

# Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease

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## Summary

*Studies of cognition and motor control have independently suggested that patients with Parkinson's disease show deficits in both attentional control and the preprogramming of movement. However, few studies have examined directly the involvement of cognitive processes in the origin of their slowed response. We examined the performance of 100 Parkinson's disease patients on simple reaction time (SRT) and a series of go/no-go cross-modality choice reaction time (CRT) tasks, in which motor response was constant; correct positive responses required attention to a progressively increasing number of dimensions of visual and auditory stimuli. The results showed that Parkinson's disease patients became increasingly impaired in response speed as choice complexity increased. Slowed response speed in Parkinson's disease involved two factors: (i)*

*a 'perceptuomotor' factor which was constant across conditions and independent of choice complexity. Depression affected this factor selectively and independently of confounding associations with impoverished motor control; (ii) a 'cognitive-analytical' factor, which played an increasingly important role as complexity of choice increased. The characteristics of the relationship between response latency and cognitive complexity indicate that the deficit was due to a constant proportional slowing in cognitive speed across all SRT and CRT conditions.*

*A cognitive deficit affecting the monitoring of stimulus-response compatibility may contribute to delayed response in Parkinson's disease. This cognitive-analytical deficit is present in early, untreated cases and, in contrast to perceptuomotor processes, is weakly related to depression.*

**Key words:** bradyphrenia; reaction time; Parkinson's disease

## Introduction

'Slowing of thought processes', or bradyphrenia (Naville, 1922), has been highlighted as a feature of subcortical dementia (Albert *et al.*, 1974; Cummings and Benson, 1984), particularly progressive supranuclear palsy. In Parkinson's disease, the existence of bradyphrenia is controversial and the nature of the affected processes underlying the clinical phenomenon is even less certain. Moreover, the possible influence of central processing speed upon motor control in Parkinson's disease is unclear despite well-known clinical observations of interactions between mental state and motor disability in the disease. In one study (Dubois *et al.*, 1988), it was found that groups of Parkinson's disease and progressive supranuclear palsy patients were both slow to move, but only progressive supranuclear palsy patients were slowed under conditions requiring greater central analysis. Analysis time correlated most strongly with indices of frontal lobe function; thus the authors concluded that the difference between subject groups could best be explained by the greater frontal-lobe dysfunction associated with progressive supranuclear palsy. However, frontal-lobe deficits are also well recognized in Parkinson's disease (reviewed by

Brown and Marsden, 1988a; Sagar and Sullivan, 1988) and recent studies have highlighted disordered attentional control in the disorder (Brown and Marsden, 1988b; Sagar *et al.*, 1988; Downes *et al.*, 1989, 1993). Rogers *et al.* (1987) noted the similarity of motor and affective signs in Parkinson's disease and primary depressive illness and attributed slowed response latencies in both groups of patients to a common dysfunction of the mesocorticolimbic dopaminergic system. These observations suggest important interactions between cognitive speed, motor speed and affective state, which may be based on dopaminergic pathology.

Attempts to separate the cognitive and motor components of performance in Parkinson's disease have often used reaction time (RT) paradigms, specifically the comparison of simple reaction time (SRT) and choice reaction time (CRT). Conflicting results have been obtained. In some studies, Parkinson's disease patients were slow on SRT tasks, in which all stimuli require the same response, but were normal on CRT tasks, in which different stimuli require different responses (e.g. Evarts *et al.*, 1981; Bloxham *et al.*, 1984; Sheridan *et al.*, 1987;

Goodrich *et al.*, 1989). Others have found no difference in the extent of slowing between SRT and CRT in Parkinson's disease (e.g. Stelmach *et al.*, 1986; Mayeux *et al.*, 1987; Pullman *et al.*, 1990).

Some studies have shown prolongation of CRT relative to SRT (e.g. Lichter *et al.*, 1988; Reid *et al.*, 1989; Jahanshahi *et al.*, 1992). Since CRT involves stimulus analysis and response selection, this finding suggests impaired central processing in Parkinson's disease which has also been supported from other sources. For example, scanning of items in short-term memory has been shown to be slowed in an elderly parkinsonian group (Wilson, 1980) and newly diagnosed Parkinson's disease patients showed borderline significant slowing of matching time in a digit-symbol substitution task (Rogers *et al.*, 1987). In RT studies, disproportionate CRT deficits may only emerge when choice of response is sufficiently taxing upon attentional resources. Many RT studies that found no selective deficit in CRT in Parkinson's disease incorporated a two-directional choice of movement as the CRT condition; however, as Evarts (1981) suggested, selection of one of two motor programs may be adequate for investigation of motor programming but too simple for the exploration of attentional control. One way to address this issue is to examine response speed in a series of tasks in which subjects are required to respond to an increasing number of stimulus attributes and to correct the results for the additive effects of impaired motor control and simple stimulus complexity.

The pattern of performance in which subjects show increasing impairment with increasing task complexity is well known in the research of ageing (Salthouse, 1985). The critical question addressed by that work is whether the pattern of greater deficits under more complex conditions represents a qualitatively different performance from milder deficits under simpler conditions. In a retrospective examination of 35 studies, Cerella (1985) found that slowed response latencies in elderly subjects could be explained by two factors: one 'sensorimotor', which was comparatively mildly affected, and the other 'central-computational', which accounted for most of their slowing. Performance in any particular task could be predicted from the relative roles played by each of these factors. If attentional requirements were low and computational analysis minimal, elderly subjects displayed only minor deficits in response latency; however, if attentional demands were high, their impairment was magnified. The explanation offered for these results is that each central computation is slowed by a constant amount; in a system of serial processing, total response time will be increased relative to that of a control group by a multiple related to the number of mental operations that occur between stimulus and response. Thus, whenever the index group shows slowed information processing relative to that of a control group, the index group will show disproportionate deficits relative to the control group over a series of tasks of increasing complexity. This disproportion will be reflected in significant group by task interactions in a statistical analysis of variance.

Application of this analysis to Parkinson's disease allows certain predictions to be made: a deficit restricted to motor

control would produce a constant deficit regardless of the cognitive complexity of the task; however, the presence of an additional central-analytical factor affecting response speed would predict an interaction between group and task, related to the cognitive complexity of the tasks.

The purpose of this study is to examine cognitive processing speed as a factor in the slowed response time of Parkinson's disease using a design and analysis that controls for motor preprogramming and task complexity. We examined the performance of Parkinson's disease patients on a series of RT tasks in which cognitive complexity was steadily increased. The nature of stimulus presentation and motor response remained constant; only the cognitive requirements involved in attention to particular stimulus attributes and the execution of choice differed across conditions. We studied newly diagnosed untreated patients, early treated patients and chronically medicated cases and concurrently assessed motor disability, depression, frontal-lobe function and memory in order to address the relationship of cognitive and motor speed to other cognitive functions, motor control, affect and dopamine deficiency. Preliminary results have been presented elsewhere (Sagar *et al.*, 1990a,b; Cooper *et al.*, 1992a).

