Digital Eye-Movement Outcomes (DEMOs) as Biomarkers for Neurological Conditions: A Narrative Review

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Abstract

Eye movement assessment is a key component of neurological evaluation, offering valuable insights into neural deficits and underlying mechanisms. This narrative review explores the emerging subject of digital eye-movement outcomes (DEMOs) and their potential as sensitive biomarkers for neurological impairment. Eye tracking has become a useful method for investigating visual system functioning, attentional processes, and cognitive mechanisms. Abnormalities in eye movements, such as altered saccadic patterns or impaired smooth pursuit, can act as important diagnostic indicators for various neurological conditions. The non-invasive nature, cost-effectiveness, and ease of implementation of modern eye tracking systems makes it particularly attractive in both clinical and research settings. Advanced digital eye-tracking technologies and analytical methods enable precise quantification of eye movement parameters, complementing subjective clinical evaluations with objective data. This review examines how DEMOs could contribute to the localisation and diagnosis of neural impairments, potentially serving as useful biomarkers. By comprehensively exploring the role of eye movement assessment, this review aims to highlight the common eye movement deficits seen in neurological injury and disease by using the examples of mild traumatic brain injury, and Parkinson's Disease. This review also aims to enhance the understanding the potential use of DEMOs in diagnosis, monitoring, and management of neurological disorders, ultimately improving patient care and deepening our understanding of complex neurological processes. Furthermore, we consider the broader implications of this technology in unravelling the complexities of visual processing, attention mechanisms, and cognitive functions. This review summarises how DEMOs could reshape our understanding of brain health and allow for more targeted and effective neurological interventions.

KEYWORDS: Parkinson's disease, mild Traumatic Brain Injury, Eye Movements, Eye-tracking, Biomarker

1. Introduction

Eye movements are a core feature of neurological assessment as characteristics can be useful for localisation and diagnosis of underlying neural deficits[1]. The study of eye movements has emerged as a fundamental tool in understanding neurological processes and the underlying mechanisms that govern them[2]. By analysing and interpreting patterns of eye movements, researchers and clinicians can gain vital insights into the functioning of the visual system, attentional processes, cognitive mechanisms, and the integrity of neural pathways[3]. Abnormalities in eye movements can manifest in various forms, such as altered saccadic patterns, impaired smooth pursuit, or abnormal pupil response. These deviations from normal eye movement patterns often serve as important diagnostic clues, aiding in the identification of specific neurological conditions and guiding subsequent investigations[4]. Furthermore, eye movement assessment offers distinct advantages in terms of non-invasiveness, cost-effectiveness, and ease of implementation[1]. With the use of modern digital eye-tracking technologies and advanced analytical methods, researchers and clinicians can precisely quantify and analyse eye movement parameters, providing quantitative data that complement subjective clinical evaluations[5].

This narrative review aims to explore the importance of digital eye movement outcomes (DEMOs) in the understanding of neurological processes and discuss how eye movement assessment can contribute to the localization and diagnosis of neural impairments, in turn, providing insights into the functioning of the visual system and cognitive processes. Comprehensively examining the role of eye movements in clinical assessment will enhance the diagnosis, monitoring, and management of neurological disorders[6]. DEMOs may have the potential to provide useful digital biomarkers, paving the way for improved patient care and deeper insights into the intricacies of neurological processes.

2. A Brief Overview of Eye Movements

The study of eye movements has provided valuable insights into various aspects of neural function, cognitive and visual processing, as well as motor performance.

2.1 Saccades

One of the most well-known types of eye movements are saccades. Saccades are rapid, voluntary movements that redirect the gaze from one point of interest to another, usually 2-3 times per second[7]. Saccades allow for exploration of physical environment by quickly shifting the fovea, the region of the retina with the highest acuity, to various locations. Saccades are essential for visual scanning, reading, and searching tasks[8]. Deficits in saccadic movements may result in issues with initiating or executing these rapid movements. Disruption to normal saccadic movement is commonly seen when there is damage to the brainstem or where there might be lesions in the frontal eye fields[9]. Medications which affect the neurotransmitter systems involved in saccades may also lead to deficits[10, 11]. As a result, saccadic abnormalities may signpost any dysfunction in brainstem regions such as the superior colliculus, basal ganglia, or other related pathways[12]. The brainstem is responsible for control of breathing, heart rate and sleep and the superior colliculi in particular are involved in visual reflexes like saccades[13].

2.2 Smooth Pursuit

In contrast, smooth pursuit eye movements are slow and smooth tracking movements used to follow moving objects[14]. When we track a moving target, our eyes move smoothly to keep the target centred on the fovea[15]. Smooth pursuit is important for maintaining a clear and stable visual representation of moving objects[16]. Smooth pursuit can include saccades in a jerk-like motion when following an object[14]. Deficits have been seen to arise in smooth pursuit movements when there are abnormalities in the brainstem and cortical regions involved in visual processing and motion perception[15].

2.3 Nystagmus

Nystagmus, refer to involuntary, repetitive eye movements[17]. These can be oscillatory or jerky in nature and occur when the eyes attempt to fixate on a specific point. Nystagmus can be caused by various factors, such as neurological conditions, inner ear abnormalities or medications[17]. Studying nystagmus can provide insights into vision impairment and underlying neurological disorders as nystagmus suggests dysfunction in the neural pathways responsible for controlling and stabilising eye movements[18].

