The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson’s disease

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Summary

In separate experiments, we studied the temporal accuracy and precision of self-paced, repetitive finger-tapping in two groups of 12 patients with Parkinson’s disease and a group of 12 controls matched to the patients with respect to age and general cognitive state. One group (I) of patients was studied initially following 12–15 h abstinence from normal levodopa medication (‘off’) and again, subsequently, ~1 h after ingestion of a single normal dose (‘on’). A second group (II) of patients, each of whom had bilaterally asymmetrical neurological signs, was tested using ‘worse’ and ‘better’ hands separately. Within each session, subjects were tested repeatedly on a tapping task during which they were required to produce a regular series of self-timed inter-tap intervals, the target duration (550 ms) of which had been established previously during an initial period of tapping in synchrony with the beats of a regular metronome. We employed Wing and Kristofferson’s (1973) model of control of motor timing to partition the total variance (TV) about the mean inter-response interval (IRI) produced during the self-paced phase of each run into separate components (‘clock’ variance (CV) and ‘motor-delay’ variance (MDV)) attributable to hypothetical ‘clock’ and ‘motor-implementation’ processes. Although the mean self-paced IRI of parkinsonian patients was generally shorter than that of controls, only during the ‘on’ medication condition (Group I) was it significantly so. By comparison with control values, and those observed during the ‘on’ medication condition, values of TV, CV and MDV in Group I were all significantly higher when subjects were ‘off’ medication. During the ‘on’ medication condition, only CV was significantly higher than the control value. In Group II, values of TV, CV and MDV associated with use of the ‘worse’ hand were all significantly higher than both control values and those associated with use of the ‘better’ hand. Values of these variables when subjects used the ‘better’ hand did not, however, differ significantly from control values. The theoretical import of these results is discussed in the light of several important procedural, statistical and computational issues and we conclude that TV, CV and MDV may all vary significantly as a function of the efficacy of dopaminergic transmission in the basal ganglia.

Keywords: Parkinson’s disease; basal ganglia; timing; tapping; motor control

Introduction

During co-ordinated movements, specific muscles must be activated or inactivated to appropriate degree, not only in correct sequence but, usually, also at appropriate times. In addressing the poorly understood issue of how such timing might be effected, two general approaches have been adopted (Summers and Burns, 1990; Ivry and Hazeltine, 1992). First, models of movement sequences have been developed within which time is not represented or controlled explicitly. In such models, the temporal structure of motor output arises effectively as an emergent property of the dynamic and
biomechanical characteristics of the processing system (e.g. Kelso et al., 1981; Rumelhart and Norman, 1982; Turvey et al., 1986). In contrast, a second approach has been to suppose that time is represented directly in the nervous system by way of the operations of a central ‘clock’, or timekeeper, different hypothetical forms of which have been employed not only in the modelling of the temporal structure of motor output (e.g. Wing and Kristofferson, 1973; Mates, 1994; Vorberg and Wing, 1996) but also, across a much wider temporal range, in psychophysical accounts of the characteristics of time perception in a variety of species, including humans (e.g. Gibbon, 1977; Church, 1984; Killeen and Fetterman, 1988; Church and Broadbent, 1990; Treisman et al., 1990; Wearden, 1991).

If time is a variable which is specified directly by a neurobiological clock during human movement (cf. Stein, 1982), what neural processes are involved? And to what extent are they distinct from those which underlie temporal perception? In an influential series of experiments, Ivry and his colleagues have begun to provide answers to these questions by examining the effects of Parkinson’s disease and of cortical and cerebellar lesions on the temporal accuracy and precision of self-paced repetitive tapping, and on perceptual thresholds of duration (Ivry et al., 1988; Ivry and Keele, 1989; Keele and Ivry, 1990). On the basis of this work, Ivry and Keele have argued that the cerebellum provides the primary neural substrate for both perceptual and motor timing, and is solely responsible for timing computations within a movement control system in which the basal ganglia and motor areas of the cerebral cortex play some other, ill-defined roles (Keele and Ivry, 1987; Ivry and Keele, 1989).

However, the results of their analysis of parkinsonian repetitive tapping performance using Wing and Kristofferson’s (1973) ‘clock’ model of motor timing control, from which they concluded that the basal ganglia play no direct role in movement timing, are neither entirely self-consistent, nor consistent with those of other comparable studies (Wing et al., 1984; Wing and Miller, 1984; Pastor et al., 1992b; Freeman et al., 1994a). Furthermore, a significant role for the basal ganglia in both motor timing and temporal perception is suggested by observations that patients with Parkinson’s disease are impaired on a variety of other tasks which require the production of appropriately timed movements, or in which the primary temporal task demand is perceptual. Such tasks include temporal tracking (Nagasaki et al., 1978; Nakamura et al., 1978; Freeman et al., 1993; O’Boyle et al., 1995), the production of simultaneous and sequential movements (Benecke et al., 1986, 1987), the reproduction and verbal estimation of temporal intervals (Pastor et al., 1992a), and auditory, visual and tactile temporal threshold discrimination (Artieda et al., 1992).

In this paper, we aim to elucidate the effects of damage to the basal ganglia on motor timing, by addressing the important issue of the inconsistencies between the results of different studies of the effects of Parkinson’s disease on the precision of self-timed repetitive tapping, interpreted within the theoretical framework provided by Wing and Kristofferson (1973). Following an exposition of their model, we review the relevant literature in detail.

This model was developed to explain the temporal characteristics of self-paced finger-tapping in a task involving two sequential, and continuous, stages. During an initial ‘synchronization’ period, a subject is required to tap in time with a series of brief, regularly spaced auditory signals produced by a metronome. Immediately following the cessation of these pacing cues, there ensues a ‘continuation’ phase, during which the subject is required to continue tapping at the same rate. Wing and Kristofferson (1973) supposed that the statistical structure of the series of intervals produced during the self-paced phase of tapping is determined by two hypothetical processes, a ‘clock’ and a ‘motor-implementation system’ such that the clock, having been more or less accurately entrained to the frequency of the pacing cues, subsequently ticks, with successive clock-intervals (\(C_j\)), with mean clock interval \(\mu_c\), which are subject to random temporal variation (\(\sigma_c^2\)). Each tick of the clock initiates the production of a response by activating the motor-implementation system which imposes a delay (\(D_j\)), with mean motor-delay interval \(\mu_d\), which is subject to independent, random temporal variation (\(\sigma_d^2\)), before the eventual occurrence of the response (\(R_j\)). The interval (\(I_j\)) between two successive responses (\(R_{j-1}\) and \(R_j\)) is therefore given by,

\[
I_j = C_j + D_j - D_{j-1}
\]

and the mean IRI is \(\mu_I = \mu_c\), with variance \(\sigma_I^2\).

Given that \(C_j\) and \(D_j\) are assumed to be random, independent variables, it can be shown that,

\[
\sigma_I^2 = \sigma_c^2 + 2\sigma_d^2
\]

Now, in the hypothetical case of a clock which ticks at a perfectly constant rate (\(\sigma_c^2 = 0\)), a response (\(R_j\)) which follows a motor-delay interval (\(D_j\)) which is randomly long (or short) will close a response interval (\(f_j\)) which is longer (or shorter) than the mean (\(\mu_f\)). Given that the delay-interval (\(D_{j-1}\)) is equal to \(\mu_d\), the next response interval (\(I_{j+1}\)) which is opened by \(R_j\) will be necessarily shorter (or longer) than the mean. This negative covariation between neighbouring response intervals, which is thus predicted to arise as a consequence of random variation in the delay imposed by the motor-implementation system, is not predicted, on the other hand, in the hypothetical case in which the motor-implementation system imposes a perfectly constant motor-delay (\(\sigma_d^2 = 0\)), following clock intervals which are subject to random variation.

The model therefore predicts that neighbouring response intervals (intervals at lag 1) will tend to covary negatively, and this negative covariation is attributed to random variation (‘noise’) in the duration of the delay within the motor-implementation system. Calculation, across the series of
response intervals, of the autocovariance, \( \gamma \), at lag 1 therefore provides an estimate of the variance attributable to the motor delays. Thus,

\[
\sigma_D^2 = -\gamma(1)
\]  

(3)

The variance attributable to the clock (\( \sigma_C^2 \)) can then be obtained indirectly (but not independently) by elimination in Equation 2. It follows from the assumptions underlying the model that the lag 1 autocorrelation, \( \rho(1) = \gamma(1)/\gamma(0) = -1/\{2+(\sigma_D^2/\sigma_C^2)\} \), should range between 0 and –0.5 and that, for lags > 1, the predicted value of autocovariance is zero.

The validity of the model is supported by experimental observations in neurologically intact subjects that (i) estimates of covariance between adjacent intervals are usually negative (e.g. Wing and Kristofferson, 1973; Turvey et al., 1989), (ii) with changes in effector, CV is more stable than MDV (Wing, 1977a, 1980), and (iii) changes in the target interval provided by the metronome tend to affect CV and not MDV (Wing, 1980). In addition, studies of patients with neurological damage have provided some evidence that the two processes can be functionally dissociated and mapped onto discrete neural systems (e.g. Keele and Ivry, 1987; Ivry et al., 1988).

