Dopaminergic effects on simple and choice reaction time performance in Parkinson's disease

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Article abstract—The present study examined whether premovement central neural processing in Parkinson's disease was related to functional motor disability and plasma l-dopa concentration. Reaction time (RT) performance in simple and choice RT tasks was assessed while plasma l-dopa levels were controlled by continuous IV l-dopa infusion in five parkinsonian patients. Five age-matched controls performed the same RT tasks for comparison. Simple RT for the patients was longer than the normal control RT at all infusion levels (p = 0.005). However, choice RT was normal when the patients were "on," but became prolonged as plasma l-dopa levels decreased (p < 0.01). The results show that there are abnormalities of premovement central neural processing in Parkinson's disease, and that simple and choice RTs are differentially affected by l-dopa replacement. This suggests that different neural mechanisms may be involved in the processing of these tasks.

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Reaction time (RT) studies can be used to analyze objectively premovement abnormalities in Parkinson's disease and may offer insight into the nature of central neural processing related to motor performance.1 RT studies measure response initiation time in motor tasks and can be separated into simple and choice types, depending on the kind of information given prior to a stimulus to move. Simple RT tasks present a single preparatory cue, providing unambiguous information on the nature of the impending movement prior to the stimulus to move. Choice RT tasks utilize more than one preparatory cue, which results in the need to consider more than one option for the impending movement and to choose the correct one when the stimulus to move is given. While previous studies have shown that parkinsonian patients exhibit prolongation of response initiation in simple RT tasks,1 in the presumably more complex choice RT task, response initiation has been found to be within normal range.12 These studies have implied that performance in choice RT tasks was paradoxically normal in Parkinson's disease. However, a problem with these investigations has been that the wide variability among patients' clinical status and therapies may have precluded finding a meaningful re-

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clinically depressed, and were capable of following instruc-
tions correctly. They were all taking a combination of l-dopa,
carbidopa prior to study, and their disability scores without
medication tanged from II to IV on the Hoehn and Yahr
scale. Five age-matched normal controls (3 men, 2 women,
aged 31 to 64 years; mean, 47.0) were studied with both tasks
for comparison. Patients and normal volunteers participated
in accordance with guidelines specified by the NIH Human
Subjects Comittees.

Experimental protocol. Clinical rating of parkinsonian
symptoms using a modified Columbia scale was performed by
two neurologists on patients at a clinical baseline and after
stabilization at each infusion rate, with simultaneous sam-
ping for plasma l-dopa, t-dopa, l-Dopa (l-,3,4-dihydroxy-
phenylalanine) was prepared in 0.45% saline to a concen-
tration of 2 mg/ml and given by continuous IV infusion with
oral carbidopa 30 mg, starting the day before testing.

Response rates of l-dopa (mg/kg/hr) were empirically estab-
lished for each patient based on the corresponding individu-
al clinical response. Three rates (high, medium, and low) were
set to achieve three parkinsonian states (optimal or on, mid,
and off). Rate adjustments were made 2 hours prior to the admin-
istration of each set of trials to allow stabilization of clinical
performance and plasma l-dopa level. Plasma samples were
stored immediately at -70 °C and later assayed for l-dopa
using high performance liquid chromatography with electro-
chemical detection.

Behavioral tasks and recording techniques. Simple and
directional-Choice visual RT tasks requiring fixation and ex-
tension movements about the wrist were performed by all
subjects. A subject was seated with the right hand secured to
a handle attached to the arm of a DC torque meter with the
wrist centered over the motor's axis of rotation. The forearm
was secured to prevent upward or downward movements when
the subject's arm was hidden from the subject's view. An electro-
tance meter recorded wrist angular displacement, and bipolar
surface electrodes were used to record EMG activity from wrist
dorsor and extensor muscles. A video screen was positioned 1
meter in front of the subjects and displayed hand positions
and target cursors as the visual cues. Target images were
displayed as rectangular boxes 1.2 cm high and 2.5 cm wide. A
(PDP) 134 minicomputer controlled the tasks and data acquisi-
tion.

For the simple RT task, a single target appeared in outline
form to the left or right of the center window, subtending a
visual angle approximately 6 to 7° from the center, as an
indication that the subject should prepare for an impending
30° wrist movement. If the hand position cursor was kept
within the center window for a variable "hold" period (800 to
1,800 msec), the offset target changed to solid form and the
center window disappeared, signifying the visual "go" stimu-
lus. The subject then had to move the position cursor into
the target by flexing or extending the wrist (figure 1A). For
the directional-choice RT task, two outlined preparatory targets
were displayed on either side of the center window (figure
1B). After the variable "hold" period, one of the targets changed to
solid form as the go stimulus and the other target disappeared.
The subject again had to either flex or extend the wrist 30° to move the cursor
into the target (figure 1B). Practice sessions were given until
subjects became familiar with the apparatus and could per-
form the tasks as rapidly and accurately as possible. For
both types of tasks, a trial consisted of aligning the position
cursor in the center starting window and then moving into the target
window with one continuous movement. After completion of
the movement, there was a variable intertrial interval (300 to
600 msec) before the reappearance of the center window and the
start of a new hold period. Simple and choice tasks were intermixed in sets of 30 trials in a pseudorandom fashion, such
that ultimately there was an equal number of trials for

Figure 1: Schematic diagram of (A) simple and (B) choice
RT tasks. The nine-dot matrix represents the hand position
cursor. For the simple RT task, when the preparatory
outlines were presented (solid) after a variable "hold" period,
the subject was instructed to flex or extend the wrist to
place the cursor on the target. Only the fixation simple RT
task is illustrated. For the choice RT task, the instructions
were the same, although two preparatory targets were
presented and the final target appeared randomly on either
the left or right of center. This required either fixation or
extension of the wrist within the same trial.

