# Postoperative rehabilitation after deep brain stimulation surgery for movement disorders

**Niels Allert, Binith Cheeran, Günther Deuschl, Michael T. Barbe, Ilona Csoti, Markus Ebke, Martin Glaser, Jun-Suk Kang, Stefan Kelm, Paul Krack, Julia Kroth, Ulrich Jobst, Markus Leisse, Antonio Oliviero, Peter Nikolaus Nolte, Johanna Quick-Weller, Martin Strothjohann, Gertrúd Tamás, Michael Werner, Muthuraman Muthuraman, Jens Volkmann, Alfonso Fasano, Sergiu Groppa**

**Angaben zur Veröffentlichung / Publication details:**

Allert, Niels, Binith Cheeran, Günther Deuschl, Michael T. Barbe, Ilona Csoti, Markus Ebke, Martin Glaser, et al. 2018. "Postoperative rehabilitation after deep brain stimulation surgery for movement disorders." *Clinical Neurophysiology* 129 (3): 592–601. https://doi.org/10.1016/j.clinph.2017.12.035.

# Postoperative rehabilitation after deep brain stimulation surgery for movement disorders

Niels Allert [a], Binith Cheeran [b], Günther Deuschl [c], Michael T. Barbe [d], Ilona Csoti [e], Markus Ebke [f], Martin Glaser [g], Jun-Suk Kang [h], Stefan Kelm [i], Paul Krack [j], Julia Kroth [k], Ulrich Jobst [l], Markus Leisse [m], Antonio Oliviero [n], Peter Nikolaus Nolte [o], Johanna Quick-Weller [p], Martin Strothjohann [q], Gertrúd Tamás [r], Michael Werner [s], Muthuraman Muthuraman [t], Jens Volkmann [u], Alfonso Fasano [v,1], Sergiu Groppa [k,*,1]

[a] *Neurological Rehabilitation Center Godeshöhe, Bonn, Germany*
[b] *St George's, University of London, London, UK*
[c] *Department of Neurology, University-Hospital-Schleswig-Holstein, Campus Kiel, Kiel, Germany*
[d] *Department of Neurology, University Hospital Köln, Köln, Germany*
[e] *Gertrudis-Clinic Parkinson-Center, Leun, Germany*
[f] *Department of Neurology, Dr. Becker Rhein-Sieg-Klinik, Nümbrecht, Germany*
[g] *Department of Neurosurgery, University of Mainz, Germany*
[h] *Department of Neurology, University of Frankfurt, Frankfurt, Germany*
[i] *Westerwaldklinik Waldbreitbach, Waldbreitbach, Germany*
[j] *Neurology Division, Department of Clinical Neurosciences, University Hospital of Geneva, Geneva, Switzerland*
[k] *Movement Disorders and Neurostimulation, Department of Neurology, Johannes Gutenberg University, Mainz, Germany*
[l] *MediClin Bosenberg Kliniken, Am Bosenberg, Germany*
[m] *Median Reha-Zentrum Bernkastel-Kues, Bernkastel-Kues, Germany*
[n] *FENNSI Group, Hospital Nacional de Parapléjicos, Toledo, Spain*
[o] *Mediclin, MediClin Reha-Zentrum Reichshof, Germany*
[p] *Department of Neurosurgery, Goethe-University Frankfurt, Frankfurt, Germany*
[q] *Medical Park Bad Camberg, Fachklinik für Neurologie, Bad Camberg, Germany*
[r] *Department of Neurology, Semmelweis University, Budapest, Hungary*
[s] *Klinikzentrum Lindenallee GmbH, Bad Schwalbach, Germany*
[t] *Biomedical Statistics and Multimodal Signal Processing Unit, Movement Disorders and Neurostimulation, Department of Neurology, Johannes Gutenberg University, Mainz, Germany*
[u] *Department of Neurology, University Hospital of Würzburg, Würzburg, Germany*
[v] *Department of Neurology, University of Toronto, Toronto, Canada*

* Corresponding author at: Head of Movement Disorders and Neurostimulation, Department of Neurology, Focus Program Translational Neuroscience (FTN), Rhine-Main Neuroscience Network (rmn2), Johannes Gutenberg University Mainz, Langenbeckstr.1, 55131 Mainz, Germany.

*E-mail addresses:* allert@godeshoehe.de (N. Allert), bcheeran@sgul.ac.uk (B. Cheeran), g.deuschl@neurologie.uni-kiel.de (G. Deuschl), michael.barbe@uk-koeln.de (M.T. Barbe), ilona.csoti@parkinson.de (I. Csoti), markus.ebke@median-kliniken.de (M. Ebke), glaserm@uni-mainz.de (M. Glaser), jun-suk.kang@med.uni-frankfurt.de (J.-S. Kang), stefan.kelm@westerwaldklinik.de (S. Kelm), Paul.Krack@hcuge.ch (P. Krack), Julia.Kroth@unimedizin-mainz.de (J. Kroth), Ulrich.Jobst@mediclin.de (U. Jobst), markus.leisse@median-kliniken.de (M. Leisse), antonioo@sescam.jccm.es (A. Oliviero), PeterNikolaus.Nolte@mediclin.de (P.N. Nolte), Johanna.Quick@kgu.de (J. Quick-Weller), m.strothjohann@medicalpark.de (M. Strothjohann), tamas.gertrud@med.semmelweis-univ.hu (G. Tamás), dr.werner@klinikzentrum-lindenallee.de (M. Werner), mmuthura@uni-mainz.de (M. Muthuraman), volkmann_j@ukw.de (J. Volkmann), alfonso.fasano@uhn.ca (A. Fasano), segroppa@uni-mainz.de (S. Groppa).

[1] These authors contributed equally.

**Contents**



## 1. Introduction

Deep brain stimulation (DBS) is highly effective for the treatment of movement disorders such as Parkinson's disease (PD) (Timmermann et al., 2015), tremor (Oliveria et al., 2017) and dystonia (Volkmann et al., 2014), but also further neurologic and psychiatric disorders (Welter et al., 2017). During DBS, continuous electrical stimulation is applied in appropriate subcortical areas to achieve clinical improvement of disabling symptoms. The unique feature of this therapeutic approach is the ability to preferentially modulate, through the choice of stimulation site, specific cerebral networks. In recent years, impressive technological development has improved the DBS technology; clinical benefits have been repeatedly confirmed in controlled studies (Krack et al., 2017). However, only few specific recommendations for perioperative care have been developed and (Deuschl et al., 2006; Krack et al., 2002) no guidelines for rehabilitation therapy following DBS exist. Moreover, no studies on therapeutic approaches such as physical, occupational, speech/language or cognitive therapy after DBS are available. Despite recent promising studies attesting efficiency of DBS for the therapy of psychiatric disorders such as treatment-refractory depressions (Youngerman and Sheth, 2017) or Tourette's syndrome (Welter et al., 2017), the main clinical application of DBS is still for the therapy of movement disorders. This review highlights the paucity of well-designed studies comparing algorithms for the postoperative care of patients with movement disorders and DBS and develops a work-up for the postoperative care based on existing evidence from available literature and guidelines as represented by the authors' consortium consensus.