The first study in which the model was applied to the analysis of the performance of parkinsonian patients involved the investigation of a 44-year-old right-handed female (M.F.) with predominantly right-sided signs (Wing and Miller, 1984; Wing et al., 1984). M.F. was tested on seven occasions over a 1-year period, during which time she took inconsistently a low daily dose of levodopa. M.F. was required to tap, using the index finger, on a touch-sensitive plate and trials were run with each hand at each of two target (metronome) intervals (450 ms and 550 ms). On average, over the period of testing, M.F.’s total IRI variance (TV) and CV were significantly larger when using the right hand than when using the left, whereas MDV did not differ significantly between the two hands. The authors also observed that TV using the right hand deteriorated to a significantly greater extent over the period of testing than did TV using the left hand, whereas MDV did not. While these changes in TV were accompanied by similar changes in CV (Wing and Miller, 1984), no confirmation was provided that the latter were statistically significant.

Ivry and Keele (1989; see also Ivry, 1986) subsequently published details of three studies involving the testing of parkinsonian patients on a very similar version of the tapping task in which subjects were required to tap, at a target interval of 550 ms, by using the index finger to depress a microswitch. In one of the three studies, involving the comparison of performance between ‘effectors’ in four subjects, both mean TV and CV were larger when using the ‘impaired effector’ than when using the ‘unaffected effector’, while there was ‘little difference’ between the effectors in MDV (Ivry and Keele, 1989; Table 4). For several reasons, however, the significance of these aggregated data is difficult to assess. First, one of the four subjects was M.F. (Ivry, 1986, p. 22), whose data were published earlier (Wing and Miller, 1984; Wing et al., 1984) and are described above. Secondly, the effect of medication in the case of another subject concerned ‘pre- versus post-medication’ (Ivry, 1986; Table 3). We suppose this subject to have been B.A.U., details of whom had already been published (Keele and Ivry, 1987, pp. 207–8; Ivry, 1986, pp. 41–2). This subject was a 75-year-old male who, shortly after having been diagnosed, was tested using his dominant hand over a period of 2 weeks, on one occasion prior to, and on five occasions subsequent to, beginning medication with levodopa. While, in this subject, MDV remained ‘fairly constant’ over the six sessions, CV declined, following the beginning of treatment, to a lower and subsequently stable level by the third session. Thirdly, no details were provided of the remaining two subjects in this group: we presume them to have had bilaterally asymmetrical parkinsonism. Fourthly, no statistical analysis of the aggregated data was possible in view of the small numbers of subjects involved.

In a second study, the performance of seven patients while maintained normally on levodopa (‘on’) was compared with their performance after they had missed their normal morning medication (‘off’). The authors reported that despite clear differences between conditions in the severity of neurological signs, there were no associated differences in TV, CV or MDV on the tapping task. In the third study, the performance of 29 patients (‘on’ levodopa) was found not to differ, in respect of TV, CV or MDV, from that of 21 elderly controls. In neither of these two studies, however, were the results of statistical comparisons provided. On the basis of their three studies, the authors concluded that the basal ganglia play no direct role in motor timing (Keele and Ivry, 1987; Ivry and Keele, 1989).

Subsequently, Pastor et al. (1992b) addressed the discrepancies between the results of previous studies in an experiment in which repetitive, alternating, 80° flexion–extension movements of the wrist were studied in parkinsonian patients, following 48 h of withdrawal from levodopa medication, and in age-matched controls. Subjects were tested both during and following (for 30 movements) the presentation of 30 auditory pacing stimuli at target intervals, on different trials, of 400 ms, 500 ms, 667 ms, 1000 ms and 2000 ms. Each subject was tested on one trial at each target interval and the IRI was defined as the interval between two successive flexion movements, recorded electromyographically from the forearm flexor. The authors reported that, during self-paced tapping, TV, CV and MDV were all significantly higher, at all target intervals, for patients than for controls. On the other hand, although mean values for all three variables were higher among a subgroup of patients classified as having ‘moderate/severe’ disease than among a subgroup classified as having ‘mild’ disease, only for TV at a target interval of 667 ms was the difference statistically significant. However, the interpretation of these data is problematic, for two reasons in particular.

First, as Wing and Kristofferson’s (1973) model is
concerned specifically with the control of motor timing, its application should involve use of a task in which the primary task-demand is that of timing accuracy, with minimal competing demand for the generation or modulation of force, or for spatial accuracy, about the control of which the model has nothing to say. Indeed, Wing (1990) has shown that the TV of self-paced tapping increases if additional attentional demands are imposed. It is clear, however, that the task employed by Pastor et al. (1992b) imposed a stringent spatial task-demand, the severity of which was likely to have increased as a function of target frequency. Furthermore, there is evidence in the authors' data that, at the highest target frequencies, their patients' ability to move at the required rate was constrained by a rate ceiling. The degree to which this task might have involved a significant demand for force control is also unclear. In these important respects, therefore, the task differed from the finger-tapping tasks used by previous investigators.

A second problem in interpreting these data appropriately arises from the fact that Pastor et al. (1992b) ran only one trial per subject at each target frequency. Aside from the unaddressed issue of within-subject sampling error, this feature of the authors' experimental design had unfortunate consequences when combined with their strategy for dealing with apparent violations of the prediction of Wing and Kristofferson's (1973) model that the lag 1 autocorrelation, \( \rho(1) \), should range between limits of 0 and \(-0.5\). Across different target intervals, the frequency of trials on which such violations occurred ranged between 28.6% and 60%, and only one parkinsonian subject and one control subject produced values of \( \rho(1) \) which fell within the predicted range during trials at all target intervals. In addressing this problem, Pastor et al. (1992b) chose to restrict subsequent analyses to data collected from only those trials which produced a value of \( \rho(1) \) which fell within the predicted range. As the authors ran only one trial per subject at each target interval, however, the adoption of this procedure had the consequences that, in subsequent comparisons between different groups of subjects, (i) the number of subjects was very much reduced; (ii) for any given target interval, groups were unbalanced in respect of previously controlled independent variables, and (iii) the size and constitution of groups varied with target interval. The potential import of these considerations is indicated by the fact that in the case of eight parkinsonian patients who were tested both when 'on' and when 'off' levodopa, statistical analyses were not possible because acceptable data were produced during both conditions only at target intervals of 667 ms, by three subjects, and 500 ms, by four subjects.

Given that the number of response intervals produced during a single trial is necessarily small, one might expect to observe a certain incidence of such violations, simply as a consequence of sampling variability. All previous investigators had run blocks of trials at a particular target interval and subsequently averaged over trials and blocks. However, although lag 1 autocorrelations calculated from such averaged values exceed the predicted bounds less frequently than do those derived from single trials, violations still persist. Ivry and Keele (1989), for example, reported violations in 18.0% of blocks of six trials among their parkinsonian patients and in 13.2% of blocks among their elderly controls. To minimize the effect of these violations, the large majority of which involved a positive estimated lag 1 autocovariance (i.e. \( \rho(1) > 0 \)), these authors chose to set MDV to zero and to attribute all of the tapping variability to the clock process (else, in the decomposition of tapping variance, CV > TV). The authors commented that the alternative use, in such cases, of negative values of MDV and of CV greater than TV 'did not change the tenor' of their conclusions. Ivry (1986) also remarked that the inclusion in analyses of only those subjects whose data did not violate the prediction (cf. Pastor et al., 1992b), had no effect on the patterns of results of comparisons of patients with controls.

Thus, for a variety of reasons, the studies we have reviewed provide an inconsistent and confusing account of the degree to which the performance of self-paced repetitive movements, and the operation of Wing and Kristofferson's (1973) 'clock', are affected by Parkinson's disease. The nature and extent of reported impairments, in respect of TV, CV and MDV, have varied, within and between different reports, according to the number and characteristics of the patients studied, to whether or not subjects were receiving dopaminergic medication at the time of testing and to the nature of the experimental designs employed. In addition, comparison of results between different studies is obscured further by significant variations in task characteristics, in methodological and computational procedures, and in the degree to which different authors provided details of the neurological status of their patients.

In an attempt to resolve these inconsistencies, we conducted two experiments, each involving a separate group of 12 patients with mild or moderate Parkinson's disease. In the first experiment, we compared, within subjects, performance between conditions of 'on' and 'off' dopaminergic medication in such a way as to maximize, in a controlled fashion, potential effects of medication. In the second experiment, conducted with patients with bilaterally asymmetrical neurological signs, we compared, within each subject while maintained on normal medication, performance with the hand more affected by the disease with performance by the hand less so-affected. In addition, we compared the performance of each group of patients, in each condition, with that of a group of control subjects matched to the patient groups in terms of age and general cognitive status. At the beginning of each experimental session, neurological assessment was made of the severity of tremor, rigidity and bradykinesia manifest in a patient's hand(s). To maximize the probability that the primary tapping task-demand was accuracy of timing, we employed a manipulandum which involved minimal demand for either the control of force or for spatial accuracy, and to facilitate comparisons between our own data and those described in the literature, we tested subjects' performance using a single target interval of 550 ms. Finally,
we examined the consequences, for the interpretation of our results, of observed violations of the predictions of autocovariance at lags 1–5, of Wing and Kristofferson's (1973) model, and of several significant variations in computational procedure which have been adopted by others. Brief details of preliminary analyses of some of the results described here have been reported previously (Freeman et al., 1994b; O'Boyle et al., 1994a, b).

