Separating Storage from Retrieval Dysfunction of Temporal Memory in Parkinson's Disease

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Abstract

■ Dysfunction of the basal ganglia and the brain nuclei interconnected with them leads to disturbances of movement and cognition exemplified in Parkinson's disease (PD) and Huntington's disease, including disordered timing of movements and impaired time estimation. Previous research has shown that whereas striatal damage in animals can result in the loss of temporal control over behavior, dopaminergic deregulation in the human striatum associated with PD distorts the memory for time. Here we show a dissociation between deficits in storage (writing to) and retrieval (reading from) temporal memory processes. Both are dysfunctional in PD and sensitive to treatment with dopaminergic agents, but produce dissimilar distortions. When time intervals are stored in memory while the subjects are dopamine depleted, the process is slowed, leading to overestimation of two different time intervals. Conversely, when retrieval occurs in a dopamine-depleted state, interference or coupling occurs between two remembered time intervals, producing overestimation of the shorter and underestimation of the longer one. Whether those two separable patterns of dysfunction in storing and retrieving temporal memories rely on distinct neural networks within the basal ganglia and/or their cortical targets remains to be answered by future research. ■

INTRODUCTION

Overall slowing, in both motor (bradykinesia) and cognitive (bradyphrenia) domains, is widely reported as the major behavioral deficit in Parkinson's disease (PD) (Marsden & Obeso, 1995; Benecke, Rothwell, Dick, Day, & Marsden, 1986; see also Obeso, Rodriguez, & DeLong, 1997; Malapani, Pillon, Dubois, & Agid, 1994; Worringham & Stelmach, 1990; Bloxham, Dick, & Moore, 1987; Frith, Bloxam, & Carpenter, 1986; Evarts, Teravainen, & Calne, 1981; Hallet & Khoshbin, 1980; Flowers, 1976). On the other hand, interference between alternative motor plans stored in memory or switching deficits between different cognitive strategies have also been recently related to the major motor and cognitive parkinsonian symptoms (Malapani et al., 1994; Taylor, Saint-Cyr, & Lang, 1986; see also Flowers, 1976). That is, bradykinesia and bradyphrenia may not be solely a general cognitive slowing but rather a consequence of interference from unwanted memories. Indeed, there are studies suggesting that an important feature of motor pattern execution, which may contribute to difficulty in acquiring new motor programs in PD, is the necessity to inhibit previously learned alternatives. For example, PD patients regularly show difficulty in neuropsychological testing requiring switching between differ-

ent motor programs or cognitive strategies (Robertson & Flowers, 1990; Taylor et al., 1986; see also Malapani et al., 1994; Benecke et al., 1986). Patients exhibit difficulties in executing a designated sequence while at the same time suppressing an alternative, currently inappropriate sequence (Worringham & Stelmach, 1990; Frith et al., 1986). Hence, dopamine deficiency in the striatum and frontal cortical areas may induce both cognitive slowing and confusion associated with intrusion of unwanted memories of previously learned motor programs.

The dopaminergic-related slowing in PD has been related to an underlying distortion of the perception and production of time intervals (O'Boyle, Freeman, & Cody, 1996; Artieda, Pastor, Lacruz, & Obeso, 1992; Pastor, Artieda, Jahanshahi, & Obeso, 1992; Pastor, Jahanshahi, Artieda, & Obeso, 1992; Volkmann, Hefter, Lange, & Freund, 1992; Ivry & Keele, 1989; Nakamura, Nagasaki, & Narabayashi, 1978). This hypothesis is consistent with extensive animal work that emphasized the role of dopaminergic brain systems and the striato-frontal circuitry in timing behavior (for a review, see Meck, 1996). Specifically, the output dopaminergic neurons originating in the substantia nigra pars compacta (SNc) and projecting to the striatum are thought to represent the pacemaker ("clock") in interval timing. Indeed, administration of dopamine receptor (DA) agonists in rats trained with the peak interval (PI) procedure (Roberts, 1981; Catania, 1970) induces a faster clock

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speed, while DA antagonists produce the inverse effect, a slower clock speed (Meck, 1986). In addition, 6-OH-dopamine lesions targeting the striatum eliminate timing behavior in rodents, and timing does not recover after administration of L-dopa to the lesioned striata. In contrast, timing is restored with L-dopa in animals with damage in the SNc, suggesting that those pacemaker-dopaminergic cells that survive the lesion act effectively again under L-dopa supplementation (Hinton & Meck, 1997). Similarly, it was suggested that damage to the human striatum produces timing distortions, slowing down the "clock" speed. Focal lesions in, and degenerative diseases of, the basal ganglia cause subjects to overestimate time in both temporal estimation (Artieda et al., 1992; Pastor, Artieda, et al., 1992) and temporal reproduction (Malapani et al., 1994; Pastor, Artieda, et al., 1992; Pastor, Jahanshahi, et al., 1992) tasks. Moreover, overestimation of time intervals was related to dopamine depletion in the human brain, since the deficit was found to be accentuated in PD patients when they were tested without L-dopa replacement treatment (Pastor, Artieda, et al., 1992; Pastor, Jahanshahi, et al., 1992).

If slowing in monitoring current time due to dopaminergic deficiency in PD was the culprit for understanding the motor and cognitive slowing these patients experience, then one might expect intervals to be systematically lengthened, that is, overestimated, with different tasks and in different time ranges (Gibbon, Malapani, Dale, & Gallistel, 1997). However, shortened or simply more variable time intervals are produced when PD patients are asked to reproduce timed self-paced, repetitive movements or to compare the duration of two tones (O'Boyle, 1997) in the range of milliseconds (O'Boyle et al., 1996; Keele & Ivry, 1990; Wing, Keele, & Margolin, 1984). Whether timing distortions in PD may result in either over- or underestimation, changes are most often attenuated by dopamine replacement therapy (Malapani, Rakitin, et al., 1998; O'Boyle et al., 1996; Pastor, Artieda, et al., 1992; Pastor, Jahanshahi, et al., 1992; Wing et al., 1984).

