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RESEARCH ARTICLE

Interval timing and Parkinson's disease: heterogeneity in temporal performance

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Abstract Interval timing deficiencies in Parkinson's disease (PD) patients have been a matter of debate. Here we test the possibility of PD heterogeneity as a source for this discrepancy. Temporal performance of PD patients and control subjects was assessed during two interval tapping tasks and during a categorization task of time intervals. These tasks involved temporal processing of intervals in the hundreds of milliseconds range; however, they also covered a wide range of behavioral contexts, differing in their perceptual, decision-making, memory, and execution requirements. The results showed the following significant findings. First, there were two clearly segregated subgroups of PD patients: one with high temporal variability in the three timing tasks, and another with a temporal variability that did not differ substantially from control subjects. In contrast, PD patients with high and low temporal variability showed similar perceptual, decision-making, memory, and execution performance in a set of control tasks. Second, a slope analysis, designed to dissociate time-dependent from time-independent sources of variation, revealed that the increase in variability in this group of PD patients was mainly due to an increment in the variability associated with the timing mechanism. Third, while the control subjects showed significant correlations in performance variability across tasks, PD patients, and particularly those with high temporal variability, did not show such task correlations. Finally, the results showed that dopaminergic treatment restored the correlation effect in PD patients, producing a highly significant correlation between the inter-task variability. Altogether, these results indicate that a subpopulation of PD patients shows a strong disruption in temporal processing in the hundreds of milliseconds range. These findings are discussed in terms of the role of dopamine as a tuning element for the synchronization of temporal processing across different behavioral contexts in PD patients.

Keywords Interval timing · Time perception · Time production · Parkinson's disease · Heterogeneity of Parkinson's disease

Abbreviations

PD	Parkinson's disease
UPDRS	Unified Parkinson disease rating scale
MTT	Multiple tap task
STT	Single tap task
CAT	Interval categorization task
SD	Standard deviation
BGTCP	Basal ganglia-thalamocortical pathway

Introduction

Time and space constitute the essential framework in life. Thus, many behaviors in daily life depend on appropriate processing of temporal information. Time is fundamental for perception of speed and quantity, for producing and understanding speech and music, and for dancing and

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performing sports. A wealth of experimental evidence suggests the existence of a common timing mechanism for motor and perceptual tasks that require temporal processing in the range of the hundreds of milliseconds (Hazeltine et al. 1997). For instance, significant correlations between interval tapping and interval discrimination tasks have been documented (Keele et al. 1985; Treisman et al. 1992; Buonomano and Karmarkar 2002). These findings indicate that individuals who are good at producing intervals through tapping are also good at discriminating intervals, even if the perceptual, cognitive, and motor aspects of these tasks are different. In addition, Ivry and Hazeltine (1995) found that the variability on both perception and production tasks increases linearly as a function of the target interval, following the scalar property of interval timing (Gibbon 1977; Meck and Benson 2002), and that the slope of this increase was similar between the tasks suggesting again a common timing mechanism.

In the same vein, functional magnetic resonance imaging (fMRI) studies have demonstrated that the basal ganglia-thalamocortical pathway (BGTCP) is activated during both perceptual and motor timing tasks (Rao et al. 1997, 2001; Schubotz et al. 2000; Meck and Malapani 2004; Pouthas et al. 2005), implicating this network as part of the neural substrate for a common "internal clock" (Buhusi and Meck 2005). Given that the basal ganglia receive dopaminergic input from the substantia nigra, it is not surprising that systemic dopaminergic modulation with agonists or antagonists produces time underestimation and overestimation, respectively (Mariq and Church 1983; Harrington and Haaland 1999; Buhusi and Meck 2002). Based on this evidence, it has been suggested that the dopaminergic modulation of information flow across BGTCP is part of the neural mechanism for temporal processing in a variety of circumstances, including motor and perceptual interval timing (Meck 1996).

The deterioration of the dopaminergic input in Parkinson's disease (PD) is accompanied by a series of motor and cognitive deficits, and also by the disruption in the execution of tapping and discrimination tasks of time intervals (Harrington et al. 1998; O'Boyle et al. 1996; Pastor et al. 1992a, b; Artieda et al. 1992). These studies have reported an increase in timing variability in PD subjects with respect to normal controls, which supports the role of dopamine and BGTCP in interval timing. However, the literature is not consistent about this point. Ivry and Keele (1989) did not find timing deficits in 29 medicated PD patients that performed both interval tapping and discrimination tasks. In addition, other studies have found normal PD performance on timed tapping (Duchek et al. 1994), rhythmic tapping and circle drawing (Spencer and Ivry 2005). It is possible that this discrepancy may be due to variability of disease characteristics. Heterogeneity has been reported for PD patients with different rates of clinical progression [measured with unified Parkinson's disease rating scale (UPDRS) and Hoehn & Yahr scores], age of onset, antiparkinsonian medication dosage, and cognitive performance on a number of neuropsychological tests (Foltynie et al. 2002; Lewis et al. 2005; Schrag et al. 2006). Hence, it is reasonable to expect the existence of heterogeneity in PD with respect to temporal processing: some with normal and others with abnormal performance on temporal tasks. A skewed sample of PD subjects could lead to experimental results with or without temporal deficits, thereby explaining the discrepancy in the results reported in the literature.

In the present study we investigated the temporal performance of PD patients and control subjects during two interval tapping tasks and during a categorization task of time intervals. These tasks cover a wide range of behavioral contexts, differing in their perceptual, decision-making, memory and execution requirements. However, all tasks involved temporal processing of time intervals in the range of hundreds of milliseconds.

Methods

Subjects

Patients with PD and age-matched controls participated in this study. All subjects volunteered and gave consent for this study, which was approved by the University of Minnesota Institution Review Board, before commencement of experiments.

At screening, subjects underwent a neurological history and examination to exclude control and parkinsonian subjects with potentially confounding neurological factors. Extensive neuropsychological evaluations were performed to delineate aspects of cognitive function. This included the mini-mental status examination (Folstein et al. 1975), Beck depression inventory (Beck et al. 1961), Wechsler abbreviated scale of intelligence (The Psychological Corporation 1999), Petrides conditional associative learning test (Petrides 1997), trail making test parts A and B (Lezak et al. 2004), and the computerized version of the Wisconsin card sort test (Grant and Berg 1948; Heaton et al. 1993).

Two subsequent visits were scheduled for subjects within 3 months of screening. These subsequent visits were performed within 2 weeks of each other and were scheduled at the same time of day for each subject.

PD group (ON/OFF medication)

Testing was performed in two different medication conditions: OFF and ON medication. An OFF medication state

was achieved by having patients withhold their medication for a minimum of 12 h prior to testing. The ON medication state was when they were on their routine antiparkinsonian medications and obtaining optimal benefit. Randomization of ON and OFF states was done to address the potential of an order effect. The UPDRS and Hoehn & Yahr staging were used to systematically evaluate the signs and symptoms of PD. For the duration of this study, no antiparkinsonian medication changes were made by the investigators.

Controls

Control subjects were also tested on the UPDRS and Hoehn & Yahr staging.

