The treatment of Parkinson’s disease with deep brain stimulation: current issues

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Abstract
Deep brain stimulation has become a well-established symptomatic treatment for Parkinson’s disease during the last 25 years. Besides improving motor symptoms and long-term motor complications, positive effects on patients’ mobility, activities of daily living, emotional well-being and health-related quality of life have been recognized. Apart from that, numerous clinical trials analyzed effects on non-motor symptoms and side effects of deep brain stimulation. Several technical issues and stimulation paradigms have been and are still being developed to optimize the therapeutic effects, minimize the side effects and facilitate handling. This review summarizes current therapeutic issues, i.e., patient and target selection, surgical procedure and programming paradigms. In addition it focuses on neuropsychological effects and side effects of deep brain stimulation.

Key Words: Parkinson’s disease; deep brain stimulation; subthalamic nucleus

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Introduction
First performed in late 1980s, deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the internal globus pallidus (GPI) or ventral intermedius nucleus (VIM) of the thalamus has developed and become a distinguished symptomatic treatment for Parkinson’s disease (PD). Especially DBS of the STN and GPI is an effective option to improve motor symptoms and manage long-term motor complications resulting from levodopa treatment, such as wearing-off phenomena and dyskinesias. Furthermore patients’ mobility, activities of daily living, emotional well-being and health-related quality of life which are impaired by motor symptoms and complications (Damiano et al., 2000; Chapuis et al., 2005; Chaudhuri et al., 2013), can be enhanced by DBS (Volkmann et al., 2001; Deuschl et al., 2006). To further optimize its efficacy technical issues and stimulation paradigms are still being developed. One aim of this review is to summarize current technical issues and stimulation paradigms. The other aim is to give an overview of the clinical effects and side effects of DBS with a focus on neuropsychological aspects.

Clinical Outcome
Numerous clinical trials – few of them already providing long-term data between 8 and 10 years of follow-up (Fasano et al., 2010; Castrioto et al., 2011) – could demonstrate an improvement of levodopa-responsive motor symptoms and motor complications, a reduction of the levodopa equivalent dose and an increase in quality of life after DBS (Table 1). These trials provide a high level of evidence namely: Level I–II due to the prospective randomized nature of the trials (Oxford Centre for Evidence-based Medicine – Levels of Evidence; March 2009). However, placebo controlled trials assessing prospectively quality of life are not available for DBS in PD.

Patient Selection
An essential aspect influencing the outcome after DBS in PD is patient selection and timing of surgery. Main indications for DBS in PD patients are levodopa-induced motor fluctuations, dyskinesias and unmanageable tremor. Preoperative indicators for a good outcome are younger age and shorter disease duration, high levodopa-response, few axial motor symptoms, absence of dementia, stable psychiatric conditions and no or non-severe comorbidities (Bronstein et al., 2011). With the exception of non-levodopa-responsive tremor, the preoperative levodopa-response is one of the most important outcome predictors (Charles et al., 2002). Several studies have shown a positive correlation between preoperative levodopa-response and motor improvement (Kleiner-Fisman et al., 2003; Kim et al., 2013).

Regarding cognitive impairment and psychiatric disorders, there are no stringent criteria available (Lang et al., 2006). Dementia is one of the most common exclusion criteria (Bronstein et al., 2011). The management of mild cognitive impairment is still handled more heterogeneously. Besides age and levodopa-equivalence dosage the axial subscore, i.e., speech, neck rigidity, posture, rising from chair, gait and postural instability, in the Unified PD Rating Scale (UPDRS) is reported to be a predicting factor for executive dysfunction after DBS (Daniels et al., 2010). Prognostic factors for the development of depressive symptoms after surgery are preoperative persistently
increased scores for depression and anxiety measured by the State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI) and Clinical Global Impression - Improvement scale (CGI-I) (Schneider et al., 2010). Therefore depression and other unstable psychiatric conditions require a careful preoperative assessment, a stabilizing treatment and a close-meshed postoperative follow-up (Bronstein et al., 2011). Concerning time point selection, age, Hoehn and Yahr stage and disease duration are important criteria. There is no clear age cut off, but patients over 70 years have a higher incidence of relevant comorbidities and cognitive impairment resulting in an increased risk for peri- and postoperative complications (Russmann et al., 2004; Lang et al., 2006; Ory-Magne et al., 2007). In the past DBS used to be performed after 11 to 13 years of disease duration in patients with advanced motor-complications (Follett et al., 2010; Williams et al., 2010; Okun et al., 2012). Recent data show high efficacy of DBS concerning an improvement of motor symptoms and quality of life in patients with shorter disease duration and early motor complications (Schüpbach et al., 2013). In this study patients with a mean age of 52 years, a mean PD duration of 7.5 years and motor fluctuations of any severity persisting for 1.7 years were treated with STN-DBS and medication or received best medical treatment. The quality of life - measured by the PD Questionnaire (PDQ-39) - improved by 26% in the stimulation group, whereas it worsened in the medication group. Psychosocial aspects were also analyzed and improved significantly in the stimulation group. The UPDRS motor score improved by 53% in the stimulation group in comparison to 4% in the medication group. These results favor the application of STN-DBS in an earlier stage of PD.