2.4 Convergence

Convergence is the inward movement of the eyes that occurs when one focuses on a nearby object. It allows for the merging of the visual inputs from both eyes, facilitating binocular vision and depth perception. Convergence is crucial for activities like reading, where the eyes need to adjust and align to maintain a clear and single image and usually occurs at ~5cm from the nose[19]. Issues with conversion typically result in double vision due to difficulties with binocular coordination when looking at objects at a close range[20]. Damage to the brainstem can evoke such problems due to its role in coordinating and controlling the extraocular muscles responsible for binocular vision[12].

2.5 Vestibular ocular reflex

The vestibular ocular reflex (VOR) is an involuntary eye movement which maintains a stabilised image on the retina irrespective of head movement during activities such as walking and running. This involves counter-rolling the eyes about the same axis as the head during movement[21]. Problems with VOR are commonly seen with head injuries[22].

2.6 Pupillary Response

Pupillary response refers to changes in the size of the pupils in response to different stimuli. The pupils can constrict (miosis) or dilate (mydriasis) based on factors like light levels, emotional states, or cognitive processing[23]. Pupillary response is an important indicator of autonomic nervous system activity and can provide insights into arousal, attention, and cognitive load. Irregular pupil response can provide insight into problems in the brainstem where the pupillary reflex originates. This could be caused by a variety of neurological conditions[23].

2.7 Ocular Microtremor

Ocular microtremor (OMT), a small, constant, involuntary oscillation of the eyes, occurs even when fixating on a stationary object[24]. Although its exact function is not fully understood, OMT has been studied as a potential indicator of brain function and neurological disorders[25-27]. OMT is thought to be related to neural activity and has the potential to provide valuable insights into cognitive processes and underlying mechanisms. A healthy

functioning range is proposed to be ~70-100Hz[28, 29]. Deficits in OMT would present as a decrease in frequency (Hz) that the eye is oscillating at.

3. Methods to Objectively Measure Eye Movements

There are various methods to record eye movements, and each has its own advantages and limitations. The choice of technique depends on the specific research or clinical requirements. Researchers and clinicians consider factors such as accuracy, precision, spatial and temporal resolution, invasiveness, and ease of use when selecting the most appropriate method for their particular study or application. Here, we outline eye movement measurement techniques that are available:

3.1 Scleral Search Coils

Scleral search coils are widely used for measuring eye movements. This technique involves placing tiny wire coils embedded in a pliable, circular plastic ring on the sclera (the white part of the eye). Eye movements are then tracked using recordings of small electric currents induced by a magnetic field[30]. By measuring the changes in magnetic field induced by the movement of the coils, precise and highly accurate measurements of eye position can be obtained[30]. Scleral search coils provide excellent spatial and temporal resolution, making them particularly useful for research settings where precise measurements are required[31]. They allow for measurement of eye movements with minimal interference as they do not obstruct the visual field and do not require the head to be mounted so permit a natural experience. However, the implantation of the coils is rather invasive and therefore requires a high level of skill to set up, limiting their use to laboratory and controlled settings[32]. Similarly, scleral search coils are limited by their invasive nature in that this can restrict sample sizes, while the coils themselves can cause discomfort and irritation and cannot be administered for prolonged use[32].

3.2 Video and Infrared eye-trackers

Another method for digital eye tracking utilises video and infrared eye-trackers. These non-invasive methods of tracking gaze are commonly used in both research and clinical settings[6]. Video and infrared eye trackers do not impact the natural viewing experience as they do not require any restraints for use. This enables a more real-world representation of eye movement. The systems use cameras to capture images or infrared light to illuminate the eye, and then track the movement of specific features, such as the pupil or corneal reflection[6]. By tracking the position and movements of these features over time, eye-trackers can provide accurate measurements of eye position and gaze direction. Furthermore, the cost of mobile video and infrared based eye-tracking devices has substantially reduced in recent years (e.g., Pupil Labs Invisible ~$5k). Video-based eye-trackers, such as video oculography (VOG), are easy to use and offer good non-invasive spatial resolution[32, 33], while infrared eye-trackers are especially useful in low-light conditions. A downside to this technique is the lower spatial accuracy seen when compared to other methods such as scleral search coils[32, 34]. Similarly, there is a limited sampling rate with video eye trackers compared to other techniques which could mean tracking of rapid eye movements and subtle gaze changes may be missed. This technique may also be limited by lighting conditions as it is susceptible to changes in brightness, reflections, and occlusions, hindering performance.

3.3 Electro-oculography

Electro-oculography (EOG) is a technique that measures the electrical potential difference between electrodes placed around the eyes[35]. As the eyes move, the electrical potential at the electrodes changes, allowing for the

measurement of a wide range of eye movements such as fixations and saccades[35]. EOG is particularly effective for detecting slow eye movements and changes in eye position over time, such as smooth pursuit and slow drifts. The non-invasive nature of EOG is appealing as it is comfortable for users and can be applied with various populations. EOG is a relatively simple and cost-effective method, although it may have limitations in terms of accuracy and precision compared to other techniques. EOG relies on electrical potential rather than precise gaze coordinates resulting in a reduced spatial resolution.