An additional dopamine-dependent timing deficit with a unique pattern was recently reported (Malapani, Rakitin, et al., 1998) in PD patients asked to reproduce an interval by delaying a key press for an interval equal to a previously demonstrated standard. Subjects were tested with the PI timing procedure, originally developed to study interval timing in animals (Roberts, 1981; Catania, 1970) and to isolate modular components of temporal processing associated with distinct brain area lesions (Hinton & Meck, 1997; Meck, Church, & Olton, 1984; Meck, 1996; Olton, Wenk, Church, & Meck, 1988). Recent work (Rakitin et al., 1998) has successfully used this technique to study normative temporal reproduction of remembered time values in humans in the seconds to minutes range. When PD patients were tested on this task with dopamine replacement therapy (referred to henceforth as the "ON drug" or the "ON

group"), performance was equal to or better than age-matched controls. When tested without dopamine replacement therapy (referred to as the "OFF drug" or the "ON group"), the same patients overestimate the shorter of two intervals (8 sec in duration) and underestimate the longer of the two (21 sec), a pattern referred to as the "migration effect." It is notable that this deficit was consistently observed in every patient OFF drug, suggesting that the underlying cognitive process is extremely dependent on intact dopaminergic function.

Given the fact that intermittent feedback did not correct the performance of PD patients OFF drug over testing, this pattern of timing inaccuracies was hypothesized to reflect a dysfunctional memory representation of time (Malapani, Rakitin, et al., 1998; Gibbon et al., 1997), rather than a "clock" speed effect. Animal data with the PI procedure show that a memory effect may be inferred when a timing inaccuracy is relatively permanent despite intermittent corrective feedback during test sessions (Meck, 1996). This is to be contrasted with the classic "clock" pattern of timing errors produced in animals under dopaminergic manipulation (Meck, 1996), that is, a dramatic rapid shift that gradually returns to veridical accuracy followed by a rebound effect in the opposite direction when the drug is removed. Animals under dopaminergic manipulation, originally trained without a dopamine agonist, show a rapid shift toward underestimation when training is continued under the agonist manipulation. However, peak estimation gradually returns to veridical accuracy as new subjective times overlay previously learned memories for duration without the drug. Thus, a faster (or slower) clock might generate a larger (or smaller) representation of subjective time, but as long as the training and testing conditions remain the same, this same larger (or smaller) representation is accessed on testing trials and should be reproduced at the appropriate, veridical, real target time. On those grounds, it was concluded that a slowing or speeding of the clock monitoring the current time would not be expected to induce an accuracy distortion since PD patients OFF drug were trained and tested in the same condition.

Interestingly, the underestimation of the longer interval was not systematic in PD patients OFF drug, occurring only when two memories have been established. Indeed, patients overestimated the duration of the long interval when it was tested alone (Malapani, Rakitin, et al., 1998), strongly suggesting that the inaccurate reproduction could not be the result of a decision bias induced in the OFF-drug state. The migration effect was hence dependent on learning two intervals. When patients are required by the task to remember two different intervals, memory for an earlier learned interval appears to affect production of a later learned interval by causing a migration of criterion times toward each other. On these grounds, this permanent accuracy distortion seen in PD patients OFF drug was ascribed to a

dysfunctional memory representation, induced either on storage and/or retrieval.

Here we addressed the question of whether the deficits of PD patients result from dysfunction in either storing (writing to) or retrieving (reading from) temporal memory. To test this hypothesis, PD patients were tested with a new experimental design, using the same experimental interval timing task (PI procedure) we used in our previous research (Malapani, Rakitin, et al., 1998). The obtained results suggest that both slowing and interference are present in PD, although masked under different task conditions. Indeed, we show that migration, due to failure to inhibit memory of a previously learned temporal interval, occurs only on retrieval, while slowing, that is, lengthened temporal memories, occurs when time intervals are stored in memory for later reproduction. Moreover, when dopaminergic deficiency is maximal (PD patients OFF L-dopa), the interference effect on retrieval is robust enough to mask the coexisting slowing during storing and hence emerges whether there is feedback or not.

Encode–Decode Experiment: Design and Predictions

The new experimental design altered the procedure (PI procedure) used in our previous work (Malapani, Rakitin, et al., 1998) by withholding feedback on the second day of testing. This was intended to emphasize temporal memory encoding (or storage) during the first session, while decoding or retrieval from temporal memory was emphasized in the second session, but occurs during both sessions. This design is referred to as the encode–decode experiment.

The design and predictions for the experiment are shown in Figure 1. The key manipulation was variation in drug state (ON or OFF medication) on two successive days. PD patients were assigned to one of four experimental groups. The ON–ON group was provided with L-dopa during both encoding and decoding sessions. The OFF–OFF group was tested without L-dopa for both sessions. The ON–OFF group was provided with L-dopa during encoding but not decoding. Finally, the OFF–ON group went through the encoding session without L-dopa but had L-dopa during the decoding session. The idea was that by crossing PD patients' drug-state with the availability of feedback, we could determine whether dopamine deficiency (associated with being in an OFF group) selectively affects memory storage, retrieval, or both. Since the second, decoding, session involves no further feedback, performance reflects retrieval from memory of duration values stored during the preceding day. Retrieval (decoding) distortions are distinguished from memory storage (encoding) distortions when the testing day is conducted ON the drug after having trained OFF the drug. No distortion in
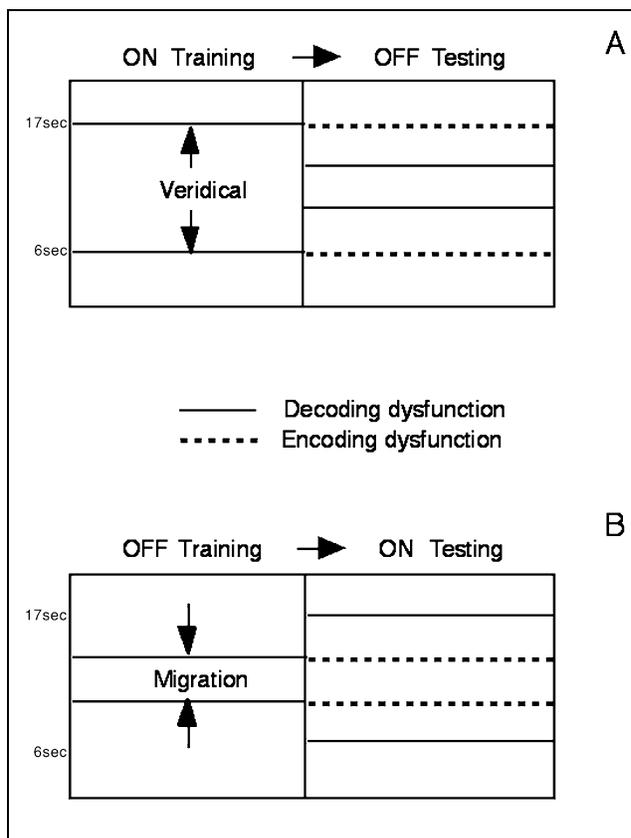
Figure 1. Predictions of the encode–decode design for two experimental groups, ON–OFF (A) and OFF–ON (B). When the encoding session is conducted ON drug, no distortion is found (upper left). But when the decoding session with no further feedback is conducted OFF drug, if migration is a retrieval distortion, it should appear during the decoding session (upper right). Conversely, the encoding session OFF drug should show migration (lower left), but if migration is solely a retrieval dysfunction, the subsequent decoding session ON drug should result in veridical memories (lower right).

