Neurobiological Bases of Interval Timing: Effects of Parkinson's Disease

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Abstract:

Temporal information processing in people with parkinson's disease [off medication] and in healthy controls was investigated using a psychophysical choice procedure and an interval production task in two time ranges, milliseconds and seconds. There were no differences between groups on a frequency bisection task [control task, non-timing]. Control subjects produced equivalent Weber fractions in the estimation [bisection] task for the milliseconds range [200 ms - 800 ms] and in the seconds range [1 - 4 seconds]. The PD group showed poorer performance only in the millisecond estimation task. For the interval production task, the parkinsonian subjects produced higher coefficient of variation values for total variance irrespective of range tested [target inter-tap intervals of 550ms and 2.25s]. The use of verbal suppression / no-suppression had little or no influence on these findings. Separate clock and motor-delay variance was estimated using the Wing and Kristofferson [1973] model. Analysis of the subset of subjects whose data did not violate the model's assumptions produced a group difference on this task but indicated that both clock and motor deficits, irrespective of range would be found if larger sample sizes are used. Coefficients of variation were higher in the seconds tapping task for both the PD and the control subjects. These findings suggest that parkinsonian individuals when tested off medication do not exhibit the scalar property, that is a constant source of variability across time. The effects of Parkinson's disease on timing performance appears to be task-dependent.

1. Introduction

Timing is a fundamental attribute which underlies information processing in humans and animals. Interval timing refers to the ability to keep track of arbitrary periods and this mechanism must be able to both start and stop events. It plays an important role in the processing and execution of motor and perceptual activities and is a subject of widespread contemporary interest [Gibbon, Malapani and Gallistel,1997, Ivry, 1996]. Recent studies have provided mixed evidence in regard to the neural basis of timing and have resulted in conflicting viewpoints in the literature. The neural structures implicated in temporal information processing in humans include the mesotelencephalic dopamine systems, and the cerebellum, but their exact contribution to timing processes is still unclear. Current evidence supports the notion that both of these neural systems are involved in interval timing but some findings have generated suggestions that they are involved in the timing of events in a duration-dependent manner.

The primary aim of the current study was to examine interval timing performance in parkinsonian participants. The study used two types of task, an estimation task where intervals are timed and classified as short or long, and a production task [finger tapping] where a subject was required to produce a specified time interval. These tasks were examined under two sets of conditions. Of greatest interest was whether the duration of the interval being timed, which was varied in a millisecond or seconds range, was a critical variable in the context of accurate timing. A secondary concern was related to the use of articulatory suppression to control for the possible use of other non-timing strategies. Originally the study intended to investigate both parkinsonian patients and subjects with cerebellar damage but due to time restrictions only preliminary data from two cerebellar patients was collected.