Apparatus

Subjects were seated comfortably on a chair facing a Laptop Computer Monitor (Dell Latitude D505) in a quiet experimental room. They were asked to tap on an ultra-sensitive touch plate (4.7 × 6 cm, E-Z Call 7727, Crest-healthcare, Dassel, MN, USA) or push a key on the computer keyboard, depending on the task (see below). The stimulus presentation and the collection of the behavioral responses were controlled by the computer on a custom made Visual Basic program (Microsoft Visual Basic 6.0 1998), with a timing precision of 5 ms.

Experimental tasks

For the two separate visits, both PD patients and control subjects performed three repetitions for each of the following timing tasks.

Timing task 1: production of multiple time intervals (MTT)

a. Experimental task. The subjects produced tapping movements on a touch-plate device synchronized to a sensory stimulus (synchronization phase), and then they continued tapping with the same interval without sensory feedback (continuation phase). At the beginning of the trial, the stimuli were presented with a constant interval (target interval). The subjects were required to push a touch-plate each time a stimulus was presented, which resulted in a movement/stimulus synchronization. After 13 consecutive synchronized movements (12 intervals), the stimulus was eliminated, and the subject continued tapping with the same interval for 8 additional intervals. Feedback was displayed on the screen, indicating the subject's mean intertap interval and standard deviation (SD) for the continuation phase of the trial. The interval separating the synchronization and the continuation phase was not included in this feedback measure or in the further analyses. The intertrial interval was 1.5 s.

b. Stimuli. The stimuli were tones (50 ms, 200 Hz, 50 dB), and the interval durations were 350, 450, 550, 650, 850 or 1,000 ms. One repetition in the task included the six interval durations. The intervals were presented pseudorandomly.

Timing task 2: production of a single time interval (STT)

a. Experimental task. For each interval there was a training and an execution period. In the training period a target interval (two stimuli separated by a particular duration) was presented at the beginning of the trial. Then the subject tapped twice on the touch-plate to produce the same interval. This was repeated for ten training trials, after which the subject entered the execution period, where he/she produced a single interval after a go signal appeared on the screen. Again, feedback was displayed on the screen, indicating the subject's intertap interval and SD across trials of the same interval during the execution period. The intertrial interval was 1.5 s.

b. Stimuli. The same stimuli and interval durations of MTT were used. Ten trials (one repetition) during the execution period were collected for a particular interval duration before changing to another one. The intervals were chosen pseudorandomly.

Timing task 3: categorization of time intervals (CAT)

a. Experimental task. The subjects were trained first to press the "m" key on the keyboard after the presentation of a 350 ms (short) interval, or to press the "n" key after the presentation a 1,000 ms (long) interval. Categorization feedback was provided, with the word "correct" or "incorrect" on the screen. At least 20 trials (short/long) were performed on this training phase. Once the subject learned to associate the short and long intervals with the response on the "m" and "n" key, respectively, intermediate intervals were also presented. Thus the subject was required to push one of the keys to indicate his/her categorical decision for the six intervals using acquired category boundaries and an implicit standard interval (middle interval = 600 ms) set during the training period.

b. Stimuli. The same stimuli and interval durations of MTT were used. The first three were considered short

intervals while the last three were long intervals. One repetition in the task included the categorization of the six intervals. The intervals were presented pseudorandomly.

c. SD calculation. The difference threshold was defined as 1 SD from the implicit standard interval. In order to calculate this threshold, a psychometric curve was constructed, plotting the probability of long interval categorization as a function of the interval (see Fig. 1). A logistic function was fitted to this data, and the difference threshold was computed as half the subtraction of the interval at 0.75*p* (probability of long interval categorization) minus 0.25*p*. Details about the logistic function fitting are given below.

Timing tasks procedure

Both the PD patients and the control subjects performed a number of tasks divided among three sessions. In sessions two and three, the subjects performed three repetitions for each of the three timing tasks in the following order: MTT, STT and CAT. Practice trials were given before collection in the three tasks until the subjects acknowledge that they understood the tasks and were comfortable with their performance.

Control tasks

In the first session, PD patients (all were ON antiparkinsonian medication) and control subjects performed the following control task.

Control task 1: Hopkins verbal learning test—revised. In this task, a list of 12 words is presented for three consecutive learning trials, and rate of learning is recorded (Benedict et al. 1998). Within the word list, three semantic categories of four words each are represented. Following these trials, a list of 24 words containing the 12 target words and 12 distractors is presented, and recognition of the 12 targets is measured. After 25 min, a delayed recall trial is administered. *T*-scores are calculated for the recall, delay, retention, and recognition portions of the task.

In addition, in sessions two and three, control subjects and PD patients randomly assigned to an ON or OFF medication state performed the following control tasks.

Control task 2: digit span subtest of the WAIS-III. Subjects completed the digit span subtest of the WAIS-III (Wechsler 1997) according to standardized procedures. For Digits Forward, the subject was required to repeat increasingly longer strings of digits exactly as read by the examiner. Two trials were administered at each string length. Digits Backward followed similar procedures except that the subject was required to repeat the string of digits in reverse order. Forward and backward spans were calculated as the longest string of digits that the individual was able to correctly repeat in order.

Control task 3: go/no-go task. On this task, subjects were presented with white letters on a black background for 250 ms followed by presentation of a black screen for an intertrial interval of 1,000 ms (Braver et al. 2001). During the first half of the task (no-go block), subjects were instructed to press the spacebar as quickly as possible for all letters except for the letter X. During the second half of the task (Target Detection), they were instructed to press the spacebar exclusively when presented with the letter X. Each portion was composed of 120 trials, with 20% X's.

Data analysis

General. Standard statistical techniques were used for data analysis including *t* test, analysis of variance (ANOVA), and linear regression (Snedecor and Cochran 1989). It is important to mention that pair-wise *t* test (within group comparisons) were performed between groups ON versus OFF medication, whereas independent *t* test (between

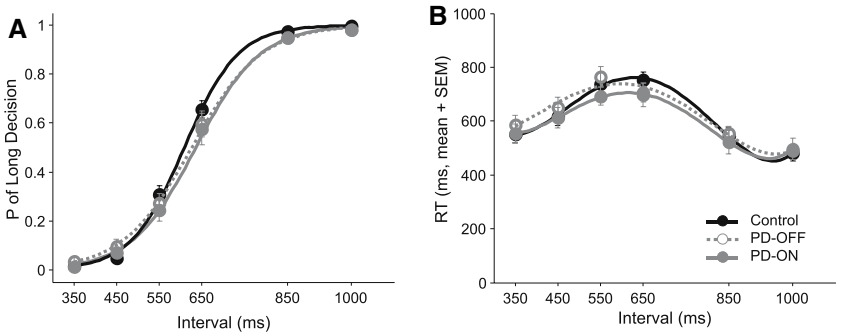

Fig. 1 **a** Psychometric functions (mean ± SEM) for the control (*black line*, *black filled circle*), PD-ON (*gray line*, *gray filled circle*) and PD-OFF (*gray dashed line*, *gray open circle*) main groups in the categorization task. The probability of long interval categorizations is plotted as a function of the interval. Logistic functions are fitted to the data. **b** Reaction times (mean ± SEM) as a function on time interval for the three main groups in the categorization task

group comparisons) were carried out between: (1) PD patients and control subjects or (2) high and low variability cluster subgroups (see "Results"). The level of statistical significance to reject the null hypothesis was $\alpha = 0.05$, that was adjusted for multiple comparisons using the Bonferroni correction in the t tests. The SPSS statistical package (version 12, SPSS, Inc., Chicago, IL, 2003) was used for all the statistical analyses.

