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PSYCHOMOTOR DEFICITS IN PARKINSON'S DISEASE

by

ROSELYNE NORMAND

A thesis
presented to the University of Ottawa
in fulfillment of the
thesis requirement for the degree of
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in
KINANTHROPOLOGY

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Roselyne Normand, Ottawa, Canada, 1987.

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ABSTRACT

The performance of seven Parkinson subjects on a discrete pursuit tracking task was studied during alleviated and unalleviated stages, and compared with the performance of seven normal individuals matched for age and sex to the Parkinson group. The subjects were requested to react to a series of target lights which provided variations in directional probability and the distance to be moved. Overall, the subjects performed 20 trials (for a total of 2000 responses each) on a subject-paced tracking pursuit task. These trials were distributed into four sessions: 1) Learning session (8 trials, under drug control), 2) four trials when "off" medication, 3) four trials 15 to 20 minutes after the ingestion of a dose, and 4) a further four trials at the peak dose effect, that is, an hour and a half after ingestion. The results of the study suggested that once given sufficient practice to learn a task, and when under drug control, the performance of the Parkinson subjects was not significantly different from their age-matched controls except for their slowness at making decisions when movement direction was less predictable, and when they had to readjust their motor responses after having overshot the target light.

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INTRODUCTION

Since it was first described by James Parkinson in 1817, the aetiology of Parkinson's disease has remained unknown. Classified as a slow, progressive and degenerative disease of the nervous system, Parkinson's disease is thought to be the manifestation of a premature aging process leading to the degeneration of a specific subcortical structure namely, the substantia nigra. This pigmented nucleus is linked anatomically and functionally to the basal ganglia, as such, its degeneration and the subsequent destruction of its principal connection with the basal ganglia (the nigrostriatal pathway) leads necessarily to the malfunctioning of the basal ganglia. This subcortical disorganization induces the manifestation of three major motor features peculiar to Parkinson's disease. The "classic triad" includes resting tremor, plastic muscular rigidity, and slowness of movement; each of which becomes more manifest and disabling as the disease progresses.

Without stopping the course of the disease and, despite their several side effects, the recent use of drug treatments has contributed to the partial alleviation of parkinsonian symptoms. Indeed, the difficulty the parkinson patient usually has in initiating (akinesia) and in executing (bradykinesia) planned motor actions can be passably improved by drug therapy. Respectively, reaction time and movement time have been identified as potential sources of information for assessing the neurological deficits of Parkinsonians and as an objective indicator of therapeutic efficacy (Cassell, Shaw & Stern, 1973; Evarts, Teravainen, & Calne, 1981; Teravainen & Calne, 1980). According to studies of the psychomotor performance of Parkinson subjects, in comparison with the motor component of a task (movement time), the preparation to action (central component or reaction time) seems to be less affected by the disease (Evarts et al., 1981; Marsden, 1982; Teravainen &

Calne, 1980, 1981). Consequently, with respect to their response to drug treatment, the central component would show less improvement than the motor one.

Rationale

Studies of the psychomotor behavior of Parkinson subjects are relatively few, and the ones that have been reported dealt mainly with the gross motor performance of the Parkinson subjects, used simple tasks and assessments were made when under drug control. Only one experiment has dealt specifically with the ability of Parkinson subjects to respond to tasks of different levels of difficulty. Indeed, Evarts et al. (1981) attempted to verify whether people suffering from Parkinson's disease had any specific problems initiating motor responses for simple or choice reaction tasks. The results of this study suggested that Parkinson subjects were, in fact, significantly slower than normal subjects at initiating simple responses, but were no different at reacting to more complex signals. The findings of this experiment were not conclusive since the authors themselves suspected the choice reaction time task to be too simple to enable an assessment of some decision making disorders accompanying Parkinson's disease.

Thus, by increasing the complexity of the task, and by considering the performance of Parkinson subjects when "on" and "off" medication, a more complete analysis of the impact of Parkinson's disease is expected, as well as the impact of drug treatment on both the decision making and the motor control abilities. The use of a complex motor task might provide indices as to what extent: 1) Parkinson's disease implies decision making and/or motor decrements, and 2) drug treatments contribute to alleviating or masking these deficits.

Statement of the problem

The basic purpose of this study was to assess the ability of Parkinson subjects to perform a complex motor task. Specifically, to assess their ability to make simple and complex decisions (involving choice), and their ability to produce fast precise movements. A sub-problem was to assess their performance when they were "on" and "off" medication. This latter step was in order to help separate the impact of Parkinson's disease itself on the motor and cognitive aspects of motor control from drug mediated responses.

Hypotheses

The hypotheses to be tested in this study were:

- 1) Parkinson subjects are significantly slower than matched control subjects when making simple decisions (simple reaction time),
- 2) Parkinson subjects are significantly slower than matched control subjects when making choice decisions (complex reaction time),
- 3) Parkinson subjects are significantly slower than matched control subjects when moving to targets at shorter distances (movement time),
- 4) Parkinson subjects are significantly slower than matched control subjects when moving to targets at longer distances (movement time),
- 5) The performance of Parkinson subjects is significantly slower when "off" medication for reaction time.
- 6) The performance of Parkinson subjects is significantly slower when "off" medication for movement time.

Definition of terms

- 1) *Reaction time*: the time interval from the presentation of a stimulus until the initiation of a motor response. It was used as a measure of cognitive function (decision making).
- 2) *Central processing*: decision making processes implying perceptual judgement and motor planning. This central activity involves the highest mental functions (cognitive functions) situated at the cortical level. Reaction time was used as a measure of the ability of the individual to process information related to making decisions.
- 3) *Movement time*: time interval from the initiation of the motor response until its completion. This measure reflects the subcortical (basal ganglia) involvement in motor actions and their control.
- 4) *Akinesia*: inability to initiate voluntary and spontaneous motor responses.
- 5) *Bradykinesia*: slowness of movement.
- 6) *Bradyphrenia*: slowness of thought.
- 7) *Hypokinesia*: total symptom complex of difficulty in starting movements (akinesia), slowness in executing movements (bradykinesia), reduction of associated movements (decreased amplitude) and clumsiness of fine movements.
- 8) *On-off phenomenon*: very sudden deterioration and improvement in bradykinesia and akinesia, in which freezing may occur suddenly and then later almost as quickly recover.

Delimitations

The population for this study was limited to a small number of Parkinson subjects (7 subjects). They were specifically at mild to moderate stages of the disease (i.e., at stage 2 or 3 on the scale used at the Parkinson's Clinic of the Ottawa Civic Hospital), they were free of any major physical and mental health problems, and were under drug treatment. The type of antiparkinsonian drug and the duration of therapy were not controlled.

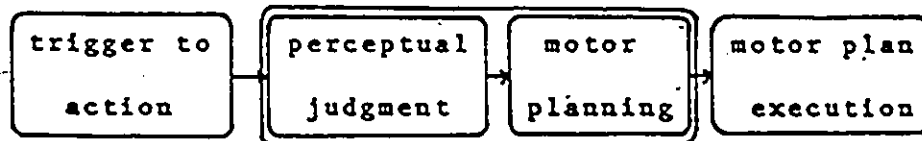
For obvious ethical reasons, it was impossible to ask of the patients, that they withdraw completely from the benefit of their medication and this, without the presence of a physician.

For practical reasons, both groups could not be tested under the same conditions. Indeed, the Parkinson group had to be tested at home while the control group was tested at the University. Moreover, we had to readjust the testing schedule of the Parkinson subjects according to their own working schedule in order to encourage their participation.

Since we were assessing the fine motor performance of the subjects on a very specific task (Tracometer), the results of the present study cannot be generalised to other tasks.

REVIEW OF LITERATURE

The division of total response time into central and peripheral processes allows a better understanding of the psychomotor activity underlying movement control. Consequently, when movements are impaired by the presence of a disease, the use of total response time may then help to clarify the role of the affected structure(s) during normal motor performance. The execution of a motor action, as suggested by Marsden (1982), involves:



The more complex the task becomes, the longer will be the central processing activity required to fulfill the adequate motor output.

As a basal ganglia disease, Parkinson's disease leads to specific motor deficits which interestingly, resemble those observed in much older normal individuals (Mortimer, Pirozzolo, Hansch, & Webster, 1982a). In the light of the large number of studies dedicated to motor control, Parkinson's disease, and aging, and in order to provide a better understanding of the overall process of motor control and cognitive function, this review of literature is divided into five sections, under two main headings. Part one is composed of two sections intended to clarify the general features of Parkinson's disease and the attempts made to alleviate its symptoms. Part two considers each component of total reaction time in order to determine at what level(s) the deficits are likely to be found, and

to what extent they may contribute to hypokinesia. More specifically, the first section aims at presenting the profile of the parkinsonian population to be studied. The second section deals with drug treatment and drug effects. Finally, sections three to five detail each component of Marsden's model of motor action.

PART ONE

Section 1: Parkinson's Disease

Parkinson's Disease and parkinsonism.

Parkinson's disease is often confounded with "parkinsonism" which is the manifestation of parkinsonian symptoms but following a different disease process. Many classifications of parkinsonism are available (Barbeau, Roy & Boyer, 1984; Duvoisin, 1977, 1984; Mortimer & Webster, 1982b; Zetuský, Jankovic & Pirozzolo, 1985) and the following provides a brief description of the main differences between the underlying deficits.

Generally speaking, there are four groups of parkinsonism namely, idiopathic, genetic, symptomatic, and postencephalitic. The first type, known as Parkinson's disease, is an irreversible degenerative disease of the basal ganglia which starts around age 50-60 and whose aetiology still remains unknown. The subsequent positive and negative deficits following the severe loss of dopaminergic neurons around the nigrostriatal bundle, become progressively more disabling as the disease progresses. The second type, source of controversies, is called "genetic parkinsonism". Indeed, while some consider its incidence as exceptional (Bannister, 1985), others maintain that family history of parkinsonism still represents 10 to 15% of the parkinsonian population (Barbeau et al., 1984; Cambier, Masson & Dehen, 1982; Duvoisin, 1977, 1984; Grimes, 1983). The third type of parkinsonism is called "symptomatic" because of the fact that parkinsonian symptoms become manifest following a malfunctioning of, or damage to brain structures and not due

only to the degeneration of the substantia nigra. This type includes multiple aetiologies such as the presence of arteriosclerosis, the sequels of brain trauma or ischemia; the presence of another disorder of the central nervous system and finally, to the side effects induced by some drug treatments (iatrogenic cause) or by exposure to toxins such as carbon monoxide. The last type, postencephalitic parkinsonism, is different from the symptomatic types for it is a sequel to a viral infection of the brain. In other words, the underlying disorders leading to parkinsonian deficits may be considered either as primary (degeneration of the substantia nigra) or secondary disorders (misFunctioning of the substantia nigra due to subsequent disorders of other structures). According to Rinne, Koskinen and Lonnberg (1980), there would be "no doubt that the progressive loss of dopaminergic substantia nigra neurons and the deficiency of the striatal dopamine play essential roles in the pathophysiology of Parkinson's disease but other neurons in the neuronal interaction of the extrapyramidal system may also be involved either primarily or as a secondary consequence".

Positive and negative symptoms.

The symptoms accompanying this basal ganglia disease are also classified as negative or positive deficits. As suggested by Cote (1982a), negative symptoms are primary functional deficits attributable to loss of specific neurons, while positive symptoms are secondary to the emergence of abnormal patterns of action in otherwise normal neurons when part of their controlling input is destroyed by the disease.

As mentioned by Gibberg (1986, p.333), "hypokinesia is probably the most important symptom and can be described as slowness or poverty of movement. There is a decrease in spontaneous movement so that when movement does occur, it takes place slowly (bradykinesia), and changes in motion are avoided or found difficult (...). Associated with bradykinesia is akinesia which relates to slowness or difficulty in initiating movement."

In Parkinson's disease, akinesia and bradykinesia are examples of negative deficits. These key motor abnormalities are indicative of a dysfunction of the basal ganglia (Marsden, 1984). Indeed, the inhibitory function of the nigrostriatal pathway is released due to a severe loss (70 to 90%) of the dopaminergic nerve cells into the substantia nigra (Birkmayer, Danielczyk, & Riederer, 1983; Cote, 1982a; Marsden, 1983; Mortimer & Webster, 1982b). - Once the pathway is destroyed, this inhibitory activity does no longer permit the efficient control of movement. This leads to problems with the initiation and execution of voluntary movements and to the loss of automatic movements (Angel, Alston, & Higgins, 1970). Manifestly, the performance of normal daily activities is modified. For instance, walking (stooped posture, no swing of the arms,...), talking (no facial expression, soft disarticulated voice,...) and writing (micrographia) undergo modifications (Duvoisin, 1984; Grimes, 1983). The affected motor system appears to lack spontaneity and drive. The extremities seem lazy and require constant coaxing to act (Angel et al., 1970). At the later stage, the parkinsonians activities may even be marked by multiple halts and stalls commonly called "freezing episodes" (Grimes, 1983). These periods of immobility are inherent to the illness. They are more likely to appear at moderate and severe stages of an untreated Parkinson's disease, but they are also an indication of an end-of-dose deterioration (or wearing off effect) (Marsden, 1976, 1984).

Tremor and rigidity are other motor features of Parkinson's disease. They are both considered as positive symptoms. Tremor is a dominant symptom though it is less disabling (Grimes, 1983; Zetuský et al., 1985). It also tends to be the motor disorder the most independent of the other motor signs (Zetuský et al., 1985). It is characterized by a rhythmical oscillatory movement (3 to 7 Hz) resulting from alternating contractions of antagonistic muscles (de Lean, 1983). It usually affects small muscle groups such as fingers, lips, tongue and larynx (Bannister, 1985; Bradley, 1984). This resting tremor increases with stress and decreases with voluntary movements (Bradley, 1984; Grimes,

1983). Rigidity, meanwhile, would result from current stimulatory and inhibitory neuromuscular activity (Birkmayer et al., 1983). This hypertonia seems to affect the agonists and the antagonists almost equally (Gibberd, 1986). Resistance to passive movements is widespread and especially evident in the larger joints. Contrary to tremor, rigidity is more likely to affect large muscle groups (Bradley, 1984). It seems to stay uniform throughout the whole range of movement.

Years ago James Parkinson (1817) defined the disease as "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses of intellect being uninjured" (Bradley, 1984). Although almost all authors are in agreement regarding their conclusions as to the presence of motor deficits following Parkinson's disease, there is less agreement around the possible cognitive decrements accompanying this basal ganglia disease. Indeed, several authors such as Benson (1984), Birkmayer et al. (1983), Hansch, Syndulko, Cohen, Goldberg, Potvin and Tourtelotte (1982), Rafal, Posner, Walker, and Friedrich (1984) and Wilson, Kaszniak, and Garron (1980), have suspected the presence of cognitive dysfunctions in parkinsonians.

