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Review Article

Sensory and Motor Visual Functions in Parkinson's Disease with Respect to Freezing of Gait Symptoms

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Abstract

Freezing of gait (FOG) is considered to be a motor disorder symptom that affects some Parkinson Disease (PD) patients; however, it is hypothesized that sensory systems may also be involved in FOG. This review article summarizes the results from previous studies focusing on visual functions in PD patients. More emphasize will be focused on freezing of gait PD patients and whether visual functions are affected to greater amount among them than non-freezing of gait PD patients. Visual functions include high contrast visual acuity, low contrast visual acuity, contrast sensitivity, Vernier acuity, mesopic vision, stereopsis, motion perception, and vergence eye movements are all affected in PD patients, with FOG patients having more deficits in some of these functions. FOG patients also had larger impairments in non-dopaminergic mediated functions such as pupil light reflex and visual processing speed test, which suggests that FOG patients have greater impairment in two functions that involve cholinergic neurotransmitters. Whether these impairments are contributing to the FOG or just associated with FOG is uncertain.

Keywords: Parkinson's Disease; Freezing of Gait; Visual Dysfunction; Eye Movement; Autonomic Nervous System

Highlights

- Freezing of gait (FOG) is thought to be a purely motor disorder in some PD patients.
- Recent studies suggest non-motor functions are also involved.
- Non-dopaminergic system could contribute to occurrence of FOG symptoms.
- Previous studies showed that different clinical and experimental visual functions are affected in FOG PD patients more than non-FOG PD patients.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects the central and peripheral nervous systems and leads to disturbance of body motor functions such as bradykinesia (slow movement), muscle rigidity, resting tremor (shaking), and postural instability [1].

Parkinson's disease is the second most widespread neurodegenerative disorder after Alzheimer's disease, and the most common neurodegenerative disease among older adults in developed countries. The estimated prevalence of PD in industrial countries is 0.3% and the incidence rate is about 8-18 per 100,000-person years [2]. With increasing age, the prevalence increases to about 1% among those who are above 60 years old, and about 4% among those who are above 80 years old [3,4].

Reduction of the dopamine neurotransmitter through cell death is considered as the primary cause of motor disturbances in PD patients [5]. The majority of cell death occurs within the basal ganglia complex, specifically in the frontal part of substantia nigra (or the black substance) which is called the pars compacta [6,7].

Non-motor Symptoms in Parkinson's Disease

The basal ganglia is connected to many different parts of brain such as superior colliculus, cerebral cortex, thalamus, and the brain stem through different channels i.e. motor, oculo-motor, associative, limbic and orbitofrontal circuits. These circuits are responsible for different functions including body movement, eye movement, perception, learning, attention, emotions, behaviors, cognitive abilities…, etc. For this reason, basal ganglia are not only involved in motor function, but they are also involved in sensory and cognitive functions. In addition, dopamine is found throughout different sites of the nervous system. These two findings have led investigators to look at other sensory and cognitive functions in PD. Non-motor disorders include anxiety, depression, cognitive dysfunction, sleeping disorders, pain, olfactory disturbances, visual hallucinations and impaired visual function have been reported in PD patients [8-11].

PD patients are also characterized by non-motor symptoms and signs that are probably not solely due to a reduction in dopamine. These deficits are believed to be due to primarily the cholinergic system dysfunctions. Different cholinergic system dysfunctions in PD patients have been reported. Within the autonomic nervous system, these include cardiovascular functions, sexual and urinary problems, gastrointestinal problems, respiratory difficulties and thermoregulation problems. In the visual system, the pupil light reflex (PLR) is mediated by the autonomic nervous system. Different parameters of pupil light reflex are affected in PD patients [8,9,12].

Deficits in the cortical cholinergic systems are also linked

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to learning and executive function. Calabresi and co-authors hypothesize that some of the cognitive deficits in PD patients are due to a combination of dopamine and acetylcholine depletion because an increase in dopamine is not sufficient to affect certain cognitive performance and acetyl cholinesterase inhibitors are useful in the treatment of dementia associated with PD. They further hypothesized that at the cellular level, dopamine and acetylcholine interact to produce the synaptic changes associated with learning and memory [13]. This interaction is altered in PD and so these patients experience problems with working memory and learning tasks. Given these findings, it is not surprising that different sensory and cognitive functions are impaired along with motor functions in PD [14], despite James Parkinson's statement in his opening chapter that "the senses and intellect being uninjured" in his detailed description of the disease bearing his name [15].

Freezing of Gait (FOG)

Freezing of gait (FOG) is a main movement disorder symptom that presents in certain PD patients especially those in the advance stages [16]. It may lead to further complications such as falls, reduction in quality of life, and lack of independence [17-19]. Freezing of gait Parkinson's disease (FOG-PD) patients experience intermittent episodes; that could last for a few seconds; of inability to produce or maintain a forward movement or to make a turn. FOG is more likely to occur when the person is walking in narrow spaces such as passing through corridors or doorways [20,21]. The pathophysiological mechanism of the FOG symptom is unclear. Even though freezing of gait is classically considered as one of the motor disturbances, recent evidence suggests that the pathophysiological underlying FOG involves both motor and non-motor systems [22,23].

The concept that the FOG disorder has a distinct pathophysiological mechanism from other motor disorders in PD arises from the fact that FOG does not respond positively to dopaminergic treatment, whereas other motor disorder symptoms do respond [22]. In addition, FOG is strongly associated with non-motor symptoms such as depression, stress, anxiety, and cognitive dysfunctions [24,25].