Cluster analysis. We used a *K*-means cluster analysis (Johnson and Wichern 1998) on the SD of temporal performance in the three tasks in order to identify two groups of subjects: low and high variability timers. The cluster analysis was performed on the z-scored (variance-standardized) SD measure for the three timing tasks. We used an iterative method in order to find the centroids of the two clusters (version 12, SPSS, Inc., Chicago, IL, 2003).

Linear discriminant analysis. The two groups obtained in the cluster analysis were analyzed further using discriminant analysis (Johnson and Wichern 1998) for two reasons: first, to validate the classification obtained in the *K*-means analysis, by calculating the percentage of subjects classified into the same group by both techniques; and second, to derive classification functions, one for each subject group (low and high variability subjects), so that other subjects, not contained in our sample, could be classified in one of the groups.

Logistic regression. This regression is given by:

$$y = \frac{(p_1 - p_4)}{1 + \left(\frac{x}{p_3}\right)^{p_2}} + p_4$$

where p_1 and p_4 correspond to the minimum and maximum values of y, y is the probability of long interval categorization, p_2 is the estimated slope and p_3 correspond to the value of x (time interval) at half of the maximum value of y. The percentage of variance explained (R^2) was greater than 90% in all the fittings.

Results

Nineteen (10M: 9F) PD patients, mean (SD) age of 61.2 (10.6) years, (range 44–78 years) and mean (SD) disease duration was 5.8 (4.5) years (range 1–15 years) participated in this study. All but one subject were right-handed. At the time of testing no disabling tremors, motor freezing, or dyskinesias were present that may have interfered with performance on the various tasks. Clinical features of PD are demonstrated in Table 3 in terms of total UPDRS scores for ON and OFF medication states.

Eighteen (8M:10F) control subjects, mean (SD) age of 59.3 (8.7) years, (range 49–77 years) participated in this study. None had a history of a neurological disorder or a disability that could interfere with their performance in the timing tasks. All but one subject were right-handed.

Neuropsychological testing and measures of mood did not demonstrate strong or clinically meaningful differences between PD patients and controls. There was no evidence of dementia based on the mini-mental status examination score in any subject. Prorated IQ scores were on average 119.9 in PD subjects and 118.8 in controls, which are in the high average range. PD subjects were comparable to controls on most neuropsychological functions with two exceptions. PD subjects were slower to complete part A of the trail-making test. Their performance on part B, which is more demanding, was not different from that of control subjects. In addition, depression levels, as measured by the Beck depression inventory, were significantly higher in the PD group than controls; however, both groups' scores indicated that they did not have clinical depression.

We analyzed separately the PD group ON and OFF antiparkinsonian medications. Therefore, we had three main subject groups: control, PD-ON and PD-OFF.

Basic timing performance in the categorization task

Our categorization task followed the method of constant stimuli in order to build psychometric curves and then calculate the categorization threshold and timing variability. Figure 1a shows the psychometric curves for the three main subject groups and two clear observations can be made. First, the curves were sigmoidal, with correct categorical responses in the extreme short and long intervals, and decision errors in the intermediate intervals. This is the typical shape of a standard psychometric function. Second, due to the above properties, the psychometric functions were well suited to measure temporal acuity. For instance, the subjects not only had categorization errors in the intermediate intervals, but also the RT increased according to the degree of timing certitude (Fig. 1b). In fact, this task is practically a time bisection task, which has been used widely in the timing literature in either human subjects (Wearden 2004) or animal models (Church and Deluty 1977). That said, it is important to clarify that better measures can be used to determine temporal acuity in perception tasks, including the parameter estimation by sequential testing (PEST) (Ivry and Keele 1989).

Variability (SD) of temporal processing

The SD increased as a function of the interval in both production tasks, which follows the scalar property of temporal processing (Fig. 2). Furthermore, in both tasks (MTT, STT), the PD-ON and PD-OFF groups showed an

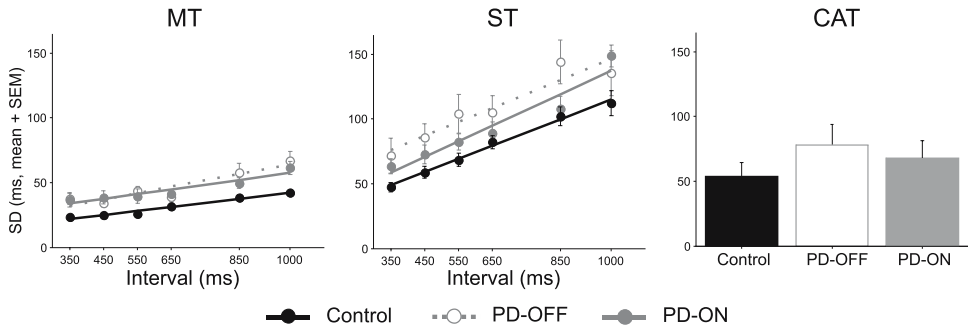

Fig. 2 Standard deviation (SD; mean ± SEM) as a function of time interval for the different timing tasks for the control, PD-OFF, and PD-ON groups. Same color conventions as in Fig. 1

increase in SD with respect to the control group. Thus, in the MTT task, this increase was statistically significant between the control and PD-ON [*t* test; $t(220) = 5.9$, $P < 0.0001$] and between the control and PD-OFF groups [*t* test; $t(220) = 6.2$, $P < 0.0001$]. For the STT task the SD results were very similar. *T* tests again showed a significant increase in SD between the control and PD-ON [$t(220) = 2.8$, $P < 0.005$] and between the control and PD-OFF groups [$t(220) = 3.9$, $P < 0.0001$].

In the CAT task the SD was significantly different between subject groups, with a significant increase in SD between the control and PD-OFF [*t* test; $t(35) = 2.5$, $P = 0.017$], but not a significant effect between the control and PD-ON [*t* test; $t(35) = 1.7$, $P = 0.104$].

Taken as a whole, the variability in temporal performance in the production and perceptual tasks was higher in PD patients, especially when OFF medication, than in control subjects.

Finally, ANOVAs comparing SD across tasks for the control, PD-ON, and PD-OFF groups independently, showed a significant effect for tasks in the three subject groups ($P < 0.0001$ for the three ANOVAs). The SD was significantly larger in the STT than in the MTT and the CAT tasks for the three subject groups (Tukey test, $P < 0.001$, all groups), and also the SD was significantly larger in the CAT than in the MTT for the three subject groups (Tukey test, $P < 0.001$, all groups).

Overall, these results suggest that the variability in the MTT task is lower than the STT and CAT tasks, probably because in the former the repetitive nature of the tapping could confer some advantage that is not present in the single interval production or categorization of the later tasks. This effect was already reported in control subjects (Ivry and Hazeltine 1995).

Cluster analysis

We performed a *K*-means cluster analysis on the SD for the three tasks with the purpose of testing the existence of two groups of subjects: low and high variability timers. The cluster analysis was performed separately for the control and the PD-OFF group. In both cases the analysis could find two segregated clusters. For the control group, the most important variable for separating low from high variability timers was the SD in the CAT task, followed by the SD in MTT and STT tasks (*F* test, $P < 0.0001$, $P = 0.02$, $P = 0.1$, respectively). Figure 3 shows the SD for the two clusters in this task, and it is evident that the low and high variability subjects are segregated.

