INTRODUCTION

Deep brain stimulation (DBS) refers to direct electric stimulation of neuroanatomical structures, usually lying in the depth of the brain. It is typically used to treat movement disorders, targeting areas involved in motor control, although it has also been used to modulate pain processing, cognition, mood, the reward network, arousal system, or to modulate

Abstract

Deep brain stimulation (DBS) has been most widely used in the management of movement disorders, but more recently to treat a growing number of neurological and psychiatric conditions. It is known to have a variety of effects upon oculomotor function, depending not only on the location of the stimulation, but also on the underlying pathology being treated. Understanding how DBS affects eye movements is important, given the widespread nature of eye movement control and its inevitable overlap with many of the networks targeted by the stimulation. Moreover, it can also offer additional mechanistic insights into neural circuits involved in complex eye movement control. Here, we discuss the application of DBS treatment across different diseases and explore how distinct stimulation locations interfere with known eye movement circuits and the ensuing oculomotor and visual effects it can produce. We also discuss more experimental DBS targets and its effects on ocular motility, as well as discussing unilateral versus bilateral deep brain stimulation and possible hemispheric asymmetry in relation to eye movement control. Contradictory findings across studies reporting DBS effects on eye movements likely relate to differences in the methodological approaches used, levodopa medication status, as well as possible variability in DBS electrode placement. We highlight the need for further research with less common DBS targets on the possible effects upon eye movements.

KEYWORDS
basal ganglia, deep brain stimulation, eye movements, neuroophthalmology, saccades
epileptic seizure spread, albeit more experimentally. DBS can be applied by using microelectrodes for recording single-unit activity within a given neuron (Basso, Pokorny,Pokorny, & Liu, 2005; Leigh & Kennard, 2004; Shaikh & Ghasia, 2019), or activity can be recorded within a population of neurons (Telkes, Jimenez-Shahed, Jimenez-Shahed,Viswanathan, Abosch, & Ince, 2016). In studies using single-unit recordings, a high percentage (around 20%) of all neurons in the targeted thalamic and basal ganglia nuclei (central part of subthalamic nucleus [STN] near the anterior part of the red nucleus, STN thalamic border or the ventral thalamus [Fawcett et al., 2007], and the posteroverentralateral portion of the globus pallidus internus [GPi] were found to be involved in eye movement control [Sieger et al., 2013]). Understanding of how DBS affects eye movements is important, given the widespread nature of eye movement control and its inevitable overlap with many of the networks targeted by DBS. Moreover, given how well-demarcated eye movement pathways are in animals and humans, assessing how DBS affects eye movements can help us understand the mechanism by which DBS is acting and offer mechanistic insights into how a disease process and its modulation with DBS alters neural functioning.

The goal of this article is to explore the broad relationship between DBS and eye movements. We will discuss the application of DBS treatment across different diseases and explore how distinct DBS locations interfere with known eye movement circuits and the ensuing visual side effects it can produce. While we will focus on the more common DBS applications used in clinical practice, we will also discuss differences between unilateral and bilateral DBS stimulation and the effect of more experimental DBS locations upon eye movements.

1.1 Indications for DBS and locations used

Deep brain stimulation is a widely used treatment across the spectrum of neurological and psychiatric diseases (Doshi, 2018; Lozano, Bernal, Bernal, Jara, & Belleville, 2014), although approved indications vary considerably between United States Food and Drug Administration and Conformite Europeenne (Doshi, 2018). While the exact effect of DBS on brain circuits remains unknown, proposed beneficial mechanisms include immediate neuromodulatory effects, synaptic plasticity and long-term neuronal reorganization (Ashkan, Rogers, Rogers, Bergman, & Ughratdar, 2017). Parkinson’s disease (PD) remains the most common indication for DBS implantation (Kocabicak, Temel, Temel, Hollig, Falkenburger, & Tan, 2015), but it is also widely used for dystonia and essential tremor (ET), and experimentally in many other diseases such as pain, Tourette syndrome (TS) and Huntington disease (HD). The most common locations for DBS include STN, GPi and ventromedial nucleus of the thalamus (VIM) (Chudy et al., 2018).

1.2 Pathophysiology of eye movement control

When investigating the influence of DBS on eye movements, it is important to consider preexisting eye movement deficits caused by the underlying condition (Srivastava, Ahmad, Ahmad, Pacia, Hallett, & Lungu, 2018), that in turn requires an understanding of the physiology of eye movement control (Table 1 and 2). Eye movements fall into two broad classes. The vestibulo-ocular reflex (VOR), fixation, smooth pursuit (SP) and optokinetic nystagmus act to stabilize the fovea in the face of motion of the head or objects of interest in the external world. Saccades, on the other hand, quickly bring the fovea upon an object or target of interest (Figure 1). The first group are largely automatic or reflexive responses while saccades are an active and inherent component of perception, action and cognition.

1.2.1 Saccades

Saccadic function can be further sub-divided depending on the saccadic stimulus provided, but it is clinically most useful to consider visually guided (reflexive) saccades and internally guided (voluntary) saccades. Some saccadic tasks are laboratory specific, such as antisaccades (looking in the opposite direction to a suddenly appearing target; Figure 1) and allow researchers to add cognitive layers on top of the final oculomotor execution (involving areas such as dorsolateral prefrontal cortex (DLPFC) and parietal eye fields (PEF). The generation of an antisaccade requires suppression of the competing reflexive saccade to the visual target while concurrently planning a saccade in the opposite direction to a calculated, non-visual target location. Memory-guided saccades are a further laboratory saccadic task where a saccade has to match the position of a stimulus that disappears prior to the start of a saccade and again probes higher-order cognitive functions.

Saccadic tasks are controlled by separate but parallel descending pathways, involving the cerebral cortex and basal ganglia (BG) (Hikosaka, Takikawa, Takikawa, & Kawagoe, 2000). The various cortical regions involved in saccade generation (Figure 2), all with reciprocal connections, project caudally primarily to the superior colliculus (SC; Figure 2)) (Terao, Fukuda, Fukuda, Ugawa, & Hikosaka, 2013). Although all saccades share this final common pathway, differing task demands can result in differential recruitment of higher-level control areas. As with voluntary body movements, voluntary saccades seem to be
| Condition | Pro-saccades | Antisaccades | Smooth pursuit | Fixation | Vergence | OKN | Other |
|-----------|-------------|--------------|----------------|----------|----------|-----|-------|
| PD        | Reported deficit | Reported deficit | Reported deficit | Reported deficit | Reported deficit | N   |        |
| ↓ A       | ↓ Inhibition of reflexive prosaccade | ↓ V           | ↓ G            | ↑ SWJ    |          |     |       |
| ↑ L       | ↑ AER       |              |               |          |          |     |       |
| STN DBS   | STN DBS     | STN DBS      | STN DBS        | STN DBS  | STN DBS  | R STN DBS |
| (Dec-Cwiek et al., 2017; Fischer et al., 2016; Goelz et al., 2017; Lohnes & Earhart, 2012; Nilsson et al., 2013; Sauleau et al., 2008; Temel et al., 2010, 2013) | Sauleau et al., 2008; Temel et al., 2010, 2013; Yugeta et al., 2010; Lohnes & Earhart, 2012; Nilsson et al., 2013; Yugeta et al., 2013; Fischer et al., 2016, Dec-Cwiek et al., 2017, Goelz et al., 2017) | STN DBS, (Nilsson et al., 2013) | ↑ G   | STN DBS and GPI DBS (Taverna et al., 2008; Yugeta et al., 2013) | ↑ Stability |
| ↑ A       | ↑ AER       | ↑ AER       | ↑ AER          | ↑ SWJ    |          |     |       |
| ↓ L       | GPI DBS     | VIM DBS      | GPI DBS (Shaikh et al., 2018) | ↓ SWJ    |          |     |       |
| Gpi DBS   | (Antoniades et al., 2015; Fridley et al., 2013) | (Kronenbuerger et al., 2010) | ↑ AER | Hypothetically improved VIM DBS (Kronenbuerger et al., 2010) |          |
| No eff    | VIM DBS     |              | VIM DBS (Kronenbuerger et al., 2010) | ↑ SWJ    |          |     |       |
| VIM DBS   | (Kronenbuerger et al., 2010) | |               | ↑ SWJ    |          |     |       |
| L-DOPA    | L-DOPA      | L-DOPA       | L-DOPA         | L-DOPA   | L-DOPA   | R STN DBS |
| (Hood et al., 2007; Lu et al., 2019; Pinkhardt et al., 2012) | (Hood et al., 2007; Lu et al., 2019; Pinkhardt et al., 2012) | (Pinkhardt et al., 2012) | No effect | (Fujhiwa et al., 2017) | No effect |
| ↓ V       | ↑ Inhibition of reflexive prosaccade | ↑ Inhibition of reflexive prosaccade | | | |
| ↑ L       | ↑ AER       | ↑ AER       | ↑ AER          |          |          |     |       |

↑, increased; ↓, decreased; A, amplitude; AER, antisaccadic error rate; BIL, bilateral; ET, essential tremor; G, gain; HD, Huntington disease; L-latency; N, normal; PD, Parkinson disease; TS, Tourette syndrome; V, velocity.
### Table 2

| Condition | Prosaccades | Antisaccades | Smooth pursuit | Fixation | Vergence | Gaze holding | OKN | VOR | Other |
|-----------|-------------|--------------|----------------|----------|----------|--------------|-----|-----|-------|
| ET     | Reported deficit | — | Reported deficit | N | N | N | N | Reported deficit↓ VOR suppression |
| VIM DBS (Kronenbuerger et al., 2010) | ↓ L | ↓ G | STN and Gpi (Bangash et al., 2019; Kronenbuerger et al., 2010) | ↑ G |
| HD     | Reported deficit | Reported deficit | Reported deficit | Reported deficit | Reported deficit | Reported deficit | N | Distractibility |
| Gpi DBS (Fawcett, Moro, et al., 2005) | ↑ V | ↑ A | ↑ L | ↑ AER |
| TS     | Reported deficit | Reported deficit | Reported deficit | N | N | N | Reported deficit↑ SWJ |
| Gpi DBS (Azimi et al., 2018) | — | — | Gpi DBS (Acknowled et al., 2011) | No effect |
| VIM DBS (Ackermans et al., 2011) | No effect |

↑, increased; ↓, decreased; A, amplitude; AER, antisaccadic error rate; ET, essential tremor; G, gain; HD, Huntington disease; L, latency; N, normal; PD, Parkinson disease; TS, Tourette syndrome; V, velocity.
more dependent on BG than reflexive ones, and are therefore more prone to disruption in BG disorders, although visually guided saccades do not completely bypass BG function and are, to a lesser degree, also affected (Hikosaka et al., 2000; Terao et al., 2013).

