MASTER'S DISSERTATION

THE INFLUENCE OF THE VESTIBULAR SYSTEM ON POSTURAL INSTABILITY IN PATIENTS WITH PARKINSON'S DISEASE

Word count: 10,213

Karen Adriaenssens

Student number: 01702041

Supervisors: Prof. Dr. Leen Maes and Drs. Maya Danneels

GHENT UNIVERSITY

ACKNOWLEDGEMENTS

During the past two academic years I had the opportunity to immerse myself in the role of vestibular assessment in patients with Parkinson's disease. It goes without saying that I learned a lot about this topic. In addition, this master's dissertation resulted in further development of my academic and professional skills. All of this would not have been possible without the help and advice of many persons. Therefore, I would like to thank all of them.

First of all, I would like to express my deepest appreciation to my supervisors: Prof. Dr. Leen Maes and PhD candidate Maya Danneels. This master's dissertation could not have been realized without their guidance, constructive feedback and sharing of knowledge and expertise. Secondly, I am grateful for the practice moments organized by other PhD candidates in audiology. Thanks to them, I learned to administer all tests of the protocol correctly. Special thanks should also go to the study participants who made time and all cooperated properly during the testing moments. Additionally, I would like to acknowledge the audiology unit of the Ghent University Hospital, since I could use an examination room and some of the testing equipment. Lastly, I would like to mention my family and friends for their support.

I hope that this master's dissertation will make readers realize that vestibular assessment is absolutely necessary in patients with Parkinson's disease and that it will provide a basis for future research on this topic. I wish you a pleasant reading.

ABSTRACT (ENGLISH)

Background and objectives: Since patients with Parkinson's disease (PD) frequently suffer from falls and instability problems, comparable to those seen in individuals with loss of vestibular function, several authors suspect vestibular degradation during the disease course. Nonetheless, research on vestibular assessment within this population is inconsistent. As a standardized test protocol specifically designed to identify vestibular dysfunctions in PD patients does not yet exist, the first aim of this master's dissertation was to introduce a possible protocol. Secondly, a pilot study was established in order to compare the vestibular function of PD patients with those of healthy controls.

Methods: Ten PD patients (eight males and two females, mean age: 67.74 years) in Hoehn and Yahr stage III of the disease and ten healthy age- and gender-matched controls (eight males and two females, mean age: 67.54 years) participated in the pilot study. All subjects underwent auditory evaluation, including tympanometry and tonal liminal audiometry, as well as vestibular and oculomotor assessment, comprising static and dynamic visual acuity (SVA and DVA) testing, the video head impulse test (vHIT), oculomotor testing, cervical and ocular vestibular evoked myogenic potential (cVEMP and oVEMP) examination and positional maneuvers. Additionally, the participants filled in the Dizziness Handicap Inventory (DHI) questionnaire. Results were interpreted statistically using the Mann-Whitney U-test and Chi-Square or Fisher's Exact test.

Results: There were no statistically significant differences in DVA loss score (logMAR), lateral and anterior semicircular canal gains, gain asymmetry (%), oculomotor parameters, cVEMP presence, cVEMP and oVEMP N1 latencies (ms) and cVEMP corrected peak-to-peak amplitudes between PD patients and controls. However, posterior semicircular canal gains seemed to be slightly but significantly higher in PD patients, oVEMPs were significantly more absent, cVEMP and oVEMP P1 latencies (ms) were significantly prolonged, oVEMP peak-to-peak amplitudes (µV) were significantly smaller and the DHI total score (%) was significantly higher. Additionally, the oculomotor traces were evaluated qualitatively and demonstrated more dysfunctional patterns in PD patients compared with controls.

Conclusion: A standardized and extensive vestibular test protocol is important in order to gain insight into the specific nature, sites and degree of vestibular degradation, possibly due to neuropathological changes in PD. VEMP testing and the DHI questionnaire might be most valuable in detecting vestibular deterioration in middle-staged PD. The importance of DVA, vHIT and oculomotor assessment should be investigated further in future research.

ABSTRACT (NEDERLANDS)

Achtergrond en doelstelling: Aangezien patiënten met de ziekte van Parkinson regelmatig valincidenten en instabiliteitsproblemen, vergelijkbaar met deze van personen met een vestibulair verlies, ondervinden, vermoeden verschillende auteurs dat er vestibulaire aantasting is naarmate de ziekte vordert. Studies met betrekking tot vestibulair onderzoek binnen deze populatie zijn nochtans inconsistent. Omdat een gestandaardiseerd testprotocol om vestibulaire disfuncties bij parkinsonpatiënten op te sporen nog niet bestaat, was het opstellen van een mogelijk protocol het eerste doel van deze masterproef. Daarnaast werd een pilootstudie opgezet om de vestibulaire functie van parkinsonpatiënten te vergelijken met deze van gezonde controlepersonen.

Methode: Tien parkinsonpatiënten (acht mannen en twee vrouwen, gemiddelde leeftijd: 67,74 jaar) in Hoehn en Yahr stadium III van de ziekte en tien gezonde, naar leeftijd en geslacht gematchte controlepersonen (acht mannen en twee vrouwen, gemiddelde leeftijd: 67,54 jaar) namen deel aan de pilootstudie. Alle proefpersonen ondergingen auditief onderzoek, waaronder tympanometrie en tonaal liminaire audiometrie, alsook vestibulaire en oculomotore testing, waaronder 'static' en 'dynamic visual acuity' (SVA en DVA) testing, de video hoofd impuls test (vHIT), oculomotorisch onderzoek, cervicaal en oculair vestibulair geëvoceerde myogene potentialen (cVEMP en oVEMP) en positioneringsmaneuvers. Verder vulden de participanten de 'Dizziness Handicap Inventory' (DHI) vragenlijst in. De resultaten werden statistisch geïnterpreteerd middels de Mann-Whitney U-test en Chi-Kwadraat of Fisher's Exact test.

Resultaten: Er waren geen statistisch significante verschillen in 'DVA loss score' (logMAR), laterale en anterieure halfcirkelvormige kanaal 'gain', 'gain' asymmetrie (%), oculomotore parameters, cVEMP aanwezigheid, cVEMP en oVEMP N1 latenties (ms) en cVEMP gecorrigeerde piek-piek amplitudes tussen parkinsonpatiënten en controlepersonen. Niettemin bleek de posterieure halfcirkelvormige kanaal 'gain' licht maar significant hoger te zijn bij parkinsonpatiënten. oVEMP's waren significant vaker afwezig, cVEMP en oVEMP P1 latenties (ms) significant verlengd, oVEMP piek-tot-piek amplitudes (µV) significant kleiner en de DHI totaalscore (%) was significant hoger. Bovendien werden de oculomotore tracés kwalitatief geëvalueerd en vertoonden parkinsonpatiënten meer disfunctionele patronen in vergelijking met de controlepersonen.

Conclusie: Een gestandaardiseerd en uitgebreid vestibulair testprotocol is belangrijk met het oog op het verwerven van inzicht in de specifieke aard, plaats en graad van vestibulaire aantasting, die mogelijks het gevolg is van neuropathologische veranderingen bij parkinsonpatiënten. VEMP testing en de DHI vragenlijst zouden het meest waardevol zijn voor het detecteren van vestibulaire disfuncties bij parkinsonpatiënten in het middelste ziektestadium. Het belang van DVA, vHIT en oculomotorisch onderzoek dient verder bestudeerd te worden in toekomstige studies.

TABLE OF CONTENTS

LIST OF TABLES, FIGURES AND APPENDICES

INTRODUCTION

Since Parkinson's disease (PD) is globally the most common movement disorder and the second most common neurodegenerative disorder after Alzheimer's disease (de Rijk et al., 1997; Reich & Savitt, 2019; Tysnes & Storstein, 2017), a lot of research has been conducted to gain insight into its pathophysiology and symptomatology. Pathologically, PD is characterized by neurodegeneration in the central nervous system. Three fundamental changes responsible for this neurodegeneration include: basal ganglia neurotransmitter pathologies (DeLong & Wichmann, 2007), alpha-synucleinopathies resulting in Lewy body accumulation (Braak et al., 2003; Del Tredici & Braak, 2016) and pathological beta-oscillations (Lee et al., 2019; Little & Brown, 2014). With regard to the symptomatology, the cardinal motor symptoms of PD are: bradykinesia, rigidity and tremor (Parkinson, 2002; Reich & Savitt, 2019; Tysnes & Storstein, 2017). Yet patients also suffer from other motor and non-motor symptoms (Balestrino & Schapira, 2020; Reich & Savitt, 2019). When Johansson et al. (2019) and Berliner et al. (2020) investigated balance perceptions in patients with PD, their participants even reported symptoms that might indicate impaired vestibular functioning. In the study by Johansson et al. (2019), patients mentioned an increasing amount of conscious effort in order to perform activities without falling and the inability to focus on multiple tasks while walking. According to Berliner et al. (2020), all subjects brought up visual and vestibular changes, including: double vision, sensation of moving, slower eye movements, perceived lag of eye movement with head or body movement, dizziness and postural instability in situations where the visual surround is moving or when shifting the visual focus. Taking into account above mentioned results, there might be an overlap between the structures affected by pathophysiological neurodegeneration in PD and the vestibular system.

1. Vestibular dysfunctions and oculomotor deficits in Parkinson's disease

1.1. Comorbid vestibular disorders

Regarding the possible existence of comorbid vestibular disorders in PD, several authors suggest that the occurrence of benign paroxysmal positional vertigo (BPPV) in this patient population might be underestimated (Becker-Bense et al., 2017; van Wensen et al., 2013). van Wensen et al. (2013) reported a BPPV prevalence rate of 5.3% in PD patients, whereas up to 11% of PD patients reporting dizziness symptoms did have objective signs of BPPV. Based on these results, Becker-Bense et al. (2017) found a PD prevalence in BPPV patients corresponding to 1.1% for the overall sampling population, 2.6% for patients ≥ 65 years and 3.5% for patients ≥ 70 years. Nevertheless, BPPV prevalence in PD patients was significantly higher than PD prevalence in BPPV patients, since van Wensen et al. (2013) showed rates ranging between 5.3% and 11%. In the light of these remarkable results, the researchers hypothesized the possibility of an underlying problem, allowing to declare the coexistence of both disorders. According to Becker-Bense et al. (2017) and based on increasing evidence, vitamin D deficiency seemed most plausible (Berridge, 2017; Jeong et al., 2013; Mpandzou et al., 2016; Yang et al., 2020). However, these results should be interpreted with caution. Given that PD usually affects the elderly – with an incidence increasing over the age of 60 years, whereas only 4% of the patients is under 50 years old (Tysnes & Storstein, 2017; Van Den Eeden et al., 2003) – prevalence rates for BPPV in the overall older population must be taken into account. Since Oghalai et al. (2000) found that 9% of their participants aged 51 to 95 years had unrecognized BPPV, the prevalence rate for BPPV in the elderly is rather comparable with the numbers found in PD patients.

1.2. Vestibular function loss

So far, laboratory testing has been undertaken with the aim of discovering vestibular function loss in PD. Concerning the caloric test and rotatory chair stimulation, Venhovens, Meulstee, Bloem, et al. (2016)

observed no significant differences between PD patients, atypical Parkinsonism patients and healthy controls. In contrast, Vitale et al. (2011) found an association between lateral trunk flexion (LTF)[1] in PD and unilateral peripheral vestibular dysfunction. All PD patients with LTF showed an asymmetry after bithermal caloric stimulation, unlike the matched controls (i.e. PD patients without LTF). Considering the limited replication studies, Tang et al. (2020) conducted similar investigations. Vestibular test results indicated abnormalities in 11 of 19 PD patients with LTF and only in 3 of 19 matched controls. However, whereas all the subjects in Vitale's study had vestibular abnormalities suggestive of a peripheral lesion, the findings in Tang's study were divided. Five LTF subjects showed peripheral abnormalities, two had a central lesion and four had mixed results.

Lv et al. (2017) investigated vestibulo-ocular reflex (VOR) gains in PD patients and healthy controls using the horizontal video head impulse test (vHIT). The researchers found significant differences between both groups, since PD patients showed slightly but significantly increased gains.

In a study by Pötter-Nerger et al. (2015) ocular vestibular evoked myogenic potential (oVEMP) assessment revealed significantly delayed latencies and reduced amplitudes in the PD patient group. Additionally, de Natale, Ginatempo, Paulus, Manca, et al. (2015) found oVEMP abnormalities in 50% of early PD patients (Hoehn and Yahr[2] stage 1.93 ± 0.7) and 47.4% of late PD patients (Hoehn and Yahr stage 2.5 ± 0.7), in comparison with 3.7% of healthy controls. However, a further study using an identical set-up only brought borderline amplitude abnormalities to light (de Natale, Ginatempo, Paulus, Pes, et al., 2015). Venhovens, Meulstee, Bloem, et al. (2016) reported aberrant oVEMP responses in PD patients, mostly in terms of delayed N1 latencies, whereas no significant differences in amplitudes compared with healthy controls were seen. Finally, in a study by Shalash et al. (2017) absent oVEMP responses were seen in 47% of the PD patients. Significantly prolonged latencies and reduced amplitudes were also evident when compared to the control group.

Pollak et al. (2009) described present cervical vestibular evoked myogenic potentials (cVEMPs) in all controls, whereas 20 of 54 PD patients showed unilaterally absent responses and four had bilaterally absent responses. In addition, Pötter-Nerger et al. (2012) found results in line with Pollak et al. (2009), namely significantly reduced cVEMP amplitudes in PD patients and no differences in latencies between PD patients and controls. More recently however, the same research group did not find abnormalities in PD patients (Pötter-Nerger et al., 2015). Besides altered oVEMP responses, de Natale, Ginatempo, Paulus, Manca, et al. (2015) reported cVEMP and masseter vestibular evoked potential (mVEMP)[3] abnormalities in PD patients as opposed to healthy controls. In a later study with an equal set-up, the researchers found no significant differences in overall c- and mVEMP latencies between both groups. Amplitudes on the other hand, were significantly smaller for mVEMPs, yet appeared normal for cVEMP responses (de Natale, Ginatempo, Paulus, Pes, et al., 2015). Venhovens, Meulstee, Bloem, et al. (2016) reported abnormal cVEMPs in PD and atypical parkinsonism patients in terms of delayed P1 latencies. Nevertheless, they did not find significant differences in amplitudes between all groups. Apart from aberrant oVEMP responses, Shalash et al. (2017) found prolonged P1 and N1 latencies in cVEMP traces. Moreover, the researchers reported decreased cVEMP amplitudes. cVEMPs were completely absent in three out of 15 PD patients.

