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Deciphering Parkinson's Disease through Eye Movements: A Promising Tool for Early Diagnosis in the Face of Cognitive Impairment

B.Buvana, R .Chaithu, N . Samyoutha

Assistant Professor1,2,3, Badruka Pharmacy College and Institution

Abstract— At any point in the progression of Parkinson's disease (PD), cognitive impairment becomes the most prominent and prevalent nonmotor symptom. Unfortunately, reliable biomarkers for assessing cognitive impairment and disease development, particularly in its early stages, are currently lacking. The cognitive scale is now the gold standard for PD patients' cognitive evaluations, although it has limited sensitivity and accuracy, particularly when it comes to detecting moderate cognitive impairment in its early stages. One of the most effective ways to learn about the connection between behaviour and brain processes is to use eye movement tracking, a cutting-edge neurophysiological monitoring tool. Researchers have recently discovered that eye movement monitoring may be used as a less cognitive and nonverbal way to assess the progression of illness in people with cognitive impairment. Patients with PD may have their cognitive state, illness severity, and disease progression monitored using eye movement monitoring, since it has a strong association with the standard cognitive evaluation scale. The instrument's detection of eye movement is more objective and repeatable than the conventional cognitive scale. According to previous research, one of the most prominent forms of cognitive dysfunction in PD patients is executive dysfunction, which is associated with increased saccade error rate, increased disinhibition on the delayed saccade task, and prolonged saccade reaction time. This provides further evidence that measuring eye movement is useful for PD diagnosis, tracking the illness's development, making differential diagnoses, and maybe even foretelling how the disease would affect people with both PD and cognitive impairment. This article provides a synopsis of the literature on the link between PD and EMD in terms of cognitive impairment.

1. Introduction

According to [1], the frequency of Parkinson's disease (PD) is expected to double by 2030, impacting over 1% of the population aged 65 and over. It is the second most frequent neurodegenerative ailment. Cognitive impairment is a significant nonmotor symptom of Parkinson's disease (PD) that may develop at any point in the disease progression, even before motor symptoms appear. It has a profound effect on patients' ability to carry out daily tasks and interact socially. raises the emotional and financial strain on families and communities as a whole, as well as on carers individually. A wide range of cognitive dysfunctions, including issues with attention, memory, visual space, language function, and executive function, may characterise Parkinson's disease dementia (PDD) [2]. Individuals with PDD have more severe forms of attention deficit, decreased executive function, and visual impairments when compared to those with Alzheimer's disease (AD).

spatial function, with little impairment to linguistic function [3]. Additionally, compared to individuals with normal cognition, those with cognitive impairment have much reduced quality-of-life and activities of daily living. However, there is currently fewer research and therapy options available for nonmotor symptoms of PD, particularly cognitive impairment, compared to motor symptoms. According to epidemiological survey data, the occurrence of cognitive impairment is 2.5-6 times greater in PD patients compared to non-PD patients of the same age group [4]. The pace of cognitive decline, the regions of the brain affected, and the severity of the disease may vary greatly; it can begin before a PD diagnosis, continue throughout the diagnosis, or manifest years or even decades after the diagnosis [5]. After twenty years of illness, the cumulative incidence of PDD might approach 80% [6], which becomes a major predictor with age [7]. Cognitively

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impaired PD patients are more likely to have dyskinesia progression and a poor prognosis, both of which complicate PD diagnosis.
When diagnosing and differentiating nervous system diseases, including neurodegenerative motor disorders like α-synuclein (α-syn) disease (including PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA)) and tauopathies (progressive supranuclear paralysis, PSP)) [8, 9], the neurological physical examination of eye movement function is crucial. A decreased saccade amplitude, prolonged saccade latency, and special saccade mode have been proposed in recent research on eye movement in PD [9, 10]. These features may be significant in the early detection, development, and differential diagnosis of PD cognitive impairment, as well as in the course of the disease itself.

