Deep Brain Stimulation: a review of the literature for established, new and experimental clinical applications and targets

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Introduction

Deep brain stimulation (DBS) is an established surgical treatment for Parkinson's disease (PD), essential tremor and dystonia. It is generally acknowledged that the development of DBS as we know it today started with the publication of Benabid, Pollak et al in 1987 on thalamic DBS for tremor.
However stereotactic surgery for PD was very common in the pre-levodopa era, and the vast majority of surgical procedures consisted of lesions, mainly pallidotomy, thalamotomy and subthalamotomy. Surgery for PD almost stopped following the introduction of l-dopa therapy in the late 60s. Unilateral thalamotomy continued to be performed rarely and in few centers for patients with intractable tremor.
It is generally acknowledged that the publication that marked the "official" birth of DBS was that of Benabid, Pollak and co-workers of 1987 on "Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease". There is no doubt that it is the fruitful cooperation of neurosurgeon Alim-Louis Benabid and neurologist Pierre Pollak, and especially their introduction of DBS in the subthalamic nucleus in 1993 that founded DBS as we know it today.
During the 60s, Sem-Jacobsen and others implanted externalized electrodes which were used for intermittent stimulation and evaluation during weeks or months, prior to subsequent ablation of thalamic and other basal ganglia targets. In the early 70s Bechtereva treated PD patients using "therapeutic electrical stimulation" through electrodes implanted for up to 1.5 years. In the late 70s and early 80s the term Deep Brain Stimulation became commonly used and few groups attempted treatment of Parkinson's disease, non-Parkinsonian tremor and dystonia with high-frequency stimulation using chronically implanted DBS systems. It is to the credit of the Grenoble Group to have reinvented, modernized and expanded modern DBS in surgical treatment of movement disorders.
Deep brain stimulation (DBS) is today an established treatment for advanced Parkinson's disease (PD), essential tremor and dystonia. New indications for, and applications of, DBS in various brain targets for various neurological and psychiatric illnesses are being reviewed here.

Thalamus DBS for Essential Tremor and Parkinsonian Tremor

In 1987 initial paper, A.L. Benabid, P. Pollak et al. noted that stereotactic thalamotomy of the thalamic nucleus ventralis intermedius (VIM) is routinely used for movement disorders. During this procedure, it has been observed that high-frequency (100 Hz) stimulation of VIM was able to stop the extrapyramidal tremor. In patients with bilateral tremor of extrapyramidal origin, who were resistant to drug therapy, the therapeutic protocol associated (1) a radiofrequency VIM thalamotomy for the most disabled side, and (2) a continuous VIM stimulation for the other side using stereotactically implanted electrodes, connected to subcutaneous stimulators. VIM thalamotomy relieved the tremor in all operated cases. Side effects were mild and regressive. VIM stimulation strongly decreased the tremor but failed to suppress it as completely as thalamotomy did. This was due in part to the fact that programmable stimulator frequency rate is limited to 130 Hz, while it appeared that the optimal stimulation frequency was 200 Hz. This therapeutic protocol appears to be of interest for patients with bilateral extrapyramidal movement disorders.

In another early publication, A.L. Benabid, P. Pollak et al. reported that stereotactic ventral intermediate nucleus (Vim) thalamotomy may improve drug resistant severe parkinsonian tremor. However, tremor may recur and bilateral thalamotomy is known to induce unacceptable side effects in a proportion of patients. A high frequency (130 Hz) chronic Vim stimulation was performed in 4 parkinsonian patients, 2 of them having previously undergone a thalamotomy on the other side. Tremor was suppressed in all patients at the price of slight paresthesias. This improvement has been lasting from 2 to 14 months. Beneficial and adverse effects were suppressed at once each time the stimulation was stopped.
In 2009, O'Sullivan and Pell published the results of their long-term experience following stimulation of the ventral intermediate nucleus (VIM) of the thalamus for tremor. Twenty-eight of these patients suffered tremor related to PD. While they did not report a measure of outcome benefit, they did report an initial adequate response with good tremor suppression in all patients. Of these, seven died due to other medical conditions or disease progression, two went on to receive STN stimulation, and seven were lost to follow up. Of the remaining 10, each continued to demonstrate suppression of tremor 10 years postoperatively.
The Multicentre European Study of Thalamic Stimulation in Parkinsonian and Essential Tremor (1999) performed VIM stimulation on 73 patients with parkinsonian tremor. In 85% of these patients tremor scores improved by >50% in both the upper and lower limbs ($p < 0.001$) at both 3 and 12 months postoperatively. Stimulation also produced a significant reduction in rigidity and akinesia. As a corollary, UDPRS II scores were improved after surgery, particularly those items specifically influenced by tremor. Axial symptoms, speech, postural stability and gait were not affected. Adverse events were reportedly very low in this study, with 4% of patients suffering an extra-axial hemorrhage without sequelae and one patient having a small intra-axial hemorrhage. Impairment of speech and stability were reported as mild adverse effects, and improved with reduction of stimulation voltage.
In 2007, Hariz et al. published the 6 year follow-up findings of the Multicentre European Study in 38 of 73 patients. Tremor remained significantly less severe at 6 years than at baseline when stimulation was on, and also to a lesser degree when stimulation was off. Total motor scores, however, were similar to those at baseline. There was also a minor improvement in appendicular akinesia and rigidity items on-stimulation compared to off-stimulation and baseline. UPDRS-II score improvements had not persisted at 6 years, reflecting progression of other symptoms with disease progression. Axial symptoms had deteriorated markedly.
In light of these findings, Hariz et al. still recommended STN stimulation in patients with tremor dominant PD, which is not only associated with tremor suppression, but also a more prominent and long-term effect on fluctuating disability. However, a role for thalamic stimulation may still be warranted in a very specific subgroup with unilaterally dominant tremor as the primary symptom.

