Review

Eye movements in Parkinson's disease: from neurophysiological mechanisms to diagnostic tools

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Movement disorders such as Parkinson's disease (PD) impact oculomotor function – the ability to move the eyes accurately and purposefully to serve a multitude of sensory, cognitive, and secondary motor tasks. Decades of neurophysiological research in monkeys and behavioral studies in humans have characterized the neural basis of healthy oculomotor control. This review links eye movement abnormalities in persons living with PD to the underlying neurophysiological mechanisms and pathways. Building on this foundation, we highlight recent progress in using eye movements to gauge symptom severity, assess treatment effects, and serve as potential precision biomarkers. We conclude that whereas eye movements provide insights into PD mechanisms, based on current evidence they appear to lack sufficient sensitivity and specificity to serve as a standalone diagnostic tool. Their full potential may be realized when combined with other disease indicators in big datasets.

Eye movements as indicators of the brain pathophysiology in PD

Global increases in life expectancy and industrialization are associated with higher prevalence of neurodegenerative conditions such as PD and related disorders [1]. PD is characterized by the motor symptoms rest tremor, **rigidity** (see Glossary), and **bradykinesia**, as well as gait and posture problems, typically manifesting on one side of the body at the initial stages of the disease [2,3]. Nonmotor clinical features such as sleep disorders, gastrointestinal dysfunction, autonomic dysfunction, olfactory deficits, and psychiatric disorders can also occur and significantly deteriorate quality of life [4,5].

Despite diagnostic criteria and guidelines [5], establishing an accurate and early PD diagnosis can sometimes prove difficult. Adding to the multifactorial nature of the disease is the complication that hallmark motor symptoms develop at different time points and are often preceded by less specific non-motor symptoms during an early, prodromal stage [4,5]. Moreover, several subtypes of the disease exist, emphasizing the importance of individualized diagnosis and treatment [6]. Over the past few years, there has been an increasing effort to characterize atypical **Parkinsonian disorders**. Even though new criteria have been proposed to improve diagnostic accuracy [7], this group of syndromes can often be mistaken for PD, especially in their early stages.

Characteristic eye movement abnormalities [8–10] are commonly observed in PD and Parkinsonian disorders (Box 1). Across neurological disorders, eye movements can help identify candidate populations of neurons and brain pathophysiological processes involved in the neurological symptoms [11,12], even in prodromal stages [13]. In PD, eye movements can provide basic research insights into how specific cognitive and executive processes are impacted, and in clinical research

Highlights

Humans use different types of eye movements to look at points of interest in the visual scene, to optimize visual processing, and to guide hand and body movements. Eye movements have the potential to reveal sensorimotor and cognitive processes in healthy and pathological brains.

Eye movement abnormalities are common in Parkinson's disease (PD) and can provide clues as to the identity of neuronal populations, mechanisms, and pathways that contribute to disease processes.

Eye movements may aid biomarker-based diagnosis and quantification of PD when combined with other biomarkers, although they currently appear to lack sensitivity and specificity to serve as a standalone diagnostic tool.

Therapeutic approaches such as deep brain stimulation, in addition to their clinical utility, offer a unique opportunity to systematically probe the brain networks that underlie human oculomotor control.

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Box 1. Hallmark oculomotor deficits in PD

Humans use a combination of different eye movements, such as saccades and smooth pursuit, to shift or stabilize gaze and to enhance focus on objects of interest in the visual environment. **Saccades** are typically examined for their latency, velocity, and amplitude, and whether they are made unwantedly and intrude fixation. They can be triggered externally by a sensory stimulus (e.g., visually guided saccades), or internally by instruction alone (e.g., self-paced saccades). Various experimental protocols have assessed the cognitive ability to predict, remember (e.g., memory-guided saccades), or suppress a target (e.g., antisaccades). In PD patients, saccades tend to be inaccurate and hypometric (fall short of their target). With disease progression, saccadic latency may increase and velocity decrease [101]. Deficits are generally worse for larger, and for self-paced and memory-guided saccades. Patients make frequent errors in the form of early, inadvertent saccades toward a memorized target or the visual stimulus in the antisaccade task [102].

Microsaccades are small, rapid eye movements that occur when a person is attempting to fixate their gaze on a stationary object. They are typically less than one degree of visual angle in amplitude and can occur at a rate of several per second. Microsaccades in PD can be altered, with changes in both the frequency and amplitude of these movements [41,42]. Square-wave jerks, also present in healthy older people, may interrupt fixation as well [103]. Reports of **ocular tremor** are controversial, and observed abnormalities might be compensatory eye oscillations resulting from head tremor rather than a fundamental feature of PD [104].

Smooth pursuit eye movements are examined for their latency and velocity relative to the target (velocity gain) and catch-up saccades made to reduce the eyes' position and velocity error relative to the target. PD patients can show preserved pursuit, although pursuit initiation may be delayed and velocity gain reduced, owing to hypometria in catch-up saccades. Pursuit deficits are more apparent in higher-level tasks involving tracking a remembered target or using visual cues for target selection [52]. Saccade, fixation, and pursuit deficits in PD patients reflect dysfunction in underlying neural networks required to generate appropriate eye movement responses, including several interconnecting pathways that involve the basal ganglia.