## Subjects

One hundred Parkinson's disease patients were recruited from the neurology outpatient clinics of the Royal Hallamshire Hospital, Sheffield. All patients fulfilled the diagnostic criteria of the Parkinson's Disease Society: akinesia plus rest tremor, rigidity or postural instability and absence of any other condition that may produce signs of parkinsonism. No patient had undergone any neurosurgical operation. Patients were not selected on the basis of any behavioural criteria. These patients were classified into three subgroups: 37 newly diagnosed, untreated patients (*de novo*) were recruited from consecutive referrals; 26 patients who had been recruited into a longitudinal study of cognition in the same way as the *de novo* cases, but had since been placed on anti-parkinsonian monotherapy with levodopa (Madopar), bromocriptine or benzhexol (early treated); and 37 chronically medicated patients who had been maintained for several years on a variety of therapies (chronic). A group of 24 age- and sex-matched, healthy control subjects was obtained from a variety of sources: spouses of Parkinson's disease patients, non-professional hospital staff and patients without hearing impairment from an ear-nose-throat clinic.

Inclusion criteria for all subjects were head injury with loss of consciousness in excess of 1 h, history of thyroid disease or diabetes, electroconvulsive therapy, major psychiatric disorder, psychoactive medication other than minor tranquilizers and hypnotics, alcohol consumption in excess of 56 units per week or any other condition known to impair central function other than Parkinson's disease. All subjects were self-declared as right-handed except two who were left-handed (both Parkinson's disease) (see Table 1).

Parkinson's disease patients did not differ from controls in premorbid IQ, as measured by the National Adult Reading Test

**Table 1** Characteristics of subject groups: mean and (range)

Subject group	Sex M/F	Age (years)	Premorbid IQ	Duration of disease (years)	Motor disability rating (KCRS)	Dementia rating (BDS)	Depression rating (BDI)
Control	12/12	61.3 (43.7–75.1)	109.0 (94–124)	—	—	1.3 (0–4)	6.4 (0–14)
<i>De novo</i> Parkinson's disease	20/17	57.7 (31.1–77.1)	107.1 (88–124)	1.6 (0.4–5.0)	19.1 (3–50)	2.9 (0–12)	8.1 (1–20)
Early treated Parkinson's disease	13/13	61.3 (44.7–78.2)	106.7 (88–121)	3.0 (0.9–7.3)	16.2 (2.5–49)	2.5 (0–9)	11.8 (2–27)
Chronic Parkinson's disease	23/14	64.3 (44.0–77.8)	105.2 (90–123)	9.1 (3.0–20)	31.3 (12.5–51.5)	4.2 (0–10)	11.4 (0–28)

M = male; F = female.

**Table 2** Characteristics of the early treated Parkinson's disease subgroup: mean and (range)

Subject group	Sex M/F	Age (years)	Premorbid IQ	Duration of disease (years)	Motor disability rating (KCRS)	Dementia rating (BDS)	Depression rating (BDI)
Levodopa	6/3	59.9 (52.5–66.1)	109.4 (89–121)	3.0 (0.9–4.7)	9.0 (2.5–21)	2.3 (0–5)	9.0 (2–15)
Bromocriptine	5/5	62.0 (54.3–78.2)	102.5 (88–117)	2.5 (1.2–4.6)	19.1 (5.5–31)	3.2 (0–9)	13.4 (3–27)
Anti-cholinergics	2/5	61.7 (44.7–75.4)	108.4 (95–115)	3.7 (1.6–7.3)	20.8 (8.5–49)	1.9 (0–4)	12.4 (5–22)

M = male; F = female.

(NART; Nelson and O'Connell, 1978) ( $t = 1.27, P = 0.21$ ) or years of education ( $t = 0.36, P = 0.72$ ). Thus group differences in test score are not attributable to differences in premorbid intellectual level or schooling. No patient was demented according to DSM-III criteria of the American Psychiatric Association (1987). The early treated group differed from the *de novo* cases in disease duration ( $t = 4.07, P < 0.001$ ) but not in clinical motor disability (score on the Kings College Rating Scale, KCRS; Brown *et al.*, 1984), global cognitive capacity (score on the memory and orientation section of the Blessed Dementia Scale, BDS; Blessed *et al.*, 1968) or severity of depression (score on the Beck Depression Inventory, BDI; Beck *et al.*, 1961). The chronic group differed from the other Parkinson's disease subgroups in disease duration ( $F = 76.8, P < 0.0001$ ), global cognitive capacity ( $F = 4.2, P < 0.05$ ) and motor disability ( $F = 15.6, P < 0.0001$ ) but not in severity of depression (see Table 2). All patients and control subjects gave their informed consent to take part in this study.

## Methods

### Simple and graded choice reaction time

Subjects were presented with a series of visual stimuli on the screen of a BBC master 128 computer. The stimuli differed in colour (yellow or purple) and in shape (circles or squares). Simultaneous to the presentation of the coloured shape, subjects

also received one of two auditory stimuli that differed in pitch (high or low). Thus there were eight possible combinations of colour, shape and tone which were delivered in a pseudorandom sequence (no single dimension of colour, shape or tone occurred more than three times in succession).

Reaction time was measured under four different conditions: (i) SRT, where subjects responded to all stimuli regardless of their nature; (ii) CRT to one stimulus dimension (CRT1), where the subject responded to a specific colour, shape or tone, e.g. all yellow stimuli and ignored all the other stimulus characteristics; (iii) CRT to two stimulus dimensions (CRT2), where a response was required only to a specific combination of two stimulus features, e.g. yellow squares or circles with a high tone; (iv) CRT to three stimulus dimensions (CRT3), where a response was required only to a specific combination of three stimulus features, e.g. purple squares with a high tone.

The stimuli appeared in the centre of the screen until the subject responded (or for a maximum period of 2.5 s) when the visual and auditory dimensions of the stimuli stopped immediately and simultaneously. The end of one stimulus automatically triggered the presentation of the next after a delay randomized between 2.5 and 4 s. Subjects were instructed to respond to the target stimuli as quickly as possible by pressing a keyboard bar with their preferred hand.

The mode of the subjects' response and the nature of the stimulus presentation did not differ across conditions; the cognitive demands were altered simply by changing the

instructions to the subject. After an initial instruction and practice session, subjects received separate blocks of CRT1, CRT2 and CRT3 (each lasting ~20 min) in that order, interspersed with suitable rest periods. The combination of stimulus dimensions that required a response (response criteria) were changed after a subject had made 10 correct responses. Within a block, the order of response criteria was constant for all subjects. In the CRT1 block, subjects were instructed to respond to any trial that contained a specific single stimulus dimension, e.g. the colour yellow. All stimulus features were individually assessed in the standard order yellow, purple, circle, square, high tone, low tone. In the CRT2 and CRT3 blocks, subjects were initially required to respond to one target dimension (in the CRT2 block) or two target dimensions (in the CRT3 block) (equivalent to CRT1 and CRT2, respectively) but, after 10 correct responses, the response criteria changed to two and three stimulus dimensions, respectively (equivalent to CRT2 and CRT3). However, for the purposes of analysis, data from these initial 10 responses of each block were included in the pooled data set for the previous block; e.g. only CRT2 responses were included in the CRT2 data set. In the CRT2 block, subjects were required to reach a criterion of 10 correct responses to each of the following stimulus dimensions: squares (CRT1); purple squares; purple circles; circles with a high tone; and yellow squares, always in that order. In the CRT3 block, the order of response criteria was yellow circles (CRT2); yellow circles with a low tone; and purple squares with a high tone. Simple reaction time was assessed at the beginning and end of each block. The response criteria were identified in upper-case white letters, positioned at the top centre of the screen throughout the procedure as a reminder to the subject. With each change of response criteria, the new target was indicated on the screen and simultaneously read aloud by the examiner. Results were calculated as mean reaction time (to the nearest 10 ms) and number of errors for each condition.

