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ORIGINAL COMMUNICATION

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What is pathological with gaze shift fragmentation in Parkinson's disease?

Abstract Oculomotor dysfunction in Parkinson's disease (PD) is mainly characterized by a fragmentation of memory-guided gaze shifts (target is reached by several hypometric saccades). Since this phenomenon can also be observed in normal subjects, we scrutinized its pathophysiological significance in PD patients. We recorded horizontal eye movements in eleven mildly- or moderately-affected PD patients and eleven control subjects. A quantitative assessment of gaze shift fragmentation was made possible by increasing its incidence over a sequence of two visually- and two subsequent memory-guided gaze shifts. Basic saccade measures (latency, velocity, etc.) were similar in the two subject groups as well as in fragmented versus non-fragmented gaze shifts. Fragmentation probability is increased in the second memory-guided gaze shift, and this clearly more so in patients than in controls. The fragmentation shows a typical gain pattern (uniform increase of gain of saccadic amplitudes across correction saccades towards 1.0 with the last saccade of the gaze shift) independent of subject group, stimulus mode, and fragmentation degree. Gaze shift fragmentation represents a physiological phenomenon, which has thus far been overlooked. It reflects a robust correction mechanism, which assures that target is reached even if the pre-oculomotor drive through the basal ganglia to the superior colliculus becomes abnormally weak or under inadequately strong inhibition – as is postulated for PD. Thus, only the abnormally high incidence of fragmentation, and of the associated amplitude reduction of the primary saccades, rather than the phenomenon per se, can be used as a diagnostic criterion in early stages of PD.

Key words Parkinson's disease · saccadic eye movements · memory-guided saccades · superior colliculus · gaze shift fragmentation

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Introduction

Parkinson's disease (PD) is characterized by three cardinal symptoms: akinesia, rigor and tremor. These deficits relate to the skeletal motor system. Less obvious to the clinician is that the oculomotor system is also affected in these patients. The deficit relates especially to saccades, a primarily voluntary oculomotor activity. The latter fact is generally taken to illustrate that the disease mainly affects internally-generated behavior, while activity evoked by external stimuli is clearly less impaired, at least at early stages of the disease [9, 22]. The oculomotor deficit consists of a special type of saccade hypometria. Having repeatedly observed this phenomenon also in normal subjects, we assessed its occurrence in PD patients and compared it with that in controls.

The findings of impairment of saccades in PD patients goes back to the work of Jones and DeJong [23], who reported that the patients abnormally often make grossly undershooting saccades when following repetitive target jumps and even more when performing self-paced saccades (also [11, 25, 27, 35]; overview, [7]). Remarkably, basic saccade measures such as latency and peak velocity are in the normal range unless the patients are severely affected [37, 38]. The phenomenon, which is

often referred to as "multiple step pattern", is especially pronounced with memory-guided saccades. The hypometric primary saccade is followed by correction saccades such that the location of the (no longer visible) target is reached, indicating that the storage of the target's spatial coordinates in memory and their retrieval is normal in PD [11, 34, 38]. The underlying pathophysiology of the phenomenon is still obscure. Some authors considered it to reflect an impaired predictive strategy in PD [8, 36]. As to its neurophysiological basis, it is nowadays assumed that a pathway from the frontal cortex through the basal ganglia to the superior colliculus (SC) is impaired in PD patients and responsible for this type of saccade hypometria. The pathway projects via the caudate nucleus (CN) to the substantia nigra pars reticulata (SNr), which in turn acts as a gate for the preparation of saccades in the SC in the form of a 'release from inhibition' [19].

To clearly distinguish this pattern of hypometric saccades, which do reach target, from other types of saccade hypometria, where the target location is missed, we use the term 'gaze shift fragmentation' in the following. A quantitative characterization of the fragmented gaze shifts in PD patients and control subjects is still missing to date. This refers to the questions (i) whether the saccades in the fragmented gaze shifts show characteristic spatial and temporal patterns, (ii) whether these patterns differ across the various gaze shift types in which they may occur, and (iii) to what extent the patterns in patients differ from those in normal subjects.

An assessment of these questions is hampered, however, by the fact that fragmented gaze shifts are only rarely encountered with the conventional saccade paradigms used. Their incidence in moderately-affected PD patients is not beyond a few percentage points when a considerable number of gaze shifts is investigated. It is true that the incidence is increased in severely-affected PD patients, but usually these patients show a more widespread deficit in oculomotor functions, which may include prefrontal cortical areas as well as pre-oculomotor structures in the brain stem. In normal subjects, finally, fragmented gaze shifts are so rarely encountered that they have attracted hardly any research interest (cf. [11]; research so far has focused mainly on the typical gaze shift behavior which includes the strategy to produce a slightly hypometric primary saccade and one or two correction saccades in the same direction, which finally settle the eyes on target; see [4]).

These considerations led us to establish a saccade paradigm, which evokes a relatively high percentage of fragmented gaze shifts. This applied not only to the patients, but also to the controls. The approach allowed us to answer the questions raised above. Surprising for us was, however, the finding that gaze shift fragmentation in patients is the same as in controls and represents a physiological phenomenon which has thus far been overlooked. Only its incidence is higher in PD patients than in controls. This led us to consider the physiological significance of the phenomenon as a basis for understanding its pathophysiological significance in PD patients.

