Journal of Neurology (2025) 272:236
https://doi.org/10.1007/s00415-025-12973-w

ORIGINAL COMMUNICATION

Reflexive and voluntary saccades as a proxy for bradykinesia and apathy in Parkinson's disease

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Received: 27 September 2024 / Revised: 21 January 2025 / Accepted: 12 February 2025

Abstract

Background Parkinson's disease (PD) encompasses motor (e.g., bradykinesia) and non-motor (e.g., apathy) symptoms.
Objective We aimed to use reflexive and voluntary saccades as a proxy for bradykinesia and apathy.
Methods Seventeen PD patients and thirteen controls (matched for age and educational level) were recruited. We assessed apathy using the Dimensional Apathy Scale (DAS) and bradykinesia using MDS-UPDRS III. Subjects were asked to fixate successively two green points (cues, 40° apart) alternating at 1 Hz. After 20 s, all stimuli disappeared, and participants were required to continue fixating on the previous locations of the cues at the same frequency for another 20 s. We measured the Maximal Amplitude (MA) (saccade amplitude from side to side) and its period. Linear mixed models assessed the effect of the group (patient/control), cue, DAS, and bradykinesia score.
Results Overall, the DAS was similarly correlated to the period ($p = 0.0157$) and the MA ($p = 0.0002$) in the absence of a cue. However, this correlation was significant only in the patient subgroup for the MA ($p = 0.0005$). In the absence of cue, bradykinesia was similarly correlated to the period ($p = .0001$) and the MA ($p = 0.0004$). However, the period was better correlated to bradykinesia than the DAS.
Conclusions While the saccade period best correlates with bradykinesia, maximal amplitude in the absence of cue better reflects the severity of apathy. Our paradigm may be a promising objective biomarker for assessing bradykinesia and apathy in PD.

Keywords Parkinson's disease · Bradykinesia · Apathy · Eye movements · Saccades

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Published online: 01 March 2025

Introduction

Parkinson's disease (PD) is a neurodegenerative disease caused by degeneration of the dopamine neurons in the substantia nigra pars compacta. This deficit generates motor dysfunction, including rest tremors, rigidity, bradykinesia, and non-motor dysfunction, such as apathy [1]. The latter refers to a loss of motivation that leads to a quantitative reduction of goal-directed behavior [2, 3] and, subsequently, the patient's quality of life [4]. Apathy is highly prevalent (up to 70 percent of PD patients [5]) and very debilitating [6].

A recent consensus was reached to define apathy clinically, with three components (lasting for at least four weeks) and the requisition of at least one to make a clinical diagnosis formally: (1) diminished initiative, (2) diminished interest, and (3) diminished emotional responsiveness [7]. Apathy can be divided into two types: (1) motivational apathy, which affects mainly de novo PD patients and is strongly associated with dopamine deficit, suggested by the improvement in motivational apathy with selective D3 dopamine agonist, and (2) cognitive apathy, mainly present in late-stage PD patients, associated with executive dysfunction and poorly responsive to dopamine [8].

Apathy is part of the neuropsychiatric triad of PD (motivational apathy, anxiety, and depression), also termed the hypodopaminergic behavioral syndrome. Recently, Béreau et al. proposed to expand this triad to a motivational, behavioral syndrome of PD, encompassing motivational apathy, anxiety, anhedonia, depression, and fatigue since there is an overlap between these symptoms [8]. Moreover, fatigue overlaps with the neuropsychiatric triad and motor symptoms since it is defined as a perception of fatigue (subjective dimension) combined with motor or cognitive fatigability (objective dimension) [9].

Bradykinesia is described as a slowness of voluntary movement and a sequence effect. The latter is a progressive speed or amplitude diminution (hypokinesia) during repetitive movements [10]. Akinesia is a delay in the initiation of movement that could eventually lead to an absence of movement. However, akinesia is often included in the concept of bradykinesia since it is difficult to distinguish clinically. These characteristics are associated with a motivational factor [10, 11], particularly marked by the sequence effect [12]. Several hypotheses have been suggested to explain bradykinesia, including (1) Bologna and colleagues' "network hypothesis", (2) Hallett and colleagues' description of bradykinesia as an energization insufficiency [11] and (3) Mazzoni and colleagues' motivation-vigour coupling, linked to an aberrant trade-off between speed and accuracy [13]. Indeed, bradykinesia is more marked when performing dual tasks [14].