### **Motor disability**

A neurologist assessed motor function using the KCRS (Brown *et al.*, 1984), which is a quantitative measure of clinical motor disability, including akinesia, tremor, rigidity and paucity of movement. Higher scores indicate poorer performance. Manual dexterity was measured under unimanual and bimanual conditions by the Fine Finger Movements Test (Corkin *et al.*, 1981). The task required the subjects to rotate a mounted spindle between the thumb and first finger as quickly as possible for 30 s.

### **Memory**

Memory was assessed using the Wechsler Memory Scale (WMS) according to published instructions (Wechsler and Stone, 1945). Forgetting in short-term memory was examined with the Brown-Peterson distractor paradigm in which recall of consonant trigrams was assessed over various distraction-filled intervals (Brown, 1958; Peterson and Peterson, 1959).

The procedure employed 0, 3, 6, 9, 15 and 30 s retention intervals with serial three subtractions forming the distraction element.

### **Executive functions**

'Frontal-lobe' capacity was assessed using the Milner (1963) (128 cards) version of the Wisconsin Card Sorting Test (WCST). Performance was scored according to the method of Heaton (1981). Cognitive sequencing and working memory were assessed with a test of digit ordering (Cooper *et al.*, 1991). In this task, subjects were read a random selection of seven digits (e.g. 5-3-6-2-7-2-1) and were required to reorder the items in memory and repeat them in ascending fashion (in this example, 1-2-2-3-5-6-7). Each subject was given 15 trials. For each trial, one point was awarded for each digit placed in its correct position until a response broke the ascending sequence (e.g. 6 followed by 4). Maximum score was seven; if a subject reported more than seven digits, only the first seven were scored. Responses that did not come from the test presentation but, nevertheless, maintained ascending sequence were tolerated but not scored.

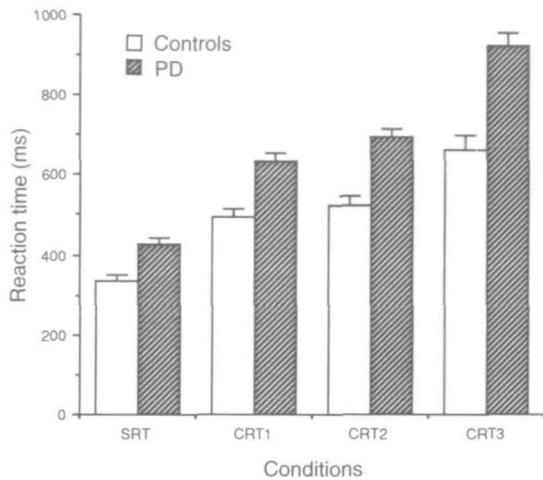
### **Statistical analysis**

Differences between data sets were evaluated by one-way and repeated measures analyses of variance (ANOVA). Planned comparisons between sets of data were made using *t* tests for two independent samples (two-tailed, unless otherwise stated). Correlations were determined with Pearson product-moment correlation coefficient, *r*.

## **Results**

### **Stimulus dimension and modality**

In order to assess differences in RT to the different categories of stimulus dimension (colour, shape and tone), a two-way ANOVA of Group (Parkinson's disease, controls)  $\times$  Category (colour, shape, tone) was performed. Since the motor response was constant across conditions, the RT data for each subject were first corrected for motor disability by subtraction of mean SRT from each of the CRT1 values to give an index, although not absolute measure, of cognitive speed. The CRT1 data within a common category of stimulus dimension were then pooled and averaged (e.g. all responses to yellow and purple stimuli were combined into the colour category). The analysis showed significant main effects of Group [ $F(1,122) = 4.16, P < 0.05$ ] and Category [ $F(2,244) = 39.17, P < 0.0001$ ] and a significant Group  $\times$  Category interaction [ $F(2,244) = 3.57, P < 0.05$ ]. Post hoc analysis revealed that, despite a correction for motor disability, Parkinson's disease patients were slower to respond than controls. Differentiation between tones produced longer response latencies than differentiation between colours ( $P < 0.0001$ ) or shapes ( $P < 0.0001$ ), whereas latencies for the visual dimensions (colours and shapes) did not differ from each other. The Group  $\times$  Category interaction was attributable



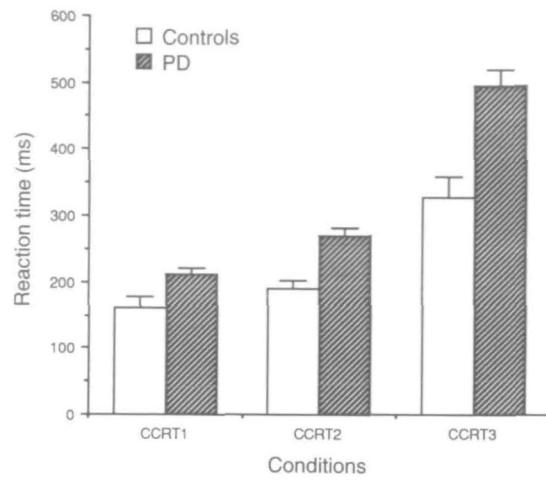
**Fig. 1** Mean RT and SEM (vertical bars) for each of the four conditions (SRT, CRT1, CRT2 and CRT3); Parkinson's disease (PD) patients were slower to respond than controls and became increasingly so as task complexity increased.

to a prolonged latency of Parkinson's disease patients, relative to controls, in their response to tone ( $t = 3.15, P < 0.01$ ) but less so to shape ( $t = 1.79, P < 0.05$ , one-tailed) and colour ( $t = 0.69, P = 0.49$ ).

### Simple reaction time and CRT in Parkinson's disease

A two-way ANOVA of Group (Parkinson's disease, controls)  $\times$  Condition (SRT, CRT1, CRT2, CRT3) showed significant main effects of Group [ $F(1,122) = 15.42, P < 0.001$ ] and Condition [ $F(3,366) = 336.68, P < 0.0001$ ] and a significant Group  $\times$  Condition interaction [ $F(3,366) = 7.24, P < 0.001$ ]. Post hoc analysis showed that, compared with controls, the total Parkinson's disease group was slower in all reaction time conditions: for SRT ( $t = 2.66, P < 0.01$ ), CRT1 ( $t = 3.48, P < 0.001$ ), CRT2 ( $t = 3.80, P < 0.001$ ), CRT3 ( $t = 3.94, P < 0.0001$ ). Moreover, the impairment in the Parkinson's disease group became more pronounced as complexity of the CRT condition increased (Fig. 1). When a similar ANOVA was carried out using  $\log_{10}$  transformed data in order to examine the interaction effect, the Group  $\times$  Condition interaction was no longer significant [ $F(3,366) = 1.02, P = 0.38$ ], indicating that the deficit in the Parkinson's disease group was proportional across conditions.

