

Movement amplitude choice reaction time performance in Parkinson's disease may be independent of dopaminergic status

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Abstract

The effect of circulating levels of plasma levodopa on reaction time performance was studied in patients with Parkinson's disease and untreated normal controls when instructed to move either a shorter or longer distance. On half the movements, subjects were pre-cued on the direction and amplitude of an impending movement. On the remaining movements, only the direction was pre-specified, and the amplitude was determined only when the cue to move was presented. Reaction time performance of patients was evaluated at three infusion levels of levodopa so that the patients were optimally, moderately, or minimally medicated. Parkinsonian patients were always slower to react and move than normal subjects. Clinical state correlated with movement time, but not with reaction time. These results contrast with those in which reaction time was related to plasma levodopa levels when movement direction and initiation were processed concomitantly, but the movement amplitude was pre-cued. It is possible that specification of the amount of muscle activity is partially independent of dopaminergic transmission.

normal subjects in all instances, do not usually show added deficits in RT with increases in movement complexity. Indeed, in some RT situations in which a behavioural choice and movement initiation are required simultaneously, PD patients can initiate movement at latencies comparable to those of normal subjects.^{4,10}

A problem with many previous investigations of RT performance in PD is that the clinical state of the patients has not been rigorously controlled. The potential difficulty of this problem was overcome in our recent investigation of choice and simple RT in relation to circulating levels of levodopa.¹⁰ We found that the paradoxical result of a seemingly normal RT when PD patients performed in a directional choice RT task was related to the circulating levels of levodopa. In our study, the choice RT in PD was not different from normal and was only slightly longer than simple RT in PD when patients were optimally medicated. However, when levodopa was reduced so that the patients were in an "off" clinical state, the choice RT was sufficiently delayed to be significantly different from normal. In contrast, the simple RT was unresponsive to changes in levodopa concentration. We concluded that the specification of directional information is a dopamine sensitive process in PD and that the failure of other investigators to see prolongation of RT in PD when movement initiation and specification are required simultaneously,^{4,11} may have been related to patient selection and fluctuating levels of levodopa.

This study was designed to investigate whether the simultaneous specification of movement amplitude and initiation of movement by PD patients is affected by levodopa administration. It is known that neurons within the basal ganglia discharge in relation to the direction of intended or executed movement.¹²⁻¹⁴ Additionally, it appears that basal ganglia neurons discharge in relation to the magnitude of an opposing load; thus they are responsive to the amount of voluntary muscle activity.^{12,15,16} It is possible that a disruption of basal ganglia function might lead to a deficit in the control of the magnitude of EMG activity. However, since PD patients seem able to scale the first agonist burst normally in relation to movement amplitude and opposing load,¹⁷ it might be expected that PD patients do not have an added deficit in RT when required to specify movement amplitude and initiation simultaneously.

In addition to slowness of movement execution, patients with Parkinson's disease (PD) typically initiate movements slower than normal.¹⁻⁴ It appears that the fundamental defect in reaction time (RT) performance in PD is a delay in starting simple movements for which all the parameters of movement, such as amplitude, direction, and which body part to move, are specified in advance.^{5,6} In normal subjects, RT is prolonged when subjects are uninformed about these parameters of movement before receiving the signal to move.^{7,8} These results are widely interpreted as indicating that the initiation process is slowed when concurrent decisions need to be made about the characteristics of the impending movement. Since the difference in movement time (MT) between normal subjects and patients with PD progressively increases with movement complexity,⁹ it might also be expected that increases in movement complexity would increasingly slow movement initiation in PD more than normal. However, PD patients, although typically slower to begin movements than

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Materials and methods

Five right handed patients with PD, aged 29 to 61 years (mean, 49.2 yr), were selected for minimal tremor, demonstration of "wearing off" response patterns to levodopa, absence of clinical depression, and capability of following complex instructions. They were all taking a combination of levodopa/carbidopa, and their disability scores without medication ranged from II to IV on the Hoehn and Yahr scale.¹⁸ Five age-matched normal subjects, aged 31 to 64 years (mean 47.0 yr), were also studied. Informed consent was obtained, and all subjects participated in the study according to guidelines specified by the NIH institutional review board for human studies. The PD patients and the normal volunteers were the same as those examined in a previous study.¹⁰