Methods
Subjects
Two groups of patients with Parkinson’s disease, and one group of control subjects, participated in the experiments. All subjects were volunteers and gave, according to the declaration of Helsinki, their informed consent to participation in the experiments, which were approved by the local Ethics Committee.

Group I (on/off medication)
Twelve patients with Parkinson’s disease [seven males and five females; mean (SD) age = 63.5 (10.5) years; range = 48–85 years] were studied while ‘on’ and ‘off’ their normal medication. All subjects were normally maintained on levodopa (with peripheral decarboxylase inhibitor) and several were taking additional medication (selegiline by five subjects and bromocriptine by two others). On Hoehn and Yahr’s (1967) rating scale of severity of the disease, four subjects were classified as Stage I, six as Stage II and two as Stage III [mean (SD) = 1.8 (0.7)], and the mean (SD) score on Webster’s (1968) ‘Parkinson’s Disease Rating Scale’ was 9.5 (3.0) (range 5.5–17.0). The mean (SD) duration of illness was 6.7 (3.8) years (range 1–14 years), and the mean (SD) score on the ‘Mini-Mental State’ (MMS) test of cognitive state (Folstein et al., 1975) was 28.8 (1.4) (range 26–30). Ten subjects were right-handed and two left-handed.

Group II (asymmetrical Parkinson’s disease)
Twelve parkinsonian subjects (six males and six females), with bilaterally asymmetrical neurological signs (tremor, rigidity and bradykinesia) were studied when performing the tapping task with the hand more affected by Parkinson’s disease (‘worse’ hand) and with the hand less so-affected (‘better’ hand). All subjects were maintained on their normal medication throughout the period of testing. Ten subjects were typically very interested to see this information, and tried hard to beat their previous ‘best scores’, we

Controls
Twelve control subjects (six males and six females) were recruited from among patients’ relations and friends. None had any history of neurological disorder, or any physical disability which may have interfered with performance of the experimental task, and all enjoyed good general health. Subjects’ mean (SD) age was 63.6 (6.7) years (range 55–74 years) and their mean (SD) score on the MMS was 29.7 (0.7) (range 28–30). All subjects were right-handed.

The experimental tapping task
During an experimental session, subjects performed a number of runs of the tapping task. One such run consisted of two continuous phases. During an initial ‘synchronization’ phase, a subject listened to a series of 15 short tone-bursts (1000 Hz, 50 ms duration) issuing, with a constant inter-tone interval (onset-onset) of 550 ms, from a computer. The subject was instructed to listen to the first few tones and then, when ready, to start tapping the index finger (see below), as accurately as possible, in synchrony with the tones (on the beat). Subjects typically started tapping on the third or fourth tone. Following the occurrence of the 15th tone, the tones ceased, and the subject was required to continue tapping without pausing and, so far as possible, at exactly the same rate, for a further 31 taps. On the 31st tap, the occurrence of a final tone-burst indicated the end of the run. The period of self-paced tapping, in the absence of the pacing tones, constituted the second, ‘continuation’, phase of a run. Throughout a run, the subject’s tapping hand was hidden from view (but not from that of the experimenter) by an appropriately placed screen, which did not otherwise interfere with performance.

At the end of a run, the subject was provided with feedback about his/her performance during the continuation phase: on a VDU screen appeared details of the ‘required interval’ (550 ms), ‘your average interval’ (the mean IRI), ‘your variability score’ (the standard deviation of the mean IRI), and the number of ‘very short’ and ‘very long’ IRIs (respectively, < or >50% of the target interval). The subject was instructed to try to use this information, on the subsequent run, to match the mean IRI to the target interval, to reduce the variability score to as low a value as possible, and to avoid producing any very short or very long intervals. As subjects were typically very interested to see this information, and tried hard to beat their previous ‘best scores’, we
believe that its provision maintained subjects' motivation and concentration at a reasonably optimal level, and promoted the best performance of which they were capable.

**Production of pacing stimuli and registration of taps**

The production and timing of pacing stimuli, and the timing of responses, were controlled using in-house software running on an Apple IIe computer. Timing was accurate to 1 ms. A subject's taps were registered using a 'tapping box' which sat on a table in front of him/her. From the upper surface at one end of the box (which measured 11 cm long×6 cm wide×3 cm deep) protruded an infra-red emitter which was separated, by 34 mm, from a receiver, so that an infra-red beam stretched between them, laterally across the surface of the box. Interruption of the beam, by the subject's finger when tapping, caused registration of the tap by the computer. The surface of the box, in the region where the subject tapped, was covered with a layer of plastic foam to minimize auditory feedback arising from the occurrence of a tap. The position of the infra-red beam was set so that it was interrupted by the subject's finger at a distance of 1–2 mm above the surface of the foam. The measured elapsed time, during the down-stroke of a tap, between the subject's finger interrupting the beam and contacting the foam surface of the box (detected using a condenser microphone attached to the bottom of the box) was of the order of a few (<5) milliseconds.

During performance of the tapping task, a subject sat in a chair with elbow and forearm resting on the table and was required to hold the box, as it also rested on the table, such that it was gripped using the thumb and all of the fingers of one hand, with the exception of the index finger which was free to allow tapping flexion–extension movements about the metacarpophalangeal joint. The subject was instructed to tap by making such movements with an excursion of 2–3 cm and, once she/he had understood how she/he was to hold the box and perform tapping movements, she/he was encouraged to find the most comfortable overall position of body, arm and hand.

Any run in which, during the continuation phase, a subject produced an IRI of a duration which was < or >50% of the target interval (i.e. outside the range 275–825 ms), was eliminated from further consideration and did not contribute to the desired target number of runs during the particular session. Such a procedure has usually been adopted in previous studies, although not invariably (Pastor et al., 1992b), to avoid the inclusion of runs containing spurious short or long intervals arising from double-triggering of the response-manipulandum (attributable, for example, to manipulandum bounce or finger tremor) or from missed, or misdirected, taps. During any experimental session, a subject rarely produced more than one or two such runs and, if she/he did so, it was usually during the first few runs of the session.

We registered taps by way of interruption of an infra-red beam in order to eliminate the potential contribution, to TV, of the variability in action typical of a mechanical manipulandum (Hopkins and Kristofferson, 1980). In addition, the use of the tapping box allowed us to eliminate the potential contribution of movements of the elbow or wrist to overall tapping variance, and to minimize potential task-demands for the generation and modulation of force and for spatial accuracy (thereby allowing the subject to concentrate processing capacity on the timing of his/her taps).

**Procedure**

Subjects in each group were tested during each of two separate sessions. At the beginning of the first session, each completed the MMS and each parkinsonian subject was assessed independently by a neurologist on the scales of Webster and of Hoehn and Yahr. Webster's ratings were used for the assessment of the severity of signs of tremor, rigidity and bradykinesia (scale of 0–3 in each case: for the hand used by patients in Group I, and separately for right and left hands for patients in Group II). At the beginning of each session, collection of data on the tapping task was always preceded by one or two initial practice runs. Other details of procedure varied according to subject group, as follows.

**Group I**

During the first testing session ('off' medication), patients were tested on 11–20 runs (mean = 16.3) of the tapping task following 12–15 h abstinence from normal medication. Subjects then ingested a single normal dose of levodopa medication and, 45–75 min later, were again assessed, by independent neurological examination at the beginning of the second testing session ('on' condition), for severity of tremor, rigidity and bradykinesia, immediately prior to being tested on a further 12–20 runs (mean = 16.4) of the tapping task. Ten subjects used the preferred hand on all tapping runs, and two used the non-preferred hand (because of the severity of neurological deficit in the preferred hand). The duration of each session was 45–60 min. The order of experimental conditions was held constant to avoid the confabulatory effects of possible infradian fluctuations in severity of neurological signs: use of a design in which the order of conditions were to be counter-balanced across subjects would necessitate testing at least some subjects in each condition on separate days, in order to maintain a sensible period of abstinence from medication in the 'off' condition. During the 'on' condition, moreover, we wished to be able to exert some degree of control over the interval elapsing between the ingestion of levodopa and subsequent testing, ideally at a time when we might expect the therapeutic efficacy of the ingestion of levodopa to be maximal. For a particular subject, the duration of this interval was determined by an independent neurologist on the basis of the time-course and pattern of neurological signs observed following drug
ingestion, our aim being to test subjects during, or immediately following, a therapeutically significant rise in plasma concentration of levodopa, and following the disappearance of 'peak-dose' dyskinesias which are observed in some patients (Marsden and Parkes, 1976).

**Group II**

During the first testing session, each patient completed a block of ~10 runs on the tapping task while using the right hand, followed by a further block of ~10 runs while using the left. Then, after a rest period of 15–45 min and during a second testing session, subjects completed a further two blocks each of ~10 runs, with the order of hands reversed. Thus, the starting hand, during the first session, with respect to the side most affected by Parkinson's disease, was counter-balanced across subjects. Over the two sessions, subjects completed 14–20 runs (mean 17.8) with the hand more affected by Parkinson's disease and 16–20 runs (mean 18.0) with the hand less so-affected. The duration of each session was 45–60 min.

