AUS DEM LEHRSTUHL
FÜR NEUROLOGIE
PROF. DR. MED. ULRICH BOGDAHN
DER FAKULTÄT FÜR MEDIZIN
DER UNIVERSITÄT REGENSBURG

Can intraoperative clinical testing predict the effects of the permanent DBS electrode in the subthalamic nucleus?

Inaugural – Dissertation
zur Erlangung des Doktorgrades
der Medizin

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Deutsche Zusammenfassung

Hintergrund und Fragestellung

Das idiopathische Parkinson-Syndrom ist die häufigste neurodegenerative Bewegungsstörung. Es handelt sich um eine neurodegenerative Erkrankung, deren motorische Kardinalsymptome Rigor, Tremor, Akinese und posturale Instabilität auf den Untergang dopaminerger Zellen in der Substantia nigra zurückzuführen sind[2 6]. Bis heute existieren ausschließlich symptomatische Therapieoptionen[14], aber keine Krankheits-modifzierende oder heilenden Therapie. Im Verlauf der Erkrankung kommt es unter der konventionellen oralen Behandlung mit Levo-Dopa oder Dopa-Agonisten zu Wirkfluktuationen mit Dyskinesien und Off-Phänomen[13]. Für die fortgeschrittene Erkrankung sind deshalb kontinuierliche Therapien wie die Tiefe Hirnstimulation (THS) entwickelt worden. Die THS im Nucleus subthalamicus (STN) ist seit 2001 in zur Behandlung des fortgeschrittenen idiopathischen Parkinson-Syndroms zugelassen und etabliert[17].

Die Implantation der THS erfolgt meist während eines stereotaktischen Wach-Eingriffs. Der Patient ist wach und ohne dopaminerge Medikation, um Wirkung und Nebenwirkungen einer intraoperativen Teststimulation anhand der klinischen Beurteilung sofort feststellen zu können. Erst nach dieser Teststimulation mittels Testelektroden, die über die bis zu fünf stereotaktischen Trajekte eingebracht werden,

erfolgt die Entscheidung für eines dieser Trajekte sowie die Festlegung der Implantationstiefe der permanenten THS-Elektrode.

In dieser Arbeit wurde untersucht, ob der Schwellenwert der Wirkung sowie der Nebenwirkungen der permanenten Elektrode und somit das therapeutische Fenster durch die intraoperative Teststimulation vorhersagbar sind.

Methoden

Die Untersuchungsprotokolle von 59 Patienten mit idiopathischem Parkinson-Syndrom wurden analysiert, die zwischen 2004 und 2015 eine bilaterale THS im STN erhalten haben.

Sowohl während der Implantation und auch postoperativ zur Programmierung der permanenten Stimulation erfolgte zur Austestung des therapeutischen Fensters eine schrittweise Steigerung der Stimulationsspannung bis zum Auftreten von Nebenwirkungen. Der Schwellenwert für eine zufriedenstellende Wirkung, entsprechend einer Reduktion von Tremor, Rigor oder Akinesie um mindestens 50% des Ausgangswertes, sowie der Schwellenwert bis zum Auftreten von Stimulation-bedingten Nebenwirkungen, wie Kapseleffekten, Parästhesien, Okulomotorikstörungen, Dysarthrie oder autonomen Symptomen, wurden für die intra- und postoperative Testung standardisiert erfasst. Da die endgültige Lage der permanenten Elektrode in Relation zum stereotaktischen Zielpunkt bekannt war, konnte den vier Polen der permanenten Elektrode jeweils eine intraoperative Stimulationstiefe eindeutig zugeordnet werden. Somit war es möglich, die Schwellenwerte für intra- und postoperative Stimulation direkt

zu vergleichen. Außerdem wurde für jeden Patienten individuell die Kategorie der Nebenwirkung beider Stimulationen verglichen.

Ergebnisse

Die postoperative Stimulation mit der permanenten Elektrode verursachte Nebenwirkungen bereits bei einem signifikant niedrigeren Schwellenwert als die intraoperative Teststimulation. Andererseits wurde ein zufriedenstellender therapeutischer Effekt mit der permanenten Elektrode erst bei einem signifikant höheren Schwellenwert erreicht. Die Nebenwirkungskategorie des individuellen Patienten zeigte sehr häufig Abweichungen zwischen beiden Stimulationen, insgesamt waren nur 33.5% der intraoperativen Nebenwirkungen in der gleichen Kategorie durch die permanente Stimulation reproduzierbar.

Diskussion und Schlussfolgerungen

Bei der Implantation der THS hängt die Entscheidung für ein Trajekt und die Implantationstiefe unter anderem von der intraoperativen Teststimulation ab[34]. Der optimale Zielpunkt hat hierbei einen möglichst geringen Schwellenwert für eine ausreichende Wirkung bei möglichst hohem Schwellenwert für Nebenwirkungen, was die Optionen bei der späteren Programmierung der Tiefen Hirnstimulation erhöhen soll. Allerdings scheinen die therapeutischen Effekte und Nebenwirkungen nicht sicher durch eine intraoperative Teststimulation vorhersagbar zu sein. Dies betrifft sowohl ihren Schwellenwert, als auch die Art der Nebenwirkung. Die intraoperative Teststimulation

führt eher dazu, dass das therapeutische Fenster der permanenten Stimulation überschätzt wird. Dies sollte bei der Beurteilung während der Implantation bedacht werden.

Ursächlich ist am ehesten eine unterschiedliche Ausbreitung des elektrischen Feldes beider Elektroden im STN und in die umliegenden Strukturen. Hierfür wiederum kommen verschiedene Faktoren in Betracht. Zunächst sind minimale Abweichungen vom Zielpunkt beim Tausch der Testelektrode mit der permanenten Elektrode nicht auszuschließen. Die beiden Elektroden unterscheiden sich außerdem deutlich, nicht nur in ihrem Durchmesser, sondern auch in ihrem Aufbau und ihrer Geometrie. Das von ihnen erzeugte elektrische Feld zeigt deshalb deutliche Differenzen, was bereits durch verschiedene Studien belegt ist[38 42].

Bisher existieren keine prospektiven Analysen, ob die intraoperative Teststimulation das Outcome der Tiefen Hirnstimulation verbessert. Die intraoperative Teststimulation erfordert eine Wach-Kraniotomie mit Zeit-intensiver klinischer Untersuchung, während der der Patient außerdem ohne dopaminerge Medikation und damit oft in einem schlechten klinischen Zustand ist. Da wir in dieser Untersuchung zeigen konnten, dass das therapeutische Fenster durch die intraoperative Teststimulation nicht sicher vorhergesagt werden kann, stellt unser Ergebnis den bisher angenommenen Nutzen der Wach-Kraniotomie in Frage. Aktuell zeigen verschiedene Studien, dass durch die erheblichen Verbesserungen der neuroradiologischen Methoden die Platzierung der Elektrode mittels intraoperativem MRT unter Allgemeinanästhesie gute Ergebnisse erzielen kann[31 51].