Vergence abnormalities are common in PD [66–69] and might be linked to vision problems in PD, such as blur, double vision [67], and convergence insufficiency [65]. In general, eye movements are tightly linked to visual perception [105,106], and hence, oculomotor abnormalities might influence visual deficits reciprocally. Yet only very few studies have simultaneously assessed oculomotor and visual deficits in PD in the same task (see Outstanding questions).

studies, eye movements have emerged as a promising objective and non-invasive tool to characterize motor and cognitive dysfunction [14–16]. However, whether there is sufficient evidence to date to reliably diagnose and differentiate between PD syndromes based on eye movement measurements is unclear.

In this review article, we present recent advances in using eye movements to quantify PD. We first link oculomotor deficits observed in PD to underlying neurophysiological mechanisms and pathways that had been identified in foundational studies of eye movement control in human and non-human primates. We then critically evaluate the evidence for using eye movements as criteria for diagnosis and as tools to assess symptom progression and treatment outcomes in PD.

Neural basis of healthy and abnormal eye movements

Utilizing eye movements as an objective approach to quantifying disease capitalizes on several unique features of eye movements. People have a natural and spontaneous ability to generate eye movements and can participate in eye movement assessment tasks with no or only minimal instruction [17]. Eye movements are continuous and provide fine-grained spatial and temporal information about sensory and cognitive processes, including information participants are not consciously aware of [18]. Eye tracking technology is now highly advanced and cost-effective; it can be portable and be used at the bedside. Different types of eye movements (Box 1) are flexibly deployed in various sensory stimulus- and task-settings, and the ability to execute and control these movements can be tested with relatively simple and noninvasive methods.

As outlined in Box 1, eye movement abnormalities in PD occur across the eye movement spectrum. Yet, most studies have focused on **saccades**, presumably because they are the easiest to measure at the bedside. Figure 1 shows a simplified and schematic overview of selected cortical brain areas

Glossary

Antisaccades: a saccade away from (often in the opposite direction of) a target.
Antisaccade task: a specialized experimental laboratory protocol in which observers are asked to look in the direction opposite to a visual target.
Basal ganglia: group of subcortical nuclei responsible for motor control and associated functions; disruption of the basal ganglia network is associated with symptoms of Parkinsonian disorders.
Bradykinesia: slowness of movement with a decrease in amplitude or speed as the movement is continued.
Deep brain stimulation (DBS): surgical implantation of electrodes to stimulate target areas in the brain. In PD, DBS of the subthalamic nucleus and other brain areas may be conducted to relieve symptoms and enable a decrease in dosage of antiparkinsonian medication.
Fixation: periods during which the eyes only move within a small spatial range (microsaccades and drift).
Frontal eye field (FEF): a region in the frontal cortex involved in the control of saccades and smooth pursuit eye movements, including eye movement inhibition and monitoring.
Gaze-evoked nystagmus: repetitive and involuntary oscillations or to-and-fro movements of the eyes that are triggered when the eyes are held in an eccentric position (not straight ahead).
Ocular tremor: constant, involuntary jitter of the eyes at a high frequency and low amplitude.
Parkinsonian disorders: a group of akinetic-rigid movement disorders that includes PD, corticobasal syndrome, multiple system atrophy, vascular parkinsonism, dementia with Lewy bodies, and progressive supranuclear palsy.
**Pupil light reflex:** in response to light, the pupil constricts, and in darkness, it dilates.
Rigidity: increased muscle tone.
Saccades: rapid, ballistic movements made by both eyes from one point in space to another, interspersed by periods of fixation.
Smooth pursuit eye movements: slow, continuous responses of the eyes to moving objects.
Square-wave jerks: involuntary saccades from and back to a fixation point.
Substantia nigra pars reticulata (SNr): a midbrain area implicated in PD and involved in the initiation of voluntary
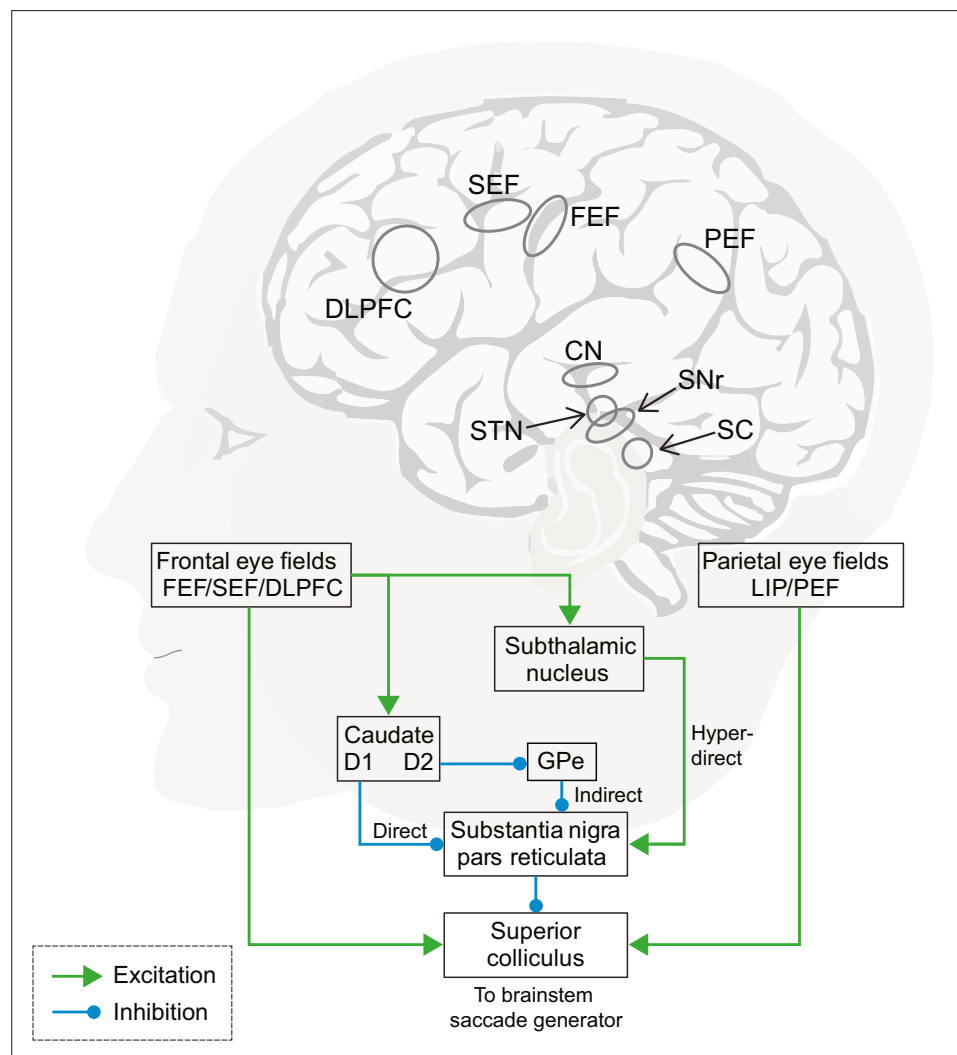
Figure 1. Brain areas involved in the generation of saccades. Brain regions are illustrated on a schematic of the human brain. The location of brain areas is approximate, and only selected areas and connections are shown. In the network schematic, green arrows indicate excitatory connections (glutamate-mediated), and blue connections indicate inhibitory connections (GABA-mediated). The SNr is the inhibitory gateway to the SC, and it can both promote and inhibit saccades. Abbreviations: CN, caudate nucleus; DLPFC, dorsolateral prefrontal cortex; FEF, **frontal eye field**; GPe, external segment of the globus pallidus; LIP, lateral intraparietal cortex; PEF, parietal eye field; SC, superior colliculus; SEF, supplementary eye field; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus. Figure inspired by Figure 7–13 in [19].