3.4 Laser based eye-tracking

More recently, laser-based eye movement devices have emerged which use infrared lasers to project a beam onto the eye's surface, and then measure the changes in the reflected beam as the eye moves[36]. These devices offer high spatial and temporal resolution, allowing for precise measurement of eye position and even accurate data on micro movements[37, 38]. Laser-based devices are often used in research settings and have the advantage of being non-invasive and portable[39]. Laser based techniques can be perceived as invasive or unsafe by users which may mean they are hesitant to participate[40]. These eye-tracking techniques are more expensive than other methods as they require stringent safety precautions and specialised equipment[40]. This could lead to reduced accessibility, limiting the widespread use of laser based eye-tracking systems.

3.5 Analytical Validation of Objective Eye Movement Measurement

Validation of eye tracking is an essential step in the development of objective eye movement measurement[41]. Many eye tracking devices have been introduced in recent years however, there is a distinct lack of appropriate analytical validation of several commercial products which tend to rely on clinical validation (group differentiation). Typically, novel eye tracking techniques can be analytically validated in numerous ways, for example, through comparison to gold/reference standard, or concurrent validity (e.g. comparing to a reference device like EOG to VOG). Analytical validation of underlying algorithms by comparison to accepted measures is essential and a prerequisite for digital biomarkers with regulatory bodies[41]. For example, the gold standard for saccade measurement is scleral search coils and various video-based systems have been validated against this[42]. Video-based systems using existing technology like tablets or smart phones have also been validated against VOG when assessing saccades, smooth pursuit, and nystagmus[43-46]. There are difficulties with comparing with VOG, as in some cases, the novel method cannot record simultaneously due to noise created[46]. Another example, is with OMT as VOG doesn't possess the sensitivity to capture it[47]. Similarly, if novel techniques were to be validated against other measurement techniques like scleral search coils, or the piezoelectric methods, individuals are put through uncomfortable, highly invasive and, lengthy protocols[47]. The current methods of measuring OMT have been shown to have a loading effect on OMT frequency, further impacting the difficulty of analytical validation of novel techniques[32, 48].

4. "Models" of Neurological Disease and Injury

Eye movement initiation and control requires a range of neural structures and brain processes and functions, so it is no surprise that impairments are prevalent within various neurological diseases (including, but not exclusive to Parkinson's disease (PD), Alzheimer's disease, Huntington's disease, dementia, multiple sclerosis) and injuries (Traumatic brain injury (TBI), Stroke etc.)[49, 50], which provide insight into underlying neural networks and processing involved in eye movement control[6]. To understand how eye movement outcomes derived from digital technologies can be used as digital biomarkers within neurological conditions, we will focus on two specific

conditions that will represent neurological disease and neurological injury. Specifically, this review will focus on PD and TBI, as these are two of the most prevalent neurological conditions worldwide and have been linked through other clinical biomarkers, which may highlight common markers of neurological dysfunction.

4.1 Parkinson's disease

PD is a progressive neurodegenerative disease with diverse pathophysiology and an unknown cause[51]. PD is signposted by a depletion of dopamine in the brain and the hallmark physical symptoms include slowness (bradykinesia), stiffness, and tremor[52]. PD also presents with a variety of cognitive symptoms such as problems with memory[53]. PD has recently overtaken Alzheimer's disease to become the fastest growing neurological disease in the world[54], with an estimated global prevalence of 8.5 million people living with the condition[55]. In PD, dopamine depletion in the substantia nigra inhibits the superior colliculus which plays a crucial role in eye movement, particularly saccade production and control. The aggregation of dopamine pathways in the basal ganglia causes overactive superior colliculus inhibition and prevents saccades from being generated[56]. Additionally, PD can impact cerebellar circuits, brain stem function and higher-level cognitive processing that can impact eye movement control. Current diagnosis of PD occurs when the disease is already in an advanced stage and non-motor symptoms usually exist for several years prior to a diagnosis[57]. In recent years, researchers continue to identify prodromal symptoms of PD such as rapid eye movement sleep disturbance, olfactory loss, and changes in cognition[58]. With motor symptoms usually manifesting after ~80% depletion of dopamine, early diagnosis through the use of subtle eye movement changes could be invaluable for people with PD (PwPD)[59].

4.2 Traumatic brain injury

A TBI typically results from a blow or jolt to the head[60] (or potentially the neck), which can range in severity from mild to severe TBI, with various symptoms accompanying the injury (e.g., headache, nausea, sleep issues, speech problems, balance deficits or limb weakness etc.). TBI is very common with 56 million people affected worldwide per year (3.8 million cases per year in the USA, 2.5 million cases per year in Europe), with additional undetected mild TBIs (concussions / mTBI) likely occurring increasingly more often across the globe (i.e., a silent pandemic) (REF). TBIs often damage and impact on the neural circuits involved in eye movement control, with dysfunction in the basal ganglia, brain stem, superior colliculus, cerebellar circuits, cranial nerves, and higher-level cognitive processing, as well as integration of vestibular function into sensorimotor control. Existing research highlights the current need for objectivity in TBI assessment, particularly in sports related mTBI. Currently, diagnosis relies on patient self-report. There are clinically validated tools used in pitch-side assessment in athletes, and in hospital emergency rooms for TBIs sustained in other ways. The sports concussion assessment tool 5[61], and the Rivermead questionnaire[62], while considering blurred vision, light sensitivity and double vision, both heavily focus on subjective symptom reporting[63]. Similarly, the vestibular ocular motor screening (VOMS) is a tool frequently utilised which reports symptoms evoked from eye movement tasks rather that the deficits themselves[20]. The VOMS utilises various eye movement metrics to evoke symptoms associated with mTBI and deficits can be seen in saccades, smooth pursuit, convergence, and VOR performance. This is obviously highly subjective due to differences in pain thresholds, but also, sports players have the tendency to downplay their post-injury symptoms to allow them to continue to play[64, 65].