**Controls**

Using the preferred hand, each subject completed 12 runs on the tapping task during a first testing session and then, following a rest-period of 20–50 min, by a further 11–12 runs (mean 11.8) during a second session. The duration of each session was 30–45 min. In testing control subjects in two sessions in this way, we attempted to match the control procedure to that followed with the patient groups as closely as possible, within the constraints imposed by testing within the clinic. This was especially the case in respect of Group I, in which the order of experimental conditions was deliberately not counter-balanced across subjects.

**Analyses of tapping data**

For the 30 response intervals during the continuation phase of each run, the mean IRI, and autocovariance at each of lags 0–5, was calculated. Autocovariance, \( \gamma(k) \), was estimated by

\[
\gamma(k) = \frac{1}{N-k} \sum_{j=1}^{N-k} (I_j - \bar{I})(I_{j+k} - \bar{I})
\]

for \( N \) intervals, at lag \( k \), where \( I_j \) is the \( j \)th interval and \( \bar{I} \) is the sample mean, given by

\[
\bar{I} = \frac{1}{N} \sum_{j=1}^{N} I_j
\]

Using Equations 2 and 3, the total tapping variance (TV, covariance at lag 0) was then partitioned into components CV and MDV, according to Wing and Kristofferson's (1973) model. Values for TV, CV and MDV were then transformed, by taking the square-root, and thus expressed as standard deviations. This transformation has usually been adopted in previous studies, although not invariably (Pastor et al., 1992b). Then, separately for each of the three variables and for mean IRI, and separately for each experimental condition, a subject's performance was taken as the mean of the values calculated for the set of runs performed during that condition.

In each subject group, the analysis of a number of runs yielded positive values of lag 1 covariance (i.e. lag 1 autocorrelations >0) or, much less commonly, negative values of CV (i.e. lag 1 autocorrelations <0.5). We chose, for each subject, to eliminate from further analysis all of those runs in which such violations occurred. Statistical comparisons (BMDP) between experimental conditions within a subject group, and between patient and control groups, were effected using, respectively, Wilcoxon's matched-pairs signed-ranks test and the Mann-Whitney U test. All tests were two-tailed, uncorrected alpha per-comparison (\( \alpha_{PC} \)) was set at 0.05 and exact \( P \)-values are reported. We exerted control over the inflation of the probability of alpha error with multiple tests by (i) conducting the minimum necessary number of planned comparisons, and (ii) employing Keppel's (1982) modified Bonferroni test (cf. Ivry and Keele, 1989) to derive a corrected value of \( \alpha_{PC} \). A family of planned comparisons was defined as all those \( n = 8 \); 3 within-group and five between-group) conducted in respect of a particular dependent variable, and the maximum family wise error-rate was set at 0.2. Hence, corrected \( \alpha_{PC} = 0.20/8 = 0.025 \).

Finally, for each experimental condition in subject group, we attempted to assess the validity of the additional prediction of the model that, for lags >1, autocovariance = 0. For lags 2–5, we first calculated, across all (pooled) runs from all subjects for a given condition, the mean autocovariance at each lag. Now whereas the theoretically predicted autocovariance function is unbiased, the observed (calculated) autocovariance function is biased. Bias in the estimator is of order \( 1/N \), where \( N \) = the number of response intervals (Anderson, 1971). We therefore compared the biased estimate at each lag with the biased expected (theoretical) value of the estimate (Vorberg and Hambuch, 1978; Vorberg and Wing, 1996), calculated using the expressions provided by Anderson (1971, p. 448). The prediction of the model, at any of lags 2–5, was considered to be violated if, at that lag, the (biased) expected value of covariance did not fall within the bounds of the 99% confidence interval of the (biased) observed mean value. Thus, in these tests, corrected \( \alpha_{PC} \) was set at 0.01.

**Results**

Both patient groups were closely matched to the control group in terms of mean age and score on the MMS, on which no patient scored <26 out of 30. Details of the severity of neurological signs in each patient group are provided, according to experimental condition, in Table 1.

**Tapping task: analysis of linear trend in IRI**

Meaningful comparison of results from different experiments in which it is supposed that the same probabilistic process...
Table 1  The severity of neurological signs, for each experimental condition, in each patient group

<table>
<thead>
<tr>
<th></th>
<th>Group I Levodopa</th>
<th>Group II Asymmetrical parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>'On'</td>
<td>'Off'</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.33</td>
<td>1.33</td>
</tr>
<tr>
<td>Median</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Range</td>
<td>0-1</td>
<td>0-3</td>
</tr>
<tr>
<td>Rigidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.25</td>
<td>1.71</td>
</tr>
<tr>
<td>Median</td>
<td>0.00</td>
<td>2.00</td>
</tr>
<tr>
<td>Range</td>
<td>0-1</td>
<td>0-3</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.17</td>
<td>1.33</td>
</tr>
<tr>
<td>Median</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Range</td>
<td>0-1</td>
<td>0-3</td>
</tr>
<tr>
<td>Combined signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.75</td>
<td>4.38</td>
</tr>
<tr>
<td>Median</td>
<td>0.00</td>
<td>4.50</td>
</tr>
<tr>
<td>Range</td>
<td>0-3</td>
<td>2-7</td>
</tr>
</tbody>
</table>

The severity of each sign was scored using a four-point scale (0-3).

is operating, requires that the process be statistically stable over time, i.e. stationary. In practice, a process [represented, in the current context, in Wing and Kristofferson's (1973) model] or its realization in a time series (a set of IRIs), is said to be stationary if its mean is constant with time and its autocovariance function depends only upon the lag. The occurrence of drifts or trend in IRI therefore implies non-stationarity in the mean of the series of intervals. We examined our data for the presence of linear trends by submitting the IRIs produced during the continuation phase, separately for each run from each subject, to analysis by linear regression. Group values of regression slope and $r^2$, for each subject group and experimental condition, are shown in Table 2, for all runs, and separately for runs with, respectively, positive or negative slope. Data from one control subject and one patient tested while 'on' and 'off levodopa were not included because their data files had become corrupted.

Linear trends in IRI, in so far as they were manifest in the data, were shallow in slope (Table 2). Furthermore, for each subject group, in each experimental condition, the median proportion of TV accounted for by linear regression was small, ranging, across all runs, between 0.035 and 0.042 among control subjects and between 0.047 and 0.080 among patients. In addition, the largest difference in the median proportion of TV explained by linear regression was, between experimental conditions in any of the subject groups, 0.032 and, in comparisons of patient with appropriate control conditions, 0.038. On the basis of these data and of arguments presented in the Discussion section, and consistent with the procedures adopted by Wing and Miller (1984), Wing et al. (1984) and Pastor et al. (1992b), we chose not to submit the IRIs to transformation for the 'correction' of linear trend prior to calculation of values of autocovariance, CV and MDV. Such a correction was applied by Ivry and Keele (1989) who reported, however, that the effects of estimating variability in terms of deviations (residuals) from a linear regression line fitted to the IRIs, rather than by using the intervals themselves, 'turned out to be minimal'.

**Tapping task: comparison of values of mean IRI, TV, CV and MDV**

We were interested in two classes of comparisons. First, in comparisons between experimental conditions within each group of patients (within-subject contrasts), we were concerned with the effect of experimental condition. Secondly, in separate comparisons between controls and each patient group (between-subject contrasts), we were concerned with the degree to which the performance of patients, in either experimental condition, differed from that of controls. Following the presentation of the results from the control group, we consider those from each group of patients in turn.

**Control group**

Control overall mean IRI, during both experimental sessions, was within 2-4 ms of the target interval of 550 ms (Table 3). There were no significant differences, between sessions (Table 3), in mean IRI ($T = 20.0, P = 0.1361$), TV ($T = 18.0, P = 0.0995$), CV ($T = 19.0, P = 0.1167$), or MDV ($T = 32.0, P = 0.5828$).

**Group I ('on' and 'off' medication conditions): within-group comparisons**

Patients tended to tap too quickly during both 'on' and 'off' conditions (Table 3), but the difference between conditions was not statistically significant ($T = 37.5, P = 0.9063$). TV,
Table 2 Analysis of linear trend in IRI: for each group, in each experimental condition, for all runs and separately for runs with positive or negative slopes in linear regression

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Levodopa</th>
<th>Asymmetrical parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Session 1</td>
<td>Session 2</td>
<td>'Off'</td>
</tr>
<tr>
<td>Runs with positive slope % of runs</td>
<td>23.2</td>
<td>52.0</td>
<td>37.2</td>
</tr>
<tr>
<td>Mean IRI</td>
<td>549</td>
<td>547</td>
<td>546</td>
</tr>
<tr>
<td>Slope</td>
<td>0.482</td>
<td>0.357</td>
<td>0.537</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.044</td>
<td>0.028</td>
<td>0.031</td>
</tr>
</tbody>
</table>

| Runs with negative slope % of runs | 76.8 | 48.0 | 62.8 | 53.8 | 57.7 | 61.7 |
| Mean IRI | 545 | 549 | 533 | 532 | 531 | 538 |
| Slope | -0.422 | -0.378 | -0.799 | -0.463 | -0.628 | -0.448 |
| $R^2$ | 0.034 | 0.032 | 0.066 | 0.054 | 0.045 | 0.054 |

| All runs Mean IRI | 546 | 548 | 540 | 535 | 534 | 540 |
| Slope | -0.229 | 0.045 | -0.402 | -0.137 | -0.203 | -0.147 |
| $R^2$ | 0.042 | 0.035 | 0.080 | 0.048 | 0.061 | 0.047 |

% of runs = group means of individual values; $R^2$ = proportion of variance accounted for in linear regression. IRIs (ms) are group means, and slopes (ms/interval) and $R^2$ values are group medians, of individual mean values across runs. Slope values in parentheses were calculated after disregarding signs of slopes. $n$ subjects = 11 controls, 11 asymmetrical parkinsonian patients and 12 patients 'on' - 'off' L-dopa.