In addition, frontal areas project to SC via an indirect BG pathway and also directly to pontine nuclei, especially the pedunculopontine nucleus (PPN), which in turn projects to dorsal vermis and fastigial nucleus in the cerebellum. There are additional minor direct projections from the frontal eye fields (FEF) to the paramedian pontine reticular formation (PPRF). The BG oculomotor pathway is concerned most with eye movements related to reward and initiation of remembered, predictive and self-paced voluntary saccades. The substantia nigra pars reticulata (SNr) is the major output of the basal ganglia for eye movements and controls saccadic eye movement via its inhibitory connection to the SC (Hikosaka et al., 2000; Hikosaka & Wurtz, 1989). Neuronal activity in the SNr appears to be selective for tasks that involve reward and cognition (Handel & Glimcher, 2000; Hikosaka & Wurtz, 1983), including memory-guided saccades (Hikosaka & Wurtz, 1983). The net result of these various connections to and from the SNr is that the indirect pathway is excitatory and the direct pathway inhibitory. The BG pathway is in this way able to regulate voluntary saccades by maintaining, enhancing, or releasing the tonic inhibition of SNr upon the SC. Reflexive saccades rely upon presentation of a visual stimulus and their cortical control relies upon PEF and its subcortical connections from the visual cortex. Of note, projections for voluntary saccades pass through the posterior limb of the internal capsule, whereas projections for reflexive saccades pass through the anterior limb (Terao, Fukuda, Fukuda, & Hikosaka, 2017). Thus, the production (and dysfunction) of saccades is a consequence of the various cortical and subcortical excitatory and inhibitory influences upon the brainstem generating structures.
1.2.2 | Saccadic parameters and the basal ganglia

Saccadic latency can be increased due to disturbed cortical processing of target selection, decision-making, and impaired inhibition. For voluntary saccades DLPF, FEF and PEF are the most important cortical structures, whereas posterior parietal cortex lesions might contribute to alterations in saccadic latency of reflexive saccades (Shires, Joshi, Joshi, & Basso, 2010; Terao et al., 2017). Subcortical projections passing through BG or indeed direct pathways to SC presumably account for latency prolongation, particularly for voluntary saccades. SC is the most important structure in saccadic initiation and higher structures are responsible for cessation of tonic inhibition of SC just before the initiation of a saccade (Terao et al., 2017). Inappropriate SC inhibition is a main cause of increased latency in PD patients, most notably for voluntary rather than reflexive saccades (Terao et al., 2017).

PD patients consistently make more unintended saccades to the visual stimulus (hyper-reflexivity), and correct voluntary saccades occur at longer latencies and with smaller amplitudes (hypometria) than controls (Mosimann et al., 2005). Oculomotor hypometria is present early in the disease, while more cognitively driven impairments such as prolonged latencies and reduced inability to inhibit saccades in antisaccade and delayed-response tasks emerge as the disease progresses (Macaskill et al., 2012; Terao et al., 2011). Saccadic latency and velocities in cognitively intact PD patients, especially for reflexive saccades, have generally been normal, with minor hypometria the most common feature of reflexive saccades (Chan, Armstrong, Armstrong, Pari, & Munoz, 2019). Cortical structures involved in saccadic initiation are located frontally (FEF, SEF—more responsible for voluntary saccades and complex saccadic tasks) and parietally (PEF—more involved in reflexive, visually guided saccades). These project to lower, subcortical structures, where SC is the convergence of all saccadic projections, including direct cortical projection to SCs and indirect projections through BG (involving CN, STN, GPe, Gpi, SNr). BG also send ascending projections through thalamus (via Gpi), back to cortical structures. SNr sends inhibitory signals to SC and produces tonic inhibition of SC, which stops only when the signal for saccadic initiation is sent. SC enables the start of the saccade by its influence on brainstem centres for vertical and horizontal gaze (riMLF and PPRF, respectively), containing burst neurons that send saccadic signal to the nuclei responsible for extracellular muscle contraction. NI are responsible for translation of saccadic velocity command to position command. Blue squares and arrows represent pathways involved in saccadic inhibition, fixation and gaze holding. Inhibition of saccades is a default mode of our brain, achieved through constant high frequency activity of SNr, resulting in SC suppression. Saccadic inhibition is required also during steady fixation, SP, during antisaccades and gaze holding in lateral position at the end of a saccade. Other structures beside SNr are involved in saccadic inhibition, involving direct projections from DLPFC, FEF, and PEF to SC, fixation cells of SC, and omnipause neurons of riMLF and PPRF. Inappropriate saccadic inhibition leads to increased square wave jerks. Gaze holding requires transformation of velocity command to position command (via NI), as well as FLOC, vermis and vestibular nuclei. A leaky NI causes inability to sustain gaze in lateral position. STN DBS influences reflexive visually guided saccades more than voluntary saccades. Yellow star 1 represents theoretical effect on pathway responsible for improvement of cortical control for reflexive, visually guided saccades. Acting directly (yellow star 2) or indirectly (yellow star 3) on SNr-SC loop, STN DBS also decreases inhibition of SC, causing decreased latency. On the other hand, Gpi improves predominantly voluntary saccades, improving top down, cortical control over SC (green star 4). Gpi DBS will likely improve voluntary saccade parameters, mainly antissaccadic error rate, due to its positive effect on the interloop control of higher, fronto-striato-thalamic oculomotor network (green star 5). Green star 6 represents a Gpi DBS potentiation of information flow between cortical and oculomotor BG loop. Star 7 represents a beneficial STB DBS effect with stabilization of SC and yet decreased threshold for saccadic initiation (see “oscillatory model” in the main text). Antisaccadic error rate increases with STN DBS, probably due to interrupted connections between STN and frontal circuits, important for saccadic inhibition. DLPFC—dorsolateral prefrontal cortex; FEF—frontal eye fields; SEF—supplementary eye fields; GPe—globus pallidus externus; Gpi—globus pallidus internus; T—thalamus; CN—caudate nucleus; STN—subthalamic nucleus; SC—superior colliculus; SNr—substantia nigra pars reticulata; DLPN—dorsolateral pontine nucleus; III., IV., VI.—cranial nerves nuclei; riMLF—rostral interstitial nucleus of medial longitudinal fasciculus, a centre for vertical gaze control; PPRF—paramedian pontine reticular formation, centre for horizontal gaze control; NI—neural integrators, including vertical NI (interstitial nucleus of Cajal and horizontal NI (the nucleus prepositus hypoglossi and medial vestibular nuclei). Green arrow—excitatory pathway; Red arrow—inhibitory pathway. Yellow star—STN DBS; Green star—Gpi DBS.
1.2.3 Smooth pursuit

Smooth pursuit eye movements, in concert with fixation, stabilize the fovea in relation to movement of objects in the surrounding environment. During head movement, the SP system combines with the VOR, fixation, and optokinetic system to maintain clear and stable vision. Visual information for SP initiation and maintenance is processed by the extrastriate cortical regions (V5, in the middle temporal visual area) and medial superior temporal visual area and thence PPC, FEF and Supplementary eye fields (SEF). Projections caudally from these regions descend ipsilaterally to pontine nuclei, then to the cerebellum (dorsal vermis, paraflocculus and flocculus). These cerebellar regions then project via fastigial nucleus, vestibular nuclei and Y-group to the oculomotor nuclei. The long and widespread nature of these pathways explains why SP abnormalities are a sensitive albeit non-specific marker of CNS dysfunction.

2 DBS AND EYE MOVEMENTS

The effect of DBS upon the various eye movements will largely depend upon its interference with, or enhancement of, oculomotor networks (Figure 2). Some DBS targets might influence more than one network simultaneously and lead to more widespread effect than other targets. Generally, one might expect stimulations of fronto-striato-thalamic networks to positively modulate parameters for voluntary saccades, although effects on fixation and SP are also possible given the role of these neural structures in fixational eye movements. Clinically relevant saccadic slowing is mostly seen in brainstem pathology to which DBS targets are relatively inaccessible, through direct mechanisms. On the other hand, DBS acting upon the cortical regions involved in programming and initiation of saccades (FEF, PEF, SEF), and related BG networks (namely SNr to SC), often affect prosaccadic and antisaccadic latencies and amplitude. Interruption of fixation through inappropriate loss of saccadic inhibition can be improved when DBS stabilizes neural connectivity to the SC, enhancing fixation, SP or gaze holding. Finally, normal SP is dependent upon both flocculo-nodular projections and projections for sensorimotor feedback of SP, that include thalamus to frontal and parietal cortical areas. Given the inherent difficulties in targeting cerebellar tracts through DBS, any effects upon SP are likely mediated through BG-thalamo-cortical networks.

In the following section, we will discuss eye movements in the context of DBS, from caudal to more rostral electrode placements in the brainstem and brain.

2.1 Midbrain DBS

The midbrain is not a standard location for DBS and is thus currently only exceptionally used for research purposes for freezing of gait and falling in patients with PD and progressive supranuclear palsy (PSP) (caudal mesencephalic reticular formation, including PPN) (Goetz et al., 2019; Servello, Zekaj, Zekaj, Saleh, Menghetti, & Porta, 2014), chronic pain (periventricular/periaqueductal grey matter (PVG/PAG) (Farrell, Green, Green, & Aziz, 2018), and cluster headaches (ventral tegmental area) (Akram et al., 2017).