Cognitive deficits.

Whether patients with Parkinson's disease inevitably exhibit specific or general cognitive abnormalities is a controversial issue. It seems that some proportion of the Parkinson population develops cognitive dysfunctions, but the causes underlying these changes are not elucidated yet. Indeed, according to Marsden (1982), these changes in cognitive functions may be due to drug treatment, or to dopamine deficiency somewhere else in the brain.

Cognitive functions are concerned with recognition, perception, identification, understanding, imagination learning and thinking (Marsden, 1982). While certain components of cognition may show decrements with Parkinson's disease, they cannot be fully related to a global state of dementia which is "usually characterized by decreased intellectual functions, impairment of judgement, confusion, disorientation and severe short and long term memory deficits" (Bentin, Silverberg & Gordon, 1981). Indeed, in light of Benson's work (1984), a subdivision of this global state of dementia into two components has been proposed namely, subcortical and cortical types of dementia. According to this author, the mental impairments associated with Parkinson's disease resemble subcortical deficiency. For instance, a parkinsonian will show an abnormal verbal output, poorly articulated and hypophonic but will tend to maintain lexical and syntactical competency until very late in the course of the disease. Concerning the mental status, the individual will tend to show memory dysfunction, abnormal cognitive processes such as the degradation of cognition, judgement and abstracting which gradually become slow, hesitant and incomplete. The term "bradyphrenia" is often used to describe this slowness at which parkinsonians process information (Birkmayer et al., 1983; Hansch et al., 1982; Rafal et al., 1984). Meanwhile, even though bradyphrenia is a cognitive dysfunction, it does not refer to intellectual impairment. Finally, as another indice of subcortical disorders, there is the "classic triad" of motor deficits, i.e. tremor, rigidity, and bradykinesia, which are peculiar to Parkinson's disease.

Most patients, sooner or later show some degree of subcortical type of dementia (Benson, 1984; Marsden, 1984; Matthews & Haaland, 1979). Some individuals may also develop cortical dementia as a second superimposed disturbance (Benson, 1984). Even though this cognitive impairment seems to be milder than the motor ones, subtle changes such as lack of spontaneity, poverty of imagination and a tendency for repetition have been noticed even at earlier stages of Parkinson's disease (Lees & Smith, 1983), but still,

greater changes appear to be more common in patients with symptoms lasting for more than six years (Marsden, 1982; Matthews & Haaland, 1979).

At light of these studies, cognitive decrements are suspected to be a feature of the parkinsonian syndrome, but it emerges a point of contention regarding which levels of cognition are more likely to be affected by the disease and whether these decrements may seem as primary or secondary deficits.

Aging effects.

Generally, Parkinson's disease is more likely to affect older individuals. It occurs at a time where the aging process has already engraved its marks. There is considerable evidence that morphological and biochemical changes associated with brain aging share many features with those seen in parkinsonism, the major distinction being the severity, the rapid progression and the earlier manifestation of these changes in Parkinson's disease (Mortimer & Webster, 1982b). Thus, part of parkinsonian deficits may be accounted for by the normal aging process (Garron, Klawans, & Narin, 1972; Loranger, Goodell, McDowell, Lee, & Sweet, 1972; Mortimer & Webster, 1982). McGeer, McGeer, and Suzuki (1977), who looked at the effect of aging on the extrapyramidal structures, suggested that the normal aging process was a tendency towards a parkinsonian like condition. For instance, at the motor level, slowness and hesitancy of most movements, fine tremors of the hands, chin and/or head, are seen in the three quarters of patients between age 70 and 101 (Barbeau, 1973). At the cognitive level, several components of cognition may undergo similar phenomena namely, the speed of processing information, memory, judgement, perception and intellectual functions.

Intellectual deficits

In a study conducted by Garron et al. (1972), the intellectual ability of 47 parkinsonians was compared with age-matched controls. The test designed for assessing the problem solving ability of the two groups was the Guilford Comprehensive Model of Intelligence. The conclusions from this research revealed that, in addition to aging effects, parkinsonians suffered from cognitive deficits in that they showed a greater bradyphrenia and intellectual decrement than their age-matched counterparts. Similarly, Loranger et al. (1972) attempted to verify whether Parkinson's disease was accompanied by intellectual impairments. For this experiment, 63 idiopathic parkinsonians (moderate to severe) (Hoehn & Yahr, 1967) underwent the standardized Weschler Adult Intelligence Scale test (WAIS). The results suggested that, compared to their control group suffering from depression, and compared to the corresponding WAIS values for their age group, the additive effects of aging, depression, peripheral motor disability, anticholinergic drugs and surgery could not entirely account for parkinsonians' intellectual impairments. Thus, structural changes associated with the syndrome were suspected to be implicated.

Perceptual deficits

As an element of cognitive dysfunction, perceptual deficits have also to be distinguished from intellectual impairments. Perception refers to the ability to consciously discriminate external sensory information. In the course of the parkinsonian syndrome, specific perceptual deficits occur. Indeed, two elements of the visuospatial system are particularly affected notably, the visuo-perceptual and the visuo-motor systems. According to Boller, Passafiume, Keefe, Rogers, Morrow and Kim's work (1984), visuospatial impairment, although not obvious at the first sight, would occur in up to 93% of parkinsonians. It is manifested by a failure to set lines to an axis similar to the model, a

difficulty to touch part of their body or to perform a route walking test. When exploring the respective roles of the visuo-perceptual and the visuo-motor factors in the visuospatial behavior of 30 parkinsonians (matched for age, sex, and education level to 30 controls) Boller et al. confirmed that both elements of the visuospatial function were impaired. All subjects were administered 14 visuospatial tests which included "visuo-perceptual" tasks, requiring minimal motor responses, and "visuo-motor" tasks. Interestingly, this decline seemed not to parallel the severity of the motor decrements which gradually get worse with time.

Other studies came to support Boller's findings as to the presence of the visuospatial impairment in Parkinson's disease (Delis, Dierenfeld, Alexander & Kaplan, 1982; Lees & Smith, 1983; Mortimer, Pirozzolo, Hansch, Webster, 1982a; Portin & Rinne, 1979; Stern, Mayeux, Rosen, Ilson, 1983). But since they mainly relate to the effects of drug therapy on cognitive performance, details about their results will be given in the following section.

Bradyphrenia.

Bradyphrenia is another cognitive defect that is likely to occur during Parkinson's disease. In 1972, Garron et al. observed that while comparing the intellectual ability of parkinsonians with their controls matched for age, sex, and education level, the former group tended to show greater slowness of thought and greater intellectual decrement than the latter. Later on, Wilson et al. (1980) attempted to reexamine this notion of bradyphrenia. For this, they picked 20 subjects with parkinsonism (medicated), and they matched them for age, sex, education level, and for verbal intellectual quotient with 16 normal controls. Also, in order to look specifically at the additive effect of aging, both groups were divided into two subgroups namely, the 64 and under and the 65 and over. All subjects underwent the "Sternberg Character Classification Paradigm" test which was

used to measure the speed and accuracy of short-term memory scanning. By way of a motor response the subjects only had to answer by pressing a "yes" or a "no" key. The results that came out of this study revealed that parkinsonian patients were slower than the controls but also that the "older" ones were slower at short-term memory scanning than their young counterparts. Knowing that young and old parkinsonians did not differ in number of medications, types of medication, or length of therapy suggested that mnemonic slowing seen in the elderly patients was more attributable to parkinsonism and advancing age than to the drugs. According to the authors, the term bradyphrenia might be an apt descriptor of this deficit.

Because they suspected that the motor responses required by the parkinsonians during certain cognitive evaluations could possibly contaminate the results, Hansch et al. (1982) used another technique to measure the central processing changes occurring in parkinsonians under drug treatment, as compared to the ones of the normal subjects. They used the long-latency positive component of event-related potentials termed P300 which is thought to reflect the information processing-related activities in humans and which may provide an objective means to evaluate cognitive function independent of specific motor responses. For this experiment, 20 male patients with idiopathic parkinsonism (mild to moderate) were compared to 20 age-matched normal controls. In addition to the auditory event-related potential parkinsonians were administered a short set of five neuropsychological tests to correlate psychometric and electrophysiological indices of their cognitive function. One of the findings of this study was the strong correlation between P300 and the Symbol Digit Modalities test. This test is a substitution test involving manipulation of both language and non-language symbols, learning and memory, visuospatial perception, and oculomotor scanning. It seems to be highly sensitive to brain dysfunction. Thus, compared to their controls, parkinsonians would have shown a slower speed of neural processing suggesting once more the presence of bradyphrenia.

Knowing that motor and neuropsychological deficits are present in Parkinson's disease, Mortimer et al. (1982a) attempted to ascertain whether the severity of the motor symptoms was associated with the degree of neuropsychological deficit. For this, they assessed the motor and neuropsychological abilities of 60 idiopathic parkinsonians compared to 60 controls matched for age, sex and education level. The motor tests consisted of measuring rigidity, tremor, and bradykinesia. The four neuropsychologic tests assessed fund of information, verbal memory, psychomotor speed and visuo-spatial performance. The results suggested neuropsychological deficits in short and long term memory, in complex visuospatial perception and reasoning. Also, according to the authors, only bradykinesia and tremor would be significantly related to the degree of neuropsychologic impairment and not rigidity. However, this statement must be qualified since the parkinsonians were under drug therapy and rigidity is highly responsive to drugs.

Conclusion.

Generally speaking, Parkinson's disease is considered as a basal ganglia disease which gradually leads to specific motor and cognitive decrements. In addition to the defects associated with the degenerative process of the syndrome, other factors such as aging and drug treatment may interfere. Indeed, the illness is more likely to affect the elderly and the use of drugs is quite necessary to alleviate the symptoms peculiar to this disease.

Section II: Drug treatment and drug effects

Dopamine.

As previously mentioned, Parkinson's disease is a disease of the basal ganglia which affects more specifically a pigmented nucleus called the substantia nigra. The dorsal zone of this nucleus, the zona compacta, uses dopamine as a neurotransmitter and forms the nigrostriatal pathway (Cote, 1982a). Dopamine is stored in the cells and fibers of the substantia nigra until released to function as a chemical messenger to other nerve cells (Duvoisin, 1984). With its inhibitory function, it plays a key role in neurotransmission within the basal ganglia; it mediates the balance between inhibitory and excitatory outflow from the nervous system (Beart, 1984). In fact, dopamine acts to restrain the acetylcholine nerve cells which are excitatory (Duvoisin, 1984).

During the normal aging process, from birth to age seventy-five, about half of the dopaminergic neurons of the substantia nigra degenerate (Mortimer & Webster, 1982b). However, in Parkinson's disease, the loss is much more severe. In fact, 75 to 90% of the functioning neurons in the zona compacta of the substantia nigra may have been destroyed (Birkmayer et al., 1983; Cote, 1982b; Mortimer & Webster, 1982b). This destruction leads necessarily to the degeneration of the nigrostriatal fibres (Cote, 1982a) and to specific disorders such as the symptoms previously described.

Antiparkinsonian drugs.

In order to alleviate the debilitating features of Parkinson's disease different drug treatments have been prescribed. The use of antiparkinsonian drugs aims either to replenish the brain dopamine deficiency, to mimic its action, to damp down or to block cholinergic activity. Consequently, they contribute to reduce the severity of the symptoms (Duvoisin, 1984).

Generally speaking, there are two groups of antiparkinsonian drugs notably, anticholinergic and dopaminergic drugs. The former block the action of acetylcholine whereas the latter enhance or imitate the action of dopamine (Duvoisin, 1984). The first group includes drugs such as Artane, Cogentin and Symmetrel. The second one includes Levodopa (L-Dopa) and Bromocriptine. No specific drug is likely to be constantly efficient on a long term basis. Indeed, when a parkinsonian has reached the peak dose effect of a certain drug and no longer obtains benefits from it; then, changes in drug therapy are needed. In order to optimize the treatment, combinations of drugs are commonly used. For instance, a combination of levodopa (precursor of dopamine in the central nervous system) with a decarboxylase inhibitor such as Carbidopa (L-Dopa/Carbidopa = Sinemet) prevents the transformation of L-Dopa to dopamine before reaching the brain. That way, about 80% less L-Dopa is needed to achieve the optimum therapeutic benefits, while strict ingestion of levodopa permits only 0.1% of the oral dose to reach the brain (Cote, 1982a). The concentration of levodopa into the blood seems to take on particular importance during the treatment. Indeed, this assumption has been verified by Shoulson, Glaubiger and Chase (1975) when they compared oral versus intravenous doses of levodopa administered to seven idiopathic parkinsonians (moderate). During this experiment, the clinical features of each patient were assessed every 30 minutes for a period of nine hours. Blood samples were also taken at regular intervals in order to correlate clinical features to plasma dopa concentration. For the group on oral doses, the concentration of levodopa fluctuated and was also followed by fluctuations in motor function. In the second group, the blood concentration in levodopa was more stable and no marked swings were observed. Similar results have been reported by Sweet and McDowell (1974). Thus, higher blood level of levodopa would allow for greater entry into the brain where it is converted into dopamine (Fahn, 1974).

Drug effects.

As previously mentioned, drug therapy aims at alleviating parkinsonian symptoms since it is unable to cure the underlying causes. Meanwhile, the beneficial effects of drug treatment seem not to help equally all parkinsonian symptoms. Unfortunately, no drug therapy has yet contributed to totally improve parkinsonian symptoms. Both short and long term treatments seem to lead to the occurrence of side effects, sometimes quite disabling for the patients. Although it was thought to be a miracle-drug at the time of its advent in the early 1970's, levodopa therapy follows the same pattern.

Among the motor symptoms, rigidity appears to be the most responsive feature. It is followed by tremor, which is usually relieved at 80% (Duvoisin, 1984). Concerning bradykinesia, it seems to be abolished as long as the syndrome is not too severe, but at the later stages of the disease, it tends gradually to be increasingly resistant to drug therapy (Duvoisin, 1984). Obviously, rigidity, tremor and bradykinesia are more likely to affect motor performance. Akinesia still remains the symptom which seems to rarely respond to the drugs that benefit the other symptoms (Angel et al., 1970). As to the cognitive components, some elements appear more likely to improve with the ingestion of drugs while others either deteriorate or remain the same.

Quite recently, the impact of levodopa treatment on parkinsonian patients has been studied by Shaw et al. (1980). In this research, 178 idiopathic parkinsonians were treated with levodopa for a period of six years. The results indicated that 70% of the patients showed an initial improvement of their total disability scores as measured by the Columbia University Disability Rating Scale. Six years later, from the former number 20% were still better than before treatment. As to the remaining group, they started suffering from involuntary movements which increased in severity and in frequency as treatment continued. Among the complications, end-of-dose deterioration occurred in 65%

of patients, "on-off" phenomena (unpredictable oscillations in motor performance) in 10% and 32% developed unequivocal dementia. In conclusion, the authors suggested that those complications might be due to an excessive stimulation of the dopamine systems since high doses were administered.