Table 3 For subject Group I ('on'/ 'off' levodopa) and controls, in each experimental condition, group mean (SD) and median IRI, and TV, CV and MDV, expressed as SDs (%variance)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Levodopa</th>
<th>'Off'</th>
<th>'On'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Session 1</td>
<td>Session 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n runs Mean</td>
<td>9.3</td>
<td>8.1</td>
<td>10.4</td>
<td>11.3</td>
</tr>
<tr>
<td>(SD)</td>
<td>(1.8)</td>
<td>(1.9)</td>
<td>(2.0)</td>
<td>(1.8)</td>
</tr>
<tr>
<td>IRI (ms) Mean</td>
<td>546.0</td>
<td>547.5</td>
<td>538.0</td>
<td>535.1</td>
</tr>
<tr>
<td>(SD)</td>
<td>(6.9)</td>
<td>(8.5)</td>
<td>(15.7)</td>
<td>(13.9)</td>
</tr>
<tr>
<td>Median</td>
<td>546.8</td>
<td>547.7</td>
<td>533.9</td>
<td>537.0</td>
</tr>
<tr>
<td>TV (ms) Mean</td>
<td>20.42</td>
<td>19.54</td>
<td>32.27</td>
<td>22.30</td>
</tr>
<tr>
<td>(SD)</td>
<td>(2.93)</td>
<td>(3.12)</td>
<td>(7.68)</td>
<td>(4.64)</td>
</tr>
<tr>
<td>Median</td>
<td>20.16</td>
<td>19.69</td>
<td>31.40</td>
<td>21.74</td>
</tr>
<tr>
<td>CV (ms) Mean</td>
<td>15.91</td>
<td>14.83</td>
<td>24.34</td>
<td>17.94</td>
</tr>
<tr>
<td>(SD)</td>
<td>(2.42)</td>
<td>(1.93)</td>
<td>(5.24)</td>
<td>(3.43)</td>
</tr>
<tr>
<td>Median</td>
<td>15.68</td>
<td>15.11</td>
<td>23.89</td>
<td>18.00</td>
</tr>
<tr>
<td>MDV (ms) Mean</td>
<td>8.23</td>
<td>8.14</td>
<td>13.50</td>
<td>8.13</td>
</tr>
<tr>
<td>(SD)</td>
<td>(1.99)</td>
<td>(1.79)</td>
<td>(4.93)</td>
<td>(2.19)</td>
</tr>
<tr>
<td>Median</td>
<td>8.09</td>
<td>7.97</td>
<td>13.58</td>
<td>8.03</td>
</tr>
</tbody>
</table>

Group values of $n$ runs are means (SD) of individual mean values, and those for IRI, TV, CV and MDV are means (SD) and medians of individual mean values.

CV and MDV (Table 3), on the other hand, were all significantly higher during the 'off' condition than during the 'on' condition (TV, $T = 0.0, P = 0.0005$; CV, $T = 0.0, P = 0.0005$; MDV, $T = 1.0; P = 0.0010$).

Comparisons with controls. As 'on' and 'off' conditions occurred, for each subject, in the same order, dependent variables derived from performance during each of these conditions were compared with performance variables derived from control sessions of equivalent period. By comparison with control subjects during session 1 (Table 3), patients during the 'off' medication condition produced significantly higher values of TV, CV and MDV (TV, $U = 10.0, P = 0.0003$; CV, $U = 9.0, P = 0.0003$; MDV, $U = 23.0, P = 0.0003$).
Table 4  For Group II (asymmetrical parkinsonism) in each experimental condition, and controls, group mean (SD) and median IRI, and TV, CV and MDV, expressed as SDs (\textit{\textsuperscript{\textit{\textvariance}}})

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Asymmetrical parkinsonism</th>
</tr>
</thead>
</table>
| \(\pi\) runs         | \begin{array}{c}
\text{Mean} \\
\text{(SD)}
\end{array} & \begin{array}{c}
\text{Mean} \\
\text{(SD)}
\end{array} & \begin{array}{c}
\text{Mean} \\
\text{(SD)}
\end{array} & \begin{array}{c}
\text{Mean} \\
\text{(SD)}
\end{array} |
| IRI (ms)              | \begin{array}{c}
456.8 \\
(7.0)
\end{array} & \begin{array}{c}
535.2 \\
(24.2)
\end{array} & \begin{array}{c}
\text{Median} \\
542.5
\end{array} & \begin{array}{c}
541.7
\end{array} |
| TV (ms)               | \begin{array}{c}
20.00 \\
(2.89)
\end{array} & \begin{array}{c}
19.84 \\
(3.61)
\end{array} & \begin{array}{c}
\text{Median} \\
19.84
\end{array} & \begin{array}{c}
19.84
\end{array} |
| CV (ms)               | \begin{array}{c}
15.39 \\
(1.96)
\end{array} & \begin{array}{c}
23.69 \\
(6.42)
\end{array} & \begin{array}{c}
\text{Median} \\
23.69
\end{array} & \begin{array}{c}
16.11
\end{array} |
| MDV (ms)              | \begin{array}{c}
8.19 \\
(1.70)
\end{array} & \begin{array}{c}
11.93 \\
(4.51)
\end{array} & \begin{array}{c}
\text{Median} \\
11.17
\end{array} & \begin{array}{c}
7.98
\end{array} |
| \(\text{\textvariance}\) | \begin{array}{c}
7.66
\end{array} & \begin{array}{c}
8.53
\end{array} & \begin{array}{c}
\text{\textvariance}
\end{array} & \begin{array}{c}
\text{\textvariance}
\end{array} |

Group values of \(\pi\) runs are means (SD) of individual mean values, and those for IRI, TV, CV and MDV are means (SD) and medians of individual mean values.

During the ‘off’ medication condition, patients also tended, although not significantly, to tap more quickly than controls (IRI, \(U = 36.0, P = 0.0377\)). During the ‘on’ medication condition, and by comparison with control performance during session 2 (Table 3), patients tapped significantly more quickly (\(U = 26.0, P = 0.0079\)) than controls. In addition, whereas TV and MDV did not significantly differ between the two groups, CV remained significantly higher among the patients than among controls (TV, \(U = 43.0, P = 0.0941\); CV, \(U = 30.0, P = 0.0153\); MDV, \(U = 73.0, P = 0.9539\)).

Given that the ‘off’ medication condition always occurred first in the patient group, it might be argued that the significant differences in variables observed between ‘on’ and ‘off’ medication conditions reflected, or were at least contaminated by, practice effects. If we assume, however, that the proportional magnitude of any effects of practice which accrued between ‘on’ and ‘off’ medication conditions was of similar order to that of any effects of practice accruing between sessions 1 and 2 in controls, potential effects of practice in each subject group can be partialled out by comparing, between groups, the difference in scores between conditions (second minus first), expressed as percentage change. Differences in these difference-scores were, in respect of TV, CV and MDV, all statistically significant (TV, \(U = 4.0, P = 0.0001\); CV, \(U = 15.0, P = 0.0010\); MDV, \(U = 13.0, P = 0.0007\)), indicating that, if our assumption is justified, the observed significant differences between ‘on’ and ‘off’ medication conditions were not attributable to practice. What little information there is in the literature on practice effects on this task suggests that they are small (Ivry, 1986, p.42; Keele and Ivry, 1987, p. 208), and some indication that a difference between groups in the magnitude of the combined influence of potential practice and fatigue effects was not an important confounding factor in our experiments is provided by a comparison of mean variance values obtained, in each group, from non-violating runs completed during the first and second halves of session 1 (Group I patients while ‘off’ levodopa). This analysis revealed that the group mean (SD) percentage changes (a negative sign indicating a decline), between the two halves of the session, in TV, CV and MDV, respectively, were \(-7\% (9.1), -7\% (17.1)\) and \(-9\% (25.9)\) for Group I patients, and \(-4\% (11.9), -3\% (23.5)\) and \(+1\% (35.8)\) for controls.

Group II (asymmetrical parkinsonism): within-group comparisons

Patients in this group also tended to tap too quickly with either hand (Table 4), but the difference between conditions was not statistically significant (\(T = 0.230, P = 0.2094\)). TV, CV and MDV (Table 3), however, were all significantly higher in the ‘worse hand’ condition than in the ‘better hand’ condition (TV, \(T = 0.0, P = 0.0005\); CV, \(T = 0.0, P = 0.0005\); MDV, \(T = 4.0, P = 0.0060\)).