Interestingly, Berardelli et al. showed that bradykinesia reflects dysfunction of at least two brain areas: underactivation of the supplementary motor area (SMA) and the dorsolateral prefrontal cortex (DLPFC) [15]. As the SMA is implicated in internally triggered movements, patients have more difficulty with movement planning compared to an "externally triggered mode" [16]. Therefore, parkinsonian patients rely more on external cues, allowing them to bypass the SMA [17]. Their skeletal muscle movements tend to slow, and their execution time increases as the cue is diminished [18]. In addition, in PD patients, the lack of auto-activation related to apathy may increase the latency of eye movement initiation without a cue [19].

Unsurprisingly, even if PD patients tend to have clinically nearly normal eye movements [20], motor system abnormalities appear to be at least partly transferable to the ocular motor system. Indeed, several studies have shown that eye movements in PD are abnormal and may, in the context of saccades, represent bradykinesia at the ocular level [21, 22]. DeJong et al. observed an "initiation delay" and an "increased transit time" in patients who were asked to look alternatively at two points as fast as possible [23]. In addition, Shibasaki observed increased reaction time during saccades in PD [24, 25]. Eye movements have the advantage over appendicular movement analysis in providing objective measures that are easily reproducible and quantifiable and allow for practical paradigms to assess cued and non-cued movements.

This study aims to examine the association of bradykinesia, assessed by the MDS-UPDRS [26], and apathy, assessed by the Dimensional apathy scale (DAS) [27–29], based on spontaneous eye movements and eye movements driven by a cue.

Method

Seventeen patients were recruited from the Movement Disorders Clinic of the Geneva University Hospital. Each patient had a Parkinson's Disease diagnosis based on the UK Brain Bank criteria, 6 of them being treated by deep brain stimulation, 11 patients being non-surgical [30]. The exclusion criteria were patients unable to consent and patients with cognitive impairment according to the MoCA test under 24 [31, 32] or another neurological disease. Visual acuity was assessed by a Snellen chart held at 36 cm of the patient's eyes and was considered as suitable above 20/70.

Every patient has been evaluated on-treatment, with a 50% increase of their usual dose, and off-treatment, after an overnight withdrawal The order in which patients completed the evaluations was randomly allocated among patients using a random number generator. To balance the conditions, every control was evaluated twice over two days.

Thirteen controls were recruited, matching with the patient group on age and educational level (education level in years: level 1 < 8, level 2 between 9 and 12, level 3 > 13). The study was approved by the local ethical committee of the Canton of Geneva (Project-ID 2019-01039).

Scales

To assess bradykinesia, the MDS-UPDRS part III was recorded for every patient in both conditions, from which we extracted the bradykinesia subscore (bradykinesia) [26] obtained by adding items 3.4 to 3.8 and item 3.14.

Apathy was quantified with the Dimensional Apathy Scale (DAS) when the patient was on medication. This multi-dimensional scale minimizing motor impairment encompasses three sub-scores (executive, emotion, and initiative). This scale measures all aspects of apathy and has recently been validated for PD [27–29]. The DAS executive sub-score (DAS) significantly differed between both groups and was the only one used for the analysis. Depression and anxiety were measured with the Hamilton Depression and Anxiety Rating Scale [33].

Procedure

Every subject executed the *ping-pong gaze paradigm*, which consisted of two parts. First, two cues appeared successively at 20° on the screen's right and left-hand sides (22 inches) at a 1 Hz frequency for 20 s. Second, the task continued for 20 s without any cue, and the patient was asked to continue looking at the location of the cues at the same frequency and amplitude (shown in Fig. 1). Participants completed one or two short practice trials (4 trials) to confirm task comprehension.

The test was performed with an eye-tracking system composed of a padded helmet with an infrared camera that collects information on eye movements (Mobile EBTH, e(ye)BRAIN, www.eyebrain.com) [34, 35]. The sampling frequency was 300 Hz, and the spatial resolution was 1920 × 1080 pixels. The patients were in a darkened room, and their head was fixed on a chin rest at 60 cm from the screen. Before each measurement, the eye-tracking system was calibrated with 13 calibration points that had to be fixed for 250 ms.

Data acquisition

The eye movements were analyzed using the software *mEyeAnalysis* (shown in Fig. 2), which detects saccades and measures their degrees and duration. We defined a saccade as a gaze shift of at least 1° amplitude. A custom script was written in RStudio to calculate saccade amplitude and latency.