Zusammengefasst stellen unsere Ergebnisse daher den Nutzen der intraoperativen Teststimulation für das Outcome der Tiefen Hirnstimulation in Frage.

Abstract

Background and Objectives:

Intraoperative test stimulation is established to optimize target localization in STN DBS, but requires a time-consuming awake surgery in off-medication state. The aim of this study was to evaluate whether stimulation-induced effects of the permanent electrode are predictable by intraoperative test stimulation.

Methods:

59 PD-patients receiving bilateral STN-DBS were clinically examined with stepwise increasing monopolar stimulation during surgery and DBS programming at matched stimulation depths. Thresholds of therapeutic effects on rigidity, tremor, akinesia as well as threshold and categories of side effects as dysarthria, paraesthesia, oculomotor dysfunction, autonomic and capsular effects were obtained from standardized examination protocols retrospectively.

Results:

The central trajectory was chosen in 48.3% for implantation of the final electrode. Postoperative stimulation via the permanent electrode caused any category of side effect at a significantly lower threshold than predicted during intraoperative test stimulation ($p<0,001$); whereas sufficient therapeutic effects were achieved at significantly higher thresholds. The category of side effects differed frequently in

individual patients, only 33.5% of intraoperative side effects were reproducible in their category with permanent stimulation.

Conclusions:

Stimulation-induced therapeutic and side effects do not seem to be reliably predictable by intraoperative test stimulation concerning their thresholds and even their categories. Hence intraoperative testing may lead to an overestimation of the therapeutic window.

Introduction

Parkinson's Disease

Idiopathic Parkinson's Disease (PD) is the most common neurodegenerative movement disorder and one of the most prevalent neurological disease with an incidence of 10 to 20 of 100,000[1]. The average age of onset is 60 years. Although PD is considered to be a disease of the elderly, it can affect people at all ages. PD is a neurodegenerative disease that leads to a dopaminergic denervation in the basal ganglia of the brain as a result of a degeneration of the dopamine-producing cells in the substantia nigra[2]. The degeneration is accompanied by deposition of alpha-synuclein and Lewy bodies[3]. These pathological changes start in the lower brainstem and olfactory bulb and proceed to predictable sites of the brain which is known as Braak stages[4].

The clinical syndrome of motor parkinsonism was first described by James Parkinson in 1817[5]. The cardinal symptoms are manifestations of a hypokinetic, extrapyramidal-motor dysfunction and include akinesia, rigidity, rest tremor and postural instability[6]. Today PD is considered to affect not only the basal ganglia, but the peripheral and central nervous system as a whole. The motor impairment is generally accompanied or even preceded by multiple non-motor symptoms, e.g. hyposmia[7], sleep disorders[8], depression, psychosis and apathy[9], autonomic dysfunction[10], as well as cognitive decline[11].

Deep Brain Stimulation

There is no approved disease-modifying treatment or even cure for PD until today; all available therapeutic options are solely symptomatic. The immediate reduction of

symptoms after intake of dopamimetics supports the diagnosis of PD[12]. During the course of the disease, this conservative oral medication with dopamimetics[13] becomes less effective because of motor complications with fluctuations, off-dystonia and dyskinesias[14]. A continuous treatment is often required in this state of the disease. Deep brain stimulation (DBS) has been available since the early 1990's[15]. Today DBS of the STN or the globus pallidus internus (GPI) is an established therapy in advanced PD[16]. Although the exact mode of action is yet not fully understood it has a highly satisfying outcome[17]. The overall motor function, measured by the Unified Parkinson's Disease Rating Scale Part III (UPDRS III), is improved by 50% at least compared to an off-medication state. The improvement maintains in the long-term, as sufficient data five[18], eight[19] and even ten years[20] after DBS implantation show. The dopaminergic medication can be reduced to 50% after STN DBS[21] which also diminishes disabling dyskinesias and medication side effects. The fluctuations of motor symptoms decrease because the continuous stimulation leads to a stabilization of basal ganglia loop activity. Furthermore the quality of life of PD patients improves under DBS treatment[22].

Objectives

Bilateral DBS of the STN is a well-established symptomatic therapy option in advanced PD[17].

The potential stimulation parameters are limited by stimulation-induced side effects emerging from current spread to surrounding structures. Therefore an optimal placement of the permanent DBS electrode in the anterior dorsolateral motor part of the

STN is required[23]. Intraoperative microelectrode recording (MER) and clinical test stimulation are routinely performed to optimize target localization and thereby improve the outcome[24] although higher complication rates have been reported, e.g. bleedings[25] [26] and specific deterioration in neuropsychological functions[27]. The discussion about usefulness of MER is lively led since DBS started to be applied[28] [29] [30] [31]. New approaches using image-guided targeting have been suggested as an alternative to the current standard procedure[32]. On the other hand, MER was found to provide additional information to preoperative magnetic resonance (MRI) images for the localization of the STN[33] and thereby may lead to a better final stimulation site than anatomical targeting alone[34].

Intraoperative test stimulation requires an awake surgery in off-medication state during which therapeutic effects as well as stimulation-induced side effects are examined immediately. Thereby the therapeutic window for permanent stimulation shall be predicted. Nevertheless in clinical practice, the effects of intra- and postoperative examinations differ considerably in some patients. Therefore the aim of this study was to systematically analyze whether the effects of permanent stimulation can reliably be predicted by intraoperative test stimulation.

Methods

Patient Selection

Data of consecutive 59 PD patients (table 1) were analyzed retrospectively after bilateral STN DBS between 2004 and 2015. All patients fulfilled the inclusion criteria for DBS having a functional disability in daily life due to severe motor fluctuations or disabling tremor with a significant improvement of UPDRS III score in a standardized L-dopa challenge. Exclusion criteria were age < 75 years, active psychiatric diseases, dementia or severe cerebral microangiopathy or atrophy. For preoperative target planning, magnetic resonance imaging (MRI) under general anesthesia was fused to stereotactic computed tomography (CT).

DBS Implantation Procedure

All patients received awake stereotactic surgery in off-medication state under local anaesthesia for burr hole trepanations without the use of sedatives.[35] During the stereotactic procedure, a “ben-gun”-array of five trajectories, central, lateral, medial, anterior and posterior, each 2 mm apart was inserted, containing FHC 22675L (FHC, Bowdoin, ME, USA) electrodes for MER and test stimulation.

Test Stimulation

One to three trajectories, with identified STN-signaling in MER were chosen for intraoperative clinical testing. Test stimulation was performed at one or two depths along the chosen trajectory inside the area with the characteristic STN signals.

Stepwise increasing currents were applied between 1 mA and 6 mA or until reproducable side effects appeared. The remaining stimulation parameters were kept constant with a pulse width of 60 µs and a frequency of 130 Hz. The improvement of rigidity, tremor and bradykinesia was documented on a standardized examination protocol in four quantitative graduations, each representing an improvement of 25% from base line. Side effects were documented by verbal descriptions of type and strength. Typical side effects were retrospectively divided into five categories: capsule effects, paresthesia, dysarthria, oculomotor dysfunction and autonomic dysregulation.

