

Oculomotor and Visuo-Vestibular Function in Parkinson's Disease

Adolfo M. Bronstein, Tim Anderson, Diego Kaski, Michael MacAskill, and Aasef Shaikh

In this chapter we will describe how Parkinson's disease (PD) affects patients' eye movements, both bedside and laboratory, preceded by brief review of the anatomo-physiological substrate of eye movements. We will provide a practical summary of how to use the eye movement examination to aid the differential diagnosis of the parkinsonian syndromes, in particular idiopathic PD from multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS). A sub-section will describe how deep brain stimulation (DBS) also influences eye movements in PD. Despite a plethora of eye movement laboratory studies in PD it is still relatively unknown what the eye movements of these patients are like in real life. Given that the eyes move in order to see better, does the akinesia of PD impose visual deprivation or delays during ecological whole-body movements? Finally, because the visual, vestibular, and oculomotor systems are tightly coupled, we will review this interaction which has bearing on the decades-long question of the contribution of central vestibular dysfunction to abnormalities of postural balance in PD. A practical implication of visuo-vestibular interactions in PD is that an observation of mini-ocular tremor in PD, with huge potential implications as a disease marker, has now been shown to be an artefact. Most authors agree that minute head oscillations, primary or transmitted from other body tremor, in these patients induce a compensatory eye movement response via the vestibulo-ocular reflex (VOR), which, on eye movement recordings but not clinically, looks like an ocular tremor.

Underlying Neural Mechanisms Involved in Eye Movements

Eye movements fall into two general classes. The first acts to stabilize the fovea in the face of motion

of the head or objects of interest in the external world (the vestibulo-ocular reflex (VOR), fixation, smooth pursuit (SP), and optokinetic nystagmus (OKN)). The second, saccades, quickly bring the fovea with its superior acuity to bear upon salient objects. The first are largely automatic or reflexive responses whilst the second, saccades, are an inherent component of the continuously active cycle of perception, action, and cognition. In PD, the most apparent clinical and laboratory impairments are with saccades. Their tight link with attentional processes indicates that they are likely to reflect not only motor function but especially cognitive impairment in PD.

Saccades

Saccades are generated to support a variety of behavioral tasks. These range from the simple (reflexively glancing at the location of a suddenly occurring visual or auditory event) to complex and volitionally planned (looking at the remembered location of an object for a specific purpose, such as a clock on the wall in order to tell the time). Some tasks are laboratory specific, such as anti-saccades (looking in the *opposite* direction to a suddenly appearing target) and devised to layer cognitive requirements on top of the final oculomotor execution. Anti-saccade production requires suppression of the competing reflexive saccade to the visual target while concurrently planning a saccade in the opposite direction to a calculated, nonvisual target location. Although all saccades share a final common pathway, differing task demands can result in differential recruitment of higherlevel control areas (see Figure 11.1).

Cerebral Control of Saccades

The functional areas controlling saccades are depicted and described in Figures 11.1 and 12.2.



Figure 11.1 Selected cortical areas involved in oculomotor control. These include the dorsolateral prefrontal cortex (DLPFC), frontal, supplementary, and parietal eye fields (FEF, SEF, PEF), posterior parietal cortex (PPC), and the middle temporal visual area (MT). An additional region not shown is the cingulate eye field (CEF) in the anterior cingulate [14].

These cortical regions, all with reciprocal connections, project caudally primarily to the superior colliculus (SC). In addition, frontal areas project to SC via an indirect basal ganglia pathway and also directly to pontine nuclei, especially the nucleus reticularis tegmenti pontis (NRTP), which in turn projects to dorsal vermis and fastigial nucleus in the cerebellum. There are minor direct projections from the frontal eye fields (FEF) to the paramedian pontine reticular formation (PPRF) [1]. The basal ganglia (BG) oculomotor pathway is concerned most with eye movements related to reward and initiation of remembered, predictive, and self-paced voluntary saccades (Figure 11.2). The net result of these various connections for the SNpr, the main output of the BG for eye movements, is that the indirect pathway is excitatory and the direct pathway inhibitory [2, 3]. In this manner the BG pathway regulates voluntary saccades by maintaining, enhancing, or releasing the SNpr tonic inhibition of the SC. Thus, the production of saccades is a consequence of the various cortical and subcortical excitatory and inhibitory influences upon the brainstem generating structures.

Smooth Pursuit

Smooth pursuit (SP) eye movements, in concert with fixation, stabilize the fovea in relation to movement of objects in the surrounding environment. During head movement the smooth pursuit system combines with the vestibulo-ocular reflex (VOR), fixation, and optokinetic system to maintain clear and stable vision. Visual information for smooth pursuit initiation and maintenance is processed by the extrastriate cortical regions MT (V5, in the middle temporal visual area) and MST (medial superior temporal visual area) and thence PPC, FEF, and 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 [1, 4]. The long and widespread nature of these pathways explains that smooth pursuit abnormalities are a sensitive albeit non-specific marker of CNS dysfunction.

Clinical Oculomotor Examination Findings in Parkinson's Disease

Decreased saccade amplitude can be detected even in clinical examination of PD patients by observing saccades made in response to verbal commands to look repeatedly between two of the examiner's fingers in the horizontal and vertical directions (Figure 11.3). The amplitude of saccades is visibly reduced when the patient is then asked to execute the same movements repetitively at their own volition (e.g. self-paced saccades), especially for

Oculomotor and Visuo-Vestibular Function in Parkinson's Disease



Figure 11.2 Schema for the cerebral control of saccades. (A, top) The posterior parietal cortex (PPC) or parietal eye field (PEF) is particularly involved in target selection (where and what to look at) and triggering reflexive (automatic) saccades. The frontal cortex (FEF, DLPFC, SEF) is particularly concerned with willed saccadic behavior (if, when, and how to look) and performance of voluntary saccades. The basal ganglia pathway is particularly concerned with volitional and not reflexive saccades. There is tonic inhibition of the SC by SNpr. There is also phasic release, or increase of inhibition, depending on the balance of activity in the direct and indirect pathways. (B, bottom) Saccade production is the result of interplay between cortical and subcortical excitatory and inhibitory influences. Red arrows denote inhibitory connections; green arrows denote excitatory connections. DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye fields; GPe: globus pallidus externa; IML: intramedullary lamina; PPRF: parapontine reticular formation; riMLF: rostral interstitial nucleus of the medial longitudinal fasciculus; SC: superior colliculus; SEF: supplementary eye fields; SNpr: substantia nigra pars reticulate; STN: subthalamic nucleus.