2. Pathogenesis of Cognitive Impairment in PD

Our understanding of the neuropathological process underlying PDD is lacking. Research has shown a correlation between the degree of cognitive impairment in PD patients and the pathological deposition of α-syn in the form of the cortical Lewy body (LB) [11]. A lack of dopaminergic (DA) neurons in the striatum caused by the loss of substantia nigra neurons is one of the main pathological features. Another is the buildup of α-synaptophysin in the inclusion bodies of neurons, which first manifests in cholinergic and monoaminergic brain stem neurons and the olfactory system, resulting in notable synaptic lesions [12]. PDD and DLB are on opposite extremities of the illness continuum, however they share many clinical features. Although they are often seen as opposite extremities of the illness spectrum, DLB and PDD have strong links with α-syn and share a lot of common clinical symptoms. The brainstem and cortical catecholaminergic, DA, and noradrenergic nuclei are more susceptible to the disease and degradation of α-syn in PD and DLB [13]. Defects in cognition and neuropsychiatry are thought to result from these illnesses' loss of monoaminergic neurons [14]. The substantia nigra, amygdala, brain, and hippocampal CA2 region are areas where α-syn lesions may be discovered in pigment neurons. The

α-syn pathology was found to be significantly correlated with an increase in activated microglia at the front of the amygdala, a progressive reduction in α-syn pathology from the anterior pericortical granules to the intermediate granule abnormal subregions and the posterior cortical granule island subregions [15, 16]. Mild cognitive impairment (PD-MCI) is characterised by a dispersion of DA neuronal defects in the caudate nucleus; in PDD, these defects spread to the periphery and neocortical regions. According to references [17, 18], the primary factor that determines PDD and DLB is the penetration of α-syn into the marginal zone (also known as the parahippocampal region) and neocortical area (also known as the frontal and temporal lobe binding area). There is substantial variation in PD pathology, according to a longterm clinical pathology research by Molly et al. [19]. Various cognitive domains may lean towards various degenerative patterns. Further factors that contribute to the development of PD include oxidative stress, mitochondrial dysfunction, cellular calcium imbalance, neuroinflammation, various faults in the neurotransmitter system, and other dysfunctional pathways and processes [20]. Also, PDD has a varied pathophysiology, according to certain research. Complex pathological alterations, such as the widespread deposition of α-syn, pathological changes similar to AD, and subcortical microangiopathy, are seen in patients with PD and cognitive impairment. Deposition of β-amyloid and tangles in nerve fibres are the primary pathological hallmarks of Alzheimer's disease [6, 21–23].

3. Characteristics of Eye Movement in Patients with PD and Cognitive Impairment

There are five main categories of eye-tracking tasks: saccade, gaze, smooth tracking, visual search, and social cognition. The two most common forms are fixation and saccade. When participants keep their gaze focused on one spot in space, it's called gazing; when they quickly move between two spots, it's called saccade. The two main types of saccades are autonomous saccades and reflected saccades. Easy focus and execution are required for reflex saccades, which are also called pro- or vision-guided saccades, to position the needle to a new object in the field of vision. The intentional tasks that arise from autonomous scanning in different models, on the other hand, may be classified as memory-guided, predictive, antiscanning, or deliberate scanning. The latter three types often need a greater degree of cognitive engagement and executive control. Saccades are the most common kind of eye movement abnormality in people with PDD.

3.1. Reflective Saccade, also known as Overlapping Saccade). There is no need to give participants complicated or even distinct instructions when administering the reflex scan task; instead, they are just instructed to stare at the target fast and precisely, and the cognitive process may be recognised using simple overlapping procedures (Figure 1(a)). Research on reflex saccade in people with Parkinson's disease and cognitive impairment, however, has shown conflicting findings [24]. Based on the findings