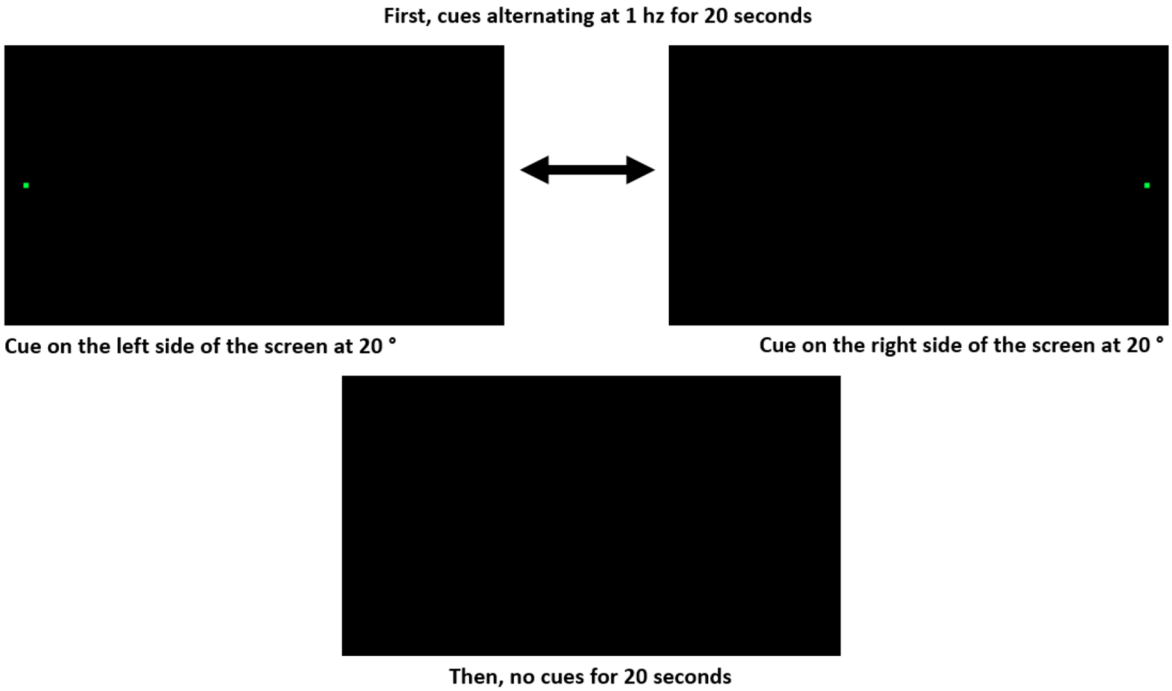

Fig. 1 Sequence of events example. The first two frames at the top display cues alternating from the right to the left side of the screen at a rate of 1 Hz for 20 s. Subsequently, the frame shows no cues for an additional 20-s period

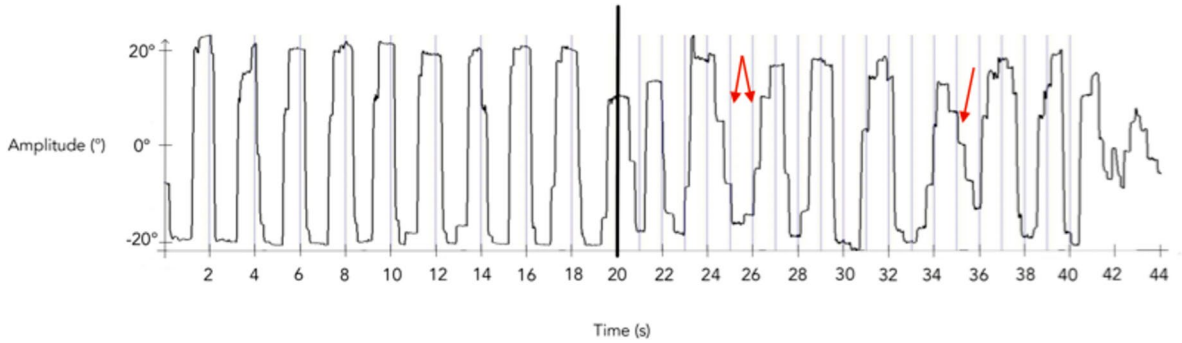

Fig. 2 Eye movement example. Amplitude on the y-axis, time on the x-axis. Arrows show examples of staircase saccades. The red interval shows an example of a period. The green interval shows an example of a maximal amplitude

We defined three outcome variables: the period (i.e., the interval between two consecutive final eye positions), and for each saccade, its maximal amplitude (MA), and peak velocity. Given that most participants experienced staircase saccades when scanning each side of the screen, we defined the MA as the maximum amplitude of the eye movement just before a change in the gaze direction. The MA minimum magnitude was set at 20° across the screen to ensure the gaze crossed the midline. We extracted the peak velocities of the measured saccades as this is recognized as a reliable variable to assess fatigue in eye movements [36].