Adapted and modified from [94].

upwards saccades, with a series of several saccades needed to reach the target. In patients with PD, reduced saccade amplitude is detectable early in the disease course, presumably reflecting neurodegeneration (Figure 11.4). The bedside anti-saccade (BAS) task has been employed in the assessment of executive dysfunction in persons with mild cognitive impairment (MCI) and dementia due to a variety of disorders including some with PD but there has been no study of the BAS task specifically in PD [5]. Other deficits on clinical examination are increased number of square wave jerks (SWJs) and impairment in smooth pursuit, VOR suppression, and OKN (optokinetic nystagmus) but these are mild and difficult to distinguish from agerelated changes.

Convergence insufficiency is present in some 40% of PD patients and may present as diplopia in a proportion (16%) during near vision (e.g. reading) [6]. It has commonly been thought that there is mild restriction of conjugate upgaze in PD but confirmatory studies with age-matched controls have been lacking. Many PD patients exhibit reduced blink rate and some a degree of lid retraction and lid lag though these latter features are more commonly seen in PSP [7]. Other ocular problems encountered in PD include dry eyes (exacerbated by antiparkinsonian drugs with anticholinergic activity), amantadine-induced corneal oedema and keratitis, decreased contrast sensitivity and reduced color discrimination, visuospatial impairments, and misperceptual disorders (illusions and hallucinations; see Chapter 8) [8].

Laboratory Eye Movement Findings in Parkinson's Disease

Starting with the landmark observations by DeLong and Melville Jones [9], laboratory studies





have dealt predominantly with saccades and less so smooth pursuit. Voluntary saccades (endogenously generated) have exhibited greater abnormalities than reflexive (exogenously induced) saccades. In reflexive tasks the sudden onset of a stimulus automatically determines the saccade target, but in voluntary saccade tasks some cognitive operation is required to select the saccade target [10]. In most voluntary saccade tasks participants must shift attention to a visual stimulus without making a saccade to that stimulus, and either initiate a saccade in the opposite direction (antisaccades), or wait for a further cue (delayed or memory-guided saccades). People with PD consistently make more unintended saccades to the visual stimulus (hyper-reflexivity), and they make the correct voluntary saccades at longer latencies and with smaller amplitudes (hypometria) than controls [11]. Oculomotor hypometria is present early in the disease, while more cognitively driven impairments (prolonged latencies and reduced inability to inhibit saccades in antisaccade and delayed-response tasks) become evident as non-dopaminergic cortical-level degeneration occurs [12, 13]. Saccadic latency and velocities in cognitively normal PD patients, especially for reflexive saccades, have generally been normal [14] or minimally abnormal [15] with minor hypometria the commonest feature of reflexive saccades [3, 12, 16].

Mild impairment of smooth pursuit (SP) is a consistent finding [17]. Interestingly there does not seem to be an underlying abnormality in the SP pathway itself. Rather, there is a saccadic abnormality whereby anticipatory saccades take the eyes ahead of the moving target perhaps again reflecting deficits in inhibition as already discussed [18].

Saccades and Cognitive Impairment in Parkinson's Disease

There have been no published systematic studies of confrontational eye movement examination in those with cognitive impairment and dementia in PD though supranuclear vertical gaze palsy may be observed in a minority of dementia with Lewy bodies (DLB) patients [19]. PD patients with mild cognitive impairment (PD-MCI) exhibit mild prolongation of reflexive visually guided saccade latency compared to those with normal cognition, but no difference in amplitude [12]. Those with PD and dementia (PDD) exhibit prolonged latency and reduced amplitude of reflexive and voluntary saccades, impaired predictive behavior, and reduced saccadic inhibition, compared to those with normal cognition and controls [11, 12]. Thus, saccadic latency correlates with cognitive status in PD, suggesting that eye movement recordings could provide useful objective markers for cognitive decline.

Ocular Dyskinesia and Other Levodopa Effects on Eye Movements

Up to 16% of advanced PD patients with levodopa-induced dyskinesias (LID) of limbs and trunk may also exhibit simultaneous ocular dyskinesia – stereotyped upward and/or horizontal conjugate gaze movements [20]. We have observed similar dyskinesia but in a smaller percentage of patients with LID, with the dominant deviation being upwards, and not appreciated by the patients themselves.

The effects of levodopa on eye movements in PD are not well established. Improvement in convergence insufficiency [21] and pursuit performance [22] has been reported but it is the influence of levodopa on saccades in PD that has been the most explored. No consistent effect has emerged and this accords with the authors' experience that dopaminergic therapy has little effect on saccadic performance, suggesting that non-dopaminergic pathways are more influential in PD saccadic dysfunction.

Eye Movements in the Atypical Parkinsonian Disorders

The careful clinical eye movement examination is most helpful in distinguishing PD (mild and nonspecific deficits) from the atypical parkinsonian disorders, which have both shared and characteristic oculomotor abnormalities.

Eye Movements in Multiple System Atrophy

Patients with MSA-C (cerebellar type) usually present with symptoms that suggest a late-onset cerebellar syndrome associated with typical cerebellar eye signs such as gaze-evoked, downbeat and rebound nystagmus, and impaired smooth pursuit [23]. Eye movements in early MSA-P (parkinsonian type) may initially be similar to those in PD, but



Figure 11.5 Schematic of typical saccade abnormalities in PD and the atypical parkinsonian disorders. It is common for healthy individuals to slightly undershoot the target and use a small secondary saccade to achieve the target. PD patients commonly show mild hypometria (undershooting) reauiring two or more corrective saccades to reach the target. In MSA and CBS the degree of saccadic hypometria is often greater than in PD with delayed launching of saccades (saccadic apraxia) an additional feature of CBS. In PSP the hallmark is early saccadic slowing with considerable hypometria developing over time. CBS: corticobasal syndrome; MSA: multiple system atrophy; PD: Parkinson's disease; PSP: progressive supranuclear palsy. Figure by Bronstein & Anderson (2021), distributed at https://doi. org/10.6084/m9.fig share.14390951 under an open CC-BY 4.0 license.

a combination of increased square wave jerks, mild or moderate saccade hypometria and impaired VOR suppression and smooth pursuit indicate that the patient is unlikely to have PD [24]. Saccade velocities are normal in patients with MSA and only a minority have a vertical supranuclear gaze palsy which if present is mild [24]. Positional downbeat nystagmus or perverted headshaking nystagmus (vertical nystagmus on horizontal head oscillation) is present in about one-third of patients with MSA-P [24, 25]. Slow saccades or significant supranuclear gaze palsy indicate an alternative diagnosis, particularly PSP (Figure 11.5).

