Coupled Temporal Memories in Parkinson’s Disease: A Dopamine-Related Dysfunction

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Abstract

Dysfunction of the basal ganglia and the brain nuclei interconnected with them leads to disturbances of movement and cognition, including disordered timing of movement and perceptual timing deficits. Patients with Parkinson’s disease (PD) were studied in temporal reproduction tasks. We examined PD patients when brain dopamine (DA) transmission was impaired (OFF state) and when DA transmission was reestablished, at the time of maximal clinical benefit following administration of levodopa + apomorphine (ON state). Patients reproduced target times of 8 and 21 sec trained in blocked trials with the peak interval procedure, which were veridical in the ON state, comparable to normative performance by healthy young and aged controls (Experiment 1). In the OFF state, temporal reproduction was impaired in both accuracy and precision (variance). The 8-sec signal was reproduced as longer and the 21-sec signal was reproduced as shorter than they actually were (Experiment 1). This “migration” effect was dependent upon training of two different durations. When PD patients were trained on 21 sec only (Experiment 2), they showed a reproduction error in the long direction, opposite to the error produced under the dual training condition of Experiment 1. The results are discussed as a mutual attraction between temporal processing systems, in memory and clock stages, when dopaminergic regulation in the striatum is dysfunctional.

INTRODUCTION

Patients with Parkinson’s disease (PD) experience difficulties when producing temporal components of movement and in programming and synchronizing motor responses. These problems are reflected in increased reaction time and movement time (Bloxham, Dick, & Moore, 1987; Evarts, Teravainen, & Calne, 1981), prolonged interonset latencies when performing sequential or simultaneous movements (Benecke, Rothwell, Dick, Day, & Marsden, 1986; Roy, Saint-Cyr, Taylor, & Lang, 1993), impaired ability to maintain a fixed rhythm in tapping tasks (Nakamura, Nagasaki, & Narabayashi, 1978; O’Boyle, Freeman, & Cody, 1996; Stelmach & Worringer-ham, 1988; Wing, Kecke, & Margolin, 1984), and increased speech production time (Lieberman et al., 1992; Volkmann, Hefter, Lange, & Freund, 1992). Parameters such as reaction time, interonset latency, rhythm maintenance, and temporal organization of speech all require accurate timing, and dysfunctions are well correlated with the clinical phenomenon of bradykinesia in PD (Benecke et al., 1986; Hallett & Khoshbin, 1980; Nakamura et al., 1978; Volkman et al., 1992). There is evidence that the timing deficits of patients with PD may not be limited to the motor domain. Nonmotor deficits include impaired temporal discrimination of pairs of stimuli in the somaesthetic, visual, and auditory modalities (Artieda, Pastor, Lacruz, & Obeso, 1992), absence of interlimb
synchronization in processing of bimodal simultaneous stimuli (Malapani, Pillon, Dubois, & Agid, 1994), and impaired time estimation (Pastor, Artieda, Jahanshahi, & Obeso, 1992).

Although all of these studies report "timing-related" deficits in PD, most of the experimental tasks used were not specifically designed to address the issue of whether an internal timekeeper is dysfunctional in PD. Recent psychophysical research suggests that several motor or perceptual tasks that require accurate timing have access to the same internal timing mechanism because normative performance varies in similar ways across tasks (Ivry & Hazeltine, 1995). A common timekeeping mechanism may be therefore used in both production and perception tasks that involve time-related decisions in the millisecond range with humans (Ivry & Hazeltine, 1995; Ivry & Keele, 1989; Keele, Pokorny, Corcos, & Ivry, 1985) and in the secondsto-minutes range with humans and animals (Church, 1984; Meck, Church, & Olton, 1984; Rakitin et al., 1998). Thus timing may be an independent process employed whenever its specific computation is needed. In fact, accurate timing is required in many behaviors across species. For example, the skilled movements of musicians, athletes, and animal predators require precise timing of activity across different groups of muscles and anticipation of time intervals into the seconds range.

Neuropsychological research provides a complementary way to address the issue of whether a common timing mechanism is used in both production and perception and to investigate possible locations of the hypothesized internal timekeepers within neural brain systems. This approach asks whether different patient groups will show either similarities or dissociations in performance on specific timing tasks as a function of the location of their neurological lesion. Patients with lesions in the cerebellum are impaired in both motor and perceptual tasks requiring accurate timing in short (milliseconds) time ranges (Ivry & Keele, 1989; Ivry, Keele, & Diener, 1988) as well as in long (seconds) time ranges (Nichelli, Alway, & Grafman, 1996). Ivry (1996) suggested that the same timing mechanism operates in both motor and perceptual tasks for the short ranges and may involve pathways that pass through the cerebellum. Performance in the same perceptual and production timing tasks was not found to be impaired in PD patients (Ivry & Keele, 1989), leading to the hypothesis that timing mechanisms do not involve the basal ganglia in humans, at least in the millisecond time ranges (Ivry, 1996). However, contrary findings recently obtained in patients with diseases originating in the basal ganglia have shown that both time estimation and motor tasks requiring accurate timing are impaired in PD patients, in short as well as long ranges (O'Boyle et al., 1996; Pastor et al., 1992) and in patients with Huntington's disease (Freeman, 1996).

Pastor et al. (1992) showed that PD patients OFF their levodopa medication underestimated time intervals in the seconds range. Following administration of levodopa, a significant improvement in time estimation was observed, supporting the hypothesis that dopamine plays a role in the modulation of internal timekeeping, consonant with a variety of work with animals in the seconds range under dopaminergic agonists and antagonists (see Meck, 1996, for review). Impaired timing of fast repetitive movements in PD patients OFF their medication is commonly found (O'Boyle et al., 1966; Wing et al., 1984), contrary to Ivry and Keele's data (1989) reporting no deficit in temporal judgment or temporal reproduction tasks in short ranges. However, it is possible that a purely motor origin may explain observed deficits in even perceptual time estimation tasks if subjects use vocal or subvocal counting to estimate time intervals, as in Pastor et al's study (1992). So the question of whether time estimation per se is impaired in PD remains to be answered.