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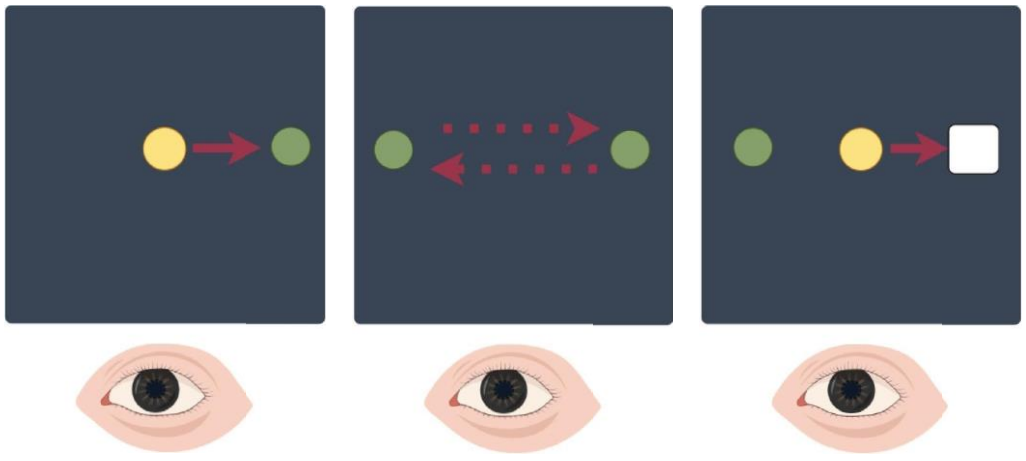

FIGURE 1: (a) Reflexive vision-guided scanning diagram: [1] the subject looks at the target point in the middle of the screen (yellow); [2] the target point appears randomly around the screen (green); and [3] the subject quickly looks at the random target point. (b) Smooth tracking diagram: the subjects looked at the target point and followed it to move at the same speed in the same direction until the target point disappeared. (c) Antisaccade diagram: [1] the subject looks at the target point that appears in the center of the screen (yellow); [2] the central target point disappears and a random target point appears around the screen (green); and [3] the subject looks in the direction opposite to the target point (white box).

MacAskill et al. [26] discovered that the reduction in vision-guided saccade is associated with the degree of cognitive decline, whereas suggestions [25] indicate that the latency and speed of eye movement in reflex saccade are comparatively conserved. Memory loss was also predicted by smaller reflex saccade amplitude, slower average speed, and shorter baseline latency in PD patients, according to a 54-month prospective study by Stuart et al. [27]. This study showed that early PD patients had impaired reflex saccade function, amplitude, and speed when compared to age-matched controls. Another research by Yu et al. [28] confirmed the impaired reflexive saccadic performance in Parkinson's disease patients, which worsened with deteriorating cognitive function. Patients with PD may be able to use reflex saccade as an indication of cognitive decline because to the negative link between prolonged latency and the Mini-Mental State Examination (MMSE) score.. Because AD solely affects complex saccade function, whereas PDD affects both reflex and complex saccade functions, Mosimann et al. [10] also suggested that impairment of reflex saccade might help distinguish between the two.

Tracking with No Delay 3.1. Figure 1(b) shows that human eyes use smooth pursuit eye movement (SPEM) to follow a tiny, slowly moving object. The basal ganglia may have a role in the aberrant SPEM seen in PD patients [29, 30]. The inability or difficulty to initiate slow, deliberate movement is a hallmark of Parkinson's disease. When compared to healthy controls, patients with PD showed more saccadic eye movements during pursuit [31]. The control group that was considered to be in the normal range showed an early

the component of smooth tracking in the direction that was proposed, a saccade to remedy the issue, and then an improved smooth tracking response. Contrarily, most PD patients employed saccade to track accurately, initial tracking was seldom generated before to scanning, and there was no evidence of improved smooth tracking after scanning. In addition, compared to the control group (low gain), patients with PD had a much decreased peak eye velocity throughout the follow-up period after scanning. Additionally, compared to those with normal working memory, PD patients with frontal brain dys-function had much greater mistake rates throughout smooth follow-up. According to single-photon emission computed tomography (SPECT), these patients exhibited low perfusion in the frontal lobe or frontotemporal cortex. This suggests that individuals with PD who experience working memory impairment may have dys-function in the frontal cortex [33, 34], leading to higher rates of predictive error during smooth tracking. An increase in irrelevant saccades or distractions, which mirrors the executive failure seen in PD patients, may be associated with SPEM abnormalities, according to other research [35].