In spite of their side effects, drug treatments such as levodopa therapy could contribute to increase the quality of life and probably life expectancy for the majority of patients with idiopathic Parkinson's disease who are able to tolerate the drug for longer than two years.

Effects of drugs on motor deficits.

More specifically, some studies have been dedicated to look at the effects of drug treatment on the motor function of parkinsonians.

Earlier in the 1970's, when the advent of L-Dopa was quite recent, Knutsson and Martensson (1971) attempted to look at the quantitative effects of levodopa on different types of movement and muscle tone in parkinsonians. Twenty one patients (19 idiopathic and 2 postencephalitic), classified as mild to severe parkinsonians, were clinically assessed during seven to eleven weeks. This clinical assessment evaluated functional disability, physical signs, tremor, rigidity, hypokinesia, manual skills, gait recordings and muscle tone. From the results it was found that following drug therapy, marked improvements were seen for rigidity and for voluntary movements such as manual dexterity. On the other hand, automatic movements, such as the swing of the arms when walking, appeared not to be modified.

Later on, Matthews and Haaland (1979) undertook a study of the relationship between the symptom's duration and the degree and rate of progression of behavioral

impairment of parkinsonians under treatment. For this experiment, 42 male parkinsonians were divided into three groups of different symptom durations, i.e. two years and under, three to five years, and finally six years and over. They were compared to a control group matched for age and education level. Two batteries of tests were administered notably, five tests for measuring cognitive function and psychometric intelligence, and five tests for assessing motor proficiency. The principal findings were that motor tasks underwent a dramatic, consistent and progressive decline in the course of both the process of the disease and the long-term treatment.

"On-off" phenomena

Thus, drug therapy tends to be quite successful in alleviating parkinsonian symptoms at first but afterwards, the results seem to be less outstanding. Indeed, not only do the patients respond less well to treatment but eventually, they will develop side effects such as the "on-off" phenomena. On-off phenomena are in fact more likely to appear after two or three years of drug therapy (Damasio, Castro-Caldas, & Levy, 1973; Shaw et al., 1980; Sweet & McDowell, 1974). This phenomenon is defined as rapid, unpredictable, and dramatic fluctuations in motor ability (Sweet & McDowell, 1974; Fahn, 1974). It is related in part to the duration of levodopa therapy and in part, to the progression of the disease (Damasio et al., 1973; Marsden, 1980; Shoulson, Glaubiger, & Chase, 1975). Before reaching its severe form, the "on-off" phenomenon goes through milder states such as: early morning akinesia, freezing episodes, end-of-dose deterioration or wearing-off effect (Marsden, 1976). According to certain studies, up to 50% of patients treated for more than five years would be affected by the on-off episodes (Damasio et al., 1973; Marsden, 1980; Shoulson et al., 1975; Sweet & McDowell, 1975). However, other authors maintained that 10% will eventually develop on-off (Shaw et al., 1980), while some found

an on-off incidence as low as 2.8% (Birkmayer et al., 1975). The possible reasons for this lie in the fact that different daily doses of levodopa were administered to the experimental groups. Thus, if the amount of the prescribed drug did not exceed the maximum tolerated by the patients, then a smaller percentage of them were likely to undergo on-off episodes.

As mentioned earlier in this section, a high plasma concentration in levodopa appears to be very important for the control of parkinsonian symptoms. Surprisingly however, on-off episodes seem to occur even at peak dose effect. They may last from a few minutes to two hours (Damasio et al., 1973). According to the same author, on-off phenomena differ from "freezing" episodes in that they are longer, more intense, and also a more complex period of akinesia with rapid onset and termination.

Antiparkinsonian drugs for a parkinson-like condition.

Knowing that antiparkinsonian drugs contributed to alleviate parkinsonian deficits, and knowing also that aging led to a parkinsonian-like condition, Newman, LeWitt, Jaffe, Calne and Larsen (1985) attempted to determine whether or not there was a relationship between normal motor deficits and Parkinson's disease by observing the effects of levodopa in healthy elderly. For this experiment, ten healthy seniors (59 to 72 years old) were matched with ten parkinsonians under drug treatment (Sinemet). The experimental group undertook a six week treatment at the rate of eight doses a day up to a total of from 200 mg to 800 mg per day. Half of the normal group was on a placebo. In order to assess the motor function of their subjects they administered the Columbia University Rating Scale as well as objective measurements of velocity, reaction time and tremor. These tests were repeated three times per phase (two phases). Interestingly, no major changes were found. Thus, although levodopa seems effective in relieving disorders of gait, posture and bradykinesia in Parkinson's disease, the dose was not adequate for the mild extrapyramidal impairment of normal elderly.

To summarize the effects of drugs on the motor dysfunction of parkinsonians, one may say that they certainly contribute to alleviating the symptoms but because of the evolution of the disease, and because of the habituation effect to these drugs, higher doses will be constantly required and eventually, when doses go beyond the maximum tolerated by the patients, side effects such as on-off episodes will be more likely to occur.

Effects of drugs on cognitive decrements.

Since motor and cognitive dysfunctions are considered as features of Parkinson's disease, it is then reasonable to expect that cognitive deficits respond the same way to drug treatment. Recently, Rafal et al. (1984) undertook to verify this hypothesis by comparing bradyphrenia and bradykinesia after doses of levodopa. Ten idiopathic parkinsonians were assessed motorically (speed of performance) and cognitively (information processing performance) by means of three different tests namely, speed of short-term memory scanning, of visuospatial orientating, and speed of information processing prior to voluntary movement. The results of this research revealed that the motor response was improved following a drug treatment, that these changes occurred without any evidence for cognitive improvements. In other words, there would be no change in bradyphrenia linked to bradykinesia or its alleviation by drug therapy.

Short-term treatment.

Probably one of the first to have shown interest in looking at the cognitive changes associated with levodopa therapy were Beardsley and Puletti who, in 1971, undertook to compare this new therapy with the conventional ones, i.e., the thalamotomy and the anticholinergic drugs. For this, two groups of parkinsonians were used. The experimental

group, or levodopa group, (but still on anticholinergic drugs), after one month's treatment with levodopa, and finally, approximately six months after the second test. Concerning the control group, they were tested twice; first, just before a thalamotomy or initiation of drug therapy other than levodopa, and second, six months later. The psychometric tests they had to undergo were the Minnesota Multiphasic Personality Inventory (MMPI) and the Wechsler Adult Intelligence Scale (WAIS). The findings of their study suggested that with levodopa no changes in personality (depression or motivation) were detected whereas at the cognitive level the specific effects were limited to an improvement of the abstract and verbal functions.

Long-term treatment.

Approximately five years after the advent of levodopa, Ricklan, Whelilan and Cullinan (1976) undertook to verify if this drug treatment was still benefiting the parkinsonians. One hundred and ninety two subjects participated in the study and were divided into four groups. The first one, the experimental group, was composed of 40 parkinsonians (mean age=65.3) who had been on levodopa for at least four years. The three other groups were used as controls; there was one group of 30 parkinsonians (mean age=66.4) who were not on levodopa, also a group of 48 patients (mean age=62.7) on levodopa for a short period of time, i.e., one to two years, and finally a group of 44 normal individuals (Mean age=65.1). Four tests were administered to all subjects notably, the WAIS, the Wechsler Memory Scale, the Bender Gestalt and the Cortical Flicker Fusion test. Because the age, sex and education levels of the subjects were equated as closely as possible, the results showed very few differences in psychometric performance between the three parkinsonian groups. Generally speaking, the long term group performed better than the other parkinsonians but the improvement seen at the early stages of the treatment

seemed not to persist later on. Concerning specific levels of the cognitive function such as the intellectual and mnemonic deficits, it seemed that they were not significantly altered by drug therapy.

Similarly, Portin and Rinne (1979) considered the long term effect of levodopa therapy on the neuropsychologic functions of parkinsonians but more specifically, they investigated the nature of the cognitive and emotional dysfunctions of 79 parkinsonian patients at four specific stages of the treatment, namely, before levodopa therapy, two to three months after, at two to three years and at eight to ten years. At each of these stages, six neuropsychologic tests were administered in order to assess 1) verbal and visuospatial skills (WAIS), 2) verbal regulation, 3) perceptual regulation, 4) motor learning, 5) memory and 6) personality variations. The general findings suggested that significant changes in mental function took place during the course of the treatment. Indeed, the pre-treatment test revealed that parkinsonians were below their control group before starting. The first year was marked by a significant improvement of the neuropsychologic functions although not up to the normal level. The second and third years showed a progressive decline, which later stabilized afterwards, but not below the pre-treatment level. Globally, cognitive functions such as perception, intellectual capacity and memory, as well as motor skills tended to deteriorate after two to three years of levodopa treatment.

While Portin and Rinne (1979) observed that, on a long term basis, levodopa led to a decline in both cognitive and motor capacity, Matthews and Haaland (1979) attempted to see if there was a relationship between the symptom duration and the degree and rate of progression of behavioral impairments in parkinsonians. They assessed three groups of 16 patients with different symptoms durations, i.e., two years and less, three to five years, and six years and over. The performance of these patients was compared to the one of 16

normal individuals matched for age and education level. Five tests were used for measuring psychometric intelligence and cognition (WAIS, Halstead Category test, Seashore Rhythm, Speech Perception, and Trail Making) whereas five others assessed motor proficiency (grip strength, static steadiness, maze coordination, finger tapping speed and grooved pegboard). As a general rule, parkinsonians performed less well than the controls. Indeed, all three groups' psychometric test scores declined with increased symptom duration. The major significant difference was found between the control group and groups two and three in performance IQ, which was measured by WAIS (based on speed, motor coordination and visual perceptual skills). Group two was not significantly different from group three in that only mild decrement appeared in the cognitive measures after three years on levodopa therapy. In addition, even in group three, where they were significantly more common, cognitive impairments were still minimal in comparison to motor deficits.

Cognitive functions during on-off episodes.

In order to look at what was happening to cognitive functions during the on-off phenomenon, 16 severe parkinsonians matched for age, sex, education and intellectual ability with 25 control subjects were administered two versions of the Modified Alice Heim test during both the on and the off episodes (Marsden, 1984). This test examined the intellectual capacity of the patients and required a minimal motor response in order to avoid the contaminating effects of changes in motor performance. Finally, the results suggested that no obvious deterioration in general intellectual abilities occurred even when the subjects became grossly immobile.

Marsden's findings agree with those of Delis et al. (1982), but some precaution has to be given towards this final study since it is a "case study". The possible fluctuations in

cognitive functions from the "on" to the "off" episodes were assessed in a severely affected parkinsonian. He underwent a series of neuropsychologic assessments and because of the severe "off" episodes, only verbal responses were required by the patient. The tests evaluated his attention, mental control, and finally, his verbal fluency. The results of this analysis revealed that, contrary to motor function, there was no dramatic fluctuation in cognitive levels from the on to the off episodes. Meanwhile, some changes did occur, for instance, long-term memory showed mild impairment and intellectual processing slowed down.

Conclusion

In brief, Parkinson's syndrome is a disease that leads gradually to severe and debilitating features. Among the therapies that have been used to alleviate its symptoms, drug treatment seems to be the most effective one. However, despite the use of such treatment, the disease continues to progress, and this leads to the eventuality that from the additive effects of both the disease and the long-term therapy subsequent problems arise, such as "on-off" episodes.

This first part of the review of literature was designed to present Parkinson's disease, its features and the way parkinsonians react to treatment. The following section deals with the assessment of the cognitive and motor deficits of parkinsonians by means of fine motor performance.

PART TWO

As mentioned earlier, Parkinson's disease is seen as a degenerative disease of the basal ganglia. By considering the cognitive and motor deficits that accompany this illness, it may be possible to suggest some of the roles played by these subcortical structures during the preparation and execution of a motor task.

Generally speaking, parkinsonians have difficulty in initiating movement (akinesia) and their motor outputs are executed slower than normal (bradykinesia). These impairments are responsible, respectively, for the increase in reaction time and for the slowness of movement time. By studying changes in the course of different tasks, one may obtain some indices about the extent and at what level basal ganglia structures are involved in voluntary movements.

Marsden's scheme of motor action suggests four main components: sensory input, perceptual judgement, motor planning and motor output. Meanwhile, for the purpose of this part of the review of literature, these four sections will be reduced to three, namely, sensory input, central processing (perceptual judgement and motor planning) and motor output; all three representing the total time to make a response.

Section I: Sensory input

Movement involves a sequence of events whose first component is often generated by an external stimulus or by an internal intention. In fact, what Heilman, Bowers, Watson and Greer (1976) as well as Sandyk (1982) respectively called "exo-evoked" and "auto-evoked" potentials are no more than environmental stimuli such as visual, auditory, or tactile stimuli, and internal triggers such as spontaneous thought and proprioception.

For voluntary movement, the sensory system is closely related to the motor system. In addition to being a prelude-element to action, it is also involved in its monitoring. Indeed, senses bring to the central mechanism indices about the external environment as well as feedback from motor activity. A defect at the sensory level may contribute to an impaired motor output.

Aging effect.

Knowing that Parkinson's disease is more likely to affect seniors it is noteworthy to look at the effects of aging on the sensory system prior to considering those induced by the disease itself.

Normal aging refers to the manifestation of a progressive decrease in the "speed of behavior" defined as the "speed with which an individual can perform a task which involves reaction motorically to an environmental stimulus" (Spirduso, 1982).

As stated by Welford (1982) "several studies have attempted to measure age changes in the different stages of reaction time from the onset of the stimulus to performance of the response. These studies have shown that speed of conduction in afferent and efferent nerves, although it slows with age, accounts for only a small fraction of the total reaction time, and can for practical purposes be ignored as a source of slowing with age." Moreover, according to Welford, a similar decline of proprioceptive sensitivity would occur in the same way. Thus, exo-evoked and auto-evoked stimuli are both slightly deficient in normal elderly and their contribution to slowness of behavior is negligible compared to that of the central processing components (Birren, Woods & Williams, 1980, Cerella, Poon & Williams, 1980; Welford, 1982).