The underlying pathophysiology of FOG has not been established [26]. Among the recent theories is the cross-talk model suggested by Lewis and Barker. In normal individuals, the basal ganglion is involved in the coordination of a number of neural activities. These neural activities include motor, cognitive and limbic processes and these processes both complement and compete with other in terms of the basal ganglion resources. In PD-FOG patients, the loss of dopamine alters the balance from competing inputs so that there is now cross talk between these inputs. In certain situations, this cross-talk put an excessive load on the processing capacity of the striatum, and combined with reduced responses from the output nuclei, this result in increased inhibition of the thalamus (i.e. a failure of disinhibition) which in turn inhibits movement [27].

Based on the cross-talk model, a PD patient walking in a crowded environment or narrow corridors has an increase in the amount of sensorimotor input. This increase in input overloads the system and produces the FOG. Simply overloading the system with sensory input may not be the only mechanism responsible for FOG.

Visual System Characteristics in Parkinson's Disease

A number of basic visual problems have been reported in PD [28,29], but few studies separated the PD patients into freezers and non-freezers. Before reviewing these functions, the pathophysiological changes in the visual system associated with PD will be reviewed.

Retina in Parkinson's Disease

Dopaminergic neurons are located in different layers of the retina with an A18 subtype of a macrine cells of the inner plexiform layer being one of the more studied cells. The highest concentration is located in the perifoveal area of the primate retina [30-33]. The inputs to these dopaminergic amacrine cells in the retina are not clearly defined, but A18 amacrine cells receive their input mainly from rod bipolar and, to lesser extent cone bipolar cells. The output of the amacrine cells is primarily to the retinal ganglion cells [33]. Autopsy studies on PD patients showed severe loss in concentration of dopaminergic neurons in the perifoveal area of the retina [34].

In general, dopaminergic neurons are involved in mediating the visual signals from cone and rod bipolar pathways to ganglion cells [35,36]. In many species, stimulating the retina with increasing light results in an increase of dopamine released especially from the amacrine cells [37]. The current theory is that dopamine plays a role in controlling the size of ganglion cell receptive fields (center-surround mechanism). An increase in dopamine reduces the size of the receptive field and may increase the strength of the antagonistic surround. In contrast, a reduction in dopamine increases the size of the receptive field center and reduces the strength of the antagonistic surround [38]. The larger receptive field combined with the weaker surround would reduce the resolving power of the visual system [31,39].

Systemic injection of the protoxin MPTP (1-methyl, 4-phenyl, 1-2-5-6 tetrahydropyridine) into primates destroys dopaminergic neurons. The effects of the protoxin MPTP on the retina were to reduce the amplitude and increase the latency of both pattern evoked electroretinogram (PERG) and pattern visual evoked potential (PVEP) signals. Both of these functions improved temporarily after administering dopaminergic treatment [40]. The PERG studies indicate that the dopamine deficit was affecting the function of the inner retinal layers. Injection of neurotoxin 6-hydroxydopamine into the retina produced similar results. Both the amplitude and phase of pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP) were abnormal especially for the higher spatial frequency stimuli [41].

Electroretinogram (ERG) studies in PD patients have reported that PERG amplitudes were reduced, which is consistent with the animal models. The flash ERG was also affected. The ERG b-wave amplitude was reduced in PD patients, which suggests that the dopamine deficit primarily affects the inner retinal layers. Visual evoked potential (VEP) results in PD were also consistent with the animal models. The VEP amplitudes were lower and the latencies of P100 and N15 signals where longer in PD patients. Moreover, there was an inverse correlation between the latency of P100 waves of VEP and the amplitude of PERG which suggests that the abnormalities of VEP signals in PD patients was mainly retinal in origin [42,43].

Dopaminergic treatment can reduce the latencies of both the ERGs and VEPs [31,44].

Optical coherence tomography (OCT) is a retinal imaging technique that can examine different retinal nerve fiber layers. OCT studies showed that the macular region is thinner in PD patients relative to healthy control subjects [45]. More specifically, the inner nuclear, inner plexiform, and outer nuclear layers are all thinner in PD patients compared to healthy subjects. This thinning in the more proximal layers of the retina is consistent with loss of dopaminergic amacrine cells in retina [46]. The anatomical and electrophysiological studies of primates and individuals with PD patients support the concept that some central visual functions deterioration may due to dopaminergic deficiency in the retina.

Higher Visual Areas in Parkinson's Disease

Visual processing begins at the retina and these signals are transmitted to the LGN by the optic nerve. The majority of fibers from the LGN project to the primary visual cortex, or "V1 area" in the occipital lobe. A smaller number of fibers project to the superior colliculus. From V1 area, the visual signal projects to the secondary visual cortex, or (V2) area. Two major pathways carry information from V2 area to higher centers. The first pathway is called the ventral, or "What" visual pathway. This pathway is also referred to as the parvo system because its inputs start from the parvo cells at retina and LGN. From V1 and V2, the ventral pathway projects to V4 area, lateral occipital cortex, and inferior temporal cortex (IT) areas. The input to the ventral pathway is mainly from the fovea and it is concerned with analyzing central vision properties like fine details, contrast and colors under daylight conditions (photopic vision). The second pathway is called the dorsal, or "Where" visual pathway. This pathway is also referred to as the magno pathway because the ganglion cells feed into the magno cell layers at the LGN which then project to the visual cortex. The projections from V1 and V2 go to areas V3A, middle temporal cortex (MT/V5), middle superior temporal cortex (MST) and posterior parietal cortex. Input to the magno system is mainly from the perifoveal area and peripheral retina. The dorsal system involved primarily in analyzing peripheral vision properties like perception under dim light conditions (mesopic and scotopic vision), localization of target, movement of objects, and depth perception [47].