---

[1] "LTF is a reversible lateral bending of the trunk with a tendency to lean to one side." (Barone et al., 2016)
[2] "The Hoehn and Yahr scale is a simple descriptive staging scale providing a general estimate of clinical function in PD and is ranging from stage 1 until 5 with increasing disability in later stages of the disease." (Goetz et al., 2004)
[3] "The masseter VEMP or mVEMP is a vestibular evoked myogenic potential corresponding to the vestibulomasseteric reflex, which appears as a bilateral and symmetric biphasic positive/negative potential (p11/n15 wave) in the averaged unrectified EMG." (Deriu et al., 2003)

Less frequently conducted measurements seen in literature regarding vestibular deterioration in PD, are: subjective visual vertical (SVV) assessment (Barnett-Cowan et al., 2010; Gandor et al., 2016; José Luvizutto et al., 2020; Scocco et al., 2014), perception of tilt (Bertolini et al., 2015) and heading discrimination studies (Beylergil et al., 2019; Beylergil et al., 2020; Yakubovich et al., 2020). Since these tests allow evaluation of central vestibular mechanisms – including visual dependency, vestibular integration, visual and vestibular self-motion perception, as well as multisensory integration – they would be an interesting addition to standard laboratory testing in the PD population. Nevertheless, extensive discussion of these measurements is beyond the scope of this master's dissertation.

1.3. Subjective balance perceptions

Subjective balance perceptions in PD patients have also been assessed in literature using validated questionnaires, such as the Dizziness Handicap Inventory (DHI). The DHI consists of 25 questions regarding dizziness and balance burden. A higher score on the questionnaire means a greater disability as perceived by the subject (Jacobson & Newman, 1990). In a recent study by Kwon et al. (2022), 86 PD patients in an early stage of the disease (Hoehn and Yahr stage I or II) showed a mean DHI score of 7.7%. Rossi-Izquierdo et al. (2014) on the other hand, investigated 32 PD patients of which 13 were classified as "fallers" and 19 as "non-fallers". Disease staging was diverse, as the patients were in Hoehn and Yahr stage I to IV. In the "fallers" group a mean DHI score of 56.46% was observed, whereas in the "non-fallers" group the patients reported a mean score of 33.26%.

1.4. Oculomotor deficits

Along with altered vestibular test results, oculomotor deficits in PD patients have been reviewed by Anderson and MacAskill (2013), generally in terms of mild hypometria of saccades. A systematic review by Frei (2021) revealed reduced smooth pursuit gains, as well as smooth pursuit eye movements consisting of both catch-up[4] and anticipatory saccades[5].

Regarding additional literature on saccadic deficits, Zhang et al. (2021) found significantly prolonged latencies during randomly displayed vertical saccade tasks in PD patients compared with healthy controls. Koohi et al. (2021) detected hypometria and slowing of voluntary horizontal saccadic eye movements without visual targets over time. Reflexive saccadic amplitude and velocity appeared to be normal in PD. Finally, Lohnes and Earhart (2011) reported that saccadic deficits might cause disrupted turn performance in PD patients, eventually resulting in freezing of gait and falls.

When expanding on smooth pursuit impairments, Pinkhardt et al. (2009) described a significantly reduced horizontal and vertical smooth pursuit gain in PD patients as opposed to healthy controls. Additionally, inspection of saccadic components during smooth pursuit eye movements revealed anticipatory saccades. Likewise, Wu et al. (2018) took saccadic eye movements during smooth pursuit tasks into account. The researchers found that PD patients were tempted to make more saccades during a smooth pursuit task in comparison with controls. Furthermore, Zhang et al. (2021) detected significantly reduced horizontal and vertical smooth pursuit gains in PD, whereas Zhou et al. (2021) only investigated the horizontal smooth pursuit and found a mildly decreased gain.

---

[4] Catch-up saccades are seen "when patients correct for position errors accumulated during SP eye movement epochs". (Pinkhardt et al., 2009)
[5] Anticipatory saccades are "saccades directed toward future target positions" (Pinkhardt et al., 2009).

2. Possible explanation for vestibular function loss and oculomotor deficits in Parkinson's disease

Despite the fact that the vestibular and oculomotor test results reviewed above show inconsistencies, most of them have in common that patients with PD appear to have altered findings in comparison with healthy controls. Besides PD and BPPV comorbidity, several studies revealed loss of peripheral vestibular function after rotatory chair stimulation, caloric testing and oVEMP and cVEMP assessment. In addition, there is increasing evidence for central vestibular impairment based on VOR, VCR, SVV, perception of tilt and heading discrimination studies, as well as oculomotor deficits in PD. Yet, the question arises: 'What could explain vestibular function loss and oculomotor deterioration in PD?'. Neuropathological investigations have shed new light on the hypothesis that there might be an overlap between the structures affected by pathological neurodegeneration in PD and the vestibular system.

Table 1: Vestibular system input-output scheme (based on Cullen (2016)). The structures marked in grey might be affected by neuropathological degeneration in patients with Parkinson's disease.

Vestibular nuclei input-output scheme			
VESTIBULAR NUCLEI	INPUT	Vestibular input	Semicircular canal afferents
			Otolith afferents
		Oculomotor input	Premotor oculomotor nuclei
			Reticular formation (including raphe nuclei, pedunculopontine nuclei, parabrachial nuclei and locus coeruleus)
		(Neck) proprioceptive input	Via central cervical nucleus
			Dorsal root afferents
		Cerebellar input	Precerebellar nuclei (with mossy fibers and climbing fibers)
			Vermis/ nodulus
			Flocculus/ paraflocculus
			Deep cerebellar nuclei (including nucleus dentatus)
		Cortical input	Parietoinsular vestibular cortex (PIVC)
			Premotor area 6 (6 PA)
			Cingulate cortex areas 23cd, 23cv, 6c
			Somatosensory area 3a
			Intraparietal sulcus area 2v
			Superior temporal cortex
	OUTPUT	Vestibulo-ocular reflex (VOR) tract	Via medial longitudinal fasciculus
			Oculomotor nuclei of cranial nerves III, IV, VI
		Vestibulocervical reflex (VCR) tract	Via medial vestibulospinal tract
			Accessory motor nucleus
		Vestibulospinal reflex (VSR) tract	Via lateral vestibulospinal tract
			Motoneurons in spinal cord
		Vestibulocerebellar tract	Vermis/ nodulus
			Flocculus/ paraflocculus
			Deep cerebellar nuclei (including nucleus dentatus)
			Lobules I–V of anterior lobe
		Vestibulosympathetic tract	Via caudal/ rostral ventrolateral medulla
			Preganglionic neurons in spinal cord controlling sympathetic nerve activity
		Vestibulo-(sub)cortical tract	Thalamus and related structures (including hypothalamus, amygdala, hippocampus and basal ganglia)
			Sulcus centralis area 3a
			Intraparietal sulcus area 2v
			Ventral intraparietal area
			Medial superior temporal area
			Dorsal medial superior temporal cortex
			Parietoinsular vestibular cortex (PIVC)
			Dorsal parieto-occipital sulcus area V6
			Parieto-occipital sulcus area V3A

Knowing that afferent and efferent vestibular pathways cross multiple brainstem and cerebellar nuclei, as well as several important (sub)cortical structures (Table 1), altered vestibular test results in PD might arise from neuropathological changes in these pathways. Recent literature suggests that the structures marked in grey in the table above might be affected in PD (Abbruzzese & Berardelli, 2003; Bertolini et al., 2015; Beylergil et al., 2019; Beylergil et al., 2020; Braak et al., 2003; Cullen, 2016; Hanakawa et al., 1999; Joyal et al., 2001; Lithgow & Shoushtarian, 2015; Meng et al., 2014; Müller & Bohnen, 2013; Putcha et al., 2014; Seidel et al., 2015; Takakusaki, 2017; Visser & Bloem, 2005; Wellings et al., 2017).

Taken together, areas of the entire vestibular system could undergo neuropathological changes during PD progression. Since the vestibular pathways are needed for several important functions, these changes might result in symptoms such as: postural instability, postural abnormalities including camptocormia and lateral trunk flexion, dizziness or light-headedness, increased visual dependency and higher-order spatial navigational deficits.

3. Objectives of this master's dissertation

Although several authors conducted research on vestibular deficits in PD patients, to date there is not one study that has investigated all five parts of the peripheral vestibular system. In addition, a standardized test protocol specifically designed to identify vestibular dysfunctions in this particular patient population does not yet exist. Nevertheless, the information obtained from vestibular testing could play an important role in fall prevention and rehabilitation programs. The first aim of this master's dissertation was thus to introduce a potential vestibular test protocol for PD patients, including a variety of tests so that the entire vestibular system would be investigated. Moreover, since there is still lack of knowledge regarding vestibular dysfunctions in PD, a small amount of patients underwent the protocol. The second aim was therefore to gain more insight in the nature and sites of possible vestibular lesions in PD.

MATERIALS AND METHODS

1. Participants

Ten PD patients (mean age 67.74 years, range 61.00-74.60) and ten healthy age- and gender-matched controls (mean age 67.54 years, range 61.30-73.40) were enrolled in this dissertation. PD patients were diagnosed neurologically and their disease severity, according to Hoehn and Yahr staging, corresponded to stage III. Patients with a clinical diagnosis of atypical Parkinsonism or dementia and clinically significant depression or anxiety were excluded from the study. Additionally, PD medication intake was not interrupted in order to minimize interference of tremor or rigidity throughout vestibular testing. Inclusion criteria for both groups were: the capability to give written informed consent and the capacity to understand instructions regarding tests integrated in the protocol. Exclusion criteria applicable to the control group comprised: neurological, auditory and vestibular disturbances. Concerning audiovestibular disturbances, subjects with a history of middle ear disorders, ear surgery or hearing thresholds exceeding 40 dB hearing level (HL) and subjects who had a vestibular disorder in the past were not included in this dissertation. The study was approved by the ethics committee of the University Hospital of Ghent (BC-07392 E08).

2. Auditory assessment

2.1. Tympanometry

Tympanometric testing was conducted in order to rule out middle ear pathologies; including tympanic membrane irregularities, ossicle dysfunctions and other abnormalities usually due to negative pressure (e.g. otitis media). The measurements were performed using a TympStar Pro device (Grason-Stadler) and stimuli were presented by means of a 226 Hz probe tone with an 85 dB sound pressure level (SPL) intensity. For interpretation of the results the shape of the tympanogram, as well as the static acoustic admittance (SAA) (mmho), ear canal volume (ECV) (mmho) and middle ear pressure (MEP) (daPa) were taken into account.

2.2. Tonal liminal audiometry

Tonal liminal audiometry (TLA) took place with the purpose of detecting hearing thresholds and possible hearing losses as well as their type and severity. The measurements were performed by means of a calibrated Equinox 2.0 audiometer (Interacoustics), supra-aural headphones and a bone conductor in a soundproof audiometric booth. For hearing threshold evaluation the Hughson-Westlake method was applied (Hughson & Westlake, 1944). Stimuli used for measuring air conduction thresholds were pure tone octave band frequencies ranging from 125 Hz to 8 kHz, as well as the half-octave frequencies 3 and 6 kHz. Bone conduction thresholds were only measured when the audiometric configuration could not be defined as normal or high frequent (due to presbycusis). Bone conduction stimuli were similar pure tone octave band frequencies, but were only ranging from 250 Hz to 4 kHz. Masking – whenever necessary – was achieved using Hood's masking method (Hood, 1960). Based upon the obtained hearing thresholds, pure tone averages (PTA) (dB HL) were calculated for both ears. The 'Bureau International d'Audiophonologie' (BIAP) recommendations for hearing loss classification were applied for determination of hearing loss severity (BIAP, 1996).

3. Vestibular and oculomotor assessment

3.1. Static and dynamic visual acuity

Static and dynamic visual acuity (SVA and DVA) testing was performed with the aim of detecting oscillopsia complaints. These complaints usually emerge as a result of increased retinal slip due to vestibular hypofunction (Gimmon & Schubert, 2019). During assessment, the subject was seated in a chair at a distance of three meters from a digital Snellen chart. Numerous series of letters, decreasing in size, were displayed and the subject was asked to read every sequence as accurately as possible in order to evaluate static visual acuity. Subsequently, the examiner took place behind the chair and manually oscillated the subject's head at a rate of two cycles per second (2 Hz). Under these circumstances, i.e. the DVA condition, the subject was instructed to read once more a series of letters. Subsequent to the assessment, a DVA loss score (logMAR) was calculated as the difference between the score in the SVA condition and the score in the DVA condition. Whenever DVA deteriorated by at least three lines in comparison with the SVA condition, corresponding to a DVA loss score of 0.3 or more, the test was perceived positive and thus suggestive of oscillopsia complaints.

3.2. Video head impulse test

The video head impulse test (vHIT) enables evaluation of the high frequent VOR function of each semicircular canal individually. In the present study ICS Impulse video goggles (Otometrics) were used and the subject was seated about 1.5 meters from a fixation point marked on the wall. By applying passive and unpredictable lateral head movements with a peak velocity ranging from 150 to 250 °/s and an amplitude between 10° and 20°, the horizontal vHIT was performed. In order to administer the vertical vHIT, the subject's head was turned 45° right- or leftwards and vertical head movements with a velocity of at least 120°/s were applied. In case of a rightward turn the left anterior and right posterior (LARP) plane was assessed, whereas a leftward turn allowed evaluation of the right anterior and left posterior (RALP) plane. In both conditions the participant had to remain a gaze of 20° in the opposite direction. Aiming at a minimum of ten good head impulses after cleaning, 20 head impulses were conducted in each test condition (horizontal, vertical LARP plane and vertical RALP plane). Outcome parameters used for interpretation were: waveform morphology (i.e. the presence of (c)overt saccades), VOR gain and gain asymmetry (%). This last parameter was computed using Jongkees formula (Jongkees, 1948).

3.3. Oculomotor testing

Oculomotor testing is always recommended during vestibular assessment, as oculomotor deficits could influence VOR test results. All participants were assessed using a VNG set-up. They wore NysStar II video goggles and were positioned 90 centimeters from a monitor at eye level.