Data analysis

Data on every saccade of every subject was included in the analyses. Data analysis was divided into three steps: (1) a comparison of the performances between patients and controls, (2) by examining a putative correlation between the eye movement performances and bradykinesia (in patients only) or apathy, and (3) by assessing if apathy (measured by the DAS) or bradykinesia have a different effect on the three outcome variables in the patients' group.

Statistical analysis

For each step, the distribution of the dependent variables (maximal amplitude, period, and peak velocity) was tested with the best fitting distribution by comparing Gaussian and other distributions with the Akaike information criterion (AIC) criteria and Linear Mixed Models (LMM) (one for each dependent variable) were run using the R package "lmer."

For step 1, firstly, the models included fixed effects (main effects) and their interactions. The participant group (patients versus controls), the state (on versus off medication), the executive part of the DAS, and the cue (present versus absent) were set as fixed effects. Putative contrasts from significant main effects or interactions were assessed as post hoc tests using the R tools "emmeans" for the discrete variables and "emtrends" for the continuous ones.

The state variable represented, on the one hand, the on- and off-medication states for patients and, on the other hand, controls' trials as "Day 1" and "Day 2," which were randomly assigned to the variable as "on" versus "off." The patient number was added as a random factor to consider inter-individual variability. Secondly, we ran two robustness tests: (1) Since six patients were under DBS, we ran the same models but added the DBS as a main effect to evaluate its impact on the dependent variables and on the other interactions; (2) The trial order (Day 1 versus Day (2) was added as a main effect to assess a possible practice effect between the first and the second trial.

In addition, to verify if the parameters of the saccades were modified while undertaking the task, we numbered each saccade. We ran an LMM using the saccade number as a random factor.

For step 2, the models included bradykinesia and the cue as fixed effects and their interactions. The state was added as a fixed effect (and its interactions) only if significant in the step 1 models. As for step 1, DBS and trial order were secondly implemented as main effects.

For step 3, to test which of the apathy or the bradykinesia had a more significant effect on the dependent variables, we built three models: Model A containing all of the main effects and the two-way interaction DAS X cue; Model B containing all of the main effects and the two-way interaction Bradykinesia X cue; and Model C, a complete model with all of the main effects and both two-way interactions of interest. AIC and Bayesian information criterion (BIC), as well as LMM comparison, were performed to compare the incomplete models (models A and B) and the complete one (model C).

We controlled the p-values of all the LMM and contrast analyses using the false discovery rate (FDR) [36] to control for multiple comparisons. We then kept only significant values $p < 0.05$.

Results

Table 1 shows the descriptive results of the cohort. Two patients were excluded from the analysis because the high blinking rate led to insufficient data quality. Therefore, fifteen patients were included in the final analysis.

Maximal amplitude (MA)

Step 1

In both groups, the analysis showed a significant main effect of the cue ($F(2155) = 165.10$, $p < 0.0001$). However, the other main effects were all non-significant: group ($F(45) = 1.42$, $p = 0.3918$), state ($F(45) = 1.41$, $p = 0.3918$), and DAS ($F(45) = 0.05$, $p = 0.8632$).

The three-way interaction between the group, the cue, and the DAS ($F(2155) = 14.38$, $p = 0.0005$) was significant. Contrast analysis showed a significant association between the MA and the DAS for patients without a cue ($R = -0.48$, $p = 0.0002$).

The two-way interactions between the DAS and the cue ($F(2155) = 37.57$, $p < 0.0001$) and between the group and the cue ($F(2155) = 7.77$, $p = 0.0164$) were significant (shown in Fig. 3). The contrast analysis of the latter showed a significant difference in the non-cued saccades between patients and controls. The other two-way interactions were non-significant: DAS-group ($F(45) = 4.60$, $p = 0.0924$), DAS-state ($F(45) = 1.65$, $p = 0.3691$), group-state ($F(45) = 0.82$, $p = 0.5364$), state-cue ($F(2155) = 1.73$, $p = 0.3492$).

The robustness tests with the DBS and the trial order showed no effects, respectively ($F(45) = 1.00$, $p = 0.4934$), ($F(45) = 0.32$, $p = 0.6922$), and no modification of the other main effects and interactions.