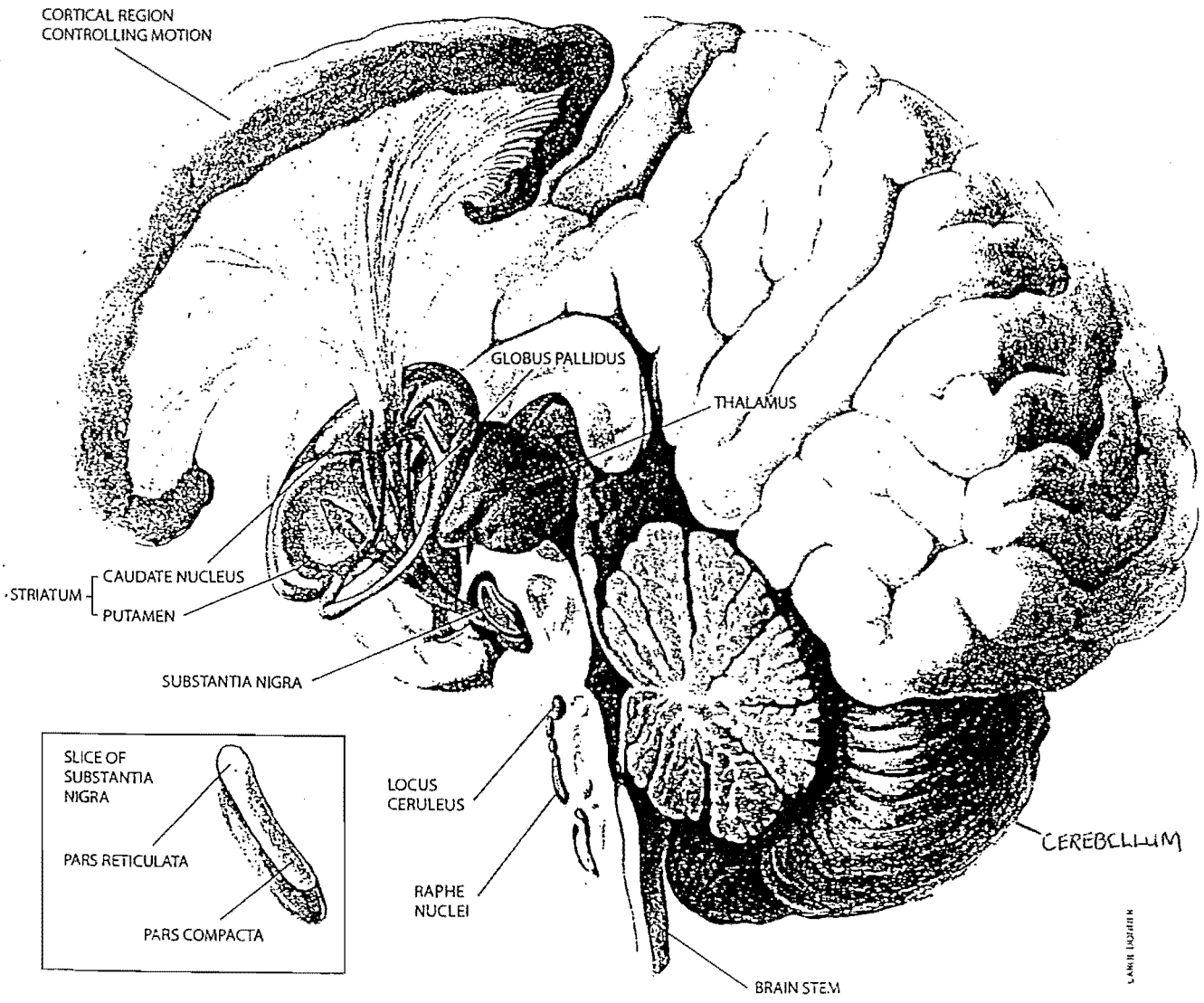
1.1. Anatomical Considerations:

The basal ganglia constitute part of the telencephalon section of the forebrain. It consists of a collection of subcortical nuclei positioned underneath the lateral ventricles [see Figure 1]. These nuclei include the caudate nucleus, the putamen and the globus pallidus and are known to affect the control of movement [Carlson, 1991]. They receive information from the neo-cortex and the cerebellum and communicate with other brain stem nuclei such as the substantia nigra, the red nucleus and the reticular formation. Parkinson's disease is a degenerative disorder of the nigrostriatal dopamine pathway between the substantia nigra and caudate nucleus and putamen of the basal ganglia. There are a number of symptoms associated with Parkinson's disease [motor and non-motor] with the most noticeable being a difficulty in the initiation or coordination of movement and a loss of balance, which is often accompanied by a rhythmic tremor of the hand or foot. These motor disturbances result from the destruction of brain stem nerve cells that communicate with other systems that underlie the cerebral cortex. Movement is controlled by the release of chemical messengers like dopamine into the striatum [see Figure 1], striatal cells then relay the dopamine transported message to other centers of the brain that project it to the cortex which then uses this information to determine muscle behaviour. However when substantia nigra neurons degenerate, dopamine signals decline resulting in disruptions to the motor system and compromised functioning and activity [Youdim and Riederer, 1997].

The cerebellum is part of the metencephalon section of the hindbrain. It has a cerebellar cortex and a set of nuclei located deep inside of it that have reciprocal projections with the cortex [see Figure 1]. The cerebellum can be sectioned into three regions, lateral which projects to the fastigial nucleus, intermediate which connects to the interpositus nucleus and the vermal region which projects to the dentate nucleus. Efferent projections leave the cerebellum via the peduncles and target

Figure 1: Location of the Basal Ganglia and the Cerebellum

[after Youdim and Riederer, 1997]



other central nervous system structures connecting with areas like the primary motor cortex [Ivry, Keele and Diener, 1988]. Two common symptoms of cerebellar dysfunction are dysmetria and dysdiadochokinesia [the inability of a person to alternate rapidly between a pair of movements that involves antagonistic muscles], signs that result from a breakdown in the ability to time the onset and offset of antagonistic muscle behaviour. Movement in a person with cerebellar dysfunction can also be hypometric [when they overshoot the target because termination of agonist activity has not occurred], especially following lesions to the hemispheres or the deep cerebellar nuclei. [Ivry & Keele, 1989].