The initial period of 3 months after implantation for DBS is critical and of major consequence for the patients, their relatives and practitioners for achieving an optimal result years and decades after the DBS-implantation. Although recent studies revealed disease course modulatory effects and an improved survival of PD patients with DBS (Ngoga et al., 2014), higher rates of revisions and removals of DBS leads have also been reported (Moro, 2016; Rolston et al., 2016); some of these could have been possibly avoided with proper rehabilitation, improving the long-range outcome. Moreover, subtle neurocognitive and psychobehavioral abnormalities like increased impulsivity or modified reward behavior have been related to DBS for movement disorders (Florin et al., 2013; Lhommée et al., 2017) or perioperative medication changes that highly influence the long-term outcome. We have begun to understand the network mechanisms of DBS action (McIntyre and Anderson, 2016), improved the patient selection

(Munhoz et al., 2016) and have set algorithms for stimulation parameters (Fasano et al., 2016b; Picillo et al., 2016), but it is now time to improve the long-term results and minimize side effects. Best long-term effects of DBS can, however, only be achieved through an optimized therapy setting including postoperative care.

## 2. Role of rehabilitation in patients with DBS

Scientific research on the specific role of neurorehabilitation in the management of patients with movement disorders after DBS is still very limited. In part this is related to differences in neurorehabilitation settings and concepts in different countries, since access to rehabilitation and the intensity of therapeutic measures also depend on the different national health care systems.

More importantly, specific goals for rehabilitation had to be developed in the last years parallel to recent developments in the field of DBS (Table 1). In this consensus work we first address issues of postoperative care. The goals for rehabilitation have to be set by DBS centers and adjusted with existing facilities evolving into active partners in the management of patients. In its classical role, neurorehabilitation focuses on symptoms not responsive to DBS or medication (Table 2). Fundamental therapies for this approach are physical, occupational and speech therapies (Table 3).

## 3. The neurophysiological basis of the clinical DBS effects in movement disorders

The prevailing hypothesis is that disorders treated with DBS are fundamentally the result of dysfunctional brain circuit activity arising from pathological connectivity interactions between subcortical nuclei and cortex (McIntyre and Anderson, 2016). DBS is believed to modulate the underlying neural activity in the proximity of the implanted electrode, thus disrupting the pathological network oscillations and inducing a more physiological activity pattern that drives the therapeutic effects (McIntyre and Anderson, 2016). Briefly, the clinical effects might mainly arise in patients with PD from the modulation of the basal-ganglia and subthalamic nucleus (STN) connections to the primary-motor cortex and supplementary motor areas (Muthuraman et al., 2017), in essential tremor (ET) through the stimulation of the dentato-thalamo-cortical pathways (Groppa et al., 2014) and in dystonia stimulation of the pallido-thalamic pathways (Fox and Alterman, 2015).

## 4. Predictors for symptom improvement with DBS

The use of strict inclusion and exclusion criteria is crucial for an optimal clinical response. In PD, the selection of patients is gener-

**Table 1**
Developments in DBS technology.

| | Novel technology | Description | Potential Benefits |
|---|---|---|---|
| **Electrode hardware** | Segmented electrode | • Allows for directional current steering<br>• Producing axially asymmetric stimulation fields | • Improved therapeutic window<br>• Fewer reprogramming sessions<br>• Focused stimulation<br>• New targets |
| | Multiple contacts vertically aligned | • Allows stimulation of several targets | • Specific modulation of several anatomical targets |
| | Multiple Independent Current Control | • One current source per contact allows precise fractionation of current | • Allows complex field shaping, similar to interleaving, but without the frequency limitations and less impact on IPG lifespan |
| **Implantation techniques** | Surgical robots | • MRI-guided, robotically actuated stereotactic intervention | • May improve implantation precision and consistency<br>• Minimizes registration errors<br>• May enhance safety |
| | Non-frame based stereotaxy | • Intraoperative MR image-guided surgery | • Simplified planning<br>• Improved implantation accuracy |
| | Objectified measurement | • Intraoperative LFP and spike recordings | • Intra-operative functional target localisation<br>• Post-operative guidance for DBS programming (contact selection) |
| | **Technology in development** | **Description** | **Potential benefits** |
| **Effects prediction** | Personalised prediction of DBS efficiency | • Patient selection upon personalized profile as derived from genotyping (surgicogenomics) or apparative phenotyping (MRI) | • Objectified decisions on DBS indication<br>• Possibly improved outcome<br>• Target selection justification |
| **DBS technology** | Closed loop or adaptive DBS | • Adaptation of stimulation parameters from physiological signal (LFP) recording and analysis | • Fewer side effects<br>• potential to be more effective in controlling symptoms<br>• IPG lifespan optimisation |
| | New targeting methods | • Advanced MRI based (diffusion and tractography based, fMRI based)<br>• PET/SPECT-based<br>• Software-based (e.g. combining different modalities) | • Improved targeting through objectified connectivity maps<br>• Mapping of effects and side effects<br>• Personalized targeting |
| | Remote control | • Telemedicine applications to transmit data (physiological recordings and stimulation status (e.g. battery life) | • Remote stimulation adaptation<br>• Improved follow-ups<br>• Better hardware surveillance |
| **Programing** | Evoked action potential based amplitude adjustment | • Adaptation of stimulation parameters from evoked potential recording and analysis | • Fewer side effects<br>• potential to be more effective in controlling symptoms<br>• IPG lifespan optimisation |
| | Assisted Monopolar screening | • Structured screening | • Improved therapeutic window<br>• faster screening<br>• fewer reprogramming sessions<br>• stimulation efficacy |

**Table 2**
Side effects.

| General side effects with DBS |
|---|
| **Motor side effects** |
| • dyskinesia |
| • axial symptoms |
| • eyelid contractions |
| • ocular disturbances |
| **Non-motor side effects** |
| • behavioral changes |
| • cognitive problems |
| **Device-related side effects** |
| • infections |
| • hardware complications |
| o dysfunction |
| o migration |
| o lead fracture |
| o lead malposition |
| **Stimulation site-related side effects** |
| **STN stimulation** |
| • paresthesia |
| • tetanic muscle contraction |
| • speech disturbances (hypophonia, dysarthria) |
| • choreiform and ballistic movements |
| • increased dyskinesia |
| • gait akinesia, freezing, impairment of balance |
| • eyelid-opening apraxia |
| • dystonia |
| • blurred vision and monocular deviation |
| • sympathetic fibers activation (sweating, ipsilateral mydriasis) |
| • block of L-Dopa effect |
| **GPI stimulation** |
| • worsening of segmental and axial akinesia |
| • phosphenes |
| • dysesthesia |
| • muscle contractions |
| **VIM stimulation** |
| • dysesthesia |
| • muscle contraction |
| • impairment of articulation, gait and balance |
| • blurred vision |

ally based on the persistence of medically refractory symptoms. Preoperative levodopa responsiveness is one of the best predictors in PD patients, whereby the improvement of motor symptoms might best mirror the postoperative outcome (Charles et al., 2002; Kleiner-Fisman et al., 2006). However, strong evidence exists that the therapeutic mechanisms of levodopa and DBS are not fully congruent. Levodopa-resistant motor symptoms do not optimally respond to DBS and represent an important issue for the postoperative rehabilitative processes. Further independent predictors for motor and non-motor outcomes are needed. We have recently shown that specific atrophy patterns in the frontal cortex might act as independent, automated predictors for the motor outcome to STN-DBS (Muthuraman et al., 2017).