Insertion of the Permanent Electrode

After identifying the optimal localization, the test electrode was replaced with the quadrupolar permanent electrode (3389, Medtronic, Minneapolis, MN, USA in 54 patients; 6147, St. Jude Medical, St. Paul, MN, USA in 5 patients).

Every test stimulation depth of the chosen trajectory was matched to the corresponding contact of the permanent electrode retrospectively. For every stimulation point of the test electrode the distance from the preoperatively determined target was registered in 0.5 mm intervals on the examination protocol. After MER and test stimulation, the final target point was defined and marked. Then, the implantation depth of the permanent electrode was determined with the second most distal contact placed on the intraoperatively defined final target. The segmentation of the permanent electrode with four contacts, each 1.5 mm in length, and with two adjacent contacts separated by 0.5 mm, was mapped in the protocol, too. Thereby the intraoperative stimulation depth

could be allocated to the corresponding contact of the permanent electrode with a 0.5 mm accuracy.

DBS Programming

Postoperative DBS programming was performed by the same examiner as during the intraoperative test stimulation between five and 13 days after surgery. Stepwise increasing currents were applied between 1 V and 6 V or until reproducible side effects appeared. The thresholds for therapeutic effects, defined as an improvement of at least 50% from baseline in rigidity, tremor or bradykinesia, as well as the thresholds for side effects were acquired for both stimulation settings.

Results

Thresholds for side effects were higher with intraoperative test stimulation than with permanent stimulation ($p<0.001$) as shown in the Kaplan-Meier estimator (Figure 1). This was replicable for every single category of side effect, and the differences were statistically significant except for capsule effects ($p=0.184$).

Thresholds of a suitable therapeutic effect were detectable in 84.8% of stimulation sites (178 / 211) for intraoperative test stimulation and still in 83.4% (176 / 211) for permanent stimulation. A strong microlesion effect obscured the delineation of thresholds in 15.2% and 16.6% respectively. Therapeutic effects of intraoperative test stimulation were achieved at significantly lower current amplitudes than in postoperative DBS programming ($p<0.001$) (Figure 2).

Thus the intraoperative test stimulation resulted in a wider therapeutic window in total with lower amplitudes for therapeutic effects and higher thresholds for side effects. Postoperative DBS programming attained a satisfactory therapeutic window for monopolar stimulation in 87.9% of the STNs, which remained constant one year after surgery (87.0%). The remaining STNs were stimulated in a bipolar stimulation mode because of unbearable side effects appearing at low stimulation amplitudes with monopolar stimulation. The average stimulation voltage of the monopolarly stimulated STNs was 2.77 V (± 0.86) after one year.

The total count of side effects was lower for the permanent stimulation than for the intraoperative stimulations (237 vs. 248, Table 2). The most likely reason is that in postoperative programming the testing stopped at 4 V in a portion of patients to shorten the procedure even if no side effects appeared until that voltage. Therefore we additionally calculated the threshold for any side effect measured until 4 V, independently of the clinical findings with higher intensities. The threshold for side effects with the permanent electrode was significantly lower than with the intraoperative electrodes (mean 3.51 V vs. 3.89 mA, mean difference: 0.38 (95%-CI 0.26, 0.49), $p < 0.001$.

The category of side effects differed frequently between intra- and postoperative stimulation. Overall only 33.5% of the side effects caused by the permanent electrode coincided in their category with the intraoperative test stimulation (Table 2). Capsule effects were most consistently predicted in 63.6% by intraoperative testing, vice versa

only 32.9% of intraoperative capsule effects recurred during permanent stimulation. The coincidence rates were even lower for the other categories of side effects.

In total 48.3% (57/118) of electrodes were implanted to the central trajectory.

Discussion

Approximately half of the permanent electrodes were implanted along the central trajectory which is in accordance with external data[36],[37] and emphasizes the influence of MER and test stimulation on final electrode location. In many centers the decision for one of the trajectories relies on the results of MER and intraoperative clinical testing. It is assumed that a wider therapeutic window offers more possibilities for postoperative stimulation parameter adjustments and thereby potentially leads to a better long-term outcome. The goal of intraoperative test stimulation is to choose the optimal stimulation site defined by the best therapeutic effects in combination with a high threshold for side effects. However, our data suggest that intraoperative test stimulation overestimates the potential therapeutic window. We found significantly higher thresholds for stimulation-induced side effects during intraoperative stimulation while a therapeutic effect was obtained at lower thresholds. The latter could partly be explained by a strong, intraoperative microlesion effect in some patients.

Yet the category of side effects was not reliably predictable which implicates that the electrodes stimulate different structures along the borders of STN. There is a variety of possible reasons for this distinct spreading of the electric field in the STN and surrounding tissues that causes a mismatch of the volume of tissue activated (VTA).

Minimal dislocations from the chosen target point during the insertion of the permanent electrode may lead to a stimulation site deviating from the assumed stimulation site in this study. Even smallest variations in the electrode location may lead to stimulations of completely different fibers[38]. In our setting the accuracy of the placement of the final electrode is controlled intraoperatively by non-stereotactic X-ray. An improvement of these placement controls during the procedure could be helpful to detect the potential dislocations in all three dimensions with the opportunity for immediate correction[39].

An earlier study found the optimal postoperative stimulation site within and around the STN more lateral and more superior compared to the preoperative MRI- based target and compared to the intraoperatively found site after intraoperative MER and test stimulation [13].

Brain shift during the procedure[40] might be another possible cause for the mismatch between intra- and postoperative stimulation sites. Even the regression of this brain shift, e.g. due to the restoration of the lost CSF during the procedure could also contribute to minimal changes of the lead position postoperatively.

As shown in experimental settings, the electric fields around the used types of electrodes differ due to their different dimensions[41]. The electrode design has a relevant impact on the stimulation effect: Changes of the diameter-height-ratio of the active contact alter the shape of VTA even if the surface area is left unchanged[42]. The 3389

Medtronic electrode has four contacts, each 1,5 mm in length with a diameter of 1.27 mm creating a surface area of 5.98 mm^2. The test electrode (FHC 22675L) offers a twofold function for MER and stimulation. Therefore its geometry is more complex with a retractable 10 mm recording tip ("micro") in a steel tube with an outside diameter of 0.46 mm, whose distal portion functions as cathode for stimulation ("macro-tip"). The remaining shaft ("cannula") is insulated from the "macro-tip" and is usually used as anode during the intraoperative test stimulation. The "macro" contact is 1 mm in length resulting in a surface area of approximately 1.78 mm^2, barely one third of the permanent electrode's. In a study using c-fos immunohistochemistry in the rat hippocampus, a macroelectrode, 150 µm in diameter, was found to have twice the radius of activation, to activate 5.8 times more neurons and to displace 20 times more tissue than a microelectrode with a diameter of 33 µm, resulting in a diameter ratio of 0.22[43]. Transferring these results to the electrodes used in this study with a diameter ratio of 0.36, an analogous impact of the electrode dimensions on the VTA is easily conceivable.