Saccade number showed no main effect of this variable ($F(2178) = 1.45$, $p = 0.3918$), but there was a significant two-way interaction between this variable and the group ($F(2178) = 6.77$, $p = 0.0269$). The contrast analysis showed a significant association between the MA and the saccade numbers in patients ($R = -0.0182$, $p = 0.0049$).

Step 2

In the patient group, the analysis showed that both the main effects of the cue ($F(1124) = 106.41$, $p < 0.0001$) and that of bradykinesia ($F(25) = 10.49$, $p = 0.0110$) were significant, as well as the two-way interaction between the bradykinesia and the cue ($F(1125) = 79.32$, $p < 0.0001$). The contrast analysis showed a significant association between the MA and the bradykinesia when the cue was absent ($R = -0.310$, $p = 0.0004$).

As in step 1, the robustness tests with the DBS and the trial order showed no effects, respectively ($F(25) = 5.59$, $p = 0.0717$), ($F(25) = 0.08$, $p = 0.8319$), and no modification of the other main effects and interactions.

Step 3

The model comparison showed a significant difference between incomplete and complete models for DAS and Bradykinesia ($\chi^2 = 41.1$, $\chi^2 = 26.8$, $p < 0.0001$).

Table 1 Participants descriptive data

	Patients on	Patients off	Controls	P value
N	17		13	
N on DBS	11		0	
Age	65.06 (10.52)		69.77 (9.84)	0.2358
Time since diagnosis	10.19 (4.15)			
Educational level	2.5 (0.52)		2.69 (0.48)	0.3164
Moca	27.07 (1.87)		27.47 (1.45)	0.0557
DAS executive	8.56 (4.94)		5.08 (3.25)	0.026
DAS emotion	9.31 (3.94)		8 (3.03)	0.7742
DAS initiative	9.5 (4.23)		7.62 (2.02)	0.1918
HAD anxiety	6.75 (3.26)		6.08 (2.69)	0.4135
HAD depression	5.81 (3.89)		2.92 (10.45)	0.0306
Ledd	642.81 (438.73)			
MDS-UPDRS III	20.88 (13.51)	28.88 (12.63)		0.0011

N on DBS number of patients on deep brain stimulation, *MOCA* Montréal cognitive assessment, *DAS* dimensional apathy scale, *HAD* Hamilton anxiety depression scale, *LEDD* Levodopa equivalent daily dose, *MDS-UPDRS III* movement disorder society—unified Parkinson's disease rating scale part III (motor examination)