timing was expected for the control group ON–ON, but migration was predicted in both sessions for the control group OFF–OFF, given previously reported findings (Malapani, Rakitin, et al., 1998).

Predictions of the encode–decode design, originally implying a deficit restricted either on storage or on retrieval solely (but not both), are shown in Figure 1. Predictions for the ON–OFF group, which went through encoding ON drug but were tested during the decoding session OFF drug, without feedback, imply one of two patterns of estimates for the second, decoding, day. If migration occurs only on retrieval from memory, then storage while ON dopamine supplementation should establish veridical memories, which may be distorted to produce migration when tested without further feedback in the OFF state. However, if migration results entirely from storage deficits, then no such distortion is expected, as the testing day represents retrieval only. Hence, migrated reproduction is predicted during the decoding session for a retrieval dysfunction, while veridical estimates would indicate a storage dysfunction

(Figure 1A). Now, if retrieval difficulty is the only dysfunction in our temporal reproduction task, then the OFF–ON group should show no migration effect when tested ON medication. We would expect to see migration in the initial, encoding, session OFF medication; then, when ON the drug during the decoding session, subjects should reveal an accurate storage process unaffected by medication state. Conversely, if migration was due solely to storage distortions, we would expect migrated estimates during the decoding session of the OFF–ON group, as shown in Figure 1B, revealing a distorted storage process during the prior encoding session OFF medication.

RESULTS

Time estimate distributions from each interval were compiled. Temporal location, or accuracy, was indexed by the time of the median estimate, while absolute variability, or precision, was indexed by the semi-interquartile range (SIQR) [SIQR = 1/2 (time of the 75th percentile − time of the 25th percentile)], and relative variability by the coefficient of variation (CV = SIQR/median). Mean median, SIQR, and CV data of the four groups are shown in Table 1.

The accuracy data for all four groups of PD patients are presented in Figure 2.

Two main effects are evident in these data. First, whenever subjects are in the OFF-drug state, migration appears, replicating our earlier PD-related effect (Malapani, Rakitin, et al., 1998). That is, compared to the ON-drug state, PD patients OFF L-dopa produce responses that are long compared to the 6-sec criterion and short compared to the 17-sec criterion. Migration was observed during both the encoding sessions, as seen in the OFF–OFF and OFF–ON groups' performances, and the decoding sessions, as seen in the OFF–OFF and ON–OFF groups' performances. These results make it apparent that the migration effect is dependent neither on the presence nor absence of feedback, and hence, was not likely attributable to a selective problem with storing temporal information in memory. This fact, coupled with the assumption that memory retrieval is required for performance during both encoding and decoding sessions, led us to attribute migration in PD patients to a dopamine-dependent dysfunction of retrieving temporal memory.

The second timing deficit evident in Figure 2 can be seen in the OFF–ON group's data from the decoding session. In that case, patients substantially overestimate both target intervals. These data from the OFF–ON group contrast with the decoding session data from the OFF–OFF group that clearly show strong migration. Apparently, restoring dopamine during the decoding session improves the retrieval deficit (manifested as migration) and allows a second deficit associated with dopamine deficiency during the encoding session to be observed. This second deficit was attributed to storing memories for the target interval, since this operation is only possible during the encoding session when feedback is available. That is, dopamine deficiency during the encoding session results in the storage of incorrect memories of the target interval that are subsequently retrieved intact while ON dopamine during the decoding session.

Dopamine-deficient storage and retrieval of temporal memories are distinguishable by changes in the variability of timing errors, in addition to the direction of those errors. These results are illustrated in Figure 3. For the PD patients in the OFF–ON group, overestimation of the intervals was associated with a proportional increase in timing variability, measured by the standard deviation. That is, the Scalar Property and Weber's Law held with subjects studied ON drug, even when timing errors occurred. Violations of the Scalar Property, however, occurred in the OFF-drug state. The short interval was associated with an increased CV compared to the long interval, indexing greater relative variability. That is, the standard deviation of estimates—expressed as a proportion of the obtained, inaccurate, means—is different for the two target intervals in all PD groups OFF L-dopa, replicating our previous findings (Malapani, Rakitin, et al., 1998). In contrast, the storage deficit still reflects the Scalar Property of timing variability and, consequently, the coefficients of variation were equal for inaccurate reproduction of the two intervals.

### Statistical Analyses of Results

Accuracy

Individual mean median data of all four groups are shown in Figure 2. The medians for all subjects of the four experimental groups were subjected to a repeated-measures analysis of variance (ANOVA), assessing drug condition (ON vs. OFF) and session (encoding vs. decoding) as the within-subjects factors, and group as the between-subjects factors. The analysis showed an overall significant effect of group [$F(3) = 15.095$; $p < .0001$], session [$F(1) = 11.362$; $p < .002$], and duration [$F(1) = 602.8$; $p < .0001$]. All three interactions, Session × Group [$F(3) = 17,026$; $p < .0001$], Duration × Group [$F(3) = 98.2$; $p < .0006$], and Session × Duration × Group [$F(3) = 35.46$; $p < .0001$] were also highly reliable (see Table 1 for absolute mean median values and SDs).