Following calibration, horizontal and vertical saccadic eye movements were assessed using a randomly shifting luminous dot which the subject had to follow as accurately as possible. When sufficient saccadic eye movements were obtained, three outcome parameters could be interpreted: accuracy (%), latency (ms) and maximum velocity (°/s). In addition, the waveform morphology was taken into account since under- and overshoot saccades are suggestive of cerebellar lesions. Secondly, horizontal smooth pursuit eye movements were investigated by means of a slowly horizontally moving luminous dot with a velocity of 0.2 and 0.4 Hz. The acquired outcome parameters comprised: the gain (%), phase (°) and asymmetry (%) of the subject's eye movements. Regarding waveform morphology, a faltering pattern would be suggestive of central dysfunctions. Thirdly, the patient was exposed to a panoramic mountain landscape in order to elicit optokinetic-induced nystagmus. The landscape was interrupted by vertical bars and moved horizontally at three velocities: 20 °/s, 40 °/s and 60 °/s. Outcome parameters for this

measure were: the mean maximum slow component velocity (SCV) (°/s) and nystagmus preponderance (NP) (%). Finally, positional and spontaneous nystagmus were evaluated by means of a luminous dot, at first displayed in the middle of the monitor and then right-sided, left-sided, above and below the center. Initially, the subject was allowed to look at the dot in the five directions, but afterwards his/her visual field was darkened. Positional and spontaneous nystagmi were merely interpreted visually. In case of aberrant results seen in all test conditions, central oculomotor abnormalities were suspected.

3.4. Vestibular evoked myogenic potentials

In order to assess otolith functioning as well as vestibular nerve activity, cervical and ocular vestibular evoked potentials (cVEMPs, oVEMPs) were measured. For both tests Neuro-Audio (Neurosoft) equipment was used.

As part of cVEMP assessment, the subject's skin was first scrubbed by means of abrasive gel with the aim of achieving impedance values below 5 kΩ and inter-electrode impedance values below 2 kΩ. The active electrode was then applied on the upper $1/3^{rd}$ of the sternocleidomastoid (SCM) muscle belly, whereas the reference electrode was positioned 1 or 2 centimeters beneath the interclavicular ligament of the sternum and the common electrode on Fz. Subsequently, the participant was asked to turn his/her head away from the testing ear towards the contralateral shoulder in order to contract the ipsilateral SCM muscle. Since constant muscle tension is important with the aim of comparing both sides, continuous monitoring of electromyographic (EMG) activity was displayed by the software. In addition, an EMG correction algorithm was used in order to obtain reliable amplitude parameters. A SCM muscle tension of at least 80 µV was targeted. Regarding stimulation, 500 Hz tone bursts with a 95 dB normalized hearing level (nHL) intensity were delivered by insert earphones. Response parameters for cVEMP interpretation were: the absolute latencies of p13-n23 or P1-N1 (ms), corrected peak-to-peak amplitude and asymmetry ratio (%). The formula utilized when calculating the latter parameter was the following: ((peak-to-peak amplitude right - peak-to-peak amplitude left) / (peak-to-peak amplitude right + peak-to-peak amplitude left)) x 100.

Similar to cVEMP testing, scrubbing the skin, applying electrodes and checking impedances must precede oVEMP assessment. The favorable nose reference electrode configuration was applied. Two active self-adhesive electrodes were positioned below the lateral eye canthus near the inferior oblique muscle, whereas reference electrodes were attached next to the medial eye canthus and the common electrode on Fz. Prior to the measurement, the subject was instructed to lie down in supine position and to remain an upward gaze, fixating the ceiling in an angle of 30° or more during the whole testing period. For stimulation, 500 Hz tone bursts at a 120 force level (FL) intensity were delivered by a an amplifier (Brüel & Kjaer, type 2718) coupled with a minishaker (Brüel & Kjaer, type 4810) that, in its turn, was placed on Fz. The following response parameters were taken into account during analysis: the absolute latencies of n10-p15 or N1-P1 (ms), peak-to-peak amplitude (µV) and asymmetry or inter-ocular ratio (&) (%). The interocular ratio was calculated by means of the formula displayed here: IOR = ((amplitude OD - amplitude OS) / (amplitude OD + amplitude OS)) x 100 %; in which OD stands for oculus dexter, whereas OS stands for oculus sinister.

3.5. Positional maneuvers

With the aim of detecting positional vertigo, positional maneuvers including the Dix-Hallpike and roll test were performed. The Dix-Hallpike maneuver is known to be the gold standard in detecting posterior and – less frequently – anterior BPPV. The maneuver was performed by turning the participant's head 45°

towards one side and subsequently bringing him/her in supine position until the head was hanging 20° below the examination table. Diagnosis of horizontal BPPV is possible by means of the roll test. In this case, the participant started in supine position, with the head being supported in an angle of 30°. Consequently, the head was rotated 90° to one side, then brought back to neutral position and finally turned 90° towards the other side. In order to interpret nystagmi properly, VNG goggles (Synapsis HF3x RevB- SN109) were used. The examiner observed the participant's eyes in either of the positions and noted, after performing the maneuvers, whether nystagmi were seen.

4. Questionnaire

In order to evaluate self-perceived dizziness or unsteadiness in patients with PD, the Dizziness Handicap Inventory (DHI) was used. The DHI questionnaire consists of 25 items which are subgrouped into three domains, namely: functional, emotional and physical aspects of dizziness and unsteadiness. Those three domains comprise seven, nine and nine questions respectively. All 25 questions must be answered 'yes', 'no' or 'sometimes'. A 'yes' response is scored four points, a 'no' response zero points and a 'sometimes' response two points, resulting in a total score ranging from 0 to 100. A higher score thus means a greater disability as perceived by the subject (Jacobson & Newman, 1990).

5. Statistics

Statistical analyses were performed using IBM SPSS Statistics version 27. The Shapiro-Wilk test of normality was applied for each variable and based upon the p-values of the respective variables, the appearance of their QQ-plots and the number of participants, non-parametric testing was preferred. In case of a continuous variable, the Mann-Whitney U-test was administered. In case of a categorical variable, the Chi-Square or Fisher's Exact test was applied. $p < 0.05$ was used as criterium for statistical significance.

RESULTS

1. Participant information and auditory test results

Between October 2020 and March 2022 ten PD patients and ten healthy age- and gender-matched controls participated in this study. The PD group consisted of eight male and two female patients with a mean age of 67.74 years (SD 4.18, range 61.00-74.60). Similarly, the control group consisted of eight male and two female participants with a mean age of 67.54 years (SD 3.78, range 61.30-73.40). PD severity corresponded to Hoehn and Yahr stage III in all patients. However, this might not be the case in PD patient 10, whose functional condition deteriorated strongly prior to his participation in the study. Vestibular test results of this patient must therefore be interpreted cautiously.

Apart from participant 15 who showed a type C tympanogram, indicating a significantly negative middle ear pressure, middle ear pathologies were ruled out in all other participants. Tympanometric testing was not possible in participant 12, since the probe tip could not seal the ear canals tightly.

The pure tone averages (PTA) (dB HL) were calculated based on the 500, 1000 and 2000 Hz hearing thresholds. Three PD patients were found to have a mild sensorineural hearing loss, compared to one control person. Presumably, the sensorineural hearing loss is in all four cases due to presbycusis. Additionally, the mean PTA corresponded to 14.92 dB HL (SD 12.51, range -1.70-36.70) in the PD group and 11.67 dB HL (SD 8.39, range -5.00-30.00) in the control group. Nevertheless, nonparametric testing by means of the Mann-Whitney U-test showed no statistically significant difference in PTA (dB HL) between both groups (U = 187.50, p = 0.735).

Table 2: Participant information and auditory test results.

Case-number	Group	Gender	Age (years)	Tympanometric configuration		PTA (dB HL)		Hearing loss type (PTA > 20 dB HL)
				right	*left*	*right*	*left*	
1	PD	male	72.8	A	A	15	8.3	
2	PD	male	71.8	As	A	**33.3**	**36.7**	sensorineural
3	PD	female	67.3	A	A	**33.3**	**36.7**	sensorineural
4	PD	female	65.8	A	A	10	6.7	
5	PD	male	67.1	A	A	6.7	3.3	
6	PD	male	61.0	A	A	0	-1.7	
7	PD	male	67.5	A	A	**26.7**	**25**	sensorineural
8	PD	male	64.7	A	A	15	15	
9	PD	male	64.8	A	A	3.3	6.7	
10	PD	male	74.6	A	A	10	8.3	
11	control	male	71.2	A	A	16.7	20	
12	control	male	69.6	leak	leak	16.7	**30**	sensorineural
13	control	female	66.8	A	As	20	20	
14	control	female	69.5	A	Ad	10	13.3	
15	control	male	66.7	A	**C**	8.3	11.7	
16	control	male	61.3	Ad	Ad	5	5	
17	control	male	69.4	A	Ad	15	18.3	
18	control	male	63.3	A	A	1.7	1.7	
19	control	male	64.2	Ad	Ad	1.7	-5	
20	control	male	73.4	A	A	13.3	10	

Abbreviations: PD = Parkinson's disease, PTA = pure tone average, dB HL = decibel hearing level.

2. Oculomotor test results

The oculomotor test results are listed in Appendix 1. Horizontal fast smooth pursuit acquisition did not take place in participant 3 for unknown reasons. In participant 10, vertical saccadic, as well as horizontal optokinetic (40°/s) acquisition was not possible because of tiredness and insufficiently visible pupils as a result. When elaborating on the test results in bold, deviant values were found in seven PD patients and two control subjects. Optokinetic testing with a 60°/s stimulus showed most deviant results, followed by vertical saccadic testing.

The oculomotor test statistics are presented in Appendix 2. Based on the Mann-Whitney U-test, no statistically significant differences in oculomotor parameters between the PD and control group were observed.

Concerning the morphology and quality of the oculomotor traces however, most PD patients seemed to have subjectively less "good-looking" results in comparsion with their age- and gender-matched control subjects. As an example, the oculomotor traces of participant 5 (PD) and 15 (control) are displayed in Table 5. It becomes clear that participant 5 exhibits less accurate oculomotor traces in comparison with participant 15. The patient's eye movements are not fluent and do not always follow the visual targets, based on the oculomotor traces of saccadic and smooth pursuit testing. Although this phenomenon is not the case in every PD patient, it is seen remarkably more often in PD patients compared with controls.

Table 3: Comparison of the oculomotor traces of participant 5 (Parkinson's disease) and participant 15 (control). The x-axis stands for time (s), the y-axis stands for pupil displacement (°).

Optokinetic testing
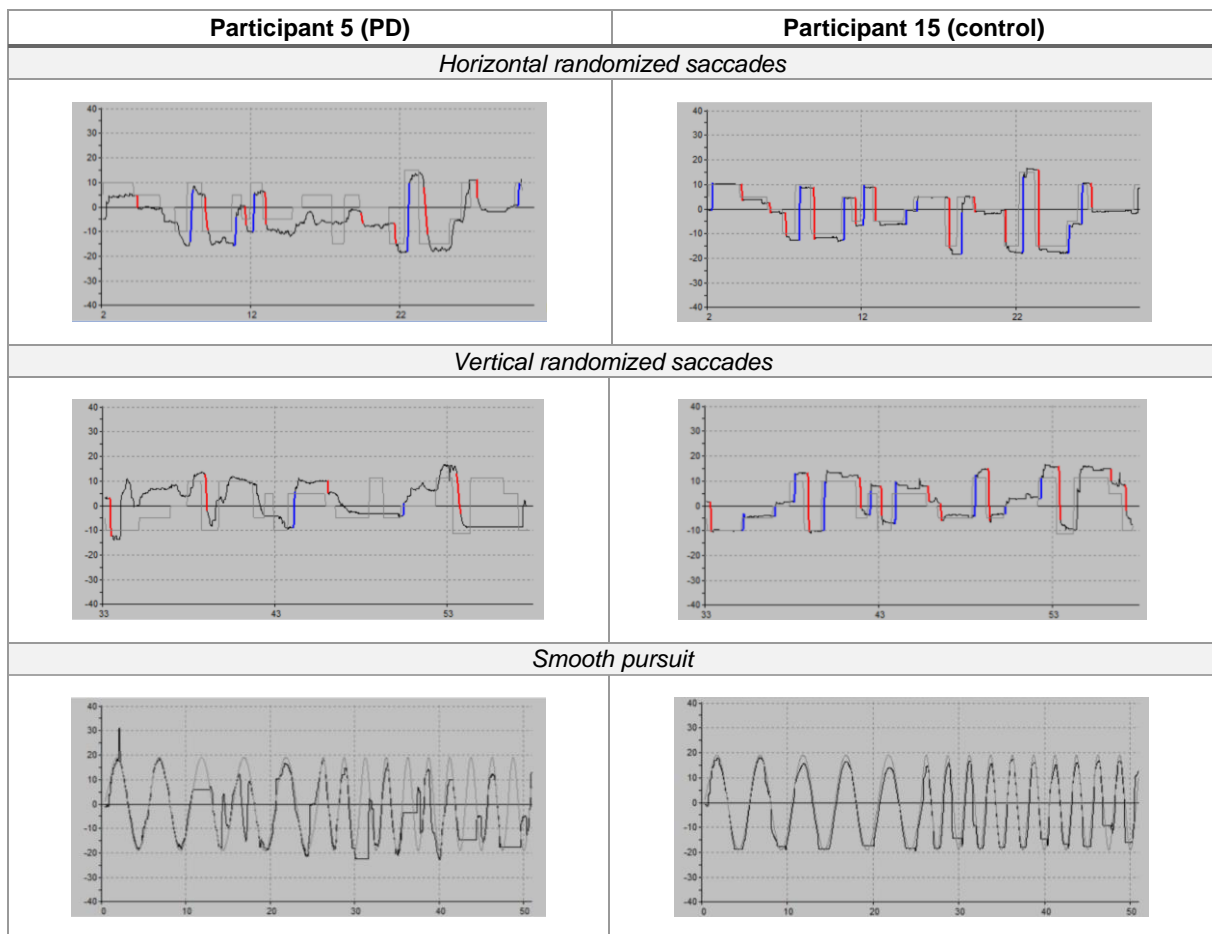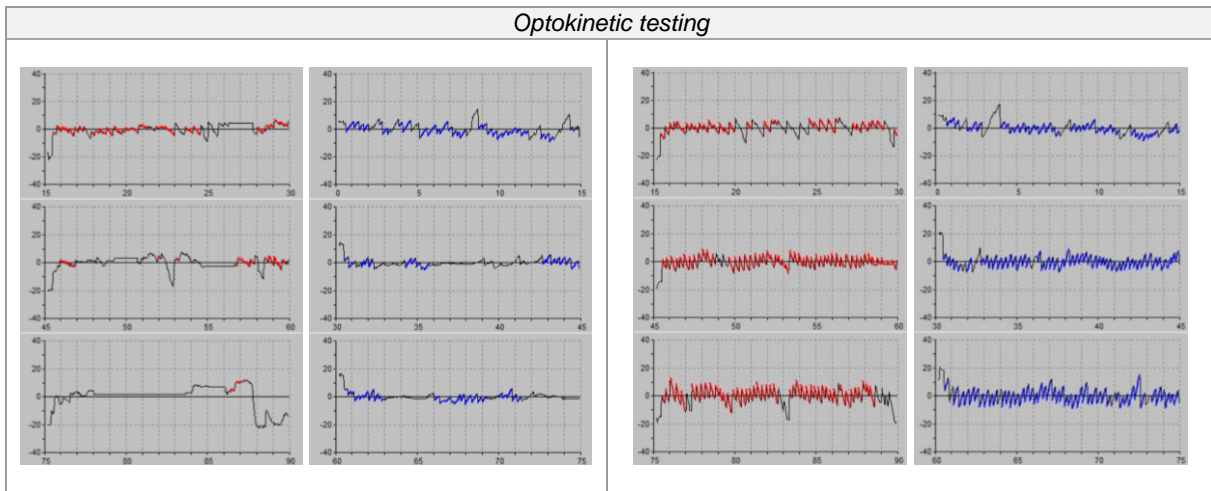
Abbreviations: PD = Parkinson's disease.

