Parkinson's-disease-related changes in the behavioural synergy between eye movements and postural movements

Cédrick T. Bonnet, Arnaud Delval, Tarkeshwar Singh, Luc Defebvre

Parkinson's-disease-related changes in the behavioural synergy between eye movements and postural movements

Cédrick T. Bonnet, PhD,[1] Arnaud Delval, MD, PhD,[2] Tarkeshwar Singh, PhD,[3] and Luc Defebvre, MD, PhD,[2]

[1] Univ. Lille, CNRS, UMR 9193 – SCALab – Sciences Cognitives et Sciences Affectives, F-59000 Lille, France

[2] Univ. Lille, Unité INSERM 1172, CHU Lille, F-59000 Lille, France

[3] Department of Kinesiology, The Pennsylvania State University, University Park, PA 16802, United States

Corresponding author:
Cédrick T. Bonnet
e-mail: cedrick.bonnet@univ-lille.fr
https://pro.univ-lille.fr/cedrick-bonnet/

RUNNING TITLE: Parkinson's-disease-related changes in eye and postural movements

KEYWORDS: Parkinson's disease-related impairments; synergic model; eye and postural movements; automatic vs. higher order behaviours; visual performance

ABSTRACT

Patients with Parkinson's disease (PD patients) have been shown to exhibit abnormally low levels of synergy in their posture control. The goal of this study is to determine how synergic interactions between vision and posture are affected in PD patients. These synergic interactions were expected to be impaired because PD affects the basal ganglia, which are involved in the modulation of both types of movement. Twenty patients (mean age: 60) on levodopa and 20 age-matched-controls (mean age: 61) performed a precise visual task (searching for targets in an image) and an unprecise control task (randomly looking at an image) in which images were projected onto a large panoramic display. Lower back, upper back, head and eye movements were recorded simultaneously. To test behavioural synergies, Pearson correlations between eye and postural movements were analysed. The relationships between eye movements and upper and lower back movements were impaired in the patients. The age-matched controls did not show any significant correlations between eye and postural movements. Overall, our results showed that the PD patients failed to adjust and control their postural stability for success in the visual task. The impaired synergy between eye and postural movements was not related to clinical variables - probably because our patients had early-stage PD. Our results showed that impairments in synergy can occur very early in PD. Hence, the analysis of this synergy might provide a better understanding of postural instability, visual task performance in the upright stance, and perhaps the risk of falls in PD patients.

INTRODUCTION

Parkinson's disease (PD) leads to major motor impairments, such as resting tremor, rigidity, hypokinesia, and postural instability (Magrinelli et al., 2016; Yang, Tang, & Guo, 2016). PD patients also have visual impairments (e.g. altered contrast sensitivity and double vision (Ekker et al., 2017; Weil et al., 2016)) and cognitive impairments (Yang et al., 2016). Here, we sought to determine how synergic interactions between vision and posture are affected in PD patients. Previously, Latash and Huang (2015) explained that analyses of impairments in synergy are relevant because they show more fundamental impairments than singular impairments such as postural instability. Latash and Huang (2015) explained that impaired synergy may be the cause of motor impairments, while postural instability may only be the result of these impairments. Recently, synergy analyses have shown that PD is associated with abnormally low indices of multimuscle synergy in postural control (Falaki, Huang, Lewis, & Latash, 2016, 2017b).Furthermore, the basal ganglia (affected in PD) are involved in the control of both eye movements and posture. More precisely, the caudate and putamen nuclei are interconnected structures that control saccadic eye movements and posture (Hikosaka, Takikawa, & Kawagoe, 2000; Visser & Bloem, 2005). Both nuclei are affected in PD (Pasquini et al., 2019; Wang, Zhang, Zang, & Wu, 2018). The neural circuits for saccades and postural control even overlap (see Figure 4 on p. 7 in French & Muthusamy, 2018), which thus provided a mechanistic basis of PD-related impairments in the relationships between the two functions.

It is still not clear whether PD-related impairments affect the synergic interactions between vision and posture (Devos et al., 2013; Ewenczyk et al., 2017). Our research group has developed a quantitative model of how eye movements and limb movements synergically interact for success in ecological, precise, visual search tasks performed in the upright stance (Bonnet & Baudry, 2016). We therefore used this model to test PD-related impairments in behavioural synergy between eye and postural movement in a precise visual search task. Precise tasks refer to tasks in which participants search for specific targets in a goal-directed fashion, whereas unprecise free-viewing tasks (used here as control tasks) involve the participant merely glancing at the environment in the absence of any goals. We expected to find that PD would impair the synergic interactions between eye movements and postural movements during a precise visual search task. The results presented below confirmed our expectations and suggested that PD patients may need to perform exercises combining eye and postural movements to recover goal-directed postural control. These combined exercises may benefit PD patients more than exercises involving eye movements alone or postural movements alone would.

MATERIALS AND METHODS

Participants

Twenty PD patients (12 males and 8 females) and 20 age- and sex-matched healthy older adults (12 males and 8 females) were included. The mean ± standard deviation (SD) age, body mass and height were respectively 60 ± 8 years, 78 ± 17 kg and 1.71 ± 0.06 m for the patients and 61 ± 7 years, 78 ± 13 kg and 1.71 ± 0.08 m for the age-matched healthy controls. The two groups did not differ on their physical characteristics ($F_s(1,38)<0.29$, $p>0.05$). To calculate of the sample size with sufficient statistical power, we used the results of our previous study of young adults (Bonnet, Davin, Hoang, & Baudry, 2019) and a bivariate normal model in G*power (Faul, Erdfelder, Buchner, & Lang, 2009). Based on our previous study, the estimated effect size f was 0.624. With a two-tailed test and alpha risk of 0.05, a power of 0.8, and a phi correlation (H0) of 0, the required sample size was 9. We decided to recruit at least

twice this number of patients (n=20) and then the same number of control participants as there were patients.

The PD patients were diagnosed by one of the two physicians in the investigating team (LD or AD). The diagnosis was confirmed immediately before the experimental session. The PD patients had a mean ± SD time since disease onset of 5 ± 2 years (range: 2–11). Their mean motor Movement Disorder Society Unified Parkinson's Disease Rating Score (MDS-UPDRS) motor score on-medication (part III; (Hughes, Daniel, Kilford, & Lees, 1992) was 21 ± 8 (range: 10–39). The patients' mean Hoehn and Yahr stage was 2.0 ± 0.5 (range: 1–3) and the mean axial score out of 24 (computed by summing the scores for MDS-UPDRS III items 18 (speech), 22 (axial rigidity), 27 (rising from a chair), 28 (posture), 29 (postural stability) and 30 (gait); Bejjani et al., 2000)) was 3.3±2.4 (range: 0–11).