Section 3.2 treats antisaccade. When individuals engage in

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antisaccade, they concentrate their gaze on the visual signal located in the middle of the detection screen. After a predetermined period, the visual stimulus signal in the centre of the screen will appear in a random direction. The participants in this research had to look in the opposite direction of the visual stimulus signal that was in the middle of the screen; the signal occurred randomly in one particular direction (Figure 1(c)). Antisaccades are only effective when the subject is able to spontaneously scan in the opposite direction from the stimulus, rather than relying on their reflexive, visually directed scan [36]. According to some research, spontaneous

There is no discernible decline in performance in later stages of PD, although early-stage symptoms such as saccade disorder and reduced saccade amplitude have been reported [37], particularly in memory-mediated saccade activity. Deterioration in saccade accuracy and extension of saccade latency are the most prominent symptoms of reverse saccade involvement, which worsens with the course of PD [26]. Waldthaler et al. [38] performed a meta-analysis and discovered that PD patients had a much higher mistake rate and reverse saccade delay, and that a longer latency of saccades was associated with higher exercise load and longer disease duration. In addition, Silvia et al. [36] demonstrated that the primary cause of the increased antiscan error rate in PD patients is not the inability to voluntarily scan in the opposite direction of the target, but rather the inability to control the reflex scan of unexpected targets. Further findings included the following: a higher Hoehn and Yahr (H & Y) score was positively linked with a greater reverse scan error rate, and the H & Y score, as an overall clinical stage evaluation tool, represented the degree of cognitive deterioration caused by the illness. While dopaminergic medication may have some correlation with PD progression, it has no discernible impact on reflex delay.

4. Possible Mechanism of Eye Movement Disorder in PDD

The decreased saccade amplitude observed in the PD patient may be due to basal ganglia dysfunction, which causes ex-

cessive superior colliculus inhibition when the fronto-ocular signal gets transmitted from the substantia nigra reticular part to the basal ganglia. Autonomous saccade works through the cortical-basal ganglia-superior colliculus pathway, whereas reflex saccade starts directly from the cortex to the superior colliculus without passing through the basal ganglia, both of which are then projected to the brainstem saccade generator (Figure 2). The DA neurons in the pars compacta of the substantia nigra regulate the direct inhibition and indirect excitation of the striatum to the inner globus pallidus/substantia nigra reticular part by stimulating D1 and D2 receptors, respectively [39]. The loss of DA neurons in the substantia nigra pars compacta in PD leads to excessive activation of the inner

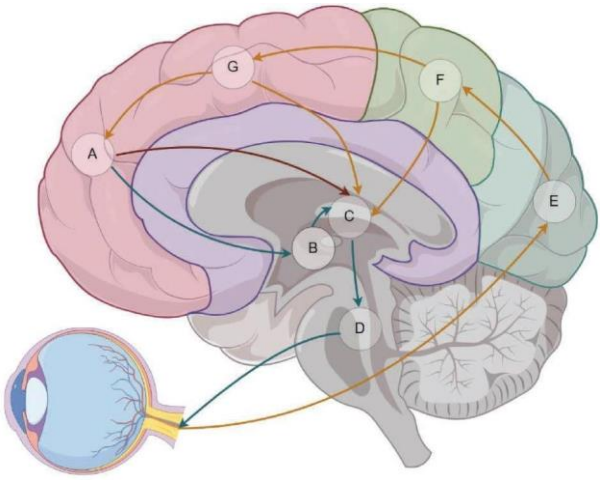
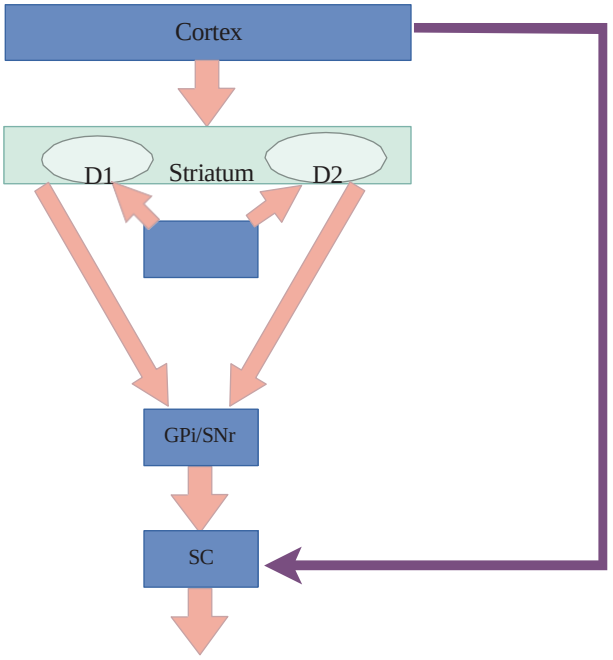