Dopaminergic neurons were found in lateral geniculate nucleus (LGN) and occipital cortex in rats [48], in the occipital, parietal, frontal cortex in nonhuman primates [49,5], and in visual cortex of cats and humans [50,51]. There are two main dopaminergic pathways in the midbrain that may also influence visual processing. The first one originates in the substantia nigra and projects into the visual cortex. The second one starts from the tegmentum and projects into the frontal cortex [52].

Visual Functions in Parkinson's Disease

There have been many reports in literature described visual deficits in moderate to severe PD patients. Harris (1998) and Armstrong (2017 &2011) have reviewed most of sensory and motor visual functions that are affected in PD patients. The list of deficits includes decreased high and low contrast visual acuity, reduced spatial and temporal contrast sensitivity, abnormal colour vision, peripheral visual field constrictions, abnormal ocular alignment, abnormal saccadic and smooth pursuit eye movements, dry eye, reduced blink rate, abnormal pupil light reaction, visual hallucinations, abnormal dark adaptation, abnormal depth perception [53,54,28].

For the purpose of this review article, deterioration of several visual functions in PD patients will be classified based on whether one of the main visual pathways (parvo or magno) is preferentially affected in the disease, and whether these functions are differently affected in patients with freezing of gait symptom. Also focus on other ocular functions that are controlled by prefrontal cortex pathway and the cholinergic system pathway will be described as well.

Visual Functions Mediated by Ventral Pathway in Parkinson's disease

Visual acuity: Several studies have shown a reduction in visual acuity in PD patients. Nowackaand co-authors showed that visual acuity at distance using ETDRS log MAR charts was reduced by 0.08 log units in PD patients (VA = 0.15 ±0.23) relative to control subjects. This reduction is approximately equivalent to a reduction in acuity of one line of visual acuity chart [32]. Another study showed that the mean visual acuity using Snellen acuity chart was poorer in the Parkinson's patients (20/39) compared with controls (20/28). This reduction was larger than reported by Nowacka, et al by 0.06 log units (15%) [55].

A reduction in high contrast acuity in PD does not always occur. Two studies reported that visual acuity for high contrast letters was unaffected by PD [56,57]. However, both studies reported that the visual acuity is significantly reduced in PD patients' when using low contrast letters. The reduction tended to be larger in more severe cases [57]. Treatment of PD may only produce a marginal, if any, improvement in visual acuity. Jones reported that the PD patient tended to have an improvement in acuity with treatment, although the improvement was not statistically significant [58].

A comparison of visual acuity using high and low contrast letters between FOG and non-FOG PD patients, and healthy normal people found that best corrected high and low contrast visual acuity in both PD patient groups was relatively worse than healthy controls. Reduction in visual acuity was larger in FOG-PD group than non-FOG-PD group, and it was more obvious when using low contrast letters. Although results were significantly different, the difference in the mean high contrast acuities between the healthy controls and non-FOG subjects for example was only 0.062 LogMAR, which was only 3 letters different [59]. PD patients have more visuospatial perception errors than healthy controls [60], and FOGPD patients have more visuospatial judgement compared to non-FPG PD and healthy controls. Furthermore, the performance on these tasks correlated with the severity of the gait disorder [61,62,20]. Thus, the degraded quality of visuospatial information could be contributing to FOG symptoms. PD patients have a higher dependence on visual cues to help them to control their posture [63], and so it is possible that FOG is due to degraded visual information involved in balance and posture. Because of the degraded visual information, the FOG PD patients are less sure of their balance in making the next movement and so they stop.

The reduction in visual acuity is consistent with the hypothesis

that the receptive fields of the ganglion cells are larger in PD. Nevertheless, it is still possible that the decrease in visual acuity is due to cortical dopaminergic reduction. The association of visual acuity reduction with the severity of the disease suggests that there could be both retinal and cortical involvement and it is impossible to distinguish between them from measuring visual acuity alone [58,55].

Other confounding factors could be responsible for any reduction in acuity. These factors include dry eye, poor blinking or abnormal fixational eye movements [28]. Another confounding factor is that the prevalence of ocular diseases is higher in PD patients. Nowacka found that nuclear and posterior subscapular cataract, age-related macular degeneration (ARMD), blepharitis and glaucoma rates were higher in PD patients compared with age-matched healthy control subjects [32].

Spatial and temporal contrast sensitivity: Spatial contrast sensitivity is usually measured by varying the contrast of sinusoidal grating until the grating pattern is just visible. This is repeated for a wide range of spatial frequencies (i.e. different widths of the grating bars). The majority of these studies on PD patients agree that there is loss in contrast sensitivity at medium and high spatial frequencies (the narrower grating bars), especially for the cases with more advanced PD [64]. The loss in contrast sensitivity was marked mostly at 4.8 cycles per degree (cpd), which was the peak region of the contrast sensitivity function in controls. The losses in contrast sensitivity of medium and high spatial frequencies were consistent with losses reported in the visual evoked potential (VEP) studies [65,66].

A study found significant reduction in contrast sensitivity in PD patients with FOG symptoms compared to PD patients without FOG symptoms using Pelli Robson contrast sensitivity chart. In addition, loss in contrast sensitivity was shown to be strong discriminator between freezer and non-freezer PD patients [59]. The severity of FOG correlated with losses of contrast sensitivity especially at lower spatial frequencies. Losses in low frequency contrast sensitivity were considered to be a stronger predictor for the freezing of gait severity more than motor impairments [67]. The loss of sensitivity at the lower spatial frequency is suggestive, but not definitive, of magno pathway loss rather than a parvo pathway loss.

