Chapter

Deep Brain Stimulation in Non-motor Symptoms of Neurodegenerative Diseases

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Abstract

Deep brain stimulation (DBS) is a functional neuromodulatory technique that involves the use of a neurostimulator to deliver electrical impulses to the brain. It primarily alleviates the motor symptoms in neurodegenerative diseases; however, it has been found beneficial in a multitude of neurological and psychiatric diseases, such as dystonia, essential tremor, Tourette syndrome, intractable pain, epilepsy, treatment-resistant depression, and obsessive-compulsive disorder. Nonmotor symptoms, such as neurobehavioral disorders, autonomic dysfunction, sleep dysfunction, and somatosensory dysfunction, play an important role in neurodegenerative diseases and have a significant impact on the quality of life. The effects of deep brain stimulation on these symptoms are not yet apparent, although early results are promising and warrant future investigations. The main problem in interpretation is the lack of studies in this field, as most have methodological issues or small sample sizes, which limit the strength of the evidence. However, it is clear that DBS has a promising future in the treatment of neurodegenerative diseases in general and will have a vital role in personalized medicine as functional neuroimaging and our understanding of brain physiology improve.

Keywords: deep brain stimulation, nonmotor symptoms, neurodegenerative diseases, neuromodulation, neurostimulation

1. Introduction

Deep brain stimulation (DBS) is a functional neuromodulatory technique that involves the use of a neurostimulator to deliver electrical impulses to the brain [1]. It has been used for several decades, primarily in advanced Parkinson's disease (PD), to alleviate the motor symptoms of the disease [2]. The exact mechanisms of therapeutic efficacy are not yet precisely defined; however, DBS is beneficial in a multitude of neurological and psychiatric diseases, such as dystonia, essential tremor, Tourette syndrome, intractable pain, epilepsy, treatment-resistant depression, and obsessive-compulsive disorder [3]. It is generally used to target specific locations in the brain that will be discussed later in the chapter. Despite this, the effects of DBS can be considered as systemic, as it influences neuronal pathways in both an upstream and a downstream manner. In that sense, it can affect a plethora of symptoms, including nonmotor symptoms in neurodegenerative diseases [4]. It is

becoming more apparent that neurostimulations will have an even more critical role in the future as our understanding of brain physiology and pathways improves with novel imaging techniques. This chapter includes the basics of how deep brain stimulation works, what are the nonmotor symptoms in neurodegenerative diseases, and what is the current evidence on the effects of DBS on nonmotor symptoms.

2. Deep brain stimulation

2.1 How does deep brain stimulation work?

The system for DBS consists of three key components: an electrode that is placed in specific cerebral structures, an implantable pulse generator (IPG), and an extension that connects the two. Even though the exact mechanism is not yet known, the current hypothesis is that DBS works via excitation and inhibition of neurons and axons that are in proximity of the placed electrode [5]. The desired effect is achieved by changing the frequency of stimulations, as low-frequency stimulations most often excite nearby neurons [1], while high-frequency stimulations reduce local neuronal activity. Details of the implantation procedure are beyond the scope of this chapter, although it is useful to know that it is implanted stereotactically. In most cases, the stimulation is bilateral, although it is possible to stimulate unilaterally as well. The targets for stimulation are deep brain structures, as well as deep white matter tracts. A key benefit of DBS is the ability to adjust stimulations wirelessly via handheld devices to improve symptom relief and reduce possible side effects [5].

Currently used method for DBS function is based on an open-loop system, which enables trained physicians to adjust various settings depending on the patient's condition [6]. This works adequately for most patients; however, changes in patient states bring challenges as modifying stimulations require a physician visit. A possible solution to this problem is the closed-loop or adaptive DBS that will enable real-time adjustment of the neurostimulations due to the continuous feedback signals. This will most likely be achieved with the help of various wearable sensors, neurochemical sensors, and electrophysiological recordings, which would all be interpreted with the Internet or mobile applications that will enable constant insight into the state of each patient [7]. Unfortunately, numerous challenges till the clinical application remain, but the prospects are bright, and hopefully such systems will be perfected in the near future.

