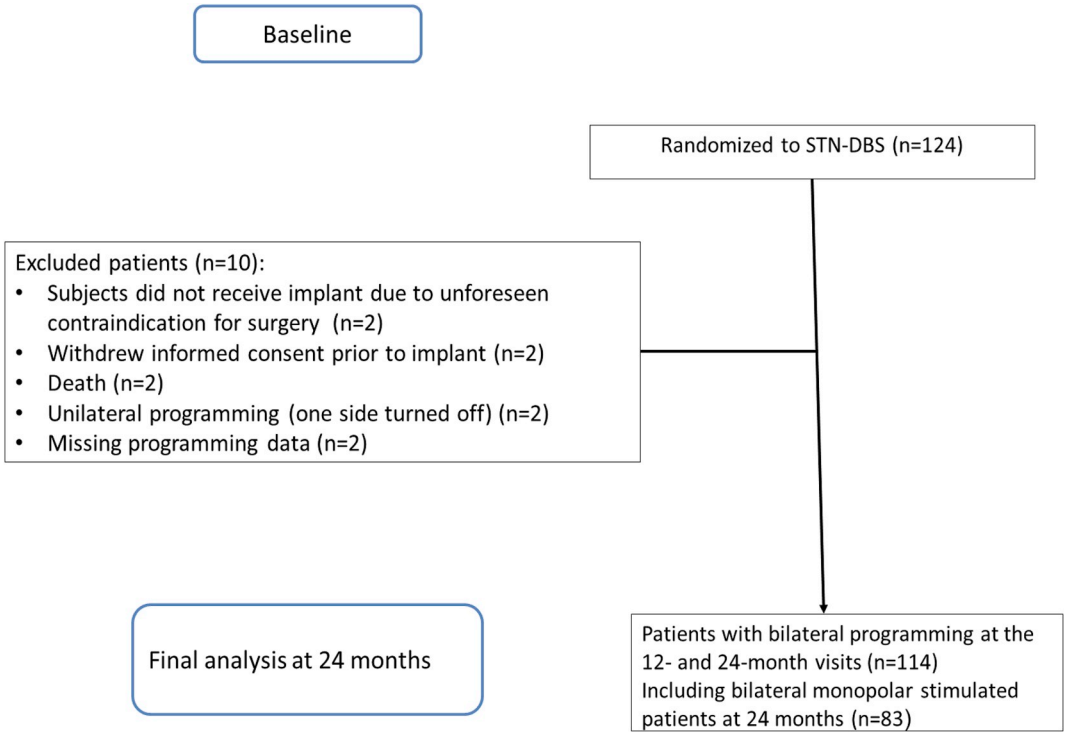

Fig. 1. Flow chart of the patient population recruited for this study.

Table 2
Stimulation settings and impedance for the whole cohort (mean of the right and left sides). Note a parallel decrease in impedance and increase in amplitude at the 5-month follow-up. Impedance being stable thereafter. Impedance calculation was limited to patients with monopolar stimulation.

Parameter	Visit	n	Mean	Median	SD	Min	Max
Amplitude (V)	Initial	112	1.8	1.8	0.8	0.0	3.7
	05 mo	113	2.5	2.6	0.6	0.7	3.7
	12 mo	114	2.6	2.625	0.7	1.0	4.2
	24 mo	114	2.8	2.725	0.7	1.1	4.4
Pulse width (μs)	Initial	111	60.0	60	8.1	0.0	90.0
	05 mo	113	62.5	60	8.7	30.0	90.0
	12 mo	114	65.1	60	12.3	60.0	150.0
	24 mo	114	65.8	60	13.5	60.0	150.0
Frequency (Hz)	Initial	111	129.8	130	16.8	0.0	185.0
	05 mo	113	137.7	130	22.2	65.0	210.0
	12 mo	114	139.1	130	23.4	60.0	210.0
	24 mo	114	142.7	130	26.3	70.0	210.0
Impedance (ohms)	Initial	113	1107.0	1042.5	279.6	481.5	2697.6
	05 mo	113	1286.2	1395.0	271.9	690.0	2697.6
	12 mo	114	1229.2	1395.0	242.3	690.0	1784.1
	24 mo	114	1188.7	1372.5	277.7	651.0	1833.5
TEED[a] (1 s)	Initial	95	33.7	27.1	26.8	0.1	142.5
	05 mo	88	69.0	57.3	46.4	11.0	257.9
	12 mo	86	84.4	67.0	62.9	11.0	303.0
	24 mo	83	93.0	75.0	67.8	17.4	317.9

and second side. There was no statistically significant difference at any visit (p-values > 0.10).