Given the rich population of structures related to eye movement control in the brainstem, investigating possible oculomotor dysfunction during midbrain DBS application is of particular relevance. There are only few case reports of PPN DBS-induced oscillopsia (Jenkinson, Brittain, Brittain, Hicks, Kennard, & Aziz, 2012). Authors are not united as to the underlying mechanism involved, some suggesting direct stimulation of the oculomotor nerve fibres (Ferraye et al., 2009) and others stimulation of fibres in the uncinate fasciculus of the cerebellum, resulting in activation of the saccadic pre-motor neurons in the brainstem (Jenkinson et al., 2012), leading to induction of small saccadic movements (Jenkinson et al., 2012).

2.2 Periaqueductal grey matter DBS

Liu et al investigated local field potentials during a saccadic task under different visual conditions via implanted electrodes in the rostroventral part of PVG/PAG in four patients with DBS for the treatment of neuropathic pain (Liu et al., 2009). They characterized different local field potential signals of
human SC, with distinctive, task-specific firing frequencies for saccades, fixation or SP visual activity. Because the saccade-related local field potentials varied predictably with the proximity of the electrode contacts to the SC, they suggested that saccade-related local field potentials may be used as a functional marker for localizing the PVG/PAG region during stereotactic surgery for modulation of pain.

### 2.3 Pedunculopontine DBS

The PPN is a collection of heterogeneous neurons located in the area between the midbrain and pons. It acts as an integrator of activity from BG, cerebellum, and motor cortex and is an important part of at least three distinct systems: rostral locomotion region, arousal system, and behavioural state control. Indeed, neurophysiological studies in monkeys showed an alteration of firing rate in PPN neurons not only before and during voluntary movements, but also during reflexive and voluntary saccades and fixation (Kobayashi, Inoue, Inoue, Yamamoto, Isa, & Aizawa, 2002; Okada & Kobayashi, 2009, 2014, 2016). The PPN influence upon saccades is probably due to direct PPN projections to SC (PPN cholinergic neurons; Kobayashi, Yoshida, Yoshida, & Inouye, 2009) and STN (predominately inhibitory, GABAergic PPN neuron projections; Mena-Segovia & Bolam, 2017). Moreover, the PPN also receives projections from FEF limbic cortex and is involved in reward-orientated eye movement behaviour (Okada & Kobayashi, 2013). The PPN is affected in PD and atypical parkinsonian syndromes such as PSP and multiple system atrophy (MSA), where it is suggested to play a role in the development of the axial symptoms, such as gait disturbance, postural instability and falling. Therefore, PPN was studied as a potential DBS target for the treatment of freezing of gait and postural instability in PD and PSP patients (Goetz et al., 2019; Servello et al., 2014). Although DBS effects on eye movements were not documented, one might have expected some influence upon oculomotor function given PPN projections to frontal cortex, SC and BG.

### 2.4 Potential future DBS targets: Interstitial nucleus of Cajal and SNr

In the 1970s and 1980s, midbrain stereotactic surgeries started being carried out for the treatment of cervical dystonia (CD). The concept was based on Hassler’s early theories for CD, emphasizing the role of the midbrain interstitial nucleus of Cajal (INC), a group of cells in the medial longitudinal fasciculus, involved in oculomotor control, head posture and vertical eye movement. An interesting review by Sedov et al analyses the database of midbrain single-unit recording of pretectal neurons (Sedov et al., 2017) obtained during such surgeries. Although midbrain lesions are no longer routinely used in CD, nor is INC an established target for DBS, Sedov et al. pointed out that INC DBS may be used as alternative future treatment strategy for CD (Sedov et al., 2017). Should this occur, eye movement dysfunction may represent one of the major concerns, because INC acts as a neural integrator (of velocity to position, for gaze holding) for vertical eye movements (Fukushima, 1991). Indeed, animal studies of bilateral lesions in the close vicinity of the INC led to a severe impairment of the maintaining eccentric gaze position, and decreased gain of the VOR (Fukushima, 1991; Leigh & Zee, 2006).

The SNr has also been suggested as a potential target for treating axial symptoms in PD (Chastan et al., 2009) and as experimental treatment for epilepsy (Loddenkemper et al., 2001; Watanabe & Munoz, 2011), but has not yet used in humans, due to potential non-ocular side effects (Bejjani et al., 1999; Watanabe & Munoz, 2011). Interestingly, bilateral SNr microstimulation in monkeys suppressed SC (Liu & Basso, 2008); perhaps unexpectedly, no eye movement problems were recorded, and instead, contralateral saccades were facilitated (Liu & Basso, 2008).

### 2.5 Subthalamic nucleus deep brain stimulation

Subthalamic nucleus deep brain stimulation (STN DBS) is the most common location for treating symptoms in PD patients. It decreases tremor, helps with drug-induced dyskinesias and motor fluctuations, and might modulate aspects of executive cognition or emotion (Bakhtiari, Altinkaya, Pack, & Sadikot, 2020; Hartmann, Fliegen, Fliegen, Groiss, Wojtecki, & Schnitzler, 2019). STN sends stimulatory glutamatergic projection to SNr, which when active, inhibits SC (Figure 2). Furthermore, the role of STN in planning of saccades is supported by the presence of saccadic subcortical premovement potentials, similar to so-called “Bereitschaftspotentials” for limb movements (Fawcett et al., 2007).

Dopaminergic degeneration impairs the direct basal ganglia (BG) pathway and pathologically enhances the indirect BG pathway (involving also STN), which leads to increased inhibitory output from SNr (Goelz et al., 2017). This affects both BG connections with SC and feedback projections to cortical structures, resulting in coexistence of inappropriate initiation and inhibition of saccades (Barbosa et al., 2019).

### 2.5.1 STN DBS and Saccades

Most studies agree that DBS STN decreases prosaccadic latency—the time taken to initiate a saccade—and increases
velocity and amplitude of visually guided saccades (Nilsson, Patel, Patel, Rehncrona, Magnusson, & Fransson, 2013; Shaikh, Antoniades, Antoniades, Fitzgerald, & Ghasia, 2018; Temel, Visser-Vandewalle, Visser-Vandewalle, & Carpenter, 2008, 2009; Terao et al., 2013; Yugeta et al., 2010). Studies comparing improvement of oculomotor function with motoric improvement, assessed using the UPDRS scale, have yielded contradictory results, some claiming there is a clear correlation between reduction of saccadic latency and UPDRS III (Antoniades, Carpenter, Carpenter, & Temel, 2012; Temel, Visser-Vandewalle, et al., 2009), and others that there is none at all (Pinkhardt et al., 2012). Indeed, saccadic parameters improved similarly to gait parameters during gait “turning” (Lohnes & Earhart, 2012). Antoniades et al. also described the effect of the lesion, inevitably produced during DBS electrode placement, on eye movements. They described that the lesion itself has known beneficial effect on general motoric features, but can negatively affect oculomotor parameters, with worsening of reflexive saccadic latency. Transient prolongation of saccadic latency returned to baseline in few weeks and was successfully shortened when stimulation was turned ON. This supports the multidimensional effect of DBS stimulation, differing from the concept of a reversible “lesion” (Antoniades, Buttery, et al., 2012).

The effect of STN DBS on voluntary saccades is more unclear. Some studies report that STN DBS affects only visually guided saccades (Fischer et al., 2016; Goelz et al., 2017; Lohnes & Earhart, 2012; Sauleau et al., 2008; Temel et al., 2008). Other data show positive effect of STN DBS on visually guided and voluntary saccades (Dec-Cwiek et al., 2017; Nilsson et al., 2013; Yugeta et al., 2010, 2013), whereas some results indicate that specific parameters (e.g. latency) are improved only for visually guided saccades, and other parameters (gain of first saccade) only for voluntary saccades (Antoniades, Carpenter, et al., 2012; Fawcett et al., 2010; Fischer et al., 2016; Pinkhardt et al., 2012; Rivaud-Pechoux et al., 2000; Temel, Visser-Vandewalle, et al., 2009; Tokushige et al., 2018). There are also studies where DBS fails to produce any effect at all (Schmalbach et al., 2014; Tokushige et al., 2018), and it was even reported to worsen saccadic performance in a study with 12 PD patients and four ET patients (Bangash et al., 2019). Because L-DOPA seems to have an opposite effect on saccadic eye movements as DBS STN (it improves voluntary saccades, but prolongs latency of visually guided saccades—for more details see the section below, and Table 1) (Dec-Cwiek et al., 2017), the variability of reported outcomes may relate to differing methodologies (ON or OFF medications) employed. In addition, disease duration and patient age vary considerably across research papers and minor variabilities in DBS electrode placements may also contribute to difference in results (Shaikh et al., 2018).

There are two theories explaining the beneficial effect of STN stimulation on pathological BG activity in PD patients. In the rate model, STN DBS decreases the excessive inhibition of SC via facilitation of STN and SNr projections (Fawcett, Dostrovsky, Dostrovsky, Lozano, & Hutchison, 2005; Hutchison et al., 2004). However, according to this theory, STN DBS would cause not only facilitation of saccades, but would also increase the frequency of unwanted saccades, so-called square wave jerks (SWJs) (Fawcett, Dostrovsky, et al., 2005; Hutchison et al., 2004). This contradicts findings in many studies (Goelz et al., 2017; Wark, 2006; Yugeta et al., 2010), where not only initiation, but also inhibition and fixational stability were improved with STN DBS. Therefore, another model, the oscillation model of BG circuits was proposed (Antoniades, Buttery, et al., 2012; Shaikh et al., 2018; Tokushige et al., 2018; Yugeta et al., 2010): beta band oscillations are increased in PD patients, and because desynchronization of beta band is required to initiate a motor command, motoric thresholds in PD are elevated. STN DBS thus decreases pathologic oscillations and facilitates motor command, but at the same time it also stabilizes SC activity and restores inhibitory saccadic control (Yugeta et al., 2013).