movements and the suppression of involuntary ones.

Subthalamic nucleus (STN): part of the basal ganglia system. The STN is a primary target site for deep brain stimulation in PD.

Superior colliculus (SC): a layered nucleus in the midbrain involved in target selection and the initiation of eye and other movements, as well as the integration of inputs from different sensory modalities.

Tauopathies: a group of neurodegenerative disorders characterized by abnormal aggregation of tau protein in the brain.

Vergence: disjunctive movements of the eyes made to reduce visual blur and achieve fusion of an object's image for binocular vision. Vergence eye movements facilitate depth perception.

for saccade control. Many of the same areas are involved in the control of pursuit and small-scale saccades (microsaccades) as well. Saccades are promoted and inhibited via projections to the **superior colliculus (SC)** [19]. Whereas frontal and parietal eye fields have excitatory (glutamatergic) connections to SC (Figure 1, green arrows), a second pathway (Figure 1, blue lines) links frontal and parietal areas to the SC through the **basal ganglia** and particularly, the **substantia nigra pars reticulata (SNr)**. The SNr tonically inhibits the SC via GABAergic projections, thus inhibiting saccades. At the same time, inhibition of the SNr itself can promote saccades. The SNr receives inputs from at least three different pathways, which have all been implicated in PD: a direct pathway with GABAergic projections through the caudate nucleus that promotes saccades, an indirect

pathway with GABAergic projections through the external segment of the globus pallidus (GPe) that inhibits saccades, and a hyperdirect pathway with excitatory input directly from the **subthalamic nucleus (STN)**, cancelling saccades. Together, this system forms an inhibitory gateway to the SC, potentially involved in reward-modulated and motivated behavior [20,21], and in deciding whether to initiate a saccade [22,23]. We will return to elements of this pathway in our discussion of **antisaccade** behavior, as well as the effects of **deep brain stimulation (DBS)** in PD.

In the human and non-human primate literature, the inhibitory control of saccades has been probed with countermanding (stop signal), go/no-go and **antisaccade tasks**. In countermanding or stop signal tasks, observers execute a speeded response (e.g., button press or saccade) to a go signal, such as the disappearance of a **fixation** spot. In a subset of trials, participants must abort that response when a stop signal (e.g., reappearance of fixation spot) is shown. This task probes the initiation and cancellation of planned movements, and the monitoring of movement consequences, subserved by the distinct networks in the frontal cortex [24,25] shown in Figure 1. Because of the tasks' sensitivity to measuring inhibitory and impulse control – executive functions that can be impacted in diseases affecting the corticobasal ganglia pathways [26] – antisaccades have gained wide recognition for use in psychiatric and neurological populations [27]. Relatedly, the antisaccade task (Box 2) has emerged as a precise means of quantifying neurological function [28,29], and an internationally standardized protocol has allowed direct comparisons of results across experimental settings and laboratories [30].