3.2. Correlation with clinical outcomes

The purpose of reprogramming is to optimize the clinical outcomes by either improve the effect on parkinsonian symptoms or avoiding side effects. Therefore, we assessed if relevant outcomes were improved by changing the programming parameters. The best measure of the stimulation efficacy is the change between the preoperative medication-off condition and the postoperative medication-off/stimulation-on condition, which was analyzed here if not otherwise mentioned. The improvement of the UPDRS III-lateralized scores was not correlated with the lateralized TEED. There was no correlation between TEED and the improvement of the UPDRS III total. For further analysis, the change of the PDQ-39 SI from baseline to 24 months was stratified into comparison "groups": those with a change in PDQ-39 SI of $> 20\%$ (n = 38) vs. those with $\leq 20\%$ change (n = 45) but TEED was not statistically significantly different between these groups. The changes of the UPDRS II, the PDQ-39 total and the subscores PDQ-39 mobility and activities of daily living were not affected by changing the contact configuration or by changing the polarity at 5, 12 or 24 months (p's > 0.05). (Table 3) Patients were further stratified into those which had a more than 50% reduction of LED and those with less than 50% reduction. The two groups did not differ in their TEED. Also, there was no correlation between TEED and the reduction of LED.

4. Discussion

In this report from the EARLYSTIM trial we summarize the changes in stimulation parameters of STN-DBS over a two year follow-up period in PD patients which have been programmed according to standardized rules [2,4,5] and we report the influence of programming on the outcomes. Both impedance of the electrodes and stimulation parameters have been systematically documented at 1, 5, 12 and 24 months allowing to calculate changes in energy delivered over time. This well controlled study in a large consecutive cohort of patients conducted in centers with high expertise in DBS using common strategies to individually adapt stimulation parameters for each patient offers the opportunity analyzing standards of stimulation and their relation to clinical outcomes. The systematic documentation of impedance allowing for calculation of energy delivered helps to better understand some practical issues of STN DBS in PD.

Stimulation energy is not related to change of the UPDRS III lateralized score itself but is related to the dominant side of the disease. This has never been reported but is intuitively plausible. According to this trial programming adaptation is seemingly necessary over at least two years. The findings show that the energy delivered is increased during this time period. By far the largest increase is occurring during the first 5 months. This has never been described before in such a large cohort and in the past this has generally been explained by the loss of the so-called "stun-effect". The stun-effect can have two main components. It may be related to a lesion-like effect of the insertion of a relatively large electrode with a diameter of 1.27 mm into the relatively small STN. The shape of the STN is ovaloid with the diameters $3 \times 5 \times 12$ mm in humans [14]. Such a stun-effect depends on electrode size. It was not rare to see permanent tremor improvement after insertion of the first larger electrodes used when thalamic DBS was started for tremor in 1987 [15]. A clinically permanent effect with the quadripolar leads used in this study, however, is typically not observed. The second explanation forwarded for the stun-effect is a postoperative edema surrounding the implanted electrode after surgery, disappearing with edema resorption.