Beta band oscillations in sensorimotor cortices and BG are present in healthy subjects during steady posture, whereas desynchronization of beta bands is observed during preparation and execution of limb and eye movements. Using STN DBS electrodes to record local field potentials during prosaccadic and antisaccade tasks, beta band desynchronization was related to preparation and execution of prosaccades, as well as early inhibition of prosaccades and execution of antisaccades (Yugeta et al., 2013). In PD patients oscillatory activity in STN is increased (Weinberger et al., 2006) and might disturb execution of movements (Hammond, Bergman, Bergman, & Brown, 2007), increasing the required motoric threshold and prolonging saccadic latency. Although the magnitude of the oscillatory behaviour does not correlate with severity of symptoms, it positively correlates with response to dopaminergic therapy. As beta oscillations are more prominent in dorsal parts of STN, and as its oculomotor region lies more ventrally, eye movements are less susceptible to beneficial effects of L-DOPA (Weinberger et al., 2006). However, STN DBS directly decreases pathologic oscillations and facilitates motor commands, but at the same time it also stabilizes SC activity and restores inhibitory saccadic control (Yugeta et al., 2013), leading to the coexistence of decreased latency and improved fixation.

2.5.2 | L-DOPA, its effect on eye movements, and interactions with DBS

The effects of L-DOPA on oculomotor deficits in PD are not comparable to its influence on the general motoric state
(Pinkhardt et al., 2012; Rascol et al., 1989). It has in fact been suggested that considerable part of oculomotor PD deficits are caused by non-dopaminergic dysfunction, especially impaired top-down frontostriatal saccadic control due to frontal lobe pathology in PD (Pinkhardt et al., 2012), explaining also why saccadic latency correlates with cognitive status in PD. Regardless, studies have shown that L-DOPA might increase latency for reflexive prosaccades and at the same time reduce error rate for voluntary antisaccades (Bakhtiari et al., 2020; Hood et al., 2007; Lu, Buchanan, Buchanan, Kennard, FitzGerald, & Antoniades, 2019). In the case of L-DOPA ON state, dopaminergic therapy seems to interfere with the effects of DBS, modestly prolonging saccadic latency, or at least diminishing any DBS-related reduction in latency of reflexive saccades. Similarly, L-DOPA ON state has been shown to decrease the antisaccadic error rate, that can be increased by STN DBS (Bakhtiari et al., 2020).

Such interactions between L-DOPA and DBS may be a consequence of L-DOPA altering the balance between the direct and indirect pathways of the BG circuit (Lu et al., 2019); as memory-guided saccades depend predominantly on the direct pathway, its facilitation might contribute to an L-DOPA positive effect on voluntary saccades. On the other hand, STN DBS is believed to directly modulate the excessive SC inhibition, due to SNr (Bakhtiari et al., 2020; Dec-Cwiek et al., 2017) influencing the common saccadic pathway and improving also reflexive saccade latency.

### 2.5.3 | STN DBS and visuospatial function

To explore the role of general attention in DBS effects on volitional saccades in PD, Fischer and colleagues conducted a study comparing STN DBS influences on visuospatial bias as a measure of attention deficit, and basic saccadic parameters (saccadic dysmetria) (Fischer et al., 2016). They found that STN DBS improves only basic oculomotor parameters but not higher-level exploration patterns. In fact, visuospatial deficits were observed with unilateral (left) ventral STN stimulation, that could interfere with everyday activities like driving. This suggests that distinct areas within the ventral subthalamic area, distinct from those involved in saccadic metrics, may be involved in self-guided visual exploration.

### 2.5.4 | Unilateral vs bilateral STN DBS

If hemispheric dominance for perceptual, motor, and cognitive processes is well understood, hemispheric specialization in saccadic control is still under debate, with some studies showing asymmetries for saccadic gain, peak velocities, and saccadic latencies (Vergilino-Perez et al., 2012; Weber & Fischer, 1995). Although DBS stimulation offers a unique opportunity to investigate hemispheric asymmetry in eye movement control, only very few studies have compared the effect of unilateral versus bilateral stimulation (Fischer et al., 2016; Goelz et al., 2017; Schmalbach et al., 2014; Temel, Visser-Vandewalle, et al., 2009; Yugeta et al., 2013). Among them, only one study (Temel, Visser-Vandewalle, et al., 2009) has assessed left and right gaze asymmetry, beyond a general effect of stimulation on eye movements, and reported faster rightward directed eye movements during bilateral STN high frequency stimulation.

Mild visual neglect with decreased fixation time and prolonged reaction time for hand and eye movements was suggested to be a consequence of STN DBS stimulation within the non-dominant hemisphere (Schmalbach et al., 2014). In another study, 17 PD patients with left-sided symptoms presented with saccadic hypometria and rightward viewing bias (Fischer et al., 2016). When comparing the effect of unilateral or bilateral stimulation, unilateral stimulation had no effect on prosaccadic latency or visual bias, whereas bilateral stimulation improved saccadic hypometria but not the visuospatial bias.

Goelz et al. used antisaccadic error rates as measure of cognitive function, and pointed out that impaired cognitive motor function, a well-described side effect of DBS STN, was observed only in bilateral but not unilateral stimulation (Goelz et al., 2017). However, any beneficial effect on eye movements (increased prosaccadic gain and decreased prosaccadic error rates) improved only in bilateral stimulation settings (Goelz et al., 2017), suggesting that unilateral stimulation effect on eye movements was generally too weak to produce either a positive or negative influence.

### 2.5.5 | STN DBS and smooth pursuit

Results for STN DBS influence on SP are contradictory, although different studies again differ in methodologies used (e.g. Nilsson et al. tested patients in L-DOPA medication ON and OFF state (Nilsson et al., 2013), whereas Pinkhardt et al. tested patients on medication ON state only (Pinkhardt et al., 2012)). Both studies, regardless of L-DOPA treatment status, found clear SP deficit (reduced velocity and gain) in PD patients. In the study of Nilsson et al, DBS significantly improved SP (Nilsson et al., 2013), but Pinkard et al. found a positive effect of STN DBS only on saccadic, but not SP performance. This suggests that SP deficit in PD may be related to extra dopaminergic mechanisms (Pinkhardt et al., 2012), perhaps explaining why dopaminergic therapy has contradictory evidence on SP deficit, from no effect at all, to improving or even worsening SP gain (Nilsson et al., 2013; Waterston, Barnes, Barnes, Grealy, & Collins, 1996).
2.5.6 | STN DBS: fixation and gaze holding

Some eye movements (fixation, SP, gaze holding) require robust saccadic inhibition to be executed properly. In PD, intrusive saccades interfere with saccadic inhibition. Bilateral STN DBS was found to increase fixational stability and reduce SWJs in PD patients (Goelz, Cottongim, Cottongim, Metman, Corcos, & David, 2019; Wark, Garell, Garell, Walker, & Basso, 2008). The underlying mechanism that enables STN DBS to improve both saccadic performance and saccadic inhibition remains unclear, although the oscillatory theory offers a possible explanation for this seemingly paradoxical phenomenon—see the section 2.5.1 for more details (Watanabe & Munoz, 2011; Yugeta et al., 2013).

2.6 | Globus pallidus internus deep brain stimulation

Globus pallidus internus deep brain stimulation (GPi DBS) is used for treating motor symptoms and tremor in PD patients. Besides its use for PD patients, GPi DBS is also common target in patients with dystonia (Doshi, 2018; Lozano et al., 2019; Meoni et al., 2017). There is also experimental data showing symptom improvement in patients with HD (Fawcett, Moro, Moro, Lang, Lozano, & Hutchison, 2005) and Tourette syndrome (Azimi et al., 2018; Doshi, 2018; Lozano et al., 2019).

2.6.1 | GPi DBS and saccades

The effect of GPi DBS on eye movements is far less studied than STN DBS, although the role of GPi in saccadic control has been specifically investigated in animal models (Shin & Sommer, 2010; Yoshida, Okamoto, Okamoto, Makita, Nanba, & Yoshizumi, 2009) and in humans after unilateral pallidotomy (Bleghker, Siemers, Siemers, Abel, & Yee, 2000; O'Sullivan et al., 2003). Pallidotomy did not affect visually guided saccades, but had some effect on voluntary saccades and was reported to negatively affect ocular fixation (Bleghker et al., 2000; O'Sullivan et al., 2003).

The influence of GPi DBS on eye movements is described in a patient with HD (Fawcett, Moro, et al., 2005), a PD patient (Straube, Ditterich, Ditterich, Oertel, & Kupsch, 1998) and in two studies comparing DBS STN and GPi effects on eye movements in patients with PD (Antoniades et al., 2015; Fridley et al., 2013). Contrary to STN DBS, GPi DBS in PD patients has no effect on prosaccades, but seems to improve predominantly voluntary saccades (antisaccadic error rates and latency). However, in HD patients with DBS GPi, the pattern was nearly opposite: GPi DBS improved prosaccadic parameters (shortened reaction time, increased amplitude, increased velocity), but deteriorated parameters in a voluntary, memory-guided saccadic task (prolonged reaction time and decreased amplitude) (Fawcett, Moro, et al., 2005).

One study directly compared GPi and STN DBS effects on saccades and observed increased numbers of saccadic intrusions and decreased latency of pro- and antisaccades only in STN, but not GPi DBS (Fridley et al., 2013). While they do not offer a clear pathophysiological mechanism underlying their findings, they suggest that in contrast to STN, which has a clear and important role in BG oculomotor circuit, the role of SNr and GPi in this circuit remains questionable and certainly less prominent. GPi does however play a role in fixational stability, probably through downstream effects on oculomotor function, resulting in increased fixational stability in GPi stimulation, as observed in their study.