Furthermore the stimulation between the "macro-tip" and the "cannula" in a bipolar mode creates an asymmetric electric field[20]. Theoretical comparisons of test- and DBS-electrode therefore utilized a bipolar model for permanent stimulation, too. But in clinical practice monopolar stimulation is most commonly applied with only one of four contacts functioning as cathode and the implantable pulse generator (IPG) case as anodic return. Here the electric field spreads more radially outwards from the active contact which results in wider tissue activation than in bipolar mode[44]. Furthermore it is

necessary to place the electric center of the permanent electrode coincident with the electric center of the test electrode to reproduce the intraoperative effects with the chronic stimulation[16] which is barely feasible or verifiable in clinical practice due to the different compositions outlined above.

In total, there are various mismatches in the design of the two electrodes that possibly lead to relevant discrepancies in VTA and stimulation effects.

While intraoperative test stimulation was performed in constant-current mode, postoperative DBS programming utilized constant-voltage mode. There is some evidence that monopolar current-controlled and voltage-controlled stimulation generate nearly identical VTA shapes in theoretical DBS models[45]. Also in clinical practice, the current of intraoperative testing is usually considered to be equal to the voltage of permanent electrode stimulation assuming fixed impedances around 1000 Ω. But clinical measurements revealed that the impedance fluctuates in a range from 500 to 1500 Ω[46]. In vitro experiments showed that the impedance is mostly influenced by the conductivity and thickness of the encapsulation layer around the electrode[47]. In an in-vitro model with typical DBS settings, the VTA was inversely correlated to the impedance with a reduction up to 52% of VTA volume just by increasing the impedance within the typical range[48]. Perioperative edema, a haemosiderine layer or later gliotic scar formation determine the electrode´s encapsulation. This changes the conductivity of the surrounding tissue and thereby contributes to different VTA intra- and postoperatively. An edema decreases the impedance, while a glial transformation has

the opposite effect[18]. Although the impedance of the “macro” contact of the test electrode cannot be measured during the surgery, we suggest a notable influence of the impedance changing over time on different stimulation effects.

Although there is evidence for the usefulness of MER in target localization and outcome improvement[11], similar clinical effects of intraoperative clinical testing have yet not been shown convincingly. As we were not able to predict the therapeutic window accurately, our results may stimulate the discussion about the necessity of awake surgery. Recent studies provided increasing evidence for good clinical results after electrode placement using intraoperative MRI[49 50 51] or CT[52] which could potentially shorten the procedure and relieve the patient from the strain of awake surgery.

In conclusion, whether test stimulation and intraoperative clinical examination improve the long-term outcome of STN DBS is called into question by our data and should be evaluated in a prospective study design. Therefore clinicians involved in DBS surgery and programming should be aware that the therapeutic effect and side effects of permanent stimulation may not be reliably predicted by intraoperative test stimulation.

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Tabellen

Table 1

Patients‘ characteristics

Patients	59
male / female	45 / 14
STNs	118
stimulation points	211
	mean ± SD
age at surgery (years)	61.53 ± 6.73
disease duration at surgery (years)	12.07 ± 5.54
preoperative UPRDS III OFF	37.44 ± 11.65
preoperative UPDRS III ON	13.14 ± 7.36
time to first DBS activation (days)	8.43 ± 4.57
preoperative levodopa equivalent dose (mg)	1181.25 ± 551.05
postoperative levodopa equivalent dose (mg)	438.80 ± 275.87
relative levodopa reduction	58,93 % ± 24.26%
levodopa equivalent dose 1 year after surgery (mg)	547.83 ± 314.44
relative levodopa reduction 1 year after surgery	49.65% ± 31.08%
chosen trajectory	
central	48.31% (57/118)
anterior	23.73% (28/118)
posterior	12,71% (15/118)
medial	10,17% (12/118)
lateral	5.08% (6/118)

Table 2

Intra- and postoperative stimulation-induced side effects and their coincidence rates

	intraoperative	postoperative	coincident	coincident in % of intraoperative effect	coincident in % of postoperative effect
total*	248	237	83	33.5%	35.0%
any side effect	198	151	51	25.8%	33.8%
no side effect	50	86	28	56.0%	32.6%
capsule effect	85	44	28	32.9%	63.6%
oculomotor effect	33	35	9	27.3%	25.7%
paraesthesia	42	37	11	26.2%	29.7%
dysarthria	24	19	4	16.7%	21.1%
autonomic effect	14	16	3	21.4%	18.8%

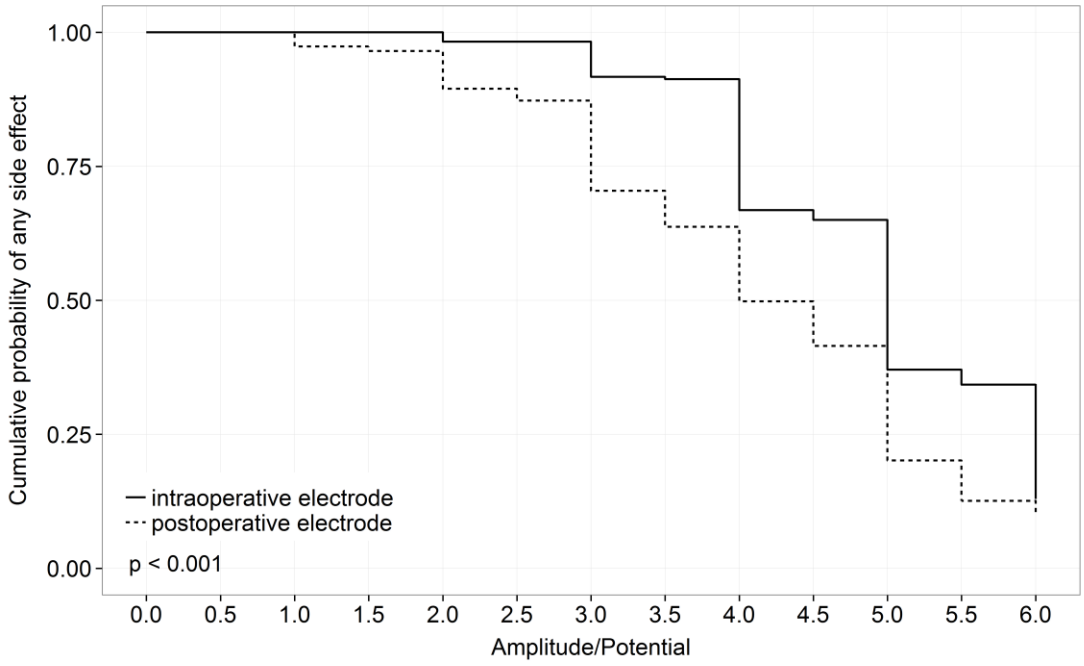
***=all side effects detected and no side effect; multiple effects per stimulation point possible**