In order to examine a measure of RT independent of motor control, corrected CRT (CCRT) was calculated as the difference between CRT and SRT at each condition (CCRT1, CCRT2, CCRT3). This was considered to represent an index, although not absolute measure, of pure cognitive RT. The CCRT was also impaired in Parkinson's disease. Two-way ANOVA of Group (Parkinson's disease, controls)  $\times$  CCRT Condition (CCRT1, CCRT2, CCRT3) showed significant main effects of Group [ $F(1,122) = 12.11, P < 0.001$ ] and Condition [ $F(2,244) = 168.49, P < 0.0001$ ] and a significant



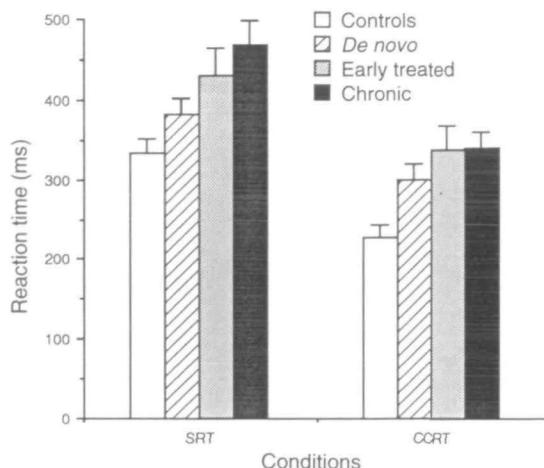
**Fig. 2** Mean corrected CRT (CRT minus SRT; CCRT) and SEM (vertical bars) for each of the three choice conditions (CCRT1, CCRT2 and CCRT3); as in Fig. 1, Parkinson's disease (PD) patients became increasingly impaired as a function of task complexity, even when response was corrected for motor speed.

Group  $\times$  Condition interaction [ $F(2,244) = 5.24, P < 0.01$ ] (Fig. 2).

Post hoc analysis revealed that controls had faster CCRTs than Parkinson's disease patients in all conditions: for CCRT1 ( $t = 2.07, P < 0.05$ ), CCRT2 ( $t = 2.71, P < 0.01$ ), CCRT3 ( $t = 3.38, P < 0.01$ ). The CCRT increased with task complexity ( $P < 0.001$ ) and the Group  $\times$  Condition interaction was attributable to the divergence of Parkinson's disease response latencies from those of controls as complexity of choice increased (Fig. 2). These analyses show that the Parkinson's disease patients were impaired under complex CRT conditions even when response was corrected for the influence of motor disability. A further series of analyses were performed in order to ascertain whether these deficits were a common feature of the disease or were more related to the factors of disease duration, treatment and depression.

### Differences among subgroups

The analysis was similar to that described above except that all Parkinson's disease subgroups were included; thus a two-way ANOVA of Group (*de novo*, early treated, chronic, controls)  $\times$  Condition (CCRT1, CCRT2, CCRT3) was performed. The analysis yielded significant main effects of Group [ $F(3,120) = 5.09, P < 0.01$ ] and Condition [ $F(2,240) = 170.89, P < 0.0001$ ] and a Group  $\times$  Condition interaction [ $F(6,240) = 3.02, P < 0.01$ ]. Post hoc analysis revealed that controls had faster CCRTs than all Parkinson's disease subgroups (for *de novo*,  $P < 0.05$ ; early treated,  $P < 0.01$ ; chronic,  $P < 0.001$ ) but the subgroups did not differ from each other. For CCRT1, only the chronic patients differed from controls ( $P < 0.05$ ); for CCRT2, the early treated subgroup was also impaired ( $P < 0.01, P < 0.05$ ); and finally, for CCRT3, all three Parkinson's disease subgroups



**Fig. 3** Mean and SEM (vertical bars) of SRT and corrected CRT (averaged across the three choice conditions) for controls, *de novo*, early treated and chronic Parkinson's disease. All Parkinson's disease subgroups were slowed relative to controls and equivalently so in both conditions.

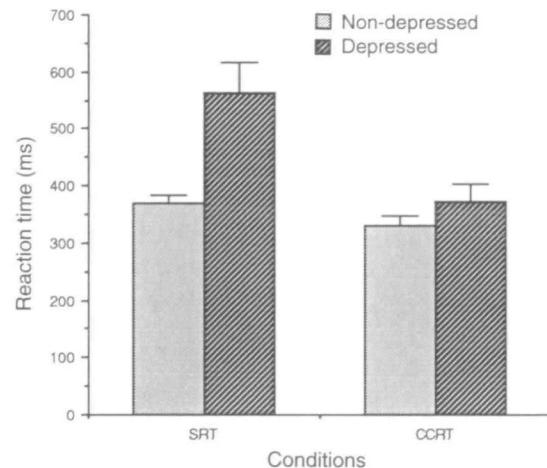
differed from controls (for *de novo*,  $P < 0.05$ ; early treated,  $P < 0.05$ ; chronic,  $P < 0.001$ ) but not from each other. These analyses suggest that the Group  $\times$  Condition interaction is due to an increasing difference between performance of the controls and Parkinson's disease patients with increasing cognitive complexity of the task.

A further series of analyses was conducted in order to establish differential effects on SRT or CCRT from different disease subgroups, treatment regime and severity of depression. For these analyses, SRT was compared with a single measure of CCRT, averaged across the three conditions, CCRT1–3.

A two-way ANOVA of Group (controls, *de novo*, early treated, chronic)  $\times$  Condition (SRT, CCRT) showed main effects of Group [ $F(3,120) = 9.85$ ,  $P < 0.0001$ ] and Condition [ $F(1,120) = 36.27$ ,  $P < 0.0001$ ] but no interaction [ $F(3,120) = 0.67$ ,  $P < 0.58$ ]. Post hoc analysis showed that controls had faster RTs than all Parkinson's disease subgroups (*de novo*,  $P < 0.05$ ; early treated,  $P < 0.01$ ; chronic,  $P < 0.0001$ ); the chronic patients were slower than the *de novo* and early treated subgroups ( $P < 0.01$  and  $P < 0.05$ , respectively). However, the total Parkinson's disease group was equivalently impaired at SRT and CCRT. This analysis indicates greater impairment in Parkinson's disease patients with longer disease duration and greater physical disability but no differential impairment overall on SRT compared with a measure of cognitive RT, corrected for motor disability (Fig. 3).

### Effects of treatment

Of the total group of treated Parkinson's disease patients, only the subgroup treated with levodopa showed a significant improvement in motor control after the institution of therapy, as shown by a significant decline in KCRS score ( $t = -3.06$ ,  $P < 0.05$ ).



**Fig. 4** Mean and SEM (vertical bars) of SRT and corrected CRT (averaged across the three choice conditions) for non-depressed and depressed Parkinson's disease subgroups. The depressed patients were slower to respond than the non-depressed patients in the SRT condition but not the CRT condition.