The group and interaction effects, when further analyzed with post hoc comparisons within each group revealed the following effects: (a) "ON–ON control group": no effect of session [$F(1) = 0.04$; $p = .8$], but a large effect of duration [$F(1) = 759.4$; $p < .0001$] and no Session × Duration interaction [$F(1) = 0.06$; $p < .8$; Figure 2A] were found. (b) "ON–OFF experimental group": no effect of session [$F(1) = 0.124$; $p = .7$], a significant effect of duration [$F(1) = 742.39$; $p < .0001$],

Table 1. Time Estimation Measures

| Group | Median | | | | SIQR | | | | CV | | | |
| | Encoding | | Decoding | | Encoding | | Decoding | | Encoding | | Decoding | |
	6 sec	17 sec	6 sec	17 sec	6 sec	17 sec	6 sec	17 sec	6 sec	17 sec	6 sec	17 sec
ON–ON	5.7 (0.1)	17 (0.2)	5.8 (0.1)	17 (0.4)	0.5 (0.06)	1.9 (0.2)	0.5 (0.07)	1.4 (0.2)	0.1 (0.009)	0.11 (0.01)	0.098 (0.01)	0.08 (0.01)
ON–OFF	5.7 (0.1)	16.8 (0.2)	8.7 (0.2)	13.7 (0.3)	0.5 (0.07)	1.5 (0.18)	1.2 (0.17)	1.5 (0.4)	0.09 (0.01)	0.09 (0.01)	0.14 (0.02)	0.11 (0.02)
OFF–ON	7.8 (0.3)	14.6 (0.3)	9.5 (0.5)	24.5 (1.7)	0.7 (0.08)	1.7 (0.1)	1.12 (0.19)	3.4 (0.6)	0.1 (0.008)	0.14 (0.02)	0.11 (0.01)	0.13 (0.01)
OFF–OFF	6.9 (0.2)	16.1 (0.8)	10.3 (0.8)	14.5 (1.02)	0.8 (0.03)	1.8 (0.1)	1.4 (0.12)	1.4 (0.15)	0.12 (0.005)	0.11 (0.01)	0.14 (0.01)	0.09 (0.005)

Mean median time estimates (standard errors in parentheses), SIQR, and CV for all four patient groups. The encoding session is shown in the left column (storage) and the decoding session (retrieval), without feedback, in the right column.
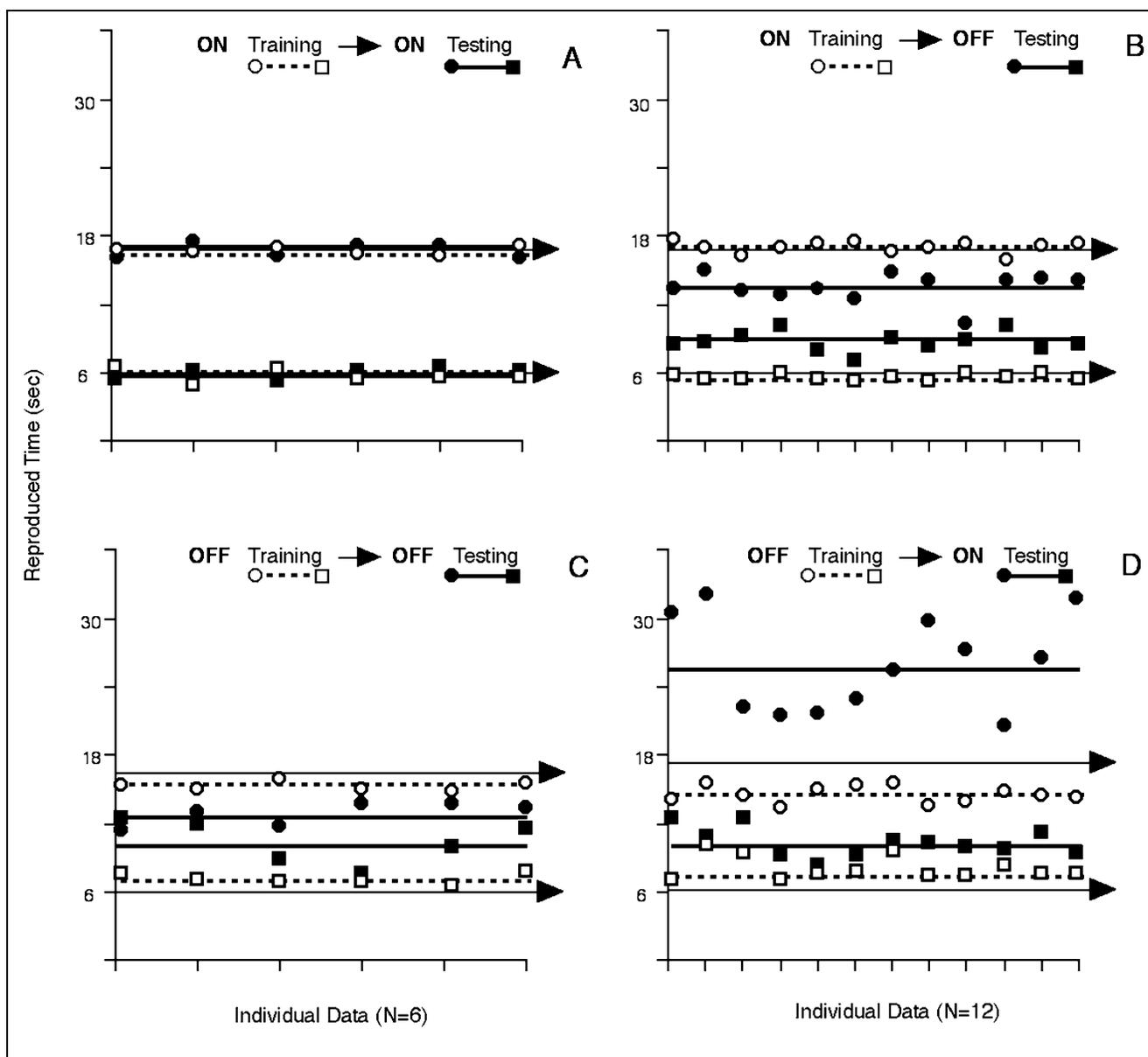
Figure 2. Median estimates for all individuals in all groups. Blue: estimates ON medication; red: estimates OFF drug; black arrows: target values (6 and 17 sec); squares: 6 sec; circles: 17 sec; dashed lines: group mean median on the first (encoding—storage) session; solid lines: group mean median on the second (decoding—retrieval) session without feedback; open points: encoding (storage); filled points: decoding (retrieval). (A) Control group ON–ON: Note the veridical estimates in both sessions. (B) Experimental group ON–OFF: Note the migrated estimates (solid red lines) on the second, decoding, day. (C) Control group OFF–OFF: Migration is seen in both days. (D) Experimental group OFF–ON: Migration is observed on the encoding day (dashed lines) but a large rightward shift is seen on the second, decoding, day ON medication (solid lines).