A hallmark of impaired inhibitory control in the antisaccade task is a significant increase in directional errors. In addition, two key findings, related to inhibitory dysfunction, are commonly observed in PD: the first, prolonged saccadic latency or reaction time, results from increased inhibition of the SC by the SNr. The second finding is a tendency to make early, premature saccades in stop-signal tasks, delayed reaction time tasks, or antisaccade tasks. This effect could relate to an independent process that bypasses the SC-basal ganglia route [31]. It is important to note that even though PD patients, as compared to healthy controls, show increased error rate, longer latency, and more premature saccades in the antisaccade task, this behavior is as variable as the disease itself, as illustrated in Figure 2, and is not specific to PD but also occurs in other neurodegenerative diseases [32].

Overall, the antisaccade task and similar protocols are useful because they not only mark PD symptoms but can also shed light on the underlying brain pathophysiology. In the context of

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Box 2. The antisaccade task

Saccades can either be elicited reflexively, by the sudden onset of a visual event or a loud sound, or voluntarily, by the desire to look at a particular object or location. Similarly, individuals can voluntarily suppress the reflexive urge to make a saccade. In the antisaccade task, the observer must suppress an automatic saccade to a suddenly appearing peripheral target (sometimes termed the prosaccade) and instead look in the opposite direction (the antisaccade). This task thus requires (i) the initiation of a reflexive saccade to the peripheral target; (ii) the subsequent inhibition of this saccade; and (iii) the initiation of a voluntary antisaccade in the opposite direction. Such flexible control of action – orienting and suppressing a movement depending on task and situational demands – characterizes executive control.

Neurophysiological studies in macaque monkeys have revealed the circuitry underlying successful saccade inhibition and reorienting in the antisaccade task [107], making antisaccades highly serviceable for the investigation of diseases affecting volitional, executive control. The examination of directional errors – commonly a short-latency prosaccade followed by a corrective antisaccade – in conjunction with single-neuron recordings in saccade-control brain areas revealed a key role of the SC and FEF in this task. The firing rate of SC [108] and FEF [109] saccade neurons is correlated with direction errors as well as prolonged latency, indicating that lack of inhibitory input to these areas might underlie poor performance in this task. A likely main source of such an inhibitory signal to the SC is the SNr (see Figure 1 in main text) in the basal ganglia [110,111]. Congruent with findings of reduced dopamine levels in the basal ganglia and associated depletion of dopamine levels in downstream areas such as the SC and brainstem [112], antisaccade performance is significantly impaired in PD patients.
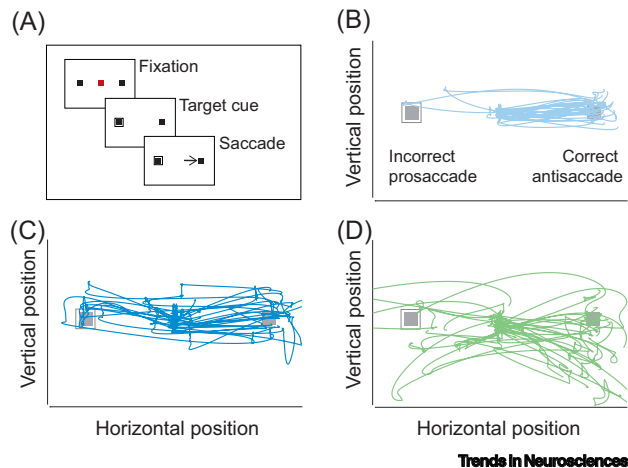
Figure 2. The antisaccade task, and interindividual variability in task performance in Parkinson's disease (PD). (A) Typical trial timeline in a standardized antisaccade task protocol [30]. Following a fixation period of randomized duration, one target location is cued. Cue onset indicates that a saccade can be initiated (here shown without a gap between fixation offset and cue onset). (B–D) Individual 2D eye position traces for three PD patients (data from [50]), revealing large heterogeneity in antisaccade deficits. Whereas the patient shown in panel B performed the task comparably to healthy individuals and only made two incorrect prosaccades, directional errors were more frequent in the other two patients, who also showed large vertical deviations.

assessing impulsivity, the antisaccade task has gained particular importance in examining effects of DBS as a treatment for PD, as we discuss in the following sections.

Another saccade protocol that consistently reveals deficits in PD patients is the memory-guided saccade task. In this task, a saccade is expected to be performed toward the location of a remembered peripheral-onset stimulus after a brief delay. PD patients typically display accuracy abnormalities (hypometria) [33,34]. Notably, these deficits are not unique to the oculomotor system but occur in memory-guided pointing movements as well [35]. Although working memory performance may be impaired in PD, hypometric memory-guided movements are believed to result from a deficient memory-to-motor signal transformation process, rather than from cognitive deficits, because manipulations of memory load do not further impair saccades [34,35]. Memory-guided saccade abnormalities do not seem to respond to levodopa treatment [36] but may improve with DBS (see below). These higher-order saccade deficits point at the involvement of brain networks that include the basal ganglia and regions in the prefrontal cortex that support working memory functions [37].