Target Point
Although mechanisms of action of DBS are not completely known up to date, modulation of pathological local (beta) oscillations (Kühn et al., 2008) and modulation of the basal ganglia-cortical network including the hyperdirect pathway seems to play an important role (Gradinaru et al., 2009). The optimal target point for DBS in PD is still a matter of debate. STN-DBS was first performed in 1993 in an advanced PD patient leading to a reduction of motor fluctuations, dyskinesias and dopaminergic medication (Benabid et al., 1994). Since then, several studies have reported an improvement of levodopa responsive symptoms (Limousin et al., 1998; Klein-Fisman et al., 2006), motor fluctuations and dyskinesia after STN-DBS (Follett et al., 2010; Okun et al., 2012). STN-DBS is usually performed bilaterally, but unilateral STN-DBS can be effective in highly asymmetric tremor-dominant PD patients (Kumar et al., 1999). Currently, STN-DBS is the most frequently used surgical therapy in PD. However, concerning the improvement of major PD symptoms no significant difference in efficacy has been shown between the STN and the GPI (Weaver et al., 2012), concerning the reduction of dopaminergic medication doses the STN is favorable (Follett et al., 2010; Moro et al., 2010). Furthermore, STN-stimulation requires lower electrical power and results in longer battery life-spans (Volkmann et al., 2001). One advantage of GPI-stimulation is a direct and significant reduction of dyskinesias. Another advantage – in comparison to STN – seems to be a better outcome regarding depression scores (Follett et al., 2010).

In contrast to STN- and GPI-DBS, stimulation of the VIM has no effects on dyskinesia, motor fluctuations, rigidity and bradykinesia but a clear and immediate effect on tremor (Benabid et al., 1996; Ondo et al., 1998). Certainly, VIM-DBS is a therapeutic option for patients with essential tremor and elderly patients with a unilateral tremor-dominant PD.

Another target point is the pedunculopontine nucleus (PPN). DBS of the PPN has been analyzed in small experimental trials. There is evidence revealing that stimulation of the PPN might have positive effects on parkinsonian gait disorder, postural instability and freezing (Pereira et al., 2008). Other reported effects concern a modification of vigilance and quality of sleep (Alessandro et al., 2010). Stimulation of the substantia nigra pars reticulata, partially in combination with the STN, remains experimental. An assumed effect on axial motor symptoms could not yet be proved, but an improvement of freezing of gait has been observed (Weiss et al., 2013).

Effects on Cognition, Behavior and Mood
Changes of neurocognitive function, behavior and mood after DBS in PD have been described in several studies with partially conflicting results. Recent data suggest that the most frequent cognitive side effect, verbal fluency deficits, may be caused by surgical implantation (Okun et al., 2012). In this study, 156 patients underwent DBS device implantation, whereof 101 patients received immediate STN-stimulation and 35 received stimulation after 3 months. Verbal fluency, measured by Delis-Kaplan Executive Function System, degraded similarly in both groups without further aggravation after 3 months. Witt et al. (2013) observed a decline in Mattis Dementia Rating Scale in 7 out of 31 patients with STN-DBS. In comparison to patients without cognitive impairment lead trajectories in these 7 patients harmed a significantly larger volume of the caudate nucleus. However, there is also evidence that stimulation itself has an effect on verbal fluency: Low-frequency (10 Hz) STN-DBS has been shown to improve verbal fluency in comparison to higher stimulation frequencies (130 Hz) and no stimulation (Wojtecki et al., 2006).