The main and the most studied effect of DBS occurs via electrical potential generated by the neurostimulations. There was a prevailing thought that the effects of DBS are dominantly local in the areas that the electrodes were placed [8]. However, recent advances indicate that neuromodulation with DBS affects entire pathways, both afferently and efferently, and thus can influence more than just the stimulated structures [9]. Both animal and human studies in vivo show this, mainly through increased neurotransmitter release from axon functional magnetic resonance imaging (fMRI) studies [10]. In a practical sense, this means that targeting motor dysfunction, for example, in Parkinson's disease, has an added effect of changing the function of other neuronal pathways and not only the motoric dopamine pathways that are primarily disrupted in the disease. Therefore, choosing the right target is essential for adequate treatment response.

2.2 Targets for stimulation

The two most common targets for DBS are the globus pallidus internus (GPi) and the subthalamic nucleus (STN), which are a part of the

cortico-basal-ganglia-thalamocortical circuit loop. They are most commonly used in Parkinson's disease for control of dopaminergic symptoms such as tremor, rigidity, and bradykinesia [5], although beneficial effects of GPi stimulation were found in dystonias as well [11]. Another possible target in PD is the ventral intermediate nucleus (VIM), an area of the thalamus, that if stimulated improves tremor-dominant variants of the disease and can also be used in patients suffering from essential tremor [12]. Furthermore, stimulating the anterior nucleus can help in medically refractory epilepsy, while benefits of thalamic stimulation were also seen in Tourette's syndrome, neuropathic pain, and traumatic brain injury as well.

Advancements in preclinical and neuroimaging research studies and neurosurgical experiences led to a discovery of several targets that could prove beneficial to numerous diseases. DBS in the ventral capsule, the ventral striatum, or nucleus accumbens (NA) has been shown to improve symptoms of obsessive-compulsive disorder [13], while NA stimulation has been shown to reduce the severity of obesity and anorexia [14]. Treating treatment-resistant depression is also possible with DBS; however it requires an individualized approach due to numerous possible targets [15]. Moreover, benefits of DBS are observed in dementia as well, with the possible targets being the fornix and the nucleus basalis of Meynert (NBM) in Alzheimer's disease [16]. In general, the most reliable evidence for DBS use comes from movement disorders, while other indications still require randomized, well-designed studies to prove efficacy. Different possible targets and adjustable nature of DBS put it at the forefront of personalized medicine in the future, especially as functional neuroimaging improves, as stimulations will be catered to each patient individually.

2.3 The mechanism of DBS

The neuromodulatory effects of DBS occur in various stages, while most of the focus in the early days of DBS was on the immediate effects. In time, it is becoming more apparent that short-term and long-term effects of DBS are just as significant, as those are opening new frontiers in therapy. All of the cells in the body function through changes in electric potential, but our neurons are special in the sense that they comprise a series of networks where this potential can be passed on to other neurons or cells [17]. This physiological basis creates the stage for neuromodulation with DBS, as different impulse settings create different effects on the cell bodies and axons of neurons. Even a single DBS pulse can influence neuronal activities for several milliseconds, while an increased frequency can prevent the cells from resetting to their base values [18]. In neurons, these pulses dissociate cell bodies of neurons from their axons and essentially "hijack" the signaling in both afferent and efferent directions [19]. Generally, the pulses inhibit cell body activity while creating action potentials in the axons [20]. The pulses also act on astrocytes and microglia in the area of stimulation, causing a change in glial activity and complete changes in ion concentrations such as potassium and calcium, which in turn influences the changes in action potentials of neurons [21]. Immediate effects of DBS are a consequence of the function of individual neurons that are stimulated in the vicinity of the placed electrode and vary greatly depending on the selected target.