Participants were excluded if they had a history or signs of vestibular, musculoskeletal or neurological disorders or diseases (other than PD in the patient group), recurrent dizziness, dementia (according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition), cognitive decline (a Montreal Cognitive Assessment (MoCA) score below 27 (Nasreddine et al., 2005)), severe motor fluctuations, or dyskinesia. Participants were also excluded if they had fallen in the previous six months (based on their reply to a simple question) and if they were taking a medication known to affect postural control. The patients were on their usual dopaminergic medication (i.e. "on-medication") during this study. The mean total daily levodopa equivalent dose was 659±339 mg. The participants were only included if they had normal or corrected-to-normal vision, i.e. if they could clearly see images. The study was approved by the local independent ethics committee (reference: 2014-74). All the participants gave their written, informed consent to participation.

Apparatus

Three video projectors (Optoma HD83, London, England) were used to project the images onto a full semi-circular panoramic display (radius: 2.04 m; height: 2 m; Figures 1A and 1C). The participants could see images projected onto the panoramic display with a maximum visual angle of 100° for left-right and 20° for up-down (Figure 1A and 1C). The participants stood with their feet placed in a standardized position (14 cm, 17°; McIlroy & Maki, 1997). Head, upper back and lower back movements were measured with a Polhemus magnetic tracking system (Polhemus Liberty 240/8-8 System, Colchester, VT) at 240 Hz. The markers were placed on (i) a helmet worn by the participant (the head marker), (ii) the upper back over the seventh cervical vertebra (the upper back marker), and (iii) a chest belt over the fifth lumbar vertebra (the lower back marker) (Figure 1C). Eye movements were recorded with iViewX software and eye tracking goggles (SensoMotoric Instruments, Teltow, Germany) attached to the helmet worn by the participants (Figure 1C). The iViewX system recorded the pupil position at a frequency of 50 Hz. Begaze software (SensoMotoric Instruments, Teltow, Germany) was used to characterize fixations in each trial. It defined a fixation as less than 13 pixels of eye movement for 80 ms. A MATLAB (MathWorks, Natick, MA, USA) script was used to project the image onto the wall and to synchronize the data from the magnetic tracking system, and the eye tracker.

The 12 images displayed to the participants were all images of rooms inside a house (the kitchen, the living room, etc.; Figure 1B). Six images were shown in the precise task, and six other images were shown in the free-viewing control task (Figure 1B). The order of the images shown in the tasks was counterbalanced so that all images were projected the same number of times to all participants. The order in which the six images per task were shown was randomized across participants. The order in which the two tasks were performed was

also randomized. The images had been used in previously reported study (Thibaut, Tran, Szaffarczyk, & Boucart, 2018).