4.3 PD and TBI: a common neurological thread

In recent years, there has been increasing suggestion that TBI severity (ranging from mild to moderate, to severe) could increase the risk of developing various neurodegenerative diseases, including PD[33]. A study of over 300,000 veterans found that a history of TBI regardless of severity was associated with a 56% increased risk of PD[66]. Similarly, a recent twin study demonstrated that a history of head injury with amnesia or loss of consciousness has been associated with increased risk of developing PD[67]. Even TBIs that occur later in life can increase the risk of developing PD by 44% when reverse causation is ruled out[67]. However, the underlying mechanisms linking TBI and PD are complex. A previous meta-analysis of 22 studies showed that history of head trauma with loss of consciousness is significantly associated with higher risk of developing PD[68]. There are several possible mechanisms for this relationship such as TBIs causing neuroinflammation, disruption of the blood brain barrier, and disruption to mitochondrial function[68].

Research highlights that an initial brain injury can trigger a cascade of events that leads to the aggregation of abnormal proteins in the brain[69]. This contributes to the neurodegenerative process seen in PD as abnormal protein, such as alpha-synuclein, accumulation in the brain is also a hallmark of PD[70]. Additionally, there is established evidence for a link between neurodegeneration development and repeated TBIs (even mTBIs) (e.g., from sport, military duties, work-related etc.), with the recent consensus statement on concussion describing this as an ongoing public health concern[71]. Even an mTBI could lead to development of neurodegenerative conditions, as although mTBIs are generally considered to be transient in nature, emerging evidence suggests that they can become chronic (i.e., symptoms last >12 weeks) and there are considerable long-term subtle deficits (e.g., undetected ongoing symptoms) and consequences associated with such injuries[72, 73]. For example, following an mTBI a sports performer is more likely to suffer a second mTBI or musculoskeletal injury if they return to sport within the same season; likely due to subtle deficits that are not detected on subjective rating scales used to denote a return to health[74, 75]. An mTBI can disrupt cellular processes and may create a vulnerable environment within the brain, making it more susceptible to the accumulation of pathological proteins and the subsequent development of neurodegenerative diseases like PD[69]. Disruption caused by mTBI can include mitochondrial dysfunction, oxidative stress, inflammation, and impaired clearance mechanisms, all of which are implicated in the development and progression of neurodegenerative diseases[76]. Another considered link between mTBI, and PD is the disruption of the blood-brain barrier. An mTBI compromises the integrity of the blood-brain barrier, meaning harmful substances can enter the brain. This can further contribute to potential neurodegeneration and the likelihood of developing neurological diseases (e.g. PD)[77].

6. Overview of Eye Movement Impairment in PD

Table 1 provides a brief overview of the eye movement impairments in PD presented in this section.

6.1 Saccades

It is well reported across the literature that deficits can be seen in saccades in PD such as undershooting from targets, reduced amplitudes, increased latencies, anti-saccades (directing gaze in the opposite direction of target), and prosaccades (directing gaze towards a target) [53]. The depletion of dopamine within the basal ganglia disrupts both direct and indirect pathways, perturbing the smooth orchestration of saccadic initiation and execution[33].

6.2 Smooth Pursuits

Similarly, the abnormal smooth pursuit seen in PD has also been linked to the disruption of basal ganglia and cerebellar circuits essential for modulating the accuracy of smooth pursuit tracking[33]. The integration of sensory inputs for smooth pursuit is compromised by altered dopamine transmission, affecting the performance of motion tracking.

6.3 Nystagmus

Problems with nystagmus would present with either pendular or more commonly, jerk-like[33]. By using eye tracking, deficits in nystagmus can be measured and attributed to problems arising from the cerebellum. Vertical optokinetic nystagmus can be strongly asymmetric in PwPD and is often an indicator of the atypical Parkinsonism, Progressive Supranuclear Palsy (PSP)[78].

6.4 Pupillary Response

Changes in pupil response are a reported feature of PD. Research has highlighted that PwPD demonstrate a larger pupil after light exposure, reduced amplitude for contraction, and prolonged contraction time at light reflex[79]. Anisocoria (different sized pupils) after light adaptation has also been reported in PwPD. It has been suggested that the parasympathetic nervous system plays a role in this, as well as the cholinergic deficits in cognitively impaired PwPD[80]. It has also been shown that pupil response reflects cognitive load and is a representation of cholinergic deficit[81]. This research showed that pupil response abnormalities are associated with PD and can be used to examine deficits in executive functioning in early PD.

6.5 Convergence

Convergence insufficiency is common in PwPD[82]. This has been associated with symptoms of exophoria (one eye drifting outwardly), and diplopia (double vision)[83]. These deficits have been linked to deterioration in the brainstem[84].

6.6 Vestibular Ocular Reflex (VOR)

PwPD have abnormal VOR gain when compared to healthy controls[85]. There were no significant differences between left and right eye in both PD and HC. This impaired VOR gain seen in PwPD has been attributed to the degeneration of VOR circuits in the braintstem[86].