Parkinson's disease Pallidum and STN

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects several regions of the central and peripheral nervous system. The symptoms of Parkinson's disease encompass the classic parkinsonian triad (tremor, bradykinesia, and rigidity) associated with dopaminergic denervation, other motor signs associated with non-dopaminergic transmission (postural instability and impairment of gait, speech, and posture), and non-motor symptoms (NMS).
Lauri Laitinen et al. had started to revive Leksell's old posteroventral pallidotomy, showing its effect on most symptoms of advanced PD including on–off fluctuations and levodopa induced dyskinesias. Lesions in the globus pallidus internus (GPi) consistently improved dyskinesias and parkinsonian motor symptoms. However, there was a risk of inducing permanent neurological deficits with pallidotomy (especially when bilateral). Lesions of the subthalamic region also improved parkinsonian symptoms, but caused hemiballism in some patients.

Evidence supporting the efficacy of STN and GPi stimulation is the broadest of any of the targets. Particularly in the last 5 years, this evidence has unequivocally demonstrated the efficacy of stimulation to these two areas in alleviating motor symptoms

STN DBS induces many of the antiparkinsonian effects of dopamine replacement therapy (DRT) and preoperative response to levodopa contributes to predict outcome following surgery. In a meta-analysis reviewing 38 studies from 34 neurosurgical centres in 13 countries, STN DBS was found to improve rigidity and bradykinesia by 63% and 52% after 12 months. With the addition of DRT, these improvements increased to 73% and 69%. The long-term outlook confirms that STN DBS persistently improves motor fluctuations, dyskinesias and all the cardinal motor manifestations of PD, with less consistent effects on bradykinesia in the on-medication condition. STN DBS does not have an acute antidyskinetic effect and dyskinesia reduction is due to the fact that levodopa-equivalent dose (LEDD) is readily reduced after surgery (on average by 55.9%).

GPi DBS improves rigidity and bradykinesia one year after implant, with a reduction of beneficial effects at 5 years. Some of these GPi patients successfully underwent subsequent STN DBS. However, some studies report stable benefits 4 or 5–6 years after surgery. The GPi has a large size and contains discrete segregated output pathways, which explains some loss of efficacy following DBS also depending on the subnuclear location of the stimulating electrode. Stimulations or lesions placed in the anteromedial/ventral GPi are associated with a greater improvement in rigidity, while those located in the central/dorsal GPi are more effective on bradykinesia. The dramatic LEDD reduction observed after STN DBS has never been reported for GPi DBS, however GPi DBS has a direct and acute antidyskinetic effect especially when stimulation is delivered through the ventral contacts. The long-term efficacy of GPi DBS on PIGD is less documented, but it was associated with fewer side effects.

Bilateral GPi DBS has a low cognitive morbidity, with some studies reporting a mild decline of semantic verbal fluency and no significant impact on cognitive functioning observed 6 months after surgery in advanced PD patients. Very few data are available for psychiatric symptoms. Recurrent manic and hypomanic episodes, each lasting several days, were reported in a patient treated by GPi DBS. The occurrence of hallucinations and delusions has been poorly investigated in patients treated by GPi DBS. In two PD male patients with preoperative hypersexuality, who underwent GPi DBS, hypersexuality did not improve after surgery. Few studies addressed the effects of GPi DBS on sleep quality in PD patients and reported subjective improvement of daytime sleepiness notwithstanding the fact that these patients did not reduce DRT.

Studies comparing STN and GPi DBS

One study directly compared the effect of GPi, STN or both in patients undergoing both implants and three studies compared patients randomly assigned to implant of either targets, bilaterally or unilaterally. A study found that STN DBS might improve bradykinesia more than GPi and a retrospective comparison in patients with young-onset PD reported a 70–80% improvement of bradykinesia after STN DBS, compared with a 30–40% improvement after GPi. However, a large randomised, prospective multicentre study on 255 patients (the VA-study) revealed a 30% improvement of the UPDRS-III motor score in both STN and GPi DBS groups, with no between-group differences. Another randomised comparative trial found similar results after unilateral procedures.

Some studies suggest GPi DBS is less efficacious than STN DBS on PIGD. By contrast, a recent meta-regression analysis (which actually only take into account a limited number of patients undergoing GPi DBS) revealed that PIGD initially improves following DBS of either STN or GPi, to gradually decline two years after implant to pre-surgery values in STN, but not GPi, implanted cases. Only two studies have attempted to directly and objectively compare the two implantation sites with respect to gait. One study revealed more improvements with STN DBS than GPi DBS but the weaknesses in the study designs may have biased the results (no randomization at baseline). The other one compared patients randomized at

baseline to receive GPi or STN stimulation and did not found overt differences. Concerning other axial symptoms, in the VA-study the falls rate and the performance on stand-walk-sit test in the condition without stimulation favored GPi DBS group.
GPi DBS does not allow reducing medication to the extent reached after STN DBS, as also confirmed by large comparative studies. Apomorphine or levodopa-induced dyskinesias are almost abolished by GPi DBS and remained unchanged after STN stimulation. However, at least in some patients, depending on the electrode trajectory, stimulation exceeding the STN nucleus may influence the ansa lenticularis and the lenticular fasciculus, mimicking the antidyskinetic effect of GPi stimulation.