Saccades fall along an amplitude continuum from large to small [38,39], and microsaccades are controlled by some of the same brain areas and mechanisms that also underlie saccades [40] (Box 1). In PD, fixational eye movements such as microsaccades are often abnormal [41,42], although disturbances are nuanced and patient-specific [43] and sometimes reported in healthy age-matched controls as well. In general, PD patients and those with progressive supranuclear palsy (PSP) show an increase in involuntary saccades during fixation (also termed saccadic intrusions, or specifically described as **square-wave jerks**, which are coupled with large microsaccades) [42]. More frequent microsaccades during fixation, especially in the horizontal direction, are associated with a decreased ability to hold fixation for long periods of time in PD [44]. Understanding microsaccade abnormalities in PD is important because these types of eye movements are known to increase visual acuity [45] and are critical for daily tasks such as reading [46]. Accordingly, microsaccade disturbances in PD might be related to low-level visual functions such as contrast sensitivity [47] and performance in high-level vision tasks such as visual search [48].

In contrast to considerable impairments in saccades, PD patients show only mild smooth pursuit deficits, typically seen as decreased eye velocity relative to the target velocity, which can then invoke saccades to allow the eyes to catch up to the target [8,49]. Not many studies

have examined the coordination of pursuit and saccades in PD. Some found comparatively normal catch-up saccade rates during visually guided pursuit [47,50]. Others reported increased catch-up saccade rates in PD patients and attributed these to a failure to inhibit saccades [51]. Whether changes in catch-up saccades during pursuit in patients are triggered by a retinal error signal or whether they are a form of saccadic intrusion could be addressed by studies that include a larger battery of different eye movement tests, further discussed in the following sections.

In general, pursuit deficits occur in healthy aging as well, and are therefore not necessarily specific to PD, thus rendering visually guided pursuit of limited diagnostic value for PD. Impaired pursuit appears to be more prevalent when tasks involve higher-level cognitive processing or deliberation, such as remembering the motion path of a target (memory-based pursuit [11]). When patients with preserved memory function had to remember the meaning of two consecutive visual cues, they tended to use saccades rather than smooth pursuit to track the target [52]. Similarly, PD patients cannot easily initiate smooth pursuit in cognitive anticipation of a visual target. This is shown in studies that report fewer, slower, and delayed anticipatory eye movements in patients as compared to healthy controls in tasks that included a target direction reversal [53] or required anticipating the start of target motion [54]. Because the same function is relatively preserved in healthy older people [55], this deficit appears to be disease-specific. Conversely, tasks that require predicting the velocity of a previously shown target that is only briefly blanked from view yielded only small performance differences between patients and controls [54]. Notably, even though patients tended to reach a lower peak velocity in these testing protocols, their eyes decelerated less after the target had disappeared (i.e., maintained target velocity at a higher rate). These findings show that patients can build up and maintain an internal representation of an object's motion direction and velocity if they have been recently exposed to the same object (i.e., in the same trial).

Indeed, some oculomotor functions are preserved in PD patients. Most notably, this includes the latency of visually guided saccades [56] and the initiation of visually driven smooth pursuit [52]. PD patients also perform corrective saccades at a comparable level to healthy controls when they must rapidly adapt to a new movement goal [57]. Congruently, movement adaptation is preserved when the trajectory of a hand movement must be corrected online [58]. All these tasks have in common that they require a sense of urgency – a movement needs to be initiated or corrected rapidly. When PD patients participated in a rapid go/no-go task that simulated the real-world requirements of batting a baseball, their ball interception performance was comparable to that of healthy controls, despite mild impairments in pursuit and saccadic tracking of the ball [50]. Notably, the same patients exhibited expected performance impairments in saccade and antisaccade tasks, including inhibitory dysfunction manifested in an abundance of premature saccades to the wrong target (Figure 2).

We speculate that this differential preservation of function for rapid action in dynamic tasks might imply the involvement of pathways that bypass dopaminergic connections through the basal ganglia, or a hyperdirect pathway linking frontal cortical eye movement areas to the basal ganglia through the STN [59] (Figure 1). Although there is no direct evidence yet that links this pathway to smooth pursuit, the STN is involved in pursuit and saccadic eye movement control and possibly in impulse control function and reward-modulated goal pursuit [60]. Moreover, STN activity serves switching from automatic to voluntary saccades to adapt to changes in task and situational demands [61]. It is directly implicated in the pathophysiology of PD [62] and serves as the main target area for DBS [63,64], as we discuss in the following section.