When elaborating on the morphology and quality of the saccadic and smooth pursuit traces of participant 2 (PD), certain dysfunctional patterns catch the eye. More specifically, the saccadic traces often show a multiple-step or staircase pattern and the smooth pursuit eye movements seem to be interrupted by catch-up and anticipatory saccades (Figure 3). Altogether, signs of multiple-step or staircase pattern were seen in eight PD patients compared with two control subjects. Nine PD patients and seven control subjects possibly showed cath-up and/or anticipatory saccades.
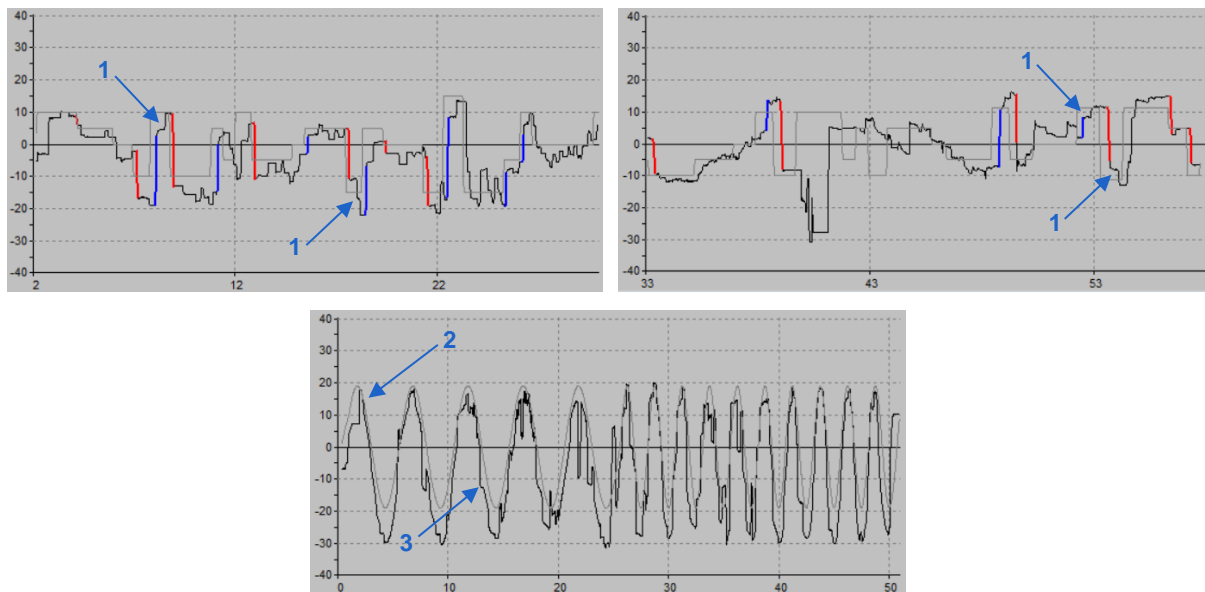
Figure 1: Horizontal saccadic, vertical saccadic and smooth pursuit traces of participant 2 (Parkinson's disease). Multiple-step/staircase patterns (1), catch-up saccades (2) and anticipatory saccades (3) are indicated by numbered arrows. The x-axis stands for time (s), the y-axis stands for pupil displacement (°).

3. Vestibular test results

3.1. Positional maneuvers

Positional maneuvers, the Dix-Hallpike and roll test in particular, were performed in all participants. When eye movements were observed through VNG goggles, none of the participants showed abnormalities. Moreover, no one indicated experiencing vertigo as dizziness perceptions were questioned. Undetected BPPV could therefore be ruled out in this pilot study.

3.2. Static and dynamic visual acuity

All participants underwent SVA and DVA testing, but due to neck stiffness, the DVA test result was not reliable in PD patient 10. Consequently, this patient was excluded from statistical analysis for this part. As a DVA loss score of 0.3 logMAR or higher is suggestive of oscillopsia, one PD patient and one control subject were found to be in the oscillopsia risk zone. The mean DVA loss score equaled 0.14 logMAR (SD 0.10, range 0.00-0.30) in the PD group and, similarly, 0.14 logMAR (SD 0.07, range 0.10-0.30) in the control group. Based on the Mann-Whitney U-test no statistically significant difference in DVA loss (logMAR) between both groups was observed (U = 41.50, p = 0.758).

Table 4: Static and dynamic visual acuity test results.

Case-number	Group	SVA (logMAR)	DVA (logMAR)	DVA loss (logMAR)
1	PD	0.1	0.3	0.2
2	PD	0.0	0.2	0.2
3	PD	0.1	0.1	0.0
4	PD	0.0	0.0	0.0
5	PD	0.0	0.1	0.1
6	PD	-0.1	0.2	**0.3**
7	PD	0.0	0.2	0.2
8	PD	0.0	0.1	0.1
9	PD	0.1	0.3	0.2
10	PD	0.0	not reliable	/
11	control	0.1	0.4	**0.3**
12	control	0.0	0.2	0.2
13	control	0.1	0.2	0.1
14	control	0.0	0.1	0.1
15	control	0.1	0.2	0.1
16	control	0.0	0.2	0.2
17	control	0.0	0.1	0.1
18	control	0.0	0.1	0.1
19	control	-0.1	0.0	0.1
20	control	0.1	0.2	0.1

Abbreviations: PD = Parkinson's disease, SVA = static visual acuity, DVA = dynamic visual acuity.
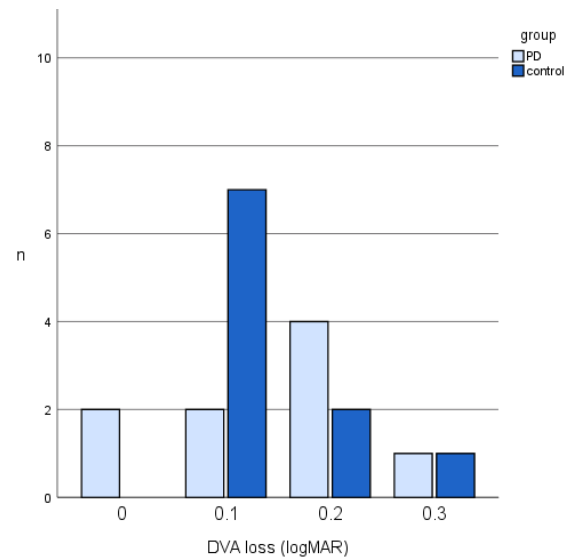
Figure 2: Bar chart depicting the dynamic visual acuity (DVA) loss scores in patients with Parkinson's disease (PD) and controls. n stands for the number of participants.

3.3. Video head impulse test

Altough we aimed for at least ten cleaned head impulses in each direction, this number was not achieved for each semicircular canal in every patient. Data analysis showed a minimum of four cleaned head impulses and a maximum of 21. In participant 14, right anterior canal head impulse acquisition was not possible. Participant 7 showed a lateral semicircular canal gain equal to 1.83. As this is an extremely high value, it was regarded as an outlier and removed for further statistical analysis. Since a vHIT gain equal to or smaller than 0.8 is suggestive of vestibular function loss when using ICS Impulse video goggles (Otometrics), a peripheral vestibular problem can be suspected in participant 1 (PD), 5 (PD), 10 (PD) and 17 (control).

Concerning the lateral, anterior and posterior semicircular canal gains in the PD group, the mean values corresponded to 1.11 (SD 0.22, range 0.58-1.36), 1.06 (SD 0.23, range 0.66-1.54) and 1.06 (SD 0.28, range 0.38-1.64) respectively. In the control group on the other hand, the mean values corresponded to 1.03 (SD 0.15, range 0.83-1.37), 1.02 (SD 0.11, range 0.85-1.29) and 0.97 (SD 0.11, range 0.69-1.20)

respectively. Using the Mann-Whitney U-test, no statistically significant differences in lateral and anterior canal gains between PD patients and controls were found (U = 135.00, p = 0.122; U = 161.00, p = 0.415). However, the posterior canal gains turned out to be slightly, but significantly different (U = 120.50, p = 0.031) (Figure 2). PD patients showed an increased posterior canal gain in comparison with controls.

With regard to the gain asymmetry in the PD group, the mean values equaled 4.70% (SD 4.55, range 0.00-14.00), 12.20% (SD 7.11, range 4.00-24.00) and 13.10% (SD 7.31, range 3.00-28.00) for the lateral, anterior and posterior semicircular canals respectively. The control group for its part, showed mean values equal to 5.50% (SD 4.33, range 1.00-14.00), 7.11% (SD 3.44, range 1.00-11.00) and 7.60% (SD 4.43, range 1.00-16.00) respectively. According to the Mann-Whitney U-test, the gain asymmetry values (%) were in none of the three planes − lateral, anterior and posterior − statistically significantly different between PD patients and controls (U = 43.50, p = 0.620; U = 72.50, p = 0.152; U = 24.50, p = 0.052).

Table 5: Video head impulse test results. The value marked in grey is regarded as an outlier.

Case-number	Group	LSCC gain		LSCC gain asymmetry (%)	ASCC gain		ASCC gain asymmetry (%)	PSCC gain		PSCC gain asymmetry (%)
		right	*left*		*right*	*left*		*right*	*left*	
1	PD	1.10	0.94	8	**0.69**	1.13	24	1.26	**0.71**	28
2	PD	1.01	0.92	5	1.20	0.99	10	1.02	1.23	11
3	PD	1.31	1.33	1	1.11	1.02	4	0.90	1.13	11
4	PD	1.28	1.22	2	1.32	1.10	9	1.01	1.25	11
5	PD	1.08	1.08	0	1.10	**0.76**	18	1.09	1.16	3
6	PD	1.83	1.35	7	1.35	1.17	7	0.88	1.21	16
7	PD	1.36	1.35	0	1.17	1.32	6	1.20	1.64	15
8	PD	0.98	0.95	2	0.98	0.83	8	1.12	1.04	4
9	PD	1.17	1.36	8	0.97	1.54	23	1.29	1.01	12
10	PD	**0.77**	**0.58**	14	**0.66**	0.85	13	**0.57**	**0.38**	20
11	control	1.10	1.00	1	1.29	1.12	7	0.96	1.13	8
12	control	1.02	1.05	1	1.09	1.07	1	1.00	1.03	11
13	control	1.35	1.01	14	0.90	1.13	11	1.02	0.89	7
14	control	1.37	1.18	7	/	1.08	/	0.95	0.94	1
15	control	1.03	1.19	7	0.89	1.00	6	1.14	1.01	6
16	control	1.03	0.87	8	0.85	0.99	8	0.88	0.95	4
17	control	1.06	0.89	9	1.03	0.90	7	**0.69**	0.96	16
18	control	0.84	0.83	1	0.93	1.13	10	0.96	0.90	3
19	control	0.93	0.89	2	1.01	1.07	3	0.82	0.99	9
20	control	1.00	0.91	5	0.89	1.10	11	1.20	0.96	11

Abbreviations: PD = Parkinson's disease, LSCC = lateral semicircular canal, ASCC = anterior semicircular canal, PSCC = posterior semicircular canal.
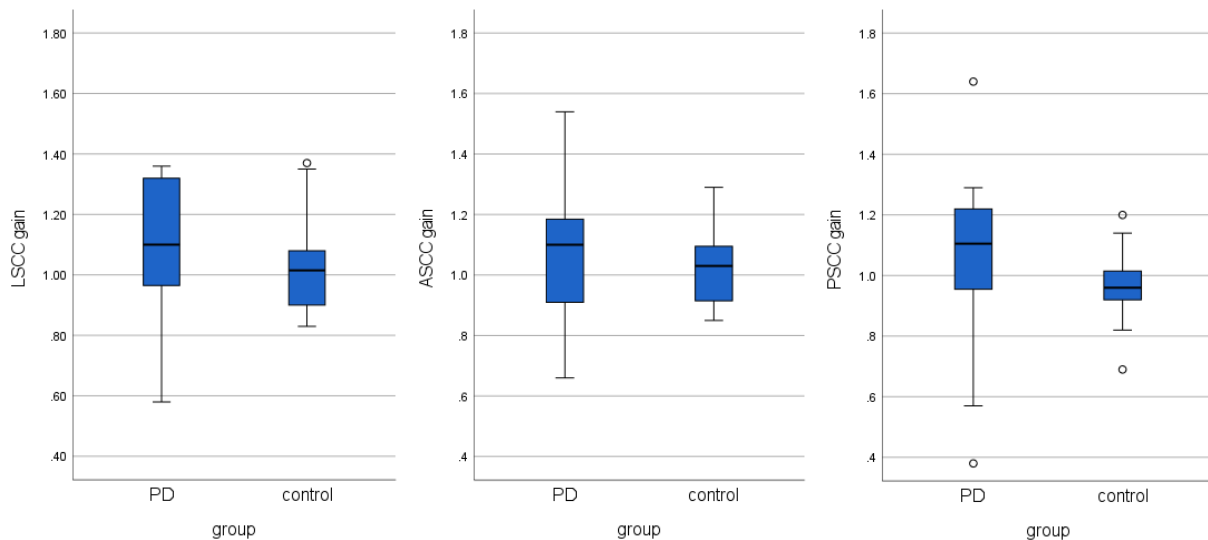
Figure 3: Boxplots depicting the lateral (LSCC), anterior (ASCC) and posterior semicircular canal (PSCC) gains in patients with Parkinson's disease (PD) and controls.