The loss of contrast sensitivity in PD is consistent with a decrease in retinal dopamine and corresponding increase in receptive field size. However, the loss in contrast sensitivity in some PD patients appears to be greater for horizontally oriented stimuli than vertically oriented stimuli. This finding suggests the cortical origin of contrast sensitivity loss rather than retinal origin [68,69,56]. Interestingly, contrast sensitivity improves in PD patients after administrating L-DOPA [68,70]. Bulens and his coauthors described 'notch losses' in the contrast sensitivity function of PD patients. These losses occur only in the medium spatial and not anywhere else in the spatial frequency domain [69]. Their interpretation is that this deficit represents selective loss visual neurons tuned to this range of frequencies. However, one should interpret their results with caution because uncorrected astigmatic refractive errors can create notch defects and differences in contrast sensitivity at different orientations [71,72].

Temporal contrast sensitivity measured using a 4-degree circle with range of flickering rates (1, 2, 4, 6, 8, and 16 Hz.) showed that PD patients had lower temporal contrast sensitivity especially at the higher flicker rates (8, and 16 Hz). These results suggest that there could be either a deficit in the magno pathway or a general reduction in the retinal gain such that the dopamine deficiency was equivalent to lowering the retinal illuminance [65].

There is an interaction between the spatial and temporal contrast sensitivity functions in normals. If the flicker rate of the grating pattern increases from 1 Hz to 10Hz in normals, sensitivity at low spatial frequencies increases and sensitivity at the medium and high spatial frequencies decreases. The changes in sensitivities are thought to be due to a decrease in the strength of antagonistic surround of the receptive fields. In some PD subjects, increasing the flicker rate to 8 Hz decreased their sensitivity at all spatial frequencies without any sensitivity enhancement at the low spatial frequencies. This suggests that dopamine is involved in controlling the ganglion cell receptive field and if it is absent or in a low concentration, the receptive field surround is not very strong for the 1 Hz stimulus so that increasing the flicker rate decreases the contrast sensitivity at all spatial frequencies [65].

Visual Functions Mediated by Dorsal Pathway in Parkinson's disease

Visual Perception under Dim Light Condition (after Dark Adaptation): The human visual system is capable of operating under a wide range of lighting conditions. The two general processes involved in this large operating range are light and dark adaptation. Light adaptation is the ability of our visual system to adjust to increasing levels of light and maintain a high relative sensitivity to changes in the stimuli relative to the background. The initial phase of light adaptation occurs within a few seconds. On the other hand, dark adaptation occurs when we go from a bright environment to a dark environment. In this situation, the visual system is optimized for detecting a small amount of light on the absolute scale. As with light adaptation, the time course depends on the change in magnitude that occurs in the background environment. If the change in the background is about a factor of 100, then dark adaptation takes only a few seconds [73]. However, if the change in light levels goes from operating based on cone input to operating based on the more sensitive rods, then the time course is 10 to 20 min [37].

The light levels in an urban environment at night fall within the mesopic range where both rods and cones are providing input. Since PD is characterized by a dopaminergic level reduction, it expected that their mesopic vision is compromised, particularly their spatial resolution in dim lighting [74]. Two studies found that there were similarities in peripherally viewing contrast sensitivity functions between dark-adapted normal individuals (by wearing neutral density filters) and light-adapted PD patients. This finding supports the view that dopaminergic neurons are involved in the light-dark adaptation processes and a decrease of dopamine release in the dark-adapted retina weakens the strength of the antagonistic surround of the receptive fields [66,38]. This suggests that visual resolution of PD patients might decrease more as background light levels decreased.

A questionnaire study showed that PD patients had difficulties with driving cars especially during night. Half of PD patients of that study were freezers but the study did not compare between freezers and non-freezers patients [67]. Alhassan found that low contrast visual acuity, and contrast sensitivity is affected to greater extend in

PD patients with FOG symptoms more than both PD patients without FOG symptoms and healthy individuals when these measurements were taken under low light levels (i.e. mesopic vision). The effect of reducing light level after 5 minutes of full dark adaptation was very obvious on contrast sensitivity values. However, reduction in high contrast visual acuity among FOG PD patients was similar to other two groups [59].

Vernier acuity: Another type of visual assessment is measuring the ability of subjects to tell when two targets are misaligned. This kind of acuity measurement is called hyperacuity. Traditional visual acuity is limited by the cone spacing in the fovea and the optical quality of the eye. The average spacing between the cones in the fovea is 0.6 minutes of arc (approximately 40 seconds of arc) and so this would be the minimum separation between two points or lines that could be resolved if the optics of the eye were perfect. The term hyperacuity arises from the fact that one's ability to judge whether two objects are in alignment ranges from 3 to 8 second of arc. These values are about 10 times better than the resolution threshold of human eyes; hence the term hyperacuity. In addition, optical image degradation has only a small or little effect on hyperacuity. This suggests that the hyperacuity task depends more on neural processing in higher visual centers beyond the retinal level to detect the small differences in the spatial locations of the two lines [75,76].

Vernier acuity is a form of hyperacuity. It is the ability to detect the slight horizontal misalignment of two vertical lines (or bars). Vernier acuity can be as low as 3 second of arc (arc sec) in individuals who have had extensive practice and approximately 20 arc sec for naïve subjects [77,78].

Previous studies on the effect of age on Vernier acuity are mixed. Some showed there are no significant differences between age groups. Others showed there are no changes in Vernier acuity threshold until age of 60 years or above. However, these studies agree that Vernier acuity is minimally affected by the optical degradation due to normal aging changes. The studies that showed a decrease in in Vernier acuity in older people, assumed that the decrements were due to aging neural processes [75,79,80,81].