In the same way, when compared with the value of their healthy age-matched counterparts, the sensory system of parkinsonians seems not to be significantly affected. These are the conclusions brought by Kupersmith, Shakin, Siegel and Lieberman (1982) and Sandyk (1982) who respectively looked at the afferent and the efferent sensory integrity in Parkinson's disease. In attempting to define further the abnormalities in the visual system of parkinsonians, Kupersmith et al. found an increased latency in the visual evoked potential of parkinsonians compared to their normal controls. Suspecting a decrease in speed of nerve conduction, they carried out a neuropathologic examination but failed to demonstrate demyelination or other lesions in the visual system that could have explained the delay. As to Sandyk (1982), he tried to find out whether there were differences in the cortical responses to successive voluntary movements from different areas of the periphery (neck, arm, and foot). His results revealed a greater delay for the extension and flexion of the foot of parkinsonians as compared with their matched controls. Meanwhile, according to Sandyk, this delay was not expected to be caused by a peripheral conduction problem.

At this level one may suspect that the use of drugs has some effect on nerve conduction but according to Damasio et al. (1973), it does not seem to be affected for better or worse by long-term levodopa.

Conclusion.

Thus, it would seem less likely that the deficits seen in parkinsonians could be due to a defect at the sensory level. Even though the sensory integrity does decline with aging, it seems not to be further modified by either the syndrome nor by the drugs used to alleviate the parkinsonians' symptoms.

Section II: Central processing

The efficiency with which an individual can react to a stimulus and be ready to start the motor response is called speed of reaction. This event occurs at the central level and comprises two steps, notably, the perceptual judgement and the motor planning.


Perceptual judgement.

Perception refers to the ability to consciously discriminate external sensory information (Stern et al., 1983) and it would depend upon two processes, namely, the recognition of the information to be perceived, and the suppression of unwanted confusing extraneous information (Marsden, 1982). The issue as to whether these types of perceptual judgement are defective or not in Parkinson's disease remains to be clarified since it is still the object of controversy.

There are mainly two schools of thought: from one, there are those who deny that some defect at the cognitive level may be partly responsible for the motor impairment of parkinsonians and from the other, there are those who accept this eventuality.

According to Marsden (1982), the perceptual judgement of parkinsonian patients would be preserved in the course of the disease. He supports the idea that basal ganglia function in movement is more motor than sensory or cognitive. In fact, Marsden's conclusions emerge from the analysis of several studies whose findings brought some elements susceptible to invalidate the presence of any impairment at the level of perceptual judgement.

Marsden referred to a study by Heilman et al. (1976) in which it was verified that a warning stimulus could contribute to increased arousal in parkinsonians and thus, reduce



their reaction time. The results revealed that effectively, in the presence of a warning signal, parkinsonian patients did not react differently than normal controls and consequently, improved their reaction time (though not-up to a normal level). Sandyk (1982) arrived at the same conclusion regarding the fact that some perceptual functions, such as the level of arousal, were spared in the course of the disease.

By comparing the performance of parkinsonians to that of a normal population for simple and choice reaction times, Evarts et al. (1981) attempted to see whether or not the use of reaction time could be useful to assess the central motor disorders associated with Parkinson's disease. By increasing the difficulty of the task (increased choices) they expected to observe a substantial increase in the time to process the task. However, the results revealed that parkinsonians had no more difficulty dealing with the complex task than people of the same age group. Thus, beside a slowness in initiating movement, parkinsonian patients did not show any particular difficulty in analysing the information. Meanwhile, what Marsden omitted to take into account when he used Evarts' conclusions was that, in their discussion, the authors mentioned the fact that the task they used for the complex reaction time might have been too simple to really detect deficits at the decision-making level (cognitive level).

Marsden also referred to a study conducted by Angel et al. (1970) in which the parkinsonians' ability to correct errors was considered. By means of a step tracking task, they analyzed the time needed to correct a voluntary movement which the subject perceived to be inaccurate. Interestingly, it was noticed that parkinsonians did not tend to make more errors than their controls, they showed no difference in perceiving error signals or in selecting the appropriate response, but the time they needed to stop a false move was much longer than their counterparts.

Thus, according to this school of thought, the difficulty of the parkinsonians in starting movement would not lie in either perceptual or in judgement defects, but in the faulty transmission of motor commands from the "decision making" system to the motor apparatus.

The second school of thought accepts the fact that perceptual judgement not only is impaired by the disease but that it may also contribute to akinesia.

A study conducted by Stern et al. (1983) focused on the ability of parkinsonians to generate voluntary movements during predictive and unpredictable sequences of movements. Even with the help of visual guidance, i.e., the form of the design being utilized (straight horizontal and vertical lines, and sawtooth), the patients could not use this information to improve their tracking. Moreover, when some segments of the design were deleted for a short period of time, the subjects could not track properly until the design reappeared on the screen. This visual dependency has already been noted by Cook, Brown and Brooks (1978). These observations suggested that parkinsonian patients might suffer from an internal spatial perceptual defect. Again, this impairment has already been found by other authors (Boller et al., 1984; Lees & Smith, 1983; Mortimer et al., 1982a; Portin & Rinne, 1979). As a final conclusion, Stern et al. (1983) suggested that perceptual motor impairment was associated with the higher-order motor control of sequential and predictive voluntary movements. This impairment occurs at the level called "perceptual judgement" and would then be partly responsible for the increase in reaction time.

Similar conclusions were derived from other studies which considered the ability of parkinsonians to anticipate a motor response. More specifically, Flowers (1978b) observed that, for a step tracking task, parkinsonians did not spontaneously use prediction as readily as normals for controlling their actions, but that they tended to be tied more directly to sensory information, responding to events rather than anticipating them. Thus

when facing an unpredictable task, parkinsonian patients were as good as their normal counterparts.

More recently, Bloxham, Mindel and Frith (1984) came to the same conclusions regarding the fact that parkinsonians had difficulty in using advanced information either to select an appropriate movement or to initiate it. However, Day, Dick and Marsden (1984) qualified this statement by adding that parkinsonians might have some difficulty in anticipating an action but that they were able to do so since their tracking lag was, most of the time, below their visual reaction time (measured during unpredictable situations).

Motor planning.

Motor planning involves the selection, sequencing and delivery of the correct collection of motor programs required to achieve the desired motor behavior (Marsden, 1984). Motor programs are in fact subunits of the motor-plan. They are sets of muscle commands that are structured before a movement sequence begins, and which allow the entire sequence to be carried out uninfluenced by peripheral feedback (Keele, 1968 in Marsden, 1982). In Parkinson's disease, motor programs would be preserved since the pattern and timing of motor action in the agonistic, antagonistic, and synergistic muscles remain intact (Berardelli, Dick, Rothwell, Day, and Marsden, 1986b; Marsden, 1984). So, this suggests that it may be in the sequencing and delivering of motor programs that parkinsonian patients would have more difficulty. Indeed, according to a study conducted by Frith, Bloxham, and Carpenter (1986), while Parkinson subjects can develop new motor programs for a novel task, they have difficulty in deploying already existing programs in novel situations.

To execute a motor plan, an individual has to move from one point of a sequence to another, the signal of arrival at each point being the trigger required to shift the motor program to the next point in the sequence (Marsden, 1982). Parkinsonians cannot execute simultaneous and sequential motor programs, nor can they deliver sufficient electrical activity to their muscles to achieve the required rate of force necessary to initiate a fast movement (Marsden, 1984; Petajan & Jarcho, 1975). In other words, parkinsonians would have difficulty in calling up and in running motor programs although the latter's basic content is intact (Marsden, 1982). It is at the level of motor planning that the delay responsible for akinesia would seem to occur.

Conclusion.

Thus, parkinsonians' longer reaction times would be more likely to be due to a defect in motor planning rather than to a dysfunction at the perceptual level. However, this latter issue remains to be clarified since no consensus has been reached as to the involvement of the cognitive functions in preparation to movement.

Section III: Motor output

The slowness with which the parkinsonians execute motor output is called "bradykinesia". This negative feature of Parkinson's disease is responsible for the drastic and common increase in movement time observed in parkinsonians. According to Teravainen and Calne (1981), assessing the parkinsonians' movement time gives indices about the clinical status of the patients since their performance at movement time correlates well with motor disability level.

Possible explanations for such slowness are offered by different studies which considered both the muscular factors underlying this slowness, and the control system being used in the execution of the motor action.

Motor units.

Studies with electromyography (EMG) have been used to explain part of the slowness of movement seen in parkinsonians. Indeed, it has been observed that parkinsonians could activate agonistic and antagonistic muscles in the correct time sequence but that they could not deliver sufficient EMG activity to achieve the required rate of force increase, for the required level of force to attain a large fast movement (Marsden, 1984). According to Berardelli, Accornero, Argenta, Meco, and Manfredi (1986a), "the first agonist burst which normally provides the impulsive force to movement is inadequate and followed by compensatory multiple bursts, and this slows down the execution of a simple ballistic movement. The slowing is such that the movement cannot any more be considered as ballistic" (p.1149). Interestingly, Petajan and Jarcho (1975) have attempted to determine the ability of parkinsonian patients to initiate a muscle contraction sufficient to activate a single motor unit. As with Marsden, they found that compared to their age-matched controls, parkinsonians had great difficulty in producing a minimal muscle contraction. However, their investigation went further in finding that a population of the low threshold motor units of the patients produced tremor instead of being involved in the initiation of slowly developing muscle contraction.

Drug treatment.

Petajan and Jarcho (1975) also looked at the effect of levodopa treatment on the ability of their subjects to recruit motor units. They observed that, as a response to treatment, the patients acquired the control of motor unit frequency as well as the ability to activate normally the low threshold motor units that initiate contraction.

Recently, Berardelli et al. (1986b) compared the size of the first agonist EMG burst of Parkinson subjects during rapid wrist movements (single joint movement) when the patients were "on" and "off" their normal drug therapy. They found that despite slowness of movement in all the tests performed, the parkinsonians "could change the amplitude and duration of the first agonist burst appropriate to the size of the movement and the background load, as in normal subjects" (p.1277). They also found that the peak velocity of movement increased when patients were "on" therapy, but that the amount of change was relatively small compared with the "off" condition.

Thus, the slowness of movement observed in parkinsonians is forced by the fact that, by themselves, they cannot energize sufficiently their muscle units to be able to work ballistically. Consequently they are limited to bradykinetic motor action.

Feedback control.

Because parkinsonians have lost the advantages of working ballistically, they are constrained to move slowly towards their objective, checking their progress on the way. They are limited to a closed-loop mode of control with which the parkinsonians can only plan and execute their movement on the basis of how the target they were following has just moved (Bloxham et al., 1984; Flowers, 1978b). According to Frith et al. (1986), this excessive reliance on feedback is mainly present in the early stages of performance in a novel task.

Conclusion.

Obviously, the motor output of patients suffering from Parkinson's disease is greatly impaired. In addition to the typical motor symptoms accompanying the syndrome and the side effects that emerge following long-term treatment, parkinsonians experienced difficulty in doing fast and smooth sequences of movements. Indeed, they are constrained to bradykinetic and saccadic movements, and they are limited to a closed-loop mode of control.

The second part of this review of literature aimed at dividing the total time to respond into peripheral and central processes in order to locate at what level the ~~important~~ changes observed in the parkinsonian patients were more likely to be found. Thus, according to the research considering this problem, the major defective sites associated with this basal ganglia disease would be peripheral and central. More specifically, the central impairment appears to involve the planning level, i.e., at the level where questions such as where, when, and how to move are raised. Given that cognitive processes linking decision to action are still controversial in studies on Parkinson's disease, then no comment can be made at present. As to the peripheral impairments, it seems that the output system is the one that suffers the most from the subcortical damage.

Given that Parkinson's disease is a disease of the basal ganglia, it is more likely that these deficient subcortical structures are responsible for the difficulty the patients have to select and execute motor programs even if the latter are maintained intact. Thus, the basal ganglia, as Marsden (1982) suggested, would be responsible for the automatic execution of learned motor plans.



METHOD

Subjects

Seven out-patients from the Parkinson Clinic of the Ottawa Civic Hospital volunteered to participate to this study. They were all men ranging from 51 to 72 years old (mean age= 61.1 yr.; S.D.= 7.8) and having a history of Parkinson's disease for 2.5 to 11 years (mean= 6 yr.; S.D.= 2.9). They were selected according to the following criteria: 1) in addition to an idiopathic type of Parkinson's disease, they had to be free of any other major physical and mental health problems (stroke, cardiovascular disease, etc...), 2) they had to be at the early stages of the disease, i.e., stage two or three (according to the scale used at the Parkinson Clinic of the Ottawa Civic Hospital), and finally, 3) they had to be under drug treatment. This selection was undertaken by a neurologist, Dr David Grimes, from the Parkinson Clinic and they were all his patients. Further details concerning the characteristics of each of these Parkinson subjects are listed in Table 1.

Seven healthy subjects (mean age= 61.3 yr.; S.D.= 7.5) from the Ottawa area volunteered to participate for this study as control subjects. These people were healthy, i.e., they were free of any major physical and mental health problems (cardiovascular disease, stroke, etc...), and they were matched for age (\pm 1 year) to the experimental group. General information about each subject was gathered on a special form (see appendix 1).

TABLE 1: CHARACTERISTICS OF THE PARKINSON SUBJECTS

SUBJECT	AGE (yr)	DURATION (yr)	STAGE	MEDICATION (mg)								
				SINEMET		BROMOCRIP-AMANTADINE		ARTANE				
				d;	dd;	f	d;	dd;	f	d;	dd;	f
1	51	2.5	2	100/25;	300/75	;3	2.5;	1.25;	1			
2	53	2.5	2	100/25;	300/75	;3	2.5;	6.25;	3			2 ; 6 ; 3
3	55	5.0	2	250/25;	1000/100	;5	2.5;	12.5;	5	100;	100;	1
4	62	5.0	2	250/25;	1150/1125	;5				100;	200;	2
5	64	8.0	2	250/25;	500/50	;2				100;	100;	1
6	71	8.0	2	100/25;	725/150	;4						2 ; 3 ; 3
7	72	11.0	2-3	100/10;	900/90	;6	2.5;	25.0;	6	100;	200;	2

d - dose; dd - daily dose; f = frequency/day

Apparatus

The apparatus used to measure psychomotor performance was the National Research Council Tracometer, a pursuit tracking task (Buck, Leonardo, & Hyde, 1981). The tracking unit (see Figure 1) displayed five targets set in a semicircular fashion. Using a control steering wheel, the subject aligned the pursuit pointer within the target light area for an uninterrupted period of 200 milliseconds (successful alignment) and then, moved towards the next target that was illuminated. One trial consisted of a random sequence of 100 target presentations, with the limitation that each of the 20 between-target movements occurred five times. The task was novel in that moving the pointer to the left was achieved by turning the wheel to the right and vice-versa.

As the subject always rested for 200 milliseconds at one target before the next was illuminated the responses could be considered as discrete movements. The difficulty of the task was varied across four movement distances and four levels of directional probability (Figure 1). When resting at position five the probability that the next movement would be to the left was 100%. When resting at position 2 the probability of moving right was 75%, but the probability of moving left was 25%. When resting at the central position (3) the probability was 50% for moving in either direction.