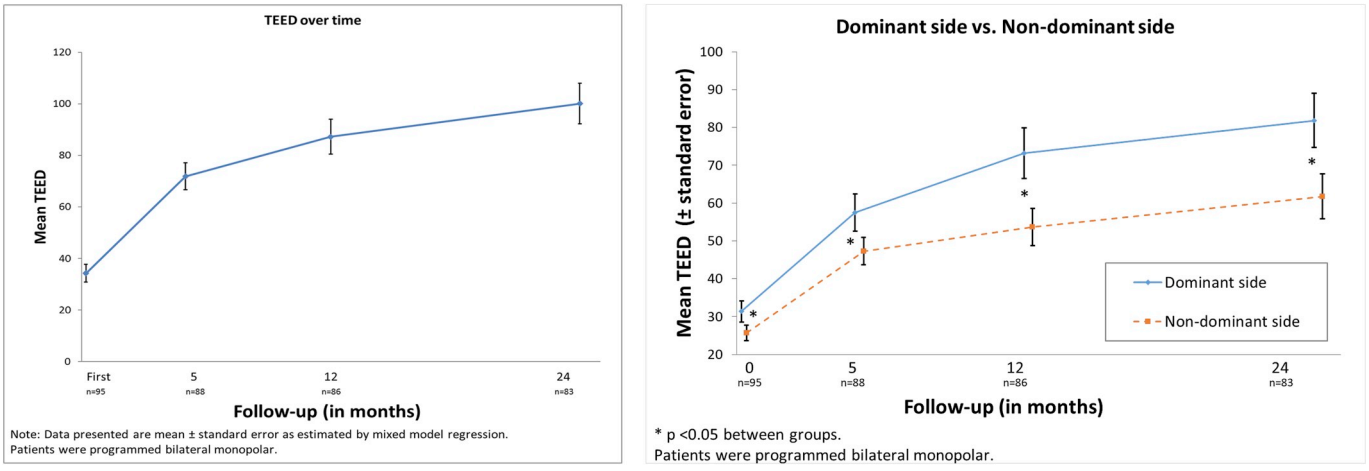

Fig. 2. (A) Mean total energy delivered (TEED) for this patient population. The energy is significantly increasing during the whole study period. (B) The dominant side is stimulated with higher TEED.

Table 3
24 months results of the two dichotomized groupings: contact-changers versus non-contact changers and typical versus atypically programmed patients regarding important outcome parameters. No significant differences were found.

Endpoint at 24 months	Mean Score	Std Error	Mean Score	Std Error	*P*-value
	Non-changers (n = 82)		Changers (n = 32)		
UPDRS II "worst" total	10	0.7	10.8	1.02	0.473
PDQ-39 Mobility subscore	23	2.49	27.9	3.8	0.345
PDQ-39 ADL subscore	22.5	1.95	26.7	3.12	0.872
PDQ-39 SI	21.8	1.47	23.5	2.36	0.483
	Typical (n = 83)		**Atypical (n = 31)**		
UPDRS II "worst" total	10.7	0.74	9.5	1.06	0.106
PDQ-39 Mobility subscore	25.2	2.39	22.4	3.68	0.314
PDQ-39 ADL subscore	25.7	1.87	21	2.99	0.817
PDQ-39 Summary index	24.3	1.62	18.5	2.58	0.139

Note: Data presented are mean ± standard error as estimated by mixed model regression. *P*-value is the group*visit interaction that will detect a difference between groups.

Our data show a mild increase in electrode impedance that is compatible with change in tissue conductance in response to disappearance of edema. However this increase in impedance has only a minor impact on TEED. We propose that the main reason of the increase shown in the first 5 months and to a lesser degree up to 12 months is related to the increase in voltage. This increase allowed a decrease in dopaminergic treatment, with a progressive weaning of long-term effects of the drugs mainly in the first weeks [16] and a progressive desensitization over months (and years) after substantial decrease of L-dopa. In the first months, indeed it is not possible to increase stimulation parameters without provoking stimulation-induced dyskinesia, particularly in those patients already being sensitized to dyskinesia with the drugs. In the long term, dyskinesia can completely disappear. This has been explained by desensitization of the molecular processes that led to dyskinesia in the first place [17] and psychotropic effects of drugs [18].

The improvement of the main outcome parameter PDQ-39 is not related to the stimulation strength in this post-hoc analysis as there is no relation with the TEED over the observed time period. But this is not surprising as quality of life is depending on many motor and non-motor variables which are not systematically related with stimulation strength [19,20].

GPi DBS is sometimes preferred over STN DBS as programming DBS is less time consuming in this target [21,22]. However, GPi DBS does not allow for decrease in drugs [21,23]. Desensitization to the behavioural side effects with STN DBS can allow for improvement in behavioural disorders as shown by the Earlystim Study [24]. The benefit of STN on akinesia seems superior [25]. Table 4 additionally summarizes the mean stimulation parameters of controlled prospective studies [25–27]. From these data it is obvious that the TEED is in a similar range for all but one [27] studies. On the other hand there is a tendency for higher TEED for pallidal than for subthalamic stimulation.

