ABSTRACT

Introduction: Over the last three decades, extensive basic and clinical research has been performed on the use of subthalamic nucleus (STN) as the preferred deep brain stimulation (DBS) target for the treatment of Parkinson's disease (PD).

Areas covered: The mechanism underlying the benefit for the motor symptoms in PD is related to the modulation of firing patterns within the hyperdirect projections from motor cortical areas, as well as within the afferent and efferent fibers to the motor STN. Advancements in neuroimaging techniques allow us to identify precisely the STN optimizing surgical targeting.

Expert opinion: In this review, we provide an update on the current uses of STN-DBS as a routine therapy as well as its experimental indications in PD, the critical aspects associated with its successful implementation and recent advances in DBS technology.

Key words: deep brain stimulation; lead technology; neurophysiology; neuroimaging side effects; subthalamic nucleus; neuroimaging; side effects.

HIGHLIGHTS BOX

1. The subthalamic nucleus (STN) is still the primary target of Deep Brain Stimulation (DBS) for Parkinson's disease (PD).
2. Cognitive decline and dopa refractory axial symptoms are not improved by this surgical procedure.
3. Age, severity of PD, and lead location are important predictors of long-term improvement.
4. Innovative techniques, such as short pulse width stimulation and directional DBS, may allow some reduction in stimulation-related side effects.

1. STN DBS: historical trends

The introduction of modern-day deep brain stimulation (DBS) in the late 1980s was a pivotal moment in the field of stereotactic functional neurosurgery. It transformed the management of medically refractory movement disorders, particularly advanced Parkinson's disease (PD), essential tremor (ET) and dystonia [1]. The surgical treatment of PD indeed has a long history that considerably precedes the discovery of levodopa. The options in the late 19th / early 20th century predominantly involved creating lesions along the corticospinal tract, producing contralateral paresis to treat hyperkinetic symptoms. However, Foerster [2], Meyers [3] and others realized the importance of the basal ganglia in motor physiology and Irving Cooper confirmed this by serendipity when he accidentally injured the anterior choroidal artery before performing a cerebral peduncle lesion in a patient with parkinsonism. The patient sustained an improvement not only in tremor but also in rigidity and bradykinesia [4]. Post-mortem studies consequently confirmed that the therapeutic effect was related to an ischemic stroke in the pallidum. This led to the introduction of pallidotomy as a new option in the treatment of PD [5]. Early procedures were carried out through an open approach with a relatively high morbidity and mortality. The subsequent introduction of human stereotactic surgery by Spiegel and Wycis allowed for accurate targeting through a burr hole approach relying on ventriculography landmarks and atlas coordinates. Stereotactic lesions were performed in the pallidum, pallido-thalamic tract and in the thalamus amongst other targets along the basal ganglia circuitry [6]. Nevertheless, ablative surgery for movement disorders was almost always unilateral due to the high morbidity

associated with bilateral surgery. Lesions are irreversible and relied on atlas coordinates for indirect targeting. Spiegel and Wycis firstly used electrical stimulation before making a lesion in a case of parkinsonism with oculogyric crisis [7]. However, the first use of chronic depth electrostimulation as a therapy per se in neurological disorders was in the early 70s by Bechtereva [8]. This neuroscientist treated PD patients using "therapeutic electrical stimulation" through electrodes implanted. Patients were treated with intermittent courses of stimulation for up to 1.5 years. Of note, clinical benefits were evident even during stimulation-free periods [9, 10].

Short-lasting stimulation was utilized prior to ablative surgery to confirm targeting accuracy. With the development of commercially available implantable stimulators, the benefit of chronic high frequency stimulation was established in 1987 by Benabid et al. after using electrical stimulation during a thalamotomy for essential tremor to confirm targeting accuracy [10]. It was observed that using stimulation at frequencies higher than 100Hz led to immediate and reversible cessation of tremor. The authors proposed that, in order to avoid the significant side effects from bilateral thalamotomies, a thalamotomy for the most disabled side and chronic high frequency DBS for the other side could be carried out [11]. The practical observation of these reversible and adaptable effects of high frequency stimulation, which mimicked the effect of a lesion in the same place, was therefore the historical starting point of the modern development of DBS as a new method. In that early juncture, DBS of the Ventral intermediate (Vim) nucleus of the thalamus initially became the only target to treat essential tremor and parkinsonian tremor [12]. The role of thalamus in the basal ganglia network is very well known since late 80s [13]. Indeed, the classic model of the basal ganglia