The present study assessed interval timing competence in the seconds range in patients with PD. The first aims of the reported research were to test if temporal processing follows normative rules with aged subjects and to see how it may break down in PD. In the first experiment we examined temporal reproduction of more than one duration. Subjects received blocked training on one duration at a time, but more than one were trained in the same session. A second experiment, in which only one duration was trained, controlled for biases and interactions that may occur when more than one duration has been learned. We evaluated the role of striatal dopaminergic activity in temporal processing by examining PD patients when brain DA transmission was impaired (OFF state) and when DA transmission was reestablished, at the time of maximal clinical benefit following administration of levodopa + apomorphine (ON state). We used a between-subject design that compared both ON and OFF states of patients to aged subjects (Experiment 1), and a within-subject design that compared PD patients in the OFF state to their own performance in the ON state (Experiments 1 and 2). The experimental questions were: (1) Is timing competence in PD patients under the treated (ON) state comparable to normative performance? (2) Is timing in the same patients when OFF medication different, either in precision or accuracy? (3) Are differences seen between timing one and more than one temporal duration?

We used the peak interval (PI) timing procedure, originally developed to study interval timing in animals (Catania, 1970; Roberts, 1981) and to isolate modular components of temporal processing associated with distinct brain area lesions (Meck, 1983, 1986, 1998a, 1998b; Meck, Church, & Olton, 1984; Olton, Wenk, Church, & Meck 1987). Recent work (Rakitin et al., 1988) has successfully used this technique to study normative temporal reproduction of remembered time values in humans in the seconds-to-minutes range.

This task has received extensive theoretical and em-
empirical study. Normative reproduction in animals and humans shows a peak in responding at the target time and variability around this peak. Both accuracy (peak location) and precision (variability around the peak) will be studied here in the context of the Scalar Expectancy Theory (SET) model of temporal information processing (Figure 1).

The timing system is assumed to be comprised of three separable components (Figure 1a): a clock system that monitors the (subjective) passage of time, a memory system that records the subjective representations of the target times, and a decision system that compares current time to remembered time to generate appropriate responding. Both animal and human data show that variability increases dramatically with increases in the target, or base duration being timed in the PI task, and this increase follows the “scalar rule” (Figure 1b). A large body of literature has established this “scalar property,” a strong form of Weber’s Law (Allan & Gibbon, 1991; Gibbon, 1977; Gibbon, Church, & Meck, 1984). In its simplest form the scalar property holds that errors of estimation are strictly proportional to the target time, so entire distributions of estimates superpose when scaled in proportions of the target duration. This means in turn that the standard deviation (not the variance) is proportional to the mean. The constant of proportionality, the coefficient of variation, \( \sigma/\mu \) (SIQR/median), is the fundamental sensitivity index of the interval time sense, comparable to the Weber fraction of temporal discrimination (Allen & Gibbon, 1991; Getty, 1975; Ivy & Hazeltine, 1995). The scalar property implies that multiplicative variance mechanisms are responsible for errors of estimation at different target durations (Gibbon, 1992; Gibbon et al., 1984).

Scalar variability may be induced in either of the three components—clock, memory, or decision—in the temporal processing system. Clock variance is illustrated in Figure 1b. Subjective time (on the ordinate) accumulates with real time (on the abscissa) at an average rate (heavy diagonal). However, within and between trials the clock rate may vary (dashed diagonals) so that the recorded target times in memory show the scalar property (distributions on the ordinate). Scalar variance may also result in a similar way from variability in the rate of the encoding and decoding process for comparison with current time. And the comparison itself may also generate scalar variability, via a ratio of current to remembered time exceeding a variable threshold for initiating and terminating responding (Gibbon, 1992).

Increases in the level of variability in patient populations are frequently cited in short-interval (e.g., tapping) tasks as indices of dysfunctional temporal processing.

![Figure 1](http://www.mitpressjournals.org/doi/pdf/10.1162/089892998562762762)

**Figure 1.** (a) Information processing schematic of the Scalar Expectancy Theory model. The clock system is assumed to involve a pacemaker that is gated into an integrator to monitor the flow of subjective time. When feedback is given, or on fixed-time training trials when the target duration is indicated by a change in the signal, the subjective time is encoded (dashed arrow) and stored in memory. On later peak interval trials these memory values are decoded (dashed arrow) and sampled for comparison with the current time value in the clock/integrator system. The comparison is made by a ratio. When the current subjective time is sufficiently close to the remembered time (ratio close to 1.0), responding is generated. (b) Clock System Variance. Subjective time is shown growing linearly with real time. Variation in the rate of the subjective integration (dashed diagonals) generates subjective time distributions for a short (S) and a long (L) time (on the ordinate) that are scale transforms of each other (the scalar property).
When variability is shown to be increased relative to normative performance of control groups, an important observation is whether or not this increased variability remains scalar in the target times being estimated (Gibbon, Malapani, Dale, & Gallistel, 1997). If so, the temporal information processing system may have increased multiplicative noise in either the clock, the memory, or the comparison mechanism but is otherwise operating normally. If, however, variability is shown to violate the scalar property, it is likely that the violation occurs in the memory representation, because increased variability in the clock system should remain scalar at different target times (see Figure 1b), and increased threshold variability in the comparison process should similarly remain scalar (Gibbon, 1992).