Comparison of the RT measures of all of the Parkinson's disease treated subgroups in an analysis of Treatment (levodopa, bromocriptine, anticholinergics)  $\times$  Condition (SRT, CCRT) showed an insignificant main effect of Treatment and an insignificant interaction with Condition; the main effect of Condition was again significant [ $F(1,23) = 5.25$ ,  $P < 0.05$ ]. This analysis indicates that SRT and CCRT were not differentially affected by different anti-parkinsonian treatment regimes, despite different effects of treatment upon motor disability.

### Effects of depression

An analysis of the data according to severity of depression showed an important dissociation (Fig. 4). In the original assessment of depression by Beck *et al.* (1961), a score of 18 was recommended as a cut-off between moderate depression and no depression. However, this level is somewhat arbitrary because a substantial number of patients were incorrectly classified using this cut-off. Later studies have recommended a cut-off of 10 between no depression and mild depression (Mayeux *et al.*, 1981). The use of the BDI to evaluate depressive symptomatology is further complicated by the significant number of somatic items on the scale. In Parkinson's disease, scores on these items may be influenced by the motor rather than the affective features of the disease, although these items do not entirely account for high BDI scores in Parkinson's disease (Levin *et al.*, 1988). Against this background, we considered that an arbitrary score of 13 represented a probable upper limit for the score of non-depressed Parkinson's disease patients on the BDI so this was used to distinguish groups of 'non-depressed' and 'depressed' patients, recognizing that a score of 14 or more did not necessarily indicate clinical depression.

A two-way ANOVA of Group (depressed, non-depressed)  $\times$  Condition (SRT, CCRT) showed significant main effects of Group [ $F(1,78) = 19.96, P < 0.0001$ ] and Condition [ $F(1,78) = 13.92, P < 0.001$ ] and a significant Group  $\times$  Condition interaction [ $F(1,78) = 9.98, P < 0.01$ ].

*Post hoc* analysis showed that the depressed group was slower to respond than the non-depressed group; CCRT was faster than SRT and the Group  $\times$  Condition interaction was due to a disproportionate impairment in SRT, relative to CCRT, in the depressed subgroup (Fig. 4). Specifically, the depressed group was slower than the non-depressed group for SRT ( $t = 3.47, P < 0.01$ ) but not CCRT ( $t = 1.19, P < 0.24$ ). The analysis was repeated using a measure of fine finger movement control as a covariate but without significantly altering the qualitative nature of the results. Depressed patients were slower than non-depressed patients at SRT [ $F(1,69) = 19.12, P < 0.0001$ ] but not at CCRT [ $F(1,69) = 0.10, P = 0.8$ ].

### Analysis of RT data in XY space

Interpretation of the significant Group  $\times$  Task interactions (e.g. Figs 1 and 2) was assisted by the method of Brinley (1965). The procedure is based on the knowledge that Group  $\times$  Task interactions may be significant for at least two reasons: first, the interaction may reflect qualitatively different deficits under different task conditions; secondly, however, the interaction may reflect a single deficit which becomes multiplied across conditions as a function of task complexity. In this experiment, for example, the Parkinson's disease patients may be slowed in RT by a constant proportion across all conditions. However, the RT of controls becomes progressively slower across the increasingly complex conditions CRT1–3 so that the *absolute* slowing of the Parkinson's disease group relative to controls is greater in the more complex conditions than in the simple conditions. As a result, the Group  $\times$  Condition interaction may be significant yet the performance of the groups does not differ *qualitatively* from one condition to the next, as suggested by the loss of significance in the Group  $\times$  Condition interaction term when the data are log-transformed.

A further analysis of response latency was performed, according to the method of Brinley (1965), by plotting the mean RTs for each stimulus target (e.g. colour yellow) of controls against the corresponding values of Parkinson's disease patients in XY space. The explanation that significant interactions are due simply to a multiplicative effect of task complexity on a constant proportional deficit predicts that the data plot will yield a straight line with a slope  $> 1$ ; this result was obtained in Cerella's (1985) retrospective review of the effects of aging on response time. If, however, the interactions are due to qualitatively different performance of the groups in different conditions, then such a plot will yield a curvilinear relationship with divergence of the Parkinson's disease performance in the more complex conditions; a departure from linearity resulting from a qualitatively different pattern of performance across conditions could not be explained by simple multiplication of a constant deficit.

When the mean RTs of Parkinson's disease patients were plotted against those of controls the resulting regression accounted for 95% of the variance (Fig. 5). The function (Parkinson's disease = 1.56, controls – 128) maps the RTs of Parkinson's disease patients onto those of controls by a simple multiplicative transformation and the addition of a constant factor. Thus, performance of the Parkinson's disease group in these experiments can be adequately explained by a constant deficit that slows performance in proportion according to the cognitive complexity of the task.

### Correlations between SRT, CRT and other test measures

Correlation coefficients were determined between SRT, CCRT, demographic variables and measures of memory, executive functions, affect and motor control (Table 3). Bonferroni corrections were applied so that a level of significance of  $P < 0.0015$  was adopted throughout.

In the total Parkinson's disease group, SRT correlated most significantly with the score on the BDI ( $r = 0.53, P < 0.0001$ ); performance on the cognitive tests, Digit Ordering ( $r = -0.44, P < 0.0001$ ) and Brown-Peterson Task ( $r = -0.36, P < 0.001$ ); performance on the tests of motor disability, KCRS ( $r = 0.35, P < 0.0005$ ) and the Fine Finger Movements Test ( $r = 0.34, P < 0.001$ ); and subjects' age ( $r = 0.32, P < 0.001$ ). By the stringent significance criteria adopted, CCRT correlated only with performance on the Digit Ordering Test ( $r = -0.44, P < 0.0001$ ). It is important to note that, SRT and CCRT did not correlate significantly with each other ( $r = 0.10, P = 0.31$ ).

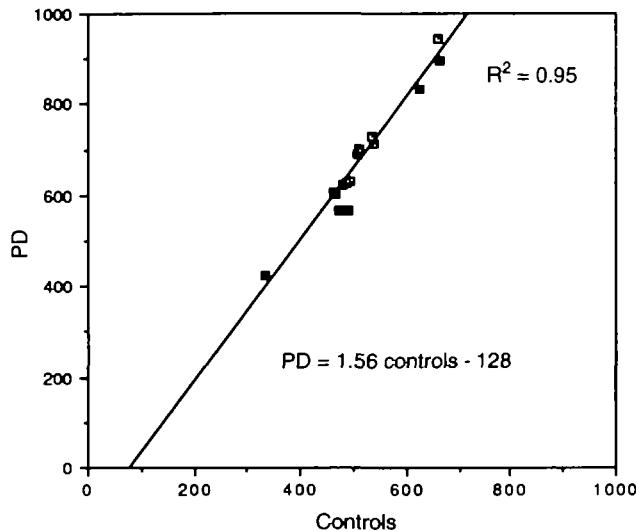
### Set-shifting or fatigue?