Long Term evaluation
A multicentre long-term study on bilateral STN or GPi DBS reported the occurrence of cognitive decline in 23% of STN patients and in 12% of GPi patients 5–6 years after surgery. Accordingly, a meta-analysis of reports on side effects of STN or GPi DBS along 10 years concluded that cognitive and behavioural adverse events were more common after STN DBS. In a prospective RCT of patients treated with unilateral GPi or STN DBS, no between-group mood variations but a greater decline on a task of phonological verbal fluency was detected 7 months after surgery in the STN group. In the multicentre VA-study that randomly assigned patients to either STN or GPi DBS, the STN group showed greater decline in visuomotor processing speed and mood worsening. In another study, apathy was unchanged in the medically treated group, whereas it progressively increased during the first months after implant in patients who received unilateral GPi or STN implants, with no relation to postsurgical medication changes.

La Pitié-Salpêtrière team reported a five years follow up of stimulation of the subthalamic nucleus in Parkinson's disease (W M Schüpbach et al). The short term benefits of bilateral stimulation of the subthalamic nucleus (STN) in patients with advanced levodopa responsive Parkinson's disease (PD) are well documented, but long term benefits are still uncertain. Thirty seven consecutive patients with PD treated with bilateral STN stimulation were assessed prospectively 6, 24, and 60 months after neurosurgery. Parkinsonian motor disability was evaluated with and without levodopa treatment, with and without bilateral STN stimulation. Neuropsychological and mood assessments were also rated.
No severe peri- or immediate postoperative side effects were observed. Six patients died and one was lost to follow up. Five years after neurosurgery: (i) activity of daily living (Unified Parkinson Disease Rating Scale (UPDRS) II) was improved by stimulation of the STN by 40% ("off" drug) and 60% ("on" drug); (ii) parkinsonian motor disability (UPDRS III) was improved by 54% ("off" drug) and 73% ("on" drug); (iii) the severity of levodopa related motor complications was decreased by 67% and the levodopa daily doses were reduced by 58%. The MADRS was unchanged, but cognitive performance declined significantly. Persisting adverse effects included eyelid opening apraxia, weight gain, addiction to levodopa treatment, hypomania and disinhibition, depression, dysarthria, dyskinesias, and apathy. We concluded that despite moderate motor and cognitive decline, probably due to disease progression, the marked improvement in motor function observed postoperatively was sustained 5 years after neurosurgery.
More recently, optimal target localization for subthalamic stimulation was investigated in Paris, GH Pitié-Salpêtrière. We wished to determine the ideal target within the STN area that showed the greatest improvement and fewest side effects for patients with PD. We were also interested in which clinical and surgical factors might be relevant for the postoperative outcome with DBS-STN. A cohort of 309 patients with Parkinson disease underwent surgery within a 13-year period. Patients were evaluated before, during, and 1 year after DBS-STN. Pre- and postoperative results were obtained in 262 patients with PD. The best motor outcome was obtained when stimulating contacts were located within the STN as compared with the zona incerta (64% vs 49% improvement). Eighteen percent of the patients presented

a postoperative cognitive decline, which was found to be principally related to the surgical procedure. Other factors predictive of poor cognitive outcome were perioperative confusion and psychosis. Nineteen patients showed a stimulation-induced hypomania, which was related to both the form of the disease (younger age, shorter disease duration, higher levodopa responsiveness) and the ventral contact location. Postoperative depression was more frequent in patients already showing preoperative depressive and/or residual axial motor symptoms.
In this homogeneous cohort of patients with PD, we concluded that (1) the STN is the best target to improve motor symptoms, (2) postoperative cognitive deficit is mainly related to the surgery itself, and (3) stimulation-induced hypomania is related to a combination of both the disease characteristics and a more ventral STN location.

Pedunculopontine nucleus

While STN DBS has demonstrated efficacy in improving the cardinal features of Parkinson's disease, its effect on axial symptoms (for example, gait) has been disappointing. Due to its known role in movement control, interest in the pedunculopontine nucleus (PPN) has been growing over recent years as a potential target for improvement in gait impairment.
In the most recent series of five patients although not reflected in UPDRS-III scores, gait and falls questionnaire scores were found to have improved significantly following dedicated PPN at 2 year follow-up. Similar effects on gait and falls were found by Moro et al. in a series of six patients implanted with unilateral PPN DBS, although their results referred specifically to an improvement in gait freezing. The suggestion of improvements in movement outcomes applying specifically to gait freezing has been supported by several other small series.
Stefani A, Lozano AM et al. reported the clinical effects of deep brain stimulation (DBS) in the PPN and subthalamic nucleus (STN). Six patients with unsatisfactory pharmacological control of axial signs such as gait and postural stability underwent bilateral implantation of DBS electrodes in the STN and PPN. Clinical effects were evaluated 2-6 months after surgery in the OFF- and ON-medication state, with both STN and PPN stimulation ON or OFF, or with only one target being stimulated. Bilateral PPN-DBS at 25 Hz in OFF-medication produced an immediate 45% amelioration of the motor Unified Parkinson's Disease Rating Scale (UPDRS) subscale score, followed by a decline to give a final improvement of 32% in the score after 3-6 months. In contrast, bilateral STN-DBS at 130-185 Hz led to about 54% improvement. PPN-DBS was particularly effective on gait and postural items. In ON-medication state, the association of STN and PPN-DBS provided a significant further improvement when compared to the specific benefit mediated by the activation of either single target. Moreover, the combined DBS of both targets promoted a substantial amelioration in the performance of daily living activities. These findings indicate that, in patients with advanced Parkinson's disease, PPN-DBS associated with standard STN-DBS may be useful in improving gait and in optimizing the dopamine-mediated ON-state, particularly in those whose response to STN only DBS has deteriorated over time. This combination of targets may also prove useful in extra-pyramidal disorders, such as progressive supranuclear palsy, for which treatments are currently elusive.