Methods

Subjects

We examined 11 mildly- or moderately-impaired PD patients (PD; Webster Rating Scale: WRS range 7–15 points, M ± SD 10 ± 3 points; Unified Parkinson's Disease Rating Scale: URS motor part, 17 ± 4 points; duration of illness, 4 ± 2 years) aged 60 ± 9 yrs (5 men and 6 women). They were compared with 11 age-matched control patients (CO; 55 ± 5 years) who suffered from vertebral pain syndromes and showed no evidence of a CNS disease (6 men, 5 women). Subjects with major cognitive deficits were excluded (*Standard Progressive Matrices Raven*-test, SPM series A–C: PD, 82 ± 11; CO, 83 ± 11). On average, PD patients showed no clear asymmetry of their skeletal motor symptoms. Their medication at the time of investigation consisted of the usual dopaminergic and anticholinergic drugs in moderate dosages. All subjects gave their informed consent to participate in the study, which was approved by the Ethics Committee of the Freiburg University Clinics.

Apparatus and stimuli

Subjects were seated in a comfortable chair in front of a computer monitor at a distance of 57 cm. Their heads were immobilized by means of a chin and a head rest. Stimulus presentation on the visual display was controlled by a laboratory computer. It consisted of a red fixation point (FP; 0.2° x 0.2°; luminance: 6.0 cd/m^2) in the center of a homogeneous green background (screen, diameter: 17"; luminance: 2.8 cd/m^2) and two white spots which served as saccade targets (T1, T2; 0.2° x 0.2°; luminance: 38.7 cd/m^2). Subjects learned in a short training session with this set-up to perform the following sequence of saccadic gaze shifts (see Fig. 1 for time structure and example):

- After a fixation period of 800 ms, FP was extinguished and subjects performed a visually-guided saccade to T1, which appeared after a gap of 200 ms at eccentricities of ± 2, ± 4 or ± 14°(positive/negative values always indicate rightward/leftward movements) (*V1 gaze shift*). Duration of T1: 3300 ms.
- 800 ms later, T2 appeared in addition to T1 (overlap), and subjects shifted their eyes onto this target (T2 jumped always in the oppo-

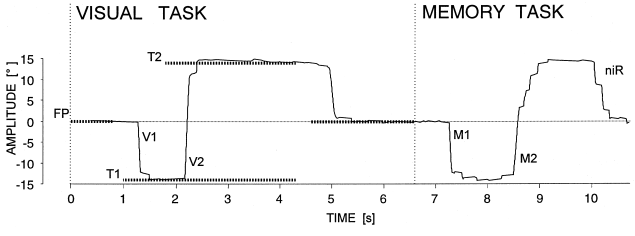

Fig. 1 Visual target presentation and example of saccadic eye movements for the experimental paradigm used (two visually-guided saccades followed by two memory-guided saccades). FP: fixation point; T1, T2: first and second visual target. Dashed, horizontal lines indicate duration and amplitude of stimuli. V1, V2: first (leftward) and second (rightward) gaze shift to T1 and T2, respectively. M1, M2: gaze shifts to the remembered locations of T1 and T2. niR: non-instructed, spontaneous gaze shift back to the center of the screen after end of trial.

site direction of T1, with amplitudes of 4, 8, 16 and 28°, relative to T1) (*V2 gaze shift*). Duration of T2: 2500 ms.
- FP reappeared for 2000 ms and subjects recentered their eyes on it.
- Extinction of FP was the sign for subjects to initiate memory-guided saccades, first to the remembered location of T1 (*M1 gaze shift*) and, after an interval of about 1 s during which the eyes were to rest on the imagined target, to T2 (*M2 gaze shift*).
- After a further rest interval of about 1 s, the trial was finished (4 s interval between second FP offset and begin of next trial). Noticeably, subjects tended to spontaneously shift gaze towards the center of the blank screen, where the reappearance of FP would indicate the beginning of the next trial. These non-instructed recentering gaze shifts were included in the analysis in those cases in which they were not contaminated by blinks or drifts. (*niR gaze shifts*).

During the experiments the room lights were dimmed, but not completely extinguished. The residual illumination helped the subjects to stay alert during the measurements. However, the fact that subjects saw the monitor frame may have allowed them to use it as an allocentric spatial reference in the memory tasks (see Discussion). On the other hand, the residual illumination helped us to prevent afterimages of the saccade targets, as did the changes in eye position during target acquisition (V1 and V2) and the rather long interval (2.3 s) after target extinction and before triggering M1.

Overall, each subject performed 120 of these trials (15 trials for eight amplitude combinations). However, since usually some trials were invalidated because of artifacts (e. g. eye blinks, eye drifts), we analysed only the ten first valid trials per subject for consistency across all subjects. We repeatedly encouraged subjects to stay alert during the recording sessions. Short breaks were given after every 15^{th}–20^{th} trial.

Eye movement measurement and data analysis

Horizontal eye movements were recorded by means of an infrared light technique (Iris System, Skalar, Delft, The Netherlands) for both eyes (linearity within 3 % for ± 25° eccentricity; optimal resolution, 2 arcmin). Horizontal eye position of both eyes as well as target position were fed into a laboratory computer (acquisition rate: 500 Hz), monitored throughout the experiment on the computer screen, and stored on a hard disk for offline analysis.

An eye movement calibration was performed at the beginning and at the end of each experimental session, using the final eye position resulting from primary and secondary saccades towards defined eccentric target locations (± 10° and ± 20°). Furthermore, throughout the sessions the validity of the calibration was ascertained by comparing it, for each gaze shift in a given trial, with the final eye position reached with the corresponding visually-guided gaze shifts V1 and V2 in that trial.