In order to determine whether performance was related to set-shifting deficits or abnormal fatigue, performance within each condition was analysed separately for the early, middle and late phase of each CRT condition; performance was analysed as both number of errors and mean RT. For the error analysis, each condition was broken down into thirds on the basis of total number of trials, including correct responses, and errors were ascribed to the early, middle or late phase according to the third in which they fell. For the RT analysis, phase was defined on the basis of the correct responses only. Of the 10 correct responses required for each CRT condition, RTs of the first three responses were averaged to provide mean RT for the early phase; responses four to seven were averaged for the middle phase; and responses eight to 10 were averaged for the late phase. For errors, a three-way ANOVA of Group (controls, *de novo*, early treated, chronic)  $\times$  Condition (CRT1, CRT2, CRT3)  $\times$  Phase (early, middle, late) showed significant main effects of Group [ $F(3,98) = 3.88, P < 0.05$ ] and Phase [ $F(2,196) = 61.48, P < 0.0001$ ] but not Condition. The Group  $\times$  Phase interaction was significant [ $F(6,196) = 2.18, P < 0.05$ ] and the Condition  $\times$  Phase interaction was also significant [ $F(4,392) = 16.14, P < 0.0001$ ]; all other

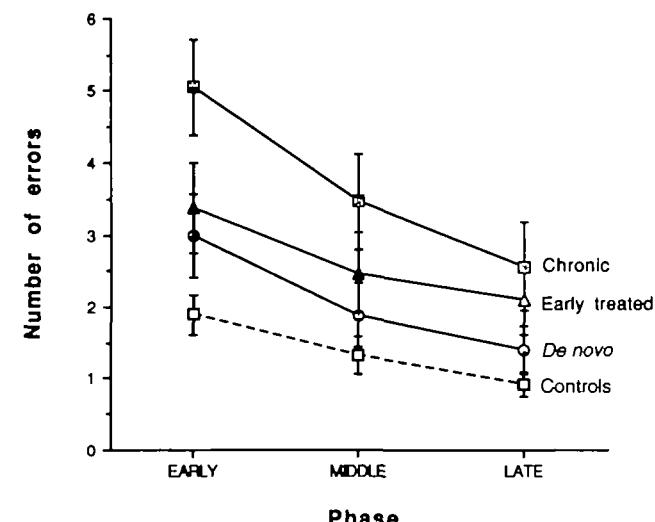
interactions were not significant (Fig. 6). Post hoc analysis revealed that more errors were made in the early phase than the later two ( $P < 0.001$ ); more errors occurred in the middle phase than the last ( $P < 0.001$ ); chronic patients made more errors than controls and *de novo* patients ( $P < 0.01$  and  $P < 0.05$ , respectively); and the Group  $\times$  Phase interaction was due to more errors by the chronic group in the early phase (chronics versus controls  $t = 4.33$ ,  $P < 0.0001$ , versus *de*

*novo*  $t = 2.36$ ,  $P < 0.05$ , versus early treated  $t = 2.32$ ,  $P < 0.05$ ). However, the disproportionate deficit in the chronic group in the early phase did not completely account for impaired performance of the Parkinson's disease group. Parkinson's disease patients continued to make more errors than controls at the middle ( $t = 2.88$ ,  $P < 0.01$ ) and late phase ( $t = 2.82$ ,  $P < 0.01$ ) of each condition.

For RT, a three-way ANOVA of Group (controls, *de novo*, early treated, chronic)  $\times$  Condition (CRT1, CRT2, CRT3)  $\times$



**Fig. 5** Mean RTs of Parkinson's disease (PD) patients plotted against those of controls for each of the 14 different target stimulus conditions (after Brinley, 1965). The function Parkinson's disease = 1.56 controls - 128 ms accounts for 95% of the total variance and implies that the Group  $\times$  Condition interaction displayed in Fig. 1 does not reflect a qualitatively differing pattern of performance across conditions by the Parkinson's disease group, compared with the control group.

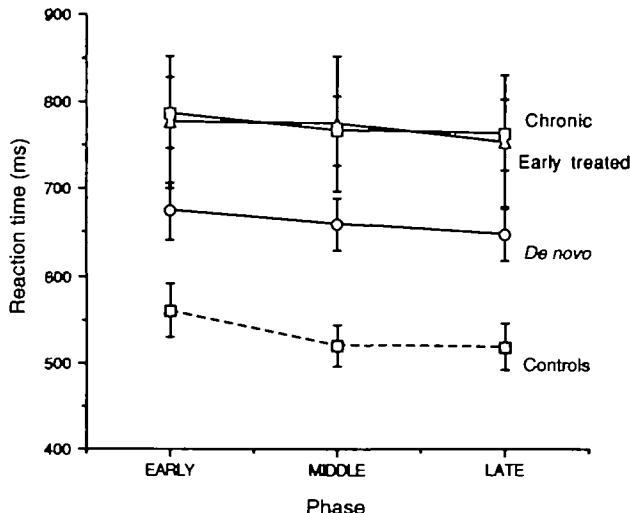


**Fig. 6** Mean number of errors and SEM (vertical bars) made by the controls group and each of the Parkinson's disease subgroups (*de novo*, early treated and chronic) at each phase (early, middle and late) of each CRT block. All subjects improved as the block progressed but the chronic Parkinson's disease subgroup made disproportionately more errors at the beginning of each new block.

**Table 3** Correlations between reaction time, clinical variables and cognitive test scores (Parkinson's disease total group)

	Simple RT		Corrected CRT	
	r	P	r	P
Age	0.32*	0.001	0.30	0.003
Disease duration	0.17	NS	0.13	NS
Blessed score	0.29	0.004	0.24	0.02
NART	0.18	NS	0.09	NS
Beck score	0.53*	0.0001	0.24	0.03
Memory quotient	0.30	0.002	0.27	0.007
Brown-Peterson	0.36*	0.0003	0.26	0.009
Digit ordering	0.44*	0.0001	0.44*	0.0001
WCST				
Categories	0.25	0.01	0.17	NS
Perseverative responses	0.18	NS	0.08	NS
Cards sorted to first category	0.06	NS	0.17	NS
KCRS score	0.35*	0.0005	0.31	0.003
Fine finger score	0.34*	0.001	0.19	NS

Significant after Bonferroni correction (see text). NS = not significant.



**Fig. 7** Mean RTs and SEM (vertical bars) for controls and each Parkinson's disease subgroup (*de novo*, early treated and chronic) at each phase (early, middle and late) of each CRT block. As in Fig. 6, the performance of all subjects improved over the block but, in this case, no Parkinson's disease subgroup showed disproportionate impairment at any particular phase.

Phase (early, middle, late) showed significant main effects of Group [ $F(3,84) = 6.52, P < 0.001$ ], Condition [ $F(2,168) = 115.07, P < 0.0001$ ] and Phase [ $F(2,168) = 6.83, P < 0.01$ ] (Fig. 7). Post hoc analysis revealed that controls had faster RTs than the early treated ( $P < 0.05$ ) and chronic ( $P < 0.001$ ) groups and the chronic group was slower than the *de novo* group ( $P < 0.05$ ). All three conditions differed from each other ( $P < 0.01$ ); RT increased as a function of task complexity. As in the error analysis, the main effect of Phase was due to inferior performance at the beginning of each block. The early phase RTs were slower than the middle ( $P < 0.05$ ) and the late ( $P < 0.001$ ) phase RTs but the RTs of the middle and late phases did not differ from each other. None of the two- or three-way interactions was significant. As in the error analysis, the longer RTs in the early phase of each condition did not entirely account for the impaired performance of the Parkinson's disease group [Parkinson's disease versus controls for early phase ( $t = 1.82, P = 0.08$ ), for middle ( $t = 2.49, P < 0.05$ ), for late ( $t = 2.3, P < 0.05$ )].