has been established on the presence of intrinsic direct and indirect pathways, both comprising a consecutive set of excitatory glutamatergic and inhibitory GABAergic projections. In this model, cortical projections are directed to the striatum, which further converge on GPi and SNr (substantia nigra pars reticulata) either directly or indirectly via GPe and STN. The output from GPi and SNr is then directed to the thalamus, which further projects back to the cortex, forming a complete cortico-basal ganglia-thalamo-cortical loop. Both direct and indirect basal ganglia pathways are modulated by endogenous dopamine release from the SNc (substantia nigra pars compacta) [14].

However, following the introduction and routine use of Levodopa, patients with PD began to develop motor fluctuations and dyskinesia and, thus, there was a need to identify new therapies to address these issues [15]. In the early 1990s, Leksell's posteroventral pallidotomy enjoyed a revival. Indeed, several studies showed that parkinsonian tremor, rigidity and hypokinesia can be effectively abolished by posteroventral pallidotomy. The significant effect of posteroventral pallidotomy is believed to be based on the interruption of some striopallidal or subthalamopallidal pathways, which results in disinhibition of medial pallidal activity necessary for movement control [16].

Subsequently, the subthalamic nucleus (STN) and globus pallidus interna (GPi) were investigated as potential DBS targets for treatment of symptoms of advanced PD[16]. The seminal work of Bergman et al. and of Aziz et al provided evidence that lesions in the STN alleviated parkinsonism in the MPTP monkey model of PD. This paved the way to explore this target in humans [17, 18].

The role of the STN in PD was explored in mainly non-human primate models treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Overactivity of the STN was identified in comparison to control animals [17]. Lesions [17, 18] or high-frequency stimulation of the STN [19] resulted in improvement in hemibody bradykinesia and rigidity. Interest in the STN was incited by the strategic position of this nucleus within the basal ganglia circuitry (Figure 1). It receives input from the cerebral cortex and external globus pallidus and sends output to the globus pallidus (internal as well as external part) [20]. The development of STN DBS was also facilitated by progress in MRI allowing direct visualization of the nucleus [21] and, thus, precise localization with imaging. The interesting findings in the primate models led Pollak and Benabid to propose STN DBS in humans. The first patient went on to receive unilateral STN DBS in Grenoble in 1993 [22]. Shortly after, the same group implanted bilateral STN DBS in a small cohort of PD patients showing an improvement of activities of daily living scores by 58-88% and motor scores by 42-84% [23]. The same research group performed a larger study of bilateral STN implantation in 24 patients with advanced PD confirming the efficacy of this target in advanced PD. The severity of symptoms off medications decreased and the levodopa dose was reduced with consequent reduction in dyskinesias [24]. Soon after, other teams around the world adopted this target with similar results [25-31].

The use of the GPi as a target for DBS has also been extensively explored including in head to head comparison with STN DBS. This target is especially useful in the treatment of the long term complications of dopaminergic treatment, mainly levodopa induced dyskinesia (LID) [16]. New experimental targets such as the

pedunculopontine nucleus (PPN) [32], the nucleus of Meynert [33] and the substantia nigra [34, 35] have been investigated but with limited evidence of efficacy. The main target for DBS in Parkinson's disease over the last 25 years has however been the STN. The important reason of this extensive use of STN is its efficacy not only for resting tremor but also its impressive effects on bradykinesia and rigidity [26].

Here, we provide an update on the current uses of STN-DBS as a routine therapy as well as its experimental indications in PD including a discussion of the crucial aspects of its implementation, insights into some of the side effects that DBS can induce and how these may be overcome, and how some of the recent advances in DBS technology may help improve patient outcomes.