Clinical treatment

The Parkinsonian signs of patients were rated independently by two neurologists using a modified Columbia scale.¹⁹ The ratings were done at clinical baseline and after stabilisation at each of three rates of levodopa infusion. Levodopa was prepared in 0.45% saline to a concentration of 2 mg/ml and given by continuous IV infusion, with oral carbidopa, 50 mg every three hours, starting the day before testing. Infusion rates of levodopa (mgm/kgm/hr) were established empirically for each patient based on the corresponding individual clinical response. Three rates (high, middle and low) were determined to achieve three Parkinsonian states (optimal or "on", mid level, and "off"). Rate adjustments were made two hours before administration of each set of movement trials to allow stabilisation of clinical performance and plasma levodopa levels. Simultaneous with the clinical ratings, blood samples were drawn and stored immediately at -70°C for subsequent assay with high-performance liquid chromatography with electrochemical detection.²⁰

Apparatus and Procedures

The subject was seated and the lower arm and hand were restrained between lightly padded supports with the elbow angle at ~90°. The hand was restrained within a handle that was coupled to a low friction, brushless DC torque motor (Aeroflex TQ-64). The hand was positioned so that flexion-extension movements about the wrist could be performed in the horizontal plane, and the wrist joint was colinear with the axle of the torque motor. A video monitor was placed approximately 1m in front of the subject. A cursor in the form of a 3 × 3 matrix of small spots representing the instantaneous orientation of the right hand and a target cursor in the form of a rectangular box that was 4° to 8° of wrist rotation from side-to-side were visible on the video screen. The subject was required to position the hand to align the two cursors only with the aide of the video display, since the hand could not be seen directly. Additional details concerning the torque motor system can be found elsewhere.²¹ Bipolar surface electrodes were used to record

the electromyogram (EMG) from wrist extensor and flexor muscles.

The subject performed a simple and choice visual RT task requiring 15° or 30° of wrist flexion. For the simple RT task, a single centrally located target appeared on the video screen for initial alignment at 0° of wrist flexion. A preparatory target with dashed lines, located at either 15° or 30° of wrist flexion appeared after 1 s. This pretarget was used by the subject to prepare the amplitude of the impending movement. After an additional 0.8 to 1.8 s delay, the central target disappeared and the pretarget changed appearance to become solid-lined; this was the signal to begin a flexion movement directed toward the target as soon and as rapidly as possible. For the choice RT task, the centrally located target and then two outlined preparatory targets, located at 15° and 30° of wrist flexion, appeared on the video screen. After a brief delay, the central and one of the pretargets disappeared and the remaining pretarget became solid lined. As before, this was the signal to begin movement. Practice sessions were given until the subject performed movements that were consistently fast and accurate. The four types of movements (simple RT to 15° and 30° and choice RT to 15° and 30°) were performed in one block of 100 trials. The trial order presentation was pseudo random, so that an equal number of trials of each type, 25, was presented. After practice, controls performed three sets of 100 trials, and patients performed one set of trials at each infusion rate. Wrist position and the full-wave rectified and low-pass filtered (50 Hz) EMG were digitised at 200 Hz for subsequent analysis.

Data analysis

Each trial was inspected off-line using semi-automatic interactive software that allowed for marking the beginning and end of movement with an electronic cursor. RT was defined as the time from the go signal to the onset of movement velocity. Trials were rejected if RT was shorter than 175 ms or longer than 850 ms. MT was measured from the beginning of movement to the first zero-cross in the velocity profile. If movements of the PD patients were hypometric, there would be zero-crosses in velocity before the hand moved the correct distance. In these cases, MT was measured as the first zero cross after the hand had moved to 3° short of the correct movement amplitude. Kinematic data from each subject and for each trial type were tabulated, averaged and analysed with *t* tests, factorial and repeated measure analyses of variance, and linear regression procedures. Unless noted, the probability levels refer to statistics from the analyses of variance.

Results

Clinical

The plasma levodopa concentration was positively correlated with the corresponding rate of levodopa infusion ($R = 0.88$,

Table Plasma levodopa levels and corresponding clinical scores for PD patients

| Clinical state | Plasma levodopa level in $\mu\text{g}/\text{ml}$ (SEM) | Clinical score (SEM) |
|----------------|--------------------------------------------------------|----------------------|
| High | 6.34 (1.50) | 3.00 (0.45) |
| Mid | 4.30 (0.96) | 6.70 (0.61) |
| Low | 3.06 (1.10) | 13.10 (1.21) |

$p \leq 0.005$) and was inversely related to the total Parkinsonian disability score ($p \leq 0.05$, table).