A further assessment of fatigue was carried out by examination of the six SRT measures, taken at the beginning and end of each of the three conditions. A three-way ANOVA of Group (controls, *de novo*, early treated, chronic)  $\times$  Condition (CRT1, CRT2, CRT3)  $\times$  Position (beginning, end) showed significant main effects of Group [ $F(3,120) = 5.88, P < 0.001$ ] but not Condition or Position. There was a significant interaction of Group  $\times$  Position [ $F(3,120) = 6.22, P < 0.001$ ] but no other two- or three-way interactions reached significance. Inspection of the data showed that, unlike any of the other groups, the chronic patients were slower to respond at the end of the conditions than at the beginning. Although this analysis indicates the presence of fatigue in the chronic

group, the major findings of this study (increasing impairment in RT in Parkinson's disease as a function of increasing cognitive demands of the task) cannot be attributed to fatigue alone for two reasons: first, none of the interactions involving Condition were significant; secondly, evidence for cognitive slowing was also obtained in the non-chronic groups which showed no evidence of fatigue.

## Discussion

The results of this study show that patients with Parkinson's disease become increasingly slow to respond as decision of choice becomes more complex. The characteristics of the relationship between response latency and cognitive complexity indicate that the deficits are due to a constant *proportional* slowing in cognitive speed across all SRT and CRT conditions. We will refer to this as a cognitive-analytical deficit. The cognitive slowing coexists with, but is independent of, a deficit that forms a simple absolute impairment independent of the cognitive complexity of the task; we will refer to this as a perceptuomotor deficit. The cognitive slowing is not related to severity of depression in this study, in contrast to perceptuomotor slowing which is strongly associated with depression.

The two major conclusions are: (i) delayed response in Parkinson's disease involves processes concerned with the monitoring of stimulus-response compatibility (internal: external mapping); (ii) depression affects particularly sensorimotor processes. This may operate through arousal and attentional focusing, stimulus registration and/or response initiation but not internal-external mapping. These points are discussed following the possible experimental complications of set-shifting deficits and fatigue.

## Relevance of set-shifting deficits and fatigue

It has been shown in some studies that Parkinson's disease patients are impaired at shifting set (Bowen *et al.*, 1975; Lees and Smith, 1983; Cools *et al.*, 1984; Flowers and Robertson, 1985; Taylor *et al.*, 1986). In our study, response latency and error data on the RT tasks were subject to analyses to investigate the importance of this factor in the increased RTs of our Parkinson's disease group. If performance were compromised by difficulty in changing from one stimulus target to the next, the deficits would probably be most pronounced at the beginning of each new block of trials. If, however, impairment were more attributable to fatigue or waning attention then performance would decline towards the end of each block. Analysis of RT and error data showed that Parkinson's disease patients (like controls) performed most poorly at the beginning of each block. The chronic subgroup of Parkinson's disease patients, in particular, made significantly more errors at the beginning of each block, relative to their error rate over the later portions of the block, possibly reflecting a deficit in their ability to shift attention from one target stimulus to the next. This group, but not the other Parkinson's disease groups, also showed some evidence of fatigue. However, these deficits did not totally

account for the poor performance of the chronic subgroup or indeed that of the Parkinson's disease group as a whole. Thus, failure to shift set and fatigue do not totally account for reduced cognitive speed in Parkinson's disease.

### **Cognitive and sensorimotor slowing in Parkinson's disease**

The specific aim of our study was to examine how response latency relates to cognitive demands in Parkinson's disease whilst controlling for known motor slowing. Our procedure was similar to a design developed independently by Dubois *et al.* (1988) in which RT was measured under conditions of graded attentional demands. Dubois *et al.* (1988) found SRT to be abnormal in Parkinson's disease but 'central processing time' was not disproportionately affected under the more complex conditions. As they suggested, however, this result was probably due to the insufficiently taxing nature of the cognitive aspects of their procedure on attentional control. In our study, patients became increasingly slow to respond as more stimulus dimensions were incorporated into the choice decision. The cognitive slowing was displayed by all Parkinson's disease subgroups, including the newly diagnosed untreated cases; indeed, duration of disease failed to correlate with either SRT or central processing speed, corrected for SRT.

Simple reaction time and corrected CRT correlated significantly with scores on other cognitive tests that were acquired from the subjects in the same test sitting as that used for the RT study. Examination of the correlation coefficients and significance values in Table 3 shows that, in general, those measures correlating significantly with SRT were similarly associated with corrected CRT. Notably, however, depression (as gauged by the BDI) and control of fine finger movements correlated more strongly with SRT than with corrected CRT. A covariate ANOVA showed that depression exerted its influence selectively upon SRT despite a confounding interrelationship between Beck score and control of fine finger movements. As with Cerella's elderly population, slowed response latency in Parkinson's disease appears to be due to two separate factors: one 'non-cognitive', that is principally related to depression and impoverished motor control, and the other 'cognitive', which delays all mental operations between stimulus and response by a constant factor. All responses are to some extent composed of these two processes but the relative importance of each one varies with the nature of the task. The most basic SRT paradigm is likely to be weighted more towards a non-cognitive sensorimotor component whilst complex CRT tasks will clearly depend more upon the cognitive component.

### **Cognitive influences on motor control in Parkinson's disease**

The data allow some interpretation of the nature of the processes involved in cognitive slowing. Theoretically, the deficits could involve any of the following stages in the stimulus-response sequence: attentional focusing, stimulus perception, stimulus

identification, mapping of stimulus features to an internal representation of the target (internal-external mapping), response selection (go or no-go) and response initiation and execution.

In this study, complexity of the CRT condition was altered according to the number of stimulus dimensions that required simultaneous attention without in any way altering the nature of the stimuli presented across conditions. Stimulus processing involves perception of the stimulus and subsequent identification of its features. Stimulus perception (as opposed to identification) should not be affected by the complexity of the choice imposed in the task. Thus, simple deficits in stimulus perception would also be expected to produce a constant, additive effect across conditions and are unlikely to account entirely for the results of this study; if factors relating to the stimulus are involved, they concern stimulus identification and its subsequent processing.

Following perception of a stimulus, the subject must relate the perceptual trace to an internal knowledge base of the stimulus characteristics (e.g. Is this a yellow square?) and subsequently compare the identified stimulus to an internal representation of the target (the stimulus that requires a response). The results of this study are compatible with a deficit in processes concerned with the monitoring of stimulus-target compatibility.