2. STN DBS: timing of surgery and clinical effects

Debate persists with regards to the ideal timing of surgery during the course of PD. Multicenter trials carried out by Deuschl et al. [29] and Williams et al. [36] reported outcomes of STN implantation11-13 years from the onset of the disease. However, Schüpbach et al. suggested performing surgery earlier (average: 7 years) after disease onset just when complications start to appear [37]. They reported outcomes from 10 patients treated with STN DBS with a follow up period of 18 months compared to 10 patients on receiving best medical treatment. Only the operated patients exhibited improvement in UPDRS motor scores, in dyskinesia scores and in quality of life (QoL) and were able to decrease their daily doses of dopaminergic drugs by 57%. The QoL was the primary outcome measure of the German-French "EARLYSTIM" multicenter trial in 2013with 2-year follow

up showing better QoL in STN DBS patients than in matched patients receiving best medical treatment [38, 39]. Recently, Schüpbach et al. from the EARLYSTIM study group reported that PDQ-39-SI at baseline was correlated to the change in PDQ-39-SI after 24 months in PD patients treated with STN DBS as well as in those treated with the best medical treatment ($p < 0.05$). Interestingly, the higher the baseline score (worse QOL) the larger the improvement in QOL after 24 months [40].

Dulski et al. have recently showed an improvement in QoL measures in the first 6 months after STN-DBS diminished slightly (being still better than before surgery) after 12 months [41]. The same results were demonstrated by several other centres. Liu et al. found that 51.1% of their patients' group reported better QoL outcomes after STN implantation. The subdomains of mobility, activity of daily living and bodily discomfort improved significantly after the surgery. Presurgical factors including QoL, dopaminergic medication burden, disease stages, depression scores, were found to correlate with QoL changes. Of note, greater presurgical QoL burden, less dopaminergic medication exposure, and earlier disease stages, were predictors of QoL improvements [42].

With regard to DBS outcome factors, axial symptoms have been recently definitely proved as predictors of DBS outcome in a cohort of 143 PD patients treated with STN-DBS and assessed before and 1, 2, 5, and 10 years after the implantation [43]. Indeed, Lau et al. found the level of axial disability was the only symptom that significantly predicted death after surgery (hazard ratio 4.30 [SE 1.50] per unit of square-root transformed axial score)[43].

It is important to consider that one of the contraindication for surgical treatment of PD is a medically refractory form of the disease (according to CAPSIT-PD) [44].

Factors against early surgery include possible inclusion of non-PD patients. Indeed, operating on patients earlier than 5 years after symptom onset may lead to the include atypical parkinsonism cases who will fail to obtain long-term benefit [45]. Moreover, the early surgery might be associated to an earlier emergence of long-term side effects of STN DBS (such as gait freezing or dysarthria) In other words, the benefit-to-risk ratio in patients undergoing STN-DBS just after the onset of motor complications could be less, given that the baseline disability at the time of surgery is mild, and the degree of potential benefit from surgery is necessarily less, when compared with PD patients with greater preoperative disability from motor complications. [45]. Lastly, motor complications developing after a few years do not necessarily get worse, but instead could remain minimally disabling for a long period of time [45]. Therefore, this approach might lead to taking a risk of implanting patients who may not receive much benefit. Nevertheless, the U.S. Food and Drug Administration has now approved STN DBS for use as early as 4 years after diagnosis [38]. Taking into account these aspects, it is important to realise that surgery should not be a "last resort" and that timing should be tailored to the needs of the individual patient.

In regard to timing of surgery, there is an ongoing debate about a possible disease modifying effect in early PD by STN-DBS. Four retrospective analyses showed STN-DBS could maintain subjects' off-medication motor signs several years after electrode implantation[26, 48-50]. On the other hand, a prospective study showed equivalent disease progression, as measured by striatal fluorodopa uptake in subjects receiving or not receiving STN DBS[51]. It is well known that stimulation induced increases in brain-derived neurotrophic factor (BDNF) [46]. There are

several studies that have hypothesized the role of stimulation-produced BDNS in promoting the survival of the nigrostriatal system, promote functionality of the basal ganglia-cortical circuitry, and decrease α-synuclein (α-syn) aggregation in the parkinsonian brain [47]. The putative neuroprotective and disease-modifying effect of STN-DBS have been supported by data in mechanistically relevant models of PD [52] but concrete evidence for a disease modifying effect of STN DBS in humans is lacking.

3. STN DBS: current trends

3.1 STN DBS Programming

The initial programming can be carried out as early as 48 hours following surgery but in people in whom there is a significant implantation effect (microlesion effect) programming is usually postponed until after parkinsonian signs recurrence [53]. However, the practical approach to the initial programming might be different in several centres.

The adjustable parameters are the contact selection and polarity, voltage amplitude, frequency and pulse width. There are several modes of DBS settings.