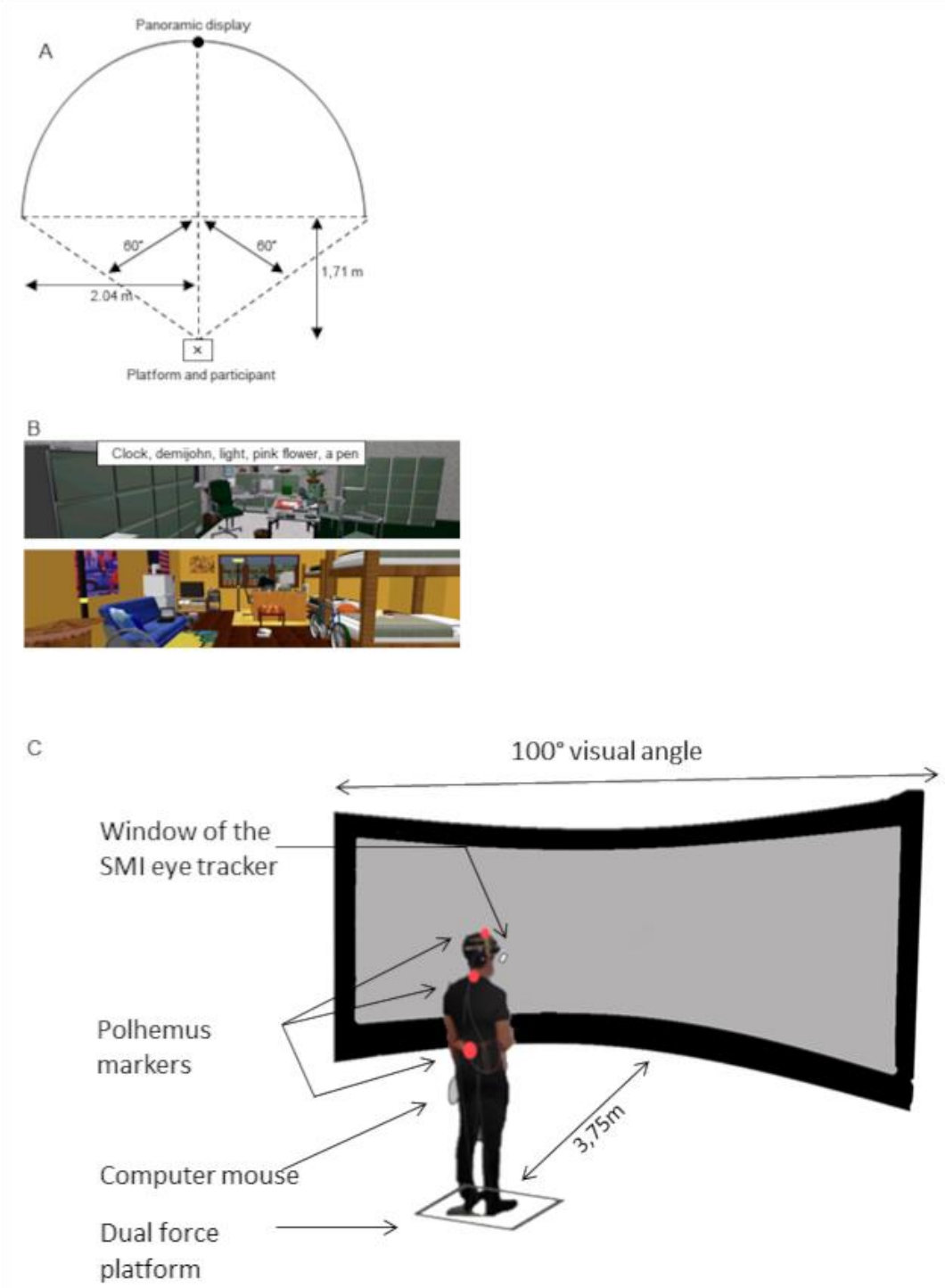

Figure 1. A. The position of the participants with respect to the semi-circular panoramic display (radius: 2.04 m; height: 2 m) onto which the 12 images were projected. The participants stood 1.71 m behind the centre of the semi-circular panoramic display and therefore could see the images subtended by a visual angle of 100° at most. B. Two images shown during the study. The top image was shown in the precise search task because the participants had a list of objects to search for. This list was shown at the top of the image. The bottom image was shown in the free-viewing (control) task in which there were no objects to search for. The participants were told to look wherever they liked in the image. C. The experimental setup, with a participant standing on the force platform, wearing the Polhemus system's three markers and with the eye tracker fixed to the helmet.

Tasks

The study was performed with two tasks (a search task and a free-viewing task) and six trials per task. Each trial lasted for 50 seconds. In each trial, the participants had to stare at a black cross (2°) projected in front of them for the first five seconds. The black cross then disappeared, and the participants were free to look wherever they wished in the image.

In the free-viewing task, the participants were instructed to look freely at the image and focus on its content. In the search task, the participants were instructed to detect the location of five objects in each image. The names of these five objects were displayed at the top of the image throughout the trial (Figure 1B, top panel). Before the tasks, the participants were shown a document with the names and pictures of the objects to be searched for. During each trial in the search task, the participants knew that they had to find as many target objects as possible. They could use the strategy of their choice, e.g. searching for one target at a time or search for them all at once. Once a target object had been found, the participant had to confirm the successful outcome by fixing the object for approximately 5 sec. They could look at the names of the five objects as many times as they liked. After each trial, the participants had to report how many objects they had found and to rate their level of confidence concerning their task performance (from 1 (low performance), to 5 (high performance)). If the participant found all five objects before the end of the trial, they had to continue looking for the same five objects again and again until the trial ended.

During each task, the participants were told to relax and stand in a comfortable position. They were allowed to move their head and other body parts to look at the images in the most comfortable way. However, they were not allowed to make voluntarily movements not related to the task (e.g. hand movements or deep breaths). The arms had to stay in the same position during each trial (in their trouser pockets, for example). The investigator checked that the participants performed the task as per the instructions.

Procedure

Once the participants arrived in the experimental room, they were familiarized with the equipment, the procedure, and the visual tasks. Next, the participants were set up with the markers and eye-tracker. The devices were then calibrated with the MATLAB script, and the participants performed the tasks. All the participants sat down and rested for approximately five minutes between tasks. The participants were allowed to stop the study at any time and for any reason.

Dependent variables

To analyse linear postural movements (lower back, upper back, and head), the range (R), SD, and mean velocity (V) in the mediolateral (ML) and anteroposterior (AP) axes were calculated. Two additional postural control variables were calculated: the general path length of postural movements and the ellipse area (Paillard & Noé, 2015). The ellipse area captures 85% of the postural sway (Kinsella-Shaw, Harrison, Colon-Semenza, & Turvey, 2006; Latash, Ferreira, Wieczorek, & Duarte, 2003). To analyse the eye movement time series, we used the same variables: R, SD, and V in both left/right and up/down directions, the path length, and the ellipse area. To analyse the characteristics of fixation, all saccades were excluded before calculating the SD and R. The latter analysis allowed us to determine whether the participants looked more carefully at objects located further away in one task than in another task.

In the search task, several performance variables were evaluated: the number of correct objects found, the percentage of incorrect objects reported, the time spent looking at the correct objects found, the eccentricity and size of correct objects found, and the self-reported confidence score. The time spent looking at the correct objects was computed with a MATLAB script by considering the characteristics of fixation (defined with the Begaze software). The head, upper back and lower back time series were all resampled at 50 Hz, i.e. the frequency of the eye movement time series. Only the last 45 seconds of data from each trial were analyzed. The five-second-long fixations on each object found in the search task could have confounded our results. To control for this, we deleted the longest fixations corresponding to the number of objects found in the eye time series.

Differences between our model of synergy and other models of synergy

The behavioural synergy model is concerned with how postural sway and eye movements are mutually controlled for success in precise visual search tasks performed in the upright stance (Bonnet & Baudry, 2016). It is important to note that our behavioural synergic model does not encompass the coordination between the eyes and the rest of the body included in other synergy models(e.g., Anastasopoulos, Ziavra, Savvidou, Bain, & Bronstein, 2011). Furthermore, the behavioural synergy model does not encompass any type of muscle activity or any reflex (such as the vestibulo-ocular reflex or compensatory eye and head movements) (Einhäuser et al., 2007). The model covers relationships between various behaviours (eye movements and body posture) and has already been validated in healthy young adults (Bonnet, Davin, & Baudry, 2019; Bonnet, Davin, Hoang, et al., 2019; Bonnet, Szaffarczyk, & Baudry, 2017).

Tests to identify stabilizing relationships between eye and postural movements

Outliers (more than 2 SD outside the quartiles) were identified and deleted (Tabachnik & Fidell, 2006). We also tested the normality of the data distribution (using a Shapiro-Wilk test) and the homogeneity of the variance (using the Mauchly test) before our analyses.

To test the behavioural synergy model, we calculated the correlations between the characteristics of eye movements (angular variables) and postural movements (linear variables). We tested our main hypothesis by selecting results from the correlations matrices for the characteristics of eye movements and postural movements performed in each task and each group separately. In our previous studies of young adults (Bonnet, Davin, & Baudry, 2019; Bonnet, Davin, Hoang, et al., 2019; Bonnet, Szaffarczyk, et al., 2017), eye and head movements had the strongest functional synergies. We therefore considered correlations between eye movements and head movements as our primary outcome.