Data analysis was performed using an interactive computer program, which automatically detected saccades by means of an eye velocity threshold (velocity threshold 50°/s). The algorithm detected saccades greater than 0.75°. Saccades smaller than 0.75° were determined interactively. Saccade detection below the noise level of 0.2° (peak-to-peak amplitude in the position trace) was not performed. Artifacts like drifts or blinks were identified by visual analysis and removed. The analysis comprised saccade reaction time (SRT) and duration as well as amplitude and peak velocity for each saccade in a given saccade sequence (i. e. of primary as well as secondary saccades). Including an analysis of SRT frequency distributions, we performed a classification of saccade types based on these distributions, distinguishing (i) anticipatory saccades (SRT < 90 ms), (ii) express saccades (90–130 ms), (iii) fast regular saccades (131–210 ms), (iv) slow regular saccades (211–400 ms) and (v) late saccades (> 400 ms; compare [14]). We calculated the gain of each saccade (ratio of eye amplitude versus eye position error) and the gain at final eye position (ratio of total eye amplitude across all saccades in a gaze shift to target displacement; the end of a gaze shift was determined by the proximity to the target position, by a fixation time > 300 ms at that position and by the direction change between T1 and T2). For measuring saccadic peak velocity maximum detection was performed after data smoothing. For smoothing we used a simple moving window average (the window extending 1 point leftward and rightward, for a total of 3 points), which preserved the peaks quite well. The dependency of peak velocity on saccade amplitude was determined by fitting a curve to the peak velocity/amplitude data (cf. [1]). These 'main sequence' curves (cf. [3, 4]) allow comparing amplitude ranges of different saccade types by calculating the asymptotic maximum of the curves (PV_m) and the initial slope of the functions (PV_m/A_{63}), and they allow determining peak velocity (PV) for any amplitude value (we chose 12°, PV_{12}; PV was obtained with the following equation: $PV = PV_m*[1-\exp(-A/A_{63})]$; A, saccade amplitude; A_{63}, amplitude at which peak velocity reaches 63 % of its saturation value; PV_m/A_{63} equals the initial slope of the function for small values of A).

Furthermore, the following measures were obtained to characterize gaze shift fragmentation: the gain of the primary saccade, the number of saccades in a gaze shift, the percentage of 'multiple step pattern' (MSP; when it consisted of 3 or more saccades, or, of 2 saccades with the first one being smaller than the second; to and fro saccades excluded), and the intersaccadic intervals within the gaze shift. Additional measures are given in the Results section.

For statistics we used the mean values of the above measures for each subject (exceptions will be noted), assessing the statistical significance of the results by analysis of variance. In the following presentations we pooled the findings for rightward and leftward gaze shifts, because statistically they showed no significant difference.

Results

Basic saccade parameters

Saccadic reaction time (SRT)

In Fig. 2, the SRT values of controls (Fig. 2A) and patients (Fig. 2B) for V1, V2, M1 and M2 (Fig. 2AB, a–d) are given as frequency histograms (M1 and M2 relative to second FP offset; compare Fig. 1). The groups' mean values (± SD) are also given in Fig. 2 (calculated from the individual subjects' median values). Statistically, SRTs of PD patients were not different from those of the controls when tested across all gaze shift types ($p = 0.69$) and separately for each of the four types ($p \geq 0.7$). The values obtained were consistent with those given in the literature for normal subjects (remind that V1 occurred in a gap task, and V2 in an overlap task; compare [6, 32] for V1 and V2; [26] for M1). A classification of primary saccades for V1, V2 and M1 was performed on the basis of the SRTs [14]. The results are given in Tab. 1. Statistically, the distributions showed no difference between subject groups (in line with a previous study for V1 [32]; M2 gaze shifts were not classified because of the lack of an external trigger). Additionally, no significant effect was found in patients versus controls when relating saccade latencies to the rather variable number of saccades per gaze shifts. Thus, all SRT aspects tested were normal in patients.

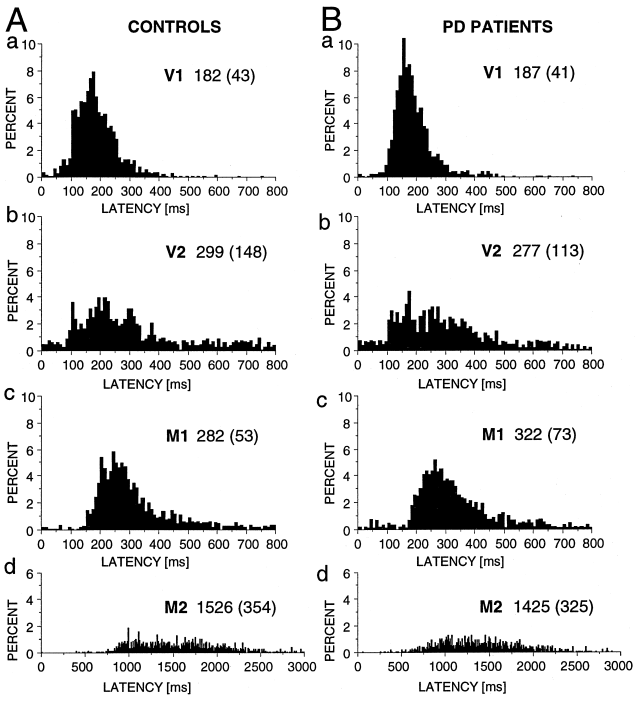

Fig. 2 Frequency histograms of saccadic reaction times in controls (**A**) and PD patients (**B**) for primary saccades in V1, V2, M1, and M2 gaze shifts (bin width, 10 ms). Inserted numbers indicate mean (SD), in milliseconds.