2.6.2 | GPi DBS and saccadic inhibition—antisaccades and fixation

Globus pallidus internus is one of the main output structures in BG and its tonic inhibition output is believed to have major effect not only on somatic motoric system, and also on tonic saccadic inhibition. During ocular fixation, the saccadic system must be inhibited (Leigh & Zee, 2006) to allow steady fixation. Loss of saccadic inhibition after pallidotomy might cause saccadic intrusions, so-called SWJs (Watanabe & Munoz, 2011).

In PD, dopaminergic degeneration leads to striatal disinhibition of GPi and SNr, two important sources of inhibitory output to SC, thalamus, and frontal cortex. Consequently, inhibition from GPi and SNr is increased leading to impaired saccade initiation, smaller saccadic amplitudes and probably also increased antisaccadic error rates. In hyperkinetic movement disorders, as are HD, Tourette syndrome and tardive dyskinesia, the inhibitory GPi and SNr output is disturbed, leading to decreased inhibition of SC and frontal cortex. However, this simple GPi inhibitory hypothesis cannot explain the known therapeutic effects of pallidotomy for both PD and hyperkinetic disorders (Lozano et al., 1997), as it does not explain the prolonged saccadic latency seen in HD or after pallidotomy.

Antoniades et al. proposed a double loop model to explain both the deficit and the dynamic improvement of antisaccades after GPi DBS treatment (Antoniades et al., 2015). In this model, the DLPFC-BG loop (originating in DLPFC, going to STN and striatum, then to ventrolateral thalamus and back to DLPFC) acts upon the oculomotor loop (originating in FEF/SEF, going to STN and striatum then to oculomotor thalamus and back to FEF/SEF). The DLPFC-BG
loop structures control more complex eye movements, including both initiation of volitional prosaccades and also inhibition of prosaccades in the antisaccadic task. Although the oculomotor loop has direct control only over relatively simple movements, such are reflexive prosaccades, it is involved in the execution of more complex, voluntary saccades, both memory-guided and antisaccades with input from the DLPFC—BG loop. Interloop information transfer occurs in the striatum, with modulation of striatal medium spinal neurons (MSN), which in normal brains fire at very low rates. In PD patients, MSN firing rate is pathologically elevated and therefore interrupts the transfer of information between loops (Taverna, Ilijic, Ilijic, & Surmeier, 2008). According to the model, GPI DBS improves interloop information flow, by widespread MSN inhibition and consequently reduced firing rate. Results of their study showed that GPI DBS reduced both prosaccade and antisaccadic latencies (although the improvement was statistically insignificant), as well as antisaccadic error rates. Therefore, they predicted that antisaccadic error rate was unlikely to have been reduced through direct GPI DBS prosaccadic inhibition, and more likely mediated by strengthening of DLPFC—BG loop influence over the oculomotor loop, responsible for both prosaccadic inhibition and initiation of volitional saccade. In support of this conjecture, they argue that neither pallidotomy nor other DBS locations have any influence on MSN, and therefore fail to improve antisaccadic error rate. Furthermore, L-DOPA acts on MSN directly, and has been shown to improve antisaccadic error rate.

2.6.3 | GPI DBS and smooth pursuit

None of the aforementioned studies describe GPI DBS effect on SP. Because GPI sends projections through thalamus to FEF responsible for SP control, it was proposed that SP parameters might change due to stimulation (Shaikh et al., 2018), but because studies investigating SP in GPI DBS are lacking, this remains purely hypothetical.

2.7 | Thalamic VIM DBS

The most common indication for thalamic DBS is ET, VIM being the most common target. Thalamic DBS has been used also for non-ET tremor, tremor dominant PD, obsessive–compulsive disorder (inferior thalamic peduncle), neuropathic pain (questionable effect of ventro-postero-lateral (VPL) nucleus), traumatic brain injury, Tourette syndrome (medial thalamus with centro-median-parafascicular complex [CM/Pf]), and drug-resistant epilepsy (VPL nucleus) among others (Whiting et al., 2018).

2.7.1 | Thalamic DBS and saccades

Specific thalamic nuclei are known to be part of the extensive saccadic network (Kronenberger et al., 2010). In animal studies, central nuclei of internal medullary lamina (IML) and pulvinar are directly involved in saccadic programming. IML is probably a source of efference copy information, coming from cortical structures, important for antisaccadic and memory-guided tasks (Leigh & Zee, 2006). Central thalamus is involved in initiation of voluntary saccades (Tanaka & Kunimatsu, 2011). Pulvinar on the other hand might contribute to saccadic suppression and directing visual attention towards a salient target (LaBerge & Buchsbaum, 1990; Leigh & Zee, 2006). However, from animals studies, especially monkey data, it appears that part of the motor thalamus—ventrolateral thalamus, a monkeys homologue for VIM, seems to be activated during visually guided saccades (Krack et al., 2003; Leigh & Zee, 2006). Kronenburger et al found that unilateral DBS stimulation of VIM in ET patients reduced the latency of visually guided saccades in three out of four patients, but also negatively affected saccadic accuracy, and suggested DBS interferes with cerebello-thalamocortical projections (Kronenburger et al., 2010). Based on knowledge from animal studies, Watanabe et al. predicted the following two effects of thalamic DBS on saccade performance in Tourette syndrome patients, although there does not yet exist confirmatory data: firstly, reduced antisaccadic error rates and secondly, increased suppression of saccade initiation due to activating afferent projections to the STN, SNr and GPI (Watanabe & Munoz, 2011). Temel et al. compared the effect of STN DBS and VIM DBS upon saccadic function and observed prominent prosaccadic latency reduction only in STN DBS (Temel, Visser-Vandewalle, et al., 2009).

2.7.2 | Thalamic DBS and Smooth pursuit

Lesions affecting the posterior thalamus can cause an ipsilateral SP deficit (Brigell, Babikian, Babikian, & Goodwin, 1984), and central thalamus (including the CM/PF complex) is believed to have an important role in motion and feedback mechanism of SP (Leigh & Zee, 2006). Ackermans et al. did not report any adverse oculomotor effect following stimulation of the CM/Pf in patients with refractory Tourette syndrome, but nevertheless pointed out that stimulation of this part of thalamus carries substantial risk of adverse effects on oculomotor function (Ackermans et al., 2011). On the other hand, case reports of ocular adverse effects in patients with ET and unilateral VIM DBS reported PSP-like features with supranuclear vertical palsy and broken SP, that completely resolved after stimulation was turned off (Patterson, Okun, Okun, & Hess, 2017).
2.7.3 | Thalamic DBS and supranuclear pathways for convergence

Changizi, Cho, Kopell, & Rucker, 2014 described a case report of a patient with subjective diplopia and “dizziness” observed during medial thalamic stimulation. They hypothesized that thalamic DBS may influence descending supranuclear convergence pathways travelling through the medial thalamus to rostral midbrain, disinhibiting convergence neurons and causing esodeviation (Changizi, Cho, Kopell, & Rucker, 2014).

3 | Oculomotor side effects from DBS

Deep brain stimulation, especially at higher intensities, may stimulate not only axons projecting from the stimulated area, or cause retrograde activation of axons projecting to the stimulated area, but also fibres passing through the stimulated area or its surrounding structures (Arle, Mei, Mei, Carlson, & Shils, 2018; Temel, Tan, et al., 2009). The latter may contribute to both positive and negative effects of DBS, depending on the stimulated structures. For example, it was suggested that GPi DBS can directly influence STN through excitation of GABAergic projections from GPi to STN, and that STN DBS can cause increased dopaminergic release by stimulation of nigrostriatal and pallido-nigral projections (Parent, 2004). Stimulation of fibres of passage can also partially explain why some DBS actions are not limited to local effect of stimulation and might reflect more distal effect of DBS (Agnesi, Connolly, Connolly, Baker, Vitek, & Johnson, 2013; Agnesi, Johnson, Johnson, & Vitek, 2013).

In the case of STN DBS, the nucleus itself is small, with several fibres passing in its direct vicinity; namely the internal capsule, (positioned laterally and ventrally in relation to STN), SNr (positioned ventrally), fibres of the oculomotor nerve (located medioventrally), and sensory thalamus (positioned dorsally to STN) (Koeglsperger, Palleis, Palleis, Hell, Mehrkens, & Botzel, 2019). As previously mentioned, the most common site of STN stimulation is its dorsolateral, sensorimotor portion. The stimulation effect can extend to oculomotor fibres, lying just medially to it or the ventrally lying midbrain rostral interstitial nucleus, causing unilateral eye deviation. Tamma et al. reported oculomotor side effects in 24% of patients undergoing STN DBS, where either central, medial or anteromedial part of STN was stimulated (Tamma et al., 2002). Respectively, if oculomotor fibres were involved, the deficit was characterized by excessive adduction or reduced abduction in the ipsilateral eye and elevation of the superior eyelid; in the case of the rostral interstitial nucleus, the deficit consisted of a lateral and upward gaze deviation. Bejjani et al described a similar crossed midbrain syndrome in 4 out of 25 patients with STN DBS who developed a reversible diplopia, dystonic posture and tremor in the contralateral limb in the acute postoperative phase (Bejjani et al., 2002).

Cortical commands for saccadic generation travel directly or indirectly to SC through the internal capsule; for reflexive saccades, fibres are located in the posterior limb and for voluntary saccades in the anterior limb of the internal capsule. Conjugate ipsilateral eye deviation has been observed where DBS electrodes stimulate the internal capsule that lies laterally and ventrally to the STN (Tommasi et al., 2008), and may in some instances progress to contralateral eye deviation (Koeglsperger et al., 2019). This effect is most commonly observed when the electrodes are placed along lateral anterosuperior border of the STN (Koeglsperger et al., 2019), and this feature may indeed help guide correct electrode placement. Similarly, if the electrode is placed too far laterally in VIM stimulation (with usual preferred target being placed 1–2 mm anterior to the ventralis caudalis), fibres of the posterior limb of the internal capsule can be stimulated, causing a variety of eye movement abnormalities (e.g. diplopia, deficit in convergence, esodeviation—see Section 2.7.3 for more details).