It is possible that the degree to which performance differed between ‘worse’ and ‘better’ hands varied according to which was the preferred hand and which the non-preferred hand. We addressed this issue by calculating, first, mean values for TV, CV and MDV, separately for performance by each hand as ‘worse’ or ‘better’ hand and, secondly, the mean difference
in performance between ‘worse’ and ‘better’ hands separately for left and right hands as the ‘worse’ hand. As all patients in this group were right-handed, and as the number of subjects for whom the ‘worse’ hand was the right (preferred) hand was equal to the number of subjects for whom the ‘worse’ hand was the left (non-preferred) hand, mean values in each case were thus calculated across data from six patients (subgroup A, left hand ‘worse’ and right hand ‘better’; subgroup B, right hand ‘worse’ and left hand ‘better’). These results are shown in Table 5, together with the results of equivalent calculations in respect of ratings of tremor, rigidity and bradykinesia. For subgroup A, mean (SD) age = 66.3 (2.5) years, duration of illness = 5.8 (2.5) years, MMS score = 29.3 (0.8), Webster score = 10.3 (2.7), Hoehn and Yahr score = 1.5 (0.6). For subgroup B, equivalent values were, respectively, 61.7 (5.4) years; 4.4 (2.6) years; 29.5 (1.2); 7.5 (2.3) and 1.5 (0.6).

In order to constrain alpha error, and because of the unacceptably low statistical power which would be involved in comparisons conducted with n = 6, we have not submitted these data to statistical analyses. It seems clear, nevertheless, that irrespective of which hand was the ‘worse’ hand and which hand the ‘better’, mean values of TV, CV and MDV were higher for the ‘worse’ hand than for the ‘better’ hand. However, the magnitude of the difference, between ‘worse’ and ‘better’ hands, in the mean values of each of the three variables, was higher if the ‘worse’ hand was the non-preferred hand (i.e. higher for subgroup A than for subgroup B). This effect, in turn, appeared to reflect differences in performance between preferred and non-preferred hands as the ‘worse’ hand, rather than as the ‘better’ hand.

**Comparisons with controls.** Both hands of patients in this group were tested during each of the two sessions. Performance with ‘better’ and ‘worse’ hands was therefore compared, separately, with the overall performance of controls over both control sessions (Table 4). Patients, when using either hand, tapped quicker than controls, but the difference in IRI was not statistically significant in either case (‘worse’ hand, U = 49.0, P = 0.1841; ‘better’ hand, U = 51.5, P = 0.2364). Similarly, TV, CV and MDV in the ‘better’ hand condition were not significantly different from control values (TV, U = 81.0, P = 0.6033; CV, U = 93.0, P = 0.2253; MDV, U = 71.0, P = 0.9539). Values of each of these variables, however, were significantly higher in the ‘worse’ hand condition than in the control condition (TV, U = 131.0, P = 0.0007; CV, U = 132.0, P = 0.0005; MDV, U = 112, P = 0.0209).

**Correlations of TV, CV and MDV with motor signs**

Separately for each patient group, and for values of TV, CV, MDV and aggregated scores for ratings of tremor, rigidity and bradykinesia (possible range = 0–12), difference scores between experimental conditions were calculated (Group I, ‘off’ minus ‘on’ levodopa; Group II, ‘worse’ minus ‘better’ hand). Then, using these difference scores, and separately,
for TV, CV and MDV, for each patient group and for the two groups combined, we calculated the correlation (Spearman’s r) between the tapping-performance variable and the aggregated score of motor signs. None approached statistical significance.

**Violations of the predictions of the model**

**Prediction 1: -0.5 < \( \varphi(1) < 0 \)**

The percentage of runs in which such violations occurred [in respect of estimated autocorrelations, \( \varphi(1) \)] ranged, across experimental conditions and subject group, between 22.9% and 35.9% (Table 6).

For a particular set of data, values of TV, CV and MDV estimated using different strategies for dealing with violations at lag 1 will vary as a function of the incidence, within the data-set, of such violations. We therefore examined the extent to which the use of one or other of the different strategies, which we described in the Introduction, might produce different patterns of difference between experimental conditions in our own data. Restricting these additional analyses to data collected during ‘on’ and ‘off’ medication conditions (Group I), we compared calculated values for TV, CV and MDV derived from the use of, respectively, our own strategy (Method A, elimination of the contribution of values from all violating runs), the strategies adopted by Ivry and Keele (1989; Method B, inclusion of observed values from all runs, irrespective of violations; Method C, for violating runs, MDV set to zero and CV to TV) and that employed by Pastor et al. (1992b; Method D, inclusion of values from only the first non-violating run from each subject). From all analyses, irrespective of method, we excluded all values derived from the very few runs (see Table 6) in which there occurred violations of the prediction of the model that \( \varphi(1) > -0.5 \) (in such runs, estimates of CV are negative).

Inspection of Fig. 1 reveals clearly that despite the expected inflation of CV and deflation of MDV associated with the use of the analytic methods utilized by Ivry and Keele (1989), values of TV, CV and MDV were, irrespective of the method employed to deal with violations of the model at lag 1, larger during the ‘off’ medication condition, than during the ‘on’ condition. The question of whether the difference between conditions in each case was statistically significant, we leave open, in the interests of our strategy for constraining alpha error. It is evident from Fig. 1, nevertheless, that for each of the variables, the size of the observed effect of medication condition and, as a consequence, statistical power (given that \( n \) was constant at 12) varied with analytic method. This was most clearly so in respect of the method employed by Pastor et al. (1992b), the smaller associated effect-sizes reflecting their lack of control of within-subject sampling error, but was also manifest following use of either of the methods employed by Ivry and Keele (1989), especially in respect of MDV, for which the size of the effect of medication condition was reduced.

**Prediction 2: \( \gamma(k) = 0 \), for \( k > 1 \)**

Violations of this prediction, in respect of estimated covariances, \( \gamma(k) \), are indicated in Fig. 2, separately for each group of subjects and each experimental condition. Aside from a marginal violation at lag 3 during the first session, mean observed values for control subjects did not depart significantly from the expected predicted values. Violations were more common, however, among the patient groups (especially Group I), and the patterns of violations, across lags 2–5, varied with both patient group and experimental condition.

**Discussion**

**Unpaced tapping performance: TV, CV and MDV**

**Patient Group I: ‘on’ and ‘off’ levodopa medication**

Our within-group analyses showed clearly that, in patients tested initially following a 12–15 h period of abstinence from normal medication, a single normal dose of levodopa caused a significant decrease in total tapping variance (TV) and in the component variances (CV and MDV) attributable to random temporal variation in the operations of hypothetical clock and motor-implementation system processes (Wing and Kristofferson, 1973). During the ‘off’ medication condition, moreover, values of TV, CV and MDV were all significantly higher than control values. During the ‘on’ condition, on the other hand, while TV was higher than the control value (\( P = 0.0941 \)), only CV remained significantly elevated above that of controls. This overall pattern of results suggests strongly that normal self-paced finger-tapping and the normal...
functioning of both theoretical processes are dependent upon the integrity of dopaminergic transmission within the basal ganglia.

The observed differences, between ‘on’ and ‘off’ medication conditions, in TV, CV and MDV, are consistent with the ‘anecdotal’ data reported by Pastor et al. (1992b) in respect of several patients tested first following 48 h withdrawal of levodopa therapy (‘off’) and subsequently, 3 days later, following ingestion of 250 mg levodopa/carbidopa (‘on’). Our results are also consistent with those of Pastor et al. (1992b) in that values for all three variables were, in both studies, significantly higher among patients while ‘off’ dopaminergic medication than among controls.

However, our results are not consistent with those reported by Ivry and Keele (1989) who observed, during the ‘off’ condition of an experiment involving seven patients, absolute values of TV, CV and MDV comparable with those reported here, but found ‘minimal change’ in any of the three variables as a function of levodopa medication. In addition, these authors reported that values of TV, CV and MDV among a group of 29 patients (including 22 who were receiving some form of dopaminergic medication at the time of testing, in addition to the seven patients mentioned above who were tested while ‘off’, medication: Ivry, 1986, p. 19 and Table 1) were not significantly different from those among a group of 21 elderly controls.

A number of factors can be identified as possible contributors to the differences between the two sets of findings. First, Ivry and Keele (1989) controlled for potential within-subject order effects (e.g. practice) in their comparison of performance during ‘on’ and ‘off’ medication conditions, by balancing the order of medication conditions across subjects: testing during ‘on’ and ‘off’ conditions was performed on separate days, usually 1 week apart, for each subject. In addition, for neither their within- nor between-subjects studies did Ivry and Keele (1989) provide details of exactly when, during the ‘on’ condition, subjects were tested in relation to previous drug ingestion, or of how long, prior to the ‘off’ condition, subjects had abstained from drug therapy. We, on the other hand, always tested subjects first following 12–15 h abstinence from normal medication, and then during a second session later on the same day, 45–75 min following a single normal dose of levodopa. We adopted this procedure in order to maximize the probability of revealing the effects of levodopa ingestion by testing subjects, first, at a reasonably controlled time of significant therapeutic response to the drug and, secondly, in the absence of unwanted variation in non-controlled independent variables which might be expected to attend within-subject designs involving extended periods between experimental conditions (e.g. temporal fluctuations, within subjects, in neurological condition or, between subjects, in therapeutically efficacious plasma concentrations of levodopa at the time of testing in the ‘on’ condition). At the same time, we controlled for potential order effects by comparing, for each dependent variable, the difference in performance between ‘off’ and ‘on’ conditions with the difference in performance between two broadly equivalent sessions, conducted with control subjects who were, as a group, matched with the patient group in terms of age and general cognitive state. Thus, unless the effects of practice on the tapping task between ‘off’ and ‘on’ medication conditions among our patients were of a different order of magnitude to those in control subjects, and this seems unlikely, we are confident that we did not maximize the likelihood of observing the effects of the ingestion of levodopa at the expense of lack of control of the effects of session order.