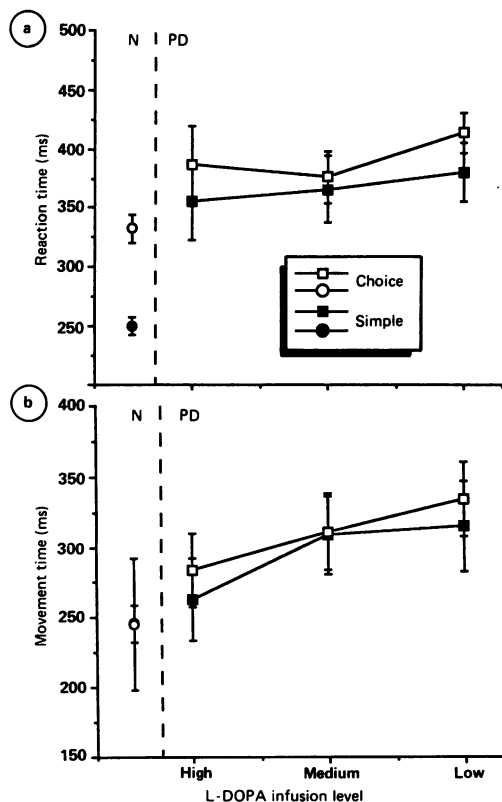
Reaction time

Simple RT was prolonged in the patients with PD at all three infusion rates compared with the RT of normal controls ($p \leq 0.01$, figure 1a, *t* tests). There was no change in simple RT in relation to the plasma concentration of levodopa. The patients' choice RT was also significantly longer than simple RT for normal subjects ($p \leq 0.0001$). There was no difference between choice and simple RT in PD patients. For normal subjects, choice RT was longer than simple RT ($p \leq 0.0001$). Choice RT for the patients with PD was also longer than the choice RT of normal subjects at all infusion levels. Choice RT did not change with concentration of levodopa. RT did not vary with movement amplitude for either the patients or the normal subjects in either the simple or choice task.

Movement time

In contrast to RT findings, plasma levodopa concentration affected MT of the PD patients ($p \leq 0.0001$, fig 1b). For the patients, MT was longer at the lower rate than at the mid or high rates of levodopa infusion ($p \leq 0.0005$). MT was the same in the simple or choice task for both the normal subjects and patients with PD.

Figure 1 Performance during simple and choice reaction time tasks. A Reaction time for normal controls (N) and PD patients. RT was greater for the patients than for normal controls in both tasks. Simple RT was faster than choice RT in normals, but not different from choice RT in the patients. The plasma levodopa level did not affect RT during either task. B Movement time for normal controls (N) and PD patients. MT was typically greater than normal for the patients, though when optimally medicated the PD patients moved nearly as fast as the normal controls. MT for the patients slowed with decreases in available levodopa. Error bars are \pm one SEM for all statistics.



Additionally, MT for the patients at the high infusion level was indistinguishable from MT of the normal subjects. However, at the two lower rates of levodopa infusion, MT was longer for the PD patients compared with normal controls ($p \leq 0.01$, *t* tests).

Discussion

RT deficits in PD patients are most evident when all movement parameters are fully prepared in advance, as in a simple RT task.^{5,10,11} When specification of movement parameters is required concomitantly with movement initiation, as in a choice RT task, PD patients initiate movements either normally or with less of a "central" delay than normal subjects.^{5,10,11} Recently, we found that choice RT of PD patients was sensitive to plasma, and presumably brain, levels of dopamine when movement direction and initiation were processed simultaneously.¹⁰ Our results suggest that in PD specification of movement amplitude, like simple movement initiation but in contrast to specification of movement direction, may not be sensitive to dopamine replacement therapy, and therefore may not be a dopaminergic process.