Measuring Vernier acuity may be useful for evaluating the magno pathway neural functions of the visual system [82,83]. Vernier acuity as a function of light level may also allow one to tease out dopamine deficiencies at the higher centers versus at the retinal level. A study found that both FOG and non-FOG PD patients had significantly worse Vernier acuity compared to normal healthy people, with FOG PD patients having the worst. Measuring Vernier Acuity under low light conditions (i.e. mesopic) reduced Vernier acuity to larger amplitude in PD patients with FOG symptoms more than other two groups [59]. This result suggests that the larger decrement in Vernier acuity at lower luminance in FOG PD patients could be due to less precise positional information leaving the retina because the ganglion cell receptive fields are larger.

Motion perception: Different studies showed motion detection deficits at high level among PD patients comparing to age-matched controls. One of the studies measured the motion perception by using the Useful Field of View test. This study showed that PD patients had more motion perception errors comparing to healthy controls; however, this study could not discriminate whether the motion detection deficit was originally retinal or cortical in PD patients [84].

Coherent motion thresholds were measured for cognitively intact PD patients and for age-matched controls. This paradigm starts with over a hundred dots moving in random directions. The percentage of dots that are moving in the same direction increase until the subject can identify the direction of nonrandom motion. This is considered a global motion task since the subject must integrate the information of a relatively large area of their visual field. PD patients required a significant higher percentage of dots moving in the same direction relative to age-matched controls [85].

Castelo-Branco and his coworkers used a hierarchical approach to study temporal and motion perception in PD subjects [86]. They categorized the visual stimuli based on where in the visual system the processing likely occurred. Contrast sensitivity to a high temporal frequency target was their low-level stimulus. Detection of this stimulus is believed to be mediated by the magno pathway. The intermediate-to- high level stimulus was global motion integration stimuli using random dot kinetogram (RDKs). This type of motion integration is believed to be mediated by the cortical dorsal pathway. They also looked at the relationship between the two stimuli. For all levels of stimuli, PD patients showed more deficits than healthy controls. However, the temporal contrast sensitivity impairment from the retinal level could not explain the motion integration deficits at the cortical level in PD patients, as there was no relationship between the two motion perception tests. From this study, it appears that motion perception in PD patients due to impairment in the cortical areas and not necessarily due to dopaminergic reduction in the retinal level.

Lee and Harris (1999) used a questionnaire to assess motion and space perception in everyday life of PD patients. The patients reported that they haddifficulties when they tried to move through narrow spaces at their home, and they had difficulties determining the movement of pedestrians and vehicles in the street.They also reported difficulties in judging distances in space (i.e. distances between objects, or when they try to reach an object) [87].

Stereopsis (Depth Perception): The reports of difficulties in judging distances could result from an impairment in stereopsis [87]. Stereopsis is a relative depth perception that arises from the integration of slightly different information from each eye in the visual cortex [88].

Flowers & Robertson showed that global stereopsis for suprathreshold complex patterns in depth was impaired in the advanced stages of PD, but perception of simple global stereopsis suprathreshold patterns in depth was not impaired in mild and moderate PD subjects [89]. Because interpretation of complex 2-D imageswas also impairedin the advanced stages, they believed that the inability to interpret complex 3-D images reflected a general visual-spatial processing deficit in higher visual and cortical levels rather than a deficit just in-depth perception. Thus, their results support the hypothesis that visual deficits in PD patients could either be of retinal origin or result from deficits in the higher visual centers [89]. Kim et al (2011) reported that local stereopsis was impaired in PD patients. This study also found that the contour stereopsis dysfunction was associated with other visual cognitive dysfunctions

(e.g. visual memory and visual perception constructive function) which suggest that the deficit in contour stereopsis is associated with dopaminergic depletion in the cortical level. However, they did not investigate the possible role of retinal dopaminergic depletion as a potential factor of depth perception deficit [90]. Sun et al (2004) foundthe number of individuals who had abnormal local stereopsis was higher in PD patients than healthy controls and there was no improvement on stereopsis after taking medications for PD group. The impairment of stereopsis correlated with the motor dysfunction, which suggests that the stereopsis deficits may be related to the severity of the disease. The interesting finding in this study is that they performed color perception tests and they found patients had more error scores than the controls. PD patients who had abnormal stereopsis had significantly worse color perception scores than PD patients with normal stereopsis. The latter finding suggests that the retinal dysfunctions in PD patients may contribute to higher visual deficits in PD patients such as contour stereopsis [91].

A study looked into comparison of both local and global stereopsis in PD patients with and without FOG symptoms using stereopsis tests that are commonly used in clinic. The study clearly showed that FOG PD patients had worse stereopsis than non-FOG PD patients on both types of tests. The deficits in stereopsis among freezer patients was bigger when using global tests. The impairment in global stereopsis was larger as the shape of depth was more complicated for a certain test. The deficit in stereopsis was not associated with the severity of the disease or with eye movement abnormalities which suggests that the deficit in stereopsis was more likely due to impairment in higher cortical areas among FOG PD patients [92].

Imaging studies of the human brain have shown activity related to binocular disparities or stereopsis in the occipital cortex, parietal cortex (V3A in particular), frontal cortex and cerebellum. Data from nonhuman primates' cellular recording has identified cells that are stimulated by contour and random dot stereo stimuli in visual areas V1 and V2 and throughout the parietal lobe visual areas. Based on these and similar findings, stereopsis was thought to be mediated by the dorsal visual pathways (i.e., the "where visual system"). Supporting this hypothesis was the report that extensive lesions in the parietal lobe resulted in partially loss of any depth perception. Nevertheless, cells in the ventral visual areas (i.e. the "what visual system") have also been to shown to respond to both contour and random dot stereo patterns in more recent experiments. Some of these cells in the inferotemporal cortex respond best to certain shapes whether the shape is formed by contours or seen in depth within a random dot pattern. These cells tend to be located in the posterior inferotemporal cortex [47].