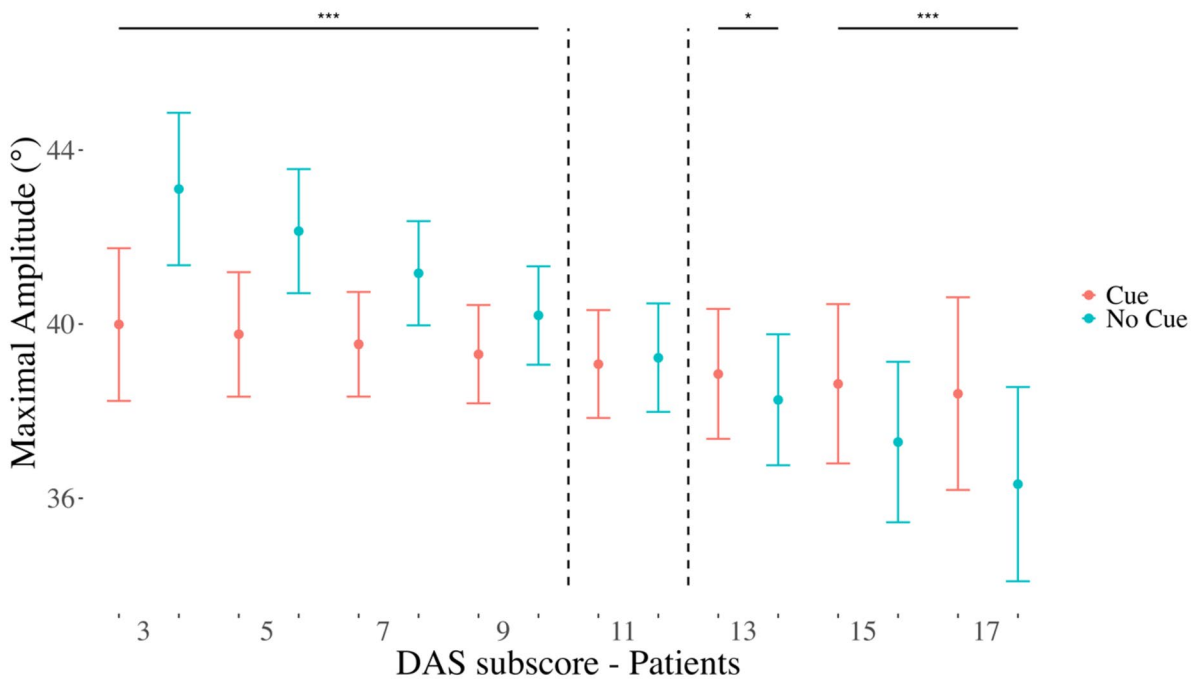

Fig. 3 Interaction between maximal amplitude, DAS, and cue. Maximal amplitude on the y-axis and the DAS executive on the x-axis for patients. Cued saccades in orange, non-cued saccades in blue. The error bars correspond to the confidence intervals. The difference between cue and no-cue is significant for DAS executive scores from 3 to 9 and 13 to 17 (***$p < .0001$, *$p = 0.0349$, FDR corrected). The trend between maximal amplitude and DAS executive for the non-cued saccades is −0.48 ($p = 0.0002$). (*DAS* dimensional apathy scale)

Period

Step 1

None of the main effects was significant: group ($F(46) = 0.12$, $p = 0.9669$), State ($F(46) = 0.01$, $p = 0.9669$), DAS ($F(47) = 2.30$, $p = 0.3728$), and cue ($F(2048) = 2.72$, $p = 0.2925$).

The two-way interaction between the DAS and the cue was significant ($F(2051) = 9.50$, $p = 0.0180$). The contrast analysis depicts a significant association between the period and the DAS for non-cued saccades ($R = 8.9$, $p = 0.0157$). The other two-way interactions were non-significant: DAS-group ($F(47) = 0.17$, $p = 0.9669$), DAS-state ($F(46) = 0.01$, $p = 0.9669$), group-state ($F(46) = 0.06$, $p = 0.9669$), group-cue ($F(2048) = 0.03$, $p = 0.9669$), and state-cue ($F(2049) = 0.02$, $p = 0.9669$).

The robustness tests with the DBS and the trial order showed no effects, respectively ($F(46) = 0.28$, $p = 0.9669$), ($F(46) = 0.00$, $p = 0.9669$), and no modification of the other main effects and interactions.

The analysis with the saccade numbers showed a main effect of this variable ($F(1940) = 14.28$, $p = 0.0028$). The three-way interaction between the saccade numbers, the group, and the cue was non-significant ($F(2061) = 0.33$, $p = 0.9571$).

Step 2

In the patient subgroup, the analysis showed a significant main effect of bradykinesia ($F(26) = 9.39$, $p = 0.0371$). The main effect of the cue was non-significant ($F(1065) = 5.49$, $p = 0.0716$).

The two-way interaction between the bradykinesia and the cue ($F(1073) = 16.51$, $p = 0.0014$) was significant. The contrast analysis showed a significant association between the period and the bradykinesia when the cue is absent ($R = 10.2$, $p = 0.0001$) (shown in Fig. 4).

As in step 1, the robustness tests with the DBS and the trial order showed no effects, respectively ($F(25) = 0.33$, $p = 0.9571$), ($F(25) = 0.15$, $p = 0.9669$), and no modification of the other main effects and interactions.

Step 3

The model comparison showed a significant difference between incomplete and complete models only for