In the neurochemical sense, the milieu of brain tissue is significantly changing as several changes occur in the concentration of neurotransmitters and neurotrophic factors. The values of crucial neurotransmitters (dopamine, noradrenaline, serotonin, and gamma-aminobutyric acid) are altered depending on the location of the modulation, which makes target selection key, as increasing serotonin [22] or noradrenaline by stimulating NA, for example, affects mood and can have an antidepressant effect [23]. However, even the presence of the electrode can significantly

impact the neurochemical properties surrounding it. It is a foreign object that necessitates reaction from microglia and astrocytes that create an immediate inflammation and edema that subsides over the long term with the creation of a fibrotic membrane by astrocytes [24, 25].

Most programs for DBS are intended for long-term function, and all these changes that happen immediately or short term after initiating the therapy have a profound effect on the structure and function over extended periods. The physiological basis for this is a result of our brains' adaptive capacity, which we call synaptic and neural plasticity [26]. Constant stimulation on the same areas and the changes mentioned above in neuronal activity and extracellular milieu lead to changes in synaptic structure and density, neurogenesis, and neuroprotection, which in turn change the properties of neural networks [27]. This is most likely mediated by neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF), similarly as in the physiological central nervous system conditions [28]. The changes in neuroplasticity and neuronal organization lead to functional improvements of various symptoms over time; this is especially pronounced in alleviating neuropathic pain, axial symptoms, obsessive-compulsive symptomatology, and several nonmotor symptoms as well [5].

Aside from the neurochemical changes, there are effects of DBS on brain oscillations present in numerous neuropsychiatric diseases. Current data points out that synchronous brain activity can be amplified in Parkinson's disease (beta oscillations in the basal ganglia [29]), Alzheimer's disease (gamma oscillations in the hippocampus [30]), and treatment-resistant depression (gamma and theta oscillations in the subcallosal cingulate gyrus [31]). Early data indicates that DBS can affect these oscillations and provide a balance to brain activity, reducing the amplification that is pathologically found [30–32]. Further research is required to detect various oscillation patterns in diseases to develop therapeutic goals for treatment, not only with DBS but with other neurostimulation techniques as well.

3. Nonmotor symptoms in neurodegenerative diseases

Nonmotor symptoms in neurodegenerative diseases are disturbances in neurobehavior, autonomic function, and sleep and sensory function that are not a consequence of motor symptoms [33]. Most of the studies are focused on nonmotor symptoms in Parkinson's disease, but they can be present in most other central nervous system disorders. The pathophysiology and incidence differ from one disease to another, although the spectrum of symptoms remains the same. In many cases, the first signs of neurodegeneration will be nonmotor disturbances as they often precede other symptoms [34]. It is important to point out that these symptoms are present as primary diseases as well, usually in the psychiatric spectrum of diseases. However, in the context of validated and approved DBS stimulation in the classical targets of stimulation, they can be considered as nonmotor symptoms in extrapyramidal diseases. It is clear that as the field matures, new nomenclature will be needed to accurately assess the effect of DBS on various neuropsychiatric symptoms, especially if those symptoms are primary targets (e.g., treatment-resistant depression or obsessive-compulsive disorder). We can divide the nonmotor symptoms into several key categories: neuropsychiatric symptoms, sleep disorders, autonomic symptoms, gastrointestinal symptoms, and sensory symptoms [33]. Nonmotor symptoms present a vital field of study as they can have a significant impact on the quality of life and are often overlooked in clinical practice.

Neurobehavioral symptoms frequently present in neurodegenerative disorders are excessive fatigue, depression, anxiety, apathy, and cognitive dysfunction.

Depression and anxiety both commonly occur at the same time in patients and often precede diagnosis with mild symptoms at the beginning, although more severe forms occur as the disease progresses [35]. On the other hand, apathy can be present as a separate symptom, mainly if there is a prominent degeneration of dopamine pathways in the limbic system [36]. Finally, cognitive dysfunction is considered as an inevitable consequence of long-term neurodegeneration. The extent of cognitive difficulties varies from mild to severe depending on the disease, with different cognitive domains affected as well [37].