For the PD-OFF group, the cluster analysis also clearly identified groups of low and high variability timers (Fig. 3 left-bottom). In this case, the most important variable for separating low from high variability timers was the SD in STT task, followed by the SD in CAT and MTT tasks (*F* test, $P < 0.002$, $P = 0.011$, $P = 0.037$, respectively). We used the clustering information of the PD-OFF analysis to classify the subjects in the ON medication condition. The results (Fig. 3 right-bottom) indicate that there was a decrease in the three tasks SD in the high variability PD group during the ON condition.

Discriminant analysis

These analyses validated the clustering results obtained independently for the control and the PD-OFF groups: there was a perfect concordance between the discriminant and clustering analyses. This means that all subjects were assigned to the same group (high/low variability) by both analyses.

The classification functions for the PD-OFF group were

$$\text{High variability group: } C = -73.887 + 0.722\alpha + 0.482\beta + 0.245\delta$$

$$\text{Low variability group: } C = -28.787 + 0.469\alpha + 0.292\beta + 0.149\delta$$

where *C* is classification function, α, β, and δ are SD during the MTT, STT and CAT tasks, respectively. Given α, β, and δ for a specific subject, *C* can be calculated for each group and the subject will be classified to the group that yields the largest *C*.

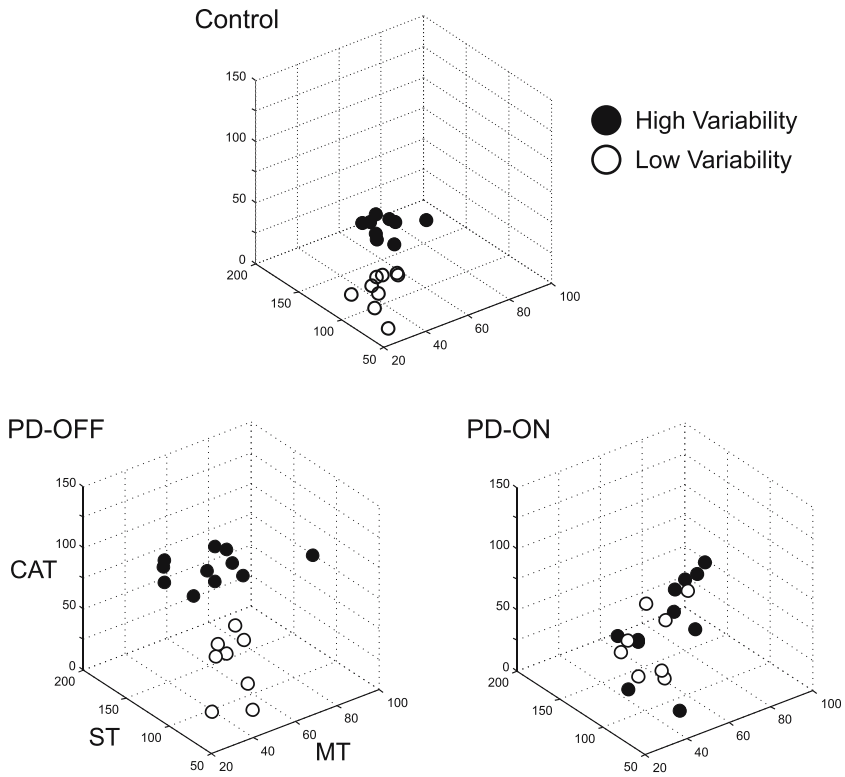

Fig. 3 3D scatter plots of the SD across the three timing tasks for the control, PD-OFF and PD-ON groups. Subjects that were classified on the cluster analysis as high variability timers are depicted in *filled circles*, and low variability timers in *open circles*

The classification functions for the control group were

High variability group: $C = -14.146 - 2.545\alpha - 8.645\beta - 18.895\delta$

Low variability group: $C = -1.697 - 2.306\alpha - 0.365\beta + 3.349\delta$.

The above notation was used. Obviously, the same procedure should be followed to find the group of a particular control subject.

Cluster groups properties: SD

Table 1 shows the SD (mean ± SD across subjects) for the different timing tasks and the six cluster-groups [three subject groups (control, PD-ON, PD-OFF) × two variability clusters (high/low)]. It is clear that there were complex relations between task and cluster-group. Therefore, all possible cluster-group pair comparisons were performed using *t* tests (Zar 1996; Table 2). The results showed the following main points: (1) the PD-OFF patients with high variability showed a significantly higher SD in the three tasks with respect to the other five cluster groups. (2) There was no significant difference in SD in the timing tasks between the PD-OFF patients with low variability and the PD-ON patients with low and high variability, and the control subjects with high and low variability. (3) The control subjects with high variability had an SD that was not significantly higher than most of the PD patient cluster groups.

Table 1 SD (mean ± SD) for six different cluster groups and three timing tasks

Task	Cluster group	SD (mean ± SD)
MTT	PD-OFF high variability (n = 11)	52.58 ± 15.39
	PD-OFF low variability (n = 8)	37.90 ± 9.48
	PD-ON high variability (n = 11)	48.45 ± 12.74
	PD-ON low variability (n = 8)	38.97 ± 15.41
	Control high variability (n = 9)	34.37 ± 6.34
	Control low variability (n = 9)	27.17 ± 5.58
STT	PD-OFF high variability	127.63 ± 34.17
	PD-OFF low variability	66.51 ± 30.29
	PD-ON high variability	96.53 ± 13.14
	PD-ON low variability	90.43 ± 21.02
	Control high variability	84.81 ± 16.14
	Control low variability	73.15 ± 9.95
CAT	PD-OFF high variability	95.77 ± 27.54
	PD-OFF low variability	52.90 ± 30.90
	PD-ON high variability	62.67 ± 37.14
	PD-ON low variability	59.35 ± 15.94
	Control high variability	74.52 ± 8.24
	Control low variability	32.54 ± 14.34

These results suggest that our PD patients were not homogenous in terms of temporal processing. There was a

Table 2 *t* Test comparisons of the SD for all tasks between cluster groups

Cluster group (*i*)	Cluster group (*j*)	Mean difference (*i* – *j*)	Sig.
PD-OFF high variability	PD-OFF low variability	39.556	0.000
	PD-ON high variability	20.445	0.024
	PD-ON low variability	27.079	0.006
	Control high variability	27.428	0.000
	Control low variability	47.707	0.003
PD-OFF low variability	PD-ON high variability	–14.111	0.018
	PD-ON low variability	–12.476	0.120
	Control high variability	–12.127	0.120
	Control low variability	8.152	0.101
PD-ON high variability	PD-ON low variability	6.635	0.401
	Control high variability	6.984	0.698
	Control low variability	27.263	0.000
PD-ON low variability	Control high variability	0.349	0.962
	Control low variability	20.628	0.005
Control high variability	Control low variability	20.279	0.003

subgroup of PD patients that showed a much higher variance in the three tasks and another group of patients with a SD that was slightly higher but not significantly different from control subjects. The results also demonstrate that the levodopa dosage equivalents (LDE) decreased significantly the SD in the timing tasks, particularly in the PD patients with high variability. Finally, the results indicate that even if the control subjects can be classified in high and low variability timers, their temporal variance is significantly lower than in PD patients.