Behavioural and physiological studies have described distinctive coding for movement direction and amplitude. For example, the RT to begin movements with an unspecified direction is typically longer than for movements with an unspecified amplitude,^{7,8} thereby indicating some independence for the two processes. Additionally, the specification of direction and amplitude appear to be not only independent but also characteristically different.^{22,23} Both processes require about the same time, about 150 ms, but have different forms. Amplitude specification begins with the selection of a presumed "default" mid-range amplitude, gradually becomes more accurate, and when enough time has elapsed, it is finally set with precision.²² In contrast, movement direction specification is a random process with subjects equally likely to choose one of the possible movement directions until the correct direction can be set after a sufficient time lapse.²³

Direct recordings of cerebral cortical cell firing suggest additional segregation of movement direction and amplitude coding. Cells in the primary motor and somatosensory cortices have discharges related to both movement direction (or position) and amplitude (or force).²⁴⁻²⁶ This may imply that the motor and sensory cortices are not primarily involved in preferentially specifying one or the other dimension of movement. In contrast, the parietal lobe, specifically area 5, has cells with discharges that are solely related to movement direction and presumably independent of movement amplitude.²⁷ Unfortunately, the supplementary motor area, the cortical target of basal ganglia output²⁸ has not been studied with similar analyses regarding its coding for specification of movement amplitude.

It appears that the basal ganglia is also

involved in processing information related to both the direction and amplitude of movement. For example, cellular discharge in several basal ganglia structures is related specifically to either the intended¹³ or the executed^{12,14} direction of movement, and the discharge of some cells is related to the magnitude of muscle activity in a single direction.¹² Thus, the relationship of basal ganglia neurons to applied loads is relatively weak, possibly indicating that the basal ganglia is not primarily involved in specifying the amount of muscle activity.

The deficit by PD patients in directional specification of movement has been examined in RT tasks when directional coding is required at movement onset.¹⁰ In these studies, movement initiation is prolonged when subjects must process directional information concurrently with movement initiation. In other studies, involving assessment of multiple segment movements for which changes in direction were required between the segments, Berardelli *et al*²⁹ reported that PD patients paused excessively long between individual segments of a sequential two-dimensional movement. It might appear from these data that changing direction during movement execution, like RT, is also slowed in PD. However, this deficit may not be related only to the requirement to change direction, but instead may be due to the sequential nature of the task. For example, Benecke *et al*³⁰ demonstrated that the time to begin the second of two independent movements executed sequentially was delayed in PD. Moreover, the inter-onset latency between the independent movements was dopamine sensitive.³¹ In their aggregate, these deficits were interpreted as indicating difficulty in selecting motor commands for sequential movements by PD patients. It may not be possible to generalise from the deficits in execution to deficits in initiating sequential movements, since Rafal *et al*⁶ showed that RT is unimpaired in PD when a sequential movement task is being prepared. Thus, there may be a difference in directional processing when the sequential movement is prepared compared with when it is executed. Since the movements in the Berardelli²⁹ study required changes in movement direction, it is possible that instead of reflecting a generalised deficit in motor programming, the excessive pauses between movement segments were related to a slowing of processing directional information, especially in a sequential motor task, in PD. This issue and the dopaminergic sensitivity of such behaviour were not evaluated and need further clarification.

In addition to reports of problems with directional coding in PD, there have been numerous investigations on whether magnitude coding is impaired in PD. Flowers³² noted that movements of PD patients are typically hypometric when they are executed rapidly, especially for movements of larger amplitude. In many patients, the entire targeted movement is performed in several segments. Successive bursts of EMG activity accompany this segmented movement,^{17,33} suggesting that PD patients have difficulty in

emitting large amounts of muscle activity required to make large movements. The slow build up in the EMG during voluntary movement that is often observed in PD³⁴ would support the notion that the mechanism controlling EMG magnitude in rapid movements is impaired in PD. Data obtained from performance on isometric tasks also indicate that PD patients have a slow EMG build up, but nevertheless ultimately achieve the correct end point.³⁵ In contrast to these data on abnormalities in voluntary EMG responses are recent results showing that PD patients can scale the size of the first agonist EMG burst when they perform movements of different magnitudes and against different loads.¹⁷ Although the magnitude of the EMG burst was diminished when PD patients were off medication, this study showed that the amplitude of the bursts in relation to intended movement size and opposing load was not altered by withdrawal of dopamine replacement therapy.¹⁷

These results indicate that the concurrent planning of movement amplitude and initiation by PD patients is insensitive to plasma, and likely brain, levels of dopamine. This contrasts with our earlier data concerning directional choice RT¹⁰ and seemingly with results from other studies indicating that some aspects of amplitude specification are affected by Parkinsonism and sensitive to dopaminergic replacement therapy.^{17,32,34} Nevertheless, we did find that the amplitude choice RT of patients was significantly slower than normal, even at the optimal levodopa infusion rate, indicating that Parkinsonism affects the concurrent specification of movement amplitude and initiation, though not necessarily through a dopaminergic mechanism.

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