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Simple and choice reaction time in Parkinson's disease

Yasar Kutukcu, William J. Marks Jr., Douglas S. Goodin *, Michael J. Aminoff

Department of Neurology, School of Medicine, Box 0114, Room M-794, University of California, San Francisco, CA 94143, USA

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Abstract

Reaction-times were evaluated in 6 parkinsonian patients and 6 normal control subjects using a simple reaction task and 3 choice reaction tasks of differing complexity. Reaction-times were measured as the time from stimulus onset to the onset of electromyographic activity in the responding muscle. Reaction-time was significantly delayed in patients compared to controls in all tasks, but to a greater extent in the more difficult tasks. The relative magnitude of the change, however, was only 4% in the simple reaction task and 8% in the more difficult choice tasks. These results suggest that the deficit in Parkinson's disease is unlikely to represent a defect in preprogramming as suggested by some investigators. Instead, our results indicate a disturbance in the cerebral processing of the auditory stimuli after their occurrence and prior to the initiation of motor activity.

Keywords: Parkinson's disease; Reaction time; Simple reaction time; Choice reaction time; Bradykinesia; Akinesia

1. Introduction

Reaction-time studies may provide insight to the mechanisms underlying the akinesia and bradykinesia that characterize Parkinson's disease. There has therefore been considerable interest in the alterations in response times that occur in patients with Parkinson's disease [2–8,14,15,17,18,20–23]. Hallett [14] argues that the entire reaction-time can be broken down into two parts or subtimes: the movement initiation or response time and the movement time. The response time represents the time between the onset of the stimulus and the onset of movement, whereas the movement time represents the time between the onset of the movement and completion of the response task. In Hallett's view, response time correlates with akinesia whereas movement time correlates with the clinical manifestation of bradykinesia. In studies of response time in patients with Parkinson's disease, a contrast is often drawn between the findings in simple reaction tasks (SRTs) and choice reaction tasks (CRTs). In SRT experiments only one stimulus is delivered and one response is required, so that it is possible to program the response prior to stimulus onset. CRT experiments, by contrast, involve two or more stimuli and two or more responses, so that preprogramming of all responses is not possible. Several groups have reported delayed response times in parkinsonian patients during SRT experiments but normal response times during CRT experiments [2,8,20,22]. These results have been interpreted as evidence that such patients have a defect in the ability to preprogram motor responses. In this view, response times in SRT tasks are similar to those in CRT tasks because the motor program is selected after stimulus occurrence in both cases [22]. Unfortunately, however, the literature is inconsistent with respect to this observation. Thus, there have been reports of delayed response times in SRT experiments with normal response times in CRT experiments [2,8,20,22]; equally delayed response times in both SRT and CRT experiments [7,18,21,23]; delayed response times in both SRT and CRT experiments, but with a disproportionate delay in the latter [5,15]; and normal response times in SRT experiments, with delayed response times in CRT experiments [4,17].

Differences in methodology probably account, at least in part, for some of these discrepancies. For example, some investigators have used experimental arrangements in which so-called SRTs were performed when several different stimuli were presented but a preceding cue indicated which of the stimuli was to occur and thus the expected response. However, Jahanshahi et al. [15] reported that parkinsonian patients required 2 to 3 s to

* Corresponding author. Tel.: +1-415-476-1986

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incorporate such cued information into fast responses, compared to controls who were able to do this in less than 1 s. In such a circumstance, a cued SRT experiment may artificially prolong the response time when the latency between the cue and imperative stimulus is short.

Another methodological factor is the manner in which response times are measured. For example, some authors do not describe how response time is measured [18], others measure response time as the time from stimulus onset to the onset of limb movement [2–8,14,15,17,18,20–23], and yet others measure it to the onset of electromyographic (EMG) activity in the responding muscle [10,18,22,24,25]. In normal subjects, however, there is a discrepancy of approximately 40 ms between the onset of EMG activity and finger movement [10,24] and even longer intervals are likely when limb movement is required [14,25]. Thus, when investigations are to be undertaken to study the central processes leading to the generation of a motor response, the time to EMG onset is a better measure than limb movement. This is because such central processes must occur before the initial activation of the muscle. Thus, the delay between EMG onset and limb movement is allocated more properly to movement time than response time. This is particularly true for Parkinson's disease, in which the delay between EMG and movement onset may exceed 150 ms [14,22,25], for uncertain reasons but perhaps because the initial EMG discharge is inadequate to produce limb movement [14].