In patients with segmental and generalized dystonia, only very few indices for an optimal postoperative clinical outcome exist. Pallidal stimulation seems to be more effective in patients with primary dystonia with no magnetic resonance imaging (MRI) abnormalities affecting limb, neck or face muscles in comparison to patients with secondary forms or phenotypes affecting bulbar or trunk muscles (Fox and Alterman, 2015). Patients with mobile dystonia are more responsive. Some genetic forms (DYT1 or DYT11) respond better than others (i.e. DYT6) (Bruggemann et al., 2015).

Similarly for ET, clinical factors may help to identify patients who are good candidates for DBS, but no unequivocal predictors exist. The underlying diagnosis (ET in comparison to cerebellar or secondary tremor forms) is one of the strongest predictors of long-term benefit from DBS (Deeb et al., 2016).

## 5. Surgical issues/perioperative care

Concomitant disorders should be evaluated and documented for the postoperative care. Information on blood clotting abnormalities, cardio-vascular or renal disorders and immune deficiencies should be gathered preoperatively. Because a variety of disorders require anticoagulation therapy, all DBS patients should

**Table 3**
Classes and levels of evidence for rehabilitation procedures for patients with PD and PD after DBS.

| Therapy | Class | Level of evidence for PD patients | Class | Level of evidence for PD patients after DBS |
|---|---|---|---|---|
| **Physiotherapy** | **I** | **A**<br>Improvement in UPDRS, balance, movement initiation, and amplitudes, mobility, timed-up and go, independence in daily life (de Dreu et al., 2012; Foster et al., 2013; Tomlinson et al., 2013) | **I** | **B**<br>Improvements on the UPDRS score after Robotic-Assisted Rehabilitation Protocol (Nardo et al., 2014)<br>Improvement in UPDRS after physiotherapy and exercises for coordination and proprioception (Tassorelli et al., 2009) |
| **LSVT-BIG (Lee Silverman Voice Treatment) therapy** | **III** | **A**<br>Improved motor performance, UPDRS, timed-up and go (Ebersbach et al., 2010, 2015) | **III** | **C** |
| **Speech therapy** | **I** | **A**<br>Improvement in sound volume, envelope of sound (Herd et al., 2012a, b) | **IIa** | **C** |
| **Occupational therapy** | **I** | **B**<br>Improvement and preservation in autonomy and mobility in daily life, preservation of the workplace (Clarke et al., 2009; Dixon et al., 2007) | **I** | **C** |
| **Talk therapy** | **III** | **C** | **III** | **C** |
| **Behavior therapy** | **III** | **C** | **III** | **C** |
| **Cognitive training** | **IIa** | **C**<br>Cognitive training is safe and modestly effective on cognition in mild to moderate PD (Leung et al., 2015) | **III** | **C** |
| **Parkinson's Disease Nurse** | **IIb** | **B**<br>Regular contact, reliable source information in social business (Hurwitz et al., 2005) | **III** | **C** |

**Class I:** benefit >>> risk (therapy should be performed), **class IIa** benefit >> risk (reasonable to accomplish therapy), **class IIb** benefit ≥ risk (therapy may be considered), **class III** no evidence known; **level A** identifies treatments established from large randomized clinical trials as effective, **level B** as probably effective, limited populations, or from one single study, **level C** as possibly effective, limited data available.

have clear prescription documentation for the perioperative management.

Several algorithms on the implantation of the electrodes and impulse generator exist (Bronstein et al., 2011; Krack et al., 2017). Since the impulse generator is typically implanted under general anesthetic and the electrode implantation is done with the patient awake to enable intraoperative testing, it is important to know if this occurred on the same or following days. No differences in the necessity for distinct rehabilitation strategies or optimized outcomes have been shown for the specific implantation strategies. Information on intraoperative or postoperative imaging (see below) as well as the images themselves should be available for the postoperative practitioner.

## 6. Perioperative motor and non-motor side effects

Patients after DBS surgery are at risk to develop perioperative motor and non-motor side effects which differ depending on the stimulation area: globus pallidus internus (GPI), ventral intermediate (VIM) or STN (see below and Table 2).

## 7. Device-related side effects

Device-related side effects such as infections, dysfunction, or migration of the leads have been reported (Rolston et al., 2016). In the case of hardware complications like lead fracture, malposition or migration, a re-operation and lead replacement might be required. The most common hardware complication was lead malposition (Rolston et al., 2016). To assess integrity of leads and extensions, traditional X-rays of the DBS system should be conducted. Impedance measurements should be performed and documented at every visit, and provide the first clue to loss of system integrity. It is worth noting that the normal impedance range depends on the system used (i.e. in the range of 2000–3000 kΩ in directional electrodes). Changes in impedance occur during the first days and weeks of stimulation, and can have an impact on therapy with constant voltage devices (Bronstein et al., 2015).

## 8. Stimulation-related side effects

Stimulation-related side effects depend on the target area (Table 2). Various side effects can be observed in STN stimulation. Apart from transient dysesthesia and tetanic muscle contraction, speech disorders such as hypophonia and dysarthria have frequently been found (Alomar et al., 2017). Further motor side effects (choreiform and ballistic movements, increased dyskinesia or axial symptoms) can occur directly after STN-DBS. Stimulation-induced dyskinesia requires the reduction of dopaminergic medication. In a few PD patients, gait akinesia and/or freezing occur or considerably worsen during the immediate postoperative period after STN-DBS. This paradoxical deterioration of gait is often associated with misplaced electrodes (i.e. dorsal and anterior to the STN) (Fleury et al., 2016). Advanced programming algorithms or even a reimplantation should be considered. The motor worsening in the ON condition was linked to the stimulation of pallodothalamic fibers in the proximity of STN or to current spread to pallidal outflow fibers with GPI stimulation (Krack et al., 2017). Hence, stimulation of ventral contacts may result in better antidyskinetic but reduced antiakinetic effects whereas stimulation of dorsal contacts result in better antiakinetic effects.

The final stimulation setting aims at an optimal compromise between motor symptom control and minimization of side effects. An adjustment of stimulation parameters including the active contacts may be required and is supported by more advanced stimulation techniques like interleaving, current steering or directional DBS (Fig. 1).