3.1 | DBS-induced eye movement deficits and its influence on quality of life

The extent to which eye movement abnormalities may significantly reduce or indeed enhance the therapeutic effect of DBS in patients has not been adequately investigated (Rowe et al., 2018). Furthermore, specific eye movement abnormalities may be under-reported by patients, although they likely interfere with everyday activities, such as reading, manual tasks and stability during walking. The indirect negative influence of eye movement disorders comes from loss of depth perception, reduced hand-to-eye co-ordination, and reduced ability to visually scan the environment (Pollock, Hazelton et al., 2011), all of which can lead to postural instability in an already vulnerable population. It has also been argued that while mild visuospatial biases induced by unilateral DBS may not interfere with simple laboratory motor tasks, such deficits may affect more complex behaviours such as driving a car (Fischer et al., 2016).

4 | General effects of DBS on eye movements—summary

There is considerable variability regarding DBS effects on eye movements in the literature. Nevertheless, beyond the specific effects of DBS upon specific eye movements (discussed above), and across specific BG disorders, it is
worthwhile recapping how the different DBS targets may act upon oculomotor structures in the BG.

- Electrodes targeting GPi will likely improve voluntary saccade parameters, mainly antisaccadic error rate, due to its positive effect on the interloop control of higher, fronto-striato-thalamic oculomotor network, within the GPi.
- Antisaccadic error rate seems to be increased with STN DBS, probably due to interrupted connections between STN and frontal circuits, important for saccadic inhibition.
- STN DBS, on the other hand, appears to improve certain saccadic parameters (especially latency) of visually guided saccades in PD, through a direct effect on the SNr-SC loop, removing a tonic inhibition of SC, and facilitating neural discharges to burst cell neurons in the brainstem. Saccadic amplitude is partially improved through a similar mechanism; however, velocity can only be influenced by a top-down influence on brainstem structures.
- STN DBS can cause ocular dysconjugacy with adduction and depression of the eye ipsilateral to the side of STN DBS (Bejjani et al., 2002) that may lead to blurred vision or diplopia. This is due to the strategic location of the oculomotor nerve fascicles arising from the oculomotor nucleus. A conjugate gaze deviation away from the side of STN DBS has also been described, due to activation of the fronto-pontine fibres within the internal capsule by a lead that is too lateral.
- Finally, thalamic VIM stimulation interrupts projections from the parieto-occipito-temporal junction to midbrain structures, and potentially also thalamocortical projections, both of which may impair SP.

5 | CONCLUSION

We have reviewed the available literature exploring DBS and eye movements. Variable findings regarding the effect of DBS on eye movements across studies are likely influenced by methodological approach, especially L-DOPA medication status, as well as by possible variability in DBS electrode placement, highlighting the need for systematic approaches in studies specifically probing oculomotor control in DBS. L-DOPA is in some aspects reported to have an opposite effects to DBS on saccades, hinting at additional non-dopaminergic effect of DBS stimulation more generally. Indeed, DBS stimulation can act on axons ortho- or retrogradely, and some effects can be produced also due to stimulation of fibres of passage. The latter is also the most common mechanism of DBS-induced eye movement side effects, which can be in many cases modulated by adjusting the parameters of stimulation.

Finally, the effect of DBS upon eye movements remains studied mostly in PD patients. Less common DBS targets are not investigated for possible effects on eye movements, despite their direct or indirect involvement in eye movement control. Several aspects of the neurophysiology of DBS-mediated oculomotor effects remain unexplored, including comparisons of uni- and bilateral stimulation, and hemispheric asymmetry in eye movement control in relation to DBS.

CONFLICT OF INTEREST

The authors report no competing interests.

PEER REVIEW

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REFERENCES

Ackermans, L., Duits, A., van der Linden, C., Tijssen, M., Schruers, K., Temel, Y., … Visser-Vandewalle, V. (2011). Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. Brain, 134(Pt 3), 832–844.
Agnesi, F., Connolly, A. T., Baker, K. B., Vitek, J. L., & Johnson, M. D. (2013). Deep brain stimulation imposes complex informational lesions. PLoS One, 8(8), e74462.
Agnesi, F., Johnson, M. D., & Vitek, J. L. (2013). Deep brain stimulation: How does it work? Handbook of Clinical Neurology, 116, 39–54.
Akrum, H., Miller, S., Lagrata, S., Hariz, M., Ashburner, J., Behrens, T., … Zrinzo, L. (2017). Optimal deep brain stimulation site and target connectivity for chronic cluster headache. Neurology, 89(20), 2083–2091.
Almer, Z., Klein, K. S., Marsh, L., Gerstenhaber, M., & Repka, M. X. (2012). Ocular motor and sensory function in Parkinson's disease. Ophthalmology, 119(1), 178–182.
Antoniades, C. A., Butterly, P., FitzGerald, J. J., Barker, R. A., Carpenter, R. H., & Watts, C. (2012). Deep brain stimulation: Eye movements reveal anomalous effects of electrode placement and stimulation. PloS One, 7(3), e32830.
Antoniades, C. A., Carpenter, R. H., & Temel, Y. (2012). Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Similar improvements in saccadic and manual responses. NeuroReport, 23(3), 179–183.
Antoniades, C. A., Rebello, P., Kennard, C., Aziz, T. Z., Green, A. L., & FitzGerald, J. J. (2015). Pallidal Deep brain stimulation improves higher control of the oculomotor system in Parkinson's disease. Journal of Neuroscience, 35(38), 13043–13052.
Arle, J. E., Mei, L. Z., Carlson, K. W., & Shils, J. L. (2018). Theoretical effect of DBS on axonal fibres of passage: Firing rates, entropy, and information content. Stereotactic and Functional Neurosurgery, 96(1), 1–12.
Ashkan, K., Rogers, P., Bergman, H., & Ughratdar, I. (2017). Insights into the mechanisms of deep brain stimulation. Nature Reviews. Neurology, 13(9), 548–554.
Azimi, A., Parvaresh, M., Shahidi, G., Habibi, A., Rohani, S., Safdarian, M., … Rohani, M. (2018). Anteromedial GPi deep brain stimulation in Tourette syndrome: The first case series from Iran. Clinical Neurology and Neurosurgery, 172, 116–119.
Bakhtiari, S., Altinkaya, A., Puck, C. C., & Sadikot, A. F. (2020). The role of the subthalamic nucleus in inhibitory control of oculomotor behavior in Parkinson’s disease. *Scientific Reports*, 10(1), 5429.

Bangash, O. K., Dissanayake, A. S., Knight, S., Murray, J., Thorburn, M., Thani, N., ... Lind, C. R. P. (2019). Modulation of saccades in humans by electrical stimulation of the posterior subthalamic area. *Journal of Neurosurgery*, 1–9. [Epub ahead of print] https://doi.org/10.3171/2018.12.JNS18502

Barbosa, P., Kaski, D., Castro, P., Lees, A. J., Warner, T. T., & Djamschidian, A. (2019). Saccadic Direction Errors are Associated with Impulsive Compulsive Behaviours in Parkinson’s Disease Patients. *Journal of Parkinson’s Disease*, 9(3), 625–630.

Basso, M. A., Pokorny, J. J., & Liu, P. (2005). Activity of substantia nigra pars reticulata neurons during smooth pursuit eye movements in monkeys. *European Journal of Neuroscience*, 22(2), 448–464.

Bejjani, B. P., Arnulf, I., Houeto, J. L., Milea, D., Demeret, S., Pidoux, B., ... Agid, Y. (2002). Concurrent excitatory and inhibitory effects of high frequency stimulation: An oculomotor study. *Journal of Neurology, Neurosurgery and Psychiatry*, 72(4), 517–522.

Bejjani, B. P., Damier, P., Arnulf, I., Thivard, L., Bonnet, A. M., Dormont, D., ... Agid, Y. (1999). Transient acute depression induced by high-frequency deep-brain stimulation. *New England Journal of Medicine*, 340(19), 1476–1480.

Blekher, T., Siemers, E., Abel, L. A., & Yee, R. D. (2000). Eye movements in Parkinson’s disease: Before and after pallidotomy. *Investigative Ophthalmology & Visual Science*, 41(8), 2177–2183.

Brigell, M., Babikian, V., & Goodwin, J. A. (1984). Hypometric saccades and low-gain pursuit resulting from a thalamic hemorrhage. *Annals of Neurology*, 15(4), 374–378.

Chan, F., Armstrong, I. T., Pari, G., Riopelle, R. J., & Munoz, D. P. (2005). Deficits in saccadic eye-movement control in Parkinson’s disease. *Neuropsychologia*, 43(5), 784–796.

Changizi, B. K., Cho, C., Kopell, B., & Rucker, J. (2014). Diplopia and Esophoria induced by medialthalamic deep brain stimulation (P6.308). *Neurology* 82(10 Supplement):P6.308.

Chastan, N., Do, M. C., Bonneville, F., Torny, F., Bloch, F., Westby, G. W., ... Welter, M. L. (2009). Gait and balance disorders in Parkinson’s disease: Impaired active braking of the fall of centre of gravity. *Movement Disorders*, 24(2), 188–195.

Chudy, D., Deletis, V., Almahrifq, F., Marcinkovic, P., Skrlin, J., & Paradzik, V. (2018). Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: Experience in 128 patients. *Journal of Neurosurgery*, 4(3), 1189–1198.

Paradzik, V. (2018). Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: Experience in 128 patients. *Journal of Neurosurgery*, 4(3), 1189–1198.

Cadin, A., & Kaski, D. (2019). An update on best practice of deep brain stimulation in Parkinson’s disease. *Frontiers in Systems Neuroscience*, 13(1), 17–25.

Fawcett, A. P., Moro, E., Lang, A. E., Lozano, A. M., & Hutchison, W. D. (2005). Pallidal deep brain stimulation influences both reflexive and voluntary saccades in Huntington’s disease. *Movement Disorders*, 20(3), 371–377.