Also other factors of stimulation intensity, the localization of the electrode and respective volume of tissue activated impact verbal fluency (Mikos et al., 2011). Regarding speech performance the cognitive (executive-function) aspect has to be clearly distinguished from the voice/articulation/loudness aspect that can be ameliorated or deteriorated by DBS depending on factors such as preoperative speech impairment (Tripoliti et al., 2008; Astrom et al., 2010; Skodda et al., 2012, 2014).

Regarding depression, there are some clinical trials reporting an improvement after STN-DBS (Witt et al., 2008; Okun et al., 2012). One explanation for these results might be an increase in quality of life and reduction of motor symptoms and complications. Others revealed a beneficial effect of GPI-DBS on depression and a worsening effect of STN-DBS (Odekerken et al., 2013). The deteriorating effect of STN-DBS might be caused by a reduction of dopaminergic medication. Apart from that, disease progression has to be taken into account as well (Houeto et al., 2002; Follett et al., 2010). Furthermore, there are reports of a detrimental effect of STN-DBS on fatigue. Okun et al. (2012) described that STN-stimulation rather than the surgical procedure appears to be responsible for this side-effect. In comparison to PD patients with STN-stimulation, their control group received implantation without stimulation for three months.
Table 1 Prospective randomized controlled clinical trials of deep brain stimulation (DBS) in Parkinson’s disease (PD)\(^{\text{a}}\)

| Reference               | Randomization | Pat.(n) | Age(year) | PD-Duration (day) | Follow-up [month] | UPDRS-III change (points) | PDQ-39 (points) | Change in LED (mg) |
|-------------------------|---------------|---------|-----------|-------------------|-------------------|---------------------------|----------------|-------------------|
| Deuschl et al., 2006    | STN           | 78      | 60±7.4   | 13.0\(\pm5.8\)   | 6                 | 19.6 (±15.1)             | 9.5±15.3        | -593±548          |
|                         | BMT           | 78      | 60.8±7.8 | 13.8\(\pm5.6\)   |                   | 0.4 (±9.5)               | -0.2±11.2       | -95±390           |
| Weaver et al., 2009\(^{\text{d}}\) | STN/GPi (blinded) | 60/61  | 62.4±8.8 | 10.8\(\pm5.4\)   | 6                 | 12.3                     | 0.4 (±9.5)      | -296              |
|                         | BMT           | 134     | 62.3±9.0 | 12.6\(\pm5.6\)   |                   | 1.7                      | 0              | 15                |
| Follett et al., 2010    | STN           | 147     | 61.9±8.7 | 11.1±5.0         | 24                | 10.7                      | 0              | -408              |
|                         | Gpi           | 152     | 61.8±8.7 | 11.5±5.4         |                   | 11.8                      | ±14.1          | -243              |
| Williams et al., 2010\(^{\text{d}}\) | STN          | 183     | 59       | 11.5              | 12                | 17.1 (±13.2)             | 0.4 (±13.3)    | -453              |
|                         | Gpi           |         |          |                   |                   | 0.3±11.1                 | 0              | n.a.              |
|                         | BMT           | 183     | 59       | 11.2              |                   | 17.1 (±7.5)              | 4.8 (±1.0)     | -391±547          |
| Okun et al., 2012       | STN           | 101     | 60.6±8.3 | 12.1±4.9         | 3 (12)\(^{\text{d}}\) | 21±1 e                   | 18.8\(\pm5.4\) | n.a.              |
|                         | STN (inactive)\(^{\text{d}}\) | 35      | 59.5±8.2 | 11.7±4.1         |                   | 20.3 (±16.3)             | 0              | -54±561           |
| Odekerken et al., 2013  | STN           | 53      | 60.9±7.6 | 12.0±5.3         | 12                | 20.3 (±16.3)             | 0              | -208±521          |
|                         | Gpi           | 55      | 59±17.8  | 10.8±4.2         |                   | 11.4 (±16.1)             | 0              | -363±19           |
| Schüpbach et al., 2013  | STN           | 124     | 52.9±6.6 | 7.3±3.1          | 24                | 17.5 (±1.0)              | 8.1±1.2        | -535±19           |
|                         | BMT           | 127     | 52.2±6.1 | 7.7±2.7          |                   | 1.2 (±1.0)               | 0.0±1.2        | 245±8.8           |

\(^{\text{a}}\) Pat.: Patients; Age: age at surgery; Change in LED: Change in levodopa equivalent dose from baseline; BMT: best medical treatment, i.e. medication only; n.a.: not available; Data are means for age, PD-Duration, UPDRS-III, PDQ-39 and LED. SDs are given in parentheses, if available.