Eye Movements in Progressive Supranuclear Palsy

The earliest and most diagnostically important eye movement abnormality in patients with PSP-RS (Richardson syndrome) is slowing of vertical saccades; slowing of horizontal saccades appears later [26]. Though slowing of downward saccades was considered a hallmark of PSP-RS [27], upward saccade velocity is as slow as, or sometimes even slower, than downward saccades, and upgaze palsy occurs more frequently than downgaze palsy [26] perhaps in part related to the upgaze limitation commonly present in the elderly. Vertical and horizontal saccades become very hypometric which, when added to the low velocity of each saccadic segment, can make the eyes take more than one to two seconds to travel from one end of the orbit to the opposite. Smooth pursuit is at least moderately impaired [28]. Small-amplitude horizontal SWJs on fixation are more prominent than in other parkinsonian disorders [29]. In addition, reduced blink rate, eye-opening and eye-closing apraxia - observed as slowness of eye opening and closing – are frequently present, and blepharospasm in some. Eye movements in patients with PSP-P (PSP-parkinsonism and PSP-PAGF (PSPpure akinesia with gait freezing) are less well studied. Supranuclear gaze palsy is usually absent during early PSP-P but develops late in the disease course in 70% of patients [30]. By definition, supranuclear gaze palsy is not evident in the first five years after disease onset in patients with PSP-PAGF, but can appear as a late feature [31].

Eye Movements in Corticobasal Syndrome

The oculomotor characteristic of clinically diagnosed CBS is saccadic apraxia [32], evidenced clinically as delay in the initiation of saccades to command or towards a target, especially towards the side of the apraxic limbs, and in the laboratory as a marked increase in saccade latency [33]. This difficulty in launching saccades is often accompanied and signaled by the patient using an auxiliary head movement in the same direction. In contrast to PSP, saccade velocities in patients with CBS are normal [34]. Smooth pursuit may be moderately impaired, but not as much as in patients with PSP. Antisaccade errors in CBS are similar in extent to those encountered in PSP [33, 34].

In summary, in the differential diagnosis of parkinsonism, slowed vertical saccades can suggest a diagnosis of PSP (and help rule out PD, MSA, or CBS), cerebellar eye signs (especially gaze-evoked, headshaking, or positional downbeat nystagmus) suggest MSA, and saccadic apraxia suggests CBS (Figure 11.4).

Effects of Deep Brain Stimulation on Eye Movements and Vestibular Function

There is a paucity of understanding how DBS affects oculomotor and balance deficits that are common in PD and lead to problems in navigation, walking, and to falls. DBS can improve, worsen, or have no effect on these functions. The focus of this section is to understand typical clinical oculomotor or balance deficits that are seen in PD with DBS, and how to manage them.

Effects of Deep Brain Stimulation on Eye Movements

Subthalamic nucleus (STN) DBS can cause ocular dysconjugacy with adduction and depression of the eye ipsilateral to the side of STN DBS [35]. Such ocular misalignment, if mild, leads to blurred vision but if moderate or severe, to diplopia. The basis of this deficit is the strategic location of the oculomotor nerve fascicles emerging from the oculomotor nucleus. The oculomotor nerve passes medially, ventrally, and posteriorly to the STN. If the active DBS electrode within the STN is in proximity to the oculomotor nerve fibers, the electrical charge may activate the ipsilateral nerve fibers causing monocular medial and downward deviation and on some occasions, tonic counterclockwise torsion and lid retraction of the ipsilateral eye [35]. These oculomotor signs can be used to guide localization of the DBS electrode. Another oculomotor side effect is conjugate gaze deviation away from the side of STN DBS due to activation of the fronto-pontine fibers within the internal capsule by a lead that is too lateral. Treatment of any of such stimulation-dependent DBS side effects usually requires moving the location of the active electrode to an alternate contact. Alternative strategies include minimizing the electric spread to the oculomotor fibers that can be accomplished by constricting the volume of tissue activation by reducing the voltage or pulse-width, switching to bipolar montage, or current steering with contemporary directional electrode leads.

Subthalamic nucleus DBS does not necessarily lead to negative visual consequences. Some who have existing visuomotor deficits may even experience benefits. There is sparse literature examining effects of STN DBS on visuomotor function [36]. It is however likely that STN DBS mediates any visuomotor benefits by modulating abnormal basal ganglia outflow that would otherwise adversely affect the superior colliculus, precerebellar pontine nuclei, or the cerebellum [2]. More studies are required to examine the mechanistic underpinning of beneficial and adverse effects of DBS on visuomotor deficits in PD. Combined PPD and STN stimulation seems to add further benefit on antisaccadic task performance, suggesting a DBS ascending effect on frontal lobe processing [37].

Effects of Deep Brain Stimulation on Vestibular Function and Balance

The effects of STN DBS on balance function are unpredictable, improving it in some patients but worsening it in others [38, 39]. These conflicting observations suggest that STN DBS affects multiple neuronal pathways. One important nearby pathway that can be modulated by the electrical field generated by STN DBS is the cerebellothalamic pathway, a major output from the deep cerebellar nuclei [40]. This probably explains stimulation-dependent increase in vertigo and other complex self-motion illusions [41]. STN DBS can also modulate vestibular activity via activation of the precerebellar nuclei and thereby the subthalamo-ponto-cerebellar projections [40]. Although these different mechanisms can describe diverse effects of STN DBS on vestibular function, such hypotheses need further experimental support.

In summary, there are various effects of DBS on oculomotor and vestibular function, depending in part on the location of the stimulation. Diplopia and blurred vision that is commonly seen in DBS patients is usually due to direct activation of the oculomotor nerve fascicles, with tonic conjugate deviation of the eyes secondary to activation of cortico-bulbar fibers. Vestibular effects of the STN DBS may be caused by activation of cerebello-thalamic fibers projecting to the cerebral cortex responsible for motion perception. The approach to addressing these DBS-induced vestibular or visual side effects is to constrict the volume of tissue activation by delivering less electrical charge or orientating the current away from the relevant anatomical target.