Table 1 Percentage of saccade subpopulations, mean (SD), in controls (CO) and PD patients (PD)

Subpopulation	V1 gaze shift		V2 gaze shift		M1 gaze shift	
	CO	PD	CO	PD	CO	PD
'Anticipated'	4 (4)	2 (2)	5 (4)	6 (4)	1 (1)	2 (2)
'Express'	15 (14)	11 (9)	8 (7)	8 (7)	0 (1)	1 (1)
'Fast regular'	51 (22)	59 (19)	21 (17)	24 (17)	16 (14)	7 (6)
'Slow regular'	29 (24)	26 (19)	38 (15)	42 (13)	62 (11)	64 (14)
'Late'	1 (1)	2 (2)	29 (25)	22 (16)	21 (12)	26 (16)

Saccadic peak velocity

The mean values of calculated peak velocity at 12° (PV_{12}) for the gaze shifts V1, V2, M1, M2, and niR amounted to 375, 392, 318, 351 and 333°/s in controls, respectively, and to 335, 386, 292, 309 and 299°/s in patients. Despite a tendency to somewhat higher values in the controls, statistics revealed no significant difference between groups with respect to peak velocity at 12°, maximum peak velocity (PVm) and initial slope of the 'main sequence' functions (PV_m/A_{63}; $p > 0.2$). Additionally, the difference between subject groups was not significant when comparing fit quality of the exponential peak velocity-amplitude functions (mean error sums of squares; $p = 0.09$). Thus, saccade velocities of patients were also in the normal range (cf. [1, 4]).

Gain at final eye position

The final eye position reached in V1 and V2 gaze shifts served to recalibrate the eye movement recording for each individual trial (see Methods). The mean gain values for the M1 shifts were close to unity (CO: 1.10, 1.05, 0.98, PD: 1.00, 0.89, 0.98, for 2°, 4°and 14°jumps, respectively). Those for M2 showed an overshoot for small target jumps, which declined towards unity with increasing target amplitude (CO: 1.31, 1.17, 1.08, 1.03, PD: 1.17, 1.07, 1.01, 1.01 for 4°, 8°, 16°and 28°jumps, respectively; amplitude effect, [$F(3,57) = 19.86$; $p = 0.0001$]). Gain of M1 and M2 showed no significant difference between controls and patients ($p > 0.18$), apart from a tendency to slightly higher gain values in controls.

Gaze shift fragmentation

Gain of primary saccades

Fig. 3A shows the gain of the first saccade in the gaze shifts as a function of target amplitude for V1, V2, M1, and M2. On average, the gain was similar in the two subject groups, decreasing slightly with increasing target amplitude ($p = 0.048$). Patients had a tendency for

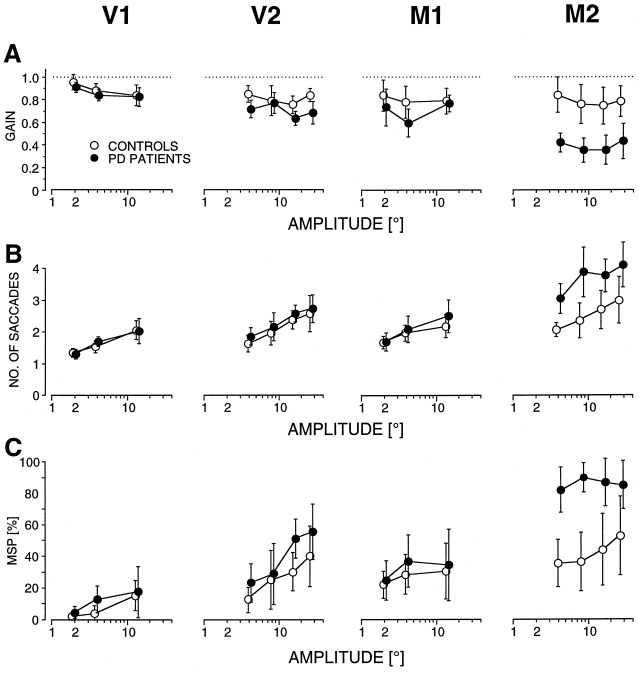

Fig. 3 A–C Conventional measures of gaze shift fragmentation. (**A**) Gain of primary saccade. (**B**) Number of saccades within gaze shifts. (**C**) Percentage of multiple step pattern, MSP. Mean values (± 95 % confidence intervals) of controls (n = 11; open circles) and PD patients (n = 11; filled circles) are plotted as a function of target amplitude (note logarithmic scales on abscissas), separately for V1, V2, M1, and M2 gaze shifts. Statistically, differences between subject groups are significant only for M2 gaze shifts in A–C).

smaller gain values. Statistically, this difference was not significant for V1 ($p = 0.35$), V2 ($p = 0.06$) and M1 ($p = 0.15$), but was highly significant for M2 [$F(1,19) = 22.72$; $p = 0.0001$].