Substantia nigra pars reticulata

Weiss D, Walach M, Meisner C et al. evaluated nigral stimulation for resistant axial motor impairment in Parkinson's disease. Gait and balance disturbances typically emerge in advanced Parkinson's disease with generally limited response to dopaminergic medication and subthalamic nucleus deep brain stimulation. Therefore, advanced programming with interleaved pulses was put forward to introduce concomitant nigral stimulation on caudal contacts of a subthalamic lead. The authors hypothesized that the combined stimulation of subthalamic nucleus and substantia nigra pars reticulata improves axial symptoms

compared with standard subthalamic nucleus stimulation. Twelve patients were enrolled in this 2 × 2 cross-over double-blind randomized controlled clinical trial and both the safety and efficacy of combined subthalamic nucleus and substantia nigra pars reticulata stimulation were evaluated compared with standard subthalamic nucleus stimulation. The primary outcome measure was the change of a broad-scaled cumulative axial Unified Parkinson's Disease Rating Scale score (Scale II items 13-15, Scale III items 27-31) at '3-week follow-up'. Secondary outcome measures specifically addressed freezing of gait, balance, quality of life, non-motor symptoms and neuropsychiatric symptoms. For the primary outcome measure no statistically significant improvement was observed for combined subthalamic nucleus and substantia nigra pars reticulata stimulation at the '3-week follow-up'. The secondary endpoints, however, revealed that the combined stimulation of subthalamic nucleus and substantia nigra pars reticulata might specifically improve freezing of gait, whereas balance impairment remained unchanged. The combined stimulation of subthalamic nucleus and substantia nigra pars reticulata was safe, and of note, no clinically relevant neuropsychiatric adverse effect was observed. Patients treated with subthalamic nucleus and substantia nigra pars reticulata stimulation revealed no 'global' effect on axial motor domains. However, this study opens the perspective that concomitant stimulation of the substantia nigra pars reticulata possibly improves otherwise resistant freezing of gait and, therefore, highly warrants a subsequent phase III randomized controlled trial.

Hyperkinetic disorders

Welter ML, Grabli D, and M. Vidailhet reviewed Deep Drain Stimulation for hyperkinetics disorders: dystonia, tardive dyskinesia, and tics. This review focuses on new insights in deep brain stimulation (DBS) for patients with hyperkinetic movement disorders: dystonia, tardive dyskinesia and Gilles de la Tourette's syndrome. The recent literature confirms the efficacy of high-frequency stimulation of the globus pallidus internus (GPi) for primary dystonia, generalized or not, with a stable effect over time. The benefit of DBS in other forms of localized dystonia remains to be demonstrated in larger studies. Some clinical and radiological predictive factors have been determined with a predominant influence of the disease duration. Tardive dystonia and myoclonus-dystonia are also improved by GPi stimulation. Encouraging results obtained in cerebral palsy may pave the way for the application of DBS in other secondary dystonia.

Dystonia

Although dystonia severity was reduced by 40–50% with improvement of disability and quality of life, the long-term effect has not been fully evaluated. The fact that some patients experienced a smaller improvement highlighted the need for predictive factors of a good outcome.

Long-term results and predictive factors for GPi-DBS in primary generalized dystonia

The long-term motor and functional efficacy of GPi-DBS in primary generalized dystonia (PGD) was suggested by previous studies. The retrospective evaluation of 30 patients with PGD treated by GPi-DBS confirmed that the excellent outcome at 1 year [-79 and -69% in the motor and disability scores of the Burke–Fahn–Marden dystonia rating scale (BFMRS), respectively] was maintained at 2 years, with a homogeneous improvement (>40% in all patients), and up to 8 years for the patients with available data. Moreover, as clinical outcome did not depend on high energies of stimulation, battery replacement was required after up to 48 months in patients who were initially stimulated using 60 Hz, whereas they were replaced every 24 months for those who received initial stimulation at 130-Hz frequency. In 26 DYT1-positive patients treated by GPi-DBS, the benefit observed at 1 year was maintained up to 10 years (mean follow-up duration 6.2 years, range 3–10 years). However, 8⁄26 patients exhibited a worsening of dystonic symptoms leading to the implantation of an additional lead in both GPi, 5 years after the first implantation, with a subsequent improvement in only four patients. Additional smaller studies also