Relationships between parkinsonian disability and RT task performance.
The present study sought to examine whether there is
an abnormality of movement central neural process-
ing in Parkinson's disease that is related to func-
tional motor disability and plasma l-dopa levels during
the "on" and "off" states. Simple and directional-
choice visual RT tasks were used to evaluate response
initiation in patients with predictable response fluctua-
tions to l-dopa ("wearing-off"). A continuous IV infu-
sion pump was used to regulate plasma l-dopa levels
during RT performance. This dose-response evaluation
allowed for a more detailed examination of how simple and
close RT tasks were affected in Parkinson's disease.

Materials and methods. Subjects. Five right-handed pa-
tients with Parkinson's disease (4 men, 1 woman, aged 22 to
61 years; mean, 49.2) were selected for study according to
the following criteria: they exhibited minimal tremor, demon-
strated a "wearing-off" response pattern to l-dopa, were not

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were significantly different either in comparing the two RT tasks or in comparing the controls and most bradykinetic patient on or off. MT correlated inversely with plasma L-dopa concentration ($r = 0.7, p \leq 0.005$), and was virtually identical for both tasks in patients at a given infusion rate, as it was for both tasks with the controls (table). Optimally treated patient MTs were not significantly different from normal, but became significantly slower at middle and low dose rates ($p < 0.05$). Figures 4 and 5 illustrate the EMG findings as the L-dopa infusion rate was decreased.

Discussion. By titrating the level of motor disability using variable rates of an IV L-dopa infusion, we found abnormalities of both simple and directional-choice RTs in patients with Parkinson’s disease. Furthermore, these premovement measurements were differentially affected by L-dopa treatment. While it has been clearly demonstrated that the initiation and execution phases of voluntary movements are abnormal in Parkinson's disease, the central neural mechanisms underlying premovement abnormalities have remained obscure. Evarts et al. found a prolongation of simple RT, but did not demonstrate selective impairment in directional-choice RT in Parkinson's disease. Similarly, Blocham et al. found that parkinsonian patients did not benefit from the preparatory cues in simple RT tasks, but nevertheless performed choice RT tasks almost as well as normal controls. Rafa et al. examined the relationship between clinical state and response initiation time, and found that slowing of premovement (or “cognitive”) processes in Parkinson’s disease did not always accompany clinical bradykinesia. Though each of these studies investigated central processes in Parkinson’s disease, none of them systematically examined RTs in precise relationship to drug or disability level. Consequently, functional changes in these measurements were not obtained.

Our results showed that while simple RT was significantly prolonged in parkinsonian patients at all three L-dopa infusion rates, it was not significantly affected by treatment. This is in agreement with other studies that found no improvement in simple RT after L-dopa treatment. We extended those findings using a dose-response method and demonstrated that patients, even at their clinical best, did not benefit from single preparatory cues to the same extent as normal controls.

In comparison, we found that directional-choice RT was not significantly different from that of controls at the highest L-dopa infusion rate (on), but became significantly prolonged when the infusion was decreased to the middle and lowest rates (off). Choice RT, therefore, was inversely proportional to plasma L-dopa concentration and directly proportional to functional motor disability, particularly to bradykinesia. This finding demonstrated that parkinsonian patients with mild to moderate disease required more time to respond to one of two directional-choice targets when they were at or near their functional worst. Further, we showed that patients were capable of improving prolonged choice RT to normal with L-dopa treatment.
To alleviate concern that increasing bradykinesia may have artificially prolonged RT, we calculated the electromechanical dissociation between the onset of the first agonist EMG burst and the earliest detection of movement. Because the sensitivity of movement detection by the torque motor system was equal for all subjects, the low amplitude and slow EMG build-up often seen in bradykinesia may have resulted in longer electromechanical dissociation intervals in bradykinetic patients. However, our findings indicated that the apparatus accurately detected movement onset even when the ensuing movement was slow. There was no significant difference in electromechanical dissociation intervals between controls and patients, regardless of the degree of bradykinesia. RT measurements, therefore, were not detectably affected by bradykinesia and were probably an accurate reflection of premovement neural processing times.