Abbildungen

Figure 1

Cumulative probability for any side effect for increasing stimulation potentials

Kaplan Meier estimator showing the cumulative probability for any side effect (capsule effect, paraesthesia, oculomotor dysfunction, autonomic effects, dysarthria taken together) for increasing stimulation potentials. Intraoperative stimulation with the test electrode (continuous line) caused side effects at significantly higher current strengths than postoperative stimulation with the permanent DBS electrode (dashed line) ($p<0.001$).



intraoperative electrode	229(0)	229(0)	229(0)	229(0)	229(4)	225(4)	225(19)	210(20)	209(76)	146(80)	142(141)	66(146)	61(184)
postoperative electrode	228(0)	228(0)	228(6)	222(8)	220(24)	204(29)	197(67)	157(82)	142(113)	42(120)	33(137)	8(140)	5(141)

Numbers at risk (cumulative events)

Figure 2

Cumulative probability for a capsule effect for increasing stimulation potentials

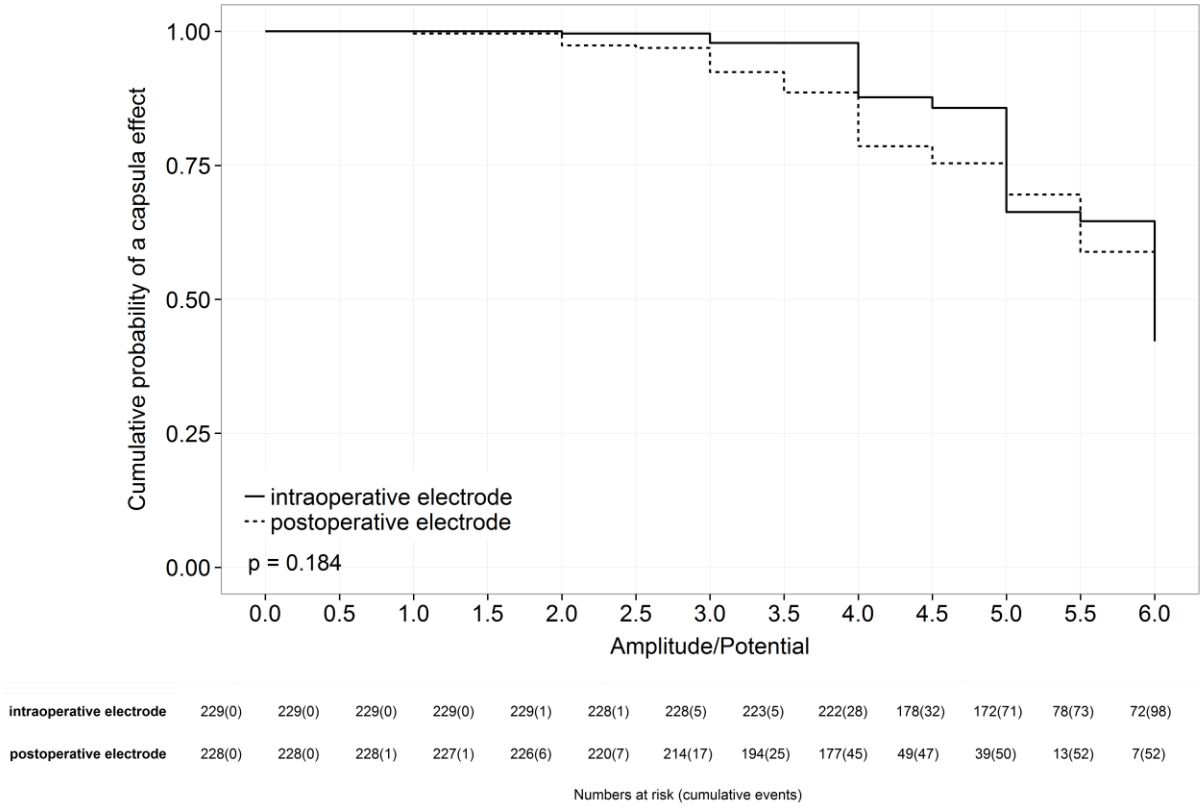


Figure 3

Cumulative probability for paraesthesia for increasing stimulation potentials

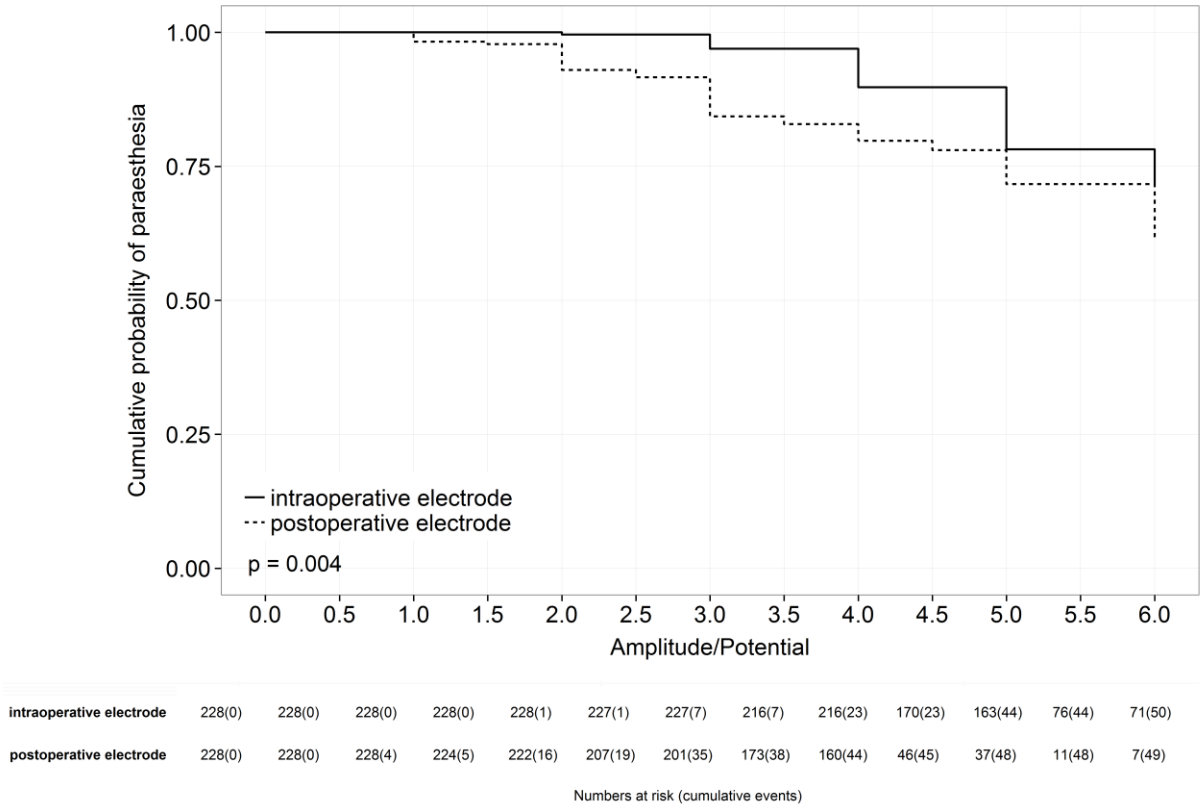


Figure 4

Cumulative probability for an oculomotor effect for increasing stimulation potentials