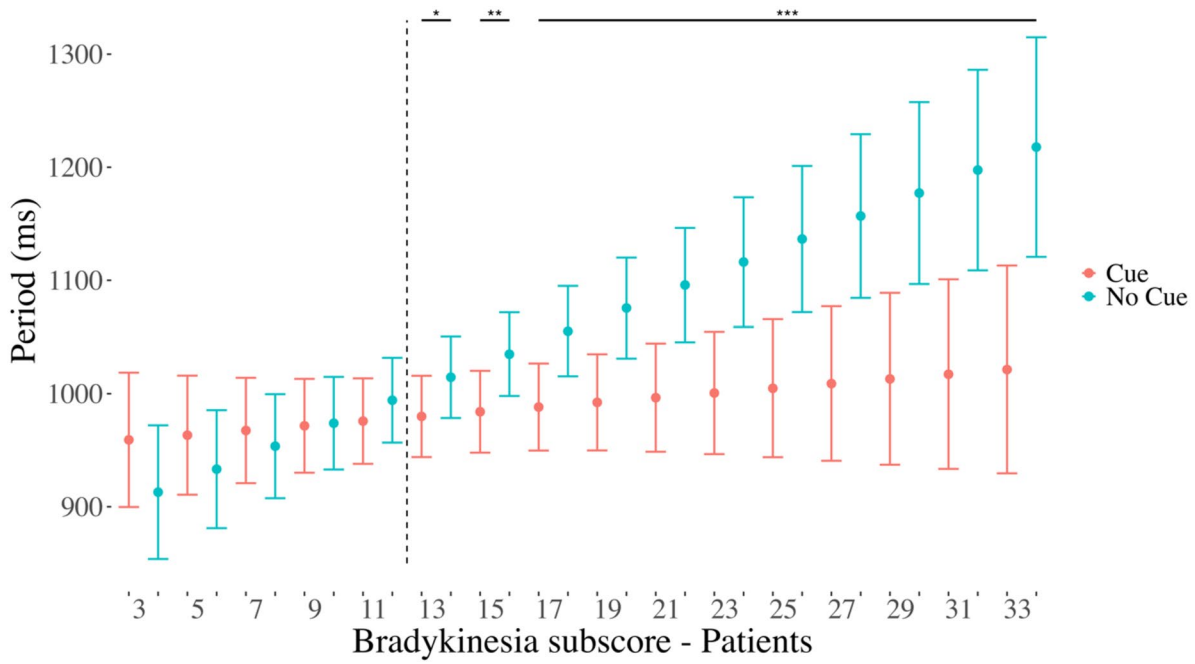

Fig. 4 Interaction between period, bradykinesia, and cue. Period on the y-axis and bradykinesia on the x-axis. Cued saccades in orange, non-cued saccades in blue. The error bars correspond to the confidence intervals. The difference between cue and no-cue is significant for bradykinesia score from 13 to 33 (***p < .0001, **p = 0.0026, *p = 0.0363, FDR corrected). The trend between period and bradykinesia for the non-cued saccades is 10.2 (p = .0001). (Bradykinesia: subscore of the MDS-UPDRS part III)

bradykinesia ($\chi^2 = 11.9$, p = 0.0060). The model comparison for DAS was not significant ($\chi^2 = 1.26$, p = 0.6112).

Peak velocity

Step 1

In both groups, the analysis showed all main effects were non-significant: group (F (46) = 3.34, p = 0.257), State (F (46) = 3.15, p = 0.268), DAS (F (47) = 1.86, p = 0.440) and cue (F (2068) = 8.29, p = 0.070).

The robustness tests with the DBS and the trial order showed no effects, respectively (F (47) = 0.04, p = 0.922), (F (47) = 0.01, p = 0.922), and no modification of the other main effects and interactions.

The analysis with the saccade numbers showed no main effect of this variable (F (2100) = 0.11, p = 0.922).

Step 2

In the patient subgroup, none of the main effects was significant: cue (F (1051) = 4.61, p = 0.197) and bradykinesia (F (27) = 0.25, p = 0.877).

As in step 1, the robustness tests with the DBS and the trial order showed no effects, respectively (F (24) = 1.10, p = 0.577), (F (24) = 0.04, p = 0.922), and no modification of the other main effects and interactions.

Step 3

The model comparison showed no significant difference between incomplete and complete models for DAS and Bradykinesia ($\chi^2 = 3.76$, p = 0.210, $\chi^2 = 0.02$, p = 0.922).

Discussion

Our study shows that the interval between a gaze shift (period) in the absence of a cue is tightly correlated with measures of bradykinesia. In contrast, the maximal amplitude of a saccade in the absence of a cue correlates with the severity of apathy and, to a lesser extent, bradykinesia.

The period evolved similarly in both groups. The impact on the period of the apathy amplitude on the one hand and of the cue on the other is the same in both groups, which does not allow us to distinguish patients from controls. However, only bradykinesia, measured with the MDS-UPDRS-III, significantly modified the period, and only in the patient group. Indeed, as described by Hallett et al. and suggested by Berardelli, bradykinesia is a deficit of muscle energization

(a predominant parameter for repetitive movements) and encompasses both preparation and reaction times before movement execution. The period of eye movements includes both, which may explain why this variable best reflects eye movements bradykinesia [11, 14].

The period is more reliable than the MA as a measure of bradykinesia. Indeed, the differences between cued and non-cued periods are significant for bradykinesia scores above 11, while the differences for the MA are only significant for scores above 21. As expected, cued eye movements show less bradykinesia than non-cued ones, as previously shown by others. Contrary to the MA, which reflects only one aspect of bradykinesia (amplitude decrement), the period encompasses both the reduction in amplitude and preparation time for movement in the opposite direction [17, 19].