For the PD patients, we also determined whether significant correlations between eye movements and postural movements could be influenced by one or more clinical variables. We performed partial correlations by controlling for the influence of five clinical variables (the MoCA score, the MDS-UPDRS motor score, the mean time since disease onset, the mean daily total levodopa equivalent dose, and the axial rigidity score). We focused on non-significant partial correlations, which might indicate that a clinical variable might weaken (and therefore be a potential cause of) significant correlations between eye movements and postural movements.

All analyses were performed with Statistica software (version 10, Statsoft Inc., Tulsa, OK, USA). The threshold for statistical significance was set to $p<0.01$.

Selection of the data to be analyzed

The SensoMotoric Instruments eye tracker recorded "0-values" (i.e. missing values) when participants' eyes were closed (e.g. during blinking) and when the pupil was greatly dilated. The latter issue was mainly due to the fact that the room lighting was turned off so that the participants could see the images more clearly. Eye movement data files in which there were more than 20% of 0-values (missing values because of blinking or pupil dilation) were excluded, and only high-quality recordings were analyzed. The remaining visual files contained 93.40 ± 5.66% of the data, on average (PD patients: 94.04 ± 5.62%; age-matched participants: 94.27 ± 5.36%). For eye movement data, outliers accounted for respectively 2.04% and 0.75% of the data per spreadsheet for the PD patients and the age-matched participants, respectively. For postural movement data, outliers accounted for respectively 0.72% and 0.75% of the data per spreadsheet for the PD patients and the age-matched participants, respectively.

RESULTS

Coupling between eye movements and postural movements in PD patients and in age-matched controls

In the search task, the PD patients had significant, positive Pearson correlations between eye and postural movements in the search task (Figure 2A, B, C, D, E and F). There were three significant positive correlations between the eyes and the upper back and three other significant positive correlations between the eyes and the lower back (Figure 2A, B, C, D, E and F). In contrast, the age-matched controls did not exhibit any significant correlations between eye movements and postural movements in the search task. In the free-viewing control task, no significant correlations were found in either group, *ns*.

When controlling for the influence of the four clinical variables (see the Methods), the six above-mentioned correlations remained statistically significant. Hence, the clinical variables had no influence on the significant coupling shown in Figures 2A, B, C, D, E and F.

Additional analyses

Description of eye and head angular yaw movements when performing the tasks

We analysed the angular rotations of the eyes and head (using the R and SD in the yaw (left-right) directions) in the free-viewing and search tasks. This descriptive analysis merely served to provide information on how much the participants rotated their eyes and head when exploring large images in visual tasks. Overall, the participants rotated their eye and body segments by between 90° and 110° (Table 1).

Table 1. Angular movements (rotations) of eye and head movements in the left-right (eye) and yaw (head) directions.

	In the free-viewing task				In the search task			
	Eye movements		Head movements		Eye movements		Head movements	
	R	SD	R	SD	R	SD	R	SD
PD patients	48.51°	10.56°	27.8°	3.39°	51.40°	9.68°	32.13°	3.96°
Age-matched controls	42.41°	7.99°	45.08°	5.29°	47.02°	7.87°	42.26°	5.44°

Note. R and SD correspond to the range and standard deviation. PD patients are patients with Parkinson's Disease.