## 9. Psychiatric side effects

Some patients develop a perioperative transient confusional state, reported in around 2–5% of patients, which is in some cases accompanied by an accessory agitation (Follett et al., 2010). Postoperative confusion is increasingly observed in elderly patients. Low-dose neuroleptic (e.g. quetiapine), sedative or anxiolytic treatment might be beneficial in these cases.

Affective disorders can be observed primarily in PD patients with STN-DBS. Apathy and depression are most likely related to a quick or radical reduction in dopaminergic medication (Fasano et al., 2016a). In contrast euphoria, hypomania and mania can be directly induced by stimulation of limbic and associative neuronal pathways, in most cases via the more ventrally located contacts of the electrode (Mallet et al., 2007). A cautious adaptation of stimulation parameters and dopaminergic medication is needed in these conditions.

## 10. Postoperative imaging

Neuroimaging studies are essential for identifying perioperative side effects (e.g. intracerebral bleedings), long-term comorbidities (i.e. gliosis along the implanted leads) or the reconstruction of the proper implantation site in case of insufficient efficacy. Either postoperative computer tomography (CT) or MRI is recommended to document the results of the DBS. CT is used in most DBS centers but this approach produces significant artefacts with the implanted electrodes and, depending on the algorithms used in individual patients, fusion errors from 1.7 mm to 3 mm are possible (O'Gorman et al., 2009).

## 11. Acute postoperative pharmacological issues and medication adaptation

The issue of medical management following DBS is an essential one, since it greatly contributes to the success of the DBS procedure in both the early phases (e.g. postoperative apathy) and in long-term follow-up (e.g. symptoms of disease progression or management of DBS-induced complications) (Fasano et al., 2016a). A layer of complexity for the development of standardized algorithms is introduced by the need to consider the clinical presentation before implantation, the perioperative workaround and postoperative outcome.

If DBS results in efficient tremor suppression, tremor medication can be reduced; however, it may still be valuable to maintain tremor suppression with reduced stimulation-induced side effects. VIM and pallidal stimulation do not usually allow for a reduction of the dopaminergic medication. After STN-DBS the levodopa equivalent daily dose usually has to be reduced, typically by 50–60%.

The critical decision is how and when to reduce oral medication after STN-DBS. Local guidelines differ considerably. A tailored approach depending on the patient's main problems, e.g. dyskinesia versus excessive OFF time should be considered. The simplification of frequency and dosage and withdraw of medication prone to causing side-effects (anticholinergic drugs for tremor suppression with potential for neuropsychiatric and cognitive adverse events) could represent an important step to improve the long-term outcome. The clinicians may consider starting the process of medication adaptation even before DBS (Fasano et al., 2016a).

In the first few weeks after DBS implantation, dyskinesias due to the microlesioning effect might require a reduction in the levodopa dosage. Further differences in the timing of medication

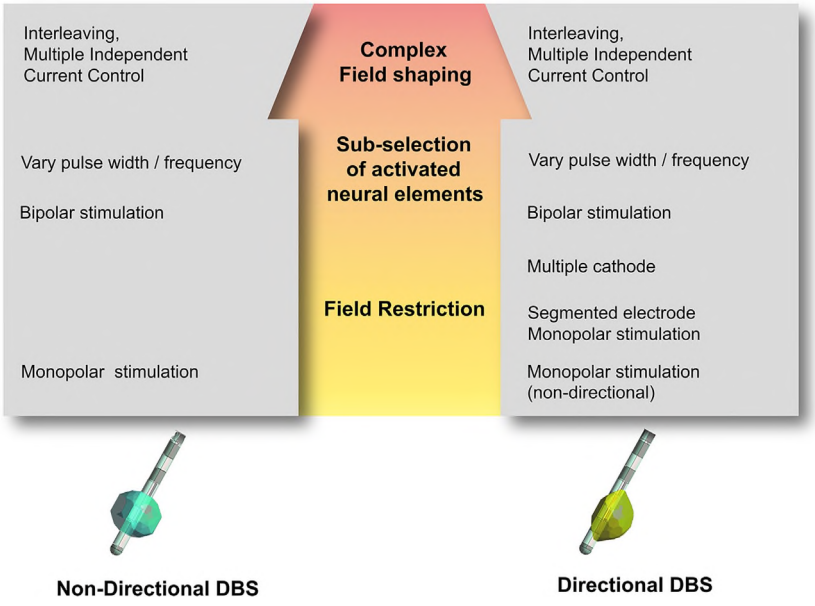


**Fig. 1.** The specification differences between the Non-Directional (left) and Directional DBS (right) with new developments for hardware adjustment of stimulation parameters. The modelled volumes of tissue activated are shown as representative figures for both types of stimulation respectively.

adjustments result from protocols regarding when stimulation is switched ON. Some centers start programming in the immediate postoperative period, usually while patients are still admitted and can be observed closely. Other centers start programming several weeks after the initial implantation awaiting the evolution of the lesioning effect that subsides and a stable clinical picture has emerged. No overall consensus exists on this proceeding.

## 12. Programming of stimulation parameters

Programming the stimulation parameters is based on clinical testing of efficacy and side effects and a trial and error approach guided by specific signs of the treated disease, the programmer's experience and existing guidelines. Several algorithms have been proposed for the most common movement disorders (Fasano et al., 2016a, 2016b). The goal of the first programming visit is establishing 'where' to deliver stimulation. Taking note of the effects on motor signs and stimulation-side effects while frequency and pulse width are kept constant (usually 130 Hz and 60 μs, respectively) and amplitude of stimulation (V or mA for constant-voltage or constant-current DBS, respectively) is slowly increased, one can establish the therapeutic potential and 'therapeutic window' for each contact. The contact with the best efficacy and/or widest therapeutic window is usually chosen for chronic stimulation (Fasano et al., 2016a, 2016b).

The second step is establishing 'how' to deliver stimulation. The goal is optimal symptom control with minimal side effects (see as well Fig. 1). During this stage, the programmer primarily adjusts the amplitude of stimulation. Variation of the pulse width adds another approach to optimize symptom control. These possibilities to improve DBS efficacy are particularly relevant for the long-term outcome.

Advanced programming methods are often required not only in the rehabilitation setting but also in later follow-up visits, both to mitigate common DBS-associated impairments and with refractory symptoms stimulation paradigms beyond the limits of the therapeutic window can be applied. Lowering of amplitude is the easiest way (usually the first step) to lessen stimulation-induced side effects but it frequently leads to a worsening of other motor symptoms. Whenever possible, decreasing the pulse width is a viable way to widen the therapeutic window of stimulation, particularly when the goal is limiting the effect on large fibers surrounding the stimulated target (Reich et al., 2015).

Low-frequency stimulation (LFS; ≤80 Hz) is one approach for improving speech (hypophonia) and other axial signs, including freezing of gait (FOG), imbalance, falls and eyelid-opening apraxia in PD (Sidiropoulos and Moro, 2014). However, improvements may be short-lived, while control of some symptoms may be inferior and bradykinesia can occasionally get markedly worse. Cycling stimulation and multiple programs (patient selection of high and LFS settings to suit intended activity) can be employed to prolong any benefits. In many cases, the best way to improve stimulation-induced side effects while keeping the benefit of DBS is focusing the electrical field within the boarder of the stimulation target.