1.2. Dopamine Pathways and Timing:

A: Empirical evidence from Animal studies:

Much of the evidence relating to contributions of brain pathways in temporal information processing has originated from studies that have investigated timing in animals. For example Meck and Church [1984] trained rats using a psychophysical choice procedure [bisection task] to choose between two levers, one of which had been designated long and the other short. The animals' response was reinforced only if it corresponded to the presented stimulus of a short or long duration. Once the animal had been trained to make these discriminations accurately they were presented with unreinforced intermediate signals. Across these various intermediate signals the probability of the animal responding to one of the levers [usually the long lever] produces a gradient from which performance-related measures can be extracted for analysis.

Evidence to suggest that the nigrostriatal dopamine and basal ganglia systems are important in timing comes from a series of animal lesion studies carried out by Meck and colleagues [reviewed in Gibbon et al, 1997, and Meck, 1996]. They

investigated the performance of rats on peak interval [PI] timing tasks after they had received lesions to the substantia nigra, the caudate putamen [dorsal striatum] or to the nucleus accumbens [ventral striatum]. Rats that sustained lesions to the substantia nigra or to the caudate putamen exhibited disruptions to their timing process and lost the ability to discriminate time intervals. However, with the administration of the dopamine precursor L-dopa timing ability was restored to those rats which had sustained lesions to the substantia nigra but not for those which received lesions to the caudate putamen indicating that dopamine levels in the latter structure were critical to normal timing performance.

One important finding related to time perception in the seconds to minutes range is the ability to selectively affect internal clock speed through pharmacological manipulation [Nichelli, 1993]. Meck [1983] showed that in rats, the administration of a stimulant drug like methamphetamine increased the speed of the internal clock and induced changes to the subjective experience of an event which resulted in an underestimation of time. When neuroleptic drugs like haloperidol were administered clock speed decreased which led to the subsequent overestimation of that time period. Once the pharmacological manipulation was discontinued animals that had been trained to discriminate time under the effects of these drugs revealed an opposite bias to time estimation, that is overestimation after methamphetamine and underestimation with haloperidol because of compensatory changes in the timing process [Nichelli, 1993]. It is the transient effects of these dopamine drugs that give rise to the notion that clock processes rather than memory processes underlie dopamine effects. By contrast evidence from bisection and other tasks like the peak procedure for example, have shown that rats who sustained lesions to their frontal cortex and hippocampal regions exhibited more permanent deficits in timing functions [Meck and Church, 1984]. The rats with fimbria fornix lesions experienced changes in behaviour consistent with the animal remembering events occurring earlier than they actually had, whereas rats with lesions to the frontal cortex exhibited the opposite effect revealing a tendency to recollect events as eventuating later than they actually had

[Olton, Meck and Church 1987].

B: Empirical evidence from Human studies:

Evidence provided by animal studies has led to the exploration of the role of dopamine and timing processes in humans. As stated earlier dopamine is involved in a number of clinical disorders like Parkinson's disease and it was therefore natural to suspect that people who had these disorders would exhibit difficulties in their ability to time events and that brain structures that were innervated by dopaminergic pathways would be activated during timing tasks [Hinton and Meck, 1997].

Recent work using functional magnetic resonance imaging [fMRI] revealed that areas of the frontal cortex, basal ganglia and thalamus show an increased blood flow during interval timing tasks [Hinton, Meck and Macfall, 1996]. The activity shown by these regions using MRI is consistent with already revealed information about the neurophysiology of timing and the importance of the basal ganglia and frontal cortex systems in animal studies [Meck, 1996].

Contrary to what might be expected given the findings in the animal research, Ivry and Keele [1989] found that parkinsonian subjects [who were receiving medication at the time of testing] did not show any problems in their ability to implement a timed response as measured by a finger tapping task. They also reported that parkinsonian subjects did not reveal a deficit in the discrimination of comparison stimuli as being longer or shorter than a sample stimuli of 400 milliseconds. However, a subset of parkinsonian subjects [N=4] did reveal some increased variability on the tapping task. This difference was thought to reflect the fact that these subjects were clinically different from the remainder based on their pre-medication status and whether their symptoms were asymmetric. Another study by Duchek, Balota and Ferraro [1994] that compared medicated parkinsonian subjects and Alzheimer patients with elderly and young controls found non-significant differences in clock delay variability and motor delay variability components of a finger tapping task.