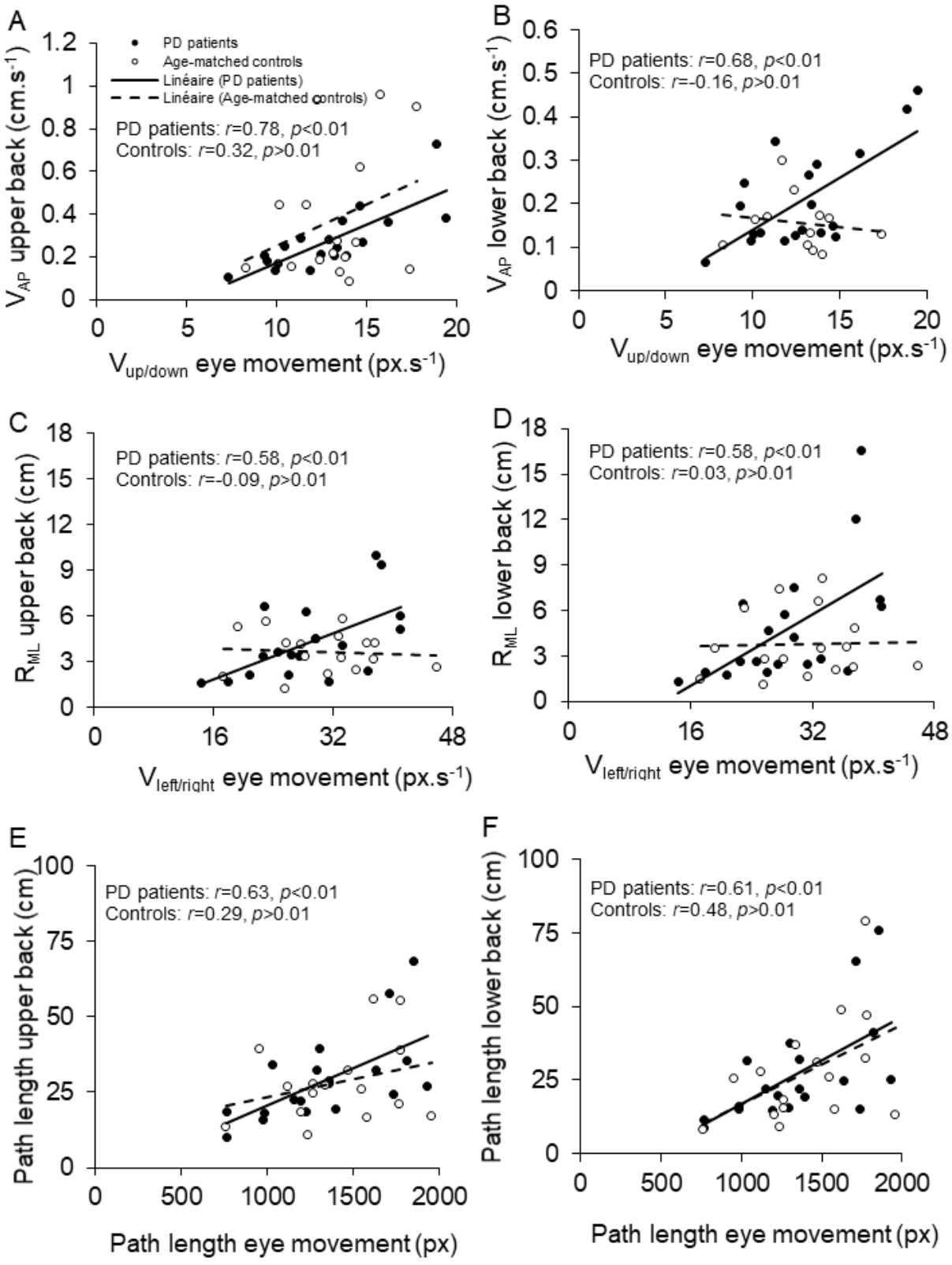

Figure 2. Significant correlations (according to Pearson's coefficient) between eye movements and body (lower back, upper back and/or head) movements in the precise search task in PD patients). Panel A shows a significant correlation between the mean velocity of eye movement in the up-down direction (Vup-down; in pixels×s^{-1}) and the mean velocity of the upper back movement in the anteroposterior (AP) axis (V_{AP} of the upper back, in $cm.s^{-1}$).

Panel B shows a significant correlation between Vup-down for eye movement and V_{AP} for the lower back movement. Panel C shows a significant correlation between the mean velocity of eye movement in the left-right direction (Vleft-right) and the range of the upper back movement in the mediolateral axis (R_{ML}, in cm). Panel D shows a significant correlation between Vleft-right for eye movement and R_{ML} for the lower back movement. Panel E shows a significant correlation between the path length of eye movement and the path length of upper back movement. Panel F shows a significant correlation between the path length of eye movement and the path length of lower back movement. All correlations were significant at $p < 0.01$.

Performance in the search task

In the search task, the PD patients performed worse than the age-matched controls with regard to several variables (Table 2). In fact, the PD patients found fewer objects than the age-matched controls (Table 2). The PD patients also made more mistakes than the age-matched controls about the objects found and exaggerated the number of objects found but these differences were not tested statistically. Despite the patients' worse performance, their confidence scores were similar to those of the age-matched controls (Table 2).

Table 2. Visual performances in the precise search task.

	Patients with Parkinson's disease	Age-matched controls	One-way ANOVA
Mean number of objects found	3.30±0.67	4.16±0.45	$F(1,38)=22.27$, $p<0.01$
Confident score	4.93±0.19	4.96±0.07	$F(1,38)=0.71$, $p>0.01$
Proportion of inaccurate objects found	3.13 %	0.78 %	
Proportion of exaggeration	11.25 %	4.51 %	
Mean duration spent to look at each object found	4.47±0.93 sec	5.04±0.70 sec	$F(1,38)=4.8$, $p>0.01$
Eccentricity of the objects found	Centered: 62±22 % Middly centered: 68±22 % Excentred: 68±20 %	Centered: 87±18 % Middly centered: 79±17 % Excentred: 84±19 %	
Size of the objects found	Smaller: 58±16 % Mid-size: 67±23 % Bigger: 74±22 %	Smaller: 82±16 % Mid-size: 80±20 % Bigger: 89±13 %	

Note. The proportion of inaccurate objects found was calculated as follows: total number of inaccurate objects found / total number of objects searched. The proportion of exaggeration was calculated as follows: number of objects declared to be found - number of objects really found)/total number of objects found. The eccentricity of the objects found corresponded to the proportion of the total number of objects in each of the three categories. The object was centered, middly centered or excentred when the closer limit of the object from the center of the panoramic display was < 20°, [20°-40°] and [40°-60°] (on the left or right of the panoramic display), respectively. The size of the objects found corresponded to the proportion

of the total number of objects in each of the three categories. The object was smaller, mid-size or bigger when their size was < 5°, [5°-10°] and > 10°, respectively.

DISCUSSION

In the visual search task, the PD patients exhibited only positive (destabilizing) correlations between eye movements and upper/lower back movements, while the age-matched controls did not exhibit any significant (i.e. stabilizing or destabilizing) correlations. Hence, the more the PD patients rotated their eyes to look at their environment, the more they swayed. The age-matched controls were better in controlling their posture because they did not exhibit any destabilizing relationships for eye movements vs. body movements. In general, the age-matched controls had a higher level of visual performance than the PD patients in the search task.

Positive correlations between eye movements and postural movements in the PD patients

In the visual search task, the PD patients showed positive correlations between eye movements and both upper body and lower body movements (see Figure 2). Hence, all the observed relationships between eye and postural movements were destabilizing. These results are not in line with those of other studies of PD-related impairments in the synergic control of the upright stance (Falaki et al., 2016, 2017b). Falaki et al. studied multimuscle synergies controlling centre of pressure movements and evidenced reduced synergy for the maintenance of postural control (Falaki et al., 2016, 2017b) and for anticipatory synergy adjustments (Falaki et al., 2016). These studies specifically focused on postural control. Our present results complement these literature reports by showing that PD impairs higher-order relationships between eye movements and postural movements and not only multimuscle synergies for postural control.

We did not observe any significant relationships between clinical variables and impaired synergy in PD patients (see the Results section). This result was expected, as all the patients had early-stage disease. Previous studies have already shown the absence of a relationship between clinical variables and postural variables in PD patients at Hoehn and Yahr stages I and II (Bonnet, Delval, & Defebvre, 2015; Chastan, Debono, Maltête, & Weber, 2008). This finding is consistent with Latash and Huang (2015)'s suggestion that impairments in synergy are as important as clinical impairments. The evaluation of impaired synergy (i.e. combined impairments in eye movements and postural movements) complements the evaluation of clinical impairments.

The existence of destabilizing relationships between eye movements and upper/lower body movements in PD patients might be due to impairments in the basal ganglia which notably have an important role in the control of both eye and postural movements (Hikosaka et al., 2000; Visser & Bloem, 2005). When the basal ganglia are damaged, the affected individuals perform more irrelevant, reflexive saccades, which limits their ability to gather relevant, goal-directed information (Hunt et al., 2018). Patients are limited in their acquisition and integration of visual information from the environment (Hunt et al., 2018). It has been proposed that the basal ganglia have a role in the organization of muscle synergies in both humans and other animals (Mileti et al., 2020). Impairments in the basal ganglia, particularly in the caudate nucleus, substantia nigra pars reticulata and putamen (Pasquini et al., 2019; Wang et al., 2018) might explain the observed PD-related limitations in adaptation of the magnitude of saccadic eye movement and postural control during a precise visual search task. These structures are also anatomically and functionally interconnected (French &

Muthusamy, 2018). The existence of destabilizing relationships between eye and upper/lower body movements in PD patients might be due to impairments in the pedunculopontine nucleus (Ewenczyk et al., 2017; see also Gallea et al., 2017). Future studies will need to establish which structures are correlated with PD-related impairments in synergic eye and postural movements.