Accuracy, according to the SET model of temporal information processing, is expected to be near veridical as long as training and testing are conducted under the same conditions. Animal data with the PI procedure show that a clock speed difference does not produce an accuracy change (Meck, 1996), unless it is introduced after training in an alternative drug condition. Animals under dopaminergic manipulation, originally trained without a dopamine agonist, show a dramatic, 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. Similarly, bias in the decision process that might lead to systematic under- or overestimation should be corrected during training when subjects are given feedback on this task. Conversely, a memory effect may be inferred when an accuracy distortion is relatively permanent despite intermittent corrective feedback during test sessions (Meck, 1996). Thus only a permanent accuracy distortion implicates a dysfunctional memory representation, induced either on storage or retrieval.

In summary, then, accuracy and nonscalar variance effects in patient populations are most likely the result of dysfunctional memory encoding or decoding, whereas additional, scalar noise may be present in patient populations at any stage of the temporal processing system.

**EXPERIMENT 1**

In Experiment 1, aged \( n = 12; \) mean age: 72 years) subjects with no neurological disease and PD patients \( n = 10; \) mean age: 55 years) were trained to remember time intervals indicated by a visual signal appearing on a computer screen for a standard duration. On a following test block, subjects were required to reproduce the same time intervals by pressing the space bar on the keyboard. Training and testing sessions for each duration were blocked (20 training and 60 test trials). Aged subjects were tested with three different durations (8, 12 and 21 sec) and their performance was contrasted with the performance of 10 young (mean age: 25 years) college students (previously reported by Rakitin et al., 1998). PD patients were tested with two durations (8 and 21 sec), in both ON and OFF levodopa states. The performance of PD patients in the OFF state was contrasted with their own performance in the ON stage, and performances in both states were contrasted with the performance of the aged group for these durations.

**Results**

1. **Young versus Aged Controls**

Distributions of responding for the three intervals are shown in Figure 2. Rakitin et al.’s (1998) young group is shown in the upper panel, our aged group is in the middle panel, and the distributions for both groups, normalized for time relative to the median time, and proportions of peak responding, are in the bottom panel. Young subjects’ peak estimates are very close to veridical, with increasing variability with increasing target durations. Aged subjects’ estimates are veridical for the 8-sec duration, close to veridical for the 12-sec duration and show a small underestimation (leftward shift) for the 21-sec duration. Normalized distributions in the bottom panel, plotted in time relative to the median time, show superposition across durations for both groups but with somewhat larger variance at all values for the aged subjects.

Means (standard deviation) of accuracy, variability, and the coefficient of variation in both young and aged groups are summarized in Table 1. The following effects were found to be statistically reliable: Accuracy: All sources of variance were significant (Age: \( F = 7.7, p < 0.05; \) Duration: \( F = 993.2, p < 0.05; \) Age \( \times \) Duration: \( F = 4.1, p < 0.05 \)). Posthoc comparisons showed that the interaction effect was due to a significant leftward shift of the aged group for the 21-sec duration \( (p < 0.05) \). Variability: A significant effect of Duration \( (F = 80.8, p < 0.05) \) and an effect of Age that “approached” significance \( (F = 3.7, p = 0.06) \) but no interaction effect was found for semi-interquartile range (SIQR). No significant correlations were found between SIQRs and the neuropsychological scores. Coefficient of Variation: A significant effect of Age \( (F = 7.3, p < 0.05) \) was found on SIQR/median. No Duration or interaction effects were found. Thus aged subjects have somewhat greater variability than young ones, which nevertheless remains scalar in their target time estimates.

2. **ON versus OFF States of PD Patients**

Distributions of responding for both ON and OFF conditions at both signal durations are shown in Figure 3. The
Figure 2. Relative frequency distributions for the three target durations (8, 12, and 21 sec) showing accuracy and variability of estimation in young college students (white, upper panel) and in aged normal controls (black, middle panel). The three functions of the two groups, when plotted in time relative to the median time and normalized as proportions of the maximum relative frequency, superpose (lower panel).

Table 1. Mean (Standard Deviation) of Accuracy, Variability, & Coefficient of Variation in Young and Aged Subjects in Experiment 1.