support the short and long-term efficacy of GPi-DBS in generalized or cervical dystonia but highlighted the possibility of heterogeneous outcomes, even in homogeneously selected patients. In 24 consecutive patients with either generalized (n = 22) or segmental (n = 2) dystonia treated by GPi-DBS, the motor and disability scores of the BFMRS improved by 44 and by 39%, 1 year after surgery, respectively. Only eight patients had a good outcome (improvement >50% of the motor BFMRS), whereas five were non-responders (improvement <25%). Finally, in a literature-based series of 44 patients, GPi-DBS appears to be a well-tolerated and effective treatment for generalized dystonia in children and adolescents (mean age at surgery: 14.2 ± 3.5 years).
In an attempt to optimize the selection of dystonic patients for DBS, the predictive factors of GPi-DBS efficacy were assessed in two retrospective studies. In the first series of 39 patients, the shorter disease duration was the main predictive factor of a good postoperative outcome, whereas the age at onset, age at surgery and severity of the disease had no significant influence. Fixed skeletal deformities may also be associated with a poorer outcome. In the second series of 40 patients, a lower BMFRS score and younger age at surgery were found to be predictive of the postoperative outcome. Interestingly, this team also focused on brain imaging data and modelling of current distribution. The predictive model suggested that the greater the volume of the right GPi and the greater the volume of stimulated tissue within the left GPi, the greater was the postoperative improvement. Data regarding the influence of DYT1 status on stimulation outcome are still conflicting: a few studies found that DYT1-positive patients had a better outcome whereas others were inconclusive.

Focal or segmental dystonia
Globus pallidus internus-DBS had proven efficiency in segmental dystonia with cervical involvement. Data regarding other forms of localized dystonia are limited to small series of individual cases and thus should be considered cautiously. In these series of patients with segmental dystonia involving various body segments, improvement was reported for neck, trunk, upper and lower limbs. In addition, facial dystonia (including blepharospasm and oromandibular dystonia) could also be noticeably improved. Such a pattern of improvement as a function of body region is in line with results previously reported in generalized dystonia. An interesting and complex issue is the evolution of speech after GPi-DBS. If dysarthria was the more frequent side effect due to GPi-DBS, patients with hyperkinetic speech disorder due to oromandibular dystonia may expect some improvement after surgery. Rare patients with severe writer's cramp have been successfully treated with unilateral DBS of the ventral oral nucleus of the thalamus. This unusual target was chosen based on encouraging results of unilateral thalamotomy in the ventral oral complex. In addition, Stimulation of the ventral intermediate nucleus of the thalamus (Vim) has been successful in three cases of dystonic tremor. However, in segmental or focal dystonia mainly involving the upper limbs or lower face, a decrease in the severity of dystonia is not meaningful without consistent improvement in manual function or speech. To date this question was not specifically addressed and even if encouraging, results of DBS in focal or segmental dystonia (except for severe cervical involvement) reported in series of patients has to be confirmed in larger studies.

Myoclonus dystonia
Myoclonus dystonia is a rare form of movement disorder with prominent action myoclonus and slight dystonia. Although genetically heterogeneous, many cases are caused by point mutations or large deletions in the [varepsilon]-sarcoglycan gene (SGCE). In severe forms of the disease, DBS has been proposed in few patients targeting the Vim or the GPi. Previously published and recent case reports, with proven SGCE mutations, consistently suggest that both Vim and GPi-DBS significantly improved myoclonus, whereas only GPi-DBS decreased dystonia.

Tardive dystonia

Two cases series confirmed that GPi-DBS is efficient and well tolerated for patients suffering tardive dystonia. In nine consecutive patients with tardive dystonia, the mean improvement in BFMRS motor and disability scores were of 74 and 89%, respectively, 6 months after surgery. Abnormal Involuntary Movement Scale score was also reduced by 70%. Quality of life and mood significantly improved; cognition was unchanged and no permanent adverse effects were reported. Very similar results were described by another team in six patients.

Secondary dystonia

The issue of DBS for dystonia secondary to brain injury is strongly debated. Patients with secondary forms of the disease have complex movement disorders with a combination of hyperkinetic and akinetic-rigid dystonia. In addition, the DBS target often displays lesions and the pathological process may progress (as in inherited metabolic disorders). Finally, beyond the reduction of dystonia severity the global motor and functional outcome is difficult to capture due to the lack of adequate tools of evaluation. However, in the recent literature, some teams have assessed the benefit of this treatment in such patients.

In a pioneering controlled study performed in 13 patients suffering dystonia-choreoathetosis cerebral palsy due to neonatal hypoxic encephalopathy, GPi-DBS provoked a 24% decrease in the mean BFMRS motor score, 12 months after surgery. Four patients were improved by 39–55%, whereas four patients were non-responders (improvement <20%). Despite a small sample, the comparison between the clinical outcome and the volume of tissue activated suggested that optimal placement of the leads was a major (but not exclusive) factor for good outcome. The disability, mental health and body pain-related quality of life were slightly improved. Several other case reports also suggest that GPi-DBS could offer a therapeutic alternative for dyskinesia due to various focal brain lesions or inherited metabolic or degenerative disorders.

Long-term side effects

In addition to well established hardware (such as infection, hemorrhage, leads or extension fractures) and stimulation related side effects (dysarthria), unusual deleterious effects were reported in a few dystonic patients chronically treated with GPi-DBS. Acquired stuttering was described in two patients under conditions that optimally suppressed dystonic symptoms, with marked disability in one. Parkinsonism was also reported in patients with cranial–cervical dystonia. These observations were in line with the worsening in akinesia observed in patients with Parkinson's disease or in dystonia with GPi-DBS. Rare stimulation-related adverse events primarily affected speech. Implantable pulse generators were replaced every 24 months on average in patients who received initial stimulation at 130-Hz frequency. No battery was replaced for up to 48 months in 20 patients initially stimulated using 60 Hz. Clinical outcome did not depend on high energies of stimulation.