In interleaving stimulation (ILS), two different stimulation programs (several electrodes with different stimulation parameters) run on the same lead in a temporally alternating sequence. ILS has been shown to be useful to improve the therapeutic window (Barbe et al., 2014; Miocinovic et al., 2014). Non-directional (axially-symmetric) current shaping enabled by multiple source constant current stimulation (MSCCS) may achieve a similar effect to interleaving, and be more economical on the implantable pulse generator (IPG) lifespan. This technology is currently used more frequently than ILS to improve the therapeutic window in sub-optimally placed leads. However, the frequency and severity of stimulation-induced side effects were similar to previous trials of STN-DBS in PD patients (Timmermann et al., 2015b). Either ILS or MSCCS can be used for the stimulation of zona incerta (useful in reducing dyskinesias) or substantia nigra pars reticulate (partially effective in improving FOG and balance) (Weiss et al., 2013). In both cases, the strategy can be implemented only if there are contacts available above or under the STN.

Directional current steering DBS (D-DBS) through segmented electrodes is the most recent technological innovation available (Steigerwald et al., 2016). D-DBS enables axially-asymmetric stimulation fields, allowing the programmer to 'steer' away from structures producing side effects and towards the therapeutic target. Intraoperative safety studies have shown potential to improve the therapeutic window (Dembek et al., 2017; Pollo et al., 2014).

**Table 4**
Evaluation of individual DBS outcome.

Responders
- Functional improvement of motor and non-motor symptoms
- Wide therapeutic window in the motor testing
- Equivalent or better motor response in the stimulation ON condition in comparison to preoperative L-Dopa testing
- Medication reduction and simplification

Non-Responders
- Identify reasons for suboptimal outcome
- Imaging (CT/MRI): detect suboptimal DBS lead placement

Programming issues
- Information transfer between implanting center and postoperative care givers
- Medication failure: review dosing schedule

Identification of residual symptoms
- Develop a care plan

Scales
- Motor symptoms
- MDS-UPDRS$_{III}$
- Hoehn & Yahr scale
- Dyskinesia Rating scale
- FOG-Q

Non-motor symptoms
- Epworth sleep scale
- Beck depression scale
- Fatigue Severity Scale

Therapy outcome
- Rehabilitation: Profile PD
- DBS: The deep brain stimulation impairment scale (DBS-IS)

Daily life impact
- PDQ-39

Self-assessment

How would you describe yourself after DBS?

|----------|----------|----------|
worse unchanged better

## 13. Assessment instruments in neurorehabilitative care

A quantification of the residual symptoms after DBS and at the beginning of the rehabilitation process is mandatory. Several scales for the assessment of the motor and non-motor symptoms in PD are presented in Table 2 and Table 4. At least one testing in the medication OFF state is needed. However, in neurorehabilitation assessment tools that help to evaluate the performance of an individual in activities of daily living (ADL) such as the Barthel index and the Functional Independence Measure (FIM) are more common although much less disease-specific.

## 14. Organisation of postimplantation care

Before selecting a proper setting of post-surgical rehabilitation, the individual needs and goals for rehabilitation have to be defined for each DBS patient individually. If only mild stimulation and medication refractory motor impairments exist, ambulatory therapeutic sessions may be sufficient. With longer disease durations and residual motor and non-motor symptoms more complex goals should be stated and combined therapies for specific symptoms should be joined by the possibility of stimulation and medication adjustment. Available therapies and the evidence level for these therapies are presented in the Table 3.

To achieve DBS-specific rehabilitation goals regular (ideally daily) access to physicians (and/or specialized nurses) trained in the programming of DBS and handling of DBS hardware is critical. Suboptimal stimulation parameters limit the potential long-term benefit of the treatment. Another essential feature of specific rehabilitation for each DBS patient is that the team (nurses and therapists) must be familiar with motor and non-motor symptoms of movement disorders. This enables them to give valuable feedback on functional changes and improves the process of DBS programming.

## 15. Specific goals for neurorehabilitation in patients with PD and DBS

Stabilization of DBS efficacy in PD patients usually requires a period of several weeks to months. DBS programming and titration of medication is, therefore, not completed during early rehabilitation and requires further adjustments. An increasing number of PD patients with STN-DBS are transferred to a rehabilitation facility after an initial programming in the DBS center. A retrospective study analyzed the need of further DBS adjustments and medication adjustments during such hospital rehabilitation and shows illustratively the inpatients rehabilitative care (Allert et al., 2011). Patients started rehabilitation on average 20 days after implantation and remained 29 days in the facility. The stimulation parameters were changed on average 7 times. Active stimulation contacts of the quadripolar electrodes were changed in half of the electrodes and amplitude was increased from 2.1 ± 0.8 to 3.0 ± 0.8 V. The daily levodopa-equivalent dosage was reduced from 529 ± 290 to 300 ± 277 mg. The patients improved considerably in daily living scores. This study supports the view of DBS programming as an important goal for early neurorehabilitation after DBS.

## 16. Specific goals for neurorehabilitation in patients with dystonia and DBS

Dystonia symptoms improve directly after DBS only to a minimal extent. Isolated generalized dystonia improves e.g., gradually in the first years after bilateral GPI-DBS implantation, whereas the optimal state can be achieved in cervical dystonia earlier, within months with optimal stimulation settings (Volkmann et al., 2012). The mobile component of dystonia responds stronger and faster to the therapy than the fixed components (Tagliati et al., 2011). Speech abnormality and dysphagia may improve less than other dystonic symptoms (Tagliati et al., 2011).

DBS programming for dystonia is associated with two specific challenges. First, unlike in DBS for PD, there is a lack of good individual outcome predictors. Whether DBS allows e.g. 20 or 80% symptom reduction in an individual patient cannot be predicted at the time of surgery. The second challenge concerns the latency of beneficial DBS effects which are often delayed by hours with the full efficacy building up over weeks and months. It is therefore difficult to determine whether the programming of specific stimulation parameters has already tapped the full potential of DBS in an individual patient. In this respect, hospital rehabilitation offers a unique opportunity to further adjust stimulation parameters and to evaluate clinical responses during a longer time period with close feedback from therapists and nurses.

## 17. Specific goals for neurorehabilitation in patients with tremor and DBS

Tremor symptoms are mostly very well controlled directly after the DBS. Essential hand tremor decreases by 80–90%, while head and voice tremor improves by a lesser extent during bilateral VIM stimulation (Flora et al., 2010). A diminishing effect is observed on the long term, especially on action tremor or in patients with multiple sclerosis, who might profit from dual-lead thalamic deep brain stimulation

After DBS for ET, physical therapy and occupational therapy should be considered. These therapies influence neurological comorbidities like gait ataxia and deficits of balance but also many further aspects of daily living as well. During rehabilitation the

patients can achieve an increased awareness and control of movements and environment with the modified motor control with DBS. Still, residual symptoms may necessitate a further adaptation of the prescribed medication.