Cowey & Porter (1979),have shown that lesions in a monkey's inferotemporal cortical area will impair detection of forms in depth generated by random dot stereo patterns, whereas lesions earlier in cortical visual centers do not impair global stereopsis. Given that processing binocular disparities involves perception of objects in depth, form in random dot stereograms and control of vergence eye movements, it is not surprising that multiple areas of the brain are involved in processing this information [93].

Given the multiple areas in the brain where stereopsis is processed, it is difficult to conclude that any impairment in stereopsis could be due to a dopamine deficiency in the parietal cortex. Nevertheless, the association of impaired stereopsis with other visual spatial problems in more severe cases may reflect changes in the inferior temporal cortex or ventral pathway.

Stereopsis is only one factor that contributes to depth perception. There are several monocular clues that also contribute to depth, but stereopsis is one of the more salient clues. Some monocular clues are static such as perspective and others are dynamic such as optic flow [47]. Impairment of any of the depth perception clues, as well as, impairment in the integration between the visual and motor systems in PD patients could lead to further movement disorders. Distance estimation of a remembered target is more inaccurate in PD patients than healthy controls during static (when they are not walking), active dynamic (when they walked toward it), or passive dynamic (moving on a wheel chair) conditions [61]. Results from this study confirmed that there are more errors in distance estimation during active movement condition than other two conditions. They attributed distance estimation deficit during active moving to two potential factors; a deficit in the proprioceptive perception, which is controlled by somatosensory system; or problems in the integration between proprioceptive and visual perception systems. In a subsequent study, they found that FOG-PD patients had more errors in distance estimation during both static and dynamic conditions than non-freezers DP patients and healthy controls [94]. The results of this study suggest that the motor disturbances that cause freezing of gait disorders could be due to two different perceptual impairments: the visuospatial (vision only) or visuomotor (vision and proprioception) deficits.

Eye Movement in Parkinson's Disease

The generation of eye movements is thought to begin in the visual motor areas (i.e. frontal eye field) in the frontal cortex. Signals are then sent to the superior colliculus and from there to extra ocular nuclei and then to the extraocular muscles. The basal ganglia and substantia nigra are located within the eye movement pathway between the frontal cortical areas and superior colliculus. Thus, it is possible that the dopaminergic pathway (basal ganglia and substantia nigra) mediate the neural activities of the eye movement pathway. Numerous studies have reported impairments in different types of eye movements in PD patients [95-98].

Vergence Eye Movement

Previous studies showed PD patients have difficulty with near visual tasks and report reading difficulties and diplopia. The clinical findings are consistent with a diagnosis of convergence insufficiency, which is inability to converge the two eyes enough when performing a near task. These findings include remote near point of convergence and reduction in fusional vergence amplitude at near compared to age matched normal individuals. Most of these functions improved after patients were treated with dopamine [99-101]. These findings suggest that the dopaminergic pathway regulates or influences convergence eye movements.

A video oculography study of vergence eye movements in PD patients showed there was a significant delay of both convergence and divergence eye movements among PD patients compared to age matched normal individuals. These delays were not correlated with

the severity, duration, or the treatments of the disease, which suggests that the dopaminergic system does not affectthe vergence system in PD patients [96].

The conflicting conclusions could be a result of multiple areas involved in the control of the vergence eye movements. Alvarez et al. (2014) compared the neural activity and convergent peak velocity in non-PD convergence insufficiency patients and control subjects using functional MRI (fMRI). The participants looked at 3 different targets representing 3 different vergence demands; far, middle, and near. The results showed that the convergence peak velocity in the patient group was lower than controls. Functional activities from frontal eye field, posterior parietal cortex and cerebellar vermis correlated with reduction of convergence peak velocity in the patient group [102]. It is possible that latency deficits are due to defects in the non-dopaminergic pathways regulating vergence eye movements and other vergence problems are due to defects in the dopaminergic pathways. Neural activities of vergence system adaptation were studied on two monkeys while their vergence system adapted to both cross and uncrossed disparities. Extracellular recordings indicated that prism adaptation was not complete in the vergence-related neurons located dorsal lateral to the ocular motor nucleus [103]. The authors concluded that other sites were responsible for prism adaptation and these sites were distal to the ocular motor nucleus. However, Takagi, et al. (2003) showed that lesions to the cerebellum vermis impaired vergence adaptation in monkeys, suggesting that central sites also play a role in prism adaptation [104]. Although neither of these studies rules out a possible role of the basal ganglion dopaminergic system in vergence adaptation, the electrophysiological studies suggest that vergence adaptation may be mediated by primarily a cholinergic system. Regardless these findings, it was found that vergence eye movement can be improved after two months of vision therapy training, and so convergence insufficiency was reduced in PD patients [105].

Fixation disparity is the small ocular misalignment of one eye or both eyes when the two eyes are fixating on an object during normal binocular vision. Schor (1980) described fixation disparity as a small error in the vergence system that is required to maintain fusion when the fast component of the vergence system changes [106]. Vergence system integrity and flexibility can be evaluated by introducing variable power of prisms in front of the two eyes. The introduced prism will create fixation disparity effect, and so good vergence system will show good adaptation to the prismatic power. Variable or bad adaptation to prismatic power stress reflects vergence system abnormalities [107]. It was found that FOG PD patients have poor vergence system adaptation to prismatic stress more frequently than non-FOG PD and healthy controls [92].