Ferraye, M. U., Gerardin, P., Debu, B., Chabardes, D., Fraix, V., Seigneuret, E., ... Pollak, P. (2009). Pedunculopontine nucleus stimulation induces monocular oscillopsia. *Journal of Neurology*, *Neurosurgery and Psychiatry*, 80(2), 228–231.

Fischer, P., Ossandon, J. P., Keyser, J., Gulberti, A., Wilming, N., Hamel, W., ... Konig, P. (2016). STN-DBS reduces saccadic hypometria but not visuospatial bias in Parkinson’s disease patients. *Frontiers in Behavioural Neurosciences*, 10, 85.

Fridley, J., Adams, G., Sun, P., York, M., Atassi, F., Lai, E., ... Yoskor, D. (2013). Effect of subthalamic nucleus or globus pallidus interna stimulation on oculomotor function in patients with Parkinson’s disease. *Stereotactic and Functional Neurosurgery*, 91(2), 113–121.

Fujiiwara, M., Ding, C., Kaunitz, L., Stout, J. C., Thayagarajan, D., & Tsuchiya, N. (2017). Optokinetic nystagmus reflects perceptual directions in the onset binocular rivalry in Parkinson’s disease. *PLoS One*, 12(3), e0173707.

Fukushima, K. (1991). The interstitial nucleus of Cajal in the midbrain reticular formation and vertical eye movement. *Neuroscience Research*, 10(3), 159–187.

Goelz, L. C., Cottongim, M., Metman, L. V., Corcos, D. M., & David, F. J. (2019). Bilateral subthalamic nucleus deep brain stimulation increases fixational saccades during movement preparation: Evidence for impaired preparatory set. *Experimental Brain Research*, 237(11), 2841–2851.

Goelz, L. C., David, F. J., Sweeney, J. A., Vaillancourt, D. E., Poizner, H., Metman, L. V., & Corcos, D. M. (2017). The effects of unilateral versus bilateral subthalamic nucleus deep brain stimulation on prosaccades and antisaccades in Parkinson’s disease. *Experimental Brain Research*, 235(2), 615–626.

Goetz, L., Bhattacharjee, M., Ferraye, M. U., Fraix, V., Maineri, C., Nosko, D., ... Chabardes, S. (2019). Deep brain stimulation of the pedunculopontine nucleus area in parkinson disease: MRI-based anatomochlinical correlations and optimal target. *Neurosurgery*, 84(2), 506–518.

Hammond, C., Bergman, H., & Brown, P. (2007). Pathological synchronization in Parkinson’s disease: Networks, models and treatments. *Trends in Neurosciences*, 30(7), 357–364.

Handel, A., & Glümcher, P. W. (2000). Contextual modulation of substantia nigra pars reticulata neurons. *Journal of Neurophysiology*, 83(5), 3042–3048.

Hartmann, C. J., Fliegen, S., Gross, S. J., Wojtecki, L., & Schnitzler, A. (2019). An update on best practice of deep brain stimulation in Parkinson’s disease. *Therapeutic Advances in Neurological Disorders*, 12, 1756286419838096.

Heuer, H. W., Mirsky, J. B., Kong, E. L., Dickerson, B. C., Miller, B. L., Kramer, J. H., & Boxer, A. L. (2013). Antisaccade task reflects from human subthalamic nucleus. *Clinical Neurophysiology*, 118(1), 155–163.

Fawcett, A. P., Dostrovsky, J. O., Lozano, A. M., & Hutchison, W. D. (2005). Eye movement-related responses of neurons in human subthalamic nucleus. *Experimental Brain Research*, 162(3), 357–365.

Fawcett, A. P., Gonzalez, E. G., Moro, E., Steinbach, M. J., Lozano, A. M., & Hutchison, W. D. (2010). Subthalamic nucleus deep brain stimulation improves saccades in Parkinson’s disease. *Neuromodulation*, 13(1), 17–25.

Fawcett, A. P., Moro, E., Lang, A. E., Lozano, A. M., & Hutchison, W. D. (2005). Pallidal deep brain stimulation influences both reflexive and voluntary saccades in Huntington’s disease. *Movement Disorders*, 20(3), 371–377.
cortical involvement in mild cognitive impairment. *Neurology, 81*(14), 1235–1243.

Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the basal ganglia in the control of purposeful saccadic eye movements. *Physiological Reviews, 80*(3), 953–978.

Hikosaka, O., & Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *Journal of Neurophysiology, 49*(5), 1268–1284.

Hikosaka, O., & Wurtz, R. H. (1989). The basal ganglia. *Reviews of Oculomotor Research, 3*, 257–281.

Hood, A. J., Amador, S. C., Cain, A. E., Briand, K. A., Al-Refaie, A. H., Schiess, M. C., & Sereno, A. B. (2007). Levodopa slows prosaccades and improves antisaccades: An eye movement study in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 78*(6), 565–570.

Hutchison, W. D., Dostrovsky, J. O., Walters, J. R., Courtemanche, R., Boraud, T., Goldberg, J., & Brown, P. (2004). Neuronal oscillations in the basal ganglia and movement disorders: Evidence from whole animal and human recordings. *Journal of Neuroscience, 24*(42), 9240–9243.

Jenkinson, N., Brittian, J. S., Hicks, S. L., Kennard, C., & Aziz, T. Z. (2012). On the origin of oscillpsia during pedunculopontine stimulation. *Stereotactic and Functional Neurosurgery, 90*(2), 124–129.

Kang, S. L., Shaikh, A. G., & Ghasia, F. F. (2018). Vergence and Strabismus in Neurodegenerative Disorders. *Frontiers Neurology*, 9, 299.

Kobayashi, H., Yoshida, T., & Inouye, M. (2009). Significant enhanced expression and solubility of human proteins in *Escherichia coli* by fusion with protein S from *Mycopoccus xanthus*. *Applied and Environment Microbiology, 75*(16), 5356–5362.

Kobayashi, Y., Inoue, Y., Yamamoto, M., Isa, T., & Aizawa, H. (2002). Contribution of pedunculopontine tegmental nucleus neurons to performance of visually guided saccade tasks in monkeys. *Journal of Neurophysiology, 88*(2), 715–731.

Kocabacak, E., Temel, Y., Hollig, A., Falkenburger, B., & Tan, S. (2015). Current perspectives on deep brain stimulation for severe neurologolical and psychiatric disorders. *Neuropsychiatric Disease and Treatment, 11*, 1051–1066.

Koeglsperger, T., Palleis, C., Hell, F., Mehrkens, J. H., & Botzel, K. (2017). Deep brain stimulation programming for movement disorders: Current concepts and evidence-based strategies. *Frontiers in Neurology, 10*, 410.

Krack, P., Batir, A., Van Blencom, N., Chabardes, S., Fraix, V., Arodoun, C., … Pollak, P. (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine, 349*(20), 1925–1934.

Kronenburger, M., Gonzalez, E. G., Liu, L. D., Moro, E., Steinbach, M. J., Lozano, A. M., … Hutchinson, W. D. (2010). Involvement of the human ventrolateral thalamus in the control of visually guided saccades. *Brain Stimulation, 3*(4), 226–229.

LaBerge, D., & Buchsbaum, M. S. (1990). Positron emission tomographic measurements of pulvinar activity during an attention task. *Journal of Neuroscience, 10*(2), 613–619.

Leigh, R. J., & Kennard, C. (2004). Using saccades as a research tool in the clinical neurosciences. *Brain, 127*(3), 460–477.

Leigh, R. J., & Zee, D. S. (2006). The neurology of eye movements. 4th. from ; http://www.loc.gov/catdir/enhancements/fy0637/2005022301.html.

Liu, P., & Basso, M. A. (2008). Substantia nigra stimulation influences monkey superior colliculus neuronal activity bilaterally. *Journal of Neurophysiology, 100*(2), 1098–1112.

Liu, X., Nachev, P., Wang, S., Green, A., Kennard, C., & Aziz, T. (2009). The saccade-related local field potentials of the superior colliculus: A functional marker for localizing the periventricular and periaque ductal gray. *Journal of Clinical Neurophysiology, 26*(4), 280–287.

Loddenkemper, T., Pan, A., Neme, S., Baker, K. B., Rezai, A. R., Dinner, D. S., … Luders, H. O. (2001). Deep brain stimulation in epilepsy. *Journal of Clinical Neurophysiology, 18*(6), 514–532.

Lohnes, C. A., & Earhart, G. M. (2012). Effect of subthalamic deep brain stimulation on turning kinematics and related saccadic eye movements in Parkinson disease. *Experimental Neurology, 236*(2), 389–394.

Lozano, A. M., Kumar, R., Gross, R. E., Giladi, N., Hutchinson, W. D., Dostrovsky, J. O., & Lang, A. E. (1997). Globus pallidus internus pallidotomy for generalized dystonia. *Movement Disorders, 12*(6), 865–870.

Lozano, A. M., Lipsman, N., Bergman, H., Brown, P., Chabardes, S., Chang, J. W., … Krauss, J. K. (2019). Deep brain stimulation: Current challenges and future directions. *Nature Reviews. Neurology, 15*(3), 148–160.

Lozano, P., Bernal, B., Jara, A. G., & Belleville, M. P. (2014). Enzymatic membrane reactor for full saccharification of ionic liquid-pretreated microcrystalline cellulose. *Bioresource Technology, 151*, 159–165.

Lu, Z., Buchanan, T., Kennard, C., FitzGerald, J. J., & Antoniades, C. A. (2019). The effect of levodopa on saccades - Oxford Quantification in Parkinsonism study. *Parkinsonism & Related Disorders, 68*, 49–56.

Macaskill, M. R., Graham, C. F., Pitcher, T. L., Myall, D. J., Livingston, L., van Stockum, S., … Anderson, T. J. (2012). The influence of motor and cognitive impairment upon visually-guided saccades in Parkinson's disease. *Neuropsychologia, 50*(14), 3338–3347.