In the present study we have reexamined the response of parkinsonian patients in SRT and CRT tasks, using EMG onset as the measure of response time. We sought to determine whether response time (measured in this manner) is, in fact, delayed in patients with Parkinson's disease. If so, we also sought to determine whether the delay is due to changes in central cerebral processing or to a delay in the initiation of movement, and whether such delays are present in SRT tasks, CRT tasks, or both.

2. Methods

Six patients with Parkinson's disease (aged 44–72 years; 3 men and 3 women) and six control subjects (aged 43–65 years; 3 men and 3 women) voluntarily participated in these experiments, which had the approval of the committee on human research at this institution. In each group, five of the six subjects were right-handed. All patients had Hoehn and Yahr scores of 2 or 2.5. The disease was symmetrical in 2 patients, predominantly left-sided in 3 patients, and predominantly right-sided in 1 patient. The duration of disease ranged from 1 to 12 years (mean $\pm$ standard deviation $= 6.7 \pm 3.5$ years). Five of these patients had been treated with medications and four were on Sinemet at the time of testing. Each of the four who had been tried on Sinemet was responsive to levodopa. Other medications included pramipexole, selegiline, pergolide, and bromocriptine. Bradykinesia and rigidity were present to a mild or moderate degree in all patients despite treatment. All treated patients were tested on medications. No patient had any clinical signs to suggest an atypical parkinsonian syndrome. On clinical evaluation, no patient was demented or depressed and no patient missed more than one point on the Mini Mental State examination [9].

Subjects participated in four sets of experiments, which were done in random order. In the *first experiment* (SRT), subjects listened to a series of 420 tones (65 dBSL; 50 ms duration) with an interstimulus interval of 2.0 s. All of the tones had the same pitch (1000 Hz), and subjects were required to respond by simultaneously extending the middle finger of both hands as rapidly as possible after each tone.

In the *second experiment* (a two-choice reaction task or 2-CRT) the arrangements were the same as in the first experiment except that two tones were presented to each subject. The frequent tones had a pitch of 1000 Hz and occurred on 86% of the trials. The other (uncommon) tone had a pitch of 2000 Hz and occurred on 14% of trials. The total number of tones presented was 420 in each block. The sequence of tones was pseudo-random with the constraint that uncommon tones did not occur consecutively. Subjects responded to the frequent tone by simultaneously extending the middle finger of both hands as rapidly as possible, and to the uncommon tone by extension of the middle finger of one hand. The experiment was performed twice; on one occasion the right and on the other occasion the left middle finger was extended to the rare tone.

In the *third experiment* (three-choice reaction task or 3-CRT) the experimental arrangements were as in the first experiment except that three tones were presented to each subject. The frequent tone had a pitch of 1000 Hz and occurred on 78% of trials, the uncommon tone was at 2000 Hz and occurred on 18% of trials, and the rare tone was at 4000 Hz and occurred on 4% of trials. These percentages were chosen so that the ratio of uncommon to frequent tones was the same as that of the rare to uncommon tones. As before, a series of 420 tones was presented to each subject. The order of the tones was pseudorandom with the constraint that two uncommon or two rare tones never occurred consecutively. Subjects again responded to the frequent 1000 Hz tone by simultaneous, rapid extension of both middle fingers. To the uncommon (2000 Hz) tone, subjects responded, in different blocks (420 tones each), by extension of either the right or left middle finger. To the rare tone, subjects responded in each run with the hand opposite to that used for the uncommon tone.