FIGURE 2: Anatomical pathways related to reflexive and voluntary saccades in Parkinson's disease. A: dorsolateral prefrontal cortex; B: basal ganglia; C: superior colliculus; D: brainstem saccade gener- ator; E: visual cortex; F: parietal frontal lobe visual field; G: frontal lobe visual field. A ⟶ B ⟶ C: autonomous saccade pathway; A ⟶ C: reflex saccade pathway.



globus pallidus/substantia nigra reticular part in the striatum, followed by over- inhibition of the thalamus (striatum-thalamus-cortical cir- cuit) and superior colliculus, resulting in motor delay and random scanning disorder (Figure 3). Abnormal deposition of α-syn in DA neurons in the substantia nigra pars com- pacta is a pathological feature of cognitive impairment in PD. When the clinical signs of PD are prominent, DA

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neurons in the substantia nigra compacta are seriously damaged, which may lead to excessive inhibition of the superior colliculus, prolongation of latency, and decrease in velocity and amplitude; this may also reduce the inhibitory effect on the superior colliculus, thus stimulating nerve impulses to produce unnecessary saccade [40] Subsequently, pathological deposits may continue to spread from the

FIGURE 3: Effect of dopaminergic neurons on saccade. SNc: substantia nigra pars compacta; GPi: internal globus pallidus; SNr: substantia nigra pars reticulata; SC: superior colliculus.

midbrain to the thalamus and cortex as the superior colli- culus circuit is gradually damaged, impairing cognition and aggravating eye movement dysfunction, which may explain

the link between eye movement dysfunction, cognitive decline, and disease progression in PD [27, 41]. Studies have also shown [42] that the lateral prefrontal cortex is a vital area for saccade control, playing a central role in executive function, while lesions in this area are associated with many executive defects. In addition, the ability to inhibit incorrect, visually evoked eye beats depends, to a certain extent, on the integrity of the lateral prefrontal cortex, which further suggests that eye movement disorders are associated with impaired executive function. Executive dysfunction is the most prominent manifestation of the cognitive impair- ment observed in PD. Amador et al.'s research also showed [36] that executive dysfunction in PD was asso- ciated with a higher antiscan error rate, increased in- hibition times in delayed reverse scan tasks, and prolonged scan response times.

5. Eye Movement Differences between PDD and Other Cognitive Disorders

section 5.1. AD. Progressive memory loss, attention impairment, and executive dysfunction are hallmarks of Alzheimer's disease (AD), the most prevalent neurodegenerative dementia [43]. Acquired oculomotor impairments in Alzheimer's disease include saccade, fixation, and smooth pursuit. Saccadic tests revealed that AD patients had fewer precise saccadic movements and more big invasive saccades [44]. Eye movements in young-onset AD were compared with those of healthy controls of the same age by Pavisic et al. [43]. Compared to healthy controls of the same age, patients exhibited aberrant patterns of eye movement in the saccade, smooth pursuit, and fixation stability tests. In addition, the findings imply that high-order visuospatial and visuoperceptual integrations may be predicted using eye-tracking paradigms that are both simple and particular, which represent fundamental oculomotor properties. Patients with AD made more mistakes and spent less time following the goal during smooth pursuit tasks. In contrast to healthy older individuals, patients with AD exhibited increased antisaccade cost, latency variability across tasks, and latency overall (Noiret et al., 2015). It took longer for AD patients to fix erroneous antisaccades and there were more uncorrected antisaccades overall. When asked to forecast when a saccade will occur, older persons with AD had more gain and gain variability compared to healthy older individuals. The majority of saccadic eye movement characteristics shown strong correlations with dementia screening tests, particularly the MMSE and episodic memory measures, as well as with prosaccade, anti-saccadic, and predictive saccade tasks. This provides further evidence that executive and selective attention impairments may underlie saccadic eye movement abnormalities in Alzheimer's disease.