Saccadic Eye Movements

Voluntary saccadic eye movements (predictive and anti-saccadic tasks) are affected in PD patients [108,109]. In predictive, or anticipatory, saccadic eye movements, saccades are made toward a predictive location. Anti-saccades are more complicated. In anti-saccadic tasks, the eye movement is in the opposite direction of a target, but with same amplitude [110]. There are two mechanisms involved in anti-saccadic eye movements. The first one is to inhibit the saccadic eye movement toward a target. The second is to generate an eye movement toward the opposite direction, but with an amount equal to the presented target. Therefore, anti-saccadic tasks require more attentional and cognitive abilities than other saccadic eye movements [110].

Mild to moderate PD patients did not show a significant difference in anti-saccadic tasks relative to normal individuals; however, patients with severe PD, had more anti-saccadic errors and increased in latencies. PD patients who were treated with anticholinergic drugs had more anti-saccadic errors than those who did not receive these drugs [111]. This suggests that acetylcholine depletion contributes to the anti-saccadic errors in PD patients. It is thought that the frontal cortex, especially the frontal eye field, controls the suppression of the movement toward a target in anti-saccadic task. Anti-saccadic errors correlated with poor performance on executive function tests in PD patients. Executive function is also mediated by areas in frontal cortex. This suggests that there is a general deficit in the frontal lobe functions in some PD patients [111]. Moreover, the anti-saccadic errors are probably due to cognitive dysfunction regulated mainly by the prefrontal cortex pathway rather than dopaminergic pathway [108].

Pupil Light Reflex in Parkinson's Disease

Pupil constriction and dilation are mediated by cholinergic (parasympathetic) and adrenergic (sympathetic) autonomic nervous systems respectively. Neural losses occur in several autonomic centers in PD patients including EW nucleus, ciliospinal center, locus coeruleus and other higher autonomic centers [112]. ANS dysfunctions in PD patients are believed to be due to mainly acetylcholine (ACh) and norepinephrine (NE) neurotransmitters depletion rather than the dopaminergic reduction [8,9,12].

Previous studies showed that the latency of constriction onset, amplitude of constriction (pupil radius after 2 minutes of dark adaptation - minimum pupil radius after reaction to light), maximum constriction velocity and maximum constriction acceleration are affected in PD patients. These studies suggest that a dopamine deficiency in the retina or cortex is not responsible for the changes in the different pupillometric parameters because there was no correlation with any other motor symptoms of the disease [113,114]. In addition, there are more PLR parameters affected in cognitive impaired PD patients than those patients who have normal cognitive function [115]. PLR parameters of cognitive impaired PD patients were similar to the pupil dysfunction reported in Alzheimer's disease patients. This suggests that both groups of patients have the same central cholinergic (parasympathetic) deficit [116].

It was reported that freezing of gait and its severity are associated with frontal cognitive dysfunction and the severity of the frontal cognitive dysfunction respectively. Patients who experience gait freezing may show a greater impairment of parasympathetic function (e.g. PLR) than those who do not experience gait freezing. This would support the hypothesis that cholinergic systems may be impaired in gait-freezing individuals [117]. Supporting this hypothesis, Alhassan found that most of constriction parameters and dilation latency of both FOG and non-FOG PD patients differed significantly from healthy individuals. PD patients with FOG symptoms showed larger pupil size under light condition and larger deficits in constriction

latency than PD patients without FOG symptoms [59].

Visual Processing Speed in Parkinson's Disease

Visual information processing speed is the ability to detect a characteristic of a stimulus that is presented for a specified time interval. The minimum presentation time required for an individual to visually identify the physical characteristics of a stimulus is called the inspection time (IT). An IT task can predict humans' general intelligence, the performance abilities and the cognitive abilities [118].

PD patients have significant deficits on reaction time (RT) tasks because RT tasks require motor responses (Gauntlett-Gilbert & Brown, 1998). However, from those studies someone cannot conclude whether such deficits are due to the motor system disorders of PD or it is more likely due to delay in the processing speed of the visible information. Because IT does not require motor responses from subjects, it can measure the perceptual processing speed. Thus, IT measurement, unlike RT measurement, can be used to dissociate between the deficits (slowness) in motor response and the delay in the information processing speed within impaired movement population such as PD [60].

Different studies have shown that PD patients have significantly slower visual processing speed compared to aged match controls. However, these studies used different visual stimuli. For example, one PD patient needed significantly longer presentation times to recognize motion-defined letters than age-matched controls and this delay in the perceptual speed did not improve after taking dopaminergic medication [119]. The limitation of this study is that the task required eye movements to track the letters so it is possible that the eye movement disorders in PD patients contributed to the delay in the processing speed. Even if eye movements are controlled, PD patients still showed significant slower processing speed than healthy controls using visual recognition tasks [120]. Moreover, the performances of those patients did not improve after receiving medications, which is consistent with Giaschi et al. (1997) results.

Johnson et al. (2004) examined the IT task by presenting a simple figure, which consists of two vertical lines. The lines differed in length and the subjects identified the longer line. Results showed that on-medicated patients required significantly longer presentation times in order to identify the longer line compared with healthy controls. Moreover, the IT score for the PD patients group was not significantly different between 'ON' and 'OFF' medication status [60].