<table>
<thead>
<tr>
<th></th>
<th>8-sec duration</th>
<th>12-sec duration</th>
<th>21-sec duration</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Aged</td>
<td>Young</td>
</tr>
<tr>
<td>Median</td>
<td>8.05 (.4)</td>
<td>8.05 (.6)</td>
<td>12.3 (.8)</td>
</tr>
<tr>
<td>SIQR</td>
<td>.35 (.2)</td>
<td>.55 (.3)</td>
<td>.66 (.3)</td>
</tr>
<tr>
<td>SIQR/median</td>
<td>.043 (.02)</td>
<td>.068 (.04)</td>
<td>.053 (.02)</td>
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</table>
accuracy of temporal reproduction in PD patients when they are ON levodopa + apomorphine medication is veridical (open symbols, upper panel). They produce peaks in responding that are very close to the targets for both durations (mean peak times of 7.8 and 21.1 sec). The same subjects show a dramatic distortion in accuracy for both durations when they are OFF their medication (filled symbols, upper panel); they overestimate the short signal and underestimate the long one. The variability of reproduction for 8 sec is also different between ON and OFF states, as can be seen in the different spread of the curves obtained for the 8-sec target. However, variability is roughly equal for the 21-sec target in both the ON and OFF states because those curves are equally broad. The scalar property, shown in the lower panel, emerges in the ON state when responses are normalized as a proportion of median time and scaled to maximum responding. The ON distributions show superposition. In the OFF state, however, a violation of superposition is observed. The 8- and 21-sec OFF distributions do not superpose, and they are broader in relative time than the ON distributions, especially for the 8-sec condition.
Means of accuracy, variability, and coefficient of variation in the ON and OFF states of PD patients are summarized in Table 2. Statistical analysis showed the following effects. **Accuracy.** A significant effect of Drug (F = 10.4; p < 0.05) and Duration (F = 557.8; p < 0.05) on the medians was found. The interaction between these two sources of variance was also significant (F = 51.6; p < 0.05). Further paired comparisons showed a significant difference between the medians obtained in the ON and OFF states for both 8 sec (F = 6.07; p < 0.05) and 21-sec durations (F = 59.2; p < 0.05). No correlations were found between accuracy and neuropsychological or motor scores in the ON state. Correlations at a significant level were found in the OFF state between the akinesia score and (1) the rightward shift in accuracy for the 8-sec duration (beta = 0.1; p < 0.05); (2) the leftward shift in accuracy for the 21-sec duration (beta = −0.05; p < 0.05). **Variability.** A significant effect of Duration (F = 73.1; p < 0.05) and Drug (F = 21.2; p < 0.05) was found for SIQR. The interaction between the two factors was not significant (F = 2.3; p = 0.1). Further paired comparisons showed a significant difference between the SIQR obtained in the ON and OFF states for 8 sec (F = 10.16; p < 0.05) but not for 21 sec (F = 0.99; p = 0.3). No correlations were found between SIQR and motor or neuropsychological scores in either drug state. **Coefficient of variation.** A significant effect of both Duration and Drug was found on SIQR/median. The interaction between the two factors was not significant. In order to test the scalar property, further paired comparisons contrasted Duration within Drug condition. Coefficients of variation for the two durations were not significantly different in the ON condition (F = 2.4; p = 0.1). However, we found a significant difference between durations in the OFF condition (F = 10.9; p < 0.05).

### Table 2. Mean (Standard Deviation) of Accuracy, Variability, & Coefficient of Variation for PD Patients ON and OFF Medication in Experiment 1.

<table>
<thead>
<tr>
<th></th>
<th>8-sec duration</th>
<th>21-sec duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD ON</td>
<td>PD OFF</td>
</tr>
<tr>
<td>Median</td>
<td>7.6 (.6)</td>
<td>8.9 (2.06)</td>
</tr>
<tr>
<td>SIQR</td>
<td>.45 (.2)</td>
<td>.82 (.5)</td>
</tr>
<tr>
<td>SIQR/median</td>
<td>.059 (.03)</td>
<td>.092 (.03)</td>
</tr>
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</table>

3. **Aged Controls versus ON & OFF PD Patients**

Statistical analysis between the three groups (Aged, PD ON, PD OFF) showed the following effects. **Accuracy.** No significant effect of Group on the median for the 8-sec target was found. Post hoc analysis showed a significant difference between the median obtained between PD ON and PD OFF groups (p < 0.05), but no significant difference between PD ON and Aged or between PD OFF and Aged. A significant effect of Group on the median for the 21-sec target was found (F = 17, 9; p < 0.05). Post hoc comparisons showed significant differences between PD ON and PD OFF (p < 0.05), PD ON and Aged (p < 0.05), and PD OFF and Aged (p < 0.05). **Variability.** A significant effect of Group (F = 8.4; p < 0.05) was found on SIQR for the 8-sec target. Further post hoc comparisons showed a significant difference between ON and OFF groups (p < 0.05) and between PD OFF and Aged (p < 0.05), but no significant difference between PD ON and Aged. For the 21-sec target, no significant effect of Group was found, and post hoc analysis showed no significant difference between any pair of the three groups. **Coefficient of variation.** A significant effect of Group was found on SIQR/median for the 8-sec target (F = 6.7; p < 0.05). Further post hoc comparisons showed a significant difference between PD OFF and PD ON as well as between PD OFF and Aged (p < 0.05). However, no significant difference was found between PD ON and Aged. For the 21-sec target, no significant effect of Group was found on SIQR/median, and the post hoc analysis showed only a significant effect between PD ON and PD OFF and no significant differences between either PD ON and Aged or PD OFF and Aged.

### Discussion

The comparisons between young and aged controls show that the scalar property for temporal information processing holds with age. The good superposition seen in Figure 2 is reflected in the large effect of duration on SIQR and the lack of an effect of duration on SIQR/median. However, aged people showed an overall increased variability compared to young college students and a slight underestimation for the longer duration target. The former effect along with the failure to find a difference in the coefficient of variation (the scalar property) suggests that temporal processing is more variable in aged people but still conforms to Weber’s Law. Thus as described earlier, this increased variance could arise either from clock variability, memory storage or retrieval variability, or criterion-decision variability.

The small underestimation seen at 21 sec (and a still smaller underestimation at 12 sec) is probably due to a dysfunction in mnemonic processing because accuracy
effects are not expected from dysfunctions in the clock system. However, to the extent that aged people show some loss of dopaminergic enervation in the striatum (Agid, Javoy-Agid, & Ruberg, 1987), and given the body of literature on clock effects induced by dopaminergic deregulation (see Meck, 1996, for review), a clock dysfunction may be also present that is small enough not to force recalibration of the remembered subjective duration with feedback during training and testing. This question is readdressed below, when large accuracy distortions in the performance of PD patients in the OFF state rule out clock effects.

The results show that the estimation of time is normal in PD patients in the ON medication state. Their peaks in responding are close to veridical for both durations, like the peaks produced by young normal control subjects. Moreover, the temporal variability in the ON state increases proportionate to the target duration. By consequence, the scalar property holds in the ON state as shown by the absence of a difference between the normalized functions for the two durations (Figure 3). These results show that temporal information processing is regulated by normative processes when the dopaminergic regulation in the brain is reestablished, as it is when PD patients are treated with the levodopa.