Sleep dysfunction and sleep-related problems are common nonmotor symptoms in neurodegenerative diseases. The pathophysiological basis is likely the variation in physiological dopamine function, as changes in dopamine are known to impact wakefulness [38]. The physiological importance of sleep comes from enabling the regeneration of brain tissue and reestablishing homeostatic conditions. Therefore, sleep disorders can increase the severity of disease progression as a vicious circle forms that disables proper neural regeneration [39]. Sleep-onset insomnia is a frequent occurrence in neurodegenerative diseases, as the progression of the disease and chronic loss of neuronal function lead to neurotransmitter disbalance that in turn causes a sleep-wake disruption. This presents as a dysfunction of the circadian rhythm in Alzheimer's disease and Huntington's disease, while in Parkinson's disease the difficulties are mostly sleeping through the night and initiation of rapid eye movement phase during sleep [40]. Sleep quality can also be affected, as difficulties in nighttime mobility and excessive fragmentation of sleep are common, as well as problems in rapid eye movement (REM) phases of sleep [41]. Furthermore, difficulties with restless legs syndrome (RLS) and involuntary limb movements create sleep difficulties, although these symptoms are more frequently found in diseases that feature dopamine dysfunction and generally have a response to dopamine therapy [42].

Autonomic dysfunction develops as a consequence of progressive degeneration in neural pathways, mostly in diseases characterized by the accumulation of Lewy bodies or α-synuclein, and is much less pronounced in diseases such as Alzheimer's or frontotemporal lobar degeneration [43]. Three main symptoms of autonomic dysfunction are issues with bladder control, nocturia, and sexual dysfunction, all of which are linked to the dysfunction in the dopamine pathways and can somewhat improve with dopaminergic therapy [44]. Moreover, gastrointestinal symptoms fall in this category as well and are an interesting subset of symptoms as the dysfunction, which often presents as constipation or anorectal dysfunction, could be a consequence of both central and enteric nervous system degeneration [45]. Interestingly, these symptoms can be present in prodromal stages of many neurodegenerative diseases, which have made the gut-brain axis an attractive research target in recent times [46].

Finally, sensory symptoms have a significant role in the clinical course of neurodegenerative diseases, especially in the prodromal stages. Hyposmia, a reduced capacity for the sense of smell, is often seen in the early stages of Parkinson's and Alzheimer's disease [47, 48]. Recent neuroimaging studies reveal a decreased volume in the olfactory regions of the brain, while neuropathological studies found a high accumulation of α-synuclein, αβ amyloid, and Tau proteins in the olfactory bulb during the early stages of neurodegenerative diseases [47, 48]. Something similar can be seen in the optical pathways as well, as there is an increase of visual hallucinations, reduced color recognition, visual acuity problems, and double vision as neurodegeneration progresses [49]. Pain syndromes are frequent as well and are more likely of neuropathic origin. Unfortunately, the mechanisms for pain in neurodegeneration are varied, and managing pain requires an individualized approach, as specific types of pain require different medications. High prevalence

of pain impacts the quality of life, as do all nonmotor symptoms in general, which makes proper measurement a necessity in the current clinical evaluation of neurodegenerative diseases.

3.1 How do we measure nonmotor symptoms?

Comprehensive measurements of all the symptoms mentioned present a challenge in everyday clinical practice. Naturally, objectifying the symptoms is crucial not only in the initial evaluation but also in the evaluation of the therapeutic effects as well. There is a wide variety of instruments available for a detailed assessment of each symptom, but this has proven to be inadequate in everyday use [50]. Best suited scales for rapid and accurate identification of nonmotor symptoms are multidomain instruments that cover most of the nonmotor symptomatology. Two scales were developed for use in Parkinson's disease; however, they are suitable for use in other neurodegenerative diseases as a quick screening of the prevalence of nonmotor symptoms.