## 18. Patient education

Programming of optimal DBS parameters is not the only requirement for successful therapy. Many patients also need psychological adjustment to their "new" life with an implanted electronic device. They also need to learn about the possibilities and limitations of their therapy, as well as address unfounded fears. Neurorehabilitation can support patients and caregivers via continuing education and by offering the possibility to exchange experiences. The safe handling of accessory devices by patients and/or caregivers is highly important. Training on appropriate use of a patient programmer needs to be re-enforced, to prevent incorrect operation of the device. In patients with significant motor or cognitive deficits caregivers must be trained as well.

## 19. Social aspects including capacity for work

In many PD patients, the onset of disease is well before retirement and therefore they are confronted with a reduced working capacity or loss of employment during the course of the disease (Koerts et al., 2016). With the new shift in the time for DBS surgery towards earlier stages in the course of the disease, the number of patients remaining in the workforce is increasing. For these patients, the preservation of the ability to work is an important rehabilitation goal. Vocationally-targeted therapy should also be considered. A complete assessment of motor, cognitive and perception abilities should be performed for patients who want to return to jobs after longer interruptions.

The burdens on family, caregivers and spouses are different, but often influence patients. In long-term relationships if one partner becomes weaker, the other is forced to cope with new and/or different roles. This is often a matter of contention, causing depression and the necessity of rebuilding everyday life. After DBS, partners must again readjust their relationship, as capacities lost in the course of disease can be resuscitated.

## 20. Driving capacity

Driving is an essential ability for many individuals and has a major impact on participation in daily activities. The evaluation of driving ability is challenging, however objective tests are necessary since reaction time, split awareness and ability to maintain concentration during driving time are in doubt in PD patients. Thorough testing and retesting of these aspects due to the progressive course of the disease and fluctuations is needed. Recent data suggest that driving permission for DBS-treated patients with PD should not be handled more restrictively than permissions for patients with PD in general (Buhmann et al., 2013). DBS centers and rehabilitation facilities should evaluate each patient's clinical state and be aware of existing regulations as local laws that will ultimately determine whether and when patients with PD after DBS are potentially eligible to drive. A formal driving evaluation can be helpful.

## 21. Long-term follow-up and DBS troubleshooting

Patients with PD who undergo bilateral STN-DBS may show sustained improvements in motor function and reductions in drug requirements for a period of 2–5 years after the procedure. During the rehabilitation and education process patients can be allowed to make small increments within the predetermined therapeutic window in between appointments, using the patient controller. Routine screening of electrode impedance and estimation of IPG replacement for primary cell IPGs is recommended during follow-up visits, as is an assessment of skin over the IPG and connectors.

Another key objective during the long-term follow-up visit is to screen for impairments associated with DBS and to monitor functional aspects of the DBS hardware. Incorporating a specific screening tool, such as the DBS-IS questionnaire, can help detect postural instability and gait difficulties, cognitive impairment, speech impairment, apathy, impulsivity and difficulties related to the DBS device (Maier et al., 2017).

As therapy demand increases with disease progression, re-implantation and revision may be considered for leads where the narrow therapeutic window is due to sub-optimal placement. Newer technologies such as ILS and D-DBS may reduce the need for this over time. Revision to a new target nucleus or implantation of a second target (e.g. VIM after STN for tremor or pedunculopontine nucleus (PPN) after STN for FOG) can be considered following detailed evaluation, and after advanced programming techniques or other therapy options (intrajejunal levodopa or subcutaneous apomorphine infusions) have been evaluated (Wijemanne et al., 2014).

## 22. New developments

Advancements in the field of DBS are highly relevant to the post-implantation care as patients might take advantage of new developments in the field of DBS technology or post-implantation care and neurorehabilitation. Adaptive DBS systems using i.e. closed-loop technology and tuning the stimulation paradigms with the online analysis of brain activity or signals from the periphery (body sensors) could be easily implanted with the next IPG change. Similarly, systems that are more effective for energy harvesting, recharging or have advantages for the interaction with other medical devices (such as MRI compatibility at 3- or 7 T) are in development and will be available in the next few years. The expansion of telemedicine applications can be adapted to interact with patients for clinical evaluation or even adjustment of DBS parameters. Advanced evaluation algorithms are needed in patients who do not adequately respond to DBS and neurorehabilitation; however, approaches for dealing with residual symptoms or new comorbidities during the advanced disease course are emerging. Implantation of further electrodes (quadripolar leads) for resistant tremor (Oliveria et al., 2017) or a synergistic application of MRI-guided focal ultrasound (Tomlinson et al., 2013) for lesioning further regions of the altered network are now tested and may enter clinical practice.

Emerging phenotyping techniques, i.e. genetic tests or non-clinical diagnostics, can improve our understanding of the outcome and side-effects of DBS in neuro-psychiatric patients and could provide important insights into interactions of stimulation and individual disease course (i.e. β-glucocerebrosidase mutation status for cognitive decline in PD patients) (de Drew et al., 2012) even years after implantation. Although not yet exhaustively studied there are first hints from both animal (Foster et al., 2013) and human studies (Ngoga et al., 2014) that DBS may have the capacity to modify the course of neurodegenerative disorders such as PD. Introducing a new network-centered approach by the use of adaptive DBS could achieve a modification of network functions, shifting towards a more physiological and effective activity, alterations that could be beneficial not only in movement disorders, but in neurological and psychiatric conditions in general.

## 23. Conclusion and future directions

Rehabilitation of patients with movement disorders after DBS necessitates a coordinated effort from a team, including caregivers, the patient, his or her family and friends and social environment, who should be well informed about the new situation and therapy plans and goals on the long term. The improvements in motor and non-motor symptoms and residual deficits should be stated together with the DBS center. Clear roles of the DBS centers and postoperative caregivers should be achieved through effective information transfer and communication. The evidence based on specific rehabilitation interventions is still very scarce but should be considerably improved in the next years.

## 24. Search strategy and selection criteria

Much of the literature in this area consists of descriptive studies, such as prevalence reports, case series, or observational studies, some of which are case-control studies. Relevant studies of all types were reviewed and considered if they add new knowledge. Potential papers were identified by searching PubMed for papers published between 1966 and March 2017, using the terms "rehabilitation", "Parkinson's" and "deep brain stimulation". In addition to seeking systematic reviews and randomised trials, we also sought to access the most up-to-date recommendations from clinical practice guidelines because such guidelines show a more consensual analysis of the evidence. We specifically sought guidelines that have been published in the past 2 years from the Canada, USA and Europe. We used the evidenced-based review of rehabilitation websites to cross-reference our findings with current evidence to ensure that no major topics were overlooked.