The same patients OFF their medication show dramatically impaired accuracy for both target durations. They overestimate the short signal and underestimate the long one compared to their own performance in the ON state. This unexpected “migration” effect, the rightward shift for 8 sec and the leftward shift for 21 sec, was correlated with the akinesia scores in the OFF state. A positive and a negative correlation were found between the akinesia score and the rightward and leftward shift, respectively, suggesting that dopamine depletion in the striatum produces the migration effect in temporal accuracy. A primary conclusion from these results is that accurate estimation of time intervals depends upon dopaminergic regulation in the striatum.

Where do these distortions lie? We propose that the migration of the peaks toward each other reflects a memory dysfunction such that the two targets appear more alike—are “coupled.” By coupling, we mean a mutual attraction between the two time values when they are laid down in memory or retrieved and compared to a current clock reading. The migration effect was consistently seen over a considerable number of trials in the OFF state. Even though subjects were receiving feedback, they were uniformly surprised that they were “off the target.” Corrective adjustment was evidently not possible for these subjects. This is evidence that the migration effect is a memory, storage/retrieval problem rather than a clock problem. A memory effect may be inferred when an accuracy distortion is relatively permanent despite intermittent corrective feedback during test sessions. As described earlier, a clock speed difference is not expected to produce an accuracy change unless it is introduced after training in an alternative drug condition. The classic clock pattern distortion produced in animals under dopaminergic manipulation (Meck, 1996) holds that subjects originally trained without a dopamine agonist show a dramatic 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. This, in turn, is followed by a rebound effect in the opposite direction when the drug is removed. In our study we analyzed first half/second half performance in the OFF condition and found no difference in accuracy early and late in training. This would be expected if the effect was a memory problem such that even under feedback subjects are unable to recalibrate because their memories continue to be laid down or are retrieved “incorrectly.” The mismatch between trained values and remembered values persists at least through the blocked training (60 trials) for each duration.

The migration, however, is demonstrably not a mixing of retrieval from two different memories. Such mixing or switching deficit is well documented in PD (Brown & Marsden, 1991; Malapani, Pillon, et al., 1994), even on levodopa medication (Owen et al., 1993). Mixing should induce relative frequency distributions of temporal estimates with two peaks, one at each criterion time, instead of one peak shifted to the right or to the left as seen here. A careful examination of individual as well as group functions showed no instances of a minor peak at the other criterion time. Rather, individual as well as group functions show unimodal peaks at a distorted, that is migrated, temporal target.

In addition to the coupling seen in accuracy when subjects are OFF the drug, there is increased variability as well that does not follow the scalar rule, either between ON and OFF states, or, importantly, within the OFF state. In the 8-sec condition, if the subjects’ dysfunction in the OFF state was one of accuracy only, while the timing mechanism operated “normally” as in the ON state but aimed at a distorted target, the OFF state function would superpose with the ON state distribution, which it does not do. Even controlling for the distorted increase in reproduced time, the coefficient of variation for 8 sec OFF is larger than that found in the ON condition. Thus, added variability is introduced in the 8-sec OFF condition. Similarly, added variability is introduced in the 21-sec condition in the OFF state, compared to the ON state because the coefficients of variation are significantly different between the two states. Importantly, this increased variability is not scalar with the distorted accuracy values OFF the drug. The coefficient of variation for 8 sec is significantly greater than that for 21 sec. Thus, the lack of dopamine regulation adds nonscalar variability in timing, just as it adds variance in many systems in PD, which is well documented in other clinical phenomena (Hallett, 1993).
In conclusion, dopaminergic deregulation in the striatum produces both accuracy and variance effects in interval timing when two different time values have been learned.

EXPERIMENT 2
The second experiment was designed to eliminate coupling by studying a condition in which only one duration must be remembered and retrieved. If the distortions seen in Experiment 1 are a result of prior training on a second duration that somehow forces migration and nonscalar variance, with only one duration in memory we should see no such distortions. It will therefore be of special interest to look for a higher coefficient of variation off the drug in the single duration condition. We chose the 21-sec duration to study in Experiment 2 because the left shift for 21 sec in Experiment 1 was in some sense more surprising than the right shift seen at the short duration. Slowness of movement and generalized slowing in PD suggests that perhaps slowed storage or retrieval might produce an overestimation of time intervals. As in Experiment 1, a new group of PD patients in Experiment 2 were trained and tested both ON and OFF medication.

Results
The results obtained in Experiment 2 are shown contrasted with the results obtained in Experiment 1 for the 21-sec duration in Figure 4. This allows a direct comparison of responding when 21 sec is the only duration trained versus 21 sec as one of two durations trained. The relative frequency distributions (upper panel) show that in both Experiments 1 and 2 subjects were fairly accurate at timing the 21-sec duration in the ON condition. A shift in accuracy occurs in the OFF state of PD patients in both experiments compared to their own performance in the ON state. However, the OFF state functions are slightly shifted to the right in Experiment 2, whereas they are dramatically shifted to the left in Experiment 1. Importantly, the 21-sec functions obtained in the ON and the OFF state for the patients in Experiment 2 superpose when plotted in relative time and normalized as proportions of the maximum (lower panel).

Mean median, SIQR, and SIQR/median in both ON and OFF states obtained in Experiment 2 are shown in Table 3. Statistical analysis of the results showed a significant (right shift) effect of drug on the median ($F = 6.9; p < 0.05$) with no significant effect on SIQR ($F = 0.01; p = 0.9$) and no effect on SIQR/median ($F = 0.1; p = 0.7$).