In conflict with these findings, other studies have found that parkinsonian patients do show deficits in their timing abilities. Pastor, Artieda, Jahanshahi, and Obeso [1992] designed a study that assessed the perception of time by patients with Parkinson's disease. They tested forty-four idiopathic parkinsonian patients on three types of time estimation and reproduction tasks and compared their performance with that of twenty normal control subjects. The first task involved a verbal estimation of the duration of a time interval where subjects were trained to estimate an interval of one second and then to use internal counting to estimate other time intervals presented to them. The reproduction of time intervals and the evaluation of motor speed, initiation and execution constituted the remaining tasks. There were twenty seven trials in these tests which each consisted of three time intervals that were presented randomly nine times. Subjects in this study were tested after their dopamine medication had been withdrawn for a period of 12-24 hours and it was found that the neurological patients showed a higher percentage of underestimation in time estimation tasks than the control subjects and that they demonstrated a greater percentage of overestimation on tasks that required the reproduction of time intervals. Following the administration of levodopa a significant improvement in time estimation and reproduction by the parkinsonian subjects was detected.

Artieda, Pastor, Lacruz and Obeso [1992] studied somaesthetic temporal discrimination thresholds [STDT] in parkinsonian subjects and normal controls using tactile, visual and auditory stimuli to look at the time intervals required for pairs of stimuli to be perceived as separate. When tested off medication parkinsonian subjects were impaired in the temporal discrimination of these three sensory modalities in comparison to control subjects. This deficit increased with disease severity but could be somewhat improved with the administration of levodopa. A problem with this study was that it was unclear about the possible mechanisms involved in this difference between the parkinsonian and control subjects on these tasks.

A study by O'Boyle, Freeman and Cody [1996] investigated temporal

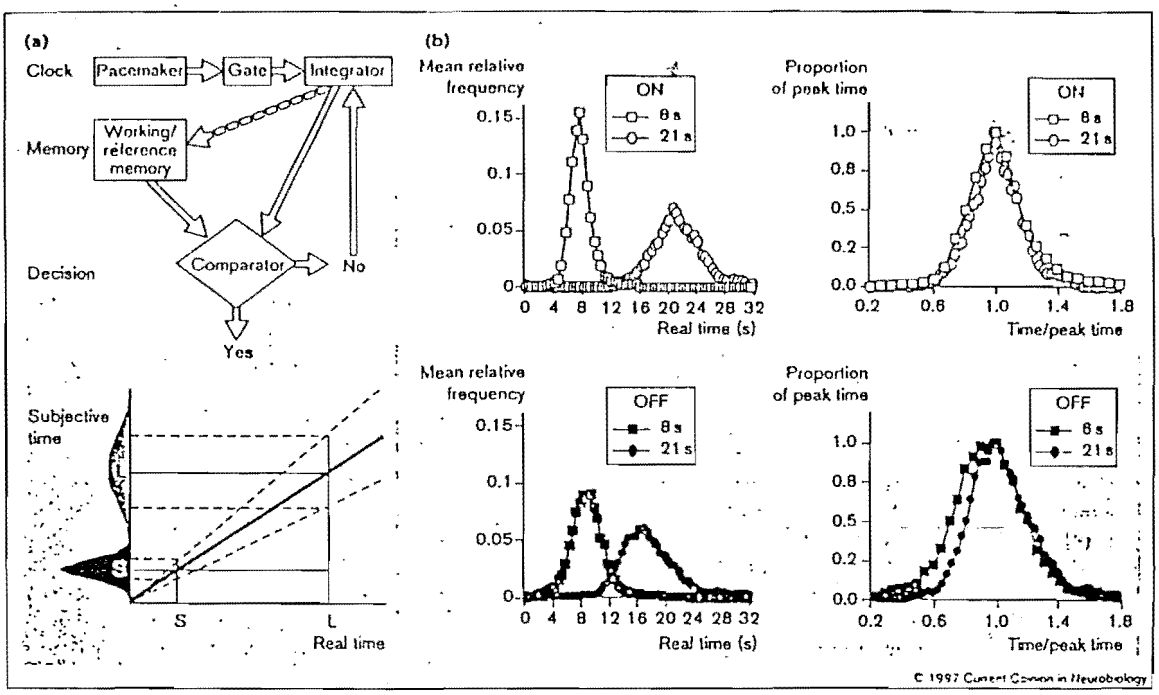
accuracy of self-paced finger tapping in two groups of parkinsonian subjects [N=12] and a group of 12 control subjects. One parkinsonian group was tested off medication [12-15 hours] and then again on medication whilst the second group who exhibited bilateral signs were tested using their 'better 'or 'worse 'hands. Each session required the subjects to complete self-paced tapping trials at a target rate of 550ms. It was found that the mean self-paced inter-response intervals of the parkinsonian subjects were significantly shorter during the 'on 'medication condition and that total, clock and motor variance values of the Wing and Kristofferson model [1973] were all significantly higher for the group during the 'off 'medication condition.