## 25. Declaration of interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article and no relevant positions in a company or competitor, having stocks, equity, or a contract of employment in a field relevant to this review work. N. Allert received honoraria for lecturing and consulting services from Medtronic. B. Cheeran has consultancy contracts with DBS device manufacturer St Jude Medical/Abbott. M. T. Barbe received speaker honoraria from Medtronic, St. Jude and GE-Medical and research funds from Medtronic. A. Oliviero declares that he is a cofounder of the company Neurek SL, which is a spinoff of the Foundation of the Hospital Nacional de Parapleji-cos. G. Deuschl has received lecture fees from Orion, Lundbeck, Medtronic, Desitin, Teva, and Pfizer and has served as a consultant for Teva, Novartis, Sapiens, and Medtronic. He has received royalties from Thieme publishers. J. Volkmann serves as a consultant to Abbott Pharmaceuticals and Medtronic Inc. and has received lecture fees from Medtronic Inc., St. Jude Medical/Abbott, and Boston Scientific. A. Fasano received speaker and/or consultant honoraria from AbbVie, Boston Scientific, Medtronic, Sunovion, Ipsen Canada, UCB pharma, Chiesi pharmaceutical, TEVA and Novartis. He also receives research grants from Weston Foundation, University of Toronto, Michael J. Fox Foundation, AbbVie, Boston Scientific, and Medtronic. S. Groppa received speaker and/or consultant honoraria from AbbVie, Medtronic, Zambon and research grants from the DFG (CRC 1193) and BMBF (KKNMS, 01GI1603B). The other authors declare no competing financial interests.


## Acknowledgements

The authors thank Dr. Cheryl Ernest for proofreading the manuscript.


## References


Allert N, Dohle C, Horn JW, Kelm S, Kirsch H, Nolte PN, et al. Rehabilitation of Parkinson's patients with deep brain stimulation. Experiences of the Neurological Rehabilitation Center Godeshohe. Nervenarzt 2011;82:462–7.

Alomar S, King NK, Tam J, Bari AA, Hamani C, Lozano AM. Speech and language adverse effects after thalamotomy and deep brain stimulation in patients with movement disorders: a meta-analysis. Mov Disord 2017;32:53–63.

Barbe MT, Dembek TA, Becker J, Raethjen J, Hartinger M, Meister IG, et al. Individualized current-shaping reduces DBS-induced dysarthria in patients with essential tremor. Neurology 2014;82:614–9.

Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol 2011;68(2):165.

Bronstein JM, Tagliati M, McIntyre C, Chen R, Cheung T, Hargreaves EL, et al. The rationale driving the evolution of deep brain stimulation to constant-current devices. Neuromodulation 2015;18:85–8.

Bruggemann N, Kuhn A, Schneider SA, Kamm C, Wolters A, Krause P, et al. Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia. Neurology 2015;84:895–903.

Buhmann C, Maintz L, Hierling J, Vettorazzi E, Moll CKE, Engel AK, et al. Effect of subthalamic nucleus deep brain stimulation on driving in Parkinson disease. Neurology 2013;82:32–40.

Charles P, Van Blercom N, Krack P, Lee S, Xie J, Besson G, et al. Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002;59:932–4.

Clarke CE, Furmston A, Morgan E, Patel S, Sackley C, Walker M, et al. Pilot randomised controlled trial of occupational therapy to optimise independence in Parkinson's disease: the PD OT trial. J Neurol Neurosurg Psychiatry 2009;80:976–8.

de Dreu MJ, van der Wilk AS, Poppe E, Kwakkel G, van Wegen EE. Rehabilitation, exercise therapy and music in patients with Parkinson's disease: a meta-analysis of the effects of music-based movement therapy on walking ability, balance and quality of life. Parkinsonism Relat Disord 2012;18(Suppl. 1):S114–9.

Deeb W, Giordano JJ, Rossi PJ, Mogilner AY, Gunduz A, Judy JW, et al. Proceedings of the fourth annual deep brain stimulation think tank: a review of emerging issues and technologies. Front Integr Neurosci 2016;10(38):1–21.

Dembek TA, Reker P, Visser-Vandewalle V, Wirths J, Treuer H, Klehr M, et al. Directional DBS increases side-effect thresholds-A prospective, double-blind trial. Mov Disord 2017;32:1380–8.

Deuschl G, Herzog J, Kleiner-Fisman G, Kubu C, Lozano AM, Lyons KE, et al. Deep brain stimulation: postoperative issues. Mov Disord 2006;21(Suppl 14): S219–37.

Dixon L, Duncan D, Johnson P, Kirkby L, O'Connell H, Taylor H, et al. Occupational therapy for patients with Parkinson's disease. Cochrane Database Syst Rev 2007;3:CD002813.

Ebersbach G, Ebersbach A, Edler D, Kaufhold O, Kusch M, Kupsch A, et al. Comparing exercise in Parkinson's disease–the Berlin LSVT(R)BIG study. Mov Disord 2010;25:1902–8.

Ebersbach G, Grust U, Ebersbach A, Wegner B, Gandor F, Kuhn AA. Amplitude-oriented exercise in Parkinson's disease: a randomized study comparing LSVT-BIG and a short training protocol. J Neural Transm (Vienna) 2015;122:253–6.

Fasano A, Appel-Cresswell S, Jog M, Zurowkski M, Duff-Canning S, Cohn M, et al. Medical management of Parkinson's disease after initiation of deep brain stimulation. Can J Neurol Sci 2016a;43:626–34.

Fasano A, Appel-Cresswell S, Jog M, Zurowkski M, Duff-Canning S, Cohn M, et al. Medical management of Parkinson's disease after initiation of deep brain stimulation. Can J Neurol Sci 2016b;43:626–34.

Fleury V, Pollak P, Gere J, Tommasi G, Romito L, Combescure C, et al. Subthalamic stimulation may inhibit the beneficial effects of levodopa on akinesia and gait. Mov Disord 2016;31:1389–97.

Flora ED, Perera CL, Cameron AL, Maddern GJ. Deep brain stimulation for essential tremor: a systematic review. Mov Disord 2010;25:1550–9.

Florin E, Müller D, Pfeifer J, Barbe MT, Fink GR, Timmermann L. Subthalamic stimulation modulates self-estimation of patients with Parkinson's disease and induces risk-seeking behaviour. Brain 2013;136:3271–81.

Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. New Engl J Med 2010;362:2077–91.

Foster ER, Golden L, Duncan RP, Earhart GM. Community-based Argentine tango dance program is associated with increased activity participation among individuals with Parkinson's disease. Arch Phys Med Rehabil 2013;94:240–9.

Fox MD, Alterman RL. Brain stimulation for torsion dystonia. JAMA Neurol 2015;72:713–9.

Groppa S, Herzog J, Falk D, Riedel C, Deuschl G, Volkmann J. Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. Brain. 2014;137:109–21.

Herd CP, Tomlinson CL, Deane KH, Brady MC, Smith CH, Sackley CM, et al. Comparison of speech and language therapy techniques for speech problems in Parkinson's disease. Cochrane Database Syst Rev 2012a;8:CD002814.

Herd CP, Tomlinson CL, Deane KH, Brady MC, Smith CH, Sackley CM, et al. Speech and language therapy versus placebo or no intervention for speech problems in Parkinson's disease. Cochrane Database Syst Rev 2012b;8:CD002812.