and also a significant Session × Duration interaction [$F(1) = 198.8; p < .0001$] were found. The interaction was further analyzed with means comparisons. A significant overestimation of the short interval was found during the decoding session OFF drug, compared to the encoding session ON drug [$F(1) = 92.95; p < .0001$]. Together with this overestimation of the short interval came an underestimation of the long interval during the decoding session OFF drug, compared to the encoding session ON drug [$F(1) = 106,086; p < .0001$; compare Figure 2B points]. It should be noted that absolute

values were found to be accurate during the encoding sessions ON drug to the extent that no significant difference was found between encoding session means of the ON–ON control and the ON–OFF experimental groups. (c) "OFF–OFF control group": no effect of session [$F(1) = 0.026; p = .8$], a significant effect of duration [$F(1) = 64.4; p = .001$], and a significant Session × Duration interaction [$F(1) = 21.9; p = .009$] were found. These patients showed larger overestimation of the short interval during the decoding session OFF drug versus the encoding session OFF drug [$F(1) =$
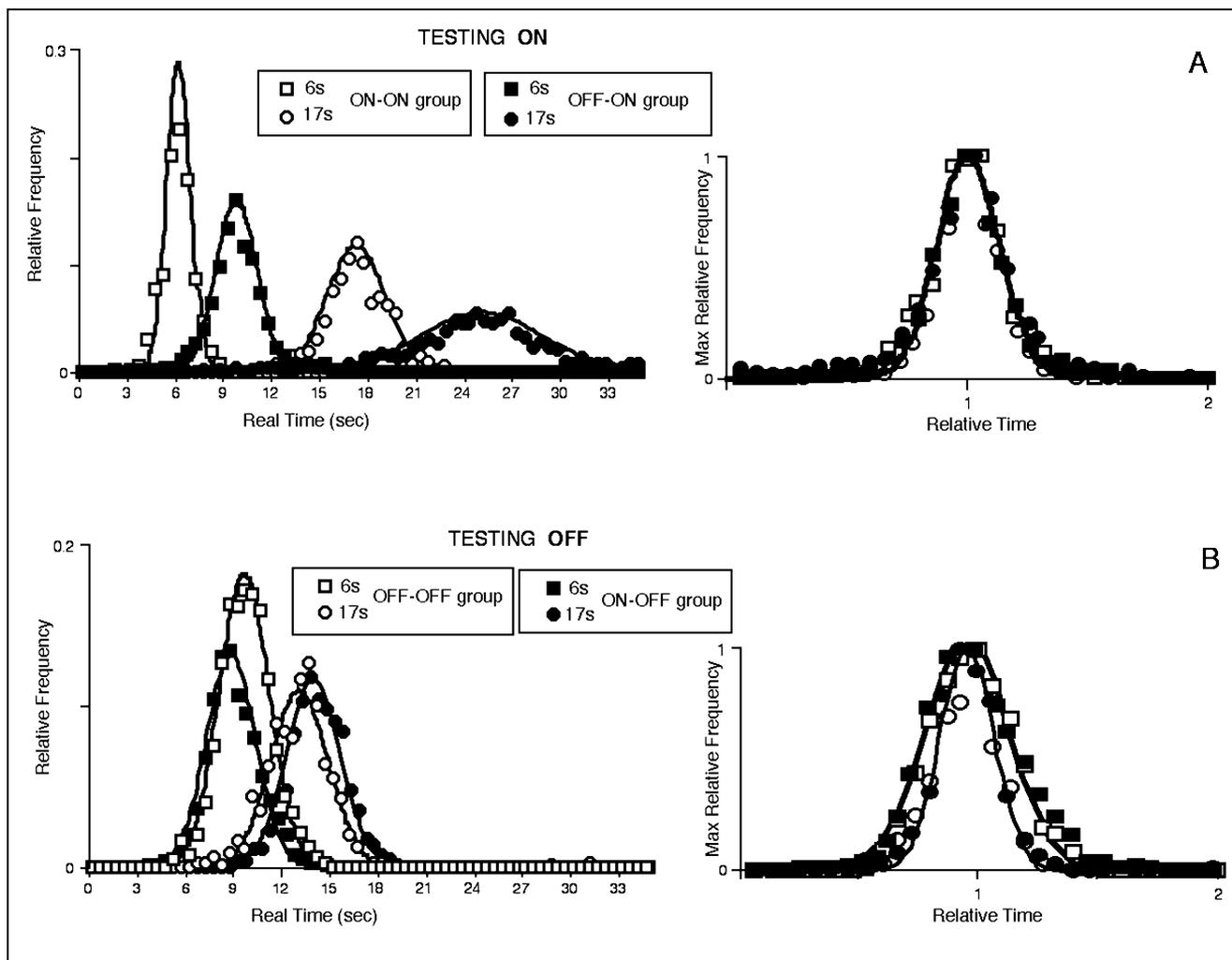
Figure 3. Migration on retrieval is associated with violation of the Scalar Property; while slowed encoding follows the scalar rule. Estimate distributions from the decoding sessions for each group in real time (left column) and time relative to the median time (right column). The smooth curves are Gaussian fits to the data. The two groups tested ON medication (ON–ON and OFF–ON) are shown in (A). The ON–ON group shows veridical estimates in the decoding session ON the drug (open points). The ON data from the OFF–ON group are right-shifted, with increased variance (filled points). In the upper right panel all four estimation distributions are shown to superpose in relative time (Scalar Property). The decoding data for the two groups tested without medication (OFF–OFF and ON–OFF) are shown in (B). Both groups show migration in the OFF-drug condition. In the lower right panel, the same data plotted in relative time show superposition for 6 sec from the two groups, and for 17 sec from the two groups. But importantly, the 6-sec distribution (heavy line curve) is broader than the 17-sec distribution (thin line curve).