The MA does not enable us to distinguish between apathy and bradykinesia. The MA decreases as the score value increases for the DAS and the bradykinesia, which show a similar trend. Moreover, the comparison analysis showed no difference in the interaction between these two variables. The results of the interaction between the MA and the bradykinesia are coherent with the concept of hypokinesia [14]. However, it is interesting to notice that the decrease in the MA is only observable for bradykinesia scores above 21. Since our patients do not display severe apathy, a higher DAS score could be correlated to the MA.

Only MA is significantly affected by the cues as the main effect. This effect was expected since PD patients depend more on external cues than controls [16] and lack auto-activation due to apathy [18]. In addition, it is concordant with the results of Cools et al., who found that patients were less efficient when switching from a high to a low-salient dimension but could switch more quickly from a low to a high-salient dimension than controls. This could be due to a dysfunction of the top-down attentional control [37]. Interestingly, the change of the MA across the task is a good reflection of the sequence effect (well-known from the routine clinical assessments, such as finger tapping) and decreases over time only in patients. This sequence effect measured on the amplitudes of the saccades mirrors the sequence effect assessed on segmental movements as shown in the literature [10, 11, 38].

Altogether, the MA represents only one aspect of the bradykinesia (motor execution). In contrast, the period captures akinesia (delay of initiation of a new movement) and bradykinesia (slowness in execution), thus being a more sensitive measure.

We observed that the peak velocity did not change during the paradigm in the patient group for both cued and non-cued saccades. Peak velocity has been described in the literature as an indicator of fatigue during oculomotor tasks [33]. Interestingly, it has been recently described that there is an overlap between Parkinsonian fatigue and apathy, as Béreau et al. [9] suggested. However, these results suggest that patients did not experience fatigue during the task and that the results can not be attributed to it.

Curiously, this study showed no Levodopa effect on ocular movements in cued or non-cued conditions. In addition, Levodopa did not help the most apathetic patients to perform the task better. This could be linked to the fact that the literature regarding the effect of Levodopa on eye movements is mixed, with some results showing a positive effect [39, 40], while others showing no effect or even a worsening of saccades, despite an effect on the motor scores [41, 42]. Moreover, late-stage PD patients tend to be less responsive to Levodopa than early-stage PD patients. In addition, our robusteness tests showed that the presence of DBS should not have modified our results on the dependent variables.

Importantly, patients included in this study were not depressed nor anxious, as shown by the low HAD scores. Therefore, we assume that our results are mainly representative of bradykinesia.

This study has some limitations. Our patient population is mixed since some patients were at the beginning of their disease and, therefore, not expected to show a dramatic change in the motor score, while others undergoing deep brain stimulation may have had reduced 'off' scores [43, 44]. Therefore, the effect of medication should be interpreted cautiously.

In conclusion, this study serves as a proof of principle. While it has been dogma for many decades that oculomotricity in PD is normal for the clinician, our data show that, on the contrary, oculomotricity can be used to measure all aspects of bradykinesia from its initiation (akinesia), be it via lack of motivation or cognition (motivational or cognitive apathy) to its execution (bradykinesia) be it via slowness of thinking (bradyphrenia) or isolated slowness in movement. This study paves the way for a confirmatory study to analyze further whether the period is more related to bradykinesia and the maximal amplitude to apathy in a more significant number of subjects. One approach to better assess the relationship between eye movements and bradykinesia would be to objectively measure the bradykinesia by recording a finger-tapping task as a control [45].

Acknowledgements The authors have no acknowledgments to report.

Author contributions (1) Research project: A. Conception, B. Organization, C. Execution. (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique. (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique. FR: 1B, 1C, 2A, 2B, 2C, 3A, 3B. DB: 2C, 3B. RP: 1A, 2A, 3A, 3B. DK: 3B. MB: 1A, 3B. RMM: 2C, 3B. PK: 1A, 2A, 3A, 3B. AZ: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

Funding A. Z. is supported by the Baasch Medicus Foundation and the Fondation Centre de Recherches Médicales Carlos et Elsie de Reuter. The funders had no role in this study's design, data collection, data analysis, and reporting.

Data availability The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflicts of interest The authors have no conflict of interest to report.

Ethical approval This study protocol was reviewed and approved by the local ethical committee of the Canton of Geneva (Project-ID 2019-01039). All the participants signed informed consent. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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