3.4. Vestibular evoked myogenic potentials

All participants successfully underwent cVEMP assessment, since a muscle tension of at least 100 µV and a number of minimum 60 samples were always achieved. With regard to the P1 latencies, N1 latencies and corrected peak-to-peak amplitudes in the PD group, the mean values equaled 14.05 ms (SD 1.23, range 12.70-16.70), 22.29 ms (SD 2.61, range 18.70-26.60) and 0.62 (SD 0.09, range 0.50-0.80) respectively. In the control group, the mean values of these identical parameters corresponded to 13.03 ms (SD 1.10, range 11.80-15.20), 20.68 ms (SD 1.22, range 18.50-22.20) and 0.70 (SD 0.12, range 0.50-0.80). The Chi-Square test showed no statistically significant difference in cVEMP presence between both groups (χ^2 = 0.10, p = 0.752) (Figure 4). Using the Mann-Whitney U-test, no statistically significant differences in corrected peak-to-peak amplitudes (U = 32.00, p = 0.094) and N1 latencies (ms) (U = 37.00, p = 0.204) were observed. Yet, P1 latencies (ms) were found to be significantly longer in the PD group in comparison with the control group (U = 27.00, p = 0.048) (Figure 5).

oVEMP assessment was not possible in participant 5. As a result, this patient was excluded from statistical analysis for this part. Concerning the N1 latencies, P1 latencies and peak-to-peak amplitudes in the PD group, the mean values corresponded to 12.49 ms (SD 0.66, range 11.60-13.70), 16.99 ms (SD 0.58, range 16.10-18.00) and 8.65 µV (SD 4.36, range 3.60-18.10) respectively. The control group for its part, showed mean values equal to 11.55 ms (SD 1.68, range 9.20-14.10), 15.63 ms (SD 1.56, range 12.90-17.90) and 14.55 µV (SD 7.49, range 2.90-30.80) respectively. As an oVEMP presence x group crosstab revealed two cells with an expected count less than 5, the Fisher's Exact test was applied instead of the Chi-Square test. According to the Fisher's Exact test, oVEMPs were significantly more absent in the PD group as opposed to the control group (p = 0.017) (Figure 6). Additionally, significantly smaller peak-to-peak amplitudes (µV) were seen in PD patients in comparison with controls (U = 61.00, p = 0.011) (Figure 8). PD patients also seemed to have significantly longer P1 latencies (ms) than controls (U = 61.00, p = 0.011) (Figure 7), whereas N1 latencies (ms) were not statistically significantly different between both groups (U = 93.50, p = 0.178).
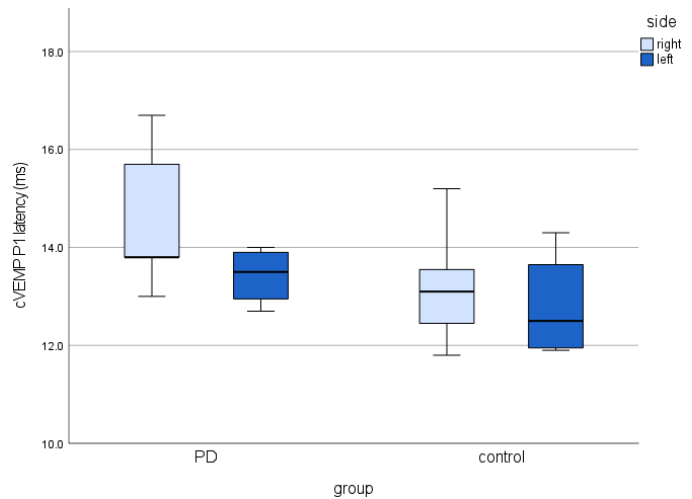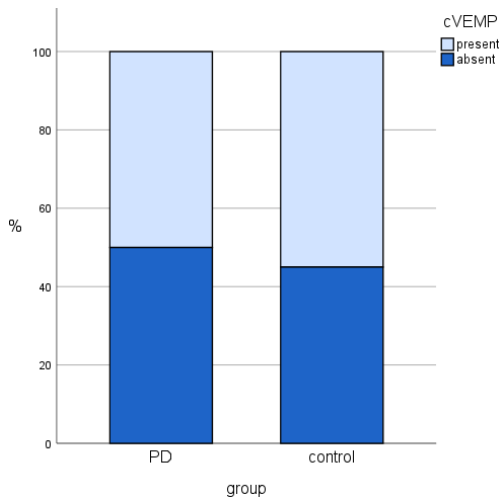
Figure 4: Bar chart depicting cervical vestibular evoked myogenic potential (cVEMP) presence in patients with Parkinson's disease (PD) and controls.

Figure 5: Boxplots depicting cervical vestibular evoked myogenic potential (cVEMP) P1 latencies in milliseconds (ms) in patients with Parkinson's disease (PD) and controls.

Figure 6: Bar chart depicting ocular vestibular evoked myogenic potential (oVEMP) presence in patients with Parkinson's disease (PD) and controls.

Figure 7: Boxplots depicting ocular vestibular evoked myogenic potential (oVEMP) P1 latencies in milliseconds (ms) in patients with Parkinson's disease (PD) and controls.
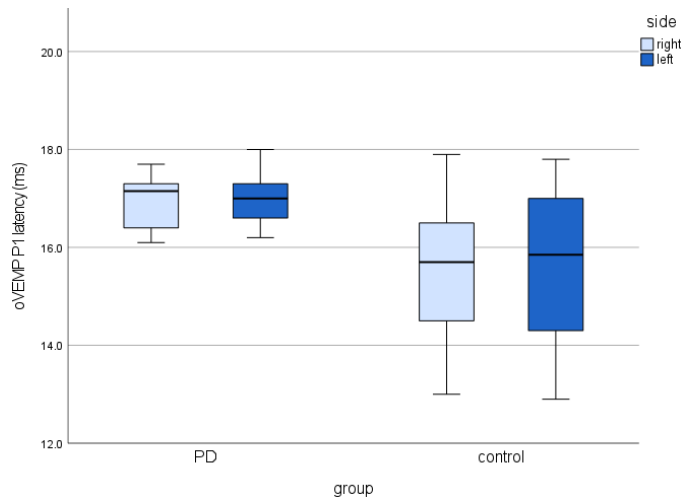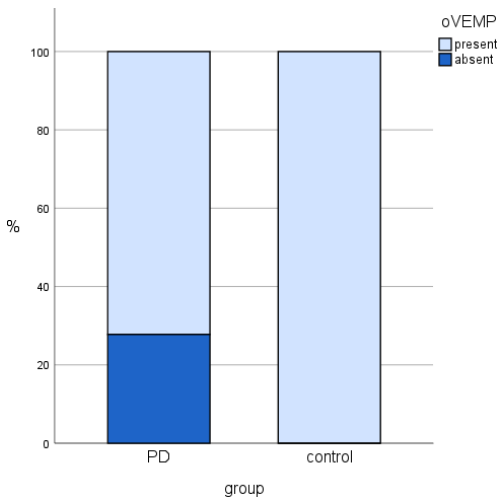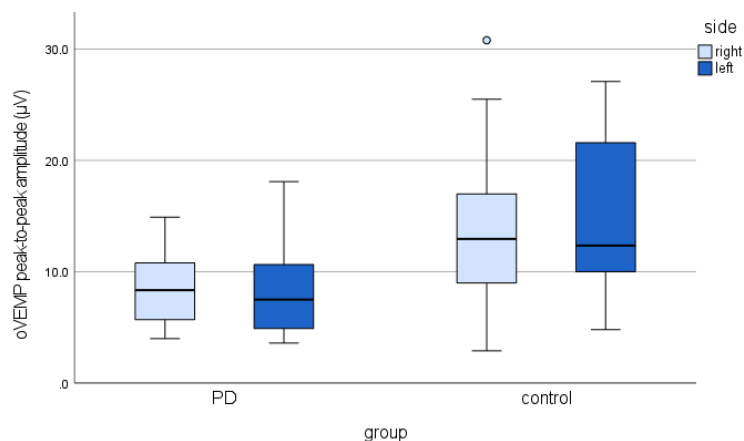

Figure 8: Boxplots depicting ocular vestibular evoked myogenic potential (oVEMP) peak-to-peak amplitudes in microvolt (µV) in patients with Parkinson's disease (PD) and controls.

Table 6: Cervical and ocular vestibular evoked myogenic potential test results.

Case-number	Group	cVEMP presence		cVEMP P1 latency (ms)		cVEMP N1 latency (ms)		cVEMP corr. peak-to-peak amplitude		oVEMP presence		oVEMP N1 latency (ms)		oVEMP P1 latency (ms)		oVEMP peak-to-peak amplitude (µV)	
		right	left	right	left	right	left	right	left	right	left	right	left	right	left	right	left
1	PD	✓	✓	13.0	13.8	18.7	20.2	0.7	0.6	✓	✓	12.4	13.7	17.0	17.3	**5.7**	**7.5**
2	PD	✓	✓	13.8	13.2	20.5	21.3	0.6	0.8	✓	✓	12.2	12.5	16.1	16.2	**7.8**	**4.5**
3	PD	✗	✗	–	–	–	–	–	–	✗	✓	–	12.2	–	17.0	–	**5.3**
4	PD	✗	✗	–	–	–	–	–	–	✓	✓	12.0	13.5	16.4	17.3	8.9	10.2
5	PD	✗	✗	–	–	–	–	–	–	–	–	–	–	–	–	–	–
6	PD	✓	✗	16.7	–	25.9	–	**0.5**	–	✓	✓	12.2	11.6	17.3	16.8	14.9	18.1
7	PD	✓	✗	13.8	–	21.4	–	0.6	–	✓	✓	12.8	13.4	17.3	18.0	10.8	11.1
8	PD	✓	✓	13.8	14.0	20.8	24.5	**0.5**	0.6	✓	✓	11.9	12.0	17.7	16.4	**4.0**	**3.6**
9	PD	✗	✓	–	12.7	–	23.0	–	0.7	✗	✗	–	–	–	–	–	–
10	PD	✓	✗	15.7	–	26.6	–	0.6	–	✗	✗	–	–	–	–	–	–
11	control	✓	✓	13.6	11.9	21.0	22.2	**0.5**	**0.5**	✓	✓	12.1	12.4	15.9	17.8	14.7	11.4
12	control	✗	✗	–	–	–	–	–	–	✓	✓	12.3	12.1	16.5	16.5	**2.9**	**4.8**
13	control	✓	✓	13.5	12.0	20.2	19.7	0.8	0.6	✓	✓	11.7	12.2	15.9	15.7	9.0	10.0
14	control	✓	✗	13.1	–	21.3	–	0.7	–	✓	✓	14.1	14.0	17.8	17.5	13.1	12.7
15	Control	✓	✗	15.2	–	22.2	–	0.7	–	✓	✓	12.2	12.9	14.9	16.0	11.8	12.0
16	control	✗	✗	–	–	–	–	–	–	✓	✓	10.4	9.7	15.5	15.2	8.2	9.1
17	control	✓	✓	11.8	14.3	18.5	21.4	0.7	0.8	✓	✓	13.8	13.3	17.9	17.0	25.5	27.1
18	control	✓	✓	11.9	13.0	19.2	20.2	0.8	0.8	✓	✓	9.3	9.2	13.0	12.9	17.0	21.6
19	control	✓	✗	13.0	–	21.6	–	0.8	–	✓	✓	9.3	9.4	14.2	13.5	12.8	12.9
20	control	✗	✗	–	–	–	–	–	–	✓	✓	10.8	9.8	14.5	14.3	30.8	23.6

Abbreviations: PD = Parkinson's disease, cVEMP = cervical vestibular evoked myogenic potential, oVEMP = ocular vestibular evoked myogenic potential, ms = milliseconds, µV = microvolt, corr. = corrected.

4. Dizziness Handicap Inventory questionnaire

All participants completed the DHI questionnaire. With regard to the scores on the different domains (physical emotional and functional), the mean values equaled 7.20/28 (SD 5.59, range 0.00-14.00), 7.60/36 (SD 6.79, range 0.00-18.00) and 10.80/36 (SD 8.70, range 0.00-28.00) in the PD group. In the control group on the other hand, mean scores corresponding to 1.20/28 (SD 3.80, range 0.00-12.00), 0.40/36 (SD 1.27, range 0.00-4.00) and 0.60/36 (SD 1.90, range 0.00-6.00) were observed. The average DHI total score was found to be 25.60% (SD 19.36, range 0.00-56.00) in PD patients and 2.20% (SD 6.96, range 0.00-22.00) in control subjects. Apart from participant 14, every control subject scored 0 on the different domains, indicating no dizziness complaints at all. By contrast, only two PD patients reported a DHI total score of 0%. In addition, four patients scored between 1 and 30% in total, indicating a mild dizziness handicap as perceived by the subject, and four patients scored between 31 and 60% in total, indicating a moderate dizziness handicap. Statistical analysis by means of the Mann-Whitney U-test showed a DHI total score (%) being significantly higher in the PD group compared with the control group (U = 13.50, p = 0.003) (Figure 9). The functional domain was found to be most affected in PD patients, followed by the physical domain and subsequently the emotional domain.

Table 7: Dizziness Handicap Inventory questionnaire results.