Significant correlations between eye movements and postural movements are absent in older adults.

On one hand, our results showed that the age-matched controls did not show any destabilizing relationships at any level in the search task; hence, the controls were more capable than the PD patients to control their stance. On the other hand, the age-matched controls did not show any statistically significant stabilizing relationships between eye and postural movements in the search task (see Results section). The latter result contrasts with our previous findings in young adults (Bonnet, Davin, & Baudry, 2019; Bonnet, Davin, Hoang, et al., 2019; Bonnet, Szaffarczyk, et al., 2017). In these three earlier studies, young adults showed significant stabilizing correlations between eye movements and postural movements in general and between eye and head movements in particular.

The literature data have evidenced an age-related reduction in functional synergies for postural control and/or motor action (Asaka & Wang, 2008; Olafsdottir, Yoshida, Zatsiorsky, & Latash, 2007). In our study, we did not find an age-related reduction in synergic eye-posture movements but we found an absence of such synergies. Thus, the absence of stabilizing (i.e. synergic) eye-postural movements in older adults was not expected. This result clearly shows that synergic relationships are fragile and can deteriorate with age. In a review, Seidler et al. (2010) suggested that basal ganglia function is affected by age. Our present results in a population of age-matched older adults might testify to the presence of a neurological impairment that is only visible at the integrated level. Therefore, an analysis of behavioural synergy might be a powerful tool for detecting age-related impairments in eye and postural movements.

Results in the free-viewing task

In the free-viewing (control) visual task, the absence of significant relationships in the two groups was expected because this task did not require any synergic behavioural relationships between eye and postural movements (Bonnet & Baudry, 2016). Our results show that precise, cognitively demanding search tasks can highlight subtle, PD-related impairments in the synergy between eye and postural movements.

Study limitations

Firstly, we did not control for (and could not determine) the respective contributions of goal-directed mechanisms and reflex mechanisms (such as the vestibulo-ocular reflex). The mechanisms' respective contributions are difficult to investigate because PD-related impairments can come from not only a combination of changes in oculomotor, postural and even vestibular systems (we believe) but also from a particular impairment (e.g. in the vestibular system). It is noteworthy that we observed PD-related impairments in the synergy between eye and upper/lower body movements but not in the synergy between eye and head movements. Hence, our findings might not be due to PD-related impairments in the vestibular system. Secondly, the medication taken by our patients might have influenced our results. This was not really an issue, since the relationships between eye movements and postural movements were already weaker in on-medication PD patients than in age-matched controls.

Hence, levodopa medication either does not change muscle synergies (Mileti et al., 2020; Rodrigues et al., 2013) or improves them (Falaki, Huang, Lewis, & Latash, 2017a; Latash & Huang, 2015). Therefore, we would have expected to see even stronger destabilizing relationships between eye movements and postural movements if the PD group had been off-medication. Future studies should focus on the contribution of medication. Thirdly, we did not find any significant stabilizing or destabilizing correlations between eye and postural movements in age-matched controls. We assume that this result was not biased because we found (i) significant destabilizing relationships in PD patients (see Figure 2) and (ii) significant stabilizing relationships in all previous studies with no more than 16 young adults (Bonnet, Davin, & Baudry, 2019; Bonnet, Davin, Hoang, et al., 2019; Bonnet, Szaffarczyk, et al., 2017).

Conclusion and future directions

We chose to perform ecological search and free-viewing tasks (rather than other visual tasks, such as gazing at specific targets displayed at a large visual angle and at high frequency) because people are more often used to looking freely at rich visual backgrounds in day-to-day situations. In this ecological context, our results are compelling insofar as they showed impairments in patients with mild PD (Hoehn and Yahr stage II, on average). The destabilizing relationships between eye movement and upper/lower body movements may contribute to the falls reported in PD patients, especially those with later-stage disease (Hoehn and Yahr stage > II). Here, we showed that the further the PD patients explored their environment, the more they swayed. We also know that the more PD patients sway, the more often they fall (Contreras & Grandas, 2012; Duncan et al., 2011). In conclusion, our first recommendation for PD patients is to avoid quick gaze shifts and especially high-amplitude gaze shifts involving rotation of the head and full body. This will certainly be difficult to comply with this recommendation in daily life. However, it is better to inform PD patients of the negative consequences of large, quick gaze shifts on their objective postural stability than to not inform them. A second recommendation (for physical therapists, this time) is to train PD patients to perform exercises that involve a combination of eye and postural movements, rather than exercises that involve eye movements alone or postural movements alone. These combined exercises might be more effective than separate exercises in enabling PD patients to recover goal-directed postural control.

ACKNOWLEDGMENT

We wish to thank Dr David Fraser (Biotech Communication, Damery, France) for his helpful advice on the English language in this paper. We thank Tanguy Davin (assistant engineer) for his help with programming MATLAB scripts to run the study, to automatize procedures both to run the study and to analyze the data. He also helped in writing the Method section. We thank France Parkinson for the grant that allowed us to perform this study (convention n° RD 1603). We also thank the ‘Conseil Regional des Hauts-de-France’ for their visionnAIRR grant (convention n°16000913).

LIST OF ABBREVIATIONS

AP = anteroposterior; ML = medio-lateral; MoCA = Montreal Cognitive Assessment score; PD = Parkinson Disease; R = range; SD = standard deviation; UPDRS = United Parkinson Disease Rating Scale; V = mean velocity.

CONFLICT OF INTEREST

In the present manuscript, there is no conflict.