It is also possible that the differences between our results and those of Ivry and Keele (1989) reflect, at least in part, differences in respective chosen strategies for dealing with runs in which there occurred violations of the prediction of Wing and Kristofferson’s (1973) model that $p(1) < 0$. In the
case of our own data, however, it is clear that the pattern of differences between conditions, in the case of each of TV, CV and MDV, was not dependent upon the particular strategy employed (Fig. 1).

A final, potentially important source of the inconsistency between our results and those of Ivry and Keele (1989) concerns the comparability of the two sets of parkinsonian patients in terms of their general degree of chronic disability and their neurological status at the time of testing. On the basis of the rating schemes of both Webster (1968) and Hoehn and Yahr (1967), all but two of our patients in Group I were ‘mildly’ impaired, the remaining two being ‘moderately’ impaired. Although Ivry and Keele (1989) did not provide any formal details of the neurological status of their patients at the time of testing, of the degree of their general disability, or of the duration of their illness, the possibility that their patients were significantly more impaired than ours is suggested by their observation that their patients, during the ‘off’ medication condition ‘were generally unable to walk and showed extreme bradykinesia in arm movements’ (p. 143). It therefore seems likely that Ivry and Keele’s (1989) patients also had a longer history of disease, and had been chronically maintained on dopaminergic medication for a longer period, than our own patients. We have shown, in our experiments with patients with asymmetrical Parkinsonism (Group III), that values of TV, CV and MDV all varied as a positive function of the severity of neurological signs, at a time when 10 of the 12 patients were maintained on normal dopaminergic medication (Table 4; see also Pastor et al., 1992b). It is well established, moreover, that the probability of unpredictable fluctuations in therapeutic response to levodopa, and in neurological status, increases with the chronicity of drug therapy (e.g. Marsden and Parkes, 1976; Nutt et al., 1984). These considerations, especially in view of the uncertainty, in Ivry and Keele’s (1989) study, about the time of testing in relation to plasma concentrations of levodopa in both ‘on’ and ‘off’ conditions, imply that results reported by these authors may not be directly comparable with those reported here.

**Group II: asymmetrical parkinsonism**

The within-subject comparisons among this group of patients, showed clearly that TV, CV and MDV during self-paced tapping were each significantly higher when subjects used the hand more affected by the disease than when they used the hand less so-affected. Values of all three variables, furthermore, were significantly higher among the patients when using the ‘worse’ hand than among controls using their preferred hand. Assuming that the bilateral asymmetry in neurological signs manifest in the two hands of these patients was indicative of a corresponding bilateral asymmetry in the effectiveness of dopaminergic functions within the basal ganglia (despite the fact that, with two exceptions, patients were maintained on normal dopaminergic medication throughout the period of testing), this demonstration that the magnitude of all three variables increased with the severity of parkinsonian signs in the effector system employed provides further evidence that normal tapping performance, and the functioning of both the clock and motor-implementation processes hypothesized by Wing and Kristofferson (1973), vary as a function of the integrity of dopaminergic transmission in the basal ganglia. Such a conclusion is reinforced by our observations that values of TV, CV and MDV were all significantly higher among the patients when using the ‘worse’ hand than among controls using their preferred hand, and is not inconsistent with the fact that values of none of these three variables among patients using the ‘better’ hand was significantly different from (although each tended to be larger than) such control values.

The interpretation of the meaning of both our within- and between-subject comparisons (and of other data in the relevant literature derived from the study of patients with asymmetrical parkinsonism) is potentially complicated, however, by the possible influence of laterality effects (Truman and Hammond, 1990) and of interactions between such effects, side of worse signs and the severity of signs. The data presented in Table 5 show that, although mean TV, CV and MDV were higher when subjects used the ‘worse’ hand than when they used the ‘better’ hand, irrespective of whether the ‘worse’ hand was the preferred or non-preferred hand, the mean magnitude of the difference between ‘worse’ and ‘better’ hands, for each of the three variables, was larger when the ‘worse’ hand was the non-preferred hand and the ‘better’ hand the preferred hand (i.e. for subgroup A). The main candidate sources of this effect would appear to be laterality differences (left versus right) in performance, or differences in the severity of signs between hands designated ‘worse’, or differences in the severity of signs between hands designated ‘better’, or some combination of, or interaction between, two or more of these factors.

This issue, which has not been addressed in the literature, cannot be resolved on the basis of the available data. Nevertheless, several clues are to be found in Table 5. First, it appears that the difference, between subgroups A and B, in the magnitude of the differences between ‘worse’ and ‘better’ hand performance, primarily reflected differences between the left (non-preferred) and right (preferred) hands as ‘worse’ hands, rather than as ‘better’ hands. Secondly, the patterns of differences, between the two subgroups, in TV, CV and MDV matched closely the patterns of differences in neurological signs. These considerations suggest that, although laterality differences in performance may have contributed, alone or in interaction, to the overall pattern of findings (as indicated by the differences in performance between preferred and non-preferred hands as ‘worse’ hand), it is more likely that the observed ‘worse’ hand versus ‘better’ hand differences in performance between the two subgroups reflected an asymmetry in the severity of signs between the hands designated ‘worse’ in one or other subgroup.

Although we believe that these considerations do not
seriously prejudice our conclusions in respect of the within-patient comparisons in Group II, they do suggest, however, that the results of the comparisons between these patients and controls should be treated with some degree of caution, because control subjects, although uniformly right-handed as were the subjects with asymmetrical Parkinsonism, were tested using only the preferred hand. It is clear, moreover, that future studies of patients with asymmetrical Parkinsonism should incorporate appropriate design features to allow either the control of these factors or their manipulation in a systematic fashion.

Leaving aside the results of a study of four patients described by Ivry and Keele (1989) because, as we have pointed out earlier, the group did not appear to consist only of patients with asymmetrical parkinsonism, the only data in the literature, of a similar nature to those described here, were reported by Wing and Miller (1984) and Wing et al. (1984) in respect of patient M.F. Our results are consistent with those reported by these authors that both TV and CV were, on average, during the course of testing, significantly higher when M.F. used the hand (right) most affected by the disease than when she used the hand (left) less so-affected. However, whereas, in the performance of our subjects, MDV was also significantly higher when subjects used the ‘worse’ hand than when they used the ‘better’ hand, this was not the case for M.F. It is difficult to draw meaningful conclusions from a comparison of the two sets of data because the two studies differed in a variety of important respects. It is of interest, nevertheless, that MDV was higher when M.F. used her ‘worse’ hand than when she used her ‘better’ hand, and that, although the difference was not statistically significant, P(0.09) approached alpha.

**Unpaced tapping performance: mean IRI**

Patients in both groups, during each experimental condition in both groups, tapped, on average, faster than the target frequency, but in neither patient group was the difference between conditions statistically significant. In each experimental condition, patients also tended to tap faster than controls, although only during the ‘on’ medication condition was the difference in mean IRI between patients and controls statistically significant. Although the mean IRI of parkinsonian subjects during self-paced tapping has been reported, in the single case of M.F., to be longer than the target interval (Wing et al., 1984) the weight of available evidence supports the conclusion that, at a target interval of 550 ms, they tend, on average, to tap too quickly, and faster than control subjects, irrespective of whether they are ‘on’ or ‘off’ dopaminergic medication (Ivry and Keele, 1989; Freeman et al., 1993). What functional and neurological factor(s), or mechanism(s), might this finding reflect?

One possibility, suggested by the work of Logigian et al. (1991), is that the frequency of voluntary tapping by parkinsonian patients is ‘attracted’ to the frequency of the neural oscillator(s) responsible for parkinsonian tremor. The mean frequency of alternating finger movements produced by our patients, however, lay between 1.85 and 1.87 Hz, quite distant from the lower bound of the range of parkinsonian tremor frequencies (3.5–12.5 Hz) recorded by Logigian et al. (1991) from the index fingers of their parkinsonian patients during paced, isometric alternating extension–flexion contractions. This lack of close frequency coupling suggests that it is unlikely that the frequency of our patients’ finger tapping was driven by, or ‘attracted’ powerfully to, the fundamental frequency of the tremor oscillator(s). Furthermore, as our patients were constrained, by the specified limits of acceptable IRIs (275–825 ms), to tap within a frequency range of 1.21–3.64 Hz, the fact that they tended to tap faster than the target frequency, and faster than controls, cannot be attributed to the occurrence of episodes of ‘hastened’ tapping at a frequency of 5–6 Hz (Nakamura et al., 1978) or 3.5–8.6 Hz (Logigian et al., 1991). Nevertheless, as it is possible that the mechanisms underlying voluntary finger tapping and pathological tremor interact in a complex fashion, centrally and/or peripherally, as a function of harmonics of the fundamental tremor frequency(ies), we cannot discount entirely a possible influence of tremorogenic mechanisms on tapping performance in our experiments. Indeed, given the large variety of possible ways in which such mechanisms might influence the characteristics of voluntary movements, it is difficult to see how this issue might be resolved unequivocally.