We have focused so far in this section on conjugate eye movements – cases in which movements of the eyes are yoked and go in the same direction – triggered by stimuli presented in the

frontoparallel plane. In the real world, these movements are always combined with disconjugate eye movements, such as **vergence**, to achieve binocular vision and to focus on objects of interest across different depth planes. Vergence abnormalities result in impaired fusion and double vision (Box 1), problems observed commonly in PD patients [65,66]. Congruently, vergence eye movements are frequently impaired in these patients as compared to healthy age-matched controls [66–69]. Reduced gain and increased convergence latency may be more pronounced for vergence driven by disparity than for vergence driven by visual blur (accommodation) [66]. This differential impairment could help understand the effect of PD on the vergence neural pathways and mechanisms. The control of disparity- and blur-driven vergence has been assumed to be partially separate anatomically, potentially relying on different brainstem nuclei and downstream connections along a cerebro-ponto-cerebellar pathway [66,70], although this notion remains debated [71]. The effect of subthalamic DBS on vergence in PD has the potential to further clarify the neural substrate underlying vergence eye movements. Another interesting aspect about vergence in PD is that patients compensate for the convergence deficit by using different types of eye movements strategically [72]. As further evidence of plasticity in this system, a preliminary study with a small group of PD patients reported recovery from convergence insufficiency following vergence training [73], although a clinical trial would be required to confirm these results.

In summary, whereas PD patients commonly show significant impairments in saccade accuracy, in the latency and error rate of antisaccades, and in vergence eye movements, pursuit can be preserved and is therefore less often targeted in studies seeking to develop eye movement-based biomarkers. This relative preservation of pursuit in conjunction with saccade impairments, as well as differential impairments in vergence, can provide valuable insights into which specific neuronal populations are impacted by the disease.

Eye movements used for diagnosis

Classifying and diagnosing movement disorders can be difficult due to their complex symptoms and varied early clinical presentation. Yet, a correct classification lays the foundation for the subsequent diagnostic process, has prognostic value, and impacts treatment choices [3]. A clinical diagnosis of PD requires not only the manifestation of cardinal symptoms – bradykinesia combined with at least rest tremor or rigidity – but also the absence of exclusion criteria [5]. In this context, the presence of specific eye movement abnormalities can assist in ruling out PD. Cerebellar oculomotor abnormalities – sustained **gaze-evoked nystagmus**, macro square-wave jerks, and saccades that are hypermetric (overshoot) – feature strongly in this category. These are abnormalities that are commonly caused by cerebellar and brainstem disorders but are absent in PD [19]. Moreover, slow or absent vertical saccades (vertical gaze palsy) in the downward direction rule out a diagnosis of PD. By contrast, vertical gaze palsy combined with large square-wave jerks [41,42] can be a characteristic symptom of PSP. In many instances, the diagnosis of PSP can be missed in the early stages. Patients are often classified as having PD, because early PSP symptoms tend to resemble those of idiopathic PD despite PSP being a **tauopathy**. In fact, slow vertical saccades may be one of the first signs of PSP and are a hallmark symptom in many patients [74,75]. Combined with other symptoms, supranuclear vertical gaze palsy can also indicate dementia with Lewy bodies, a Parkinsonian disorder that commonly causes dementia. Similarly, gaze-evoked nystagmus can be present in other disorders within the parkinsonian spectrum such as, for instance, multiple system atrophy. Abnormal nystagmus is diagnostically specific for this disorder, because nystagmus is not usually present in either PD or PSP [19].

A systematic comparison between groups of patients with PD, PSP, and multiple system atrophy as well as patients with rapid eye movement (REM) sleep behavior disorder – associated with the

prodromal stage of some parkinsonian disorders – revealed that saccade abnormalities manifest early during the disease and differentiate PSP from other patient groups [15]. In this study, participants engaged in simple, uninstructed free viewing of short video clips, a task that allows measuring spontaneous and continuous eye movement behavior, including changes in pupil size (Box 3). The gaze of patients with PSP was more biased toward the screen center than that of other patient groups, and PSP patients exhibited fewer and smaller vertical eye movements (saccades and microsaccades) than all other groups. Across all patients, vertical saccade frequency and amplitude deficits correlated with motor symptom severity. The observed significant reduction in vertical saccade rate and amplitude – pointing to involvement of midbrain regions for vertical saccade control – differentiate PSP patients from other patient groups and suggest differences in the pathophysiology between these disorders. Patients in the prodromal group (REM sleep disorder group) revealed saccade alterations mimicking abnormalities observed in the other patient groups, implying that saccade parameters could be used as early disease markers [76]. To substantiate this conclusion, however, longitudinal studies are necessary, in which patients are tracked as they convert from a prodromal stage to manifest disease, and this process might take a considerable amount of time given the heterogeneity in disease progression.

A clinical bedside assessment of horizontal and vertical saccades, fixational stability and gaze-evoked nystagmus may provide important information in the differential clinical diagnosis of PD. However, the usefulness of eye movements in defining PD subtypes remains to be determined. Subtyping relies entirely on clinical symptoms (87% of studies included in a systematic review; [77]), and eye movements are not yet part of this assessment. Given the large variability in eye movement abnormalities in PD patients, it may prove difficult to define parameter ranges that separate one PD subtype from another. It may be that eye movements will contribute to a biomarker-based classification approach of PD subtypes, in combination with other disease indicators, rather than being used on their own.