In the case of *unipolar stimulation*, one or more lead contacts are programmed as the cathode (negative) and the neurostimulator case as the anode (positive); the diffusion of the current can then be modelled radially [54].

In contrast, *bipolar stimulation* consists of one or more contacts on the lead being programmed as cathode and one or more as anode. This is associated with a narrower and more focused current field with maximal effects surrounding the cathode [55] and can reduce unwanted side effects due to lateral current spread.

This type of stimulation requires higher current intensity to achieve similar benefits compared to unipolar mode [56].

Interleaving stimulation is an alternative programming approach for optimizing the electrical field available through some DBS platforms to improve PD symptoms with fewer stimulation-induced side effects compared to the unipolar and bipolar modes. In this DBS setting, two programs can be simultaneously delivered in an alternating way and are thus "interleaved" on the same lead. Each of the two programs is characterized by specific amplitude, pulse width and active electrode contacts [57] and allow the programmer to 'shape' the electrical field as well as having theoretical advantages in desynchronising the synchronised oscillatory activity seen in the STN in PD patients .

All recent attempts at refining programming approaches have been developed to increase the side-effect threshold. Indeed, therapeutic efficacy of STN-DBS depends on applying the stimulation field to the superolateral portion of the STN or its immediate surroundings. The spread of stimulation into adjacent structures may cause side effects reducing optimal clinical outcome [58, 59].

Current steering, lower frequency and shorter pulse widths are the DBS settings showing promising clinical outcome and good safety profiles in several trials.

The concept of *current steering* is based on the utilisation of multiple independent current sources and constant-current delivery using eight-channel per lead devices, which have been shown to allow well-defined distribution of current with significant motor improvement in PD [60]. Van Dijk et al. demonstrated that the

steering-DBS lead was able to stimulate a significantly higher percentage of STN cells compared to the conventional stimulation settings. The orientation of the lead in the target is the key aspect in achieving the optimal stimulation outcome [61].

Lower frequency stimulation (<90 Hz, LFS) is a setting showing beneficial effects especially on speech intelligibility, articulation, general grade of dysarthria and laryngeal coordination [62-65]. These data were confirmed by Fabbri et al., who showed that LFS improved speech intelligibility both in the absence of L-dopa effect and with concomitant L-dopa intake among patients with severe speech impairment chronically stimulated with conventional high frequency stimulation [66]. In particular, articulation, respiration, phonation and prosody have been found to improve with LFS [67]. Phonemic verbal fluency switching improved with LFS without an improvement of phonemic verbal fluency score [67].
LFS DBS has been also shown to have beneficial effects on improving freezing of gait in several studies[68-70]. Moreau et al. have showed a significant reduction of freezing of gait episodes in a cohort of 13 PD patients treated with STN DBS at 60 Hz frequency [71]. 60 Hz STN stimulation significantly improved also swallowing function and axial symptoms in a cohort of 7 PD patients [72].

A recent programming approach explored the impact of using stimulation settings based on pulse durations <60 μSec on the therapeutic window of STN neurostimulation in PD. This is labelled *short pulse width* [73]. Reich et al. demonstrated that short pulse width stimulation allowed focusing of the

neurostimulation effect on smaller diameter axons close to the electrode while avoiding stimulation of distant pyramidal tract fibres [73]. These results were confirmed by a recent randomized, double-blind study [74]. Dayal et al. have recently shown that speed of gait and perceptual speech scores improved at 30μs settings [75].

Of note, the optimization of clinical results depends on careful programming of electrical parameters and changes in antiparkinsonian drug dosages. In this regard, improvement of parkinsonian signs can be achieved in the majority of patients even after long-term stable stimulation, especially when postoperative care is personally managed by a neurologist expert in movement disorders, who is directly responsible for stimulation programming and simultaneous drug adjustments [76]

3.2 DBS lead technology

Directional DBS (dDBS) is increasingly becoming the standard of DBS lead technology. dDBS has the advantage of shaping the electrical field in the axial plane compared to all previous lead designs which were characterized by omnidirectional stimulation field generated by cylindrical electrodes that only allow shaping the electrical field along the lead axis [77]. In recent years, several new electrode designs have been proposed allowing to shape the electrical field perpendicular to the lead (Fig.2)[78].

dDBS electrodes can steer stimulation, using (three) segmented contacts 360 degrees around the lead. In 2014, two experimental intraoperative studies with novel directional DBS leads performed in two different centres provided some

evidence to support the use of dDBS [79, 80]. Both of these studies suggested that dDBS widened the therapeutic window and lowered the current needed for beneficial effects compared to omnidirectional stimulation [79, 80]. This innovative approach through a specific orientation of the stimulation allows a reduction of the total activated tissue and, thus, enhances the accuracy of DBS in commonly used targets. Of note, directional leads have the advantage to spread the stimulation in most effective way but do not supplement a badly placed lead. Thus, directional DBS is not able to improve overall coverage of the desired target since does not expand the field of capture although it can direct stimulation in the selected stimulated target.