Eye Movements in the Real World

Evolving technology has made it feasible to record gaze in naturalistic settings. A systematic review of studies of real-world eye movements in PD concluded that eye movement strategies were used to compensate for the more severe somatomotor symptoms despite presence of typical oculomotor impairments [42]. These studies show that oculomotor performance in real-world tasks is closely linked to visual and cognitive impairments. Of note, PD can add massive delays upon visual target acquisition – up to half a second for large gaze re-orientations [43].

Impaired or even frozen gait in PD can be facilitated by strong visual cues [44]. Although striking, the mechanism remains unclear. For example, do stripes on the floor act directly as a visual target to drive the feet toward them, or indirectly, by shifting attention downwards towards the lower limbs themselves? When external visual cues (e.g. floor stripes) are provided, with or without the view of the lower limbs being occluded, gaze tracking indicates that both those with PD and controls fixate the cues one or more steps ahead of the current foot position. Such external cues are sufficient to improve parkinsonian gait, with direct visualization of the limbs unnecessary [45]. Freezing-of-gait (FOG) can be induced by changing gait direction. Body turns ideally consist of an orderly sequence of rotations, commencing with saccades and followed in order by the head, trunk, and feet. In

PD however, *en bloc* turning is common, and with parkinsonian saccades being hypometric, more saccades are needed, leading in part to a longer duration of the entire turn [46].

Cognitive decline in PD is common so it is relevant to consider how much impairment might constrain neuropsychological test performance, independent of cognitive decline. Gaze recordings of images from neuropsychological tests (e.g. the Rey complex figure and interlocking pentagons), show that saccadic hypometria leads to a restricted range of areas being fixated [47]. Meanwhile, gaze strategies in neuropsychological tasks are relatively normal in PD with normal cognition but become progressively worse in PD-MCI and then PDD [48]. Surprisingly, there has been little investigation of eye movements during reading in PD, although reading speed correlates with gait performance [49, 50].

Eye tracking during completion of the Symbol-Digits Modalities Test (SDMT), which requires decoding of symbols on a page by referring to a "key" at the top of the page, was able to identify the time point when people had learned the symbol-digit associations sufficiently to write responses without continually needing to look up the key [51]. Poorer performance in PD participants with mild cognitive impairment was not due to impaired oculomotor control, validating the SDMT as a cognitively specific assessment tool in PD.

Visuo-Vestibular Interaction in Parkinson's Disease

Parkinson's disease patients suffer from prominent postural problems and it is therefore reasonable to ask whether vestibular dysfunction may be partly responsible for these. Here, however, we will not review gait and postural control in PD as a whole because this topic is vast, reviewed often, and lies outside the remit of this visuovestibular-oculomotor chapter [52–54].

Vestibulo-Ocular Reflex and Otolith Function

Despite decades of study, whether the VOR is affected in PD still remains somewhat controversial. In 1982 Reichert et al. reported reduced or absent nystagmus in 36 PD patients to a bithermal caloric stimulation, a finding that was associated with postural instability, suggesting perhaps a link between impaired vestibular function and postural control in PD [55]. Abnormal caloric-induced nystagmus was later reported in over 80% of PD patients but the response was heightened not reduced in over half and was not related to clinical PD motor symptoms [56]. A recent study with well-selected PD patients did not report abnormalities in the caloric vestibular test [57]. By contrast, in two small studies in patients with Pisa syndrome (lateral trunk flexion), one found unilateral vestibular hypofunction in each case and the other, greater subjective visual vertical errors than those without Pisa syndrome, consistent with otolith dysfunction [58, 59]. Notably however, the subjective visual vertical is preserved in non-selected PD patients [57, 60].

The VOR assessed with rotating chairs in the dark is challenging in PD. Reduced rotational function in the dark with paradoxical enhancement during fixation-mediated VOR suppression in early reports was likely due to drowsiness [61]. The advent of easily available computerized measures of the VOR has led to further work, with modestly elevated VOR gains in PD than controls using the video head impulse test (vHIT; i.e. 1.20 versus 0.99, respectively) [62]. Whilst this result may be consistent with the increased caloric nystagmus reported by Cipparrone et al., subtle differences in VOR gains observed may be due to the technical challenge of utilizing the vHIT in patients with neck rigidity/stiffness. Besides, the increased vHIT gain in PD patients runs counter to the initial papers reporting reduced vestibular caloric responses. Furthermore, the normal interplay between VOR activation and suppression required during ecological head-eye coordination tasks is essentially preserved in PD, again indicating preserved vestibular function [43, 63, 64].

There has been interest in exploring neurophysiological brainstem function in PD, not least following reports that noisy galvanic vestibular stimulation (nGVS) or caloric vestibular stimulation can reduce severity of some PD symptoms (see Cronin et al. for a comprehensive review [65]). The vestibular-startle, elicited by free-fall, is preserved in PD but abnormal in atypical parkinsonism [66] as the latter is known to have brainstem reticular formation pathology. Reduced or absent vestibular-evoked myogenic potential (VEMP) responses in PD patients correlate with contralateral rigidity, bradykinesia score, ipsilateral dyskinesia score, as well as sleep, mood, and memory impairment [67]. The cVEMP (a loud click-evoked vestibulo-collic reflex thought to be otolith mediated) in PD has been reported as frequently abnormal (although not unanimously [68]), despite group latency values being preserved [57, 67, 69–73].

Otolith dysfunction in PD could theoretically arise from degeneration in the vestibular nuclei of PD patients, disrupting connections between vestibular nuclei and the dorsal raphe nuclei, and reducing the effect of dopamine on the excitability of vestibular nuclei. Nevertheless, in routine clinical practice, peripheral vestibular function is usually normal in PD patients.

It is important that in PD patients with complaints of vertigo or recent falls, not only should orthostatic blood pressure be measured but also a Dix-Hallpike maneuver undertaken to exclude benign positional paroxysmal vertigo (BPPV), the commonest cause of episodic vertigo regardless of any co-existing neurological disorder.