Worldwide the subthalamic nucleus is the preferred target as documented by the numbers of publications [28]. As adapting stimulation parameters is indeed more time consuming for STN than GPi DBS, the preference of the target ultimately also depends on available resources in different health care systems. The present study argues in favour of relative simple and straightforward management of DBS parameters in the vast majority of patients.

Monopolar stimulation of one contact was judged optimal in 73% of the patients and only 27% had atypical stimulation indicating that patient and physician wanted to further optimize the treatment result. The reasons to choose more complex programming reflect either insufficient clinical outcome or an unsatisfactory benefit-side-effect relation. Increasing frequency or selection of a double monopolar setting may further increase efficacy [4]. In case of side effects due to current diffusion such as dysarthria, bipolar stimulation can allow to better focus the current to the STN, but at the price of a slightly higher current consumption which explains monopolar stimulation as first choice [4]. Decrease of pulse width below 60 μs is another strategy described more recently, not available yet with during the conduct of the study [29]. Decreasing frequency described as a specific strategy to fight stimulation-induced freezing has been used in only a minority of our patients [30].

The data show that the contact-changers did not differ significantly regarding the major clinical outcomes. Such outcomes are measured in the stimulation-on and medication-off condition, the condition when medication has only its poorest effect. This reflects the worst condition for UPDRS III ("worst") and UPDRS II ("worst" total) or for aspects of life quality related to mobility reflecting more an average of the past two weeks (PDQ-39, mobility subscore and PDQ-39 ADL subscore). With this type of post-hoc analysis investing time and effort into careful programming seemingly leads to clinical outcomes which are statistically not significantly different from the cases which are easy to program. But the individual fate of the patient often makes a time-consuming programming worthwhile. By using the Kinetra® or Soletra® neurostimulators advanced programming was not applicable and we achieved good results by simply increasing TEED over time and choosing the most effective contact [6]. Advanced programming like directional steering or interleaving pulsing might have allowed additional benefit in patients with difficult programming challenges.

A study like this has weaknesses, because the motivation for parameter changes cannot be exactly tracked. Also the location of the electrode with respect to the target point is unknown. We do not have the outcome parameters directly before and after changing the stimulation parameters, but this is not feasible within such a large clinical study. In addition, we point out that this is a selected EARLYSTIM-population and that not all findings may need to be transferred to the entire group of DBS-patients and the study only covers a period of 2 years. On the other hand, this is to our knowledge the first study which

Table 4
Mean stimulation parameters of the current and previous [24–26] studies. It is evident, that the TEED used for the subthalamic nucleus is lower than for the pallidum and that the TEED for the STN is within the same order of magnitude for all but one [26] study.

stimulated area	Current study	Deuschl et al., 2006	Odekerken et al., 2013	Follett et al., 2010	Follett et al., 2010	Odekerken et al., 2013
	subthalamic nucleus				internal pallidum	
voltage (V)	2.8	2.9	2.6	3.16	3.95	2.9
pulse width (μs)	65.8	63	63.9	75.9	95.7	73
stimulation frequency (hz)	142.7	139	135	165	168	137.5
Impedance[a]	1188.7	1000	1000	1000	1000	1000
TEED (V^2 * μs * Hz/Ohm)	**61.9**	**73.6**	**58.3**	**125.1**	**250.9**	**84.4**

[a] 1000Ω used in case of lacking data.

has systematically addressed programming results and their relation to clinical outcomes. It has shown that knowing more about the electrode position would be desirable and should be captured in future studies.

The lesson of this study is a confirmation of current recommendations for programming DBS [5,8,10]. Following these standardized procedures this will lead to these homogenous results.

Contributorship

(1.Research project: (A) Conception; (B) Organization; (C) Execution. 2.Manuscript Preparation: (A) Writing of the first draft; (B) Review and Critique).

KK, LT: 1 B, C; 2 A, GD, WMMS, C.S.-B., Y.A.: 1 A, 1 B, 1 C, 2 B

PK, J.-L.H., J.R.; A.H., Y.A., A.S., L.T.; M.V.: 1 B, 1 C: 2 B

All others: 1 B, 1 C; 2 B

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