Eye movements as tools to assess disease progression and treatment effects

The previous section focused on using eye movements as a potential tool to diagnose PD or to differentiate PD from related disorders. Eye movement alterations might not only indicate disease duration and motor burden [29], but can also reveal cognitive impairments, and thus help identify patients who might be at risk for rapid cognitive decline [78]. Applying hierarchical cluster analysis to data on latency and directional errors in the antisaccade task yielded different patterns of cognitive abilities in PD patients. These different patient clusters, however, did not differ from each other in terms of cognitive impairment. These findings indicate that various saccade performance profiles might be related to similar cognitive function in PD patients [79] and provide an important cautionary note that even though eye movement abnormalities may reliably occur in PD, sensitivity and predictive power are currently lacking. However, in newly diagnosed patients, eye movement tests can potentially provide insights into when cognitive functions begin to decline [80] and help identify early signs of cognitive impairment, which in turn, serves as a prognostic factor for disease severity. A study in newly diagnosed, drug-naive PD patients – allowing the researchers to disentangle cognitive impairments related to disease from those related to medication – revealed that antisaccades were already significantly impaired in early PD, and in particular the antisaccade error rate was higher in patients than healthy controls [81,82]. Some cognitive domains were also significantly impaired, even before medication was initiated in this newly diagnosed patient group.

Moreover, eye movements could potentially be used to assess the effects of antiparkinsonian medications or other treatments on motor control. The effect of medication on saccades has been investigated by several groups. The most widely studied parameter is prosaccade latency,

> **Box 3. Alterations in pupil physiology in PD**
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> In a healthy person, the pupils dilate and constrict with changes in illumination. This **pupil light reflex** is the result of antagonistic actions of the iris sphincter and dilator muscles, which are innervated, respectively, by the parasympathetic and sympathetic nervous systems. In neurodiagnostic applications, the pupil light reflex is an important test of autonomic nervous system function. As compared to age-matched, healthy controls, PD patients exhibit a delayed pupil light reflex and a decrease in the amplitude, velocity, and acceleration of the constriction response [113]. Constriction velocity appears to be one of the most sensitive indicators in PD patients, linked to disease duration and severity [114]. Notably, alterations in the pupil light reflex occur in the absence of clinically noticeable autonomic nervous system dysfunctions, indicating that pupil markers could potentially contribute to the diagnostic process during prodromal disease stages, and before impairments in saccade parameters are seen [115].
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> Under constant light conditions, the pupil's diameter also responds sensitively to a large range of cognitive processes [116]. There is evidence that such cognitively modulated pupil responses are reduced in PD patients. In an interleaved pro- and antisaccade task, pupil dilation in healthy controls depended on the type of task and response; that is, the pupil was larger prior to stimulus appearance for correct antisaccades than for correct prosaccades or erroneous antisaccades. PD patients' pupil diameter depended less on task and response type, suggesting deficits in voluntary movement preparation in PD [117]. Similarly, PD patients show diminished changes in pupil size in response to different levels of expected reward, and these effects are particularly pronounced when testing patients in an off-medication state [118].
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> Cognitive modulations of pupil size are served by a neural circuit receiving descending cortical inputs via the locus coeruleus or the SC, which in turn receive cortical inputs from areas such as FEF [119]. This circuitry overlaps with some of the areas and pathways impacted by PD, and thus, abnormalities in the pupil response in PD patients could be mediated by loss of dopaminergic neurons in areas such as the locus coeruleus [120]. Pupil size is emerging as a useful tool to index cognitive and autonomic function impairments in PD, although it is important to note that changes in the pupil light reflex are not specific to PD. They also occur in other neurodegenerative diseases, such as Alzheimer's disease [121], and across a wide range of brain injuries, implying that they currently lack specificity to be useful as a biomarker to differentiate between these disorders.

which is prolonged in PD and appears to be further prolonged when patients are on dopaminergic medication compared to off medication [83–85]. The paradoxical increase in the degree of oculomotor abnormality, in the presence of a symptomatic treatment that can normalize somatic motor function, is noteworthy. Of greater significance is the finding that antisaccade latency, while significantly prolonged by PD, either improves [83] or is unaffected by symptomatic medication [85]. This may make it a useful biomarker of disease modifying drugs in future studies, and further work is needed in this area.

Eye movements may also be affected by therapeutic electrical stimulation of parts of the basal ganglia for treatment of motor symptoms of PD. In contrast to the effect of antiparkinsonian medication, DBS of either the STN (Figure 1) or the globus pallidus internus (GPi) reduces prosaccade latency [86,87] in parallel to improvements seen in motor symptoms. Whereas DBS improves accuracy in memory-guided saccades [88], the effect of DBS on antisaccade error rate is less clear. Some studies suggest that stimulation of the GPi, but not the STN, improves performance on the antisaccade task when patients are on their antiparkinsonian medication [89]. By contrast, another study found that DBS of the STN can impair antisaccade performance, and this was observed in patients who were off medication when tested [90]. It is possible that these conflicting results stem from testing patients in various states of medication as well as varied disease duration. Indeed, testing patients in ON and OFF DBS states and ON and OFF dopaminergic medication yields three key observations [87]. (i) DBS increases antisaccade error rate in patients who were OFF medication when tested. (ii) DBS and medication state interact, and medication reduces the detrimental effects of DBS on antisaccade performance. (iii) DBS effects on patients' saccade task performance differ widely from one patient to another, similarly to what has been described for antisaccade task performance, as discussed in the preceding text (Figure 2). It appears that effects of DBS on saccade and antisaccade performance are dependent on the individual (e.g., medication state and disease duration) and testing context as well as potentially on the exact location [91] and frequency of stimulation [92]. In addition, DBS of the STN disrupts the normal modulation of saccadic reaction time according