Multi-Sensory Integration and the Vestibular System

Early experiments in the motor, ocular-motor, and postural systems indicated that PD patients were visually "dependent" [63, 74, 75]. Specifically, postural responses elicited by a large moving visual display were larger and less susceptible to adaptation in PD patients than controls [74]. Such findings can be interpreted either as an upregulated visuo-motor postural loop or a downregulated vestibulo-proprioceptive loop. The latter is in agreement with Purdon Martin's classical experiments on postural responses in post-encephalitic Parkinsonian patients where, based on similar postural responses to a tilting support surface in Parkinsonian patients and subjects with bilaterally absent vestibular function, he concluded that the main cause of instability in Parkinsonism was central vestibular dysfunction [76]. However, any investigation of postural responses in Parkinsonism could be confounded by the severe global motor difficulties these patients experience. For this reason researchers switched to perceptual rather than motor assessments of vestibular function.

Nakamura et al. investigated the perception of head rotation (vestibular, cervical, or combined)

in PD with a remembered saccade paradigm [77, 78]. The confound introduced by the motor system (in this case the oculomotor system) was confirmed by the finding that, despite remembered saccades being hypometric, the actual perception of head rotation was preserved in PD patients, indicating preserved vestibular function. In further perceptual experiments measuring the relative strength of visual-vestibular inputs, again bypassing any motor influence, PD patients were normal [60].

Galvanic (DC electrical) vestibular stimulation in PD patients elicits normal or even increased postural responses [79], a finding incompatible with vestibular dysfunction being the cause of the postural disturbance in PD. Similarly, the long latency component of the stretch reflex to limb displacement is also enhanced in PD [80]. Taken together these results indicate that any sensory channel visual, vestibular, or proprioceptive - when individually (experimentally) stimulated induces normal or large postural responses in PD patients. Therefore, PD does not disrupt simple, mono-sensory, reflex responses. Rather, the underlying problem responsible for instability and ultimately falls is hypokinetic (small) and slow (bradykinetic) postural responses, which are not scaled to the magnitude of the perturbation [81, 82]. It seems that any sensory processing contribution to the postural problem in PD is negligible compared to the central disruption of integrative motor programs.

Perceiving the direction of self-motion heading - is a type of multi-sensory integration that depends on visual and vestibular information. Precision of heading perception is typically assessed in a heading discrimination task where subjects are presented with a whole-body linear translation (leftward/rightward), of varying intensity, and are asked to indicate the perceived direction of motion to derive a threshold. Such paradigms have been used in PD patients using linear translations on a motion platform. One study found increased vestibular thresholds in PD [83], but another that used the same method reported no impairment [84]. Patients with normal performance were less severely affected so it has been proposed that heading discrimination may only be impaired in later stages of the disease. PD

patients also appear to be less accurate in judging forward tilt but only in a multi-cue condition such as combining tilt movements with translations [85].

Sensory paradigms in the fMRI scanner may help understand central sensory-motor integration without motor interference by PD. One study has used fMRI in PD patients to study cortical activation in areas involved in visual motion processing [86]. PD patients exhibited significantly reduced activity in the medial temporal area and cingulate sulcus visual areas in response to simulated optic flow. Activation of the cingulate sulcus visual area was inversely correlated with disease severity, suggesting that impaired visuospatial performance in PD may be a result of impaired neural processing within visual motion and visuo-vestibular regions [87].

Is the So-Called Pervasive Ocular Tremor in Parkinson's Disease the Result of a Normal Visuo-Vestibular Interaction?

In 2012 Glitchel and colleagues reported "pervasive ocular tremor" that was universally present in a cohort of 112 PD patients, and mostly absent in healthy controls [88]. The presence, or not, of "ocular tremor" in PD has been the object of recent controversy [88]. The eye oscillations described had an average fundamental frequency of 5.7 Hz (i.e. within the range of the limb tremor in PD: 4-7 Hz), a mean horizontal amplitude of 0.27 degrees, and mean vertical amplitude of 0.33 degrees. The tremor persisted for the duration of the recording, although the waveform characteristics were variable. The authors did not use head restraint but recorded head movements using a magnetic tracker in a subset of patients and controls; no head oscillation was detected in any subject implying that the observable ocular tremor was independent of head motion. Nevertheless, given the lack of other reports of ocular fixation instability across decades of eye movement recordings in patients with parkinsonism, the possible origin of the pervasive ocular tremor generated significant discussion and controversy.

A subsequent study reported ocular oscillations during oculography in two consecutive PD patients attending a balance clinic. These were accompanied by a recordable head tremor that had the same fundamental frequency and high coherence with both the eye oscillations and a recordable limb tremor [89]. The eye oscillations were in the opposite direction (anti-phase) to the head oscillation and dampened by physically restraining the head. This suggests that the ocular tremor is a compensatory eye movement secondary perhaps to a head tremor transmitted from the limbs. Indeed, despite extensive oculographic recordings in PD, ocular tremor had not previously been described [90]. Further, during fundoscopy of many hundreds of PD patients over decades we (personal observations) and others have not observed such tremor of the globes [90].

It transpires that the existence of "ocular tremor" depends on the technique and equipment used to record the eye movements in a person with PD (see Kaski and Bronstein for a review [91]). In our experience, when recording eye movements with video-oculography – the almost universal technique nowadays – in PD patients it is very common to see the eye image oscillating considerably within the field of view of the camera, due to tremor of the limbs being transmitted mechanically to the head. The recorded gaze signal, however, can be completely steady. This reflects that, despite the head motion, with an intact VOR, the patient's eyes remain steady in space, which is what an eye tracker using corneal reflection stabilization measures. In the original report of the phenomenon, corneal reflection stabilization was not applied [88]. We subsequently analyzed 681 recordings from 188 patients and 66 controls and indeed observed a tremulous pupil signal in many, though not all, patients at around 4 Hz frequency, matching the characteristics reported by Gitchel et al. Crucially, a nearidentical signal existed in the corneal reflection signal. The Fast Fourier Transform power of both oscillations was strongly correlated with clinical UPDRS tremor ratings. When the two signals were subtracted, the oscillation disappeared (Figure 11.6) [92]. This indicates that so-called ocular tremor is indeed a consequence of head motion, secondary to somatomotor tremor.