In the *fourth experiment* (three-choice reaction task with more equal probabilities or 3-CRT-EP), the experimental arrangements were as for the third experiment except that only 210 tones were presented and the relative probability of occurrence of the three tones was altered so that the frequent (1000 Hz) tone had a probability of 38% whereas the two rarer tones (2000 Hz and 4000 Hz) each

had a probability of 31%. Thus, it was difficult for subjects to predict which tone was likely to occur, although there was a slightly more frequent tone, and both rare tones occurred with equal probability. Subjects responded to the tones as described for experiment 3.

Statistical analysis was performed using multiple regression on correct individual responses to each tone. The categorical variables of response task and group were coded using 0/1 dummy variables to account for the four tasks and the two groups; these dummy variables were then included in the final regression equation as predictor variables of response time. Condition-dependent differences between parkinsonian patients and controls in response times were determined by appropriate interaction terms in the regression equation. Response latency, in all circumstances, was measured as the interval between onset of the tone to onset of the compound muscle action potential (CMAP) in the responding muscle. Trials with response latencies shorter than 50 ms were considered errors. In analayzing the response to the frequent tone, latency was measured for the response of the left hand, as in our previous studies [16], because responses from this hand were faster than from the right hand. Cerebral responses were recorded simultaneously from electrodes placed on the scalp and these results are reported elsewhere [13]. Responses other than the required one or that anticipated the stimulus were considered 'error responses.' As in earlier studies, bimanual responses to the frequent tone were also considered errors if the absolute difference between the CMAP onsets in right and left arm exceeded 50 ms [18].

3. Results

Mean correct response latencies in the different experiments for the patients with Parkinson's disease and the normal control subjects are shown in Table 1. The latencies indicated in the text are taken from the coefficients of the regression equations for the individual responses and, thus, do not correspond precisely with the mean values shown in the Table.

Response latency to the frequent (1000 Hz) tone increased progressively in the SRT, 2-CRT, 3-CRT, and 3-CRT-EP experiments in all subjects (Table 1, $p < 0.0001$). In all of these experiments, parkinsonian patients were slower to respond than normal controls (delay = 7 ms; $p = 0.001$), but they were especially slow in the fourth experiment (Fig. 1) where the response times in normal subjects was the longest (delay = 22 ms, $p = 0.028$ for the interaction between group and task). The range of response latencies was 50–1183 ms. In the SRT task, this range was 50–718 ms.

In both normal subjects and patients with Parkinson's disease, the left hand responded faster than the right in the bimanual response to the frequent tone ($p < 0.0001$). This difference was particularly notable in our second experiment ($p < 0.0001$). Except for the simple reaction task, the difference in response latency between the left and right hand was significantly smaller in the parkinsonian patients compared to the normal controls ($p < 0.0001$).

Response latency to the uncommon (2000 Hz tone) was longer than to the frequent tone in all experiments and in both normal subjects and parkinsonian patients ($p < 0.0001$). The response latency to this tone was, like that to the frequent tone, delayed in the patients with Parkinson's disease compared to normal subjects (Fig. 1), especially in the two 3-choice experiments (delay = 40 ms, $p = 0.0013$ for the interaction between group and task).

Response latency to the rare (4000 Hz) tone was also delayed relative to the frequent tone in both normal subjects and patients with Parkinson's disease ($p < 0.0001$). Again, response latency to this tone was delayed in the patients with Parkinson's disease (Fig. 1) compared to normal subjects (27 ms; $p < 0.0005$). This delay was not significantly different between the third and fourth experiments.