3.3 Technical procedure

From a technical point of view, STN DBS lead implantation can be performed under local anaesthesia (LA) or general anaesthesia (GA) with different groups advocating their particular approach. However, asleep DBS is emerging as a surgically favored process.

No significant differences have been found in the postoperative Unified Parkinson's disease rating scale and levodopa equivalent drug dosage between the GA and the LA groups [81]. In this regard, Chen et al. showed in a cohort of 133 PD patients that bilateral GPi and STN DBS using the asleep method resulted in motor, quality-of-life, and medication reduction outcomes comparable to those of the awake method[82]. A Class III evidence study by Brodsky et al. showed that asleep intraoperative CT imaging-guided implantation was not significantly different from awake microelectrode recording-guided implantation in improving motor outcomes at 6 months [83].

On the other hand, the metanalysis by Ho et al. highlighted that DBS under GA may lead to lower overall complication rates but that awake DBS may lead to less treatment-induced side effects. However, there were no significant differences in clinical motor outcomes between the two techniques. [84].

In line with the metanalysis of Ho et al., a retrospective comparison between asleep and awake DBS with micro-electrode recording (MER) has shown the potential for decreased complications in cohorts operated under general anaesthesia[85]. Consequentially, trends are towards asleep procedures and less micro-recording.

3.4 Effect on non-motor symptoms

Improvements in autonomic symptoms have been reported following DBS. Halim et al. reported three cases of early onset PD with marked improvement in sweating and/or bowel and bladder function after STN DBS [86]. In particular, several studies showed evidence that STN DBS is effective for decreasing detrusor hyperreflexia in PD cases [87] possibly through modulation of the cortical control of urinary bladder [88].

STN-DBS has showed significant benefit also in other non-motor symptoms of PD including insomnia [89] and pain [90]. Sudomotor dysfunction, most often hyperhidrosis, is extremely common in PD patients and has been shown to be alleviated by STN DBS [91, 92].

4. Complications and side effects

Patients should be informed of the potential adverse effects of STN implantation that can be broadly divided into surgical risks and side-effects related to

stimulation (short-term and long-term). Surgical complications include brain hemorrhage, infection, seizures and targeting inaccuracies.

Bleeding causing death or neurological disability is, thankfully, a very rare complication but dependent on surgical background. Patient factors associated with increased risk include the use of anticoagulants, untreated hypertension and advancing age. Surgical factors include the use of microelectrode recording, the number of brain's passes and sulcal or ventricular transgression. Proponents of the image-guided and image-verified approach to DBS report significantly lower rates of hemorrhage [93].

Infections can occur after the primary surgery, either early or in a delayed fashion, or may follow skin-erosion or battery changes. Post-operative local or intracranial infections usually occur within one to 3-months after surgery, commonly at the IPG level and are often caused by Staphylococcus Aureus. Surgical removal of the IPG and cables to prevent lead infection is the most efficient treatment [94]. New cables and IPG can be implanted after eradication of the infection a few months later. Late infections caused by chronic erosion of the skin or skin injury might be avoided by preventive repositioning of the IPG prior to skin breakdown [94]. The risk of DBS hardware infection can be greater at the IPG replacement than at the primary procedure [95]. However, screening for methicillin-resistant Staphylococcus aureus (MRSA) and eradication prior to elective DBS IPG change as well as topical vancomycin in the IPG pocket during surgery are effective measures to reduce the infection rate [96].

Other hardware-related complications include breakage or damage of the leads, cables or IPG. Post-operative lead migration (defined as an unintended post-operative displacement of the DBS lead) is usually related to technical errors during implantation with failure of lead fixation at the burr hole site or poor siting of the lead/cable connector resulting in traction on the brain leads [97].