PUBLIC ACCESS REPOSITORY

Data of the results are available on a public access repository (Figshare) and can be found at: https://figshare.com/articles/dataset/Parkinson-posture/14269973

CONTRIBUTION OF THE AUTHORS

- Cédrick T. Bonnet: all parts of the work: conception, acquisition of all participants, analysis, interpretation, draft of the full manuscript, revision, collaboration, integrity of all parts of the manuscript, final approval.
- Arnaud Delval: conception, recruitment and inclusion (medical assessment) of the PD patients, acquisition, analysis, interpretation, revision of the full manuscript for important intellectual content, collaboration, integrity of all parts of the manuscript, agreement to be accountable for all aspects of the manuscript, final approval.
- Tarkeshwar Singh: analysis and interpretation of data for the manuscript, revision of the full manuscript for important intellectual content, collaboration, integrity of all parts of the manuscript, agreement to be accountable for all aspects of the manuscript, final approval.
- Luc Defebvre: principal investigator of the study in the hospital, conception, recruitment and inclusion (medical assessment) of the PD patients, acquisition, analysis, interpretation, revision of the full manuscript for important intellectual content, collaboration, integrity of all parts of the manuscript, agreement to be accountable for all aspects of the manuscript, final approval.

REFERENCES

Anastasopoulos, D., Ziavra, N., Savvidou, E., Bain, P., & Bronstein, A. M. (2011). Altered eye-to-foot coordination in standing parkinsonian patients during large gaze and whole-body reorientations. *Movement Disorders*, *26*(12), 2201-2211. doi: 10.1002/mds.23798

Asaka, T., & Wang, Y. (2008). Effects of Aging on Feedforward Postural Synergies. *Journal of Human Kinetics*, *20*(1), 63-70. doi: 10.2478/v10078-008-0018-6

Bejjani, B. P., Gervais, D., Arnulf, I., Papadopoulos, S., Demeret, S., Bonnet, A. M., … Agid, Y. (2000). Axial parkinsonian symptoms can be improved : The role of levodopa and bilateral subthalamic stimulation. *Journal of Neurology, Neurosurgery, and Psychiatry*, *68*(5), 595-600. doi: 10.1136/jnnp.68.5.595

Bonnet, C. T., & Baudry, S. (2016). A functional synergistic model to explain postural control during precise visual tasks. *Gait & Posture*, *50*, 120-125. doi: 10.1016/j.gaitpost.2016.08.030

Bonnet, C. T., Davin, T., & Baudry, S. (2019). Interaction between eye and body movements to perform visual tasks in upright stance. *Human Movement Science*, *68*, 102541. doi: 10.1016/j.humov.2019.102541

Bonnet, C. T., Davin, T., Hoang, J.-Y., & Baudry, S. (2019). Relations between Eye Movement, Postural Sway and Cognitive Involvement in Unprecise and Precise Visual Tasks. *Neuroscience*, *416*, 177-189. doi: 10.1016/j.neuroscience.2019.07.031

Bonnet, C. T., Delval, A., & Defebvre, L. (2015). Parkinson's Disease-Related Impairments in Body Movement, Coordination and Postural Control Mechanisms When Performing 80° Lateral Gaze Shifts. *IEEE Transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society*, *23*(5), 849-856. doi: 10.1109/TNSRE.2014.2369455

Bonnet, C. T., Delval, A., Szaffarczyk, S., & Defebvre, L. (2017). Levodopa has primarily negative influences on postural control in patients with Parkinson's disease. *Behavioural Brain Research*, *331*, 67-75. doi: 10.1016/j.bbr.2017.05.033

Bonnet, C. T., Szaffarczyk, S., & Baudry, S. (2017). Functional Synergy Between Postural and Visual Behaviors When Performing a Difficult Precise Visual Task in Upright Stance. *Cognitive Science*, *41*(6), 1675-1693. doi: 10.1111/cogs.12420

Chastan, N., Debono, B., Maltête, D., & Weber, J. (2008). Discordance between measured postural instability and absence of clinical symptoms in Parkinson's disease patients in the early stages of the disease. *Movement Disorders*, *23*(3), 366-372. doi: 10.1002/mds.21840

Contreras, A., & Grandas, F. (2012). Risk of Falls in Parkinson's Disease : A Cross-Sectional Study of 160 Patients. *Parkinson's Disease*, *2012*, 1-10. doi: 10.1155/2012/362572

Devos, H., Vandenberghe, W., Tant, M., Akinwuntan, A. E., De Weerdt, W., Nieuwboer, A., & Uc, E. Y. (2013). Driving and off-road impairments underlying failure on road testing in Parkinson's disease : Driving Skill Impairments in PD. *Movement Disorders*, *28*(14), 1949-1956. doi: 10.1002/mds.25701

Duncan, R. P., Leddy, A. L., Cavanaugh, J. T., Dibble, L. E., Ellis, T. D., Ford, M. P., … Earhart, G. M. (2011). Accuracy of Fall Prediction in Parkinson Disease : Six-Month and 12-Month Prospective Analyses. *Parkinson’s Disease*, *2012*, e237673. doi: 10.1155/2012/237673

Einhäuser, W., Schumann, F., Bardins, S., Bartl, K., Böning, G., Schneider, E., & König, P. (2007). Human eye-head co-ordination in natural exploration. *Network: Computation in Neural Systems*, *18*(3), 267-297. doi: 10.1080/09548980701671094

Ekker, M. S., Janssen, S., Seppi, K., Poewe, W., de Vries, N. M., Theelen, T., … Bloem, B. R. (2017). Ocular and visual disorders in Parkinson's disease : Common but frequently

overlooked. *Parkinsonism & Related Disorders, 40*, 1-10. doi: 10.1016/j.parkreldis.2017.02.014

Ewenczyk, C., Mesmoudi, S., Gallea, C., Welter, M.-L., Gaymard, B., Demain, A., … Vidailhet, M. (2017). Antisaccades in Parkinson disease : A new marker of postural control? *Neurology, 88*(9), 853-861. doi: 10.1212/WNL.0000000000003658

Falaki, A., Huang, X., Lewis, M. M., & Latash, M. L. (2016). Impaired synergic control of posture in Parkinson's patients without postural instability. *Gait & Posture, 44*, 209-215. doi: 10.1016/j.gaitpost.2015.12.035

Falaki, A., Huang, X., Lewis, M. M., & Latash, M. L. (2017a). Dopaminergic modulation of multi-muscle synergies in postural tasks performed by patients with Parkinson's disease. *Journal of Electromyography and Kinesiology: Official Journal of the International Society of Electrophysiological Kinesiology, 33*, 20-26. doi: 10.1016/j.jelekin.2017.01.002