Cluster groups properties: slope analysis

We used the slope method to analyze further the SD of the different cluster groups in the MTT and STT tasks. This analysis assumes that the total variability in a timing task can be decomposed in the variability associated to the timing mechanisms and the variability resulting from duration-independent processes. Thus, the slope method uses a linear regression between the variability and the interval duration, and the resulting slope and intercept correspond to the time-dependent and time-independent processes, respectively (Ivry and Hazeltine 1995). The main objective here was to test whether the time-dependent variability (slope) was different between cluster groups. Figure 4 shows the regressions between the SD and interval in the MTT task for each subject and cluster group. It is evident that the PD-OFF patients with high variability (Fig. 4a) can be separated in two subpopulations: subjects that showed high variability but negative slopes (Fig. 4a, gray area), and subjects with large and positive slopes. The first subgroup did not follow the scalar property of interval timing, suggesting a deep disruption in its temporal processing mechanism. Indeed, these three subjects also showed also negative slopes in the STT task (data not shown), and a *t* test between the slopes and intercepts in the ON and OFF condition did not showed statistically differences in the MTT [slope: $t(2) = -0.03$, $P = 0.97$; intercept: $t(2) = -1.33$, $P = 0.31$] and STT [slope: $t(2) = -1.04$, $P = 0.409$; intercept: $t(4) = 3$, $P = 0.95$] tasks. Therefore, these results suggest that a subgroup of PD-OFF patients with high variability do not follow the scalar property of timing processing and administration of their antiparkinsonian medication does not induce an improvement in their temporal performance.

In contrast, the remaining PD-OFF patients with high variability showed very large slopes (Fig. 4a). With the purpose of determining whether the clustering of these PD-OFF patients with high variability was related to an increase in the time-dependent variability and not due to duration independent processes, we performed *t* test for the slope and intercept between all cluster groups. The main results were the following: (1) the slope in the MTT and STT tasks for PD-OFF patients with high variability was significantly larger than the PD-OFF patients with low variability [MTT: $t(14) = 2.9$, $P = 0.01$; STT: $t(14) = 2.8$, $P = 0.01$], and larger than the same high variability PD patients but ON medication [MTT: $t(7) = 3.1$, $P = 0.017$; STT: $t(7) = 2.6$, $P = 0.05$]. (2) The slope of the PD-OFF patients with high variability was significantly larger than the two cluster groups of control subjects in the MTT [High variability: $t(15) = 3.1$, $P = 0.007$; Low variability: $t(15) = 3.9$, $P = 0.001$] and the STT [High variability: $t(15) = 2.9$, $P = 0.01$; Low variability: $t(15) = 3.7$, $P = 0.002$]. (3) The intercept of the PD-OFF patients with high variability was not significantly different from the other PD and control cluster groups in the MTT and STT

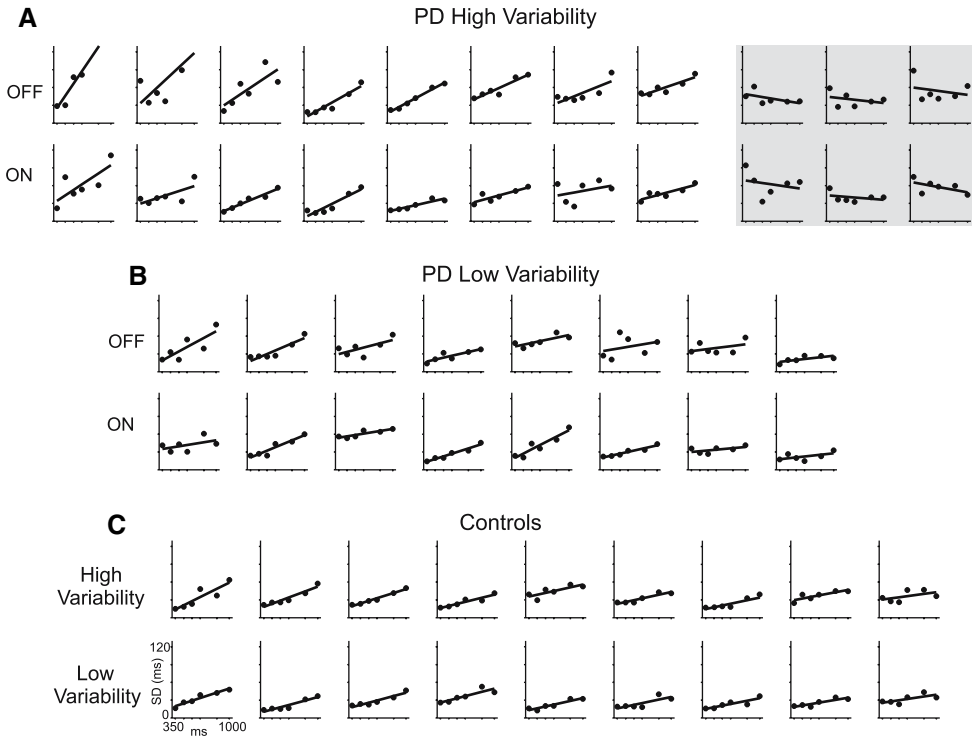

Fig. 4 Individual subject regressions between the SD and the time interval during the MTT task across cluster groups. The subjects were ordered in descending order according to their slope. **a** PD patients with high variability, OFF and ON medications. The three subjects on the right inside the gray area are the subjects with negative slopes and that did not follow the scalar property. **b** PD patients with low variability, OFF and ON medications. **c** Control subjects with high and low variability in the cluster analysis. The maximum SD value was set to 130 ms, which even if eliminated some data from the first two PD patients with high variability in **a**, was an appropriate scale to visualize the range of SDs across all cluster groups

tasks. Table 3 shows the intercept and slope (mean ± SD across subjects) for the MTT and STT tasks across all cluster-groups.

The separation of the total variability in time dependent and independent components using the slope analysis suggests three main points. First, the observed PD-OFF clustering was mainly due to a disruption of the timing mechanism in the high variability group, since these patients showed either a significant increase in slope or did not follow the scalar property of interval timing. Two, the increase in time-dependent variability was observed only in the PD-OFF but not the PD-ON condition, suggesting that the treatment with LDE produces a clear improvement in temporal performance in PD patients. Finally, the time-independent component of the total variability, that may include processes such as the stimulus detection, attention, memory, and motor implementation and execution, did not show significant differences across the cluster groups. This result confirms the notion that the high variability PD-OFF subgroup showed specific deficits in temporal processing. However, their sensory-motor and cognitive performance was similar to control subjects. Indeed, the following two sections are focused on providing independent evidence on support of these findings.

Cluster groups properties: neurological evaluations

The UPDRS and Hoehn & Yahr staging (mean ± SD across subjects) for the different tasks and cluster-groups are shown in Table 4. We performed *t* tests among all possible cluster-groups. The results showed that: (1) the UPDRS and the Hoehn & Yahr scores for PD-OFF patients with high variability were not significantly different from the PD-OFF patients with low variability or the two subgroups of PD-ON patients; (2) the high and low variability subjects of the control groups did not show statistically significant differences in these two measures. These results support the idea that the high variability PD subgroup showed deficits in temporal processing and not specific motor impairments that could be reflected in the SD of the timing tasks.