Discussion
Experiment 2, in which only one duration was reproduced, was designed to control for biases and interactions that may occur when more than one duration has been learned. Results showed a small but reliable overestimation of the 21-sec duration in PD patients OFF medication when it is the only duration to be remembered and reproduced. In contrast, the same duration is underestimated in Experiment 1, when it is associated with a memory for a shorter duration. This is evidence that the underestimation of the long signal obtained in Experiment 1 was due to the dual training requirement. Indeed, Experiment 2 suggests this left migration may have masked a right shift that would have been obtained in PD patients OFF the drug if the second, short interval had not been trained as well. Again here, as in Experiment 1, an analysis of first half/second half performance in the OFF condition showed no difference in accuracy early and late in training. Thus, as in Experiment 1, the classic “clock pattern” obtained in animals after administration of dopaminergic antagonists (Meck, 1996) also is not seen in this experiment. Rather, the relatively permanent, although small, right shift is maintained under continued feedback, consistent with a memory distortion. The nonscalar variance evident in Experiment 1, when two durations were trained, is not paralleled by an increase in coefficient variation OFF the drug in Experiment 2. Rather, variance OFF the drug is scalar with variance ON the drug as indexed by no significant change in SIQR/median. Together with the right shift in accuracy, it strongly suggests that the temporal processing distortions in Experiment 1 were the result of the dual memory feature for both the migration and the added variance seen there.

GENERAL DISCUSSION
The experiments reported here have both behavioral and functional anatomical implications.

Behavioral Implications
The first conclusion that can be drawn from the present data is that normal clock functioning, reproduction of accurate time estimation exhibiting the scalar property, is obtained whenever dopamine regulation is normal. Young subjects, to a lesser extent aged subjects, and PD patients ON levodopa supplementation treatment all showed accurate time estimation. Our interest centers on what components of the timing process are impaired when dysfunctional temporal reproduction is found. Two differing dysfunctions are observed, in accuracy and variability of temporal reproduction in PD patients OFF medication.

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. The preponderance of evidence suggests that this effect is a memory rather than a clock or decision
process effect. The accuracy dysfunction observed goes in a different direction when only one memory has been established instead of two. If the dysfunctional reproduction was a result of a decision bias induced in the OFF medication state, one would expect a distortion in the same direction for both remembered times in Experiment 1 and a similar distortion of the single remembered time in Experiment 2. Moreover, as argued earlier, a slowing or speeding of the clock monitoring the current time would not be expected to induce an accuracy distortion because subjects are trained and tested in the same condition.

Figure 4. Relative frequency distributions for the 21-sec target duration plotted together for Experiments 1 and 2 (upper panel; white and black triangles for ON and OFF functions, respectively, of Experiment 2). The 21-sec functions in both drug conditions obtained in Experiment 2, when plotted in time relative to the peak time and normalized as proportions of the maximum relative frequency superpose with the ON state function of Experiment 1 but not with the OFF state function of Experiment 1 (lower panel).

Table 3. Mean (Standard Deviation) of Accuracy, Variability, & Coefficient of Variation for PD Patients ON and OFF Medication in Experiment 2.

<table>
<thead>
<tr>
<th>21-sec duration</th>
<th>PD ON</th>
<th>PD OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>20.1 (1.9)</td>
<td>22.1 (2.05)</td>
</tr>
<tr>
<td>SIQR</td>
<td>.875 (.4)</td>
<td>.885 (.4)</td>
</tr>
<tr>
<td>SIQR/median</td>
<td>.043 (.01)</td>
<td>.04 (.02)</td>
</tr>
</tbody>
</table>
On these grounds we would ascribe the migration to mnemonic processing. There is also internal evidence supporting a memory rather than a clock or decision dysfunction here. In Experiment 2, subjects showed normal, scalar variance for the 21-sec target time even when a small distortion in the reproduced target time was present. When subjects estimated 21 sec ON medication, they reproduced nearly veridical estimates. When OFF medication, they showed an increase in their estimate, but this increase was associated with scalar variance. This suggests that variability in the clock process underlying reproductions of both the veridical and distorted times had not changed. In Experiment 1 we found two different kinds of distortion when OFF the drug. First, the target times themselves migrated, but second, variance around these new (incorrect) target values did not show the scalar property. Importantly, this is the case for the 8-sec duration in which the distortion was in the same direction as the 21-sec-only condition in Experiment 2 where variance increases according to the scalar rule. Thus the greater SIQR for 8 sec OFF in Experiment 1 was not due solely to the scalar increase expected on the basis of a new, longer target time. Rather additional variance was induced by the dual training condition.

There are, then, two effects induced by dopaminergic deregulation. One of these is distortion in the target time to be reproduced, which goes in opposite directions when one versus two memories are present. The second is an additional source of nonscalar variability, which also is present only when two memories are resident in long-term store. When only one memory must be remembered and reproduced, this source of variability is not present. Rather the scalar interval timer operates normally but on a distorted (in this case overestimated) value, as in the 21-sec-only condition in Experiment 2.

We hypothesize that either the encode or the decode system, or both, are responsible for distortions in the timed values to be reproduced. Although the memory system appears to be implicated in these accuracy and variance effects, clock distortions may be present as well, which are not observable in these conditions because training and testing occurs under the same conditions. Additional study aimed at dissociating these two kinds of effects, when trained single- or dual-target values are tested in the alternative drug state, without additional reinforced training, is currently in process in our laboratories.