A study found that the dopaminergic pathway and dopamine levels in healthy subjects did not regulate visual information processing speed [121]. Results from Johnson et al. (2004) supported this hypothesis as the IT deficits was not improved significantly when patients were on their 'ON' medication time vs. 'OFF' medication time. It is possible that IT deficits in PD patients are distinct from the motor impairments [60].

Since it is hypothesized that FOG symptoms among some PD patients may be independent from the dopaminergic reduction, and the greater cholinergic system dysfunction may be involved. If this hypothesis were correct, then one would expect that FOG PD patients could have slower IT score compared with the non-FOG patients. Results of a study supporting this hypothesis found that PD patients with FOG symptoms had significant slower IT than PD patients without FOG and healthy controls using simple IT task [122].

There is reasonable evidence that the cholinergic autonomic nervous system mediates IT [123]. IT was significantly slower in patients with Alzheimer's disease compared with healthy controls [124] and nicotine acetylcholine receptors (nAChRs) are involved in IT processing. Thus, manipulating nicotine acetylcholine pharmacologically may affect the IT score in healthy subjects [125]. There is evidence that nicotine acetylcholine receptors (nAChRs) are reduced in PD patients especially in the nigrostriatal pathways [126]. It is possible that these receptors are also reduced in the areas, which are responsible for visual processing, which could explain the slower IT times for PD patients.

General Discussion

Previous studies suggested that FOG PD patients had greater impairment in visual functions that were mediated by the magno (dorsal) pathway than non-FOG PD patients or healthy controls. First of all, FOG PD patients showed larger reduction in different spatial vision measurements under mesopic conditions. This finding suggests that the deficit was due to decreased dopamine level at the retina affecting the dark adaption processes. Previous studies did not show a selective loss of functions mediated by either the magno or parvo pathways; however, magno pathway mediated visual functions (i.e. the Pelli Robson contrast sensitivity at low light levels, and the Vernier acuity) were the best tests at distinguishing between the 3 groups [59]. In addition, it was shown that impairment of global stereopsis was more frequent than the local stereopsis in FOG PD patients. These results suggest that stereopsis deficits in PD were due to impairments in higher visual centers rather than degraded input from each eye or inadequate vergence eye movements [92]. Supporting these findings, it was found that FOG PD patients did have a preferential impairment in visual function mediated by the dorsal (magno) visual pathway rather than the ventral (parvo) visual pathwy [127].

It is believed that the visuospatial information that is processed by the dorsal stream is used in taking motor actions; thus, the term "vision for action" used to describe the dorsal pathway processes [128]. However, that does not exclude the contribution of visual information that is processed by ventral visual system. Inputs from both systems have been shown to contribute to the motor responses as both systems are connected extensively [128].

FOG PD patients have more deficits in visuospatial judgement, motion perception, and visual perception of the surrounding space than non-FOG PD patients and that might contribute to their freezing symptoms and walking performance [129]. FOG PD patients underestimated the actual distances to a target during both static and dynamic conditions more than non-FOG PD patients and normal individuals [94]. It is unclear as to how much of this deficit was due to the loss of stereopsis since individuals can also use monocular depth clues and whether deficits in visual resolution hindered their ability to judge distances.

It is not clear as to how much the reduction in the basic visual functions of visual resolution, contrast sensitivity and depth

perceptioncontribute to visuospatial and motion perception problems during walking among FOG PD patients. Impaired visual acuity was found to be associated with reduction of different gait parameters such as step length and gait velocity in older adults [130-132]. Impaired contrast sensitivity was also found to be associated with reduction of different gait parameters such as step width, step length, gait velocity and fear of falling [133-136]. Impairment in depth perception was found to be associated with difficulties in avoiding obstacles during gait in older adults [137]. It would be important to measure different visual functions among PD patients along with walking through gate assessments. This would give more information as to whether the reduction in basic visual functions in PD patients can contribute to walking through gates difficulties.

Studies have shown that visual cues may facilitate or improve the movement and walking through gates in PD patients [138]. Visual cues such as stripes on the floor is one clue. The stripes enhanced the optic flow and the perception of these stripes was improved ability of persons with PD to walk through gates [139]. Because FOG PD patients had greater impairment of contrast sensitivity test particularly in low light levels, using high contrast visual cues in a well-lit environment may help them overcome their FOG symptoms [67,140].

The results of different studies that showed FOG PD patients had larger deficits in some pupil light reflex measurements and visual processing speed test are believed to reflect the cholinergic system dysfunction. This may suggest that FOG PD patients had a larger deficit in the central cholinergic system which could contribute to the FOG symptom and other motor disturbances. The contribution of cholinergic system to motor functions has been studied in PD rat models. It was found that the fall rates were more frequent in rats, that were injected with dual 192 IgG-saporin /6-hydroxydopamine (6-OHDA) than rats with either isolated cholinergic or isolated dopaminergic lesions [141]. This drug partially destroys both cortical cholinergic and dopaminergic systems respectively. It is hypothesized that after dual cholinergic-dopaminergic lesions, the attentional resources mediated by the cholinergic pathways can no longer compensate for the impairment of striatal control of movement in complex environment, as a result, falls occurs [141].

In conclusion, results of different studies showed that FOG PD patients had more deficits in different visual and other perceptual functions than non-FOG PD patients and healthy individuals. These findings may suggest that the non-motor functions (i.e. sensory visual functions) can predict the occurrence of FOG symptoms better than the motor dysfunctions. The loss in contrast sensitivity can predict the FOG symptom better than the motor dysfunctions [67]. Given these findings, PD patients are encouraged to check their eyes in routine basis and make sure their vision is fully corrected in order to avoid any movement difficulties especially in crowded and/or dim lighted environment.

Declaration of Competing Interest

The author declares no competing financial interests.

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