Figure 11.6 Here we illustrate the principles of pupil center-corneal reflex video-oculography and how it can remove artefacts due to somatomotor tremor in PD. (A) A PD patient with tremor. The pupil is centered in the camera field of view. The red arrow is the vector showing the relative position of the corneal reflex and the pupil center. (B) The head has moved substantially relative to the camera while the eye maintains a constant gaze direction in space. The relative positions of the pupil and corneal reflex within the image are unchanged. (C) The eye after a saccade, making a pure rotation within a stationary head. The pupil center and the corneal reflection have moved differentially within the image. (D) The horizontal pupil center position of a person with PD and substantial somatomotor tremor, showing a substantial oscillation due to head movement. The patient is tracking a target stepping 20 degrees rightwards and then leftwards. (E) The corneal reflection signal shares the same oscillation. (F) Simply subtracting the corneal reflex signal from the pupil position reveals a stabilized gaze signal, showing that the patient was actually maintaining steady fixations upon fixed targets, interrupted only by saccades and micro saccades. That is, the substantial oscillations are solely due to head motion, with no residual ocular tremor.

What are the clinical implications of these observations? It seems that ocular tremor in PD does not exist. Rather, the observations are indicative of a head tremor, either transmitted to the neck muscles from the trunk or limbs, or even from the neck muscles themselves [93] in the presence of an intact VOR and manifest as an ocular tremor if the head is not fixed.

References

- Leigh RJ, Zee DS. *The Neurology of Eye* Movements, 5th Ed. Oxford University Press; 2015, xx, 1109.
- Hikosaka O, Takikawa Y, Kawagoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol Rev 2000; 80(3): 953–978.
- Terao Y, Fukuda H, Ugawa Y, Hikosaka O. New perspectives on the pathophysiology of Parkinson's disease as assessed by saccade performance: a clinical review. Clin Neurophysiol 2013; 124(8): 1491–1506.
- Buttner U, Buttner-Ennever JA. Present concepts of oculomotor organization. Prog Brain Res 2006; 151: 1–42.
- Hellmuth J, Mirsky J, Heuer HW, et al. Multicenter validation of a bedside antisaccade task as a measure of executive function. Neurology 2012; 78(23): 1824–1831.
- Schindlbeck KA, Schonfeld S, Naumann W, et al. Characterization of diplopia in non-demented patients with Parkinson's disease. Parkinsonism Relat Disord 2017; 45: 1–6.
- Corin MS, Elizan TS, Bender MB. Oculomotor function in patients with Parkinson's disease. J Neurol Sci 1972/3; 15(3): 251–265.
- Weil RS, Schrag AE, Warren JD, et al. Visual dysfunction in Parkinson's disease. Brain 2016; 139(11): 2827–2843.
- DeJong JD, Jones GM. Akinesia, hypokinesia, and bradykinesia in the oculomotor system of patients with Parkinson's disease. Exp Neurol 1971; 32(1): 58–68.
- Walker R, Walker DG, Husain M, Kennard C. Control of voluntary and reflexive saccades. Exp Brain Res 2000; 130(4): 540–544.
- Mosimann UP, Müri RM, Burn DJ, et al. Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies. Brain 2005; 128: 1267–1276.
- 12. Macaskill MR, Graham CF, Pitcher TL, et al. The influence of motor and cognitive impairment upon visually guided saccades in Parkinson's

disease. Neuropsychologia 2012; **50**(14): 3338–3347.

- Terao Y, Fukuda H, Yugeta A, et al. Initiation and inhibitory control of saccades with the progression of Parkinson's disease – changes in three major drives converging on the superior colliculus. Neuropsychologia 2011; 49(7): 1794–1806.
- Anderson TJ, MacAskill MR. Eye movements in patients with neurodegenerative disorders. Nat Rev Neurol 2013; 9(2): 74–85.
- Stuart S, Lawson RA, Yarnall AJ, et al. Prosaccades predict cognitive decline in Parkinson's disease: ICICLE-PD. Mov Disord 2019; 34(11): 1690–1698.
- Chan F, Armstrong IT, Pari G, et al. Deficits in saccadic eye-movement control in Parkinson's disease. Neuropsychologia 2005; 43(5): 784–796.
- 17. Pinkhardt EH, Jurgens R, Becker W, et al. Differential diagnostic value of eye movement recording in PSP-parkinsonism, Richardson's syndrome, and idiopathic Parkinson's disease. J Neurol 2008; 255(12): 1916–1925.
- Pinkhardt EH, Kassubek J. Ocular motor abnormalities in Parkinsonian syndromes. Parkinsonism Relat Disord 2011; 17(4): 223–230.
- Nakashima H, Terada S, Ishizu H, et al. An autopsied case of dementia with Lewy bodies with supranuclear gaze palsy. Neurol Res 2003; 25(5): 533–537.
- 20. Grotzsch H, Sztajzel R, Burkhard PR. Levodopainduced ocular dyskinesia in Parkinson's disease. Eur J Neurol 2007; 14(10): 1124–1128.
- Racette BA, Gokden MS, Tychsen LS, Perlmutter JS. Convergence insufficiency in idiopathic Parkinson's disease responsive to levodopa. Strabismus 1999; 7(3): 169–174.
- Sharpe JA, Fletcher WA, Lang AE, Zackon DH. Smooth pursuit during dose-related on-off fluctuations in Parkinson's disease. Neurology 1987; 37(8): 1389–1392.
- 23. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008; 71(9): 670–676.
- Anderson T, Luxon L, Quinn N, et al. Oculomotor function in multiple system atrophy: clinical and laboratory features in 30 patients. Mov Disord 2008; 23(7): 977–984.
- Lee JY, Lee WW, Kim JS, et al. Perverted head-shaking and positional downbeat nystagmus in patients with multiple system atrophy. Mov Disord 2009; 24(9): 1290–1295.
- 26. Chen AL, Riley DE, King SA, et al. The disturbance of gaze in progressive supranuclear palsy:

implications for pathogenesis. Front Neurol 2010; 1: 147.

- Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996; 47(1): 1–9.
- Troost BT, Daroff RB. The ocular motor defects in progressive supranuclear palsy. Ann Neurol 1977; 2(5): 397–403.
- 29. Altiparmak UE, Eggenberger E, Coleman A, Condon K. The ratio of square wave jerk rates to blink rates distinguishes progressive supranuclear palsy from Parkinson disease. J Neuroophthalmol 2006; **26**(4): 257–259.
- 30. Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSPparkinsonism. Brain 2005; 128(Pt 6): 1247–1258.
- 31. Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Mov Disord 2007; **22**(15): 2235–2241.
- Stell R, Bronstein AM. Eye movement abnormalities in extra pyramidal disease. In: Marsden CD, Fahn S (eds.). *Movement Disorders 3*. Butterworth-Heinemann Ltd; 1994, 88–113.
- Vidailhet M, Rivaud-Pechoux S. Eye movement disorders in corticobasal degeneration. Adv Neurol 2000; 82: 161–167.
- Boxer AL, Garbutt S, Seeley WW, et al. Saccade abnormalities in autopsy-confirmed frontotemporal lobar degeneration and Alzheimer disease. Arch Neurol 2012; 69(4): 509–517.
- Bejjani BP, Arnulf I, Houeto JL, et al. Concurrent excitatory and inhibitory effects of high frequency stimulation: an oculomotor study. J Neurol Neurosurg Psychiatry 2002; 72(4): 517–522.
- Shaikh AG, Antoniades C, Fitzgerald J, Ghasia FF. Effects of deep brain stimulation on eye movements and vestibular function. Front Neurol 2018; 9: 444.
- Khan AN, Bronstein A, Bain P, Pavese N, Nandi D. Pedunculopontine and subthalamic nucleus stimulation effect on saccades in Parkinson disease. World Neurosurg 2019; 126: e219–e31.
- Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR. Axial disability and deep brain stimulation in patients with Parkinson disease. Nat Rev Neurol 2015; 11(2): 98–110.
- 39. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the

subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003; **349**(20): 1925–1934.

- 40. Bostan AC, Strick PL. The cerebellum and basal ganglia are interconnected. Neuropsychol Rev 2010; **20**(3): 261–270.
- Shaikh AG, Straumann D, Palla A. Motion illusion-evidence towards human vestibulo-thalamic projections. Cerebellum 2017; 16(3): 656–663.
- 42. Stuart S, Alcock L, Galna B, Lord S, Rochester L. The measurement of visual sampling during realworld activity in Parkinson's disease and healthy controls: a structured literature review. J Neurosci Methods 2014; 222: 175–188.
- 43. Anastasopoulos D, Ziavra N, Savvidou E, Bain P, Bronstein AM. Altered eye-to-foot coordination in standing parkinsonian patients during large gaze and whole-body reorientations. Mov Disord 2011; **26**(12): 2201–2211.
- 44. Glickstein M, Stein J. Paradoxical movement in Parkinson's disease. Trends Neurosci 1991; 14 (11): 480–482.
- 45. Vitorio R, Lirani-Silva E, Pieruccini-Faria F, et al. Visual cues and gait improvement in Parkinson's disease: which piece of information is really important? Neuroscience 2014; 277: 273–280.
- 46. Lohnes CA, Earhart GM. Saccadic eye movements are related to turning performance in Parkinson disease. J Parkinsons Dis 2011; 1(1): 109–118.
- 47. Matsumoto H, Terao Y, Furubayashi T, et al. Small saccades restrict visual scanning area in Parkinson's disease. Mov Disord 2011; 26(9): 1619–1626.
- 48. Archibald NK, Hutton SB, Clarke MP, Mosimann UP, Burn DJ. Visual exploration in Parkinson's disease and Parkinson's disease dementia. Brain 2013; 136(Pt 3): 739–750.
- 49. Jehangir N, Yu CY, Song J, et al. Slower saccadic reading in Parkinson's disease. PLoS One 2018; 13 (1): e0191005.
- 50. Moes E, Lombardi KM. The relationship between contrast sensitivity, gait, and reading speed in Parkinson's disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2009; 16(2): 121–132.
- Pascoe M, Alamri Y, Dalrymple-Alford J, Anderson T, MacAskill M. The symbol-digit modalities test in mild cognitive impairment: evidence from Parkinson's disease patients. Eur Neurol 2018; **79**(3–4): 206–210.
- 52. Cano Porras D, Siemonsma P, Inzelberg R, Zeilig G, Plotnik M. Advantages of virtual reality in the rehabilitation of balance and gait: systematic review. Neurology 2018; 90(22): 1017–1025.

- 53. Marazzi S, Kiper P, Palmer K, Agostini M, Turolla A. Effects of vibratory stimulation on balance and gait in Parkinson's disease: a systematic review and meta-analysis. Eur J Phys Rehabil Med 2020; . DOI: 10.23736/S1973-9087.20.06099-2
- 54. Olson M, Lockhart TE, Lieberman A. Motor learning deficits in Parkinson's disease (PD) and their effect on training response in gait and balance: a narrative review. Front Neurol 2019; **10**: 62.
- Reichert WH, Doolittle J, McDowell FH. Vestibular dysfunction in Parkinson disease. Neurology 1982; 32(10): 1133–1138.
- Cipparrone L, Ginanneschi A, Degl'Innocenti F, et al. Electro-oculographic routine examination in Parkinson's disease. Acta Neurol Scand 1988; 77 (1): 6–11.
- Venhovens J, Meulstee J, Bloem BR, Verhagen WI. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. Eur J Neurosci 2016; 43(12): 1636–1646.
- Scocco DH, Wagner JN, Racosta J, Chade A, Gershanik OS. Subjective visual vertical in Pisa syndrome. Parkinsonism Relat Disord 2014; 20(8): 878–883.
- 59. Vitale C, Marcelli V, Furia T, et al. Vestibular impairment and adaptive postural imbalance in parkinsonian patients with lateral trunk flexion. Mov Disord 2011; 26(8): 1458–1463.
- Bronstein AM, Yardley L, Moore AP, Cleeves L. Visually and posturally mediated tilt illusion in Parkinson's disease and in labyrinthine defective subjects. Neurology 1996; 47(3): 651–656.
- White OB, Saintcyr JA, Tomlinson RD, Sharpe JA. Ocular motor deficits in Parkinson's disease. 3. Coordination of eye and head movements. Brain 1988; 111: 115–129.
- 62. Lv W, Guan Q, Hu X, et al. Vestibulo-ocular reflex abnormality in Parkinson's disease detected by video head impulse test. Neurosci Lett 2017; 657: 211–214.
- Bronstein AM, Kennard C. Predictive ocular motor control in Parkinson's disease. Brain 1985; 108: 925–940.
- Waterston JA, Barnes GR, Grealy MA, Collins S. Abnormalities of smooth eye and head movement control in Parkinson's disease. Ann Neurol 1996; 39(6): 749–760.
- Cronin T, Arshad Q, Seemungal BM. Vestibular deficits in neurodegenerative disorders: balance, dizziness, and spatial disorientation. Front Neurol 2017; 8: 538.
- 66. Bisdorff AR, Bronstein AM, Wolsley C, et al. EMG responses to free fall in elderly subjects and

akinetic rigid patients. J Neurol Neurosurg Psychiatry 1999; **66**(4): 447–455.