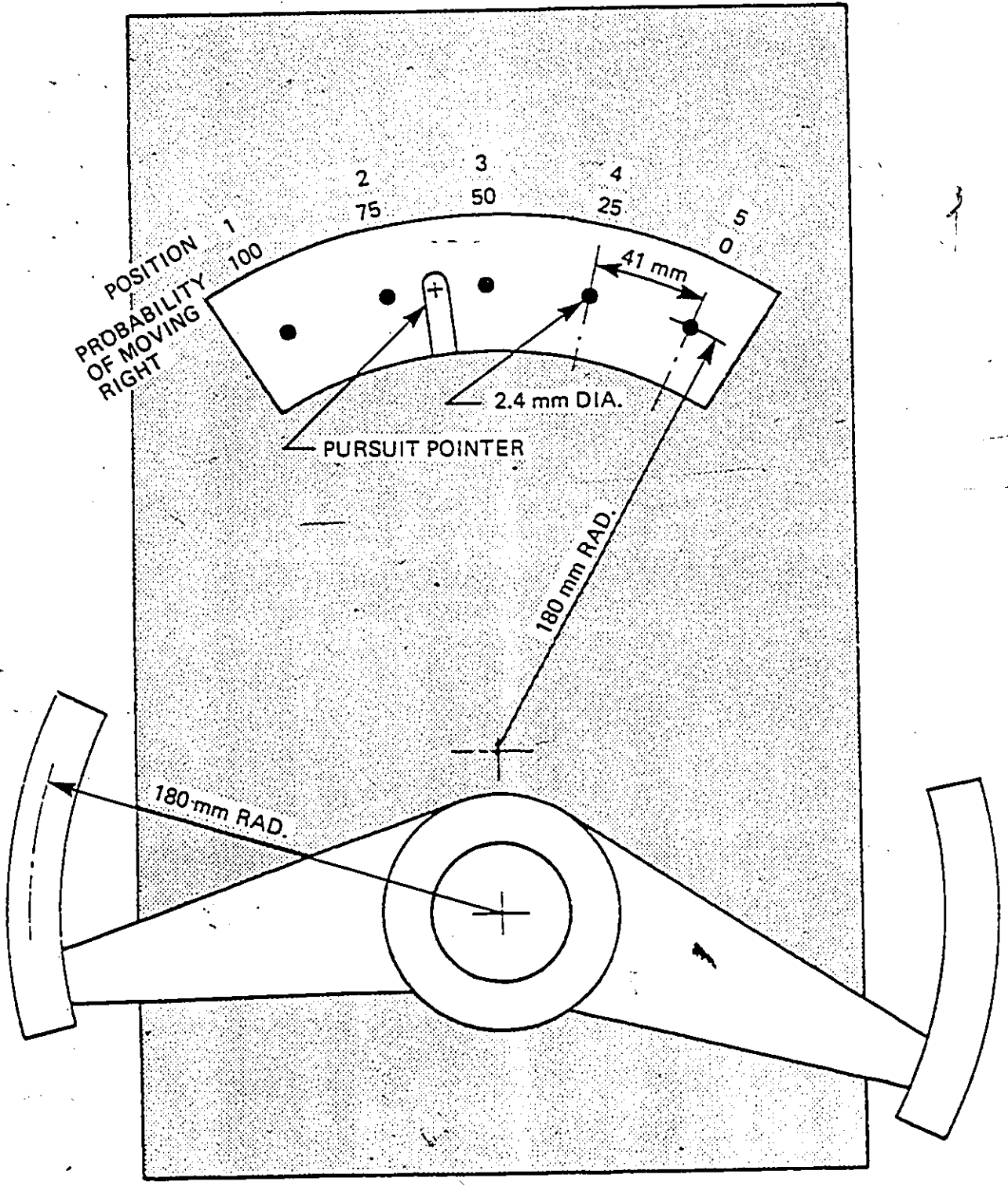


Figure 1. Front View of Pursuit-Tracking Task

Procedure

All subjects completed twenty trials distributed into four sessions. The first one, the learning session, consisted of eight trials performed successively with intertrial pauses of approximately one minute. Eight trials were considered to be sufficient for learning since the results of a previous study with seniors demonstrated that no significant learning occurred after eight trials on the tracometer (Normand, Kerr, and Metivier, 1987). For this learning session the parkinsonian subjects were under drug control. At the second session, the subjects undertook four trials while they were "off" medication, i.e., when they were no longer under the effects of their drugs. In practice, this meant that they were tested one to three hours after the time when they normally should have taken their medication. The exact time interval was determined in conjunction with the attending physician and pharmacist. Immediately after this second session, the Parkinson subjects took their medication. Thirty minutes after the ingestion of their dose, they underwent four further trials (third session). Finally, four last trials were conducted about one hour and a half after the third session, i.e., at the peak dose effect. All control subjects were given the same number of trials per session. Table 2 illustrates the testing schedule for both groups.

The tracking unit was positioned on a table such that the center of the unit coincided with the center of the chair. The subjects were asked to sit directly in front of the tracking unit. The chair was adjusted in such a way that the target display of the tracking unit was below the line of sight. Indirect ambient lighting was used in order to avoid reflection.

All the Parkinson subjects were tested in their own homes. For four of them the experimental procedure was conducted within one day, whereas for the three others, the testing had to be extended over two consecutive evenings: Day 1 - session 1 (learning session) and Day 2 -sessions 2, 3, and 4.

TABLE 2: TESTING SCHEDULE FOR BOTH GROUPS

SESSION	NUMBER OF TRIALS PER SESSION	EXPERIMENTAL CONDITION	TIME INTERVAL BETWEEN SESSIONS	TEST DURATION
1	8	Learning		40 min.
2	4	off*		25 min.
3	4	on		20 min.
4	4	peak		20 min.

* For this session, the Parkinson subjects were "off" medication. Their dose was postponed for one to three hours in order to be at an unalleviated state.

** Four Parkinson subjects could be tested within the same day. For these subjects the time interval between the first and the second session varied from two to three hours. Concerning the three people who had to be tested over two days, there were 24 hours between sessions one and two.

P: Parkinson subjects; C: Control subjects

The control subjects were tested at the University, and went through the four sessions within a day.

Before starting the experiment each subject was 1) informed of the purpose of the study, 2) instructed about the task requirements (see appendix 2) and finally, 3) was asked to fill a consent form (see appendix 3). The number of trials to be executed was given to each subject before each session.

The overall pace of the test trial was subject dependent in that a new target was not presented until alignment with the prior target was successfully achieved. The average length of the 8-trial test session was 40 minutes. The emphasis was placed on speed and accuracy of performance. In order to verify whether the subjects were following this latter instruction, they were asked once per session about the strategy they had adopted, that is, 1) if they put more emphasis on speed, on accuracy, or equally on both, and 2) if they tried to anticipate the light before it appeared. A summary of the answers given by the participants is presented in appendix 4. At the end of each trial, the subjects received knowledge of results in the form of the total number of seconds to complete the trial.

Design and Analysis

The main variables of interest were 1) total response time; the total time on average to complete a single response, 2) correct reaction time; the interval between the presentation of the target light and the initiation of the response executed in the correct direction, 3) non-overshoot movement time; the time interval between the initiation of the response and the beginning of a successful alignment (uninterrupted 200 milliseconds) with the target, without overshooting the target light, 4) overshoot movement time; the

time between the initiation of the response and the beginning of a successful alignment after having overshoot the target light, 5) error rate; the percentage of movements initiated in the wrong direction per trial, and 6) overshoot rate; the percentage of overshoots per trial.

Three different analyses of variance (ANOVA) were used to interpret the results:

- 1) GROUP * BLOCK * TRIAL (2 * 5 * 4) ANOVA with repeated measures on the last variable.

This first analysis was used in order to consider the overall performance of the two groups over the five blocks of trials, and for this purpose only TRT was used.

- 2) In order to obtain a clearer picture of the psychomotor performance of the subjects during the experiment, the components of TRT (CRT, NOMT, OMT, error and overshoot rates) were analyzed separately for each of the three phases involved in this experiment namely: a) *Learning*, b) *Treatment*, and c) *Extended practice*.

a) *Learning*: GROUP * BLOCK (Blocks 1 & 2) * TRIAL (2 * 2 * 4) ANOVA with repeated measures on the last variable.

This analysis was used to compare the ability of both groups when learning a new task. A previous study indicated that for seniors most improvement in performance occurs over the first eight trials (Normand et al., 1987).

b) *Treatment*: GROUP * BLOCK (Blocks 3 & 4) * TRIAL (2 * 2 * 4) ANOVA with repeated measures on the last variable.

To consider the effects of Parkinson's disease on the psychomotor performance by comparing the unalleviated (Block 3) and the alleviated (Block 4) stages: after performance had stabilized.

c) *Extended practice* : GROUP * BLOCK (Blocks 4 & 5) * TRIAL (2 * 2 * 4) ANOVA with repeated measures on the last variable.

To compare the performance of the control and Parkinson groups when the latter group was considered to be familiar with the task and "on" medication at (or near) the peak dose effect.

- 3) GROUP * TRIAL (8, 9, & 13) (2 * 3) ANOVA with repeated measures on the last variable. This analysis was used as a *Bridge* between the first and the second analysis. It was intended to provide an overall picture of the performance of the groups at the end of the learning session (trial 8), at the first trial when "off" medication (trial 9), and at the first trial when back "on" medication (trial 13). as for analysis no.1, only TRT was considered. For a single trial missing data may not permit a more complete analysis of all the sub-components of TRT.

An analysis of the simple main effects was used to describe the interactions and a post-hoc analysis (Scheffe Test) was conducted to describe the main effects.

RESULTS

Group means for the main variables are presented in Table 3, and each of these variables will be considered separately.

Total Response Time (TRT):

For the total time, on average, to make a single response, there was a significant BLOCK effect ($F(4,48) = 20.17, p < .001$) across all five blocks (analysis no.1, Table 4). Post-hoc analysis indicated that, for both groups, most of the learning occurred during the first two blocks (Blocks 1 vs 2, $p < .001$), but that some significant learning also occurred thereafter for the Parkinson group. More specifically, the TRT of the latter significantly improved from Block 2 to Blocks 4 and 5 ($p < .01$), and from Block 3 to Blocks 4 ($p < .05$) and 5 ($p < .01$). No significant difference was found between Blocks 2 and 3, and between Blocks 4 and 5 (see figure 2). In light of figure 2 we can see that most of the learning occurring after Block 2 was attributable to the Parkinson subjects, whereas the performance of their controls tended to stabilize after the first eight trials. Indeed, even though the learning curves of both groups, overall, tended to parallel each other, the fact that the Parkinson group was, at a certain stage, "off" medication, seems to have contributed to postpone the stabilization of their learning compared with the control group.

TABLE 3: MEANS AND STANDARD DEVIATIONS FOR THE MAIN VARIABLES OVER THE FIVE BLOCKS (msec)

Group	Variable							
	TRT		CRT*		NOMT		OMT*	
	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD
Parkinson	1570.0	25.5	395.8	8.7	1172.0	35.6	1607.2	50.5
Control	1361.4	19.7	335.6	6.1	1014.0	30.3	1277.0	39.1

* Groups are significantly different ($p < .05$)

TABLE 4: RESULTS OF THE ANALYSES OF TOTAL RESPONSE TIME (TRT)

VARIABLE	ANALYSIS	MAIN EFFECT	INTERACTION	LEVEL OF SIGNIFICANCE	INTERPRETATION
TRT	Overall (no.1)	Block		.001	Learning effect
	Bridge (no.3)		Group* Trial	.025	Due to p when "off" medication

p - Parkinson subjects

The significant GROUP * TRIAL interaction found in analysis no.3 ($F(2,24) = 4.77, p < .025$) (see Figure 3), appears to be due to the performance of the Parkinson subjects: given that the performance of the controls did not vary significantly over the three trials. More specifically, it is the performance of the Parkinson group when "off" medication (trial 9) which caused the interaction ($p < .05$) since trials 8 and 13 were not significantly different.