Case-number	Group	DHI physical domain (/28)	DHI emotional domain (/36)	DHI functional domain (/36)	DHI total score (%)
1	PD	4	6	10	20
2	PD	12	10	14	**36**
3	PD	14	18	12	**44**
4	PD	10	0	12	22
5	PD	0	0	0	0
6	PD	0	0	0	0
7	PD	0	4	4	8
8	PD	10	8	8	26
9	PD	12	16	28	**56**
10	PD	10	14	20	**44**
11	control	0	0	0	0
12	control	0	0	0	0
13	control	0	0	0	0
14	control	12	4	6	22
15	control	0	0	0	0
16	control	0	0	0	0
17	control	0	0	0	0
18	control	0	0	0	0
19	control	0	0	0	0
20	control	0	0	0	0

Abbreviations: PD = Parkinson's disease, DHI = Dizziness Handicap Inventory.
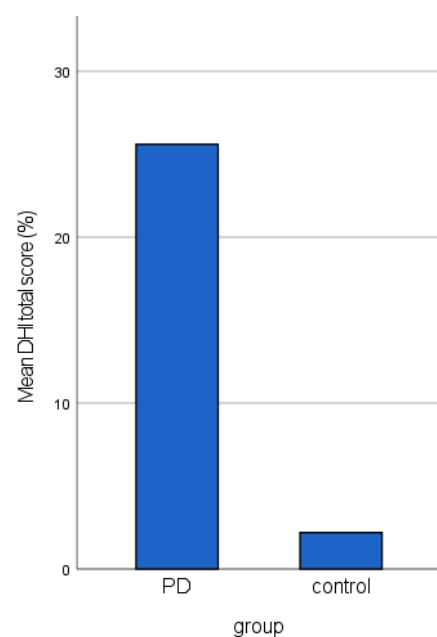

Figure 9: Bar chart depicting the mean Dizziness Handicap Inventory (DHI) total score (%) in patients with Parkinson's disease (PD) and controls.
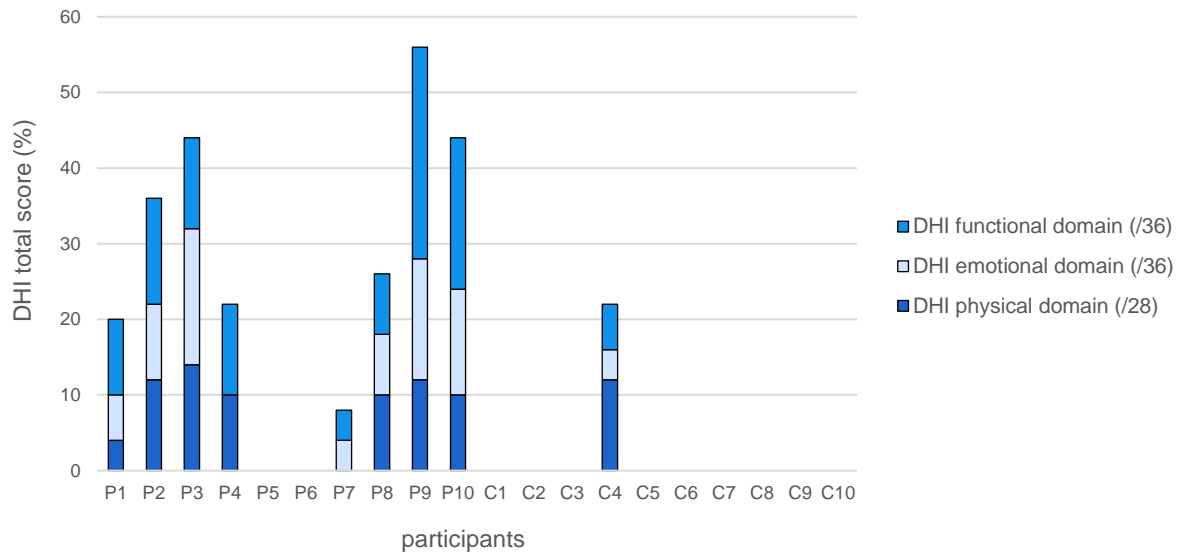
Figure 10: Bar chart depicting the Dizziness Handicap Inventory (DHI) total scores (%) in patients with Parkinson's disease (PD) and controls. P stands for Parkinson, C stands for control.

DISCUSSION

The aim of this master's dissertation was twofold. First of all, it intended to design a vestibular test protocol for PD patients, including a variety of tests in order to measure the function of the entire vestibular system. Secondly, it attempted to compare the vestibular function of PD patients with those of healthy controls, since knowledge on this topic is still limited.

1. Critical view on the protocol

As it was the first time that a study on this topic included several tests in an effort to investigate all parts of the vestibular system, the acquired insights and reflections may be valuable for future research. Nevertheless, the chosen protocol did have shortcomings that should not be overlooked.

First of all, the statement regarding this study dealing with all parts of the vestibular system should be nuanced. Since only the vHIT was used for semicircular canal evaluation, the protocol does not cover all frequencies for which the semicircular canals are sensitive. As a result, information about the low and mid frequency function of the canals is missed. Nonetheless, it should be noted that including caloric and rotational assessment would considerably prolong the duration of testing. Secondly, testing was time consuming and took about two hours per participant because of the extensive protocol. As a consequence, it sometimes became apparent that the examinations were quite exhausting, both for PD patients and elderly controls. The tiredness became most evident during oculomotor assessment. Since the oculomotor tasks require attention and clearly visible pupils, fatigue was one of the factors that influenced the results negatively (cfr. missing data in the PD group). In future research it might be indicated to use a different examination sequence (e.g. oculomotor testing before DVA and vHIT) or to split the testing in more and shorter sessions. Additionally, it is likely that – besides fatigue – upper eyelid ptosis might have impacted the oculomotor test results (cfr. missing data in the PD group). Finsterer (2003) defines ptosis as "an abnormally low-lying upper eyelid margin in primary gaze, resulting in narrowing of the palpebral opening and fissure and covering part of the eye". As oculomotor acquisition took place by means of a VNG system, coverage of the pupil is problematic. Alternatively, an electronystagmography (ENG) system could be used, since this does not require the eyes to be completely open. Another advantage of ENG acquisition is the fact that it reduces artefacts caused by eye blinking. Third, cVEMP results should be interpreted cautiously. Since it was demonstrated in literature that cVEMP response rates decrease drastically above the age of 65 years in the healthy population (Maes et al., 2010), we could ask ourselves whether it is worthwhile to maintain this test in the protocol. Nevertheless, cVEMP testing is the only way to detect saccular deficits and is thus of great interest in PD patients experiencing falls. Future research on this topic should definitely deploy a larger sample size in search of possible differences between PD patients and healthy controls. In addition, the age of PD patients should always be taken into account before drawing any conclusions on their saccular function. The fourth point of criticism is a suggestion regarding BPPV screening. According to the current protocol, positional maneuvers were performed with the aim of ruling out undetected BPPV. In the future it might be interesting to include a small inquiry with questions regarding a BPPV history as well. This way, information about a possible BPPV history will be gathered well-structured and not coincidentally. Fifth, this study lacks information about central vestibular (integration) deficits. In order to examine whether PD patients suffer from central vestibular dysfunctions, future researchers on this topic may be recommended to include 'subjective visual vertical', 'perception of tilt' or 'heading discrimination' examinations. Administration of these tests is unfortunately not evident, since particular test equipment (e.g. a motion platform) must be available. Last but not least, more patients should be investigated before drawing strong conclusions on the quality of the current protocol. This pilot study only included ten PD patients and ten matched control subjects.

2. Oculomotor and vestibular test results: Parkinson's disease patients versus controls

Despite the shortcomings of the protocol as described above, this study led to insights in the nature and sites of vestibular lesions in PD patients. Some of these insights could confirm the findings of previous research on this topic. However, the limited sample size does not allow us to draw reliable conclusions.

Unlike descriptions in previous literature, oculomotor parameters were not found to be significantly different in PD patients as opposed to controls. In particular, the significantly reduced saccadic amplitudes (hypometria) and prolonged saccadic latencies, as reported by Koohi et al. (2021) and Zhang et al. (2021), are in contrast with the findings of the current study. Additionally, no significantly reduced smooth pursuit gains were observed, contrary to research by Pinkhardt et al. (2009) and Zhang et al. (2021). Nevertheless, some PD patients did have signs of hypometric saccades, albeit not to a significant extent. This is in line with Anderson and MacAskill (2013), who concluded that saccadic amplitudes are often subtly decreased in tests using simple visually guided paradigms. When utilizing cognitively demanding visual tasks, such as memory-guided saccades and antisaccades, the hypometria would be more substantial. Concerning the cause of reduced saccadic amplitudes, Anderson and MacAskill (2013) assumed that basal ganglia degeneration might be responsible and result in saccadic hypometria early in the disease course. Increased saccadic latencies on the other hand, would occur later in the disease course. As regards reduced smooth pursuit gains, Frei (2021) enumerated both studies that found significantly diminished gains and studies that did not. Likewise, in this study there is no clear trend towards decreased gains in PD patients. Frei (2021) hypothesized that smooth pursuit eye movement pathways – linking the cortex to the basal ganglia, with the substantia nigra playing a mediating role – may be the basis for smooth pursuit abnormalities seen in PD. When it comes to the morphology and quality of the oculomotor traces, multiple-step or staircase patterns in saccadic traces, as well as catch-up and anticipatory saccades during smooth pursuit eye movements caught the eye. The multiple-step pattern was reported earlier by Anderson and MacAskill (2013), Koohi et al. (2021) and Zhang et al. (2021), who suspected it to be a compensation mechanism for hypometria during saccadic tasks. Catch-up and anticipatory saccades on the other hand, have already been mentioned by Frei (2021), Pinkhardt et al. (2009), Wu et al. (2018) and Zhou et al. (2021). According to Frei (2021), an inability to suppress extraneous saccades and a possible attentional or executive dysfunction would cause both catch-up and anticipatory saccades. Nonetheless, it should be noted that these morphologic abnormalities, and primarily the catch-up and anticipatory saccades, were also seen in the control group. There has indeed been research indicating a reduced smooth pursuit gain and an increased number of saccades during smooth pursuit eye movements in the healthy elderly population, aged 65 to 77 years (Frei, 2021; Sharpe & Sylvester, 1978). As a result, relying on smooth pursuit abnormalities as a biomarker for PD is not possible in persons over 65 years of age.

Since positional maneuvers did not provoke nystagmi or other abnormalities in any of the participants, BPPV presence could be ruled out in this pilot study. To date, an increased BPPV prevalence in PD patients has been reported by Becker-Bense et al. (2017) and van Wensen et al. (2013), but has not been confirmed by other researchers.

Regarding DVA testing, no statistically significant differences between PD patients and healthy controls were observed. Additionally, only one PD patient and one control subject were found to be at risk of oscillopsia. Since it was the first time that DVA was examined in this patient population, a comparison with previous findings is not possible. Nonetheless, DVA testing could be valuable as PD patients brought up both vestibular and visual changes in qualitative studies (Berliner et al., 2020; Johansson et al., 2019).

The vHIT indicated slightly but significantly increased posterior semicircular canal gains. Gains of the anterior and lateral canals also seemed increased, although not significantly. Slightly increased gains in PD patients were reported earlier by Lv et al. (2017). To declare this rare phenomenon, the authors speculated the possibility of a vestibular compensation mechanism, controlled by the cerebellum, in early-staged PD patients. We suspect though that central vestibular function loss in terms of inadequate VOR adaptation by the cerebellum might cause increased gain values. Other, non-pathology-related factors that could declare higher gains are goggle slippage and eye blinking artefacts. Besides increased semicircular canal gains, gains lower than 0.8 were observed in eight PD canals as opposed to one control canal. Remarkably, the gain values were considerably smaller in PD patient 10 compared with the control subjects, as well as the other patients. As mentioned earlier, the functional condition of PD patient 10 deteriorated strongly just prior to the study. Assuming that this patient would be in Hoehn and Yahr stage IV instead of stage III, we could hypothesize that peripheral vestibular functioning might degrade as disease staging increases. Since the gain asymmetry values were not found to be aberrant in all patients, isolated semicircular canal deterioration might not be the case. Altogether, there are arguments for peripheral and central vestibular deterioration, based on vHIT results. As both lower and higher gains were prominent in this study, it is evident that the mean gain values do not differ strongly between PD patients and controls.

Significant differences between PD patients and controls especially became apparent after VEMP data analysis. PD patients showed significantly prolonged P1 latencies (both in cVEMPs and oVEMPs), more absent oVEMP responses and smaller oVEMP peak-to-peak amplitudes in comparison with control subjects. These are abnormalities that have already been reported in previous literature as a consequence of peripheral and/or central vestibular deterioration. Regarding disease staging, de Natale, Ginatempo, Paulus, Manca, et al. (2015) concluded that delayed latencies were more prevalent in early PD, whereas reduced amplitudes or absent responses – whether or not in combination with delayed latencies – were found to be more common in later stages. Taking into account that lower amplitudes or absent VEMP responses would rather reflect peripheral vestibular abnormalities, whereas latency prolongation could indicate central vestibular problems (Venhovens, Meulstee, & Verhagen, 2016), early PD might involve central vestibular dysfunction and late PD loss of peripheral vestibular functioning. In addition, since Pötter-Nerger et al. (2015) found altered oVEMPs and relatively normal cVEMPs, the researchers hypothesized an intact lower brainstem function and impaired upper brainstem function in mild to moderate PD. Both observations (de Natale, Ginatempo, Paulus, Manca, et al., 2015; Pötter-Nerger et al., 2015) question Braak's hypothesis concerning pathologic alpha-synuclein spreading in PD, which would follow an ascending course originating in the brainstem and proceeding towards subcortical and cortical structures (Braak et al., 2003). In this study, lower amplitudes and absent VEMP responses were more prominent as opposed to delayed latencies. As most of the PD patients were in Hoehn and Yahr stage III or the middle stage of the disease, statements regarding a possible correlation between VEMP abnormalities and disease staging are not possible based upon the acquired data. However, it should be noted that PD patient 10 – who might be in Hoehn and Yahr stage IV – did show multiple abnormalities, since only cVEMP responses with prolonged latencies on the right were found. Yet, this single case cannot verify the findings of previous authors.

The greatest statistical effect was seen in DHI test results. Statistically significant differences in DHI total scores (%) between PD patients and controls have already been described in other studies (Kwon et al., 2022; Rossi-Izquierdo et al., 2014). The findings of the current study could thus confirm once more that vestibular assessment is absolutely necessary in the PD population. As the PD patients showed an average DHI score of 25.60%, their self-perceived dizziness handicap should be interpreted as more severe compared to the patients investigated by Kwon et al. (2022) – who scored 7,7% on average – and as less severe compared to the patients questioned by Rossi-Izquierdo et al. (2014) – who scored 33,26% on average. Taking into account that patients in the study by Kwon et al. (2022) were in Hoehn

and Yahr stage I or II and that patients in the study by Rossi-Izquierdo et al. (2014) were in stage I to IV, the factor that might most likely declare the differences in DHI scores between all studies is disease staging.

As this study only included elderly subjects, both in the PD and control group, degradation of the vestibular system due to aging should be taken into account. In 2019, the classification committee of the Bárány Society published the diagnostic criteria of age-related vestibular loss or presbyvestibulopathy (PVP). PVP is defined as "mild or incomplete vestibular losses attributable to the normative aging process, consistent with other age-related sensory losses such as presbycusis or presbyopia which are similarly incomplete losses (i.e. in contrast to deafness, or blindness, respectively)" (Agrawal et al., 2019). It is very likely that the aberrant vestibular test results seen in the control group are a consequence of PVP. However, since PD patients show remarkably more vestibular abnormalities, that are not always mild, PD is thought to have a more dominant influence on the vestibular system than PVP.

CONCLUSION

In conclusion, this master's dissertation demonstrated the importance of a vestibular test protocol, comprising a variety of tests in order to measure the function of the entire vestibular system in PD patients. Only by extensive vestibular testing we can gain insight into the specific nature, sites and degree of vestibular degradation, possibly due to Parkinson related neuropathological changes. The abovementioned criticisms on the chosen protocol should be taken into account in search for an ideal vestibular protocol, specifically designed for PD patients. Vestibular assessment in patients with PD is important as the vestibular system might be involved in frequently reported motor and non-motor symptoms, including postural instability and higher-order spatial navigational deficits. Early detection of a vestibular problem also enables healthcare professionals to initiate rehabilitation programs, customized to each patient. Regarding the results of the pilot study, we found that VEMP examinations might be most valuable in detecting vestibular deterioration in Hoehn and Yahr stage III of the disease. An important sidenote is that cVEMPs are often absent due to normal aging, making oVEMPs more interesting in the elderly population. Additionally, the study demonstrated that the DHI questionnaire is of great importance in revealing subjective balance perceptions in PD patients. The importance of vHIT, DVA and oculomotor assessment in PD patients should be investigated further in future research, comprising a greater sample size.