- Shalash AS, Hassan DM, Elrassas HH, et al. Auditory- and vestibular-evoked potentials correlate with motor and non-motor features of Parkinson's disease. Front Neurol 2017; 8: 55.
- Cicekli E, Titiz AP, Titiz A, Oztekin N, Mujdeci B. Vestibular evoked myogenic potential responses in Parkinson's disease. Ideggyogyaszati szemle 2019; 72(11–12): 419–425.
- de Natale ER, Ginatempo F, Paulus KS, et al. Paired neurophysiological and clinical study of the brainstem at different stages of Parkinson's disease. Clin Neurophysiol 2015; 126(10): 1871–1878.
- 70. de Natale ER, Ginatempo F, Paulus KS, et al. Abnormalities of vestibular-evoked myogenic potentials in idiopathic Parkinson's disease are associated with clinical evidence of brainstem involvement. Neurol Sci 2015; 36(6): 995–1001.
- Pollak L, Prohorov T, Kushnir M, Rabey M. Vestibulocervical reflexes in idiopathic Parkinson disease. Clin Neurophysiol 2009; 39(4–5): 235–240.
- Potter-Nerger M, Govender S, Deuschl G, Volkmann J, Colebatch JG. Selective changes of ocular vestibular myogenic potentials in Parkinson's disease. Mov Disord 2015; 30(4): 584–589.
- 73. Potter-Nerger M, Reich MM, Colebatch JG, Deuschl G, Volkmann J. Differential effect of dopa and subthalamic stimulation on vestibular activity in Parkinson's disease. Mov Disord 2012; **27**(10): 1268–1275.
- 74. Bronstein AM, Hood JD, Gresty MA, Panagi C. Visual control of balance in cerebellar and parkinsonian syndromes. Brain 1990; **113**(Pt 3): 767–779.
- 75. Cooke JD, Brown JD, Brooks VB. Increased dependence on visual information for movement control in patients with Parkinson's disease. Can J Neurol Sci 1978; 5(4): 413–415.
- 76. Martin JP. *The Basal Ganglia and Posture*: Lippincott; 1967.
- Nakamura T, Bronstein AM. The perception of head rotation in Parkinson's disease. Acta Otolaryngol Suppl 1995; 520(Pt 2): 387–391.
- Nakamura T, Bronstein AM, Lueck C, Marsden CD, Rudge P. Vestibular, cervical and visual remembered saccades in Parkinson's disease. Brain 1994; 117(Pt 6): 1423–1432.
- Pastor MA, Day BL, Marsden CD. Vestibular induced postural responses in Parkinson's disease. Brain 1993; 116(Pt 5): 1177–1190.

- Rothwell JC, Obeso JA, Traub MM, Marsden CD. The behaviour of the long-latency stretch reflex in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1983; 46(1): 35–44.
- Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. Brain 2001; 124(Pt 11): 2131–2146.
- Delval A, Tard C, Defebvre L. Why we should study gait initiation in Parkinson's disease. Clin Neurophysiol 2014; 44(1): 69–76.
- Beylergil SB, Ozinga S, Walker MF, McIntyre CC, Shaikh AG. Vestibular heading perception in Parkinson's disease. Prog Brain Res 2019; 249: 307–319.
- Yakubovich S, Israeli-Korn S, Halperin O, et al. Visual self-motion cues are impaired yet overweighted during visual-vestibular integration in Parkinson's disease. Brain Commun 2020; 2(1): 1– 15.
- Bertolini G, Wicki A, Baumann CR, Straumann D, Palla A. Impaired tilt perception in Parkinson's disease: a central vestibular integration failure. PLoS One 2015; 10(4): e0124253.
- Putcha D, Ross RS, Rosen ML, et al. Functional correlates of optic flow motion processing in Parkinson's disease. Front Integr Neurosci 2014; 8: 57.
- 87. Amick MM, Schendan HE, Ganis G, Cronin-Golomb A. Frontostriatal circuits are necessary for visuomotor transformation: mental rotation in

Parkinson's disease. Neuropsychologia 2006; 44 (3): 339–349.

- Gitchel GT, Wetzel PA, Baron MS. Pervasive ocular tremor in patients with Parkinson disease. Arch Neurol 2012; 69(8): 1011–1017.
- Kaski D, Saifee TA, Buckwell D, Bronstein AM. Ocular tremor in Parkinson's disease is due to head oscillation. Mov Disord 2013; 28(4): 534–537.
- Leigh RJ, Martinez-Conde S. Tremor of the eyes, or of the head, in Parkinson's disease? Mov Disord 2013; 28(6): 691–693.
- Kaski D, Bronstein AM. Ocular tremor in Parkinson's disease: discussion, debate, and controversy. Front Neurol 2017; 8: 134.
- 92. MacAskill M, Myall D. "Pervasive ocular tremor of Parkinson's" is not pervasive, ocular, or uniquely parkinsonian. 2020. Doi: 10.31219/osf. io/s8rwt
- Roze E, Coelho-Braga MC, Gayraud D, et al. Head tremor in Parkinson's disease. Mov Disord 2006; 21(8): 1245–1248.
- 94. Coe BC, Trappenberg T, Munoz DP. Modeling saccadic action selection: cortical and basal ganglia signals coalesce in the superior colliculus. Front Syst Neurosci 2019; **13**: 3.
- 95. Bronstein AM, Gresty MA, Rudge P. Neurootological assessment in the patient with balance and gait disorder. In: Bronstein AM, Brandt T, Woollacott M, (eds.). *Clinical Disorders of Balance, Posture and Gait*. Hodder Arnold; 1996.