A second possibility, arising within the context of Wing and Kristofferson’s (1973) model, is that the tendency of parkinsonian patients to tap too quickly during the continuation phase reflected a primary impairment of processes of entrainment of the ‘clock’ process to the pacing cues during the synchronization phase: according to the model, μ_c is equal to μ_e. Necessary entrainment processes might include, for example, registration, encoding and acquisition of the target frequency, storage of a relatively stable representation of (oscillation at) that frequency and subsequent retrieval of (access to) the stored representation. Such a notion is consistent with the data presented in Table 2, and with our preliminary data that the larger anticipatory synchronization error of parkinsonian patients during paced tapping tends to be more variable than that of controls (O’Boyle et al., 1995).

**Violations of the predictions of covariance at lags 1–5 of Wing and Kristofferson’s (1973) model, and the issue of statistical stationarity**

The incidence of observed violations of the model prediction that 0 > p(1) ≥ -0.5 (Table 6) was similar to that reported by previous investigators (Ivry and Keele, 1989; Pastor et al., 1992b). We also observed a number of violations of the model predictions of zero covariance at lags 2–5 (Fig. 2), violations being least common among control subjects and most common among Group I (‘on’–‘off’ levodopa...
medication) patients. Equivalent data have not been reported in previous studies of parkinsonian patients. Taken at face value, the occurrence of such violations implies that, as the temporal statistical structure of response intervals produced during self-paced tapping is not as predicted by the model, the model cannot be applied validly, or at least without revision, to the understanding of data in which they occur. This is, therefore, an important issue and we consider briefly three different possible explanations for the occurrence of these violations. These explanations are not mutually exclusive and their relative validity might be expected to vary among different subject groups, or even within subjects on different occasions, and with the characteristics of the tasks employed by different investigators.

First, violations at lag 1 have usually been attributed to sampling error associated with the use, in each run, of a small number of response intervals for the estimation of covariance. However, while one might suppose that the true incidence of violations of the prediction of $\gamma(1) < 0$ is uncertain because violations have been diagnosed invariably on the basis of the biased estimator, $\hat{\gamma}(1)$, it is difficult to assess the adequacy of this explanation without a systematic means of determining, for a particular subject group, just what incidence of such violations might be expected by chance.

A second possible explanation is that the occurrence of violations at one or more of lags 2–5 signifies that one or more of the assumptions upon which the model is built are invalid (at least in respect of the particular body of data in question). Aside from the hypothesized existence of clock and motor-implementation system processes, the major assumption at the heart of Wing and Kristofferson's (1973) model is that of the independence of the two processes, so that the control of motor timing is deemed to be open-loop. The basic model also involves the secondary assumptions that successive $C$s are independent of one another, as are successive $D$s. The non-validity of one or more of these assumptions will be manifest in a significant departure of the temporal statistical structure of response intervals from that predicted by the basic model. So far as the secondary assumptions are concerned, Wing (1977a, 1979) has shown that adequate fitting of the model to data from neurologically intact subjects requires relaxation of the assumption of statistical independence of successive motor-delay intervals. In addition, Wing (1977b) has also shown that during self-
paced tapping, normal subjects are, to some extent, sensitive to occasional perturbations in the delay between the time of occurrence of a tap and the time of occurrence of auditory feedback provided shortly following each tap. On the basis of his results, which we have replicated (McIntosh and O’Boyle, 1995), Wing (1977b) proposed that, while the control of timing of repetitive self-paced tapping is normally open-loop, subjects do monitor available feedback and are able to use it to adjust C, and thereby make compensatory adjustments to IRIs, on occasions when the difference between feedback intervals and the desired IRI exceeds some threshold value. In view of these observations, we tried to limit the availability of sensory (specifically visual and auditory) feedback in our experiments. In principle, nevertheless, it is possible that the different patterns of violations at lags 1–5 observed among our subject groups reflected, to some extent, differing patterns of violation of the various independence assumptions built into the model which may, in turn, have reflected the employment of different performance strategies which varied according to the functional and neurological resources available to a particular group of subjects in a given experimental condition. These speculations, should they prove to have any foundation, suggest that the precise nature of timing impairments among a particular group of neurological patients might better be sought by examining the functional implications of the characteristics of the version of the model which best predicts the temporal statistical structure of the data, than by ‘forcing’ an interpretation of the data within the theoretical confines of a basic model known to rest on one or more invalid assumptions.

A third explanation, related to the second, of the observed violations is that they primarily reflected the operation of processes which were not statistically stationary. Irrespective of the direction of slope, but as a positive function of slope-magnitude, a monotonic trend in the duration of response intervals will give rise to increased covariation at all lags and, therefore, to reduced estimates of MDV and increased estimates of TV and CV. It is possible, therefore, that the violations of predicted covariance which we observed at lags 1–5 (all of which involved observed values which were more positive than expected) reflected, at least in part, the presence of trends in IRI in our data. For the same reason, it is also possible that our various estimates of CV and MDV were compromised to some extent.

Despite these considerations, we did not attempt to ‘correct’ or transform our data to eliminate the potential influence of linear trend in IRI because, first, its contribution to differences in variability between conditions in our data appeared to be small (Table 2) and, secondly, it is not clear how the diagnosis and elimination of non-stationarity in short series of intervals should best be effected. Leaving aside the issue of diagnosis, we note that only one of the two alternative major procedures available for the de-trending of time series has previously been employed (e.g. Ivry and Keele, 1989) or recommended (e.g. Vorberg and Wing, 1996) in association with the use of Wing and Kristofferson’s (1973) model. This has involved fitting a (linear) regression line to the raw IRIs prior to subsequent estimation of autocovariance, CV and MDV from the residuals. A second procedure, which is used routinely in the analysis of econometric time series, involves the differencing of successive intervals. The use of one or other of these procedures involves different theoretical assumptions and consequences which have yet to be explored adequately in the context of the literature on the control of motor timing. As this is not the appropriate forum for such exploration, we merely draw attention to the fact that the correct choice of procedure will depend upon the characteristics of non-stationarity in the data. These, in turn, will reflect the nature of the process generating the non-stationarity: the fact that non-stationarity in the data implies non-stationarity in the process has previously been ignored in the motor-timing literature. As a consequence, the theoretical consequences of employing one procedure for de-trending data when, in fact, the other is appropriate, can be significant (Maddula, 1992).

These are difficult, but important, issues which will require resolution before data produced by subjects suffering from neurological insult can be interpreted fully within the context of statistical models of the control of motor timing. Nevertheless, we believe that our results, contrary to those of Ivry and Keele (1989), but consistent with those of Pastor et al. (1992b), show clearly that the total variability in response intervals produced during self-paced tapping, and the component variances attributable to Wing and Kristofferson’s (1973) ‘motor-delay’ and ‘clock’ processes, can all vary significantly as a function of the integrity of dopaminergic transmission in the basal ganglia. Together with previous observations of impairments of motor timing in parkinsonian performance on tasks studied outside Wing and Kristofferson’s (1973) theoretical framework (see Introduction), these data suggest that dopaminergic processes within the basal ganglia play a more important role in moderating the precision of motor timing in the normal brain than that proposed by Keele and Ivry (1987) and by Ivry and Keele (1989). Furthermore, the demonstration that parkinsonism can give rise to impairments of temporal perception (Artieda et al., 1992; Pastor et al., 1992a), and the finding that the characteristics of time estimation in rats can be manipulated systematically by the administration of dopamine receptor agonists and antagonists (Meck, 1983, 1986), provide additional and converging evidence which implicates basal ganglionic dopaminergic transmission in temporal processing, and which suggests that timing computations are not, as suggested by Ivry and his colleagues, the sole, or primary, preserve of the cerebellum (Keele and Ivry, 1987; Ivry et al., 1988; Ivry and Keele, 1989; Keele and Ivry, 1990).

Nevertheless, our data do not allow us to determine the degree to which the observed differences in CV, between experimental conditions, reflected a direct or an indirect role of dopaminergic transmission in the control of motor timing, especially as an increase with condition in CV was almost
invariably accompanied by an increase in MDV. As a consequence, we are as yet unable to ascribe a specific role in timing functions either to dopaminergic transmission or to the basal ganglia. Some of the problems involved in attempting to do so are indicated by recent evidence that (i) loss of dopamine in the pallidum of parkinsonian patients results in excessive inhibition of primary and non-primary motor cortical projection areas (Alexander and Crutcher, 1990; DeLong, 1990), several of which are known to be active during the production of normal, self-paced, simple movements (e.g. Boecker et al., 1994; Kawashima et al., 1995), and (ii) the consequent depression of cortical activity can be normalized (Ceballos-Baumann et al., 1994) and parkinsonian motor signs alleviated (Laitinen et al., 1992) by posteroventral pallidotomy which, it is thought, interrupts the excessive inhibitory output from the pallidum. These data raise the possibility that functional impairments observed in parkinsonian patients may reflect primarily an interference with the normal functions subserved by thalamo-cortical areas to which the damaged basal ganglia project, rather than with those subserved by the basal ganglia themselves. That this may be a serious possibility in the current context is suggested by evidence, from studies of both brain-damaged (Freund and Hummelsheim, 1985; Freund, 1989; Halsband et al., 1993) and neurologically intact (Lang et al., 1990) individuals, which implicates premotor and supplementary motor areas of the cerebral cortex in motor timing functions.

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