Number of saccades

As might be expected from the lower gain values of the primary saccades (Fig. 3A), patients also showed a tendency to higher numbers of saccades per gaze shift to reach the target (Fig. 3B). The effect was pronounced for M2 (group difference highly significant, [$F(1,19) = 13.37$; $p = 0.0017$] and was weak for V1, V2 and M1 (difference not significant, $p = 0.35$), independent of target amplitude. The number of saccades increased with increasing target amplitude for all four gaze shift types ($p < 0.005$) in both subject groups.

Multiple Step Pattern (MSP)

The difference between patients and controls became more pronounced when the saccade patterns were classified in terms of MSP (see Methods). For M2, patients produced clearly more MSP than controls [$F(1,19) = 18.5$; $p = 0.0004$] and this for all target amplitudes tested. A similar trend was found for V1, V2 and M1, but the difference between controls and patients was statistically not significant ($p = 0.29$, 0.11, 0.49, respectively). MSP percentage as a function of target amplitude increased in both subject groups for V1 and V2 ($p \leq 0.001$), but not for M1 and M2 ($p > 0.11$). MSP percentage as a function of gaze shift type in the sequence increased as well. MSP percentage for a 12° target step (MSP_{12}), calculated from regression fits of the data, increased from V1 (CO: 13 %; PD: 16 %) over V2 (CO: 23 %; PD: 33 %) and M1 (CO: 29 %; PD: 35 %) to M2 (CO: 38 %; PD: 82 %). For MSP_{12}, the difference between subject groups was statistically significant for M2 ($p < 0.0001$), but not for V1, V2 and M1. Noticeably, discrimination of patients from controls on the basis of MSP percentage with M2 was high; the lower 95 % confidence limits of median MSP percentage in patients was 63 %, while the corresponding upper limit for controls amounted to 58 %.

There was no correlation between disease severity in terms of URS and percentage MSP ($r^2 < 0.1$), in line with the rather homogeneous PD group and the relatively small number of subjects investigated.

Characteristics of gaze shift fragmentation

A major objective of our study was to characterize the phenomenon of gaze shift fragmentation in more detail than has been done hitherto (mostly in terms of MSP). By assessing both temporal and amplitude aspects, we aimed to reveal possible differences of the fragmentation between patients and controls as well as across different gaze shift types (here V1 to M2).

Table 2 Intersaccadic intervals (ISI), mean (SD), within M1 and M2 gaze shifts of controls (CO) and PD patients (PD)

	M1		M2	
	CO (ms)	PD (ms)	CO (ms)	PD (ms)
ISI-1	238 (51)	266 (72)	224 (54)	267 (89)
ISI-2	248 (73)	255 (85)	214 (61)	240 (89)
ISI-3	207 (139)	235 (167)	196 (56)	255 (83)
ISI-4	217 (69)	164 (93)	229 (93)	272 (129)
ISI-5			171 (9)	202 (121)

Intersaccadic intervals (ISIs) within gaze shifts

Tab. 2 gives our subjects' mean ISIs for M1 and M2 gaze shifts. Note that the ISIs are in the range of regular saccade latencies (about 200 ms). Statistically, there was neither a significant difference between subject groups ($p = 0.2$) nor between M1 and M2 gaze shifts ($p = 0.6$; the same held qualitatively for V1 and V2 shifts). Furthermore, we found no difference across the ISIs concerning their order within the fragmented gaze shifts (for ISI_1, ISI_2, ISI_3, ISI_4; $p = 0.4$).

Proceeding from an earlier report about abnormally short ISIs in memory-guided gaze shifts of PD patients [35], we analysed the ISI frequency distributions of all gaze shift types investigated. ISIs always peaked around 200 ms, but there was a small separate peak below 100 ms. Further analysis of this subpopulation revealed that the corresponding secondary saccades occurred mostly in association with direction changes (staircase-like sequence of saccades interrupted by one with opposite direction), in both controls and patients. Finally, length of ISI did not affect the gain of the subsequent saccades (ratio of saccade amplitude to eye position error that remained after the previous saccades; correlation coefficient $r^2 < 0.05$).

Gain characteristics within gaze shifts

On a single trial basis, the pattern of saccade amplitudes within fragmented gaze shifts varied considerably. However, a typical pattern emerged when averaged and expressed in terms of normalized amplitudes across the gaze shifts. This is shown for M2 in Fig. 4A where cumulative saccade amplitudes are given in the order of saccade occurrence (1^{st}, 2^{nd}, ...), after having separated the shifts containing only one saccade (panel $n = 1$) from those containing two saccades ($n = 2$), and so forth. Note that, apart from the first and the last saccades, the gaze shift goal is reached by about equal-sized steps, both in control subjects and patients. Note also, that the number of subjects showing gaze shift fragmentation decreased

with increasing numbers of saccades within the shift (the number of patients/controls showing 5 saccades with M2 gaze shifts (Fig. 4A) amounted to 7/10 (panel 5), the corresponding numbers for the 6 saccade gaze shifts were 8/2). In Fig. 4B the data are replotted in terms of gain (quotient of saccade amplitude to remaining position error prior to the saccade). Mean gain is close to unity in gaze shifts containing only one saccade. In the shifts containing five saccades, for instance, gain of the first saccades is by far too small and gradually rises with the number of saccades performed, approximately reaching unity with the last one (amplitude of final saccade fits the remaining eye position error, which is small and thus associated with correspondingly large confidence intervals of the final gain value). Going from shifts with n = 1 to n = 6 saccades, the effect develops in a graded way: the gain of the primary saccade determines the starting level of a gain curve, which is rather stereotypical with nearly linear increase. Qualitatively similar findings were obtained for the V1, V2 and M1 gaze shifts, for which, however, the data base was much smaller. The effects were similar in both controls and patients, suggesting that we are dealing here with one and the same phenomenon (see Discussion).