Table 1
Mean response latencies and standard deviation for correct responses for the simple (SRT), two-choice (2-CRT) and three-choice (3-CRT) reaction tasks in patients with Parkinson's disease (PD) and normal controls[a]

Response	Condition	RT-Control (ms)	RT-PD (ms)	Right–Left difference in RT (Controls)	Right–Left difference in RT (PD)
CF	SRT	160 (83)	166 (97)	4.5	5.2
CF	2-CRT	196 (109)	203 (117)	7.4	6.1
CF	3-CRT	283 (147)	291 (172)	5.5	4.0
CF	3-CRT-EP	363 (156)	384 (192)	6.1	4.5
CR1	2-CRT	290 (89)	299 (107)	–	–
CR1	3-CRT	461 (153)	503 (170)	–	–
CR1	3-CRT-EP	473 (175)	508 (214)	–	–
CR2	3-CRT	422 (153)	453 (170)	–	–
CR2	3-CRT-EP	418 (189)	442 (189)	–	–

[a]CF = Correct response to the frequent tone; CR1 = Correct response to the uncommon tone; CR2 = Correct response to the rare tone; RT = Reaction time; EP = equal probability of occurrence of each of two rare stimuli. See text for details.

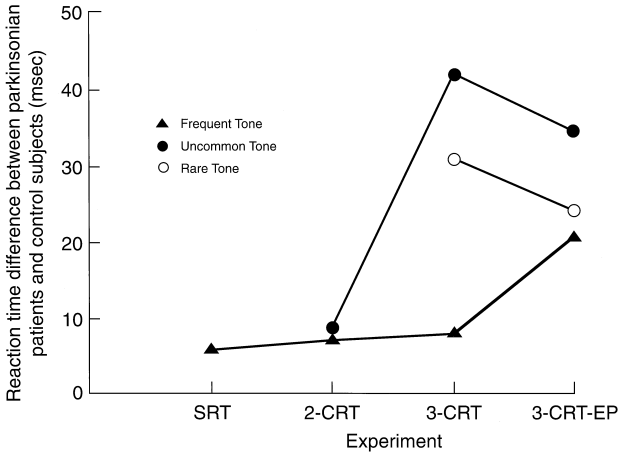

Fig. 1. Reaction-time differences between parkinsonian and normal subjects for each of the four experimental conditions described in the text. For each condition the difference in response time to the different auditory stimuli is indicated.

In all experiments, the averaged compound muscle action potential to each tone was reduced in peak-to-peak amplitude by over 50% ($p < 0.0001$) and increased in duration by approximately 50% ($p < 0.0001$) in patients with Parkinson's disease compared to normal controls. The error rates were also different between the two groups of subjects. In the first experiment the overall error rate in the parkinsonian patients was 5.4% compared to 2.5% in controls ($p < 0.0001$). In the second experiment the error rate was significantly higher ($p < 0.0001$) for both patients with Parkinson's disease (10.8%) and controls (6.0%) and was again significantly higher in patients compared to controls ($p < 0.0001$). Similarly, the error rates in the third and fourth experiments for parkinsonian patients (11.5% and 10.7%, respectively) were higher than the comparable rates (4.8% and 7.0%) in control subjects ($p < 0.0001$).

4. Discussion

Our principal findings are that there is a highly significant slowing of response time in both SRT and CRT tasks in patients with Parkinson's disease and that this delay is increased 3- to 5-fold with increase in task difficulty (as judged by an increase in the response time to the same stimulus in normal subjects). Such a result is consistent with the findings of several other authors [5,15]. Nevertheless, several differences between our study and those of others are of note. First, the response times that we recorded using CMAP onset in our SRT task are 100 ms or more shorter than the response times recorded by others using onset of limb movement as the terminal point of response time [2–8,14,15,17,18,20–23]. The relative shortness of the response time in our SRT task may be due to the ease of the task (an unaimed finger movement) or to the regular interstimulus interval that we employed. Indeed, both the parkinsonian patients and the controls showed a progressive increase in response time as the reaction task became more difficult (Table 1), suggesting that both groups were capable of preprogramming their responses in the easier tasks, especially the SRT task. Presumably, however, this short response time also relates, in part, to the delay between CMAP onset and limb movement. This delay is relatively larger in patients with Parkinson's disease compared to normal controls, particularly in CRT tasks [14,25] and this may account for the smaller difference between parkinsonian patients and controls that we found in the present study compared to others [2–8,14,15,17,18,20–23]. This increased delay may be due to an initial EMG burst that is inadequate to produce movement in parkinsonian patients. Such an interpretation is supported by our observation that the recorded CMAPs in parkinsonian patients are smaller in amplitude and longer in duration than in controls.