6.7 Ocular Microtremor

Previous research suggests that OMT is decreased in PwPD[87]. A link between OMT and brainstem activity has been proposed. It is suggested that brainstem activity excites the ocular nerve and causes the eye muscles to tremble[88-90]. This would suggest that deficits in OMT would signify impairments in the brainstem which is synonymous with characteristics of PD pathology.

Table 1 – Brief overview of eye movement impairment in PD and TBI

	PD	TBI
Saccades	• Reduced frequency • Reduced velocity • Reduced amplitude • Increased latency	• Reduced frequency, • Reduced peak velocity, • Reduced duration[5, 91] • Increased error[92] • Reduced acceleration,

	• More pro and anti-saccade errors[53] • Hypometria (undershooting saccades)	• Reduced amplitude[93]
Smooth Pursuits	• Saccadic intrusions [33]	• Poorer visual tracking than controls[94] • Large saccadic intrusions • Gain reduced[95]
Nystagmus	• Abnormal in some patients with the presence of square wave jerks[33] • Vertical Optokinetic Nystagmus can be strongly asymmetric in PwPD and is often an indicator of PSP[78].	• Presences of vertical optokinetic nystagmus • gaze-evoked nystagmus, • benign paroxysmal • positional nystagmus, and vertical and horizontal positional nystagmus post injury[18].
Pupillary Response	• Larger after light adaption • Anisocoria • Reduced amplitude of constriction • Prolonged contraction after light reflex[79]	• Increased pupil latency[96] • Reduced dilation velocity and maximum diameter[97]
Convergence	• Convergence insufficiency common in PD[82] • Impaired and associated with exophoria and diplopia[83]	• Convergence insufficiency[98]
VOR	• Increased VOR gain[85]	•
Ocular Microtremor	• Reduced frequency[87]	Not yet known.

7. Overview of Eye Movement Impairment in TBI

Table 1 provides a brief overview of eye movement impairments in TBI presented in this section.

7.1 Saccades

A TBI damages and disrupts these circuits causing saccadic deficits. mTBI can also cause malfunctioning of the superior colliculus, a critical coordinator of saccades, which further contributes to delayed initiation and compromised accuracy of saccades seen post injury[99]. Those who have experienced a TBI present with reduced saccade frequency, duration, and peak velocity[5, 91]. When compared to controls, those who had experienced a TBI also showed increased saccade error[92]. Deficits have been seen to persist for varying periods post-injury in mTBI[72, 100].

7.2 Smooth Pursuits

Smooth pursuit deficits caused by an mTBI, emanate from compromised cerebellar circuits, vital for the coordination and adjustment of seamless tracking of moving objects. Simultaneously, an mTBI causes dysfunction in cortical regions which can disrupt the integration of sensory inputs necessary for maintaining accurate smooth pursuit[99]. TBI causes poor visual tracking abilities with larger saccadic intrusions and reduced smooth pursuit gain[94, 95]. The same findings were seen for both chronic and acute TBI and were related to problems with cognition such as memory[95, 101].

7.3 Nystagmus

A recent review of nystagmus in TBI found evidence for several types of nystagmus post injury. The reviewed studies showed vertical optokinetic nystagmus, gaze-evoked nystagmus, benign paroxysmal positional nystagmus, and vertical and horizontal positional nystagmus post injury. Within these studies, symptoms persisted for between 3 days to 6 months post injury[18].

7.4 Pupillary Response

A TBI causes increased latency in pupil response when compared to HC[96]. Reduced dilation velocity and maximum pupil diameter are also seen in chronic mTBI compared to HC when assessing pupil light response[97].

7.5 Convergence

Abnormal convergence associated with mTBI manifests from altered oculomotor nuclei and cranial nerve nuclei functions[99]. This disturbs the harmonious coordination of eye movements for binocular vision. Convergence insufficiency is seen in around 50% of adolescents with a TBI[98]. Convergence insufficiency in adolescents with a TBI has been associated with poorer neurocognitive performance and increased symptom scores[102].

7.6 Vestibular Ocular Reflex (VOR)

Problems with VOR seen post mTBI result from disruption in the connections between the vestibular and oculomotor systems. Signals generated from the peripheral vestibular system are sent to the eye muscles and combined with visual inputs. Damage to the vestibular system, particularly damage to the semicircular canals in the inner ear, causes disruption between the vestibular, and visual inputs[22]. As a result, symptoms like blurred vision and dizziness arise, emphasising the need to address the underlying neural mechanisms for effective management.

8. DEMOs as Neurological Biomarkers

Biomarkers are defined as outcome measures that reflect pathogenic, physiological, or biological processes, which are classified into different biomarker categories based on their context of use (e.g., monitoring, prognosis, diagnosis, predictive, response, safety, risk biomarkers). Clinical validation of eye movements as potential biomarkers in PD and TBI already exists, as multiple studies have shown that eye movement deficits can differentiate these groups from controls (or other clinical cohorts). They can be used to monitor the conditions, or predict particular health events, and can change over time or with interventions.