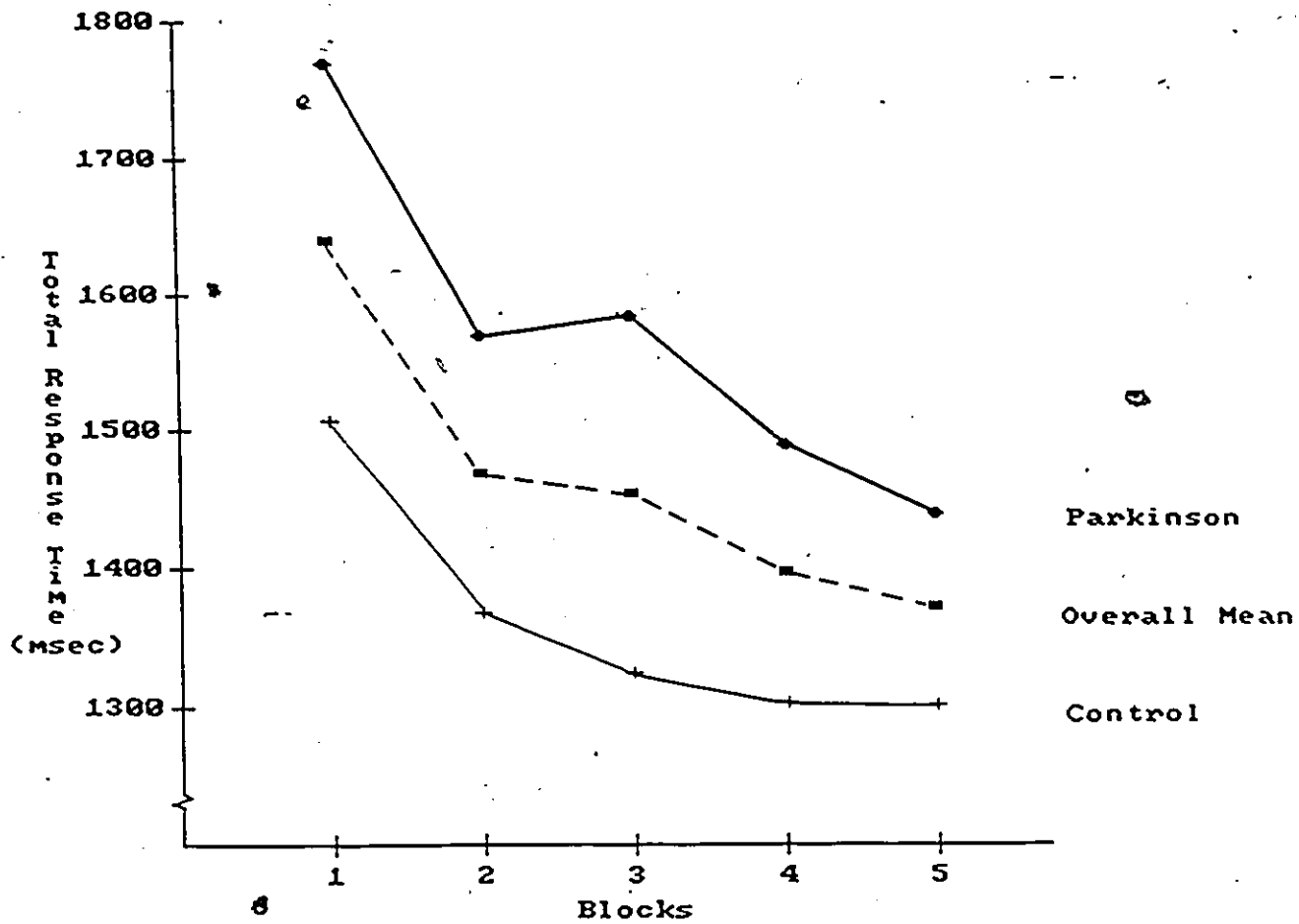


Figure 2: Total Response Time By Group For The Five Blocks

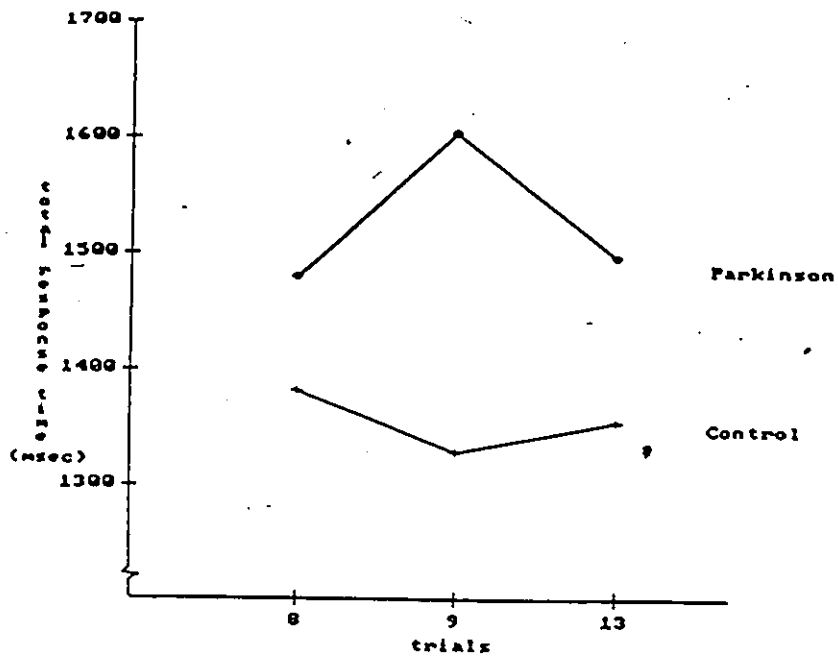


Figure 3: Total Response Time by group for trials 8,9 and 13

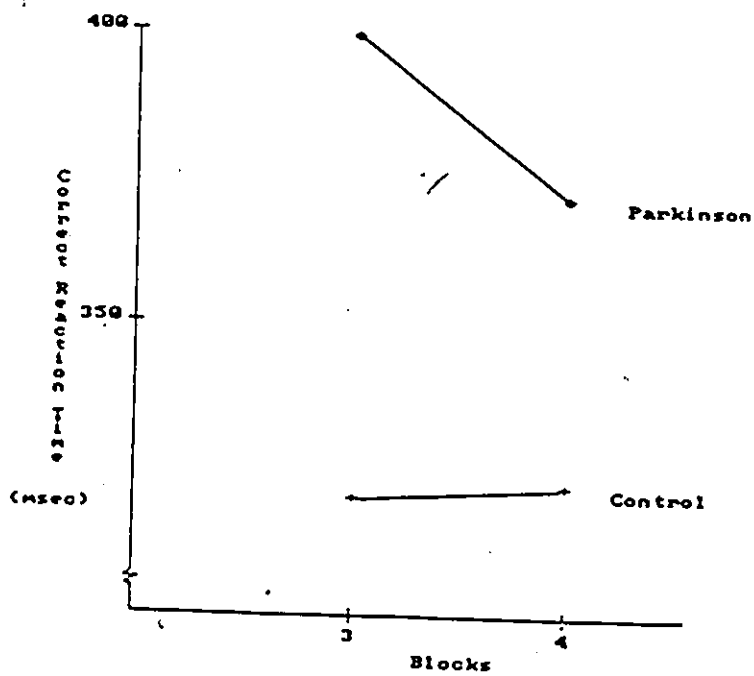


Figure 4. Correct Reaction Time By Group For Blocks 3 and 4 (msec)

Correct Reaction Time (CRT):

Table 5 illustrates the performance of both groups for CRT during the three phases of the experiment (analysis no.2).

The analysis of CRT produced a GROUP effect ($F(1,12) = 8.22, p < .025$) for the Learning phase, and for the Treatment phase a GROUP effect ($F(1,12) = 6.47, p < .05$) and a GROUP * BLOCK interaction ($F(1,12) = 11.24, p < .01$). Overall this revealed that the Parkinson group was significantly slower than the control group (at both simple and choice RTs) during the learning phase and when "off" medication (Blocks 1, 2, & 3). However, when considering the performance of the two groups during Blocks 4 and 5 (Extended practice), there was no significant group difference for simple RT but the Parkinson group was significantly slower for choice RT. Thus, we can see that until they become familiar with the task, and including when they were "off" medication, the CRT of the Parkinson group was significantly slower. When they had "learned" the task (after 12 trials or 1200 movements), and when "on" medication, their performance was no different from the one of their control subjects except for their ability to react to less predictable signals.

The GROUP * BLOCK interaction was strongest over Blocks 3 and 4 (see Figure 4), due to the performance of the Parkinson subjects when "off" medication. The CRT of the latter subjects was significantly slower ($p < .01$) at Block 3 (off) compared to Block 4 (on), and the performance of the control subjects did not fluctuate significantly over these two blocks.

The PROBABILITY effect was significant for all three phases a) Learning ($F(3,36) = 44.31, p < .001$); b) Treatment ($F(3,36) = 140.95, p < .001$); c) Extended practice ($F(3,36) = 86.21, p < .001$). This effect reflected the ability of the subjects to react to signals of

TABLE 5: RESULTS OF THE ANALYSIS OF CORRECT REACTION TIME (CRT)

VARIABLE	ANALYSIS	MAIN EFFECT	INTERACTION	LEVEL OF SIGNIFICANCE	INTERPRETATION
CRT	Learning	Group		.025	\bar{P} were slower than \bar{C}
	(no.2)	Block		.01	Improvement of both gr. from Blocks 1 to 2
		PL		.001	As PL decreased CRT increased
	Treatment	Group		.05	\bar{P} slower than \bar{C}
	(no.2)	Block		.025	\bar{P} slower when "off"
			Group*Block	.01	Due to performance of \bar{P} when "off"
				.001	(same as for Learning)
			Group*PL	.01	For PL (100&75%) \bar{P} are slower than \bar{C} at Block 3 but \bar{P} * \bar{C} at Block 4. For PL (50&25%) \bar{P} slower \bar{C}
	Extended	PL		.001	(same as for Learning)
	practice		Group*PL	.05	For PL (50&25%) \bar{P} slower than \bar{C}
	(no.2)				

\bar{P} = Parkinson subjects; \bar{C} = Control subjects; PL = Probability level

different probability levels: i.e., as the direction became less probable, the participants took longer to react. The GROUP * PROBABILITY interaction found for both Treatment ($F(3,36) = 4.55, p < .01$) and Extended practice ($F(3,36) = 3.16, p < .05$) phases (see Figure 5), is suspected to be due to changes in the ability of the Parkinson subjects to react to signals of different probability levels and this, during Blocks 4 and 5 (Extended practice). Indeed, during these two last blocks, the Parkinson group was no longer significantly slower than the control group at making simple decisions (simple RT) but when direction became less predictable (50% & 25%; complex RT), the Parkinson subjects were still taking significantly longer to react ($p < .01$).

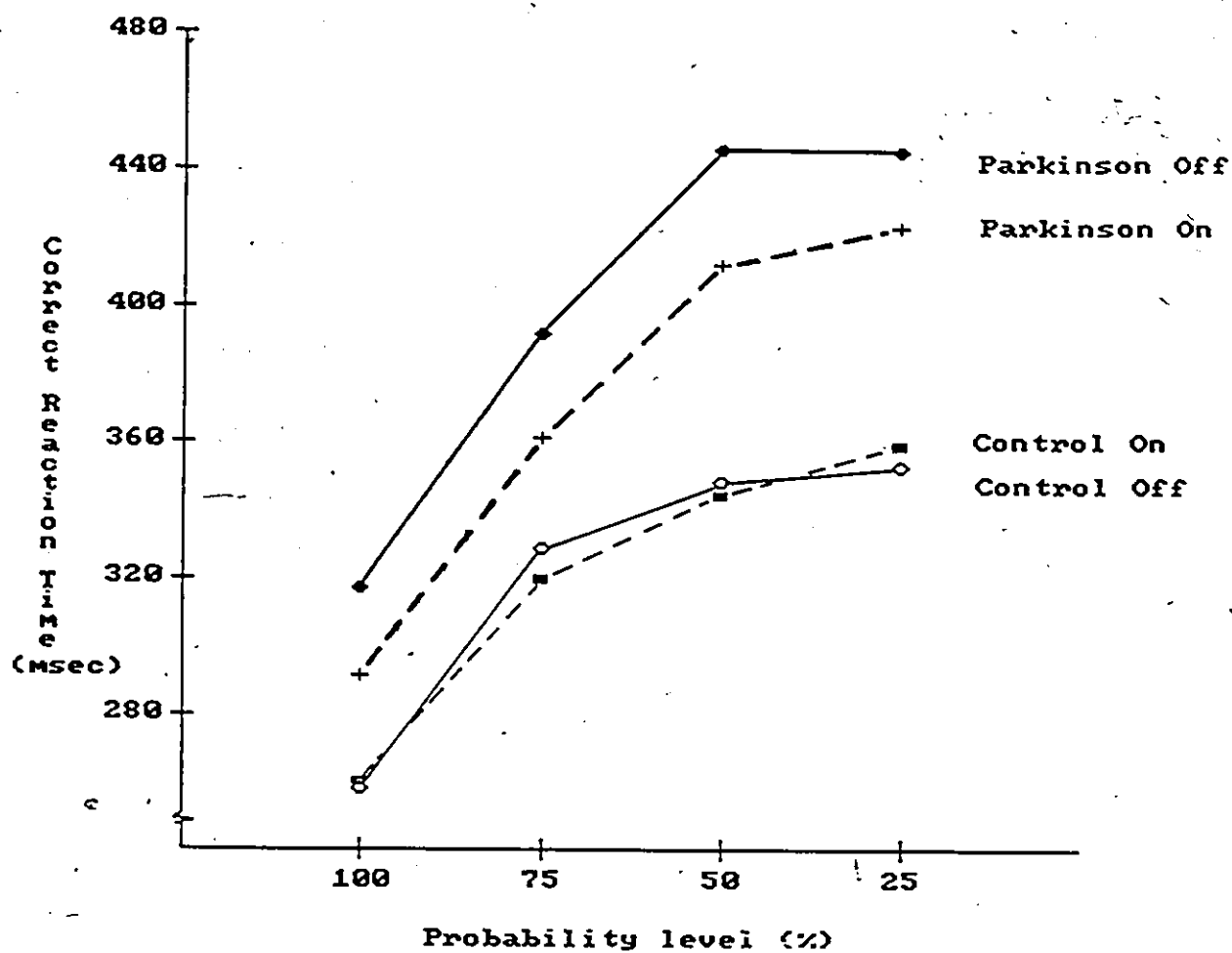


Figure 5. Correct Reaction Time for different probability levels when "off" (block 3) and "on" (block 4) medication

Non-Overshoot Movement Time (NOMT):

The results of the analysis of the movements without overshoot are listed in Table 6.

The BLOCK effect ($F(1,12) = 22.99, p < .001$), seen during the Learning phase, indicates that both groups significantly improved over Blocks 1 and 2. However, the analysis of the GROUP * BLOCK interaction ($F(1,12) = 4.93, p < .05$) revealed that the control group learned faster than the Parkinson group at making precise movements.

The main DISTANCE effect a) Learning ($F(3,36) = 205.66, p < .001$); b) Treatment ($F(3,36) = 182.84, p < .001$); c) Extended practice ($F(3,36) = 201.21, p < .001$) present during the three phases of the experiment (see Table 6), simply reflected the fact that both groups showed longer movement times for longer distances. Where the groups tended to be significantly different was for longer distances ($p < .05$). Indeed, the analysis of the GROUP * DISTANCE interaction during the Learning ($F(3,36) = 2.93, p < .05$) and the Treatment ($F(3,36) = 3.30, p < .05$) phases revealed that the Parkinson group was significantly slower than the control group when moving over the two longest distances (123 & 164 mm) (see Figure 6) and this difference appeared to be significantly greater when parkinsonians were "off" medication ($p < .01$). However, when the groups were given extended practice (Blocks 4 & 5), they were no longer different at making longer movements.

The BLOCK * DISTANCE interaction was present for all phases. During Learning ($F(3,36) = 5.01, p < .01$) (see Table 6), it revealed that both groups improved significantly from Block 1 to Block 2. At the Treatment phase, the BLOCK * DISTANCE ($F(3,36) = 3.32, p < .05$) as well as the GROUP * BLOCK * DISTANCE ($F(3,36) = 3.39, p < .05$) interactions supported the fact that when parkinsonians were "off" medication (Block 3), their performance was much slower ($p < .01$) whereas when "on" medication (Block 4),

TABLE 6: RESULTS OF THE ANALYSIS OF NON-OVERSHOOT MOVEMENT, TIME (NOMT)

VARIABLE	ANALYSIS	MAIN EFFECT	INTERACTION	LEVEL OF SIGNIFICANCE	INTERPRETATION
NOMT	Learning	Block		.001	Learning effect
	(no.2)		Group*Block	.05	<u>C</u> learned faster than <u>P</u>
		Distance		.001	As <u>dist.</u> to move increased NOMT became longer
			Group*Dist	.05	<u>P</u> slower for longer mvt dist (123&164mm)
			Block*Dist	.01	Improvement with learning
	Treatment	Distance		.001	(same as for Learning)
	(no.2)		Group*Dist	.05	(same as for Learning)
			Block*Dist	.05	<u>P</u> slower than <u>C</u> when off
			Gr*Bl*Dist	.05	At block 4 <u>P</u> started to be no different than <u>C</u>
	Extended practice	Distance	Block*Dist	.001	(same as for Learning)
				.025	Due to difficulty at making precise movements for the longest distance at Bl 5 only.