REFERENCES

Abbruzzese, G., & Berardelli, A. (2003). Sensorimotor integration in movement disorders. *Movement disorders : official journal of the Movement Disorder Society*, *18*(3), 231-240. https://doi.org/10.1002/mds.10327

Agrawal, Y., Van de Berg, R., Wuyts, F., Walther, L., Magnusson, M., Oh, E., Sharpe, M., & Strupp, M. (2019). Presbyvestibulopathy: Diagnostic criteria Consensus document of the classification committee of the Bárány Society. *Journal of vestibular research : equilibrium & orientation*, *29*(4), 161-170. https://doi.org/10.3233/ves-190672

Anderson, T. J., & MacAskill, M. R. (2013). Eye movements in patients with neurodegenerative disorders. *Nature reviews. Neurology*, *9*(2), 74-85. https://doi.org/10.1038/nrneurol.2012.273

Balestrino, R., & Schapira, A. H. V. (2020). Parkinson disease. *European journal of neurology*, *27*(1), 27-42. https://doi.org/10.1111/ene.14108

Barnett-Cowan, M., Dyde, R. T., Fox, S. H., Moro, E., Hutchison, W. D., & Harris, L. R. (2010). Multisensory determinants of orientation perception in Parkinson's disease. *Neuroscience*, *167*(4), 1138-1150. https://doi.org/10.1016/j.neuroscience.2010.02.065

Barone, P., Santangelo, G., Amboni, M., Pellecchia, M. T., & Vitale, C. (2016). Pisa syndrome in Parkinson's disease and parkinsonism: clinical features, pathophysiology, and treatment. *The Lancet. Neurology*, *15*(10), 1063-1074. https://doi.org/10.1016/s1474-4422(16)30173-9

Becker-Bense, S., Wittmann, C., van Wensen, E., van Leeuwen, R. B., Bloem, B., & Dieterich, M. (2017). Prevalence of Parkinson symptoms in patients with different peripheral vestibular disorders. *Journal of neurology*, *264*(6), 1287-1289. https://doi.org/10.1007/s00415-017-8470-7

Berliner, J. M., Kluger, B. M., Corcos, D. M., Pelak, V. S., Gisbert, R., McRae, C., Atkinson, C. C., & Schenkman, M. (2020). Patient perceptions of visual, vestibular, and oculomotor deficits in people with Parkinson's disease. *Physiotherapy theory and practice*, *36*(6), 701-708. https://doi.org/10.1080/09593985.2018.1492055

Berridge, M. J. (2017). Vitamin D deficiency accelerates ageing and age-related diseases: a novel hypothesis. *The Journal of physiology*, *595*(22), 6825-6836. https://doi.org/10.1113/jp274887

Bertolini, G., Wicki, A., Baumann, C. R., Straumann, D., & Palla, A. (2015). Impaired tilt perception in Parkinson's disease: a central vestibular integration failure. *PloS one*, *10*(4), e0124253. https://doi.org/10.1371/journal.pone.0124253

Beylergil, S. B., Ozinga, S., Walker, M. F., McIntyre, C. C., & Shaikh, A. G. (2019). Vestibular heading perception in Parkinson's disease. *Progress in brain research*, *249*, 307-319. https://doi.org/10.1016/bs.pbr.2019.03.034

Beylergil, S. B., Petersen, M., Gupta, P., Elkasaby, M., Kilbane, C., & Shaikh, A. G. (2020). Severity-Dependent Effects of Parkinson's Disease on Perception of Visual and Vestibular Heading. *Movement disorders : official journal of the Movement Disorder Society*. https://doi.org/10.1002/mds.28352

BIAP. (1996). *Recommendation 02/1: Audiometric Classification of Hearing Impairments*.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of aging*, *24*(2), 197-211. https://doi.org/10.1016/s0197-4580(02)00065-9

Cullen, K. E. (2016). Physiology of central pathways. *Handbook of clinical neurology*, *137*, 17-40. https://doi.org/10.1016/b978-0-444-63437-5.00002-9

de Natale, E. R., Ginatempo, F., Paulus, K. S., Manca, A., Mercante, B., Pes, G. M., Agnetti, V., Tolu, E., & Deriu, F. (2015). Paired neurophysiological and clinical study of the brainstem at different stages of Parkinson's Disease. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, *126*(10), 1871-1878. https://doi.org/10.1016/j.clinph.2014.12.017

de Natale, E. R., Ginatempo, F., Paulus, K. S., Pes, G. M., Manca, A., Tolu, E., Agnetti, V., & Deriu, F. (2015). Abnormalities of vestibular-evoked myogenic potentials in idiopathic Parkinson's disease are associated with clinical evidence of brainstem involvement. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *36*(6), 995-1001. https://doi.org/10.1007/s10072-014-2054-4

de Rijk, M. C., Rocca, W. A., Anderson, D. W., Melcon, M. O., Breteler, M. M., & Maraganore, D. M. (1997). A population perspective on diagnostic criteria for Parkinson's disease. *Neurology*, *48*(5), 1277-1281. https://doi.org/10.1212/wnl.48.5.1277

Del Tredici, K., & Braak, H. (2016). Review: Sporadic Parkinson's disease: development and distribution of α-synuclein pathology. *Neuropathology and applied neurobiology*, *42*(1), 33-50. https://doi.org/10.1111/nan.12298

DeLong, M. R., & Wichmann, T. (2007). Circuits and circuit disorders of the basal ganglia. *Archives of neurology*, *64*(1), 20-24. https://doi.org/10.1001/archneur.64.1.20

Deriu, F., Tolu, E., & Rothwell, J. C. (2003). A short latency vestibulomasseteric reflex evoked by electrical stimulation over the mastoid in healthy humans. *The Journal of physiology*, *553*(Pt 1), 267-279. https://doi.org/10.1113/jphysiol.2003.047274

Finsterer, J. (2003). Ptosis: causes, presentation, and management. *Aesthetic plastic surgery*, *27*(3), 193-204. https://doi.org/10.1007/s00266-003-0127-5

Frei, K. (2021). Abnormalities of smooth pursuit in Parkinson's disease: A systematic review. *Clinical parkinsonism & related disorders*, *4*, 100085. https://doi.org/10.1016/j.prdoa.2020.100085

Gandor, F., Basta, D., Gruber, D., Poewe, W., & Ebersbach, G. (2016). Subjective Visual Vertical in PD Patients with Lateral Trunk Flexion. *Parkinson's disease*, *2016*, 7489105. https://doi.org/10.1155/2016/7489105

Gimmon, Y., & Schubert, M. C. (2019). Vestibular Testing-Rotary Chair and Dynamic Visual Acuity Tests. *Advances in oto-rhino-laryngology*, *82*, 39-46. https://doi.org/10.1159/000490270

Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G. T., Counsell, C., Giladi, N., Holloway, R. G., Moore, C. G., Wenning, G. K., Yahr, M. D., & Seidl, L. (2004). Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Movement disorders : official journal of the Movement Disorder Society*, *19*(9), 1020-1028. https://doi.org/10.1002/mds.20213

Hanakawa, T., Fukuyama, H., Katsumi, Y., Honda, M., & Shibasaki, H. (1999). Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. *Annals of neurology*, *45*(3), 329-336. https://doi.org/10.1002/1531-8249(199903)45:3<329::aid-ana8>3.0.co;2-s

Hood, J. D. (1960). The principles and practice of bone conduction audiometry: A review of the present position. *The Laryngoscope*, *70*(9), 1211-1228. https://doi.org/https://doi.org/10.1288/00005537-196009000-00001

Hughson, W., & Westlake, H. (1944). Manual for program outline for rehabilitation of aural casualties both military and civilian. *Trans Amer Acad Ophthal Otolaryng Suppl*, *48*, 1-15.

Jacobson, G. P., & Newman, C. W. (1990). The development of the Dizziness Handicap Inventory. *Archives of otolaryngology--head & neck surgery*, *116*(4), 424-427. https://doi.org/10.1001/archotol.1990.01870040046011

Jeong, S. H., Kim, J. S., Shin, J. W., Kim, S., Lee, H., Lee, A. Y., Kim, J. M., Jo, H., Song, J., & Ghim, Y. (2013). Decreased serum vitamin D in idiopathic benign paroxysmal positional vertigo. *Journal of neurology*, *260*(3), 832-838. https://doi.org/10.1007/s00415-012-6712-2

Johansson, H., Franzén, E., Skavberg Roaldsen, K., Hagströmer, M., & Leavy, B. (2019). Controlling the Uncontrollable: Perceptions of Balance in People With Parkinson Disease. *Physical therapy*, *99*(11), 1501-1510. https://doi.org/10.1093/ptj/pzz117

Jongkees, L. B. W. (1948). Value of the caloric test of the labyrinth. *Archives of Otolaryngology*, *48*(4), 402-417. https://doi.org/10.1001/archotol.1948.00690040414003

José Luvizutto, G., Souza Silva Brito, T., de Moura Neto, E., & Aparecida Pascucci Sande de Souza, L. (2020). Altered Visual and Proprioceptive Spatial Perception in Individuals with Parkinson's Disease. *Perceptual and motor skills*, *127*(1), 98-112. https://doi.org/10.1177/0031512519880421

Joyal, C. C., Strazielle, C., & Lalonde, R. (2001). Effects of dentate nucleus lesions on spatial and postural sensorimotor learning in rats. *Behavioural brain research*, *122*(2), 131-137. https://doi.org/10.1016/s0166-4328(00)00390-9

Koohi, N., Bancroft, M. J., Patel, J., Castro, P., Akram, H., Warner, T. T., & Kaski, D. (2021). Saccadic Bradykinesia in Parkinson's Disease: Preliminary Observations. *Movement disorders : official journal of the Movement Disorder Society*, *36*(7), 1729-1731. https://doi.org/10.1002/mds.28609

Kwon, K. Y., Park, S., Lee, E. J., Lee, M., & Ju, H. (2022). Impact of subjective dizziness on motor and non-motor symptoms in patients with early stages of Parkinson's disease. *Journal of integrative neuroscience*, *21*(1), 3. https://doi.org/10.31083/j.jin2101003

Lee, S., Liu, A., Wang, Z. J., & McKeown, M. J. (2019). Abnormal Phase Coupling in Parkinson's Disease and Normalization Effects of Subthreshold Vestibular Stimulation. *Frontiers in human neuroscience*, *13*, 118. https://doi.org/10.3389/fnhum.2019.00118

Lithgow, B. J., & Shoushtarian, M. (2015). Parkinson's disease: disturbed vestibular function and levodopa. *Journal of the neurological sciences*, *353*(1-2), 49-58. https://doi.org/10.1016/j.jns.2015.03.050

Little, S., & Brown, P. (2014). The functional role of beta oscillations in Parkinson's disease. *Parkinsonism & related disorders*, *20 Suppl 1*, S44-48. https://doi.org/10.1016/s1353-8020(13)70013-0

Lohnes, C. A., & Earhart, G. M. (2011). Saccadic eye movements are related to turning performance in Parkinson disease. *Journal of Parkinson's disease*, *1*(1), 109-118. https://doi.org/10.3233/jpd-2011-11019

Lv, W., Guan, Q., Hu, X., Chen, J., Jiang, H., Zhang, L., & Fan, W. (2017). Vestibulo-ocular reflex abnormality in Parkinson's disease detected by video head impulse test. *Neuroscience letters*, *657*, 211-214. https://doi.org/10.1016/j.neulet.2017.08.021

Maes, L., Dhooge, I., D'Haenens, W., Bockstael, A., Keppler, H., Philips, B., Swinnen, F., & Vinck, B. M. (2010). The effect of age on the sinusoidal harmonic acceleration test, pseudorandom rotation test, velocity step test, caloric test, and vestibular-evoked myogenic potential test. *Ear and hearing*, *31*(1), 84-94. https://doi.org/10.1097/AUD.0b013e3181b9640e

Meng, H., Blázquez, P. M., Dickman, J. D., & Angelaki, D. E. (2014). Diversity of vestibular nuclei neurons targeted by cerebellar nodulus inhibition. *The Journal of physiology*, *592*(1), 171-188. https://doi.org/10.1113/jphysiol.2013.259614

Mpandzou, G., Aït Ben Haddou, E., Regragui, W., Benomar, A., & Yahyaoui, M. (2016). Vitamin D deficiency and its role in neurological conditions: A review. *Revue neurologique*, *172*(2), 109-122. https://doi.org/10.1016/j.neurol.2015.11.005

Müller, M. L., & Bohnen, N. I. (2013). Cholinergic dysfunction in Parkinson's disease. *Current neurology and neuroscience reports*, *13*(9), 377. https://doi.org/10.1007/s11910-013-0377-9

Oghalai, J. S., Manolidis, S., Barth, J. L., Stewart, M. G., & Jenkins, H. A. (2000). Unrecognized benign paroxysmal positional vertigo in elderly patients. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, *122*(5), 630-634. https://doi.org/10.1067/mhn.2000.105415

Parkinson, J. (2002). An essay on the shaking palsy. 1817. *The Journal of neuropsychiatry and clinical neurosciences*, *14*(2), 223-236; discussion 222. https://doi.org/10.1176/jnp.14.2.223

Pinkhardt, E. H., Kassubek, J., Süssmuth, S., Ludolph, A. C., Becker, W., & Jürgens, R. (2009). Comparison of smooth pursuit eye movement deficits in multiple system atrophy and Parkinson's disease. *Journal of neurology*, *256*(9), 1438-1446. https://doi.org/10.1007/s00415-009-5131-5

Pollak, L., Prohorov, T., Kushnir, M., & Rabey, M. (2009). Vestibulocervical reflexes in idiopathic Parkinson disease. *Neurophysiologie clinique = Clinical neurophysiology*, *39*(4-5), 235-240. https://doi.org/10.1016/j.neucli.2009.07.001

Pötter-Nerger, M., Govender, S., Deuschl, G., Volkmann, J., & Colebatch, J. G. (2015). Selective changes of ocular vestibular myogenic potentials in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, *30*(4), 584-589. https://doi.org/10.1002/mds.26114

Pötter-Nerger, M., Reich, M. M., Colebatch, J. G., Deuschl, G., & Volkmann, J. (2012). Differential effect of dopa and subthalamic stimulation on vestibular activity in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, *27*(10), 1268-1275. https://doi.org/10.1002/mds.25061