Previous studies have examined CRT in Parkinson's disease with a paradigm incorporating a choice of movement to one of two or more target destinations. Under these conditions, studies have reported normal CRT relative to SRT in Parkinson's disease, a finding which has been ascribed to a deficit in motor preprogramming (see Introduction). According to this notion, normal subjects, unlike Parkinson's disease patients, can prepare their response in anticipation of a predetermined movement; hence SRT is impaired in Parkinson's disease. Under CRT conditions, however, the uncertainty of the response that will be required negates this anticipatory advantage so that the performance of Parkinson's disease subjects becomes comparable to that of normal subjects. In our study, the nature of the response output for each stimulus presentation was constant; choice was 'go/no-go' and not choice of direction of movement. Because subjects would be able to preprogram the response for all stimuli, we cannot address the effectiveness with which Parkinson's disease patients select, prepare and implement one motor program over another (Marsden, 1989; Goodrich *et al.*, 1989); however, our results are unlikely to be due to a motor preprogramming deficit in Parkinson's disease, even if one were present. The observation that patients with Parkinson's disease are disproportionately slowed under conditions where only the complexity of choice is manipulated indicates that deficits in processes that precede motor programming contribute to slowed response latency in Parkinson's disease. Moreover, the virtually complete linearity of the relationship between stimulus complexity and RT across all conditions indicates that these premotor cognitive deficits have a very similar effect on SRT and CRT.

In the present study, subjects were required to make, in

addition to motor programming, a decision whether to execute the prepared movement or to abandon it and not respond. Because the probability of response varied across conditions, the pattern of results could theoretically arise from a difference in sustained attention or motor readiness between the groups which was magnified under conditions of low response probability. These possibilities require further exploration. However, several observations suggest that the results are unlikely to be due solely to these factors. First, the Parkinson's disease group showed a disproportionate slowing to the more difficult tone dimension, relative to the two visual dimensions, in the CRT1 condition despite an equal response probability across dimensions in that condition. Secondly, depression involves psychomotor retardation and loss of sustained attention but did not particularly affect conditions with low response probability; in fact, the reverse pattern was obtained. Thirdly, in a separate study, prolonged SRT in Parkinson's disease was found not to be due to deficits in attentional focusing or stimulus predictability (Jordan *et al.*, 1992). Fourthly, the cognitive slowing showed no relationship to motor disability so that, if motor readiness is involved, it is dissociable from clinical motor disability. Taken together, these considerations suggest that, if the cognitive-analytical deficit is affected by response probability, the mechanism does not involve sustained attention or motor readiness.

In summary, deficits in attentional focusing, stimulus perception and response initiation would be expected to produce simple, additive effects on RT. These processes are probably involved in the constant deficit across conditions. However, the key observation that RT was influenced in a proportional manner by the complexity of choice across all SRT and CRT conditions, when stimulus set and response mode were constant, suggests that a deficit in the identification of stimulus features and their subsequent mapping onto an internal representation of the target (internal–external mapping) contributes to the origin of slowed motor response in Parkinson's disease.

### **Nature of the deficit in cognitive speed**

The results of this study do not support a specific deficit in conjunctive attention in Parkinson's disease (i.e. the synthesis of information from multiple sources) which would predict increasing impairment under more complex conditions over and above that which results from cognitive complexity. By contrast, the cognitive deficit in Parkinson's disease appears to affect some fundamental aspect of information processing that occurs subsequent to perception and precedes movement. The behavioural phenomenon of slowed response need not be mediated at a neuronal level by slowed transmission. Slowed response is a cardinal feature of ageing and research in that area has centred upon the notion of a reduced neural signal-to-noise ratio (Welford, 1981). It is suggested that elderly subjects compensate for this deficit by the accumulation of a stimulus signal over an extended period of time and thus, given a sufficient study period, are able to respond accurately but with an increase in latency. In Parkinson's disease, Bloxham *et al.*

(1987) suggested that a depletion of dopamine in the basal ganglia leads to an increase in neuronal noise, the behavioural consequence of which is that the patients always perform as if they had a secondary task demand. The pathophysiological basis of this reduction in signal-to-noise ratio is, of course, speculative. However, one possibility worthy of further exploration lies in the role of dopamine in stimulating neural activity in the direct pathway from the striatum to the output nuclei, which disinhibits the thalamus, whilst, at the same time, diminishing activity in the indirect pathway which inhibits the thalamus. Lack of dopamine may thus lead to loss of amplification of cortically initiated signals and difficulty in distinguishing signal from noise.

The notion of a reduced capacity to distinguish signal from noise may be related to disordered attentional control. Processes of selective attention that underlie a subject's ability to respond correctly to a stimulus target involve mechanisms that lead not only to its appropriate identification but also to the active inhibition of competing influences (Tipper, 1985). Distractibility, or defective control of interference, has been described in patients with frontal lobe lesions, particularly those involving the orbitofrontal cortex (Fuster, 1989).

### **Neurochemical basis of slowed cognitive speed**

One difficulty with this hypothesis is that the relationship of slowed central processing to striatal dopamine deficiency remains uncertain (Rafal *et al.*, 1984; Pullman *et al.*, 1988), although a relationship to mesocorticolimbic dopamine deficiency has been proposed (Rogers *et al.*, 1987). Moreover, reduced capacity to distinguish signal from noise or to focus attentional resource could also result from non-dopaminergic deficits. For example, cholinergic blockade (scopolamine) in normal subjects impairs recall of attended words whilst simultaneously improving recall of unattended words (Dunne and Hartley, 1985) and reduces target detection in high-probability locations whilst facilitating detection in low-probability locations (Dunne and Hartley, 1986). Furthermore, suppression of noradrenergic activity by clonidine facilitated attentional disengagement and impaired attentional maintenance in normal subjects (Clark *et al.*, 1989); a similar result was recently reported in Parkinson's disease (Wright *et al.*, 1990).

In the present study we compared the performance of patients receiving different anti-parkinsonian medications (dopaminergic and anticholinergic). The results do not indicate any difference between treatments in their effect on cognitive speed, despite differences in effect on motor control. However, in other studies, we have shown a beneficial effect of dopaminergic therapy on a task of working memory, and deleterious effects of anticholinergic medication on recall tasks (Cooper *et al.*, 1992b), suggesting that dopamine effects on cognition may be critically task- and dose-related. The majority of cognitive deficits in early disease are unaffected by treatment and are poorly correlated with motor disability (Cooper *et al.*, 1991). Further study is necessary to clarify the relationship of these findings to impaired cognitive speed.

## Conclusion

The prolonged RTs of Parkinson's disease patients in this study were largely explained by two factors: (i) A 'perceptuomotor' factor which was constant across conditions and independent of choice complexity. Depression affected the perceptuomotor factor selectively and independently of confounding associations with impoverished motor control. A simple alerting-arousal deficit is likely to be involved. (ii) A 'cognitive-analytical' factor, which played an increasingly important role as complexity of choice increased. This may be based upon an increased neural signal-to-noise ratio and loss of inhibitory attentional control processes.

These deficits were apparent even in untreated newly diagnosed patients. Cognitive factors affecting the evaluation of stimulus-target compatibility are involved in impaired response speed in Parkinson's disease and are most apparent under conditions that emphasize attentional demands.

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