Section 5.2 will cover DLB. Mosimann et al. [46] conducted experiments that tested PDD and DLB patients' reflexive saccade abilities, as measured by gap and overlap tasks, as well as their complex saccade abilities, including prediction, decision, and antisaccades. Saccadic eye movement alterations were seen in both DLB and PDD patients, with a protracted delay of horizontal saccades of all kinds, as well as defective predictive saccades and inhibition of saccades. Like patients with PDD, those with DLB have an increased delay of reflexive and voluntary saccades, the degree of which is correlated with the severity of the condition, according to a research [47]. Vulvovaginal palsy is a symptom that may be seen in some DLB patients. Horizontal and vertical saccades were less rapid and accurate, and the patients' variability was higher. Supravertical gaze paralysis is seen in a small number of DLB patients. People with DLB had trouble with basic saccadic eye movement tasks as well as more advanced ones, and they also had trouble with reflexive and saccadic execution. Furthermore, studies have shown that akinesia and stiffness often accompany convergence issues [48].

6. Feasibility and Advantages of Using an Eye Movement Instrument to Evaluate Cognitive Impairment in PD

As of right now, there isn't a solid biomarker that can detect neurodegeneration or monitor the development of cognitive impairment in PD. Neuropsychological screening measures are now the gold standard for clinical diagnosis of PDD. Screening techniques with greater accuracy need substantial time and resources, including experienced medical personnel and significant training, yet they are adequate in diagnosing AD and moderate cognitive impairment (MCI). In addition, the degree of education of the receiver and the expertise of the assessor have a significant impact on the outcomes [49–52]. On the other

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hand, eye tracking may provide quantitative parameters and millisecond-level precision [53]. To objectively quantify cognitive impairment in PD patients, we used a particular eye-scanning technique to investigate the cognitive process behind visual abnormalities. With the use of eye movement tracking technology, it is possible to record the dynamic features of behaviour in the natural world in a way that is more objective, trustworthy, and scalable. This paves the way for the processing and quantitative analysis of objective data [54]. Patients with cognitive impairment may have their illness development monitored nonverbally and with less cognitive load using eye movement monitoring [55]. Recording eye movements does not need any extra behavioural reactions, unlike many conventional neuro-psychological evaluations. Eye movement tracking is ideal for patient research since it is noninvasive and does not have any contraindications [43]. Evidence is mounting that standard cognitive evaluation instruments and data gathered from eye movement monitoring have a strong association. Eye movement monitoring seems to be a viable tool for assessing and tracking the cognitive state, severity, and development of neurological disorders [36]. Screening for cognitive problems in neurological illnesses has piqued the interest of eye-tracking technologies in recent decades. Using an electro-phthalmography equipment, Thickbroom and Black [56] were the first to discover aberrant eye movement in multiple sclerosis. They measured eye movement during monitoring responsibilities. Eye movement abnormalities may include either the extrapyramidal or supratentorial cones, as was shown in another research [57] that included ALS patients. Based on these results, watching eye movements might be a useful diagnostic technique for gauging illness course and prognosis. Eye movement tracking may have use in the differential diagnosis of Parkinson's syndrome[58,59] since several age-related degenerative disorders are associated with aberrant patterns of eye movement. These patterns vary among PD, cortical-basal syndrome, PSP, and MSA. A growing body of research suggests that indicators that monitor eye movement may do more than just digitally record the eye's spatiotemporal trajectory and movement characteristics; they can also reflect sophisticated cognitive information and even forecast the onset of particular cognitive impairment. These markers differ because of variations in disease features, individual variances in perception, and the severity of cognitive impairment [55]. During gaze and smooth tracking tasks, several brain regions were discovered to be active, including the thalamus, anterior cingulate cortex, auxiliary motor area, superior colliculus, and frontal insular cortex [60, 61]. Tasks requiring executive function, such as scanning, smooth tracking, visual search, and social cognitive processing, engage a network of cortical and subcortical regions [62]. Thus, the eye movement tracking index offers a wealth of information for investigating the brain's inner workings, the connections between behaviour and cognition, neural processes, and brain function [63, 64]. Saccade activity impairment may be an early indicator of cognitive impairment in PD, as shown by Walton et al. [65] in their study of patients with PDD compared to those with PD without cognitive impairment. Patients with PDD were more impaired with regard to complicated saccade and reverse saccade movements. Prolonged saccade delay was shown to be more than 60% sensitive and 88% specific in differentiating PD from PDD, according to Mosimann [66] and other research. Even at an early stage, the amplitude of the reflex saccade in PD patients reduced somewhat, according to a case-control research [26] conducted by Macaskill et al. In addition, later stages of the illness are generally associated with greater saccade delay in older individuals with increased motor and cognitive impairment. If a patient has full cognitive function, their scan latency should be about the same; if they have cognitive impairment, it would progressively be longer. The varying amplitudes and latency of spontaneous saccades, together with their gradual deterioration, suggest that they might be a valuable objective tool for evaluating the illness status. According to these results, the reflex saccade parameters for motor and cognitive symptoms in PD might be reliable indicators of these conditions, and they could be used as biomarkers to monitor the development of the illness and the efficacy of neuroprotection and neurorecovery treatments. When it comes to motor illnesses like Parkinson's, eye-tracking studies are ideal for assessing cognitive function because They are less impacted by motor retardation in PD since they do not rely on motor responses and simply need basic eye motions.