8.1 Diagnosis

There is growing evidence for the use of DEMOs to differentiate clinical populations[5, 103-106]. Many recent studies have demonstrated that various eye movements can differentiate between those with and without mTBI. For example, computerised eye tracking systems have been used in military personnel with mTBI, and those who were symptomatic demonstrated deficits in several eye movements when compared to healthy controls[107]. Specifically, those with mTBI had smaller saccadic amplitudes, smaller peak velocities, smaller accelerations, and longer durations[107]. Similarly, in athletes, those with mTBI performed significantly longer saccade duration and reduced saccade accuracy[108]. For smooth pursuit, those with mTBI showed increased positional error variability, reduced radius and reduced velocities when compared to controls, and was attributed to impaired predictive timing. In this study they also included a sleep deprived cohort, and those with mTBI still performed

significantly worse in the smooth pursuit tasks[109]. The ability of DEMOs to differentiate between groups supports the use of eye tracking as a potential diagnostic tool for TBI diagnosis.

The use of eye-tracking could also be implemented in the diagnostic stage of PD. For example, early diagnosis of PD holds several benefits such as allowing for optimal treatment strategies to be formed earlier[59]. Eye tracking could not only be used in clinics to assist clinician assessment but could also be implemented in routine optician appointments which are more frequent with age as eyesight declines. Any abnormalities that arose here could allow the person to be referred to a neurologist for further investigation. With motor symptoms of PD only arising after substantial depletion of dopamine in the brain, utilising eye movement characteristics to gain further insight into neuronal integrity is invaluable. Even in the prodromal stages of the disease, changes in pupil response and blinking have been seen to differ from that of healthy controls[105, 110]. The Braak Hypothesis suggests that sporadic PD originates in the gut, and triggers alpha-synuclein spread via the vagal nerve towards the brainstem and substantia nigra before spreading to the rest of the brain[111, 112]. Therefore, this suggests again that eye-tracking may be sensitive to the early, and prodromal phases of PD development. The use of eye tracking to enable early diagnosis could allow both PwPD and their doctors to follow their symptoms longitudinally. This is beneficial as early diagnosis would allow for the development of personalised care plans, tailored to the individual's needs. For instance, neuroprotective therapies could be applied prior to the high loss of dopamine levels seen by the time of motor symptom manifestation[59]. Recent studies have shown the ability of saccadic eye movements to differentiate between PwPD and those without. For example, when comparing PwPD and healthy controls, anti-saccades and memory-guided saccades are known to be able to differentiate between the two groups[113]. Subtle changes are even present at the early stages of the disease[114].

There is evidence for the use of eye movements as a tool for differential diagnosis within PD. For instance, impaired reflexive saccade performance has been shown to differentiate between PD Dementia and Dementia with Lewy Bodies[56]. Furthermore, in PD, people with the PARKIN mutation present with distinct hypometric saccades (overshooting target) when compared to age matched controls[115]. Various eye movement characteristics show capabilities for group differentiation for both of these conditions, thus supporting the potential for eye tracking as a valuable and essential diagnostic tool. Early diagnosis would also help with differential diagnosis, differentiating subtypes of the disease and permit an alternative way to follow disease progression[116]. This is useful to distinguish from other neurological conditions, and idiopathic PD from other genetically identified Parkinsonism's. For example, people with Parkinson's Disease 1 (PARK1) display increased latency of reflexive voluntary saccades but normal velocity and duration, Parkinson's Disease 2 (PARK2) patients present with hypometric saccades and smooth pursuit deficits but normal gain, and Parkinson's Disease 6 patients present with normal gain and velocity but increased latency of horizontal prosaccades[117].

8.2 Prognosis / Prediction

Evaluating eye movements permits more accurate assessment and better management of neurological impairment and may provide better insights for prognosis and predicting trajectory of the conditions.

Abnormal saccadic movements in both mTBI and PD illustrate issues with executive dysfunction and problems with attention, motor planning, and decision making[53, 118, 119]. As a result, impairments could serve as precise markers of altered cognitive processes within the context of neurological impairment. In both mTBI and PD, the

evaluation of eye movements extends beyond motor impairment, revealing the intricate involvement of cortical and subcortical regions crucial for executive functioning. This approach not only enhances diagnostic precision but also offers a comprehensive framework for tailoring interventions.

In mTBI, studies have shown that those who present with VOR elicited symptoms have a longer expected recovery time, and are at a higher risk of re-injury[22]. Similarly, in sports related concussion, those with convergence insufficiency are also deemed to be at risk of pro-longed recovery time (≥28 days) when compared to those with normal convergence[120]. The predictive value of eye tracking in concussion has also been demonstrated in children. In a retrospective sample of 432 paediatric patients with concussion, 88% presented with ocular/ vestibular issues[121]. Findings showed that the provokable symptoms associated with VOR, and smooth pursuit, predicted prolonged recovery time[121]. These kinds of insights would permit better management of mTBI and allow for sufficient recovery times to be adhered to in order to prevent risk of future injury.

In PD, saccadic eye movements are strongly related to cognition and recent literature is increasingly supporting the use of eye tracking to measure complex cognitive information[114]. Using eye-tracking, researchers demonstrated the ability of pro-saccades to predict cognitive decline in PD[53]. Similarly, saccadic, pupil, and blink data showed high sensitivity when differentiating PwPD, PwPD and mild cognitive impairment, and people with Parkinson's Disease Dementia[122]. Impaired saccade execution in reflexive tasks, measured using EOG, has also been shown to discriminate between Dementia with Lewy Bodies and Alzheimer's, and PD Dementia and PD, further illustrating the potential usefulness of eye tracking in differential diagnosis and cognitive decline[56].