Side-effects from stimulation include dysarthria, cognitive decline, motor and sensory disturbances, worsening of balance and psychiatric disorders.

Dysarthria is one of the commonest side effects of bilateral STN DBS; 10-15% of patients can develop some form of deterioration in speech intelligibility 1 year after surgery. DBS active contact location has been associated with speech disturbance resulting in medial disturbance (cerebellar) or lateral speech disturbance (capsular), the onset of which are at times acute but can also be significantly delayed by several months [98-101].

On the other hand, psychiatric disorders of STN DBS are generally acute and can be triggered by the implantation effect even before commencing stimulation as a result of oedema around the DBS lead. These can include paranoia, mania, severe depression, acute psychosis and apathy but are often self-limiting [102-106].
Several studies have reported the aggravation of impulsive control disorders (ICD) and the development of de novo ICDs after DBS [107-110]. Amami et al. observed patients for 3 years after DBS, and their de novo ICDs were transient [111]. Merola et al. observed 150 patients for 4 years on average after DBS for

which there were 11 de novo ICDs [112]. Overall, it remains still unclear how DBS affects the change in ICDs over a longer period of time and which factors are associated with the de novo ICDs after the surgery. In common clinical practice emergence of ICDs post -DBS can usually be addressed by reduction in medication. Whereas pre-op ICD provoked by medication is actually a positive indication for DBS rather than a contra-indication.

In this regard, clinicians in the DBS team can deal with these side effects balancing titration of stimulation and withdrawal of dopaminergic medication [113]. In parallel, pharmacological treatment with an atypical antipsychotic might be necessary for a short-term period after the surgery. Due to their rapid dissociation from the D2 receptor, quetiapine and clozapine are the antipsychotics of choice in PD being least likely to induce extrapyramidal symptoms [114]. However, the efficacy of either drug for the specific treatment of post-DBS neuropsychiatric symptoms has not been examined.

Increasing weight and obesity after DBS in PD has been showed in long term follow up assessment [115]. This potential SE should encourage clinicians to provide diet management with a physical training schedule appropriate for patients.

Long-term outcome

The long-term motor benefits of STN DBS are maintained 10 years and beyond, although the magnitude of improvement tends to decline over time [116]. Functional scores in on-medication state worsen more quickly than those

recorded in off periods consistent with the degeneration of non-dopaminergic pathways. Dyskinesia, motor fluctuations and activities of daily living in off periods remain improved at 5 years [116].

However, there is a progressive deterioration in speech intelligibility, axial motor symptoms and cognition [26, 117, 118]. These are mainly attributed to progress of the disease with appearance of non-dopaminergic features, while DBS still provides good control for other motor symptoms. Furthermore, by allowing reduction in dopamine replacement therapy dosage, DBS reduces medication induced side-effects.

Axial symptoms and gait decline after DBS are challenging to treat. Testing whether there was a relationship between gait performance and STN-DBS frequency in chronically stimulated patients with PD revealed that optimal frequency varied between patients (between 60 and 140Hz). Moreover, contact site in the right STN and severity of axial symptoms were independent predictors of optimal frequency ($P = 0.009$) with lower frequencies associated with more dorsal contacts and worse axial symptoms [119].

5. Future directions in stimulation technology

There is ongoing interest in an experimental DBS technology known as *adaptive DBS* (aDBS). the system is programmed to stimulate only when necessary and not continuously. aDBS works by being subject to feedback control and adjustments are automatized (Fig.3) [120]. The application of high frequency aDBS might be managed in two different ways: a binary approach with effective stimulation

either on or off and a scalar approach with the stimulation voltage being varied up to and including therapeutic values [120]. This alternative approach to stimulation is linked to the pathological beta synchronised oscillatory activity (13-35 Hz), which is a well-recognised electrophysiological biomarker in Parkinson's Disease [121]. This approach is a phase-dependent modulation based on closed-loop paradigms, which allows to optimize the stimulation protocols for perturbation of pathological oscillatory activity. In this regard, spiking activity of motor cortex neurons and beta activity of local field potentials in the subthalamic nucleus have both been used independently of each other as neuronal signals to trigger deep brain stimulation for alleviating motor symptoms [122]. Recently, Swann et al. tested an innovative aDBS algorithm using a cortical narrowband gamma (60-90 Hz) oscillation related to dyskinesia to decrease stimulation voltage when gamma oscillatory activity is high (indicating dyskinesia) and increase stimulation voltage when it is low [123]. This study showed promising results with the double benefit of a significant saving of energy without worsening clinical symptoms [124]

STN-DBS for PD is likely to work by modulating a wide cortico-subcortical network with the STN at its centre. Advancements in neuroimaging techniques have been instrumental in defining these structures in order to refine the therapy to optimise efficacy and minimise side effects [59, 125].