7. Summary and Prospect

There are currently few options for detecting cognitive impairment in early Parkinson's disease. Research methods and tools for the detection of cognitive dysfunction are currently limited, and there are still challenges to conducting objective and large-scale screenings of cognitive impairment in the community. This is mainly due to the high cost, stringent testing requirements, and invasive nature of cerebrospinal fluid, peripheral blood, or neuroimaging [67]. Saccade monitoring has the potential to be a dependable and user-friendly biomarker, as several research on neurodegenerative diseases have shown that saccade controls have degraded to different degrees. There is a lot of activity in the area of cognitive testing that uses eye movement. Saccade has gained popularity as a method for assessing cognitive abilities and eye movement control because to its readily measurable dynamic

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features and well-defined anatomical circuits. Research is being conducted with the objective of making the tools more accurate and reliable. Many studies on Alzheimer's disease have shown a strong relationship between EMG parameters and cognitive performance; however, there is a dearth of research on the topic of cognitive impairment and EMG in Parkinson's disease patients, and what little there is is mostly cross-sectional. Different methods used to identify people, instruments, and durations of follow-up in previous longitudinal research may explain why their findings vary. To validate the role of eye movement in Parkinson's disease development, more longitudinal follow-up studies are required. The elderly also often have trouble with memory-guided scanning and reverse scanning. When it comes to scanning tasks, patients with mild cognitive function typically have no problem. However, when it comes to patients with severe cognitive impairment, eye movement is typically not an option because patients with severe cognitive impairment struggle to cooperate in order to implement the corresponding saccade paradigm. The acquired data can end up being inaccurate because of this. That is why it is essential to establish quantitative standards in order to have useful and effective assessment criteria. Furthermore, most studies found that individuals with PD used more dopaminergic drugs—drugs that might influence eye movement—during the test. To avoid this confounding impact, future research should compare PD patients taking medication with those who do not. Furthermore, there is a lack of consistency in the equipment used to detect eye movement and in the standards used to measure saccade indicators such as error rates, proper antisaccade delay, and error latency in the available research. The outcomes of the study might be skewed due to bias or mistake. In order to make the results more credible and consistent, it could be helpful to fix the possible problems with the spatial/temporal resolution, noise, calibration, etc., of existing eye-tracking hardware and software. Eye movement tracking in conjunction with other biomarkers and clinical tools has the potential to provide the most effective method for predicting cognitive deterioration and, eventually, for early, more tailored therapy of PDD.

Ethical Approval

The manuscript does not contain clinical studies or patient data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All authors had full access to all the content in the study and are responsible for the completeness and accuracy of the content. Xianglian Liao and Jian Yao are mainly responsible for manuscript drafting and manuscript editing. Hongyin Tang, Yilan Xing, Xin Zhao, and Daao Nie contributed to the literature search, and Guihua Li and Ping Luan were responsible for reviewing and guiding the manuscript. All the authors have read and approved the final manuscript. Xianglian Liao and Jian Yao contributed equally to this work.

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