Falaki, A., Huang, X., Lewis, M. M., & Latash, M. L. (2017b). Motor equivalence and structure of variance : Multi-muscle postural synergies in Parkinson's disease. *Experimental Brain Research, 235*(7), 2243-2258. doi: 10.1007/s00221-017-4971-y

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1 : Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160. doi: 10.3758/BRM.41.4.1149

French, I. T., & Muthusamy, K. A. (2018). A Review of the Pedunculopontine Nucleus in Parkinson's Disease. *Frontiers in Aging Neuroscience, 10*, 99. doi: 10.3389/fnagi.2018.00099

Gallea, C., Ewenczyk, C., Degos, B., Welter, M.-L., Grabli, D., Leu-Semenescu, S., … Vidailhet, M. (2017). Pedunculopontine network dysfunction in Parkinson's disease with postural control and sleep disorders. *Movement Disorders: Official Journal of the Movement Disorder Society, 32*(5), 693-704. doi: 10.1002/mds.26923

Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the Basal Ganglia in the Control of Purposive Saccadic Eye Movements. *Physiological Reviews, 80*(3), 953-978. doi: 10.1152/physrev.2000.80.3.953

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease : A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry, 55*(3), 181-184. doi: 10.1136/jnnp.55.3.181

Hunt, D., Stuart, S., Nell, J., Hausdorff, J. M., Galna, B., Rochester, L., & Alcock, L. (2018). Do people with Parkinson's disease look at task relevant stimuli when walking? An exploration of eye movements. *Behavioural Brain Research, 348*, 82-89. doi: 10.1016/j.bbr.2018.03.003

Kinsella-Shaw, J. M., Harrison, S. J., Colon-Semenza, C., & Turvey, M. T. (2006). Effects of Visual Environment on Quiet Standing by Young and Old Adults. *Journal of Motor Behavior, 38*(4), 251-264. doi: 10.3200/JMBR.38.4.251-264

Latash, M. L., & Huang, X. (2015). Neural control of movement stability : Lessons from studies of neurological patients. *Neuroscience, 301*, 39-48. doi: 10.1016/j.neuroscience.2015.05.075

Latash, Mark L., Ferreira, S. S., Wieczorek, S. A., & Duarte, M. (2003). Movement sway : Changes in postural sway during voluntary shifts of the center of pressure. *Experimental Brain Research, 150*(3), 314-324. doi: 10.1007/s00221-003-1419-3

Magrinelli, F., Picelli, A., Tocco, P., Federico, A., Roncari, L., Smania, N., … Tamburin, S. (2016). Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation. *Parkinson's Disease, 2016*, 1-18. doi: 10.1155/2016/9832839

McIlroy, W. E., & Maki, B. E. (1997). Preferred placement of the feet during quiet stance : Development of a standardized foot placement for balance testing. *Clinical Biomechanics (Bristol, Avon)*, *12*(1), 66-70. doi: 10.1016/s0268-0033(96)00040-x

Mileti, I., Zampogna, A., Santuz, A., Asci, F., Del Prete, Z., Arampatzis, A., … Suppa, A. (2020). Muscle Synergies in Parkinson's Disease. *Sensors*, *20*(11), 3209. doi: 10.3390/s20113209

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA : A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699. doi: 10.1111/j.1532-5415.2005.53221.x

Olafsdottir, H., Yoshida, N., Zatsiorsky, V. M., & Latash, M. L. (2007). Elderly Show Decreased Adjustments of Motor Synergies in Preparation to Action. *Clinical biomechanics (Bristol, Avon)*, *22*(1), 44-51. doi: 10.1016/j.clinbiomech.2006.08.005

Paillard, T., & Noé, F. (2015). Techniques and Methods for Testing the Postural Function in Healthy and Pathological Subjects. *BioMed Research International*, *2015*, 1-15. doi: 10.1155/2015/891390

Pasquini, J., Durcan, R., Wiblin, L., Stokholm, M. G., Rochester, L., Brooks, D. J., … Pavese, N. (2019). Clinical implications of early caudate dysfunction in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *90*(10), 1098-1104. doi: 10.1136/jnnp-2018-320157

Rodrigues, S. T., Aguiar, S. A., Polastri, P. F., Godoi, D., Moraes, R., & Barela, J. A. (2013). Effects of saccadic eye movements on postural control stabilization. *Motriz: Revista de Educação Física*, *19*(3), 614-619. doi: 10.1590/S1980-65742013000300012

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., … Lipps, D. B. (2010). Motor control and aging : Links to age-related brain structural, functional, and biochemical effects. *Neuroscience & Biobehavioral Reviews*, *34*(5), 721-733. doi: 10.1016/j.neubiorev.2009.10.005

Tabachnik, B. B. & Fidell, L. S. (2006). *Using Multivariate Statistics, 6th Edition*. Consulté à l'adresse /content/one-dot-com/one-dot-com/us/en/higher-education/program.html

Thibaut, M., Tran, T.-H., Szaffarczyk, S., & Boucart, M. (2018). Impact of age-related macular degeneration on object searches in realistic panoramic scenes. *Clinical and Experimental Optometry*, *101*(3), 372-379. doi: https://doi.org/10.1111/cxo.12644

Visser, J. E., & Bloem, B. R. (2005). Role of the Basal Ganglia in Balance Control. *Neural Plasticity*, *12*(2-3), 161-174. doi: 10.1155/NP.2005.161

Wang, J., Zhang, J.-R., Zang, Y.-F., & Wu, T. (2018). Consistent decreased activity in the putamen in Parkinson's disease : A meta-analysis and an independent validation of resting-state fMRI. *GigaScience*, *7*(6). doi: 10.1093/gigascience/giy071

Weil, R. S., Schrag, A. E., Warren, J. D., Crutch, S. J., Lees, A. J., & Morris, H. R. (2016). Visual dysfunction in Parkinson's disease. *Brain: A Journal of Neurology*, *139*(11), 2827-2843. doi: 10.1093/brain/aww175

Yang, Y., Tang, B., & Guo, J. (2016). Parkinson's Disease and Cognitive Impairment. *Parkinson's Disease*, *2016*, 1-8. doi: 10.1155/2016/6734678

GRAPHICAL ABSTRACT. Our results showed that in the precise visual search task i) the PD patients showed significant positive linear correlations between eye movement and upper back/lower back movements (discussed as destabilizing relations); ii) the age-matched controls showed no significant relations in all our analyses