Current research in DBS is particularly focused on identifying the pattern of cortical connectivity that predicts the maximum response to treatment [59]. STN-DBS is proposed to work by interrupting synchronised oscillations between STN

and the cortex through modulating the hyper-direct pathways [126, 127]. Akram et al. explored the cortical connectivity or "fingerprint" of stimulation volumes through these hyperdirect pathways [59]. Specifically, by using probabilistic tractography from modelled volume of tissue activated (VTA) of all DBS contacts to predefined cortical areas excluding tracts passing through the thalamus and striatum and only including tracts passing through the internal capsule (hyperdirect pathway). This methodological approach led to the development of a DBS-cortical connectivity matrix using the output from the previous step, to test the predictive significance of cortical connectivity (Fig.4) [59]. Consequently, studies on DBS-connectivity represent the future innovative DBS approach to identify the most effective target for different motor symptoms. Indeed, DBS-cortical connectivity along the hyperdirect pathways to M1 is predictive of maximum improvement in tremor, to SMA was predictive of maximum improvement in bradykinesia and to both SMA and PFC was predictive of maximum improvement in rigidity [59]. Mahlknecht et al. used probabilistic tractography to demonstrate that direct pyramidal tract activation might commonly occur at stimulation thresholds used in clinical practice, potentially contributing to emergence of long-term side-effects such as speech disturbances with chronic stimulation [128].

In summary, the use of advanced MRI diffusion/connectivity approaches have identified functional subregions of the STN. Although, the distance between these sweet spots is beyond the resolution of current surgical targeting strategies, other approaches, such as dDBS, combined with MR connectivity, may help to optimise DBS programming.

6. Conclusion

Subthalamic nucleus deep brain stimulation is a symptomatic treatment. It does not halt disease progression but it aims to reduce the motor disabling symptoms of tremor, bradykinesia and rigidity. Unfortunately, cognitive decline as well as dopa refractory axial symptoms, e.g. freezing of gait and balance impairment, are not improved by this surgical procedure. However, Karachi et al have recently demonstrated that freezing of gait severity post-surgery is related to preoperative severity whatever its dopa-sensitivity; and falls are related to lower postoperative cognitive performance and atrophy of cortico-subcortical brain areas [129].
Today, STN-DBS remains the primary target used in PD due to two main reasons: the effectiveness in ameliorating some important PD symptoms and the ability to reduce the drug load.

There remain several challenges in the treatment of PD: the lack of interventions to halt disease progression; the lack of effective treatments for dopa refractory axial symptoms, speech, gait, balance and cognitive decline. However, despite these challenges, the dramatic improvement brought on by DBS remains beyond doubt, allowing patients to enjoy an extended period of good quality of life.

7. Expert Opinion Section

Over the last decades, extensive basic and clinical knowledge has been acquired on the use of deep brain stimulation (DBS) of the sensorimotor dorsolateral region of the subthalamic nucleus (STN) for Parkinson's disease (PD). It remains the primary target used in this neurodegenerative condition due to the effectiveness in improving motor signs. STN-DBS is a symptomatic treatment. Indeed, there are no proofs of a disease modifying effect of STN DBS in humans.

Unfortunately, cognitive decline as well as dopa refractory axial symptoms (e.g. freezing of gait and balance impairment), are not improved by this surgical procedure. This is a significant aspect that needs to be taken into account during the process of patients' selection. STN DBS can improve motor function in PD for over 10 years.

This treatment is associated to some complications which are divided in two groups: surgery-related complications (i.e. infections, bleeding)and stimulation-related side effects (i.e. dysarthria, dyskinesias, depression, and hypomania).

A key factor to minimize DBS-induced side effects is to avoid stimulating structures and brain regions involved in these adverse events. A major advance toward this objective is the use of directional leads, which may deviate and steer current away from these structures.