8.3 Monitoring and Response to Intervention

The use of eye tracking in mTBI has the potential to aid monitoring of the condition and support treatment. Eye tracking can support intervention strategies in mTBI and could mitigate the development of long-term neurological diseases, such as PD. As an objective measure, eye tracking removes the subjectivity associated with self-report of symptoms. This is a known issue, particularly in sports related head injuries, with players underreporting their symptoms to avoid removal from play. People may also hold misconceptions of their abilities, further leading to potential misreporting of symptoms[123, 124]. This considered, previous research does indicate that self-reported symptoms associated with mTBI don't reflect the observed eye movement deficits[125]. This could also be due to underlying physiological problems, such as autonomic or somatic dysfunction, that cannot be directly measured via questionnaire[126]. In support of this, research shows that patients still exhibit physiological issues after self-reported symptoms are resolved. For instance, once self-reported symptoms resolve, and normal activity is resumed, people are left at a higher risk of secondary TBI, musculoskeletal injury, or have persistent sensory, motor, or cognitive issues[74, 75, 127, 128]. Eye movement assessment could provide a vital tool for ensuring proper recovery is achieved. Despite the high instance of oculomotor dysfunction that persists post-TBI, and the discomfort this can cause to those who experience it, there are few interventional studies exploring oculomotor rehabilitation. A recent review found that suggested optimal oculomotor rehabilitative training requires around six to eight weeks of twice-weekly, one hour sessions, with some even requiring up to 10 weeks[129]. While this is a long time, it reflects the intricacies involved in effective rehabilitation post-TBI. The reviewed studies typically used computer based training and showed significant improvements in strabismus (squint), reading, pursuit, fixation, and saccade performance[129]. This suggests that through the use of eye

tracking, and appropriate intervention, the mechanisms involved in eye movement control can recover back to normal. More recently, research has shown that the improvements seen with oculomotor training are retained over three and, six-month follow-up. 90% of the eye movement perimeters that were abnormal at baseline, significantly improved with oculomotor training[130]. No improvement was seen in the placebo group. This sample included people who had experienced a TBI more than one year ago to avoid the six to nine-month natural recovery span. This demonstrates that underlying neurophysiology is not fully recovered, and eye tracking may provide insight into these systems and support the return to play protocol to help ensure there is a reduced risk of repeat injury[74, 75, 127, 128].

In PD, eye tracking has potential to provide insight into brainstem function, higher order processing and consequently, disease severity [117]. There is evidence for eye tracking in PD as a monitor for response to intervention (such as anti-Parkinson's medication), disease severity and decline. Levodopa is used to treat the dopamine deficiency in PD and can be prescribed in various dosages and can be taken at various intervals and frequencies in a day. Being able to objectively assess a person's individual response to the medication, whether negative or positive, would be an invaluable addition in ensuring optimal care is given. Levodopa can cause different side effects, some of which can be adverse[131]. Managing medication agreement could be a real benefit to both PwPD, family members, carers, and clinicians alike. Eye movement features, such as saccadic latency, have been shown to be prolonged with the use of Levodopa treatment[132, 133]. Researchers have used saccade tasks to test the effect of levodopa on executive function in PD on and off (12 hours) medication[134]. Authors demonstrated for the first time that levodopa can improve voluntary anti-saccadic performance, whilst slowing pro-saccades. This suggests eye movement outcomes could be useful measures for monitoring medication in PD. Using EOG over 7.5 hours, eye blink rate was able to accurately detect wearing off of medication, and dyskinesias as a non-invasive alternative to plasma levodopa levels[135]. While this was assessed in a small sample, it shows promise for the use of eye movements as a potential objective, passive monitor for disease progression compared to more subjective measures such as patient diaries. The use of eye movements to detect changes in symptoms could allow for non-invasive monitoring of disease progression.

More recent evidence postulates the role of additional neurotransmitter systems in the pathology of PD. In PD, the loss of dopaminergic neurons leads to a cascade of changes in neurotransmitter signalling. One major change is the increased GABAergic activity (inhibitory) from the output nucleus of the basal ganglia to other areas, including the thalamus and the superior colliculus[136]. Such increased inhibition over the superior colliculus is associated with changes in saccades[137, 138]. In addition to dopamine and GABA, acetylcholine is also implicated in PD. Acetylcholine contributes to memory, learning and attentional processes as well as involuntary movement control[139]. Eye movement control is also coordinated by cholinergic pathways and PD is characterised by an imbalance between dopamine and acetylcholine in the brain[140, 141]. Anti-cholinergic medication can be used in PD to treat this increase in acetylcholine in the brain[142]. In healthy adults, anticholinergics cause a decrease in fixations, saccades and smooth pursuits[143]. As a result, this suggests that eye movement outcomes could also have the potential to be a useful indicator of medication effectiveness for anticholinergics, as well as levodopa in PwPD. Eye movement assessment in PD also has potential for wider application in the monitoring of disease severity and decline. For example, oculomotor training has been implemented as part of vestibular rehabilitation for balance and gait problems that arise in PD[144]. Participants underwent three training sessions a week for 6 weeks which resulted in significant balance improvements being

seen post-training when compared to baseline. This shows how the pathways involved in oculomotor control in PD are interconnected with those that are involved in postural control. Consequently, eye tracking could allow for increased understanding of subtle changes within the brain as PD progresses, and act as a potential monitor for disease severity and decline.