P = Parkinson subjects; C = Control subjects; Bl = Block; Dist = Distance

they were not different from their controls (see Figure 6). Concerning the BLOCK * DISTANCE interaction ($F(3,36) = 3.84, p < .05$) found for Blocks 4 and 5 (Extended practice), a further analysis revealed that this interaction was due to a slowness at making precise movements for the longest distance (164 mm) at Block 5 only.

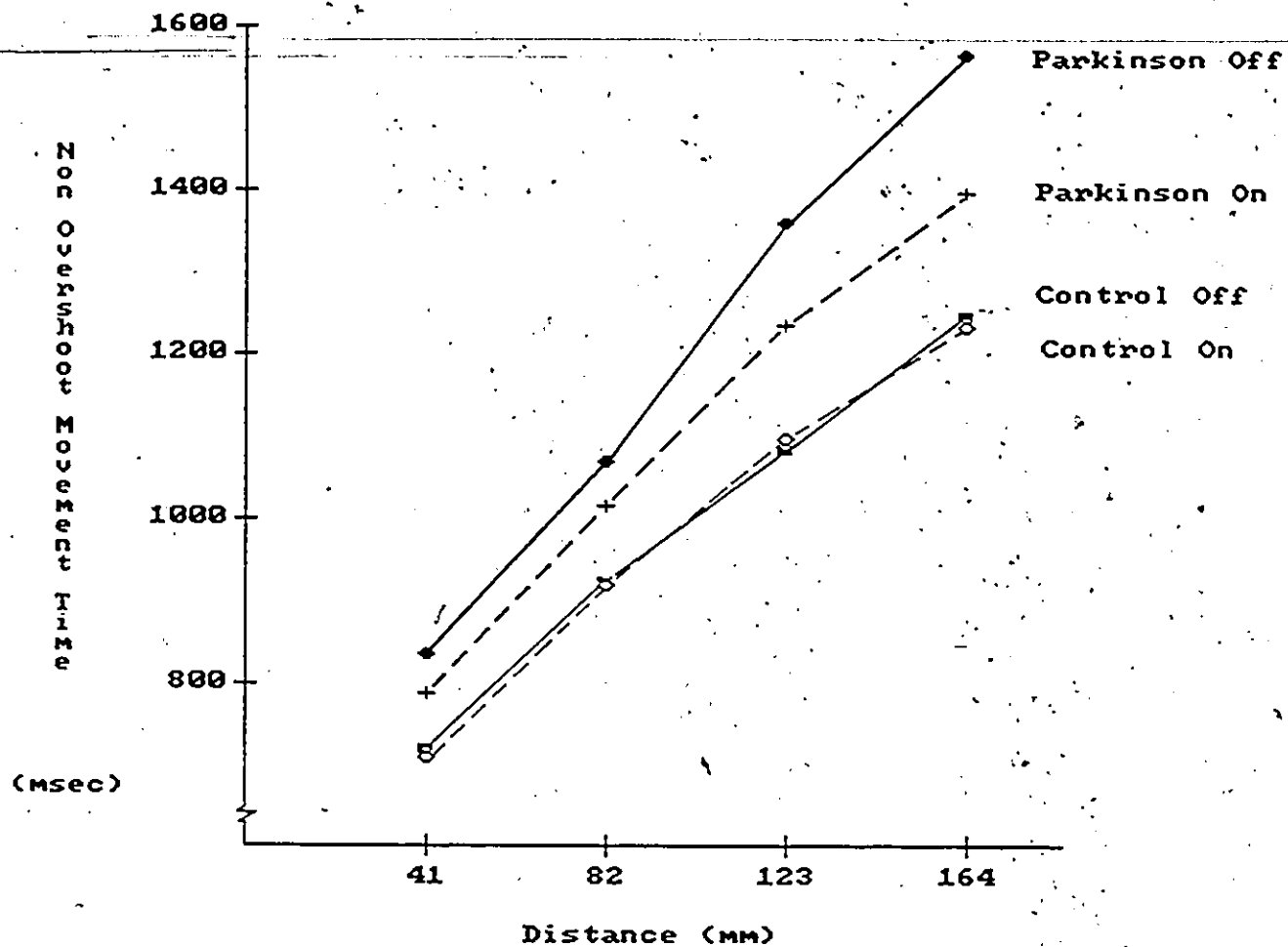


Figure 6. Non-Overshoot Movement Time (msec) By Group For Different Movement Distance When "Off" (Block 3) and "On" (Block 4) Medication

Overshoot Movement Time (OMT):

Given the fact that some data were missing (due to a low overshoot rate for the longest distance), only the three first levels (41, 82, and 123 mm) of OMT were considered in this analysis. The results of this analysis (analysis no.2, Table 7) revealed that a significant GROUP effect was present during the three phases of the experiment a) Learning ($F(1,12)= 5.14, p <.05$); b) Treatment ($F(1,12)= 5.50, p <.05$); c) Extended practice ($F(1,12)= 4.94, p <.05$). Indeed the Parkinson subjects were significantly slower at moving and at correcting their movements throughout the testing.

The significant Block effect seen in the Learning phase ($F(1,12)= 5.14, p <.05$) simply reflected that both groups improved significantly from Block 1 to Block 2. As to the DISTANCE effect present in all three phases a) Learning ($F(2,24)= 34.06, p <.001$); b) Treatment ($F(2,24)= 100.50, p <.001$); c) Extended practice ($F(2,24)= 33.47, p <.001$), it meant that as the distance to move increased, the time to cover this distance was longer.

TABLE 7: RESULTS OF THE ANALYSIS OF OVERSHOOT MOVEMENT TIME (OMT)

VARIABLE	ANALYSIS	MAIN EFFECT	INTERACTION	LEVEL OF SIGNIFICANCE	INTERPRETATION
OMT	Learning	Group		.05	<u>P</u> slower than <u>C</u>
	(no.2)	Block		.001	Learning effect
		Distance		.001	As distance increased OMT became longer
Treatment	(no.2)	Group		.025	(same as for learning)
		Distance		.001	(same as for learning)
	Extended practice	Group		.05	(same as for learning)
		Distance		.001	(same as for Learning)

P = Parkinson subjects; C = Control subjects

Errors and Overshoots:

In terms of error and overshoot rates, both groups were not significantly different even though the control group had a "tendency" to be less cautious than their counterparts (see Table 8).

Concerning the analysis of the error rate (see Table 9), the results suggested that as the movement direction became less probable, the subjects tended to make more errors in initiating the movement in the wrong direction. This main PROBABILITY effect was present during the three phases a) Learning ($F(3,36)= 136.00, p <.001$); b) Treatment ($F(3,36)= 102.99, p <.001$); c) Extended practice ($F(3,36)= 141.17, p <.001$) but a BLOCK * PROBABILITY interaction ($F(3,36)= 17.97, p <.001$) during the Learning phase indicated that from Block 1 to Block 2 both groups significantly improved by making less mistakes when they initiated their movements, for the probability levels 75% and 50%. The GROUP * BLOCK * PROBABILITY interaction ($F(3,36)= 17.97, p <.001$) seen in the last phase (Extended practice) simply reflected that, specifically for the least probable movement direction (25 %) at Block 5, the Parkinson group tended to make more errors.

As to the overshoot rate (see Table 10), the significant BOUNDARY DISTANCE effect seen at the three phases a) Learning ($F(3,36)= 58.91, p <.001$); b) Treatment ($F(3,36)= 28.51, p <.001$); c) Extended practice ($F(3,36)= 26.31, p <.001$) meant that as the subjects moved towards a target further from the boundary, they made more overshoots when compared to targets placed closer to the boundary of the display.

The BLOCK * BOUNDARY DISTANCE interaction ($F(3,36)= 7.71, p <.001$) occurring at the Learning stage reflected the fact that both groups improved significantly from Block 1 to Block 2: particularly for targets farthest from the boundary of the display.

TABLE 8: RATE (%) OF ERRORS AND OVERSHOOTS FOR BOTH GROUPS
OVER THE FIVE BLOCKS

	VARIABLE	
GROUP	ERROR RATE	OVERSHOOT RATE
Parkinson	24.5	26.8
Control	29.2	28.9

TABLE 9: RESULTS OF THE ANALYSIS OF ERROR RATE

VARIABLE	ANALYSIS	MAIN EFFECT	INTERACTION	LEVEL OF SIGNIFICANCE	INTERPRETATION
Error Rate	Learning (no.2)	Probability		.001	As PL became lower the Error rate increased
			Block*PL	.001	Error rate decreased with the learning of the task
	Treatment (no.2)	Probability		.001	(same as for Learning)
	Extended practice (no.2)	Probability	Gr*Bl*PL	.001	(same as for Learning) Due to <u>P</u> who made more error at PL 25% for block 5 only

P = Parkinson subjects; PL = Probability level; Gr = Group; Bl = Block

TABLE 10: RESULTS OF THE ANALYSIS OF OVERSHOOT RATE

VARIABLE	ANALYSIS	MAIN EFFECT	INTERACTION	LEVEL OF SIGNIFICANCE	INTERPRETATION
Overshoot Rate	Learning (no.2)	BD		.001	Overshoot rate increased as BD increased
			Block×BD	.001	Overshoot rate decreased with learning
	Treatment (no.2)	BD		.001	(same as for Learning)
	Extended practice (no.2)	BD		.001	(same as for learning)

BD = Boundary distance

DISCUSSION

The purpose of the present study was to assess the ability of Parkinson subjects to make simple and complex decisions (involving choice), and their ability to produce fast precise movements. In order to help separate the impact of Parkinson's disease on the motor and cognitive aspects of motor control from drug mediated responses, parkinsonians' performance was assessed when they were "on" and "off" medication.

Overall, the hypotheses tested in this study were partially confirmed.

Compared to matched control subjects, people suffering from Parkinson's disease proved to be slower at making simple and choice decisions (Learning and "off" phases; Blocks 1, 2, & 3), but once the task was "learned" (Extended practice phase; Blocks 4 & 5), their performance was slower only for decisions involving choice (for low probable movement direction: 25 % and 50 %).

Concerning the hypotheses which speculated that parkinsonians were slower at moving to targets at varying distances, it was confirmed for OMT but not completely for NOMT. Indeed, during the Learning and the "off" phases (Blocks 1, 2, and 3), Parkinson subjects were found to be slower than control subjects when moving to farthest targets (123 & 164 mm), but this difference disappeared during the Extended practice phase (Blocks 4 and 5). With respect to the ability to correct a movement after having overshoot the target (OMT), parkinsonians appeared to be slower than control subjects and this effect remained for all phases (Learning, Treatment, and Extended practice).

As to the two last hypotheses, which stated that the performance of Parkinson subjects when "off" medication was slower than when "on", they were again partially confirmed since parkinsonians proved to be slower at making simple decisions (probability levels: 100% and 75 %) and at moving to farthest targets (123 and 164 mm) during the unalleviated phase (Block 3) compared to the alleviated phase (Block 4).

In order to show the direct relationship between the results and the original hypotheses, each measurement variable (CRT, NOMT, OMT, error and overshoot rates) will be discussed separately.

Correct Reaction Time (CRT):

Concerning the ability to make simple and choice decisions (Correct RT) compared to the performance of normal control subjects, Parkinson subjects at first appeared to be akinetic (during the "learning" and when "off", they had difficulty in initiating motor responses), but this difference narrowed and was not significant during the two last blocks (Extended practice). A possible explanation may be that, when asked if they put more emphasis on speed or on accuracy, or both, the Parkinson patients first tended to emphasize accuracy over speed (two first blocks) and then, they changed to a balance between speed and accuracy (see appendix 4). On the other hand, the control subjects tended to maintain a consistent emphasis on speed and accuracy. As to their ability to react to signals of different probability levels, the Parkinson subjects took significantly longer to initiate a less, predictable movement than a highly probable one. This relationship varied across blocks of trials and, in particular, changed when compared with the control subjects. The difference between Parkinson and control subjects being greater for less probable decisions. Overall, this behavior, which would suggest the presence of bradyphrenia, was still present even after considerable practice on the task: i.e., when the task might be considered to be learned (Extended practice).

The difficulty in initiating a motor response (akinesia) where the movement is predictable (equivalent to a simple RT), is present in Parkinson's disease but only when the patients are "off" medication, and when they are in the initial stages of learning a novel task. At both these stages the two groups are significantly different at all levels of probability. However, over the last two blocks the two groups were only significantly different when dealing with less probable signals. The slower speed of mental processing of the Parkinson subjects appears to be impaired (bradyphrenia) even when they are under drug control: at least when they face less probable signals.

Since most studies on RT and Parkinson's disease have used a relatively low number of trials (from 15 to 240) compared to the present study (2000 movements), we observed that the results previously obtained, correspond mostly to the ones obtained when the subjects were at the learning stage (Blocks 1 & 2). Indeed, as with previous studies, the present study found the RTs of the Parkinson subjects to be significantly slower than normal for a novel task (Angel et al., 1970; Bloxham et al., 1984; Cassell et al., 1973; Evarts et al., 1981; Frith, Bloxham, & Carpenter, 1986; Marsden, 1982, 1984; Rafal et al., 1984; Teravainen & Calne, 1981; Wilson et al., 1980) and this, when the patients were under drug control. Moreover, in the two first blocks of the present study, parkinsonians did not show more difficulty to respond to changes in probability level or choice RT (Teravainen & Calne, 1981), suggesting that Parkinson subjects did not show mental processing deficiency (bradyphrenia) for more complex tasks when "on" medication. As it was found in Normand et al. (1987), eight trials appeared to be sufficient for the normal control subjects to become familiar with the task.

When "off" medication (Block 3), it was observed that the performance of the Parkinson subjects (CRT) was significantly slower than the control group for both simple and choice RTs. When back "on" medication (Block 4), the performance of the Parkinson

group was not significantly different for highly probable movements (simple RT), but they were significantly slower at reacting to less predictable movements (choice RT).

Up to now, very few studies have considered the performance of parkinsonians when "on" and "off" medication. Indeed, the main work has been that of Rafal et al. (1984) and Teravainen and Calne (1980) who found the patients to show slower RTs in an unalleviated state. The findings of Rafal et al. (1984) concerning the presence of bradyphrenia during the "off" period suggest that the patients' complex RTs tend to be more vulnerable to an unalleviated state than simple RTs. They suggest that choice RT can be remediated by drug therapy. As with Rafal et al. (1984), Cummings (1986) states that dopamine treatment improves the parkinsonian performance on complex RT tasks but does not facilitate simple RT; which suggests that abnormalities of dopaminergic functions are contributing to response latencies of the more complicated procedures. Perhaps the combined effects of aging and an unalleviated form of Parkinson's disease may contribute to enhance the neural noise in the central nervous system. In other words, the deterioration of dopaminergic activities when the Parkinson subjects are "off" medication together with the changes accompanying "normal" aging may lead to a substantial disorganization responsible for the fact that it takes longer and stronger signals for parkinsonians to make an accurate identification of the material presented (Welford, 1980).