In contrast, frequency of occurrence and amount of fragmentation does depend on subject group and type of gaze shift, as already suggested by Fig. 3. In Fig. 4C we specify this finding in more detail, by plotting the fragmentation's frequency of occurrence (ordinates) for the gaze shifts containing n = 1, 2, 3, ... saccades (abscissas) in patients and controls, separately for the gaze shift types investigated. Qualitatively, the frequency distributions of patients resemble those of controls but are shifted towards higher numbers of saccades per gaze shift. The effect is small for V1, V2, and M1 and very pronounced with M2 (and niR, see below). For instance, the controls' distribution for M2 peaks at n = 2 and the percentage of gaze shifts containing n > 2 saccades is < 40 %, while the corresponding peak in patients is at n = 3 and the percentage of gaze shifts containing n > 2 saccades is > 60 %. Thus, the pathophysiological aspect of gaze shift fragmentation in moderately-affected PD patients lies in its increased probability of occurrence and is largely dependent on an appropriate challenge of the saccade system (here the M2 condition; compare Discussion).

Non-instructed Recentering (niR) gaze shifts

After the last gaze shift (M2) in each trial, subjects' eyes had achieved an eccentric orbital position. During the following break and before the next trial started, subjects spontaneously shifted gaze back to about the center position. These niR gaze shifts were highly fragmented, much more in patients than in controls (see Fig. 4C, niR). The percentage of MSP was clearly higher in patients than in controls (76 % vs. 24 %; [$F(1,10) = 39.45$; $p = 0.0001$]), a finding which resembled that for M2. The sensitivity of the fragmentation effect to distinguish a patient from controls was similar to that with M2, so that niR may be considered a useful tool for clinical routine diagnostics. However, about half of our patients and controls produced eye blinks during the break

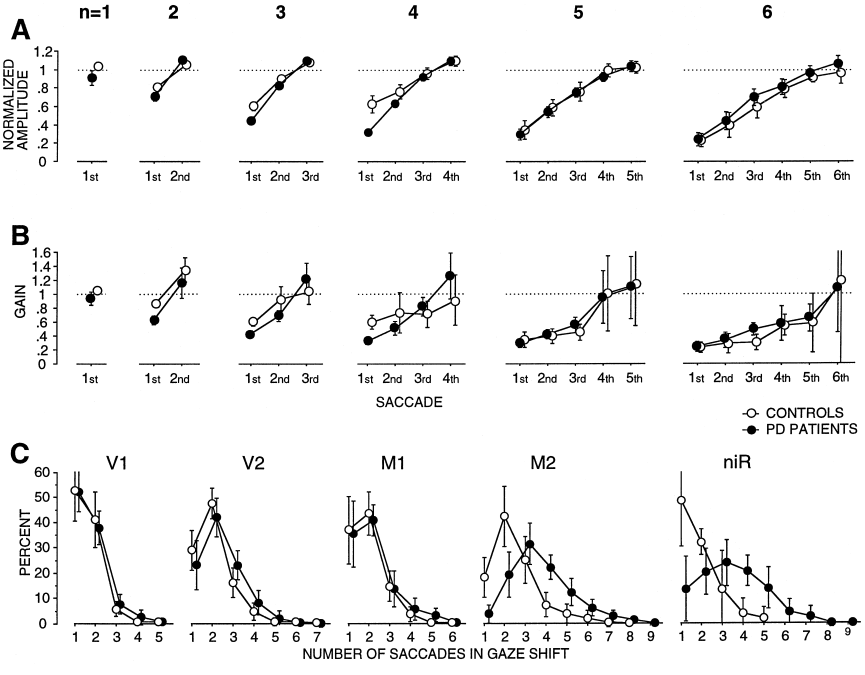

Fig. 4 A–C Characterization of gaze shift fragmentation. In (**A**) normalized cumulative saccade amplitude (ordinate) is plotted for each successive saccadic step in the M2 gaze shifts (primary saccade, 1st; secondary saccades 2nd, 3rd, ...; abscissas). Panel 'n = 1', 'n = 2' ... represent gaze shifts containing one saccade, two saccades, and so forth. The data is replotted in (**B**) in terms of saccade gain related to remaining position error. (**C**) gives the percentage of gaze shifts containing 1, 2, 3 or more saccades (abscissa) separately for V1, V2, M1, M2 and niR. Presentation otherwise as in Fig. 3.

so that not enough data could be obtained for statistics. It remains to be shown whether this problem may be overcome by modifying the saccade paradigm (e. g. shorter trial duration).

Discussion

Gaze shift fragmentation in PD (and related diseases involving a basal ganglia hypofunction) is considered a pathological phenomenon. We show here that the fragmentation per se is a physiological phenomenon and that only the abnormally high incidence in patients is pathological. The assessment of occurrence probability required the design of a saccade paradigm that facilitates the normally existing, but rather subtle tendency for fragmentation. Our data show that the fragmentation represents one and the same phenomenon across the various gaze shift types evoked and across the two subject groups. Furthermore, it sheds some light on the correction mechanism that prevents a gaze shift from falling short. In the following, we first consider the physiological significance of the fragmentation phenomenon before addressing its pathophysiological aspects in PD and finally consider the correction mechanism.