The term "central delay" has been used to characterize the longer response latency observed in choice compared with simple RT performance. It has been thought to represent additional processing needed in the selection or formulation of a central motor program in choice RT tasks.16,22 In previous studies, measures of central delay in Parkinson's disease may have been shorter than normal in part because simple RT was prolonged to a greater extent than choice RT. This might have implied normal (or even exceptionally fast) central neural processing in Parkinson's disease.24 However, when calculating the relative central delay at each dose level, we found that it increased by 123% from the on to off state (figure 3). This demonstrated that neural processing of directional-choice tasks slowed as parkinsonian disability increased. Nevertheless, for a given dose level, central delay remained apparently faster in patients than controls.

The paradoxically faster than normal central delay in Parkinson's disease may be explained by the existence of independent neural mechanisms for simple and choice RT tasks. Recently, Alexander et al22 proposed that there may be several parallel basal ganglia-thalamo-cortical pathways subserving different functions. They reported that, at a fundamental level, these separate pathways can be grouped according to those involved mainly with motor activity and those involved with more complex behavior, including cognition. The main qualitative difference between the simple and choice RT tasks in our study was that the simple task was largely dependent on the subject's attention and preparation to move (because the target was known in advance), while the directional-choice task required an additional cognitive factor to select movement in one of two directions.

Given the difference between RT tasks, the neural mechanisms underlying RT performance might also be separated along a similar scheme (motor and complex) as that proposed to link the basal ganglia and cortex. Motor connections from sensorimotor cortex project largely to the putamen, while complex pathways from cortical association areas terminate principally in the caudate.23 Together with the specific cortical regions to which each pathway ultimately projects, these circuits may comprise two completely separate physiologic substrates subserving simple and choice RT tasks. This would allow for independent processing of RT tasks and offer a reason why simple and choice RTs were found unequally affected by L-dopa. The apparently faster than normal central delay in Parkinson's disease could then be explained as a discrepant value obtained by taking the difference between latencies from two physiologically distinct RT mechanisms.

The motor circuit, connecting cortex and putamen, projects almost exclusively back to the supplementary motor area (SMA).14 Using single-cell recording techniques in behaving primates, Tanji et al14 have shown that the SMA contains a significant proportion of neurons exhibiting preparatory-set related activity. The attention and preparation underlying the simple RT task in our study was analogous to motor readiness of preparatory-set behavior. Simple RT performance, therefore, may be associated with the SMA. In addition, the SMA and its connections are nondopaminergic.24

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<td>Simple reaction time</td>
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<td>Normal controls</td>
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<td>331 ± 36</td>
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Reaction and movement times are mean (in msec) ± SEM. Plasma L-dopa levels are mean (in μg/mL) ± SEM.

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Our finding that simple RT performance was not significantly affected by dopamine replacement further substantiates the possibility that the motor circuit, particularly the SMA, may serve as a substrate for processes involved in simple RT tasks.

It follows that simple RT may be at least partially dependent on non-dopaminergic physiologic mechanisms. Parkinson's disease is known to involve several neurotransmitter systems, and it has been suggested that a widespread decrease of norepinephrine (NE) may contribute to clinical deficits such as slowness in response initiation. For example, a significant relation between the dopamine and NE levels of the NE metabolite 3-methoxy-4-hydroxyphenylglycol has been found in parkinsonian patients. Simple RT also may be highly dependent on arousal systems to maintain attention and motor readiness. Arousal is thought to be predominantly mediated by NE and acetylcholine, supporting the participation of additional non-dopaminergic mechanisms in the processing of simple RT.

Choice RT performance, in contrast, is dependent on cognitive processes more complicated than attention or preparation alone and may be subserved by components of the complex basal ganglia-thalamo-cortical pathway. This circuit links the caudate with higher association areas, and projects back to regions of the prefrontal cortex. The circuit is thought to be involved with higher cortical processing and complex motor behavior. We found that choice RT, which was normal in optimally treated parkinsonian patients, was significantly affected by dopamine deficiency. Our results are consistent with recent experimental findings that also implicate the complex circuit in cognitive processes dependent on dopaminergic mechanisms. Taylor et al. have shown that cognitive dysfunction specific to Parkinson's disease may be caused by disturbed caudate outflow and the resulting functional abnormalities in prefrontal cortex. They argue that the prefrontal region is particularly vulnerable because it is the cortical target of caudate activity as well as a terminal projection of dopaminergic mesocortical fibers from the ventral tegmental area, both of which are affected in Parkinson's disease.

Studies by Weinberger et al., measuring regional cerebral blood flow (rCBF) over dopaminergic prefrontal cortex (DLCP), present more evidence to suggest that prefrontal dopaminergic mechanisms may underlie choice RT performance. They demonstrated that cognitive motor functioning in Parkinson's disease correlated with rCBF in the DLCP. In addition, l-dopa treatment resulted in an increase in rCBF over DLCP during functional testing of this cortical region, a result that parallels our finding that choice RT performance improved with l-dopa treatment. We have shown that simple and choice RTs are both affected by dopamine replacement, but differentially affected by dopamine replacement. Examination of the neural mechanisms involved suggests that simple and choice RTs are differentially affected by the basal ganglia-thalamo-cortical parallel circuits designed to control motor and cognitive functions independently.

Acknowledgment

This work is dedicated to the late Edward V. Feustel whose unflagging striving for excellence and accuracy will always be remembered.

References


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