The present results do not completely support the findings of the literature since the slowness of thought of the Parkinson group was present during both conditions, i.e., when "off" (Block 3) and when "on" (Blocks 4 & 5: Extended practice). Had we compared the "off" data to the first two blocks we would have fully supported the findings of Rafal et al. (1984). Moreover, with extended practice the difference between control and Parkinson subjects becomes more apparent (for low probable levels: 25 and 50%), even when the latter are "on" medication.

No group difference was found for correct RT at Blocks 4 and 5. The feature which remained was the presence of bradyphrenia when the patients had to initiate movements towards less predictable target lights ($p < .05$). Thus, the results of the present study seem to support the idea that, as the Parkinson subjects become more and more familiar with the task, and when they are under drug control (at Blocks 4 & 5), their difficulty in initiating (akinesia) simple movements disappears but their ability to react to less probable (more complex) signals (bradyphrenia) remains.

Overall, the results obtained for correct RT correspond to the conclusions of Frith et al. (1986) who state that the "initiation difficulties (of parkinsonians) are particularly likely when the movement involves the deployment of a motor program in novel circumstances"... however, "if the task is performed repeatedly, then special programs will develop and performances become skilled" (p.667).

According to Marsden (1982), the main problem of Parkinson subjects is to automatically execute learned motor plans. Meanwhile, in light of the work presented by Frith et al. (1986) and in light of the present study, it may be suggested that once they are given the chance to practice sufficiently, the Parkinson subjects are capable of learning a new skill to a level where it can be performed (to some extent) automatically. These findings run counter to Flowers' conclusions (1978a) which maintained that Parkinson subjects could not learn a new task, and that even prolonged practice might not be beneficial to them.

In previous studies, akinesia was seen as a difficulty in "calling up" a motor program (Marsden, 1982), as a problem in initiating preprogrammed movements (Bloxham et al., 1984), as well as a faulty transmission of motor command from the decision making system to the motor apparatus (Angel et al., 1970). Recently, Dick, Cowan, Day, Berardelli, Kachi, Rothwell, and Marsden (1984) and Berardelli et al. (1986a) found that

in fact, the corticomotoneurone connections and the ability of the Parkinson patients to plan a motor program remained intact. Thus, in light of this recent study, and following the conclusions of Stern et al. (1983) suggesting the involvement of the basal ganglia in the monitoring rather than in the initiation of movements, it would be more appropriate to see akinesia as a difficulty in deploying already existing programs in novel situations. Therefore, as soon as the situation becomes more familiar, motor sets (modification of an existing motor program for use in a new situation; Frith et al., 1986) are then developed and the difficulty in initiating movements (simple RT) is significantly improved.

Non-Overshoot Movement Time (NOMT):

With regard to the ability to execute a correct motor response (NOMT), no significant difference was found between the two groups except for making precise movements over longer distances (123 & 164 mm) while the Parkinson subjects were in the process of learning, and when they were "off" medication (Blocks 1, 2, & 3). These results suggest that, as soon as the Parkinson subjects felt comfortable with the task and were under drug control (Blocks 4 & 5: Extended practice), they had less difficulty monitoring longer movements.

The literature on movement time (MT) and Parkinson's disease supports the presence of bradykinesia (Berardelli et al., 1986a; Cassell et al., 1973; Evarts et al., 1981; Marsden, 1982, 1984; Teravainen & Calne, 1980, 1981). According to Teravainen and Calne (1980, 1981), MT would be itself the best measure of hypokinesia since it was generally more affected by the disease, and since it responded more to treatment than RT.

The results obtained in the present study diverge appreciably from the latter conclusions. Indeed, in the present study, bradykinesia was far from being an important feature. Even if the parkinsonian group tended to be slower than the control group for

NOMT, the overall difference remained non significant. In fact, the only sign of bradykinesia noticed was observable when the patients tried to execute long, precise movements during the learning session, and when "off" medication.

As mentioned earlier, given that most studies have used a small number of responses to assess the motor performance of Parkinson subjects, it is not surprising that their results tended to correspond to the ones obtained here when the subjects were in the learning stage (Blocks 1 & 2).

In a recent study by Berardelli et al. (1986b) it was found that this "failure to energize muscles" (bradykinesia) would be most apparent in large movements. Although our study looked at fine motor performance, we still observed the Parkinson subjects to be significantly slower at moving over longer distances (123 & 164 mm) and this, during the Learning and the "off" stages. According to Kerr (1982, p.231), "moving to a target light requires the continual monitoring of the movement in order to compare the current position with the desired outcome and to make appropriate corrections". Thus, this slowness at making long and precise movements might be mainly related to a monitoring difficulty which was present during the learning of a novel task; and which became worse when Parkinson subjects were "off" medication ($p < .01$).

Interestingly, Berardelli et al. (1986b) and Dick et al. (1984) suggested that this slowness of movement seen in Parkinson subjects might be due to a defective motor command sent to the motor cortex. Given that the corticomotoneuron connection has been found intact even in bradykinetic patients who were "off" treatment, and since these Parkinson subjects appeared to be able to change the amplitude and duration of the first agonist burst appropriate to the size of the movement and the background load, as in normal subjects, Berardelli et al. (1986b) concluded that "perhaps the premotor cortex and the supplementary motor area (area of the cerebral cortex that receives a major output

from globus pallidus via the thalamus; Evarts & Wise, 1984), deprived of their normal basal ganglia input by Parkinson's disease, do not compute the command signal to the motor cortex to match the size of the movement required". Kerr, Dall, and Grimes (1987) also implied that the motor control problems of Parkinson subjects were related to problems in generating and monitoring movements of a particular force.

In light of the present results on Blocks 4 and 5, i.e., when the task might be considered to be learned and when the Parkinson subjects were back on medication, the difficulty the Parkinson subjects previously had at monitoring long and precise movements disappeared. Thus as the case for akinesia, bradykinesia would then tend to improve with prolonged practice.

The basal ganglia are seen as an aid in the monitoring of ongoing movement (Stern et al., 1983). According to Cummings (1986), they have important analytic and synthetic functions that modify, focus, and direct incoming and outgoing impulses. With Parkinson's disease, these functions appear to be defective. Indeed, Parkinson subjects have a tendency to perform all actions at a slow and steady pace so that a reasonable degree of control may be maintained (Marsden, 1984). Meanwhile, rather than considering bradykinesia as a static phenomenon, the present results suggest that the difficulty the Parkinson subjects had at monitoring long and precise movements tended to disappear as the patients became more familiar with the task (Blocks 4 & 5). Therefore, concomitant with the changes observed for akinesia, we can suggest that when given the chance to practice sufficiently, the Parkinson subjects were capable of learning a new skill to a level at which the monitoring of that new motor set was executed in a manner equivalent to control subjects. Bradykinesia may then be defined as a difficulty in monitoring new motor sets. According to the present results, akinesia and bradykinesia would be closely related.

Overshoot Movement Time (OMT):

In comparison with their age-matched controls, the Parkinson subjects appeared to be significantly slower at correcting a motor response after having overshoot the target light (OMT). Interestingly, this behavior remained the same at any level of OMT, over all five blocks of trials.

The results obtained by Berardelli et al. (1986a) support these findings. Indeed, these authors observed that the Parkinson subjects had difficulty in running motor programs particularly when they had to switch from one program to another. Even if the Parkinson subjects made no more overshoots than the normal control subjects, they took much longer to correct their false moves (Angel et al., 1970; Berardelli et al., 1986a; Marsden, 1982).

When looking more closely at the results of the present study, it is interesting to notice that, contrary to the normal group whose mean scores (OMT) over the five Blocks was faster than the value of TRT, Parkinson subjects tended to be slower at OMT than at TRT (see Table 3). This observation suggests that the Parkinson subjects were in fact unable to execute fast corrective movements below the value of their CRT. In other words, these findings may suggest that when the Parkinson subjects had to modify their motor response, the mental set required to prepare the corrective movement took almost as much time as for the initiation of a correct motor response ($OMT > CRT + NOMT$).

Error and Overshoot rates:

In terms of error and overshoot rates, the Parkinson group tended to make less false moves than the control group but these differences were not significant.

In the studies reviewed, it was found that the parkinsonians were not abnormally prone to make more false moves indeed, they even tended to make less errors and to be more accurate than control subjects (Angel et al., 1970; Berardelli et al., 1986a; Marsden, 1982). The results of the present study corroborate the findings of the latter authors but do not support Flowers' conclusions (1978a). Indeed, Flowers (1978a) found that the error score of parkinsonians was considerably worse than normal and that, as opposed to control subjects, there was no possible improvement in error score for them. In light of the present results, not only did we notice that Parkinson subjects were not different than control subjects but that, as with the latter, they were also able to reduce their false moves. This improvement in both, error and overshoot rates, occurred during the first block of trials, i.e., during the first 400 movements.

Conclusion:

Overall, the results of this study suggest that once they are given sufficient practice to learn a task (1200 responses), and when they are under drug control, Parkinson subjects are not significantly different from their age-matched controls except for their ability to make decisions when movement direction is less probable (25% & 50%), and when they have to readjust their motor responses after having overshoot the target light. In other words, these findings propose that bradyphrenia (slowness of thought or slowness of decision making), which was masked during learning, may be a more important feature of Parkinson's disease than previously thought since it remained after extended practice while the patients were in an alleviated state. As to the tendency of the Parkinson subjects to be slower than control subjects at initiating (akinesia) and executing (bradykinesia) simple and long movements, it gradually improved with practice to reach a point (during extended practice) where both groups were no longer distinct.

Given the characteristics of the present task, which allowed a large number of movement responses (2000 movements), it was possible, during this study, to observe that, in the learning of this novel task, akinesia and bradykinesia were respectively seen as a difficulty in deploying and monitoring already existing motor programs in novel situations. Since the Parkinson subjects during the extended practice had no more difficulty than control subjects at initiating simple response and executing movements, it was suggested that with prolonged practice, Parkinson subjects were able to develop motor sets, i.e., to modify an existing motor program for use in a new situation.

The major contribution of this study is to have demonstrated that Parkinson subjects could benefit from extended practice at a novel task to such a point that their performance became not significantly different from that of their matched controls. As to their ability to make decisions implying more choices, the nature of the differences between both groups became more obvious with extended practice since parkinsonians proved to be significantly slower at making more complex decisions.

In order to obtain a clearer picture of the true effects of Parkinson's disease on psychomotor performance, future studies on the tracometer would benefit from increasing their Parkinson group and from extending the learning session from eight to twelve trials (1200 responses) before testing the Parkinson patients at an unalleviated state. Indeed, given the fact that eight trials seemed not to be sufficient for the Parkinson group to feel comfortable with the task, the results at the "off" phase may have been contaminated by learning.

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GENERAL INFORMATION SHEET

Name: _____

Resident Number: _____

Address: _____

Phone Number: _____

Date of Birth: _____

Present Age: _____

Date of Admission: _____

Main Diagnosis: _____

Stage (if applicable): _____

Other Relevant Diagnoses: _____

Past Medical History: (i.e. date at onset, length of time requiring hospitalization, recent surgeries - 1 yr, epilepsy, etc.)

Medication & Timetable: _____

Physician: _____

Previous occupation(s): _____

Hobbies, interests: _____

Activities at Centre (i.e. Physiotherapy, occupational therapy, recreology): _____

Miscellaneous: _____

C

Appendix B

INSTRUCTIONS ABOUT THE TASK

This machine measures your ability to respond to a stimulus by measuring the time you take to react to a light (reaction time) and the time you take to perform the task, i.e., is to move towards the target light and turn it off (movement time). This machine also measures errors (starting in the wrong direction) and overshoots (overshooting the target light).

The machine includes a wheel, a pointer, and five target lights. The wheel and the pointer go in opposite directions which means that when you want to move the pointer to the right, you turn the wheel to the left or vice-versa.

There is a cross on the pointer. To turn off the target light, you have to cover the light with the cross for an uninterrupted period of 200 milliseconds otherwise the light will not turn off.

The display shows five target lights that will appear one at a time. No other target will appear before you complete a successful alignment.

The task is to move the pointer towards the target light and to align it for a period of 200 msec for the light to turn off and for the next one to appear. Try to accomplish the task as fast and as accurately as you can. Try not to grasp the wheel too tightly and do not forget to blink the eyes often.

One trial consists of 100 target movements. The experiment includes 20 trials (2000 movements) distributed into four sessions. The first session aims at learning the task. It includes eight trials and lasts approximately 40 minutes (Parkinson subjects are under drug control). The second one is run when the Parkinson subjects are at an unalleviated state (off medication) and this, in order to look at the effects of the disease on the movement components. For this session, the dose of the parkinsonians has to be postponed from one to three hours. The third session is conducted thirty minutes after the administration of the postponed drugs to examine how fast the medication become effective. Finally the last session, whose objective is to look at the performance of the subjects at their peak dose effect, is held about two hours after drug ingestion (or one hour and a half after the third session).

Appendix C
CONSENT FORM

Je _____ reconnais que le test m'a été expliqué et
j'en comprends les composantes.

J'accepte de participer à cette étude, toutefois il est entendu que je
serai libre de m'en retirer en tout temps si j'en manifeste le désir.

(Signature)

(Témoin)

Signature du médecin en service

CONSENT FORM

I _____ acknowledge that the test has been explained to
me and I understand what is required.

I agree to participate in this study with the understanding that I am
free to quit whenever I wish.

(Signature)

(Witness)

Signature of the attending physician

Appendix D

INVENTORY OF THE ANSWERS

a) *Parkinson group:*

STRATEGY- 4/7 subjects said they first started by putting more emphasis on accuracy but that they adopted another strategy afterwards, i.e., they concentrated on speed and on accuracy. The other Parkinson subjects, 3/7, revealed that they kept the same strategy all along, i.e., they put as much emphasis on speed as on accuracy.

ANTICIPATION- 4/7 Parkinson subjects did not try to anticipate the next light while the three others maintained that they tried sometimes.

b) *Control group:*

STRATEGY- 5/7 control subjects said they were putting as much emphasis on speed as on accuracy all along the 20 trials. The remaining subjects (2/7) opted for accuracy.

ANTICIPATION- 5/7 control subjects did not try to anticipate the direction of the next light while 2/7 tried sometimes.