**Functional, Anatomical Implications**

Our experiments indicate that temporal information processing in humans depends on dopaminergic regulation in the striatum. Previous work with animals has implicated dopaminergic transmission systems in the striatum as being required for any timing performance at all. 6-OHDA lesions in both the substantial nigra and the striatum dramatically impair interval timing assessed with the PI procedure in rats (Meck, 1998a), whereas spatial discrimination is spared (Robbins, Giardini, Jones, Reading, & Sahakian, 1990). Importantly, interval timing is corrected after levodopa administration in animals with lesions in the substantial nigra, but no such correction occurs when animals are lesioned in the striatum (Meck, 1998a). This suggests that dopaminergic modulation of striatal circuits is necessary in order for timing functions to be processed through the striatum.

The dopamine-containing nigrostriatal tract degenerates in Parkinson’s disease (Agid et al., 1987), and the resulting dysfunction of striatal circuits leads to disturbances of movement and cognition, including the disordered timing of movement, clinically known as bradykinesia and/or akinesia (Hallett, 1993; Marsden, 1992; Marsden & Obeso, 1994; Saint-Cyr, Taylor, & Nicholson, 1995). The results obtained in this study suggest that more specific timing processes, in particular storage and retrieval of the memory for time, also involve the striatal circuits. Moreover, the deficit in time reproduction found in the OFF condition is correlated with the akinesia score, suggesting that the same dysfunctional timing mechanisms may underlie disordered timing of complex movements in PD.

Recent neurophysiological evidence obtained in behaving animals (Graybiel, Aosaki, Flaherty, & Kimura, 1994) suggests that difficulties in timing complex movements and even cognitive and psychomotor behaviors could result from reduced temporal coordination of activity in the modular, distributed circuits within the striatum. Coordination of the input-output circuitry through the striatum seems to rely on the synchronized pause of activity in striatal interneurons (TANs) that are spatially distributed throughout the “motor” and “cognitive” striatum, temporally coordinated and predictive of reward. These neurons require tonic dopaminergic input in order to express the synchronized pause because after unilateral dopaminergic lesions induced by MPTP injections in primates, responses are lost on the side of the infusion, and moreover, systemic injections of apomorphine reinstate the responses (Aosaki, Graybiel, & Kimura, 1994).

A plausible explanation for the results obtained in this study is that the depletion of dopamine in PD OFF patients and the resulting reduced temporal coordination of activity between striatal modules and striato-cortical circuits impairs the storage and retrieval processes of temporal memory under the dual-task condition, as well as possibly impairing clock functioning. Whether a distinct role for temporal memory may be attributed to the dopamine-containing nigrostriatal tract or the striatal interneurons cannot be answered yet. Our current program of work assessing patients with focal and degenerative lesions in different parts of the striatal cir-
cuitry (preliminary results reported by Malapani, Rakitin, et al., 1994) should provide more evidence on this question.

**METHODS**

**General Procedure**

The general procedure is diagrammed in Figure 5. In both experiments subjects were required to remember and reproduce time intervals of a standard duration in blocked sessions, with one duration presented in each session block. A block of trials on a given duration consisted of: (1) the *training phase* of 10 fixed time (FT) trials of the appropriate signal duration to allow subjects to learn the duration to be tested later, followed by 10 peak interval (PI) trials (described below) with intertrial (ITI) feedback to allow subjects to become familiar with the response requirements of the task; (2) the *testing phase* of 60 trials including 75% PI trials and 25% FT trials, presented randomly. Two-thirds of PI trials were followed by ITI feedback. For one-third of these trials no feedback occurred, and the subject was instructed to simply continue to the next trial. Sessions generally lasted 1.5 to 2 h.

During FT trials a blue rectangle appeared on the computer screen and subjects were instructed to attend to the period of time that the rectangle remained blue. At the end of this interval the rectangle changed color from blue to magenta. On PI trials, the same blue rectangle appeared on the screen, signaling the onset of the interval to be timed, but instead of changing color at the criterion time, it remained on the screen for a duration of up to 3 times the criterion time.

Subjects were instructed to try to estimate when they thought the criterion time had elapsed by pressing the space bar on the keyboard (indicated by inverted black triangles in the left panel of Figure 5). They were told to make multiple guesses and that they should begin responding before they thought the criterion time had elapsed and continue at a high rate until they felt the criterion time had passed, after which they could terminate the trial and continue to the next by pressing the Enter key. To prevent counting during this phase, digits were imposed over the target stimulus in a randomized manner, and subjects were instructed to read this distractor aloud (cf. Rakitin et al., 1998). Feedback was presented during the ITI in the form of a histogram (Figure 5, right panel) showing the distribution of the responses they made on the previous trial plotted on a relative time scale (tenths of the target interval) so that subjects obtained no information about the absolute value of the criterion duration. They received two kinds of information from this figure. First, the spread of the histogram revealed how stringent their response criterion was. Second, the location of the peak of the histogram indicated accuracy. If most of their responding was clustered to the left of the criterion time ("T" on the abscissa), they were responding too early; if their responses clustered to the right of "T," this indicated that they were responding too late.

![Figure 5](http://www.mitpressjournals.org/doi/pdf/10.1162/089892998562762)
Data Acquisition and Analysis

In all three experiments 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.

Experiment 1

Subjects

Twelve aged control subjects with no neurological disease or intellectual impairment and ten patients with idiopathic PD and no clinical evidence of dementia participated in the study. Tables 4 and 5 show the general characteristics and the neuropsychological scores of the aged group and the PD group, respectively. 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 two groups according to their dopamine supplementation treatment at the time of the study, allowing a direct evaluation of the influence of dopa transmission on their performance: ON PD patients (n = 10), with severe fluctuations under levodopa treatment [Hoehn and Yahr stages = II (n = 3), III (n = 4), IV (n = 3)], were assessed 90 min after acute administration of a supraliminar dose of levodopa-carbidopa (250 mg) and just after an injection of 1.5 ml of apomorphine (when the effect of levodopa was maximal); OFF PD patients (n = 10) were assessed when dopamine supplementation treatment had been withdrawn for at least 18 h (when the parkinsonian disability was maximal).