First is the nonmotor symptom questionnaire (NMSQuest), a scale developed to provide a useful screening tool, as it contains 30 items that have yes and no questions covering various domains of nonmotor symptoms [51]. It is designed to be completed by patients themselves, and there is no grading of the severity of symptoms, just whether they exist or not. Nonetheless, it has proven to be an effective screening tool in further validation studies that can afterward lead to a more focused examination of reported symptoms [52]. On the other hand, the nonmotor symptom scale (NMSS) is developed to be rated by clinicians, and it incorporates the severity and impact of the symptoms on the daily life of the patients [53]. Similar to the NMSQuest, it has 30 items, spread across 9 domains, but the overlap is in 23 of the 30 items; therefore using both of them has clinical sense. It is crucial to point out that these scales have inevitable shortcomings as more nonmotor symptoms come into focus over time. Therefore, a modified NMSS is currently in active development that should improve its use in all neurodegenerative diseases. Furthermore, it is required to use the scales focused on each domain to precisely measure the severity of each symptom on its own, as only focused scales go into enough details to have a complete overview of the effect that each symptom has on the quality of life. In any case, as the focus of symptomatology studies turn toward nonmotor symptoms, it is to be expected that more comprehensive scales will be developed that are adequate for use in clinical and clinical trial settings.

4. Effects of DBS on nonmotor symptoms

The focus of clinical practice and research in DBS is on the effects it has for motor symptoms in advanced Parkinson's disease. As previously said, the nonmotor symptoms in neurodegenerative diseases are only recently coming into focus, as is the effect of DBS on them. Most robust studies come from the research done in Parkinson's disease and from patients whose targets for neuromodulation are STN and GPi; however, research from other diseases and stimulation targets will also be assessed in the coming paragraphs [54].

4.1 Neurobehavioral symptoms

Effects of DBS on neurobehavioral outcomes are a complex subject as there are possible advantages and disadvantages, depending on the initial patient selection and the deep brain target of neuromodulation. Cognitive dysfunction, as a frequent

symptom in most neurodegenerative diseases, can have varying severity depending on the disease and between each patient individually [55]. In classical DBS targets, the STN and GPi, there are mixed results regarding the effect on cognition. Generally, stimulation of these areas will not improve cognitive function, and there is even a mild risk of cognitive decline, which has been found minor in more extensive trials and not clinically relevant [4]. There is a caveat to this, as DBS in patients with pronounced cognitive dysfunction tends to increase the severity of symptoms more than in those who do not have significant cognitive impairment [56]. The same can be observed in patients who had problems with depression or anxiety in the past before being diagnosed with a neurodegenerative condition [57]. STN stimulations, in particular, led to an increase in apathy and hallucinations, while there was a minor improvement in impulsive behavior (impulse buying, gambling, excessive sexual behavior) compared to the control groups [58–60]. Benefits of DBS were found in symptoms of depression as well but mostly in milder cases without pronounced symptoms [61].

On the other hand, phase I clinical studies in Alzheimer's disease with DBS targeting the fornix [62] or the NBM [63] show encouraging results on cognitive impairment in the early stages of the disease while being safe and well tolerated. There is currently a lack of studies in this field, but more are being conducted at the time of writing. Furthermore, early research shows that patients who suffer from depression could benefit from DBS, especially severe types that are resistant to therapy. Similar to Alzheimer's disease, there are promising early results, but proper targets and correct settings for stimulations are not yet clear, and larger, controlled studies are needed [15]. To summarize, the effects of DBS on neurobehavioral symptoms are significantly impacted by the target locations for stimulation, as both beneficial and harmful effects are present. Therefore, appropriate patient selection is critical, as the impact it can have on the quality of life depends much on an individual basis.

4.2 Autonomic dysfunction

Dysfunctions in the autonomous nervous system are the more frequent nonmotor symptoms in neurodegenerative diseases. Generally, there is a lack of extensive studies featuring a high number of patients, and studying the effects of DBS on autonomic dysfunction is usually not the main focus. Dysautonomia is more frequently found in movement disorders than other diseases in the neurodegeneration disease spectrum [43]. Early studies that focus on STN and GPi stimulation reveal that DBS has a beneficial effect on urinary symptoms, especially in reducing nocturia, frequency, and urgency [64]. The most likely mechanism, revealed by urodynamic evaluation, is through increased bladder capacity and reflex volume, and the effect seems to persist over time after initial surgery [65, 66]. Similarly, neuromodulation with DBS appears to be beneficial in gastrointestinal function as well, especially in the early phases after surgery. Significant improvement was found in constipation, salivation, and gastric emptying, as the contractions of the whole gastrointestinal tract improved [67–69]. However, studies show that there is no effect on dysphagia, possibly due to a different mechanism that causes it compared to problems with emptying the gastrointestinal tract [70]. Sexual dysfunction is not significantly impacted by DBS, with most patients reporting a slight improvement, especially in younger patients [71].