Mena-Segovia, J., & Bolam, J. P. (2017). Rethinking the pedunculopontine nucleus: From cellular organization to function. *Neuron, 94*(1), 7–18.

Meoni, S., Fraix, V., Castrioto, A., Benahid, A. L., Seignuret, E., Vercueil, L., … Moro, E. (2017). Pallidal deep brain stimulation for dystonia: A long term study. *Journal of Neurology, Neurosurgery and Psychiatry, 88*(11), 960–967.

Møsimaann, U. P., Muri, R. M., Burn, D. J., Felblinger, J., O'Brien, J. T., & McKeth, I. G. (2005). Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies. *Brain, 128*(Pt 6), 1267–1276.

Nilsson, M. H., Patel, M., Rehncrona, S., Magnusson, M., & Fransson, P. A. (2013). Subthalamic deep brain stimulation improves smooth pursuit and saccade performance in patients with Parkinson's disease. *Journal of NeuroEngineering and Rehabilitation, 10*, 33.

Okada, K., & Kobayashi, Y. (2009). Characterization of oculomotor and visual activities in the primate pedunculopontine tegmental nucleus during visually guided saccade tasks. *European Journal of Neuroscience, 30*(11), 2211–2223.

Okada, K., & Kobayashi, Y. (2013). Reward prediction-related increases and decreases in tonic neuronal activity of the pedunculopontine tegmental nucleus. *Front Integr Neurosci*, 7, 36.

Okada, K., & Kobayashi, Y. (2014). Fixational saccade-related activity of pedunculopontine tegmental nucleus neurons in behaving monkeys. *European Journal of Neuroscience, 40*(4), 2641–2651.

Okada, K. I., & Kobayashi, Y. (2016). Reward and behavioral factors contributing to the tonic activity of monkey pedunculopontine
tegmental nucleus neurons during saccade tasks. *Frontiers in Systems Neuroscience, 10*, 94.

O’Sullivan, J. D., Maruff, P., Tyler, P., Peppard, R. F., McNeill, P., & Currie, J. (2003). Unilateral pallidotomy for Parkinson’s disease disrupts ocular fixation. *Journal of Clinical Neuroscience, 10*(2), 181–185.

Parent, A. (2004). Giovanni Aldini: From animal electricity to human brain stimulation. *Canadian Journal of Neurological Sciences, 31*(4), 576–584.

Patterson, A., Okun, M. S., & Hess, C. (2017). High-voltage VIM region deep brain stimulation mimicking progressive supranuclear palsy. *Tremor Other Hyperkinet Mov (N Y), 7*, 449.

Pinkhardt, E. H., Jurgens, R., Lule, D., Heimrath, J., Ludolph, A. C., Becker, W., & Kassubek, J. (2012). Eye movement impairments in Parkinson’s disease: Possible role of extrapopaminergic mechanisms. *BMJ Neuro, 12*, 5.

Pollock, A., Hazelton, C., Henderson, C. A., Angilley, J., Dhillon, B., Langhorne, P., … Shahani, U. (2011). Interventions for visual field defects in patients with stroke. *Cochrane Database Systematic Review* (10): CD008388.

Racette, B. A., Gokden, M. S., Tychsen, L. S., & Perlmutter, J. S. (1999). Convergence insufficiency in idiopathic Parkinson’s disease responsive to levodopa. *Strabismus, 7*(3), 169–174.

Rascol, O., Clanet, M., Montastruc, J. L., Simonetta, M., Soulier-Estève, M. J., Doyon, B., & Rascol, A. (1989). Abnormal ocular movements in Parkinson’s disease. Evidence for involvement of dopaminergic systems. *Brain 112 (Pt 5),* 1193–1214.

Rivaud-Pechoux, S., Vermenisch, A. L., Gaynard, B., Ploner, C. J., Bejjani, B. P., Damier, P., … Pierrot-Deseilligny, C. (2000). Improvement of memory guided saccades in parkinsonian patients by high frequency subthalamic nucleus stimulation. *Journal of Neurology, Neurosurgery and Psychiatry, 68*(3), 381–384.

Robinson, F. R., Straube, A., & Fuchs, A. F. (1993). Role of the caudal fastigial nucleus in saccade generation. II. Effects of muscimol inactivation. *Journal of Neurophysiology, 70*(5), 1741–1758.

Rowe, F. J., Hanna, K., Evans, J. R., Noonan, C. P., Garcia-Finana, M., Dodridge, C. S., … Rodgers, H. (2018). Interventions for eye movement disorders due to acquired brain injury. *Cochrane Database Systematic Review, 3*, CD011290.

Sauleau, P., Pollak, P., Krack, P., Courjon, J. H., Vighetto, A., Benabid, A. L., … Tilikete, C. (2008). Subthalamic stimulation improves orienting gaze movements in Parkinson’s disease. *Clinical Neurophysiology, 119*(8), 1857–1863.

Schmalbach, B., Gunther, V., Raethjen, J., Wailke, S., Falk, D., Deuschl, G., & Witt, K. (2014). The subthalamic nucleus influences visuospatial attention in humans. *Journal of Cognitive Neuroscience, 26*(3), 543–550.

Sedov, A., Popov, V., Shabalov, V., Raeva, S., Jinnah, H. A., & Shaikh, A. G. (2017). Physiology of midbrain head movement neurons in cervical dystonia. *Movement Disorders, 32*(6), 904–912.

Servello, D., Zekaj, E., Saleh, C., Menghetti, C., & Porta, M. (2014). Long-term follow-up of deep brain stimulation of pedunculopontine nucleus in progressive supranuclear palsy: Report of three cases. *Surg Neurol Int, 5*(Suppl 8), S416–420.

Shaikh, A. G., Antoniades, C., Fitzgerald, J., & Ghasia, F. F. (2018). Effects of Deep Brain Stimulation on Eye Movements and Vestibular Function. *Front Neurol, 9*, 444.

Shaikh, A. G., & Ghasia, F. F. (2019). Saccades in Parkinson’s disease: Hypometric, slow, and maladaptive. *Progress in Brain Research, 249*, 81–94.

Shin, S., & Sommer, M. A. (2010). Activity of neurons in monkey globus pallidus during oculomotor behavior compared with that in substantia nigra pars reticulata. *Journal of Neurophysiology, 103*(4), 1874–1887.

Shires, J., Joshi, S., & Basso, M. A. (2010). Shedding new light on the role of the basal ganglia-superior colliculus pathway in eye movements. *Current Opinion in Neurobiology, 20*(6), 717–725.

Siegler, T., Bonnet, C., Serranova, T., Wild, J., Novak, D., Ruzicka, F., … Jech, R. (2013). Basal ganglia neuronal activity during scanning eye movements in Parkinson’s disease. *PLoS One, 8*(11), e78581.

Srivastava, A., Ahmad, O. F., Pacia, C. P., Hallett, M., & Lungu, C. (2018). The relationship between saccades and locomotion. *Journal of Movement Disorders, 11*(3), 93–106.

Straube, A., Ditterich, J., Oertel, W., & Kupsch, A. (1998). Electrical stimulation of the posteroventral pallidum influences internally guided saccades in Parkinson’s disease. *Journal of Neurology, 245*(2), 101–105.

Tamma, F., Caputo, E., Chiesa, V., Egidi, M., Locatelli, M., Rampini, P., … Priori, A. (2002). Anatomo-clinical correlation of intraoperative stimulation-induced side-effects during HF-DBS of the subthalamic nucleus. *Neurol Sci, 23*(Suppl 2), S109–110.

Tanaka, M., & Kunimatsu, J. (2011). Contribution of the central thalamus to the generation of volitional saccades. *European Journal of Neuroscience, 33*(11), 2046–2057.

Taverna, S., Ilijic, E., & Surmeier, D. J. (2008). Recurrent collateral connections of striatal medium spiny neurons are disrupted in models of Parkinson’s disease. *Journal of Neuroscience, 28*(21), 5504–5512.

Telkes, I., Jimenez-Shahed, J., Viswanathan, A., Aboch, A., & Ince, N. F. (2016). Prediction of STN-DBS electrode implantation track in Parkinson’s disease by using local field potentials. *Frontiers in Neuroscience, 10*, 198.

Temel, Y., Tan, S., Vlamings, R., Sesia, T., Lim, L. W., Lardeux, S., … Baunez, C. (2009). Cognitive and limbic effects of deep brain stimulation in preclinical studies. *Frontiers in Bioscience (Landmark Ed), 14*, 1891–1901.

Temel, Y., Visser-Vandewalle, V., & Carpenter, R. H. S. (2008). Saccadic latency during electrical stimulation of the human subthalamic nucleus. *Current Biology, 18*(10), R412–R414.

Temel, Y., Visser-Vandewalle, V., & Carpenter, R. H. (2009). Saccadometry: A novel clinical tool for quantification of the motor effects of subthalamic nucleus stimulation in Parkinson’s disease. *Experimental Neurology, 216*(2), 481–489.

Terao, Y., Fukuda, H., & Hikosaka, O. (2017). What do eye movements tell us about patients with neurological disorders? - An introduction to saccade recording in the clinical setting. *Proceedings of the Japan Academy, Ser. B, Physical and Biological Sciences, 93*(10), 772–801.

Terao, Y., Fukuda, H., Ugawa, Y., & Hikosaka, O. (2013). New perspectives on the pathophysiology of Parkinson’s disease as assessed by saccade performance: A clinical review. *Clinical Neurophysiology, 124*(8), 1491–1506.

Terao, Y., Fukuda, H., Yugeta, A., Hikosaka, O., Nomura, Y., Segawa, M., … Ugawa, Y. (2011). Initiation and inhibitory control of saccades with the progression of Parkinson’s disease - changes in three major drives converging on the superior colliculus. *Neuropsychologia, 49*(7), 1794–1806.

Tokushige, S., I., Matsuda, S. I., Oyama, G., Shimo, Y., Umemura, A., Sasaki, T., … Terao, Y. (2018). Effect of subthalamic nucleus deep
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