Design

Stimuli and trial types used were those described in the general experimental procedure. Aged subjects were tested for two sessions on three durations (8, 12, and 21 sec). The design of the study counterbalanced the order of testing as follows: (8-12-21), (8-21-12), (12-8-21), (12-21-8), (21-8-12), (21-12-8). Subjects received a different order of intervals in each of their two sessions. PD subjects had two sessions per day on each drug condition, for four consecutive days. During each session, reproduction of two durations (8 and 21 sec) was assessed in blocked minisessions. The design of the study (Table 6) was counterbalanced for the drug condition and the training order for the duration. Half of the patients were tested in an OFF-ON-ON-OFF design, and the other half in a ON-OFF-OFF-ON design. During each session,

Table 4. Characteristics of Aged Subjects.

<table>
<thead>
<tr>
<th>n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.2 (4.8)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.7 (2.2)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/4</td>
</tr>
<tr>
<td>WRIQ</td>
<td>106.7 (17.3)</td>
</tr>
<tr>
<td>DSPANfor</td>
<td>5.5 (1)</td>
</tr>
<tr>
<td>DSPANbac</td>
<td>4.8 (1.4)</td>
</tr>
<tr>
<td>CVLT1.5T</td>
<td>54.5 (8.4)</td>
</tr>
</tbody>
</table>

Table 5. General Characteristics, Motor & Neuropsychological Evaluation for PD Patients ON and OFF Medication in Experiment 1.

<table>
<thead>
<tr>
<th>n</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX (m/f)</td>
<td>9/1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 (8)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>9.8 (2.4)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>MMS</td>
<td>29.1 (1.2)</td>
</tr>
<tr>
<td>MADRS</td>
<td>9.5 (7.4)</td>
</tr>
<tr>
<td>WCST (cr)</td>
<td>5.4 (2.9)</td>
</tr>
<tr>
<td>UPDRS</td>
<td>20 (10) 47.7 (14.5)</td>
</tr>
<tr>
<td>Tremor</td>
<td>0.3 (0.6) 3.4 (3.2)</td>
</tr>
<tr>
<td>Akinesia</td>
<td>9.3 (5.6) 20.6 (7.3)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>5.0 (3.1) 10.6 (4.1)</td>
</tr>
<tr>
<td>Levodopa dose</td>
<td>250 mg</td>
</tr>
<tr>
<td>Apomorphine dose</td>
<td>4 ml</td>
</tr>
</tbody>
</table>
patients estimated the duration of both 8- and 21-sec signals in a block (see “General Procedure” section). The presentation of the signals was also counterbalanced, so the order was 8-21 and 21-8 in both ON and OFF states.

Data Analysis and Comparisons

The measurements of interest were accuracy of subjective time estimates indexed (nonparametrically) as mean median, variability of subjective time (SIQR), and the nonparametric coefficient of variation (SIQR/median). Statistical analyses for comparisons between the Young and Aged groups were performed with univariate analyses of variance (ANOVA) for repeated measures. One between group independent factor (Young versus Aged) and one within factor (Duration) were tested for the median, SIQR, and SIQR/median as dependent variables. Sources of variance were Duration, Age, and the Interaction between Duration and Age. Spearman’s rank correlation coefficients were calculated between the accuracy and precision measurements and neuropsychological scores in the Aged group. To compare performances of PD ON versus PD OFF patients, we contrasted the performance of PD patients in the ON medication state to their own performance in the OFF state. Univariate analyses of variance (ANOVA) for repeated measures with Duration and Drug as the two within factors were used to test median, SIQR, and SIQR/median as dependent variables. Sources of variance were Duration, Drug, and the Interaction between Duration and Drug. Spearman’s rank correlation coefficients were calculated between accuracy and variability measurements and motor and neuropsychological scores of the patients. Finally, one between-group ANOVA analysis tested for differences on median, SIQR, and coefficient of variation of the two target times (8 and 21 sec) between PD ON, PD OFF, and Aged. Post hoc triangular comparisons (Fisher’s protected LSD) tested for differences between pairs of groups.

Experiment 2

Subjects

Nine patients with idiopathic PD and no clinical evidence of dementia took part in the study (Table 7). Patients were assessed twice and were divided into two groups according to their dopamine supplementation treatment at the time of the examination, allowing a direct evaluation of the influence of dopa transmission on their performance: ON PD patients ($n = 9$), with severe fluctuations under levodopa treatment [Hoehn and Yahr stages = II ($n = 3$), III ($n = 3$), IV ($n = 3$)] were assessed 90 min after acute administration of a supraliminal dose of levodopa-carbidopa (250 mg) and just after an injection of 1.5 ml of apomorphine (when the effect of levodopa was maximal); OFF PD patients ($n = 9$) were assessed when dopamine supplementation treatment had been withdrawn for at least 18 h (when the parkinsonian disability was maximal).

Design

All subjects were trained and tested with the 21-sec time interval, in both ON and OFF levodopa states. Four patients were tested in an ON-OFF design and the other five in an OFF-ON design. Stimuli and trial types used were those described in the general experimental procedure.

Data Analysis and Comparisons

Because no significant difference was found on any measure between subjects tested ON then OFF versus OFF then ON medication, data from both groups were pooled.
Data were analyzed similarly to Experiment 1. We used paired t-test comparisons to contrast the performance of PD patients in the ON state on median, SIQR, and SIQR/median of reproduced time measures, with their own performance in the OFF state.

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