10.363; $p = .03$], as well as a more extreme under-estimation of the long interval in the decoding session OFF drug, compared to the encoding session OFF drug [$F(1) = 11.58$; $p = .02$]. (d) "OFF–ON experimental group": large effects of session [$F(1) = 31.2$; $p = .0002$], duration [$F(1) = 149.4$; $p < .0001$] as well as Session × Duration interaction [$F(1) = 23.8$; $p = .0005$] were found. Subsequent means comparisons showed no significant difference for the short interval on encoding OFF compared to decoding ON the drug [$F(1) = 2.29$; $p < .15$]. Reproduced values for this interval were overestimated (see Table 2) in both the encoding sessions and the decoding sessions of the OFF–ON group. In the same group, however, a large difference between estimates for the long signal was found between

the encoding and decoding sessions [$F(1) = 71.002$; $p < .0001$].

Variability

Absolute and relative variability as indexed by the SIQR and the CV (SIQR/median) are shown in Table 2. A large literature confirms the Scalar Property entailing Weber's Law for time estimation and production in both humans and animals (Rakitin et al., 1998; Gibbon, 1977, 1992; Gibbon et al., 1997). Thus, we expect a very large effect of duration (short vs. long) on SIQR, and this was indeed found.

Our interest centers on the CV, which should be constant within groups across duration if Weber's Law

Table 2. Clinical and Neuropsychological Profiles of the Four PD Groups

	Group 1 (ON–ON)	Group 2 (ON–OFF)	Group 3 (OFF–ON)	Group 4 (OFF–OFF)
n	6	12	12	6
F/M	2/4	5/7	4/8	3/3
Age	52 (5.2)	56.5 (2.7)	54.7 (3.03)	56.8 (2.9)
Education	4.2 (0.2)	4.08 (0.58)	4.33 (0.4)	4.5 (0.56)
Evolution (years)	10 (2.3)	9.67 (0.89)	10.75 (1.5)	11.3 (2.4)
Hohen and Yahr	3.4 (0.5)	2.9 (0.4)	3.04 (0.2)	2.66 (0.3)
UPDRS—on	17.4 (3.01)	15.2 (2.5)	13.54 (2.5)	15.8 (1.7)
UPDRS—off	51.2 (5.6)	43.4 (4.1)	42.7 (4.5)	43.5 (3.3)
% improvement	66.2 (3.5)	66.7 (3.6)	70.9 (4.6)	62.8 (4.4)
MMS	29.4 (0.4)	28.8 (0.4)	29.1 (0.2)	29.1 (0.4)
MATTISE				
global	140.4 (1.2)	140.6 (1.05)	140.7 (0.8)	141.1 (0.9)
attention	36.4 (0.2)	36.7 (0.1)	36.5 (0.2)	36.3 (0.3)
initiation	34.2 (1.2)	35.6 (0.5)	35.8 (0.5)	36.5 (0.3)
constancy	5.8 (0.2)	5.9 (0.08)	6 (0)	6 (0)
concept	38.2 (0.6)	38.03 (0.4)	37.8 (0.4)	38 (0.4)
memory	24.8 (0.2)	24.3 (0.2)	24.6 (0.18)	24.3 (0.2)
Grober and Booschke				
encoding	16 (0)	16 (0)	16 (0)	16 (0)
recognition	16 (0)	15.2 (0.2)	14.7 (0.3)	15.6 (0.3)

holds. Repeated-measures ANOVA on the CVs showed no overall effect of group [$F(3) = 0.2$; $p = .8$], duration [$F(1) = 2.6$; $p = .1$], or session [$F(1) = 1.06$; $p = .3$], nor was there a Session × Group interaction [$F(3) = 0.8$; $p = .4$]. However, the interaction of Duration × Group was indeed significant [$F(3) = 5.85$; $p < .002$], indicating that for some groups the CV differed across duration. Given the overall effect of the interaction of duration and group on CVs, the confirmation or violation of Weber's Law within each of the four experimental groups was tested with post hoc repeated-measures on CVs between duration within each drug and session condition. The analysis showed: (a) For the control group ON–ON, no effect of duration [$F(1) = 0.002$; $p = .9$], session [$F(1) = 5.02$; $p = .08$], and no Session × Duration interaction [$F(1) = 4.08$; $p = .09$] were found; (b) For the experimental ON–OFF group, there was no effect of session [$F(1) = 0.3$; $p = .2$], but there was significant effect of duration [$F(1) = 15.9$; $p < .002$], carried by the Session × Duration interaction [$F(1) = 5.6$; $p < .03$]. Mean comparisons of the CVs (see Table 1 for absolute values) showed no significant difference in CVs between the short and long estimates in the encoding session ON drug, but the CVs obtained in the same

patients during the decoding session OFF drug differed reliably [$F(1) = 0.6$; $p = .05$]. This effect was due to a significant increase of CVs for the short interval when OFF drug during the decoding session (Table 1); (c) The analysis of the control OFF–OFF group showed no effect of session [$F(1) = 0.7$; $p = .4$] but a significant effect of duration [$F(1) = 611.8$; $p = .02$] and no Session × Duration interaction [$F(1) = 0.94$; $p = .3$]. Increased CVs for the short estimates largely carried the effect in the OFF-drug decoding session (Table 1); (d) The analysis of the experimental OFF–ON group did not show a significant effect of duration [$F(1) = 3.7$; $p = .08$], or session [$F(1) = 0.8$; $p = .3$], or a Session × Duration interaction [$F(1) = 0.017$; $p = .8$].