to target probability, in line with the notion that the basal ganglia perform Bayesian statistics for competing movement selection [93]. When asked to saccade to a target in one of two locations associated with a low or high probability of target appearance, saccade latencies to the likely target location were shorter than those to the unlikely location for healthy controls and patients OFF stimulation. However, ON stimulation, patients were no longer able to tailor their responses to stimulus probability, and saccade latencies to unlikely stimuli did not increase as they were expected to [94].

Even though the scientific and clinical focus has been on the assessment of saccades and antisaccades, studies have also looked at the effect of STN DBS on fixational eye movements in PD [95] and found that the amplitude and frequency of microsaccades are increased following DBS. In many patients, DBS also increased the prevalence of square-wave jerks, but with high interindividual variability in results. Moreover, STN DBS might alter the temporal pattern of microsaccades. Microsaccades in general are temporally more variable (i.e., less regular or clustered) in PD than in healthy controls. DBS can partially restore microsaccade rhythmicity and clusteredness in PD patients [43]. These results demonstrate that the STN may play a role in modulating the temporal dynamics of microsaccades.

Few studies have looked at the effects of DBS on smooth pursuit in PD or related disorders. Assessing oculomotor control in a group of nine PD patients who had undergone STN DBS surgery and were tested OFF medication found reduced smooth pursuit gain with DBS off, whereas switching the stimulator on brought the gain back up toward unity [96]. Likewise, pursuit velocity accuracy, defined as the percentage of the time during which pursuit velocity was within 20% of target velocity, was increased by DBS. These results demonstrate the potential of DBS to mitigate pursuit dysfunction in PD. Given the therapeutic effects that DBS of the basal ganglia has on saccades and pursuit in PD, it will be important to investigate in the future whether these benefits extend to vergence eye movements as well.

In summary, the modulatory effects of subthalamic DBS on the characteristics of saccades, microsaccades, and pursuit serve not only as important treatment indicators but also provide a unique opportunity to investigate how the basal ganglia interact with other neural structures that control eye movements [97,98]. This knowledge, together with our understanding of the neurophysiology of eye movements, can help elucidate the mechanism of action of DBS, which are still not well understood.

Concluding remarks

PD is a heterogeneous disorder where diagnosis, progression, and treatment are currently monitored using standardized clinical rating scales such as the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS [99]). Although clinical examination of saccades has, for a long time, formed part of the assessment of neurodegenerative conditions such as Huntington's disease and PSP, it does not feature in scales for assessing PD despite the evidence that eye movements are abnormal [9,10]. Future translational research in PD will be dependent on finding more precise and objective measures of disease that follow standardized protocols (see Outstanding questions). Measurements of eye movement abnormalities are strong candidates for this. Investigators are increasingly turning to more complex multivariate approaches and machine learning algorithms to address reliability concerns [28,100]. Multicenter and large collaborative studies [16,32] including thousands of patients and consensus-based eye movement protocols pave the way to big data approaches, linking clinical, behavioral, and cellular-molecular dimensions. Importantly, differential impairments in saccades and pursuit eye movements in PD allow testing assumptions about different populations of neurons along overlapping brain

Outstanding questions

Researchers are beginning to understand the neural mechanisms that underlie changes in eye movements in PD. How are these changes related to disease progression, and how are they impacted by medication or DBS?

Whereas saccades are commonly impaired in PD, other oculomotor functions, such as smooth pursuit, can be preserved. Are there specific neuronal populations in areas that jointly control saccades and pursuit that are impacted by PD?

Deficits in visual function (e.g., acuity, contrast sensitivity) can occur as non-motor symptoms in PD, and are associated with dopamine deficiency and related morphological changes in the retina. Assessing visual and oculomotor abnormalities within the same studies and tasks can help characterize underlying mechanisms and address the potential link between the two. Are visual abnormalities related to or even caused by oculomotor abnormalities?

To ensure consistent results across studies, eye movement measurement, interpretation, and reporting need to follow standard protocols. Reaching methodological consensus is easier for simplified tasks such as pro- or antisaccades, but can be more challenging for complex paradigms. How can eye movement protocols that incorporate naturalistic task requirements be standardized?

The sensitivity and specificity of eye movements as a biomarker of PD need to be further determined. How well can eye movements help distinguish PD from other conditions with shared symptoms?

Eye movements are beginning to be used to quantify neurodegenerative disease and monitor its progression. Can eye movements be used to measure the efficacy of treatment in clinical trials?

pathways that may be impacted by the disease. Treatment approaches such as DBS, in addition to their therapeutic value, provide scientists with a unique opportunity to systematically probe and investigate the brain networks that underlie human eye movement control.

Declaration of interests

The authors have no conflicts of interest to declare.

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