There is an ongoing research activity on developing a DBS devices programmed to stimulate only when necessary and not continuously labelled "adaptative DBS". These systems should capable of modulating stimulation in response to sensor feedback. The aim underlying this research is overcoming important issues such as the delicate balance between beneficial and adverse effects and limited battery longevity that are currently associated with DBS treatment.

Several DBS settings have been developed over the years. Short pulse width stimulation has showed specific efficacy on speech. Low frequency stimulation is another emerging setting to improve balance and gait difficulties.

Debate persists with regards to the ideal timing of surgery during the course of PD. Indeed, for some patients, the improvement of motor complications after STN-DBS may come too late in disease evolution, and earlier intervention with neurostimulation might provide improved motor benefits before the disability provoked by other symptoms has set in.

Multicenter trials reported outcomes of STN implantation about 11-13 years from the onset of the disease. However, other researchers suggested performing surgery seven years after the disease onset, just when complications start to appear. However, STN DBS now is U.S. Food and Drug Administration approved for use as early as 4 years after diagnosis and may be superior to medical therapy at that time.

Of note, dyskinesia and motor fluctuations often remain improved, whereas improvements in axial symptoms and quality of life in the first few years tend to decline over time. Age, severity of PD and the position of electrodes are important predictors of long-term improvement.

STN-DBS for PD is likely to work by modulating a wide cortico-subcortical network with the STN at its centre. The mechanism is related to the modulation of firing patterns within the hyperdirect projections from motor cortical areas, as well as within the afferent and efferent fibers to the motor STN. Previous studies highlighted the role of the intraoperative recording to reach a more accurate localization of the upper part of the STN recording area, which is the target area associated with a significant clinical effectiveness in PD. However, aadvancements

in neuroimaging techniques have been instrumental in defining these structures in order to refine the therapy to optimise efficacy and minimise side effects. However, treatments that may slow or reverse disease progression should be analyzed more specifically in future proposals.

FIGURES LEGEND

Figure 1. The STN is the key target of the surgical treatment of PD. It is functionally divided in three parts: the dorsal-lateral aspects of the rostrocaudal third of the nucleus are involved in motor control; the ventral-lateral-rostral portions of the nucleus are comprised in the associative circuits; in the mediorostral portions of the nucleus lies the limbic STN.

Figure 2. Concept of directional DBS. If the spot evoking the best therapeutic effect ("sweet"spot, green) lies equidistant to, but in a different direction from the DBS electrode than the spot causing limiting adverse effects ("sour" spot, red), a current flow from a cylindric contact strong enough to cover the "sweet" spot will also cause side effects by current spread to the "sour" spot (upper row). Instead of using all 3 segmented contacts of a directional electrode in the same location, one can steer the current flow away from the "sour" spot by activating only 1 or 2 of the segmented contacts which are

oriented towards the “sweet” spot (From: Steigerwald F, Matthies C, Volkmann J. Neurotherapeutics. 2019; 16:100-104. doi: 10.1007/s13311-018-0667-7).

Figure 3. Example of bilateral adaptive DBS (aDBS) based on LFP beta oscillation power in the STN of both sides. A. LFP's are recorded from the non-stimulating DBS electrode contacts resulting in a left (blue) and right (red) LFP signal. B. After filtering around a patient specific beta peak, in this case 20 ± 3 Hz, its amplitude can be calculated real-time (lower two traces). When beta power exceeds a threshold, stimulation is delivered (upper two traces). C. In this example, high frequency (130 Hz) stimulation is provided with gradually increasing and decreasing voltage to limit stimulation induced paraesthesiae. The stimulation across the two sides is discontinuous and independent (From: Beudel M & Brown P. Parkinsonism Relat Disord. 2016; Suppl 1: S123-6. doi: 10.1016/j.parkreldis.2015.09.028).

Figure 4. STN and VTA modelling, co-registration and analysis pathways. The graph on the left shows examples of STN, DBS lead and VTA modelling in SureTune package. Transformation from native space to MNI space is shown for STN and VTA models. Tractography to M1 is shown in red, to SMA in blue and to PFC in green. The graph on the right shows group average STN in green and total VTA area in red-yellow (IC: internal capsule; PFC: prefrontal cortex; SMA: supplementary motor area; M1: primary motor area; VTA: volume of tissue activated; from Akram H. et al. Neuroimage. 2017; 158:332-345. doi: 10.1016/j.neuroimage.2017.07.012).

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