Conclusion: these new results confirm that GPi-DBS has long-term efficacy and safety in severe generalized and cervical dystonia but highlight that late unusual complications, although rare, may occur. Other conditions such as tardive dystonia or myoclonus dystonia could also represent good indications. Further large studies with specific focus on functional outcome are warranted to address the question of DBS in severe and impairing segmental/focal dystonia. Although clinical predictive factors of favorable outcome for GPi-DBS in dystonia have emerged in the past years, there is a need for a reliable marker that will help to accurately select dystonic patients that will benefit from DBS. Overall, the main unanswered questions are raised by the use of DBS in secondary dystonia. Given the heterogeneity of dystonia both from clinical and causative standpoints, the potentialities of new targets within the basal ganglia should also be explored.

Novel clinical applications or stimulation targets

Obsessive Compulsive Disorder

The treatment of severe forms of obsessive-compulsive disorders (OCD) is a major challenge in psychiatry. OCD is characterized by intrusive, anxious thoughts and repetitive, ritualized behaviors. It is one of the most disabling of the chronic psychiatric disorders and has considerable repercussions on family relationships, social life, and the ability to function at work. Pathophysiological models suggest that obsessive compulsive disorder (OCD) might be associated with dysfunctions in cortico-striato-pallido-thalamo-cortical neuronal circuits. Luc Mallet, Valérie Mesnage, Jean-Luc Houeto et al. reported two cases of patients who had Parkinson's disease and a history of severe OCD. Parkinsonian disability improved postoperatively in both patients, and 2 weeks after bilateral subthalamic nucleus procedure, their compulsions had disappeared and obsessive symptoms improved (58% improvement for patient 1 on the Yale-Brown obsessive compulsive scale, 64% for patient 2). The improvements in these two patients suggest that high-frequency stimulation could improve function in the subcortical-limbic circuitry in patients with severe OCD. High-frequency subthalamic stimulation in patients with Parkinson's disease has proven efficacy and there is no evidence to suggest a major risk for patients with OCD. Despite the partial efficacy of medical treatment, the management of patients with severe OCD remains a challenge.

Then STOC Study Group reported on a randomized, double-blind, crossover study comparing stimulation of the subthalamic nucleus with sham stimulation in severe obsessive-compulsive disorder. The current treatment of OCD consists of a combination of serotonin-reuptake inhibitors and cognitive–behavioral therapy; with this treatment, however, 25 to 40% of patients have persistent symptoms and lasting functional repercussions. In the hope of reducing the disability and debilitation of patients whose OCD is highly refractory, ablative neurosurgical stereotactic treatments have been attempted, but the efficacy of these treatments has been variable. In contrast, deep-brain stimulation, which has been proved effective in the treatment of movement disorders, is a therapeutic alternative that is adaptable and reversible, permitting the modulation of the dysfunctional neural networks that are involved in the pathophysiology of OCD. Different parts of the orbito–fronto–striato–thalamo–cortical circuit, including the ventral striatum, internal capsule, and nucleus accumbens, have been targeted for stimulation, as described in several case reports and in a report on a prospective open-label study; the long-term results have been variable but promising. Furthermore, studies of stimulation in patients with Parkinson's disease have highlighted the putative role of the subthalamic nucleus in behavioral integration and the efficacy of subthalamic nucleus stimulation in reducing repetitive behaviors, anxiety, obsessive–compulsive symptoms, and OCD. These results, combined with the long-term effects of stimulation of the subthalamic nucleus and the ability to target small, well-defined structures with the use of validated procedures, led them to propose the subthalamic nucleus as a target for the treatment of highly resistant OCD.

In a 10-month, crossover, double-blind, multicenter study assessing the efficacy and safety of stimulation of the subthalamic nucleus, eight patients with highly refractory OCD have been randomly assigned to undergo active stimulation of the subthalamic nucleus followed by sham stimulation and eight to undergo sham stimulation followed by active stimulation. The primary outcome measure was the severity of OCD, as assessed by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), at the end of two 3-month periods. General psychopathologic findings, functioning, and tolerance were assessed with the use of standardized psychiatric scales, the Global Assessment of Functioning (GAF) scale, and neuropsychological tests. After active stimulation of the subthalamic nucleus, the Y-BOCS score (on a scale from 0 to 40, with lower scores indicating less severe symptoms) was significantly lower than the

score after sham stimulation (mean [+/-SD], 19+/-8 vs. 28+/-7; P=0.01), and the GAF score (on a scale from 1 to 90, with higher scores indicating higher levels of functioning) was significantly higher (56+/-14 vs. 43+/-8, P=0.005). The ratings of neuropsychological measures, depression, and anxiety were not modified by stimulation. There were 15 serious adverse events overall, including 1 intra cerebral hemorrhage and 2 infections; there were also 23 non serious adverse events. STOC Study Group concluded that these preliminary findings suggested that stimulation of the subthalamic nucleus may reduce the symptoms of severe forms of OCD but is associated with a substantial risk of serious adverse events.

Gilles de la Tourette's syndrome

Tourette syndrome (TS) is characterized by motor and vocal tics associated with various psychiatric manifestations, which can cause major familial and social disability. In patients with severe and debilitating tics, the best available drug therapy is often ineffective and has serious potential adverse effects. Tourette syndrome (TS) is thought to result from dysfunction of the associative-limbic territories of the basal ganglia, and patients with severe symptoms of TS respond poorly to medication.