The amount of fragmentation clearly depends on the gain of the primary saccade; initial saccade gain decreases along with increasing fragmentation, approaching zero in an exponential way (see averaged data in Fig. 4B; note that the measure gain is independent of gaze shift amplitude). Furthermore, amount as well as incidence of fragmentation depends on the gaze shift type, being clearly larger with M2 than with M1, V2 and V1 (Fig. 4C). How can this tendency of primary saccades (and the subsequent secondary ones) to fall short be explained?

As mentioned before (Methods) our subjects were allowed to see the monitor frame during the experiment and may have used it as a reference with the memory tasks. One could speculate that this explains why the incidence of gaze shift fragmentation in our study increased only moderately with M1 (by about 55 % as compared with V1), similarly in patients and controls. However, previous authors (Crawford et al. [11]) observed a similar increase for their control subjects in conditions without residual background illumination, using the classical single memory saccade paradigm. The corresponding increase for patients observed in this previous study was only slightly more pronounced than in the present one, but apparently was enough to yield a statistically significant difference between subject groups, unlike in our study. However, there remains the dramatic increase seen with M2 and niR in the present study.

M2 gaze shifts are particular in that they combine several complicating factors, like internal triggering (vs. external, in terms of target appearance with V1 and V2, and fixation point extinction with M1), in-memory representation of the target (vs. visual with V1 and V2), and a high complexity of the task in terms of a sequence of movements which requires a behavioral plan (similarly for niR). We wish to point out again that the in-memory representation of final eye position appears not to be disturbed in PD [11, 34, 38]. It is true that a dysfunction of spatial working memory has been observed for the ranking of targets within sequences [20], but this issue is hardly of relevance for the very short sequences of two targets we used. Furthermore, the fact that our findings for M2 resembled those for niR, which represented a simple 'recentering' saccade on the visible screen, largely rules out that internal coordinate transformations required for the M1 and M2 tasks contributed much to the observed group differences. In view of the complexity of the M2 task and of the fact that noise in a biological system gives it a somewhat stochastic property, an intermittent occurrence of saccadic hypometria of varying degrees per se does not appear surprising. Yet the hypometria considered here displays specific aspects. For instance, it can hardly be attributed to noise in the saccade-executing brainstem machinery, since basic features like velocity were normal in the hypometric saccades. Nor can cortical mechanisms be accused, since their functions (target selection, saccade timing and spatial coding of target position) were unimpaired in the fragmented gaze shifts. These findings differentiate the saccade hypometria considered here from other forms of hypometria (e. g. the one observed with drowsiness; see below) and suggests that it arises in the pre-motor drive at some intermediate processing stage between cortex and brainstem machinery.

There is a vast amount of literature, which suggests that the performance of tasks with the complexity of M2 involves the fronto-striatal loops and basal ganglia functions [10, 12, 15, 17, 19, 24, 28, 33]. These loops play a crucial role in behavior that involves internal drives and movement sequences. The way in which the pre-saccadic drive is transmitted through the basal ganglia route is noteworthy in that it is implemented in the form of a 'release from inhibition'. This view is based on animal work (see Introduction) which suggests that the cortico-striatal system provides a command signal which determines when and where to reorient gaze by disinhibiting a given neuron population on the topographic map of visual space of the SC.

It is true that cortical oculomotor commands in part bypass the basal ganglia and the SC, impinging directly on the brainstem saccade machinery (e. g., afferent paths from frontal cortex, FEF [16] and parietal cortex [2]). But the increase in fragmentation probability in basal ganglia hypofunction as in PD provides convergent evidence. In this view the SNr, as the outlet of the basal gan-

glia for saccades, exerts an inhibitory control of SC neurons, with the basal ganglia dysfunction in PD then leading to an abnormally weak drive signal in the SC for saccade generation [19]. The subnormal drive in the SC results from either an excess of tonic inhibition, which would tend to prematurely terminate the saccades in a given gaze shift, or an abnormally weak excitation of SC neurons by insufficient phasic release from inhibition, which repeatedly causes saccades in the shift to fall short, or both.

This view would be compatible with current concepts of SC function. For illustrative purposes (but not trying to interfere with current debates on these concepts), we refer to the 'moving-peak' hypothesis of SC function for saccade preparation [29, 30], also because it allows us to address the correction mechanism, which brings the eyes finally on target. According to this hypothesis, the SC comprises two functionally distinct parts: (i) A fixation zone (foveal area) where neurons are active when the eyes are on target, and (ii) a saccade zone (extrafoveal region) where neurons show a peak of activity during preparation of a saccade in a given direction, with the distance from the fixation zone coding saccade amplitude. In association with saccade generation, the activity peak travels towards the fixation zone, the activation of which in turn terminates the saccade. Saccadic hypometria would result from a subnormal size of the peak and/or an undershoot of the peak's movement. Unknown mechanisms then evoke a new peak at the site where the previous one vanished, and so forth, until the fixation zone is reached (eye on target). This mechanism, or a functionally analogous one, could represent the neuronal basis of the fragmentation phenomenon and explain why the saccade parameters are normal in the fragmented gaze shifts, apart from the hypometria.

Fragmented gaze shifts that differ from the ones considered here are occasionally observed when a subject becomes drowsy. Phenomenologically, saccadic hypometria in these gaze shifts tends to increase and the saccadic shift finally tends to change into a 'drift' towards target. Saccadic peak velocity then is decreased, indicating an involvement of the brainstem saccade machinery. Fragmented gaze shifts of this type were occasionally observed in our patients and controls. Since they were rare, they could not be included in the quantitative analyses. To point out the difference between these two types of fragmented gaze shifts, we resort to the following theoretical consideration.