In addition, we also compared the maximum tapping speed between the cluster-groups (Table 4) using *t* tests. The results showed that the maximum tapping speed was significantly different between the PD and control subjects ($P < 0.0001$ for all cluster-group comparisons). Nevertheless, no significant differences were found between the high and low variability subgroups in the PD-OFF [$t(17) = -0.43$, $P = 0.672$], PD-ON [$t(17) = 1.59$, $P = 0.13$], or between the control groups [$t(16) = 1.24$, $P = 0.231$]. These results corroborate that the high variability timers (PD and controls) did not show tapping impairments that could cause their increase in their temporal variability.

Finally, we did not find statistical differences between PD cluster-groups for subject age, disease duration or LDE (*t* tests, all $P > 0.05$). Eight PD patients had fluctuations in their medication responsiveness (motor fluctuators). However, they were distributed across the high/low variability

Table 3 Intercept (β) and slope (mean ± SD) from the slope analysis in the MTT and STT tasks for the six different cluster groups

Cluster group	β MTT	Slope MTT	β STT	Slope STT
PD-OFF high variability	–2.84 ± 23.7	0.094 ± 0.04	–4.5 ± 56.6	0.207 ± 0.08
PD-OFF low variability	13.9 ± 14.8	0.036 ± 0.02	16.2 ± 48.9	0.078 ± 0.08
PD-ON high variability	9.9 ± 15.9	0.049 ± 0.02	14.4 ± 39.9	0.129 ± 0.06
PD-ON low variability	14.4 ± 17.5	0.035 ± 0.02	7.9 ± 53.4	0.128 ± 0.08
Control high variability	9.47 ± 11.9	0.037 ± 0.01	8.5 ± 28.6	0.087 ± 0.06
Control low variability	7.22 ± 5.7	0.031 ± 0.01	12.5 ± 19.9	0.076 ± 0.05

Table 4 Different variables (mean ± SD) for the six different cluster groups

Cluster group	UPDRS	Hoehn & Yahr	Fast tapping	Age (years)
PD-OFF high variability	49.3 ± 29.83	1.9 ± 1.1	66.8 ± 29.9	61.8 ± 11.4
PD-OFF low variability	44.13 ± 17.7	1.6 ± 0.5	72.3 ± 22.6	60.3 ± 9.9
PD-ON high variability	35.9 ± 14.4	1.8 ± 0.6	90.8 ± 18.8	61.8 ± 11.4
PD-ON low variability	34.0 ± 10.8	1.6 ± 0.4	78.5 ± 12.9	60.3 ± 9.9
Control high variability	4.1 ± 3.3	0.0 ± 0.0	106.1 ± 16.1	62.6 ± 8.0
Control low variability	1.3 ± 0.9	0.1 ± 0.2	118.3 ± 24.6	55.9 ± 6.4

subgroups. Five motor fluctuators were low variability timers, whereas three motor fluctuators were high variability timers.

In summary, after evaluation of various clinical aspects of the PD subjects, it appears that the differences in temporal performance within cluster-groups is not due to common ascertainable clinical features of disease including motor impairments.

Cluster groups properties: memory and attention scores

It could be argued that the deficiencies in PD patients, particularly those in the high variability cluster subgroup, were not related to disruptions in central timing operations, but to cognitive process that are required for the performance of the timing tasks. For instance, auditory perception and attention, as well as short- and long-term memory are involved in our three timing tasks. Therefore, in order to determine the cognitive status of PD patients and controls, we examined their performance in the Hopkins verbal learning test, the digit span, and the go/no-go tasks. These control tasks evaluate long-term memory, short-term memory and attention levels. Tables 5 and 6 show the scores (mean ± SD) for the different measures associated with these three tasks, across cluster-groups. The digit span and go/no-go tasks were performed in two visits, both ON and OFF anti-parkinsonian medications (Table 5), whereas the Hopkins verbal learning test was conducted only in the ON medication state (Table 6).

Two measures were taken in the digit span task: the digit backward score that measures verbal working memory, and the digit forward score that evaluates short-term verbal/auditory attention. The *t* test analyses showed no significant differences in the digit backwards and forward scores between the high and low variability subgroups in the PD-ON [backwards: $t(17) = -2$, $P = 0.067$; forward: $t(17) = -1.8$, $P = 0.078$], PD-OFF [backwards: $t(17) = -1.5$, $P = 0.15$; forward: $t(17) = -1.9$, $P = 0.057$], or the control cluster-groups [backwards: $t(16) = 1.68$, $P = 0.112$; forward: $t(16) = 0.52$, $P = 0.607$]. Hence, these results suggest that the temporal impairments observed in these PD patients are not related to working memory or auditory attention deficits.

The go/no-go task performance was quantified with the following measures: no-go hit and false alarm rates, target detection false alarm rate, and average reaction time during the go trials on the no-go task. These measures not only reflect the ability of subjects to inhibit responses, but also their capacity to maintain high levels of attention in order to inhibit or trigger a behavioral response. The cluster subgroup comparisons again showed no significant differences in these measures between the high and low variability subgroups in the PD-ON, PD-OFF, or the control groups ($P > 0.05$, *t* test, all comparisons).

Finally, the Hopkins verbal learning test determines the subject's capabilities to recall, retain and recognize words in a long-term memory context. *T*-scores for the recall, delay, retention, and recognition portions of the task were compared between high and low variability timing subgroups using *t* tests (see Table 6). No significant

Table 5 Digit span and go/no-go task scores (mean ± SD) for the six different cluster groups

Cluster group	Digit span backward	Digit span forward	No-go hit rate	No-go false alarm rate	RT go trials
PD-OFF high	5.0 ± 0.8	6.4 ± 1.3	0.94 ± 0.1	0.33 ± 0.2	162.2 ± 59.4
PD-OFF low	5.8 ± 1.3	7.6 ± 0.9	0.90 ± 0.2	0.24 ± 0.2	142.9 ± 42.2
PD-ON high	4.7 ± 0.9	6.2 ± 0.8	0.89 ± 0.1	0.33 ± 0.2	159.9 ± 90.9
PD-ON low	5.8 ± 1.3	7.1 ± 1.1	0.92 ± 0.1	0.31 ± 0.1	154.2 ± 69.7
Control high	5.3 ± 1.2	7.2 ± 1.1	0.98 ± 0.0	0.18 ± 0.1	160.3 ± 33.1
Control low	6.4 ± 1.4	7.4 ± 1.1	0.97 ± 0.0	0.13 ± 0.1	129.4 ± 43.6

Table 6 Hopkins verbal learning test (HVLT) *T*-scores (mean ± SD) for four different cluster groups

Cluster group	HVLT recall	HVLT delay	HVLT recognition	HVLT retention
PD high variability	50.3 ± 8.7	52.5 ± 9.2	51.5 ± 9.3	51.2 ± 6.8
PD low variability	54.5 ± 10.0	53.8 ± 8.1	52.4 ± 7.9	50.4 ± 5.3
Control high variability	56.5 ± 8.8	54.8 ± 7.1	53.8 ± 7.5	51.0 ± 5.6
Control low variability	54.2 ± 12.7	50.7 ± 10.6	53.0 ± 5.8	46.7 ± 7.6

differences for all the Hopkins verbal learning test measures were observed between the high and low variability subgroups in the PD-ON or the control groups ($P > 0.05$, all comparisons). Therefore, these results suggest a clear independence between timing performance in our three timing tasks and the long-term memory abilities of PD and control subjects.