Both parkinsonian patients and normal control subjects responded faster with the left than right hand in the bimanual tasks, although the degree of asymmetry was significantly less in the parkinsonian patients. This asymmetry is consistent with our earlier reports and probably reflects hemispheric specialization or dominance related to a response to an auditory tone [12,13,19].

The magnitude of the delay in response time that we found in parkinsonian patients, especially for the less difficult tasks, is quite small compared to previously published findings [2–8,14,15,17,18,20–23]. This may also be accounted for by the relatively large delay between CMAP onset and limb movement that can occur in Parkinson's disease, because others have used limb movement to measure response time. We chose by our methodology to include this delay in the movement time rather than in the response time, so that response time better reflected selection and activation of central movement programs rather than reflecting a delay in the initiation of movement after the central program has been executed. The delayed response times in parkinsonian patients compared to controls occurred despite an error rate exceeding that in normal subjects in all four experiments. The reason for this increased error rate is uncertain.

Our results provide insight to the changes in central organization governing the responses in a reaction time task in Parkinson's disease. Much of the recent literature on this subject has focused on implications with regard to which stage of information processing is affected in Parkinson's disease. Some authors, who have reported normal response times in CRT tasks but delayed response times in SRT tasks, have focused on a possible defect in the patient's ability to preprogram movements [22]. By contrast, authors who have found equally delayed response

times in both experimental circumstances have emphasized possible involvement of stages such as stimulus encoding or response execution, because these are presumed to be common to the two kinds of tasks [23]. Similarly, those authors who have found a disproportionate delay in CRT compared to SRT emphasize the additional involvement of stages such as stimulus identification, stimulus–response 'mapping' and response selection that are presumed to be unique to the CRT task [15]. Although our results indicate that involvement of cerebral processing must occur prior to the onset of muscle activity, it is not possible to implicate any specific stage of information processing. Indeed, based on our previous studies of cerebral potentials in normal subjects engaged in SRT and CRT experiments, the various stages of information processing (at least if envisioned to proceed serially) cannot be correlated consistently with the cerebral activity associated with performance of reaction-time tasks [1,11]. Such cerebral activity reflects parallel processing to a considerable degree and is manifested by a variable coupling between cerebral events and motor output [1,11].

Our findings indicate that there is no major disturbance of the ability to preprogram movements in Parkinson's disease. First, the delay (4% of the normal) in response time in the SRT experiments was minimal, as would be anticipated if preprogramming is unaffected in Parkinson's disease. Second, the fact that SRTs were considerably shorter than CRTs (presumably because of preprogramming) in both patients and controls is against a preprogramming defect in Parkinson's disease. This is also supported by our analysis of the cerebral readiness potentials in these patients, which demonstrated that both patients and controls had similar cerebral processing preceding the anticipated response [16]. Finally, the delay (8%) in parkinsonian patients compared to controls in the 3-CRT and 3-CRT-EP experiments was significantly greater than the delay in SRT experiments, and this also would not be expected if the defect were in the preprogramming of the response. Instead, this last observation implies that the delay is due to a defect in the central (possibly cognitive) processing of the stimuli, perhaps due to a greater difficulty in switching between motor programs in patients. In this circumstance it would, perhaps, be better to characterize such a deficit in response time as bradyphrenia rather than bradykinesia, because bradykinesia implies a defect subsequent to the commencement of movement.

In summary, our results suggest that response time is more appropriately evaluated using EMG onset rather than limb movement. When this is done, the increased response time in parkinsonian patients relative to normal controls is quite small in SRT tasks, is significantly larger but still small in CRT tasks, and is related to a defect in the cerebral processing of the imperative stimulus that becomes more manifest as the cognitive requirements of the task (i.e., the task difficulty) increase.

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