Between 1999 and June 2008, 37 cases of patients with Tourette's syndrome operated on for DBS have been reported in the literature. These patients were enrolled in open label studies with stimulation applied in the ventralis oralis (Voa)/CM-Pf-Thal, the posterolateral GPi, the internal capsule or the nucleus accumbens. One study proposed a double blind evaluation of the effect of the CM-Pf-Thal stimulation in five patients for a short period (1 week) with a significant decrease in tics with bilateral stimulation. All these studies reported a decrease in tic severity and frequency with a mean of 60%, the poorer effect was noted with the internal capsule (-25%) and the nucleus accumbens (-41%). Despite the number of patients operated on, some questions are still a matter of debate: When to operate? In which target? How to evaluate? However, the main obstacle to answer these questions is the absence of well conducted double-blind studies in the previous literature. Recently, a randomized double-blind cross-over protocol has been performed in three patients with very severe and disabling Tourette's syndrome with a view to evaluating the efficacy of the bilateral DBS of the CM-Pf-Thal and/or the ventromedial part of the GPi. A dramatic improvement in tic severity was obtained with bilateral stimulation of the GPi [-65, -96 and -74 in the Yale Global Tic Severity Scale (YGTSS)]. Bilateral CM-Pf-DBS produced 64, 30 and 40% reductions in tic severity. The association of thalamic and pallidal DBS showed no further reduction in tic severity (-60, -43 and -76%), whereas motor symptoms recurred during the sham condition. No neuropsychological, psychiatric or other long-term adverse effect was observed. In this study, GPi-DBS of the ventromedial part seems to be more efficient than CM-Pf-Thal-DBS. An open follow-up revealed a persistent effect 20–60 months after surgery with an excellent tolerability. However, this study concerns only three patients and no evaluation of the quality of life and social integration was performed. In the series reported by the Italian team with 15 patients (age 30 ± 8.7 years) operated on for thalamic stimulation (Voa/CM-Pf) with an open-label 24-months follow-up, the significant decrease in tics severity (-52%, YGTSS) and obsessions and compulsions [-31%, Yale–Brown Obsessive Compulsive Scale (YBOCS)] was accompanied by a significant improvement in anxiety, depression and social impairment. In this study, about half of patients had an improvement in tic severity less than 50%, however, with an aggravation of obsessive–compulsive symptoms (OCS) in two (YBOCS: 31 and 26 after surgery vs. 23 and 25 before surgery; YGTSS: 52 and 45 after surgery vs. 79 and 78 before surgery). In these two patients, the team proposed the implantation of electrodes within the anterior limb of the internal capsule/nucleus accumbens (ALIC/NA). Two other patients with Tourette's syndrome were operated on, one for implantation of four electrodes in a single session (CM-Pf and ALIC/NA, YGTSS: 86, YBOCS: 38) and the other for stimulation of the ALIC/NA alone (YGTSS: 94, YBOCS: 35). In the first two patients, additional ALIC/NA stimulation failed to significantly decrease obsession and compulsion (-9 and -26%) with a 34% additional decrease in tic severity. In the two latter, both tics and OCs were dramatically

improved by ALIC/NA stimulation (-75 and -57%, respectively), with variable effect on depression, but an improvement in their social adaptation. No major side-effect was noted in these four patients. Another case of a Gilles de la Tourette's patient with bilateral NA-DBS has also been reported in 2009. Three years after surgery, this severe patient showed a 58% decrease in tic severity and 56% decrease in obsessions and compulsions. Self-mutilations and the urge to destroy glass have stopped just after surgery. These two last cases suggest that ALIC/NA-DBS could be proposed in patients with severe tics and OCS. Interestingly, in a young parkinsonian patient (parkin mutation, 38 years), with childhood tics which reoccurred in adulthood prior to the diagnosis of Parkinson's disease, subthalamic nucleus (STN)-DBS produced a 57% decrease in parkinsonian motor signs and a 97% reduction in tics frequency, 1 year after surgery. In a 44-year-old patient with Tourette's syndrome, 1 year after surgery, dorsolateral GPi-DBS provoked a 88% decrease in tics severity. However, despite this excellent result, the patient emphasized having difficulties adjusting to the new situation, the absent necessity of being an inpatient and recognizing that the illness had been a big part of her life. In this patient, the relatively prompt recovery after surgical intervention was problematic. Even this particular difficulty to reintegrate into a normal life or to elaborate a new project after surgery was frequently described in parkinsonian patients operated on for STN stimulation.

New targets, new indications, new technology

DBS and Depression

A large number of depressive patients cannot be helped with evidence-based treatment steps (e.g., pharmacotherapy, psychotherapy, and electroconvulsive therapy). Up to 40% of patients responding to antidepressant therapy suffer from clinically relevant residual symptoms despite optimized treatment. These patients suffer from debilitating, life-threatening symptoms, face a reduced quality of life (QoL), and are a burden for society. For these patients, suffering from so-called treatment-resistant depression (TRD), deep brain stimulation is currently under research as a possible treatment option.