In conclusion, the memory and attention abilities of PD and control subjects were similar in the high and low-variability subgroups, and consequently, the timing deficits in the PD cluster-subgroups were not due to cognitive impairments.

Correlation analysis

We performed a correlation between the SD for the three tasks in order to determine whether this analysis could suggest a common neural mechanism across the tasks in control subjects, as well as to evaluate the level of inter-task correlation in PD patients. The results, depicted in Fig. 5, show a significant correlation of SD among the three tasks in the control group. This indicated that some control subjects were consistently good timers across tasks and others were bad timers in the three timing paradigms. Thus, these data support a common mechanism for interval timing across our tasks in the controls.

Interestingly, there were no significant correlations for the SD between the tasks in the PD-OFF group (Fig. 5), suggesting a disruption in a theoretical common timing mechanism in such patients. In contrast, there were significant correlations between the MTT and the STT and CAT tasks when the same patients were ON medicine. This finding is noteworthy, since it is suggests that antiparkinsonian medication caused an inter-task synchronization on temporal processing.

These last results were more evident when we segregated the PD patients in high and low variability timers using the clustering results. We found that the correlation of SD was not significant between tasks for patients with high variability and OFF medicine (Fig. 6); however, the same patients ON medicine showed a significant correlation between MTT and STT. On the other hand, patients with low variability and OFF medicine showed significant correlations between MTT and STT and CAT tasks. However, when the same patients were ON medicine, these subjects showed a dramatic increase in the tasks correlations as is depicted in Fig. 6.

In summary, the correlation analyses suggest, according with previous studies, that there is a common timing mechanism for production and perception of time intervals. More importantly, this analysis also suggests that PD patients OFF medicine, and particularly the high variability timers, show a disruption on temporal processing that resulted in a lack of SD correlation between the three tasks. Thus, in PD patients the timing variability not only showed an overall increment, but also changed in an inconsistent fashion across timing tasks. Finally, we demonstrated that antiparkinsonian medications produce an increase in inter-task SD congruency across subjects, acting probably as a tuning element of the timing mechanism.

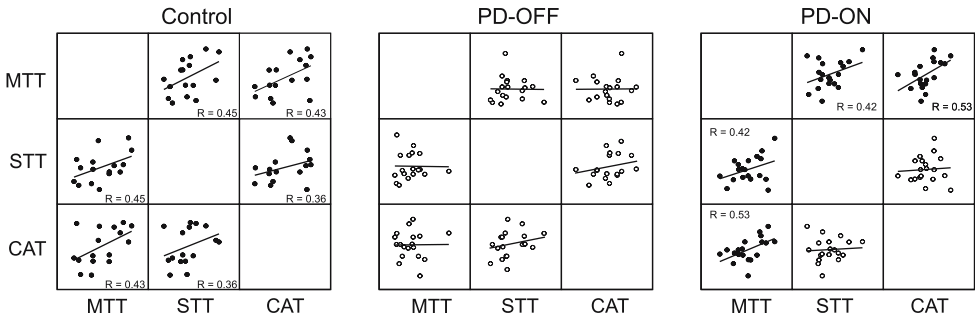

Fig. 5 SD correlation matrices across timing tasks for the control, PD-OFF and PD-ON groups. *Filled* and *open circles* correspond to significant and non-significant task correlations, respectively

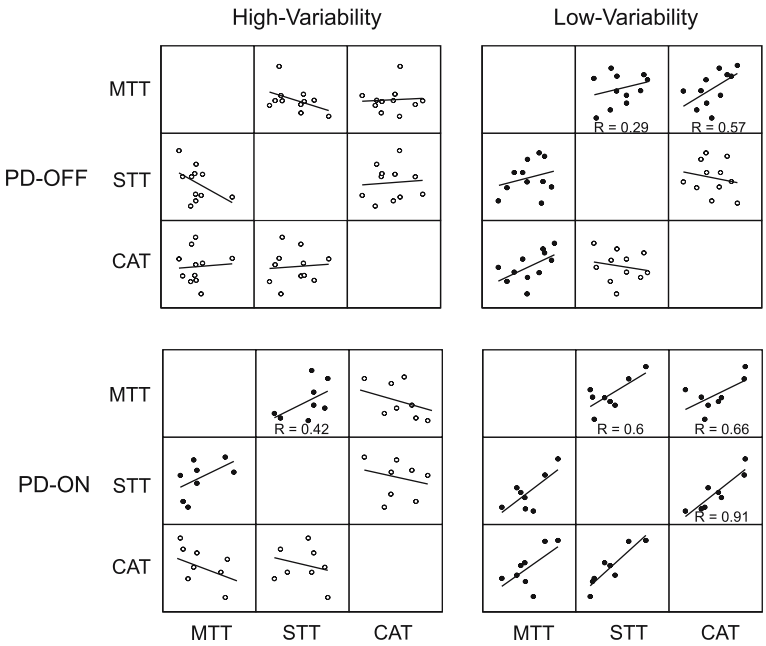

Fig. 6 SD correlation matrices across timing tasks for the high and low variability subgroups in PD patients ON and OFF medication. *Filled* and *open circles* correspond to significant and non-significant task correlations, respectively

Discussion

PD heterogeneity for temporal performance

The present study explored the abilities of PD patients to process temporal information across different timing tasks using intervals in the range of hundreds of milliseconds. Cluster and discriminant analyses revealed heterogeneity of temporal performance in our PD population; with a subgroup of high variability timers throughout all tasks, and a subgroup of PD patients with a temporal variability that did not differ substantially from control subjects. Thus, our results corroborate that the PD population encompasses a spectrum of clinical phenotypes, with subgroups that can be defined on the basis of different rate of clinical progression (measured with UPDRS and Hoehn & Yahr scores), age of PD onset, dose of levodopa, different cognitive performance in a number of neuropsychological tests (Foltynie et al. 2002; Lewis et al. 2005; Schrag et al. 2006), and now temporal processing.

Timing research has made important efforts to dissociate central from peripheral sources of timing variability (Wing and Kristofferson 1973). For example the slope analysis (Ivry and Hazeltine 1995), where a linear regression between the timing variability and the interval is performed, assumes that the slope is associated with the time-dependent component following the scalar property of interval timing (Gibbon et al. 1997). In addition, it is assumed that the intercept represents the time-independent source of variability, which should be constant across all the intervals tested and that may include processes such as the stimulus detection, attention, memory, and motor implementation and execution (Ivry and Hazeltine 1995; Spencer and Zelaznik 2003). The slope analysis on the present data showed that the increase in temporal variability in the PD-OFF patients was related to an increase in the slope but not in the intercept during the MTT and STT tasks. Hence, based on the slope model assumptions, our results indicate that the PD-OFF cluster subgroup with high variability was specifically impaired in their ability to

process temporal information with respect to the other cluster subgroups, including control subjects. Furthermore, three PD-OFF patients with high variability simply did not follow the scalar property, showing negative slopes (Fig. 5a, gray area). This observation corroborate previous studies where it has been reported that PD patients do not follow the scalar property in a peak-interval task using 8 or 21 s intervals (Buhusi and Meck 2002, 2005). Therefore, our results suggest that the heterogeneity in PD-OFF patients is due to a malfunction of the timing mechanism in the hundred of milliseconds range that can be reflected in a disruption of the scalar property or a large increase in the time-dependent variability.