DISCUSSION

A mutual attraction between the temporal estimates of two different intervals, evident as overestimation of the short interval and underestimation of the long interval, was found in all subjects in the OFF-drug state in this study. This migration effect confirms results we obtained in previous research (Malapani, Rakitin, et al., 1998; Gibbon et al., 1997). The present study, however, brings

new insight to our understanding of the origin and characteristics of the effect.

A brief summary of the results obtained in the present study shows that: (a) normal reproduction of time intervals (both long and short) occurs in the dopamine-replenished (ON drug) state; (b) migration (a lengthening of the short interval and a shortening of the long interval in reproduction) is seen during both the encoding and decoding sessions when patients are in a dopamine-depleted (OFF drug) state; (c) however, when the patients are in the OFF-drug state during the encoding session, and then in the ON-drug state during the decoding session, a novel and strikingly disproportionate overestimation of the long intervals was then observed during the decoding session.

The results of the within-group analysis of the data confirmed the predictions stated in the Introduction for the control group who were ON drug during the encoding session and again ON drug during the second, decoding, session (the ON–ON group). For both days, reproduction was accurate (compare predictions Figure 1 to results Figure 2). The accurate reproduction on the second (decoding) day validates the procedure as producing no substantial changes when retrieval takes place while ON drug a day later without feedback. The two experimental groups, ON–OFF and OFF–ON, studied under opposite medication states on the 2 days, showed different patterns of accuracy distortions. Going back to the predictions of the experimental design that motivated this study, the data confirmed the decoding distortion predictions for the ON–OFF group (Figure 1). Patients showed migration OFF drug (Figure 2), implicating memory retrieval as the source of migration. On the basis of the data obtained from this group, we might conclude that migration in temporal memory results solely from dysfunction of the decoding system in comparison with the current elapsing time. This conclusion is also consistent with the migration seen for the initial, encoding, day OFF medication of the OFF–ON group (Figure 2).

However, the data obtained in the decoding session of our second experimental OFF–ON group revealed a second distortion. If migration were due solely to retrieval distortions, then subjects trained OFF drug, but tested ON drug should retrieve accurate memories on the testing day (Figure 1). In contrast, the OFF–ON group shows a large overestimation of both time intervals in the decoding session (Figure 2). The delay between encoding and decoding sessions is not responsible for this rightward shift, as no such effect was found in the control ON–ON group. Rather, the results obtained in the OFF–ON group support the hypothesis that when feedback is no longer present, the faulty, slowed storage resulting from being OFF drug during the prior encoding session is revealed. Thus, there are two distinct profiles of dysfunctional temporal processing in PD. The retrieval dysfunction shortens the longer and lengthens the shorter interval, while the storage dysfunction lengthens both. The lengthening of reproduction might occur if the storage process has been slowed such that the stored values are written to memory as longer than the trained targets. The presence of two dysfunctions also implies that migration, especially for the longer memory, is sufficiently strong to mask the slowed storage.

The asymmetry between storage and retrieval distortions in central tendency was mirrored by an asymmetry in Weber's Law violations, for the dispersion of estimates about the central tendency. The slowed rightward shift during storage was nevertheless scalar, showing that Weber's Law applies whether the memory values are distorted or accurate. In contrast, migration in the OFF-drug state was associated with a violation of the Scalar Property. The violation reflects an overall increase in noise, which is not multiplicatively related to the time being estimated. Rather, increased noise is added to the performance at both time intervals, resulting in an inflated CV for the short, as opposed to the long, duration.

The fact that the storage dysfunction not only produces a unidirectional shift for both estimates but also shows the normative scalar rules of timing, suggests that the storage dysfunction is simply a slowed mnemonic process, which does not induce any additional, nonscalar noise. The retrieval system, however, appears to be quite different. The retrieval distortion operates like a mutual attraction, mainly affecting the long estimate. While the longer memory is retrieved as shorter than veridical, the short one is lengthened by about the same amount, whether the distortion occurs during storage or retrieval. Hence, migration for the shorter duration may simply reflect lengthened storage. The long duration, however, must undergo movement in opposite directions for storage and retrieval. Thus, it seems likely that migration with two memories reflects the unique asymmetry of time's arrow: The short duration must be "passed through" before reaching the long duration, so that the short memory must be suppressed on retrieving the long.

In conclusion, our results here show a clear dissociation between deficits in storage and retrieval temporal memory processes, both dysfunctional in PD and sensitive to treatment with dopaminergic agents. The discovery of separable dysfunctional temporal memory processes suggests that the neuroanatomical substrate of these functions may also be separable. One hypothesis is that the storage process may rely on a rather simple (excitatory?) corticostriatal neural path, in which neural outflow may be slowed but does not induce additional variance. In contrast, the necessity of inhibiting the alternative stored information while reading from memory may require the involvement of an additional, inhibitory, striato-pallidal circuit during retrieval only. Whether those two separable patterns of dysfunction in storing and retrieving temporal memories rely on

distinct neural networks within the basal ganglia and/or their cortical targets remains to be answered by future research.

METHODS

PI Procedure

The procedure we used is the PI timing procedure, in which the subject compares a currently elapsing interval to a remembered interval and responds when the former is judged to approximate the latter. The procedure was originally developed in animals, and has been used to isolate modular components of interval timing associated with distinct brain area lesions (Meck et al., 1984; Catania, 1970; see also Olton et al., 1988; Gibbon, Church, & Meck, 1984). Recent work (Malapani, Dubois, Rancurel, & Gibbon, 1998; Rakitin et al., 1998; see also Gibbon et al., 1997) has successfully used this technique to study temporal reproduction of remembered time values in humans in the seconds to minutes range.