4.3 Sleep

Sleep disorders have a significant impact on the quality of life, as they lead to fatigue and daytime sleepiness. Sleep quality is often disrupted in

neurodegenerative diseases and has been a subject of study after initiating DBS. Polysomnographic studies show that DBS in STN leads to an objective improvement sleep quality [72], which is seen in subjective-based studies as well [73, 74]. Improvement in sleep and pain was also observed in dystonia patients who were treated with STN DBS [75]. Interestingly, daytime sleepiness does not seem to be affected by DBS [76]. A possible reason for this could be a lacking effect on REM sleep, as DBS patients have an increased risk of developing REM sleep behavioral disorder in the case of STN stimulations [77]. The effect on restless legs syndrome appears to be positive in moderate to severe cases, but new cases of the syndrome can appear after initiating DBS [78, 79]. Overall, it seems that constant stimulations improve sleep quality over the long term by influencing nighttime mobility and sleep maintenance.

4.4 Sensory functions

Somatosensory dysfunction is often reported in neurodegenerative diseases and presents a significant burden in everyday life of the patients. Problems with the sense of smell and taste arise in the early phases of neurodegeneration. Subjective improvement in both smell and taste was reported in a recent prospective study [64]. It appears that the improvement in smell stems from improved odor information processing, as only odor discrimination and identification were improved, while the detection was not affected by DBS [80, 81]. There are improvements in visual function as well, mostly due to the effect on ocular smooth motor function and improving problems with saccade movement [82]; however, the amount of evidence in this field is severely limited and still inconclusive.

Fortunately, the DBS effects on pain are more apparent. Most studies suggest a beneficial effect of DBS on pain [83], especially in patients who suffer from pain in off periods [84]. There are varied types of pain that can be present in patients, but it appears that STN DBS has a substantial effect in curbing dystonic and musculoskeletal pain, while central and neuropathic pain are less affected [85]. However, severe neuropathic pain can be treated with DBS if the target for stimulations is the periaqueductal gray matter, possibility due to an increased release of endogenous opioids [86, 87]. There are promising results in chronic pain as well, with the anterior cingulate cortex showing potential, though it is too early to tell due to a lack of studies in this field [88]. This finding underlines the importance of selecting the right target for neuromodulation depending on the wanted results, which holds promise for the future of DBS.

5. Conclusion

Nonmotor symptoms represent a challenge in the treatment of neurodegenerative diseases and have a significant influence on the quality of life. DBS shows promise in alleviating these symptoms, depending significantly on the target of stimulation. The main problem is the lack of studies in this field, as most have methodological issues or small sample sizes, which limit the strength of the evidence. Likewise, only a handful of studies have nonmotor symptoms and primary end points. The number of approved indications for DBS is still small and mostly focused on extrapyramidal symptoms, and therefore, most studies are focused on the effects of DBS in STN or GPi. However, it is clear that DBS has a promising future in the treatment of neurodegenerative diseases in general and will have an important role in personalized medicine as functional neuroimaging and our understanding of brain physiology improves.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

DBS	deep brain stimulation
PD	Parkinson's disease
IPG	implantable pulse generator
fMRI	functional magnetic resonance imaging
GPi	globus pallidus internus
STN	subthalamic nucleus
VIM	ventral intermediate nucleus
NA	nucleus accumbens
NBM	nucleus basalis of Meynert
BDNF	brain-derived neurotrophic factor
REM	rapid eye movement
RLS	restless legs syndrome
NMSQuest	nonmotor symptom questionnaire
NMSS	nonmotor symptom scale

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