Putcha, D., Ross, R. S., Rosen, M. L., Norton, D. J., Cronin-Golomb, A., Somers, D. C., & Stern, C. E. (2014). Functional correlates of optic flow motion processing in Parkinson's disease. *Frontiers in integrative neuroscience*, *8*, 57. https://doi.org/10.3389/fnint.2014.00057

Reich, S. G., & Savitt, J. M. (2019). Parkinson's Disease. *The Medical clinics of North America*, *103*(2), 337-350. https://doi.org/10.1016/j.mcna.2018.10.014

Rossi-Izquierdo, M., Basta, D., Rubio-Rodríguez, J. P., Santos-Pérez, S., Ernst, A., Sesar-Ignacio, Á., Alberte-Woodward, M., Guijarro-Del Amo, M., Estany-Gestal, A., San Román-Rodríguez, E., Faraldo-García, A., Zubizarreta-Gutiérrez, A., & Soto-Varela, A. (2014). Is posturography able to identify fallers in patients with Parkinson's disease? *Gait & posture*, *40*(1), 53-57. https://doi.org/10.1016/j.gaitpost.2014.02.003

Scocco, D. H., Wagner, J. N., Racosta, J., Chade, A., & Gershanik, O. S. (2014). Subjective visual vertical in Pisa syndrome. *Parkinsonism & related disorders*, *20*(8), 878-883. https://doi.org/10.1016/j.parkreldis.2014.04.030

Seidel, K., Mahlke, J., Siswanto, S., Krüger, R., Heinsen, H., Auburger, G., Bouzrou, M., Grinberg, L. T., Wicht, H., Korf, H. W., den Dunnen, W., & Rüb, U. (2015). The brainstem pathologies of Parkinson's disease and dementia with Lewy bodies. *Brain pathology (Zurich, Switzerland)*, *25*(2), 121-135. https://doi.org/10.1111/bpa.12168

Shalash, A. S., Hassan, D. M., Elrassas, H. H., Salama, M. M., Méndez-Hernández, E., Salas-Pacheco, J. M., & Arias-Carrión, O. (2017). Auditory- and Vestibular-Evoked Potentials Correlate with Motor and Non-Motor Features of Parkinson's Disease. *Frontiers in neurology*, *8*, 55. https://doi.org/10.3389/fneur.2017.00055

Sharpe, J. A., & Sylvester, T. O. (1978). Effect of aging on horizontal smooth pursuit. *Investigative ophthalmology & visual science*, *17*(5), 465-468.

Takakusaki, K. (2017). Functional Neuroanatomy for Posture and Gait Control. *Journal of movement disorders*, *10*(1), 1-17. https://doi.org/10.14802/jmd.16062

Tang, H., Chen, Y., Cen, Z., Ouyang, Z., Lou, D., Tan, Y., & Luo, W. (2020). The link between lateral trunk flexion in Parkinson's disease and vestibular dysfunction: a clinical study. *The International journal of neuroscience*, 1-6. https://doi.org/10.1080/00207454.2020.1825419

Tysnes, O. B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. *Journal of neural transmission (Vienna, Austria : 1996)*, *124*(8), 901-905. https://doi.org/10.1007/s00702-017-1686-y

Van Den Eeden, S. K., Tanner, C. M., Bernstein, A. L., Fross, R. D., Leimpeter, A., Bloch, D. A., & Nelson, L. M. (2003). Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *American journal of epidemiology*, *157*(11), 1015-1022. https://doi.org/10.1093/aje/kwg068

van Wensen, E., van Leeuwen, R. B., van der Zaag-Loonen, H. J., Masius-Olthof, S., & Bloem, B. R. (2013). Benign paroxysmal positional vertigo in Parkinson's disease. *Parkinsonism & related disorders*, *19*(12), 1110-1112. https://doi.org/10.1016/j.parkreldis.2013.07.024

Venhovens, J., Meulstee, J., Bloem, B. R., & Verhagen, W. I. (2016). Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. *The European journal of neuroscience*, *43*(12), 1636-1646. https://doi.org/10.1111/ejn.13253

Venhovens, J., Meulstee, J., & Verhagen, W. I. M. (2016). Vestibular evoked myogenic potentials (VEMPs) in central neurological disorders. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, *127*(1), 40-49. https://doi.org/10.1016/j.clinph.2014.12.021

Visser, J. E., & Bloem, B. R. (2005). Role of the basal ganglia in balance control. *Neural plasticity*, *12*(2-3), 161-174; discussion 263-172. https://doi.org/10.1155/np.2005.161

Vitale, C., Marcelli, V., Furia, T., Santangelo, G., Cozzolino, A., Longo, K., Allocca, R., Amboni, M., Marciano, E., & Barone, P. (2011). Vestibular impairment and adaptive postural imbalance in parkinsonian patients with lateral trunk flexion. *Movement disorders : official journal of the Movement Disorder Society*, *26*(8), 1458-1463. https://doi.org/10.1002/mds.23657

Wellings, T. P., Brichta, A. M., & Lim, R. (2017). Altered neurofilament protein expression in the lateral vestibular nucleus in Parkinson's disease. *Experimental brain research*, *235*(12), 3695-3708. https://doi.org/10.1007/s00221-017-5092-3

Wu, C. C., Cao, B., Dali, V., Gagliardi, C., Barthelemy, O. J., Salazar, R. D., Pomplun, M., Cronin-Golomb, A., & Yazdanbakhsh, A. (2018). Eye movement control during visual pursuit in Parkinson's disease. *PeerJ*, *6*, e5442. https://doi.org/10.7717/peerj.5442

Yakubovich, S., Israeli-Korn, S., Halperin, O., Yahalom, G., Hassin-Baer, S., & Zaidel, A. (2020). Visual self-motion cues are impaired yet overweighted during visual-vestibular integration in Parkinson's disease. *Brain communications*, *2*(1), fcaa035. https://doi.org/10.1093/braincomms/fcaa035

Yang, B., Lu, Y., Xing, D., Zhong, W., Tang, Q., Liu, J., & Yang, X. (2020). Association between serum vitamin D levels and benign paroxysmal positional vertigo: a systematic review and meta-analysis of observational studies. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, *277*(1), 169-177. https://doi.org/10.1007/s00405-019-05694-0

Zhang, J., Zhang, B., Ren, Q., Zhong, Q., Li, Y., Liu, G., Ma, X., & Zhao, C. (2021). Eye movement especially vertical oculomotor impairment as an aid to assess Parkinson's disease. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *42*(6), 2337-2345. https://doi.org/10.1007/s10072-020-04796-6

Zhou, H., Wang, X., Ma, D., Jiang, Y., Li, F., Sun, Y., Chen, J., Sun, W., Pinkhardt, E. H., Landwehrmeyer, B., Ludolph, A., Zhang, L., Zhao, G., & Wang, Z. (2021). The differential diagnostic value of a battery of oculomotor evaluation in Parkinson's Disease and Multiple System Atrophy. *Brain and behavior*, *11*(7), e02184. https://doi.org/10.1002/brb3.2184

Appendix 1: Oculomotor test results.

Casenr.	Group	Hor. saccades			Ver. saccades			Hor. SP		Hor. OKN test (20°/s)			Hor. OKN test (40°/s)			Hor. OKN test (60°/s)		
		lat. (ms)	vel. (°/s)	acc. (%)	lat. (ms)	vel. (°/s)	acc. (%)	slow: gain (%)	fast: gain (%)	vel. R (°/s)	vel. L (°/s)	NP	vel. R (°/s)	vel. L (°/s)	NP	vel. R (°/s)	vel. L (°/s)	NP
1	PD	196	267	87	**405**	393	112	103	84	14.2	17.5	11% L	16.6	10.7	**22% R**	**9.1**	**8.3**	4% R
2	PD	178	354	99	**266**	301	101	107	118	18.1	27.8	**21% L**	22.4	42.3	**31% L**	34.2	34.7	1% L
3	PD	20	314	**75**	0	338	**192**	98	/	17.9	18.3	1% L	29.0	29.1	0%	30.7	27.3	6% R
4	PD	163	450	101	175	347	99	103	105	14.8	18.8	12% L	26.8	25.1	3% R	23.0	26.3	7% L
5	PD	254	206	92	230	**164**	108	74	**68**	14.4	17.6	10% L	19.3	19.1	0%	**9.3**	16.0	**27% L**
6	PD	140	317	93	151	196	**73**	103	106	19.3	17.0	6% R	30.6	28.0	4% R	32.9	31.2	3% R
7	PD	196	324	101	222	227	79	110	111	21.0	17.0	11% R	17.3	22.1	12% L	22.9	24.6	4% L
8	PD	175	309	98	168	305	99	114	120	22.1	16.3	15% R	35.1	31.1	6% R	39.2	32.9	9% R
9	PD	203	**118**	**61**	218	**113**	81	75	**38**	**8.5**	**8.7**	1% L	**6.9**	**8.9**	12% L	**8.3**	**9.6**	7% L
10	PD	223	318	**131**	/	/	/	**55**	**57**	21.8	22.2	1% L	/	/	/	**7.8**	**3.7**	**35% R**
11	control	131	331	104	145	263	95	99	89	16.1	19.5	10% L	30.6	29.5	2% R	25.1	23.2	4% R
12	control	141	312	102	171	349	111	106	104	19.9	20.0	0%	35.2	31.6	5% R	39.4	29.8	14% R
13	control	178	331	98	192	293	102	88	118	19.5	21.6	5% L	36.4	36.9	1% L	48.3	41.2	8% R
14	control	193	326	101	182	343	86	106	112	14.4	13.6	3% R	13.6	15.6	7% L	14.6	20.2	16% L
15	control	187	465	105	161	320	105	96	91	21.7	20.5	3% R	36.7	37.4	1% L	50.8	46.5	4% R
16	control	199	272	94	237	264	96	95	104	12.6	19.6	**22% L**	19.6	17.3	6% R	22.0	16.5	14% R
17	control	228	259	100	**262**	347	120	102	103	13.0	13.7	3% L	17.7	20.0	6% L	33.9	**9.0**	**58% R**
18	control	143	328	93	133	285	96	99	94	14.9	11.3	14% R	20.2	18.1	6% R	21.7	16.5	14% R
19	control	210	332	98	231	234	98	103	103	18.9	19.3	1% L	27.4	30.6	5% L	29.2	30.2	2% L
20	control	145	356	104	199	281	105	107	109	19.2	22.6	8% L	33.3	36.5	5% L	36.5	51.2	17% L

Abbreviations: casenr. = casenumber, PD = Parkinson's disease, hor. = horizontal, ver. = vertical, SP = smooth pursuit, OKN = optokinetic, lat. = latency, ms = milliseconds, vel. = velocity, °/s = degrees per second, acc. = accuracy, R = right, L = left, NP = nystagmus preponderance.

Appendix 2: Oculomotor test statistics.

	PD		Control		Mann-Whitney U-test		Wilcoxon signed-ranks test	
	n	*mean (SD, range)*	*n*	*mean (SD, range)*	*U*	*p*	*Z*	*p*
Hor. randomized saccades: latency (ms)	10	174.80 (62.91, 20.00-254.00)	10	175.50 (33.50, 131.00-228.00)	45.50	0.734	-0.51	0.610
Hor. randomized saccades: velocity (°/s)	10	297.70 (88.12, 118.00-450.00)	10	331.20 (55.42, 259.00-465.00)	32.00	0.173	-0.36	0.721
Hor. randomized saccades: accuracy (%)	10	93.80 (18.29, 61.00-131.00)	10	99.90 (4.15, 93.00-105.00)	28.50	0.103	-1.07	0.286
Ver. randomized saccades: latency (ms)	9	203.89 (107.24, 0.00-405.00)	10	191.30 (41.74, 133.00-262.00)	40.00	0.683	-0.18	0.859
Ver. randomized saccades: velocity (°/s)	9	264.89 (94.10, 113.00-393.00)	10	297.90 (40.10, 234.00-349.00)	37.50	0.540	-1.01	0.314
Ver. randomized saccades: accuracy (%)	9	104.89 (35.34, 73.00-192.00)	10	101.40 (9.50, 86.00-120.00)	42.00	0.806	-0.12	0.906
Hor. slow SP: gain (%)	10	94.20 (19.34, 55.00-114.00)	10	100.10 (5.97, 88.00-107.00)	48.00	0.879	-0.15	0.878
Hor. fast SP: gain (%)	9	89.67 (29.41, 38.00-120.00)	10	102.70 (9.21, 89.00-118.00)	41.50	0.775	-0.65	0.515
Hor. OKN test (20°/s): vel. to the right (°/s)	10	17.21 (4.26, 8.50-22.10)	10	17.02 (3.21, 12.60-21.70)	46.50	0.791	-0.05	0.959
Hor. OKN test (20°/s): vel. to the left (°/s)	10	18.12 (4.78, 8.70-27.80)	10	18.17 (3.85, 11.30-22.60)	40.00	0.450	-0.204	0.838
Hor. OKN test (20°/s): NP (%)	10	8.90 (6.66, 1.00-21.00)	10	6.90 (6.84, 0.00-22.00)	40.00	0.447	-0.83	0.406
Hor. OKN test (40°/s): vel. to the right (°/s)	9	22.67 (8.66, 6.90-35.10)	10	27.07 (8.62, 13.60-36.70)	29.50	0.205	-0.89	0.374
Hor. OKN test (40°/s): vel. to the left (°/s)	9	24.04 (10.37, 8.90-42.30)	10	27.35 (8.74, 15.60-37.40)	35.00	0.414	-0.42	0.678
Hor. OKN test (40°/s): NP (%)	9	10.00 (10.57, 0.00-31.00)	10	4.40 (2.22, 1.00-7.00)	36.50	0.484	-1.12	0.262
Hor. OKN test (60°/s): vel. to the right (°/s)	10	21.74 (12.28, 7.80-39.20)	10	32.15 (11.84, 14.60-50.80)	29.00	0.112	-1.68	0.093
Hor. OKN test (60°/s): vel. to the left (°/s)	10	21.46 (11.19, 3.70-34.70)	10	28.43 (14.03, 9.00-51.20)	38.00	0.364	-0.76	0.445
Hor. OKN test (60°/s): NP (%)	10	10.30 (11.30, 1.00-35.00)	10	15.10 (16.05, 2.00-58.00)	36.00	0.287	-0.59	0.553

Abbreviations: PD = Parkinson's disease, hor. = horizontal, ver. = vertical, SP = smooth pursuit, OKN = optokinetic, vel. = velocity, NP = nystagmus preponderance, n = number of participants, SD = standard deviation.