**Surgical Aspects**

Target point localization is attained by preoperative imaging and intraoperative neurophysiology. Most frequently, stereotactic magnetic resonance imaging (MRI) is used for target identification and target coordinates are calculated relative to the stereotactic frame placed on the patient’s head (Dormont et al., 2010). Further options apart from direct targeting are fusion of MRI and computed tomography (Liu et al., 2001) and stereotactic ventriculography, which is still but rarely used by some teams (Benabid et al., 2009).

Intraoperative neurophysiology consists of intraoperative microelectrode recording (MER) and test stimulation and is used to improve targeting accuracy. For MER multiple trajectories can be recorded simultaneously or successively (Benabid et al., 2009). MER of the STN is characterized by typical activity patterns, proprioceptive responses to passive movements and asymmetrical spikes at high frequency in a bursting manner (Benabid et al., 2009). Some studies suggest a significantly better clinical outcome after microelectrode recording (Mann et al., 2009; Reck et al., 2012), but longer surgery duration has to be taken into account. Intraoperative test stimulation can be performed under both local anesthesia and general anesthesia. However, local anesthesia allows a communication with the patient during the operation and thereby a more precise assessment of side effects and the effect on a variety of symptoms, i.e. rigidity, tremor, coordination and speech. In contrast, general anesthesia is a helpful option to reduce patient’s stress and pain (Lefaucheur et al., 2008; Benabid et al., 2009). After identifying the best track the final lead is implanted and subcutaneously connected to the implantable pulse generator (IPG). Typical sites for the IPG are infracavicular area and lower abdomen. At present, there are rechargeable and non-rechargeable IPGs available. Depending on stimulation parameters – higher stimulation amplitude and pulse width result in shorter battery life spans (Ono et al., 2007) – non-rechargeable IPGs need to be replaced after approximately 5 years by surgery and are favored for elderly patients and patients with few technical skills.

**Programming**

The main aim of programming is reducing motor-symptoms and complications and simultaneously avoiding or minimizing side effects of stimulation.

Stimulation devices of the first generation delivered electrical stimulation in a voltage-controlled mode whereas following devices predominantly use the constant-current mode or can be switched into this mode. In comparison to constant-current devices, where the stimulation field is kept stable in size, the stimulation field produced by constant-voltage devices is vulnerable to changing tissue impedances (Lempka et al., 2010; Okun et al., 2012). The most frequent programming parameters are monopolar stimulation, impulse duration 60–90 µs and frequency 130 Hz (Volkmann et al., 2006). Considering individual symptoms, the amplitude is increased carefully with a simultaneous reduction of dopaminergic medication during several programming sessions. However, the increase of amplitude is limited by stimulation-related side effects such as gait disorder and disequilibrium, dysarthria, oculomotor dysfunction, paraesthesia and increased muscle tone. To decrease these
side effects, the stimulation field can be minimized by bipolar stimulation, but the necessity of higher stimulation intensities has to be taken into account (Volkmann et al., 2006). Alternatively, the design and the configuration of the stimulation field is achieved by current steering with multiple stimulus sources. Current steering is possible with a new device and allows for an individual shaping of the stimulation field by shifting the current towards another contact (Barbe et al., 2014). Interleaving stimulation is another method to shape the stimulation field by using alternating stimulation of different programs on two electrode contacts. Amongst others, this can be advantageous in patients with motor symptoms that require different contacts or amplitudes for the best therapeutic effect (Wojecki et al., 2011). Apart from altering the stimulation field, a current pilot study (CUSTOM-DBS) could show that a lower pulse width of 30 µs results in a wider therapeutic spectrum with higher side effect thresholds (Volkmann et al., 2014).

A further stimulation technique under development is directional DBS. In comparison to current devices with omnidirectional stimulation (using one or more contacts of a quadripolar or octopolar electrode) smaller directional electrodes are used to adapt the stimulated area. Presently available data are based on intraoperative measurements and need to be verified by chronic implantation (Pollo et al., 2014).

**Perspective**

During the last 25 years, DBS has developed and become an established therapy for PD. Nevertheless, there are ever-growing findings concerning the effectiveness of DBS and the pathomechanisms of side effects resulting in development of new devices and stimulation paradigms. The main aim is a further reduction of side effects and better adaption to individual courses of PD. *Inter alia*, further development of closed loop stimulation, *i.e.*, adaptive and individual stimulation depending on recorded beta activity of the STN might be an important step for the future (Rosin et al., 2011; Little et al., 2012).

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