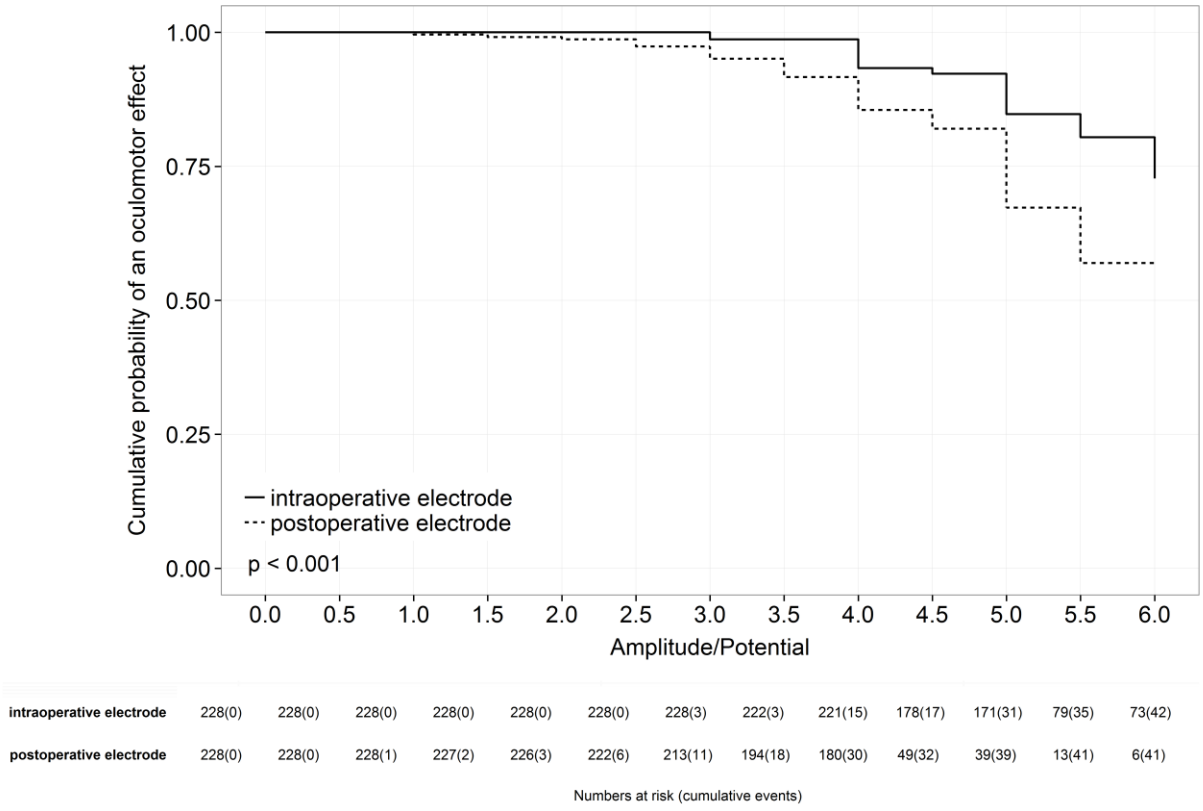


Figure 5

Cumulative probability for autonomic side effects for increasing stimulation potentials