8.4 Common trends in DEMOs across neurological conditions

Eye movement abnormalities are common features across a wide range of neurological conditions. Despite the diverse underlying pathologies, certain ocular deficits frequently emerge as shared characteristics across neurological conditions. Many people with neurological diseases exhibit changes in saccadic functioning, particularly PD, Alzheimer's Disease (AD), and Multiple Sclerosis (MS). These conditions show features of reduced velocity, accuracy, and delayed initiation. Changes in smooth pursuit such as decreased gain are seen in PD, MS and stroke. Similarly, convergence insufficiency is commonly seen in PD, and mTBI and MS. Eye movement deficits are consistent across neurological injury and disease suggesting that eye movements assessment could act as a sensitive tool for indicating neurological function. Exploring trends in DEMOs across neurological conditions would increase our understanding of the underpinnings of ocular control and provide useful diagnostic and monitoring biomarkers irrespective of condition.

The commonalities in eye movement deficits across neurological conditions, suggest that DEMOs could also be used to measure response to intervention in clinical trials throughout an array of neurological impairment. Cases of stroke and MS demonstrate great variation based on lesion location and therefore, PD and mTBI are used as vehicles for demonstration here as much less variation is seen within these conditions. PD and mTBI are two of the most prevalent neurological conditions worldwide and have been linked through other clinical biomarkers, which may highlight common markers of neurological dysfunction. The prevalence of PD and mTBI highlights the clinical relevance and meaningfulness of eye movement assessment, but there is also an established body of research surrounding DEMOs in these conditions. Clinical validation of eye movements as potential biomarkers in PD and TBI already exists, as multiple studies have shown that eye movement deficits can differentiate these groups from controls[5, 125, 145, 146]. PwPD and those with mTBI are a relatively accessible sample due to the nature of the conditions. These conditions are not necessarily as disabling as other neurological conditions, and people therefore are more likely to participate in research and clinical trials.

8.5 Current limitations and future prospects for DEMOs in neurology

Digital measurement of eye movements can present challenges in clinical and research settings. Whilst providing precise measurement of eye movements, digital measurement is not a fast process and requires expensive, specialised equipment which potentially limits widespread uptake. Moreover, these digital techniques rely on specialist training to derive meaningful data, potentially further restricting widespread adoption of such techniques. Eye movement assessment demands active assessment rather than passive monitoring which could be deemed a less attractive option for implementation into clinical practice. The lack of longitudinal evidence to support the use of digital measurement of eye movements in neurological conditions limits our understanding of any deterioration in DEMOs, or how they respond to interventions. This is made clear through the rare use of DEMOs as pre, and post-intervention measures, thus hindering the potential of DEMOs as sensitive biomarkers for the effectiveness of treatments for neurological conditions.

In parallel with the recent advances in eye tracking technology, comes the possibility of more accessible and appealing methods of eye movements assessment. For example, the development of wearable eye tracking technology (glasses), and the integration of eye-tracking via mobile phones and tablet, could permit the passive, continuous monitoring of eye movements in a real-world environment. This shift into more readily available technology, could reshape future eye movement data collection. With this will come the need for data to understand how to interpret the context of data captured, particularly in passive monitoring[147]. While these commercial devices may offer lower sampling rates, they could still provide valuable insights in a clinical and home setting, especially when data can be collected longitudinally. In turn, this will permit the further exploration of DEMOs across different neurological populations. This could have implications in clinical trials and healthcare application in enabling more frequent and convenient assessment of neurological conditions and treatment efficacy. The use of eye-tracking and DEMOs could be extended to patient home use, revolutionising how disease progression and response to treatment are monitored.

9. Conclusion

Here we use evidence from two well studied populations where eye movements have been used as potential biomarkers: mTBI and PD. In mTBI, utilising eye tracking as an objective assessment could have revolutionary impacts for improving diagnosis, supporting recovery, and minimising the potential long term impacts such as ongoing post-concussive symptoms and preventing the development of degenerative diseases. Similarly, players can skew their baseline performance to be more forgiving post-injury. This is typical as players do not want to lose time out of the game. Eye tracking would be highly beneficial in providing objective assessment to overcome this. Due to the nature of head injuries, there is a need for a portable, non-invasive, objective way of assessing symptoms. In sports related concussions this could be pitch-side assessment, and in other head injuries, this would be at the site of accident. This will ensure that the individual receives the correct and best possible care and reduce the risk of future complications. This could also enhance the return to play protocol to support players safely back to health.

The evidence for the value of eye movement assessment in neurological injury and disease is undeniable. There is a clear need for quick, non-invasive eye tracking methods that can accurately and reliably detect deficits in eye movements in clinical populations such as Parkinson's Disease. As we navigate the future of neurological research and clinical practice, this review posits that eye movement analysis stands at the forefront, guiding us toward a more profound understanding of neurological processes. It not only refines our diagnostic acumen but also serves as a catalyst for advancements in personalized medicine, promising improved patient outcomes and deeper insights into the intricate workings of the brain. In essence, the exploration of eye movements becomes a gateway to unlocking the intricacies of neurological disorders, paving the way for a new era in neurological care.

Author contributions

All authors contributed to the conceptualisation and writing of the manuscript. All authors have read and approved the final version.

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Competing Interests

The authors confirm there are no competing interests.

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