In Fig. 5 we present calculated saccade gain and displacement values for the assumption of an error feedback mechanism (cf. below) with constantly too-low gain (panels A, B; presumed to represent the 'drowsy state') and compare them with those obtained with an almost linearly-increasing gain (C, D; 'alert state') as seen in Fig. 4B. With an initial gain value of 0.8 for the 'drowsy state' (A), a large first saccade is followed by two

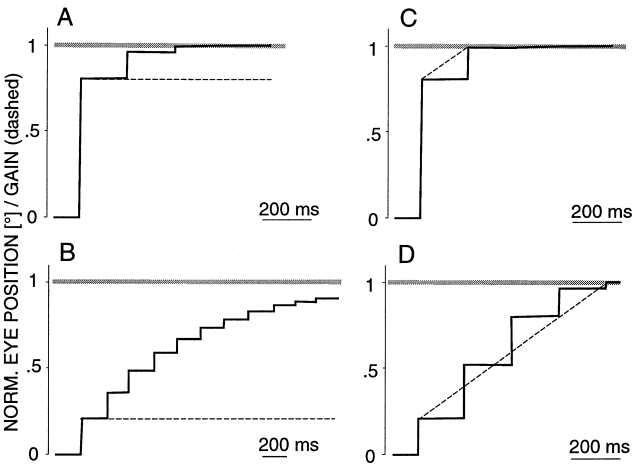

Fig. 5 Calculated examples for saccade amplitudes in fragmented gaze shifts with saccade gain held constant (**A**, 0.8; **B**, 0.2; dashed horizontal lines) versus linearly-rising gain (initial value 0.8 in **C** and 0.2 in **D**).

smaller 'correction' saccades (gaze shift is 'switched off' when target is reached). With an initial gain of 0.2 for the 'drowsy state', an asymptotic trajectory of the gaze shift results, in which the eyes do not reach target, at least within a given time (B). For the 'alert state' and an initial gain value of 0.8 (C), the resulting gaze shift does not look much different from that in A. However, when initial gain is set at 0.2, the linearly-increasing gain assures that only a few (and almost equal-sized) saccades are produced, which do reach target (D), unlike in (B).

We do not insist that the gain curves in Fig. 4B increase exactly in a linear way (note that equal-sized saccades would result in a slightly non-linear gain function). We rather prefer to emphasize the monotonic behavior of the gain curves in Fig. 4B across the gaze shifts containing 1 to 6 saccades. We take it as evidence that the correction mechanism is the same with low versus high degrees of fragmentation. One could object that the slope of the gain curves decreases somewhat with increasing fragmentation (in a monotonous way, though), but we conceive that this might be related to the non-linear behavior of the gain of the first saccade in the gaze shifts (see above). Furthermore, we do not insist that the correction mechanism operates with the error feedback assumed in Fig. 5 C, D. Alternatively, one could conceive of a simpler, but functionally equivalent mechanism which essentially maintains the drive for saccades despite their premature disruption, as long as eye position does not match the internal notion of target position. However, both notions would be compatible with the concepts of SC function described above.

The correction mechanism in fragmented gaze shifts has thus far received little attention in the literature, unlike other extra-retinal correction mechanisms. For instance, saccadic gaze shifts are normally performed, phenomenologically speaking, with the 'strategy' to

bring the eyes ballistically in the vicinity of the target (large primary saccade) before accurately homing them in on target location (small correction saccades). In addition, small perturbations of saccade execution are accounted for by the correction saccades, which show normal ISIs. In contrast, large errors appear to be corrected at especially short ISIs (overview [4]). Thus, the correction in fragmented shifts is extraordinary in that the errors may be large and yet the ISIs are in the normal range (with few exceptions only; see Results). This applied equally to controls and patients, a finding, which suggests that the correction mechanism is the same in both subject groups and therefore unaffected in PD patients.

Finally, we come back to the concept of an abnormally weak pre-motor drive in PD and raise the question whether it can be applied in an analogous way to certain skeletal motor symptoms in PD. Although there are major differences between oculo- and skeletal motor systems, noteworthy analogies can be found. It has been shown that the initial agonist burst of ballistic arm movements of PD patients is often inadequately small and requires repetitive bursts to achieve sufficient speed [18], so that the EMG may become entrained at a tremor frequency [31], a finding that cannot be attributed to a prolonged reaction time [13, 28]. Additionally, an increase in the complexity of skeletal movements is associated with an increased number of bursts in the EMG [5] and, unlike controls, PD patients display multiple phase velocity profiles in complex tasks [21].

In conclusion, gaze shift fragmentation is a physiological phenomenon. It occurs when pre-oculomotor centers like the SC receive an abnormally weak drive signal from the cortico-striatal loops or are under inadequately strong inhibition. The resulting saccadic hypometria is accounted for by a thus far not adequately appreciated correction mechanism, which iteratively restarts saccadic activity and thereby prevents falling short of the gaze shift. Impairment of the basal ganglia route in PD increases the probability of this fragmentation, but spares the correction mechanisms. The observation of this fragmentation per se cannot be used as a diagnostic criterion in early stages of PD, but only the proof of its abnormally high incidence. Special saccade paradigms are required to assess fragmentation probability, like memory-guided saccades in a sequence, or non-instructed recentering saccades.

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