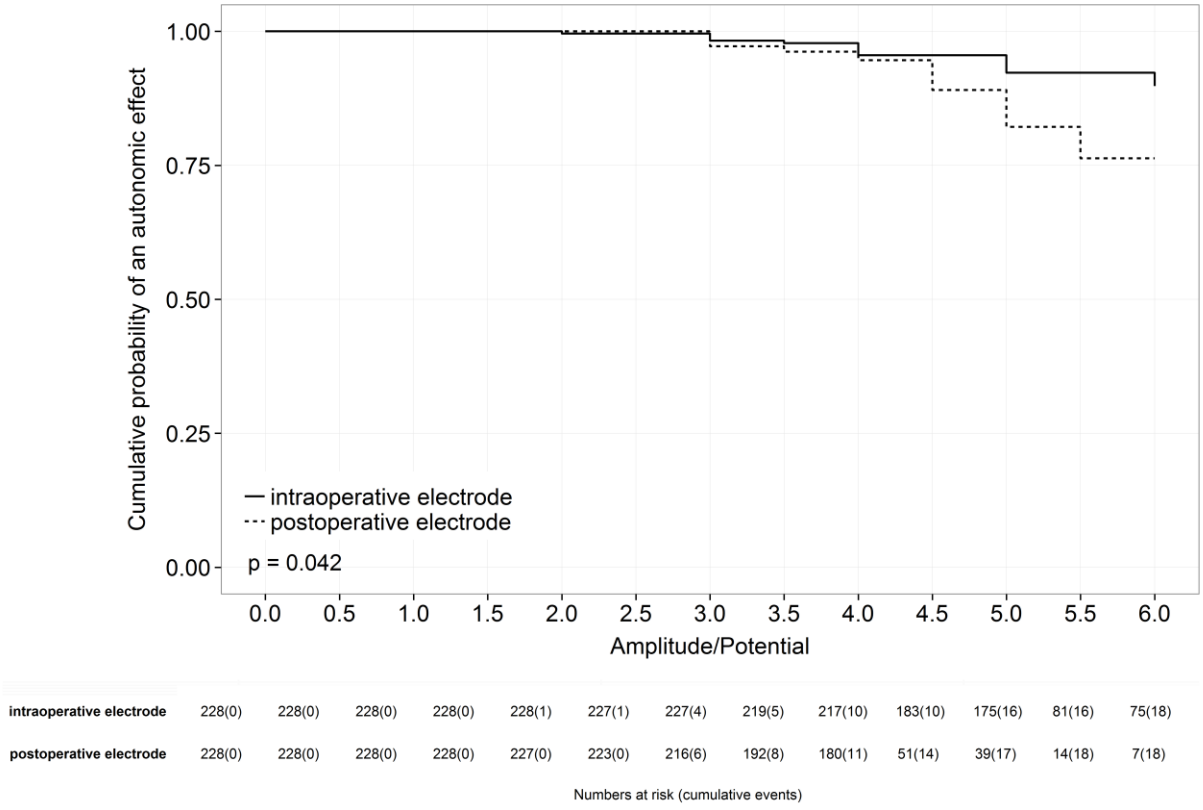


Figure 6

Cumulative probability for dysarthria for increasing stimulation potentials

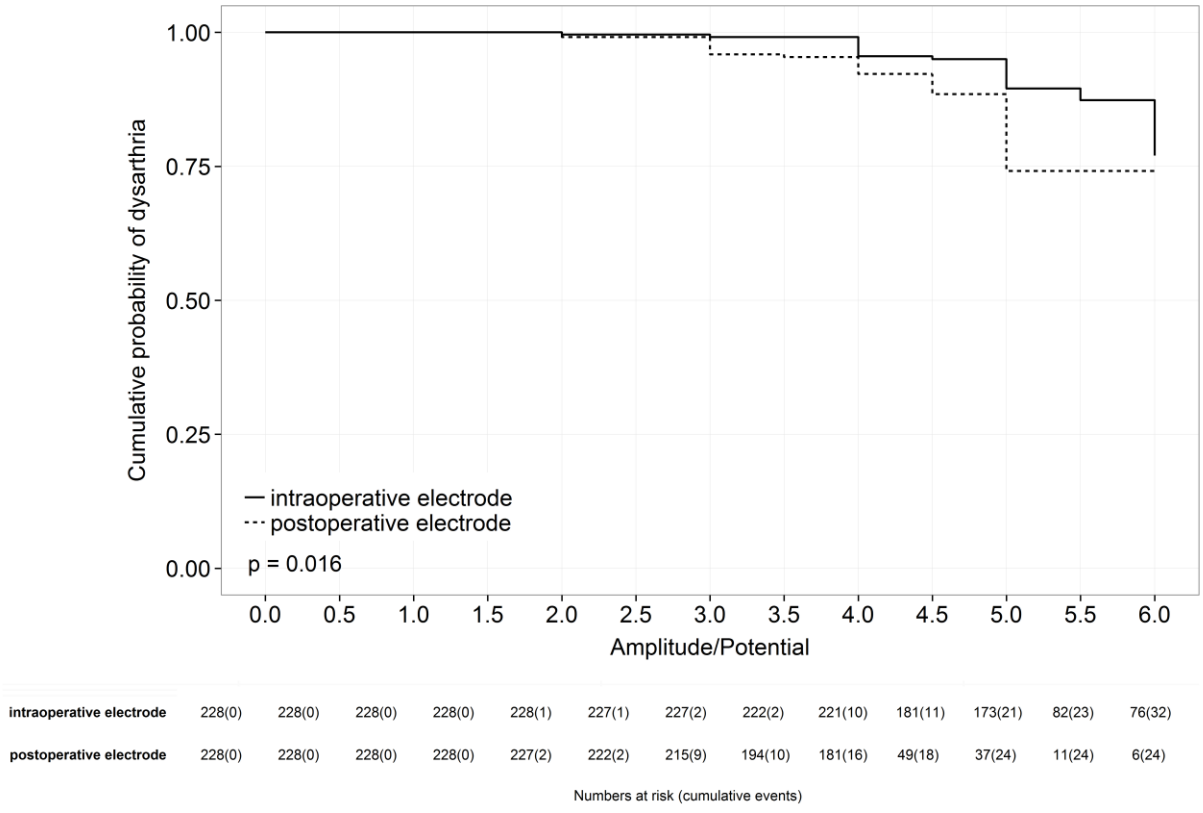


Figure 7

Cumulative probability for a therapeutic effect for increasing stimulation potentials

Kaplan Meier estimator showing the cumulative probability for a therapeutic effect (defined as an improvement of at least 50% from base line examination in rigor, tremor or akinesia) for increasing stimulation potentials. Intraoperative stimulation with the test electrode (continuous line) achieved a therapeutic effect at a significantly lower current strength than postoperative stimulation (dashed line) with the permanent DBS electrode ($p<0.001$).

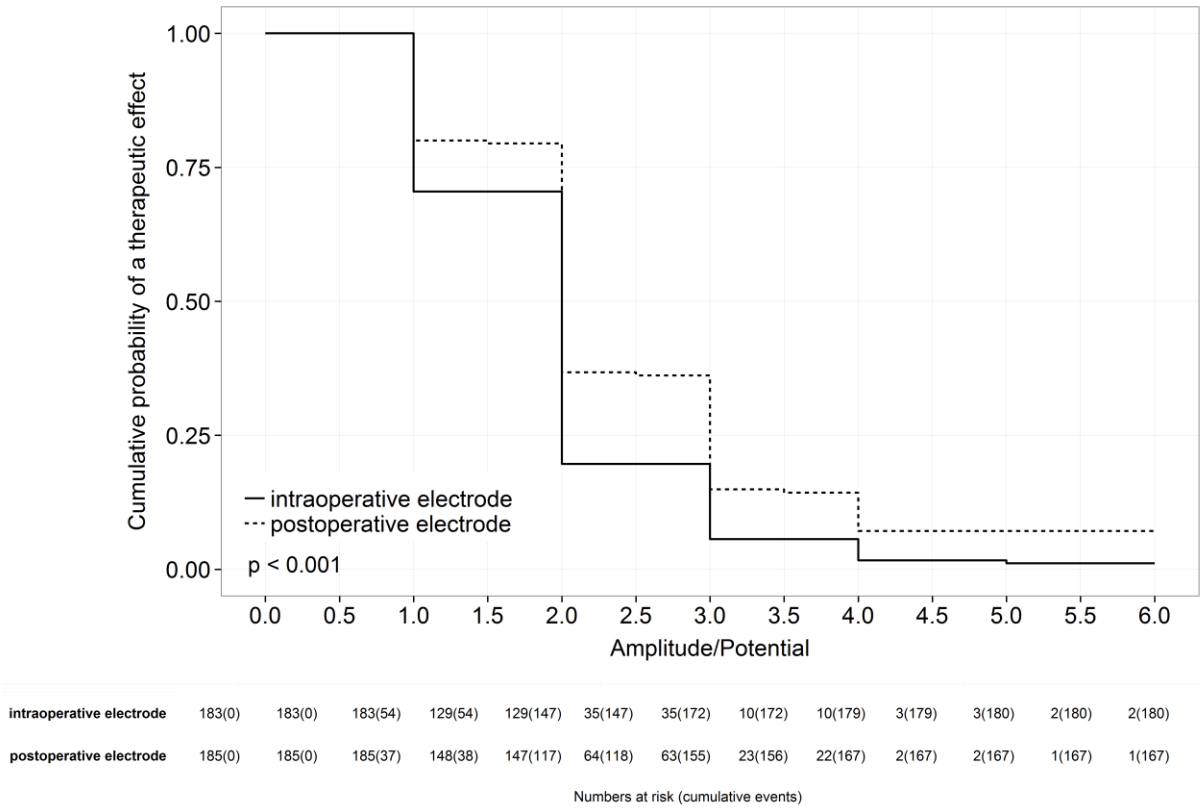
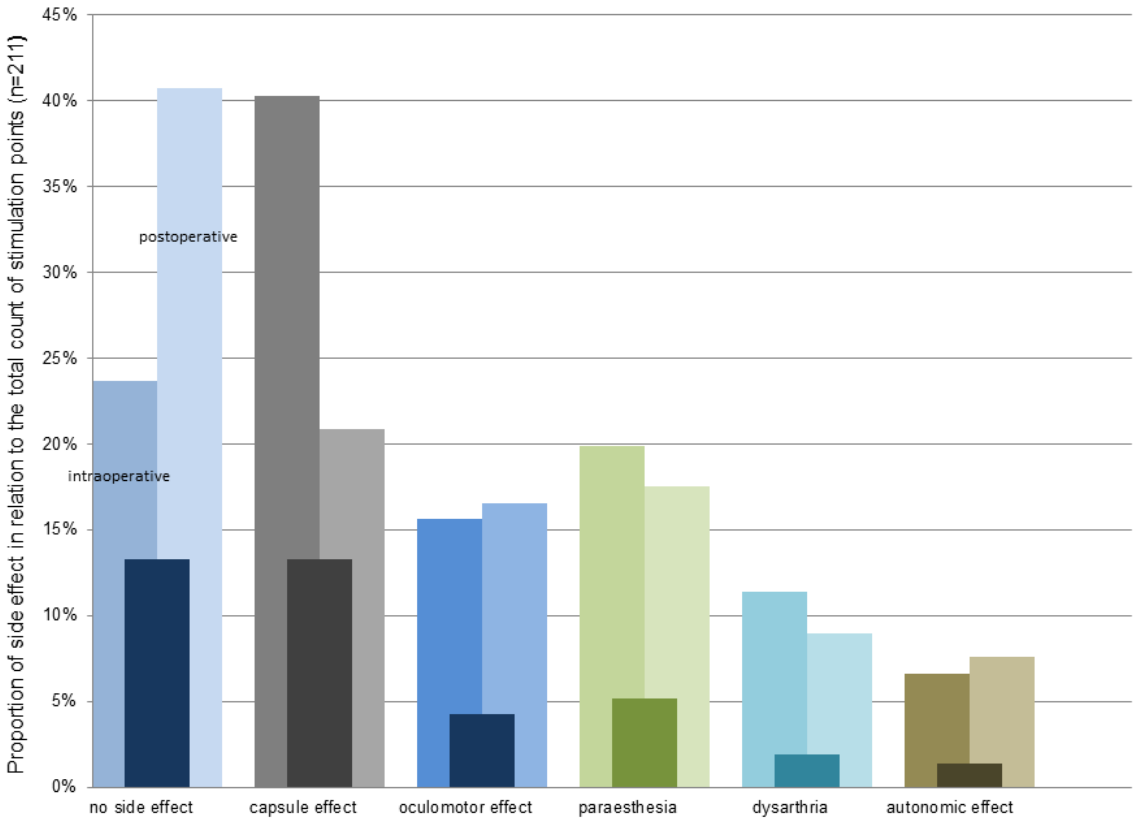