Time production training occurred during the first experimental session. Productions of two intervals (short and long) were trained in separate blocks of trials. Half of the participants were trained on the short interval first and half were trained with long interval first. Training for each interval consisted of a total of 80 trials divided into two sets of 10 and one set of 60 trials. The first two sets of trials, or pretraining blocks, served to acquaint participants with the interval to be tested in the third set of trials, the encoding session block (see below).

The first pretraining block consisted of 10 "fixed-time trials." On each trial, a blue square (2.1 × 2.1 in.) was presented on the monitor. After the target interval had elapsed, the blue square turned magenta. Participants were instructed to try to remember the time interval delineated by the appearance of the blue square on the screen up to the subsequent color change. Participants were informed that they should refrain from counting or tapping so as to avoid extraneous timekeeping. To further discourage counting, random digits were intermittently superimposed over the rectangle, and participants were instructed to read the digits aloud (Rakitin et al., 1998). The second pretraining block consisted of 10 "peak trials" in which participants were asked to reproduce the time interval that they had just observed in the preceding fixed-time trials. In these peak trials, the blue square did not turn magenta, but instead remained blue. Participants were instructed to respond by pressing the space bar just before they felt that the end of the target interval should occur and holding it until the target time had elapsed. That is, participants were to "bracket" the termination of the target interval by pressing, holding, and then releasing the space bar. The time when the key is pressed is referred to as the "start" time, and the time when the key is released is

referred to as the "stop" time. Digit distracters were employed, as described above. Participants ended the trial by pressing the "enter" key. Alternately, the trial ended when a period equal to three times the target interval had elapsed. During the intertrial interval (ITI), participants were shown a histogram that provided feedback about their response on the previous trial in relative time. Additional messages informed the participants if they had responded too short or too long with respect to the target time (see also Rakitin et al., 1998).

Design of the Encode–Decode Experiment

We used the PI timing procedure we previously described (Malapani, Dubois, et al., 1998; Malapani, Rakitin, et al., 1998; Rakitin et al., 1998), for the first (storage) session of the timing experiment, which we call the "encoding" session. In order to replicate our previous results with different time durations, the target values for the following experiments were 6 and 17 sec. That is, on the first day, the encoding session, patients were trained on a short (6 sec) and long (17 sec) interval and they were then asked to compare a currently elapsing interval to the remembered interval and respond when the former is judged to approximate the latter. The encoding session was conducted in blocked mini-sessions, counterbalanced for order of training with each duration. On the following day, subjects were assessed without further training in the second—"decoding"—session, in which we focus on retrieval. No feedback was provided during the decoding session.

"Encoding session": In the third block of the first session, participants received 20 fixed-time trials, 30 peak trials with feedback during the ITI, and 10 peak trials without ITI feedback. Digit distracters were used in all trials for all groups.

"Decoding session": The following day, participants received in the second session one block of 60 peak trials without feedback for each of the two target intervals. Distracter digits were used in all trials. The order of testing of the two intervals was counterbalanced.

Data Acquisition and Analysis

All data were collected in 0.5-sec time bins, so as to permit assessment of the Scalar Property, and to measure accuracy and variability of time reproduction. Peak functions for individual subject's blocks were created by collapsing responding from all trials into a single frequency distribution. Group distributions were obtained as follows: each individual's time estimate distribution was pooled within conditions, and then the median of the pooled distribution was aligned with the group mean median for that condition and averaged across subjects. This method for representing the spread of individual subject's time estimate distribution controls for accuracy variation across subjects. That is, the SIQRs

from the group distribution are a fair representation of the mean SIQR from individuals.

Subjects

Thirty-six patients diagnosed with idiopathic PD participated in this study. PD patients were assigned to one of four experimental groups and the key manipulation was variation in drug state (ON or OFF drug) on two successive days (encoding and decoding sessions). Table 2 shows the general characteristics and the neuropsychological scores of the four PD groups (ON–ON, OFF–OFF, ON–OFF, and OFF–ON).[1] Results are expressed as means (standard deviation). The diagnosis of PD was based on the existence of an akineto-rigid syndrome with or without resting tremor; and the absence of neuroleptic treatment, focal signs on clinical examination, and/or CT–NMR scans, or symptoms suggesting Progressive Supranuclear Palsy or Multiple System Atrophy. Patients with a Mini-Mental State Examination score below 27 and a Montgomery and Asberg Depression Rating score greater than 18 were excluded. None of the patients had undergone thalamotomy or were taking anticholinergic drugs. Patients were assessed twice and were divided into four groups according to their dopamine supplementation treatment at an in-session of the study, allowing a direct evaluation of the influence of dopa transmission on their performance. ON-drug PD patients, with severe fluctuations under L-dopa treatment were assessed 90 min after acute administration of a supraliminar dose of L-dopa–carbidopa (250 mg). OFF-drug PD patients were assessed when dopamine supplementation treatment had been withdrawn for at least 18 hr (when the parkinsonian disability was maximal).

Data Analysis and Comparisons

The measurements of interest were accuracy of subjective time estimates indexed (nonparametrically) as mean median, variability of subjective time (the SIQR), and the nonparametric CV (SIQR/median). Statistical analyses for comparisons between the four PD groups were performed with multivariate analysis of variance (MANOVA) for repeated measures. One between-group independent factor (group) and two within-factors (duration and session) were tested for the median, SIQR, and SIQR/ median as dependent variables. Post hoc comparisons (Fisher's protected LSD) were tested for differences between pairs of groups (encoding ON or OFF drug and decoding ON or OFF drug). We then further compare within each group the effect of session and duration. In that way we contrasted the performance of PD patients in either ON-drug or OFF-drug state during the encoding session to their own performance in the same or different drug state during the decoding session. ANOVA for repeated measures with duration and session as the two within-factors were used to test median, SIQR, and SIQR/median. Sources of variance were duration, session, and the interaction between duration and session. Spearman's rank correlation coefficients were calculated between accuracy and variability measurements and motor and neuropsychological scores of the patients.

Note

1. Data shown represent the ON-L-dopa scores for all patients. An informed consent statement was obtained for each of these subjects after the nature and possible consequences of the study were explained.

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