The analysis of various features of subjects including memory and attention abilities in the cluster subgroups, support that the performance heterogeneity in our timing tasks was mainly due to a disruption in temporal processing in a subpopulation of PD patients. Indeed, the differences in temporal performance within cluster-groups are not due to obvious differentiating clinical features including motor impairments of the PD subjects. High and low variability PD timers showed similar disease duration, LDE, as well as UPDRS and Hoehn & Yahr scores. Furthermore, the maximum tapping speed between the cluster-groups was also similar. The same can be said for memory and attentional capabilities, since the performance of high and low variability PD and control subjects was very similar in our three control tasks. It is well known that timing tasks possess stimulus detection, attention, memory, decision and motor components (Gibbon 1977; Wearden 2004). Most of these components are included in the Hopkins verbal learning test, the digit span, and the go/no-go tasks, since they evaluate with different degrees long-term memory, short-term memory, and attention levels using auditory or visual cues. Therefore, our results clearly rule out the possibility that the PD heterogeneity for temporal performance is due to deficiencies in performance in the non-temporal aspects of our timing tasks. That said it is important to consider that some studies have shown deficits in kinaesthesia (Klockgether et al. 1995) and the perception of visual and auditory stimuli in PD patients (Bandini et al. 2002; Pekkonen et al. 1998). However, such deficits were probably not reflected in the timing processing since the performance of PD patients in the control tasks was not different between cluster subgroups.

Cluster and discrimination analysis

A note of caution regarding cluster analysis is in order here. As admitted before, *K*-means cluster analysis is very dependent on the variables that are entered, the number of sought clusters, and the subjects included in the population (Lewis et al. 2005; Schrag et al. 2006). Here, we used the variability in temporal performance across three timing tasks as clustering variables; a choice in variables that pursued the hypothesis that individual subjects with timing deficiencies will show a consistently poor performance across tasks. This hypothesis was confirmed. In addition, the subsequent discriminant analysis had perfect agreement with the clustering results, validating the existence of high and low variability PD timers. With this analysis, we derived discriminant classification functions that can be used to segregate PD patients into high and low variability timers. Finally, the results of the clustering analysis demonstrated that high variability timers were more sensitive to dopaminergic therapy, since they showed a significantly larger decrease in timing variability, when ON medication, than the low variability subgroup. Hence, all these evidences support the hypothesis of timing heterogeneity.

As a final point, it is important to note that control subjects were also successfully divided in two clusters. However, the analysis showed that the timing-dependent variability (slope) of both groups of control subjects was statistically lower than in the PD-OFF patients with high variability. Thus, even if timing abilities are not homogenous in normal human subjects, our results suggest that PD patients, and particularly those with high temporal variability, show an impaired ability to process time in the hundreds of milliseconds range.

Heterogeneity over the dopaminergic system and interval timing

Here we described an interval timing heterogeneity among PD patients. Needless to say that this heterogeneity should have an anatomo-functional substrate. Since the treatment with LDE produces a specific improvement in temporal performance in PD patients, it is reasonable to suspect that the high versus low variability timers show differential dopamine deficiencies. Indeed, recent lesion and pharmacological experiments (Meck 2006a, b) have suggested that the timing mechanism depends on the integrity of the nigrostriatal dopaminergic system (including the substantia nigra pars compacta and the caudate-putamen) and the cerebellum (Spencer and Ivry 2005). In contrast, the mesolimbic and the mesocortical dopaminergic systems (including the ventral tegmental area, the ventral striatum and the prefrontal cortex) are associated with working memory and quantification of reward, in that order (Goldman-Rakic et al. 2004; Schultz 2006). However, the last two systems are not directly involved in temporal processing. Therefore, these findings suggest the possibility that PD patients with high or low temporal variability show a differential dopaminergic degeneration involving

preferentially the nigrostriatal or the mesolimbic/mesocortical systems, respectively (Rammsayer 1997). Of course, additional experiments are needed to test this hypothesis.

Task correlation in timing variability

We correlated the timing variability across tasks in order to test the existence of a common timing mechanism among our three timing tasks. Indeed, significant correlations were found in the MTT, STT and CAT tasks in control subjects. These results support the hypothesis of a centralized timing clock stated in different studies (Keele et al. 1985; Treisman et al. 1992; Buonomano and Karnahan 2002).

One of the most suggestive findings in the present paper is the lack of significant inter-task SD correlations in PD patients OFF medication. This effect indicates that PD patients not only show an increase in timing error and variability, but also that the increase in SD was not correlated across tasks. Therefore, our results suggest that the deterioration of the dopaminergic input in PD patients causes a strong disruption in the common timing mechanism. This disruption may be associated with a generalized noise increase in temporal processing, which leads to an increase in timing variability across tasks, and may also consequently obscure the task correlations. An alternative explanation is that the lack of SD correlation in PD patients was related to an increment in the non-timing related variability involved in the three timing tasks. However, this is unlikely, since the slope analysis revealed a specific increase in time-dependent variability in the PD-OFF patients.

Dopamine as a tuning factor during interval timing

The lack of inter-task SD correlation was reverted by the administration of the usual dopaminergic medications in PD patients. Thus, the medication decreased the overall timing variability in the three tasks, as reported previously (Pastor et al. 1992a, b; Artieda et al. 1992; Malapani et al. 1998). In addition, the medications induced congruency in the timing variance across tasks in PD patients. This inter-task temporal congruency was more dramatic in low-variability timers, where the SD correlation was even higher than in the controls (Fig. 3).

A recent fMRI study (Elsinger et al. 2003) reported a decrease in brain activation within the motor cortex and the supplementary motor area (SMA) in PD patients during a MTT task. Interestingly, these authors found that the decrease in timing variability produced by the dopaminergic therapy was accompanied with an increase in the activation of SMA, motor cortex and putamen. Hence, it is probable that the increase in the inter-task SD correlation observed in our PD-ON group was due to an increase in activity of BGTCP. In this sense, neurophysiological experiments in PD patients and animals provide another clue. The restoration of the activity across BGTCP by levodopa in PD patients is also followed by an increase in high frequency oscillations (70 Hz) within this pathway (Brown 2003; Cassim et al. 2002). The high frequency oscillations across BGTCP have been reported during movement (Cassidy et al. 2002). Therefore, a mechanism by which dopamine could increase the inter-task temporal congruency among tasks in PD patients is through an increase in both neural activity and high frequency synchronization across BGTCP.

Overall, the results of the present study suggest that the deterioration of the dopaminergic input to BGTCP produces a profound disruption in temporal processing in a subgroup of PD patients. This disruption is manifested by an increase in timing error and time-dependent variability, as well as by the lack of variability correlation among timing tasks. Interestingly, these issues can reach almost normal standards after dopaminergic therapy. Hence, our findings support the notion that the BGTCP and dopamine are intimately involved in temporal processing in the range of hundreds of milliseconds.

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