Hurwitz B, Jarman B, Cook A, Bajekal M. Scientific evaluation of community-based Parkinson's disease nurse specialists on patient outcomes and health care costs. J Eval Clin Pract 2005;11:97–110.

Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord 2006;21(Suppl 14):S290–304.
Koerts J, König M, Tucha L, Tucha O. Working capacity of patients with Parkinson's disease – a systematic review. Parkinsonism Relat Disord 2016;27:9–24.
Krack P, Fraix V, Mendes A, Benabid AL, Pollak P. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 2002;17 (Suppl 3):S188–97.
Krack P, Martinez-Fernandez R, Del Alamo M, Obeso JA. Current applications and limitations of surgical treatments for movement disorders. Mov Disord 2017;32:36–52.
Leung IH, Walton CC, Hallock H, Lewis SJ, Valenzuela M, Lampit A. Cognitive training in Parkinson disease: a systematic review and meta-analysis. Neurology 2015;85:1843–51.
Lhommée E, Boyer F, Wack M, Pélissier P, Klinger H, Schmitt E, et al. Personality, dopamine, and Parkinson's disease: Insights from subthalamic stimulation. Mov Disord 2017;32(8):1191–200.
Maier F, Lewis CJ, Eggers C, Kühn AA, Krug H, Volkmann J, et al. Development and validation of the deep brain stimulation Impairment Scale (DBS-IS). Parkinsonism Relat Disord 2017;41:133–4.
Mallet L, Schupbach M, N'Diaye K, Remy P, Bardinet E, Czernecki V, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci USA 2007;104:10661–6.
McIntyre CC, Anderson RW. Deep brain stimulation mechanisms: the control of network activity via neurochemistry modulation. J Neurochem 2016;139(Suppl 1):338–45.
Miocinovic S, Khemani P, Whiddon R, Zeilman P, Martinez-Ramirez D, Okun MS, et al. Outcomes, management, and potential mechanisms of interleaving deep brain stimulation settings. Parkinsonism Relat Disord 2014;20:1434–7.
Moro E. Neurosurgery: complications of DBS surgery [mdash] insights from large databases. Nature Rev Neurol 2016;12:617–8.
Munhoz RP, Picillo M, Fox SH, Bruno V, Panisset M, Honey CR, Fasano A. Eligibility criteria for deep brain stimulation in parkinson's disease, tremor, and dystonia. Can J Neurol Sci 2016;43(4):462–71.
Muthuraman M, Deuschl G, Koirala N, Riedel C, Volkmann J, Groppa S. Effects of DBS in parkinsonian patients depend on the sturtural integrity of frontal cortex. Sci Rep 2017;7:43571.
Nardo A, Anasetti F, Servello D, Porta M. Quantitative gait analysis in patients with Parkinson treated with deep brain stimulation: the effects of a robotic gait training. NeuroRehabilitation 2014;35:779–88.
Ngoga D, Mitchell R, Kausar J, Hodson J, Harries A, Pall H. Deep brain stimulation improves survival in severe Parkinson's disease. J Neurol Neurosurg Psychiatry 2014;85:17–22.
O'Gorman RL, Jarosz JM, Samuel M, Clough C, Selway RP, Ashkan K. CT/MR image fusion in the postoperative assessment of electrodes implanted for deep brain stimulation. Stereotact Funct Neurosurg 2009;87:205–10.
Oliveria SF, Rodriguez RL, Bowers D, Kantor D, Hilliard JD, Monari EH, et al. Safety and efficacy of dual-lead thalamic deep brain stimulation for patients with treatment-refractory multiple sclerosis tremor: a single-centre, randomised, single-blind, pilot trial. Lancet Neurol 2017;16(9):691–700.
Picillo M, Lozano AM, Kou N, Puppi Munhoz R, Fasano A. Programming deep brain stimulation for Parkinson's disease: the Toronto western hospital algorithms. Brain Stimul 2016;9:425–37.
Pollo C, Kaelin-Lang A, Oertel MF, Stieglitz L, Taub E, Fuhr P, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. Brain 2014;137:2015–26.
Reich MM, Steigerwald F, Sawalhe AD, Reese R, Gunalan K, Johannes S, et al. Short pulse width widens the therapeutic window of subthalamic neurostimulation. Ann Clin Transl Neurol 2015;2:427–32.
Rolston JD, Englot DJ, Starr PA, Larson PS. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: analysis of multiple databases. Parkinsonism Relat Disord 2016;33:72–7.
Sidiropoulos C, Moro E. Low-frequency subthalamic nucleus stimulation in Parkinson's disease. Mov Disord 2014;29:1569. https://doi.org/10.1002/mds.25963.
Steigerwald F, Muller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: a pilot study using a novel neurostimulation device. Mov Disord 2016;31:1240–3.
Tagliati M, Krack P, Volkmann J, Aziz T, Krauss JK, Kupsch A, et al. Long-Term management of DBS in dystonia: response to stimulation, adverse events, battery changes, and special considerations. Mov Disord 2011;26(Suppl 1): S54–62. https://doi.org/10.1002/mds.23535.
Tassorelli C, Buscone S, Sandrini G, Pacchetti C, Furnari A, Zangaglia R, et al. The role of rehabilitation in deep brain stimulation of the subthalamic nucleus for Parkinson's disease: a pilot study. Parkinsonism Relat Disord 2009;15:675–81.
Timmermann L, Jain R, Chen L, Maarouf M, Barbe MT, Allert N, et al. Multiple-source current steering in subthalamic nucleus deep brain stimulation for Parkinson's disease (the VANTAGE study): a non-randomised, prospective, multicentre, open-label study. Lancet Neurol 2015;14:693–701.
Tomlinson CL, Patel S, Meek C, Herd CP, Clarke CE, Stowe R, et al. Physiotherapy versus placebo or no intervention in Parkinson's disease. Cochrane Database Syst Rev 2013;9:CD002817.
Volkmann J, Mueller J, Deuschl G, Kuhn AA, Krauss JK, Poewe W, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. Lancet Neurol 2014;13:875–84.
Volkmann J, Wolters A, Kupsch A, Muller J, Kuhn AA, Schneider GH, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol 2012;11:1029–38.
Weiss D, Walach M, Meisner C, Fritz M, Scholten M, Breit S, et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. Brain 2013;136:2098–108.
Welter ML, Houeto JL, Thobois S, Bataille B, Guenot M, Worbe Y, et al. Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. Lancet Neurol 2017;16(8):610–9.
Wijemanne S, Waln O, Shahed JJ. Concurrent bilateral vim and STN DBS in a patient with ET/PD (P7.055). Neurology April 8, 2014, 82:10 Supplement P7.055; published ahead of print April 8; 2015. p. 1526-632X.
Youngerman BE, Sheth SA. Deep brain stimulation for treatment-resistant depression: optimizing interventions while preserving valid trial design. Ann Transl Med 2017;5:S1. https://doi.org/10.21037/atm.2017.03.40.