Recently, the results of deep brain stimulation close to the subgenual cingulate region cg25 (Brodmann area 25) in six patients with refractory major depressive disorder were reported by Mayberg and colleagues. The authors chose this target on the basis of their previous findings that this region is implicated in acute stimulus-induced sadness, is metabolically overactive in treatment-resistant depression, and that clinical improvement after pharmacotherapy, psychotherapy, or limbic leucotomy is correlated with decreases in its metabolic activity. After 2 months of stimulation, five patients responded; four maintained a response after 6 months. Antidepressant effects were associated with marked reduction in cerebral blood flow in cg25 as measured by positron emission tomography.

The subcallosal cingulate gyrus (SCG), including Brodmann area 25 and parts of 24 and 32, is the portion of the cingulum that lies ventral to the corpus callosum. It constitutes an important node in a network that includes cortical structures, the limbic system, thalamus, hypothalamus, and brainstem nuclei. Imaging studies have shown abnormal SCG metabolic activity in patients with depression, a pattern that is reversed by various antidepressant therapies. The involvement of the SCG in mechanisms of depression and its emerging potential role as a surgical target for deep brain stimulation has focused recent interest in this area.

Long-Term Effects of Nucleus Accumbens Deep Brain Stimulation

Bettina H Bewernick et al. reported that deep brain stimulation (DBS) to the nucleus accumbens (NAcc-DBS) was associated with antidepressant, anxiolytic, and procognitive effects in a small sample of patients suffering from treatment-resistant depression (TRD), followed over 1 year. Results of long-term

follow-up of up to 4 years of NAcc-DBS are described in a group of 11 patients. Clinical effects, quality of life (QoL), cognition, and safety are reported. Eleven patients were stimulated with DBS bilateral to the NAcc. Main outcome measures were clinical effect (Hamilton Depression Rating Scale, Montgomery-Asperg Rating Scale of Depression, and Hamilton Anxiety Scale) QoL (SF-36), cognition and safety at baseline, 12 months (*n*=11), 24 months (*n*=10), and last follow-up (maximum 4 years, *n*=5). Analyses were performed in an intent-to-treat method with last observation carried forward, thus 11 patients contributed to each point in time. In all, 5 of 11 patients (45%) were classified as responders after 12 months and remained sustained responders without worsening of symptoms until last follow-up after 4 years. Both ratings of depression and anxiety were significantly reduced in the sample as a whole from first month of NAcc-DBS on. All patients improved in QoL measures. One non-responder committed suicide. No severe adverse events related to parameter change were reported. First-time, preliminary long-term data on NAcc-DBS have demonstrated a stable antidepressant and anxiolytic effect and an amelioration of QoL in this small sample of patients suffering from TRD. None of the responders of first year relapsed during the observational period (up to 4 years).

Nucleus Basalis of Meynert (NBM) in dementia

Cell counts in numerous human post-mortem studies show that up to 96% of NBM neurons are lost in both Alzheimer disease and Parkinson's disease Dementia patients compared to age-matched controls. Strong correlations have been shown between NBM neuronal loss, resultant cortical cholinergic deficits and the degree of cognitive impairment in both diseases.

A promising result using Low Frequency Stimulation (LFS) to treat dementia comes from the single case report of Freund et al. (2009) NBM DBS resulted in marked improvement in memory function: score on AVLT (sum) doubled to 25 indicating significant improvement in immediate episodic memory, and the patient was also able to perform AVLT (recog) for the first time, recognizing six words, demonstrating some amelioration of long term memory function. Visual perceptual abilities increased with CDT score rising to 9 and TMT-A time falling to 2.5 min. Performance also improved on tests of processing speed and praxis, with additional benefits observed in attention, concentration, alertness, drive and spontaneity returned to the concept of stimulating the NBM as a therapeutic intervention in dementia. There are no cures for dementia at the present time and management consists of inadequate symptomatic treatments. There is a need for further therapies to better relieve symptoms or to slow or halt progression or even reverse the course of these illnesses. Evidence suggests that degeneration of the NBM represents a common pathophysiological substrate between the major forms of dementia, and a recent case report indicates that low frequency stimulation of this nucleus to up regulate its activity represents a way of directly improving some of the cognitive deficits associated with dementia.

Hariz M, Blomstedt P. and L. Zrinzo reported about future of brain stimulation: new targets, new indications, and new technology. In the last quarter of a century, DBS has become an established neurosurgical treatment for Parkinson's disease (PD), dystonia, and tremors. Improved understanding of brain circuitries and their involvement in various neurological and psychiatric illnesses, coupled with the safety of DBS and its exquisite role as a tool for ethical study of the human brain, have unlocked new opportunities for this technology, both for future therapies and in research. Serendipitous discoveries and advances in structural and functional imaging are providing abundant "new" brain targets for an ever-increasing number of pathologies, leading to investigations of DBS in diverse neurological, psychiatric, behavioral, and cognitive conditions. Trials and "proof of concept" studies of DBS are underway in pain, epilepsy, tinnitus, OCD, depression, and Gilles de la Tourette syndrome, as well as in eating disorders, addiction, cognitive decline, consciousness, and autonomic states. In parallel, ongoing technological development will provide pulse generators with longer battery longevity, segmental electrode designs allowing a current steering, and the possibility to deliver "on-demand" stimulation

based on closed-loop concepts. The future of brain stimulation is certainly promising, especially for movement disorders-that will remain the main indication for DBS for the foreseeable future-and probably for some psychiatric disorders. However, brain stimulation as a technique may be at risk of gliding down a slippery slope: Some reports indicate a disturbing trend with suggestions that future DBS may be proposed for enhancement of memory in healthy people, or as a tool for "treatment" of "antisocial behavior" and for improving "morality."

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