Figure 8

Proportions of different side effects in % of stimulation sites for intraoperative and postoperative stimulation.

Proportions of different side effects in % of stimulation sites for intraoperative stimulation (left column) and postoperative stimulation (right column). Intense colored columns in the middle represent coincidental rates for intra- and postoperative stimulation in relation to the total count of this particular side effect. Overall only 33.5% of the side effects caused by permanent electrode coincided in the same category with the intraoperative test stimulation.



Lebenslauf

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Sprachen

Deutsch	Muttersprache
Englisch	fließend
Französisch	gute Kenntnisse
Latein	großes Latinum

Akademische Ausbildung

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Beruflicher Werdegang

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01-06/2015	Ultraschall der hirnversorgenden Arterien
07-12/2015	Notaufnahme
01-09/2016	Intensivstation
06/2014- 09/2016	Ambulanz für Bewegungsstörungen und Tiefe Hirnstimulation
06/2014 – 09/2016	Ambulanz für Botulinumtoxin
10/2014 – 09/2016	Lehrtätigkeit: Neurologie für Logopäden, Staatliche Logopädieschule Regensburg

Wissenschaftlicher Werdegang

Dissertation Universität Regensburg, Fakultät für Medizin:

"Can intraoperative clinical examination really predict the effects of Deep Brain Stimulation in the Subthalamic Nucleus?"

01/2015 – 08/2016	Datensammlung
02/2015	GCP Training (ICH-GCP/AMG)

Publikationen

Reviews und Case Reports

Benefit of ELISpot in Early Diagnosis of Tuberculous Meningoencephalitis: Case Report and Review

Josefine Blume, Josef Köstler, Robert Weissert in eNeurologicalSci 2015

Suspected Postnatal Depression revealed as Hereditary Diffuse Leukoencephalopathy with Spheroids

Josefine Blume, Robert Weissert (eingereicht in Movement Disorders Clinical Practice, 08/2016)

Wissenschaftliche Artikel

Can intraoperative clinical testing predict the effects of the permanent DBS electrode in the subthalamic nucleus?
J Blume, J Schlaier, E Rothenfußer, J Anthofer, F Zeman, A Brawanski, U Bogdahn, M Lange
(eingereicht in Stereotactic and Functional Neurosurgery, 07/2016)

Poster

1st Congress of the European Academy of Neurology (Berlin, 2015)
Safety and Feasibility of G-CSF compassionate use in ALS patients
A Khomenko, D Baldaranov, HP Müller, S Johannesen, I Kobor, J Blume, TH Bruun, J Grassinger, T Grimm, T Kammermaier, V Haringer,A Ludoph, G Schuierer, R Laage, A Schneider, J Kassubek, W Schulte-Mattler, U Bogdahn

1st Congress of the European Academy of Neurology (Berlin, 2015)
Biomarker Discoveryin G-CSF mediated clinical ALS stabilization
S Johannesen, A Khomenko, D Baldaranov, A Khomenko , I Kobor, J Blume, TH Bruun, J Grassinger, T Grimm, T Kammermaier, V Haringer, A Ludoph, G Schuierer, R Laage, A Schneider, W Schulte-Mattler, U Bogdahn

20th International Congress of Parkinson's Disease and Movement Disorders (Berlin, 2016)
Can intraoperative clinical examination really predict the effects of STN DBS?
J Blume, J Schlaier, E Rothenfußer, J Anthofer, F Zeman, A Brawanski, U Bogdahn, M Lange

Vorträge

IAPRD 2015 – XXI World Congress on Parkinson's and Related Disorders (Milan, 2015) and
67. Jahrestagung der Deutschen Gesellschaft für Neurochirurgie (DGNC) (Frankfurt, 2016)
Can intraoperative clinical examination really predict the effects of STN DBS?
J Blume, J Schlaier, E Rothenfußer, J Anthofer, F Zeman, A Brawanski, U Bogdahn, M Lange

Eidesstattliche Erklärung

Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet. Insbesondere habe ich nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder andere Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeit erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Regensburg, 20.02.2017 Josefine Blume