Further evidence implicating dopaminergic systems in temporal processing has come from pharmacological studies that show that the production and estimation of time can be influenced by the administration of drugs. Gibbon and colleagues [1997] reported that neurologically intact subjects when tested after taking dopamine agonists like methamphetamine produced temporary distortions in their accuracy on a bisection task. When trained off and tested on agonists an underestimation of trained target intervals was found but when the subjects were trained on the agonist and then tested off a tendency to overestimate was revealed. The reverse pattern of estimation was seen when dopamine antagonists like haloperidol were administered. These systematic over and underestimations of time are associated with scalar variability [see Figure 2]. The scalar property involved in this response variability can be seen when the internal clock reaches a criterion early and the level of variability declines however when a late response to this criterion is made this variability increases.

Rammsayer [1993] designed an experiment to investigate the effect of pharmacologically induced changes in D2 receptor activity on temporal information processing. The purpose of the experiment was to test the notion that change in the pacemaker speed of the internal timing mechanism in a time perception task was caused by changes in D2 receptor activity and to study the effect of pharmacological changes in the activity of D2 receptors on these time estimation tasks.

Figure 2: Scalar Interval Timing and the Scalar Timing Model.

[after Gibbon, Malapani, Dale and Gallistel, 1997]



Scalar interval timing. (a) Information-processing components of the scalar timing model (top) generate subjective time distributions (bottom), which are scale transforms of each other. S, short (real) time; L, long (real) time. (b) Time estimation performance of Parkinson's disease patients (left column) exhibits scalar variability when they are ON medication (note that the normalized distributions in the upper right-hand panel superimpose), but not when OFF their medication (the normalized distributions in the lower right-hand panel do not superimpose).

The subjects consisted of 36 healthy male volunteers who were given either haloperidol which blocks striatal D1 and D2 receptors or remoxipride which selectively blocks mesolimbic and mesocortical D2 receptors or a placebo and were tested on an auditory temporal discrimination task. The experimental session consisted of a block of duration discriminations in the milliseconds range, described as a time perception task and one block in the seconds range described as a time estimation task with each block consisting of 50 trials. Rammsayer [1993] found that haloperidol produced a large decrease in performance on the milliseconds range task but remoxipride did not exhibit any drug effect on this task when compared to the placebo. Performance on the seconds range task was greatly affected by haloperidol but in this case there was also an effect of remoxipride. Rammsayer claimed that this differential effect between haloperidol and remoxipride on the time perception [milliseconds] task suggested that the internal timing mechanism was more likely to be dependent upon the D2 receptor influence on dopamine antagonistic effects on the basal ganglia rather than the mesolimbocortical system which would have been affected by both haloperidol and remoxipride.

A study by Rammsayer and Classen [1990] in parkinsonian patients found the same effect of D2 receptor blockers on time perception performance and suggested that this marked decrease in performance in the millisecond range was dependent upon the potency of haloperidol in blocking striatal D2 receptors whereas remoxipride blocked mesolimbic and mesocortical regions.

1.3. Cerebellum and Timing:

A: Empirical evidence from Human studies:

Another line of inquiry that has recently emerged in the literature suggests that the cerebellar system may be involved in interval timing processes especially those concerned with very brief time ranges [milliseconds]. Unlike the empirical evidence surrounding the role of dopamine pathways in interval timing the evidence for cerebellar involvement has originated from human research [McCrone ,1997].

The principal study here examined the performance of cerebellar subjects in judging brief duration stimuli [Ivry and Keele, 1989]. They compared four neurologically impaired groups including subjects with Parkinson's disease, cerebellar lesions and cortical or peripheral neuropathy, with control subjects who were either elderly or college aged. Subjects were tested on two types of task, a motor timing task [finger tapping], and a temporal discrimination task which required the comparison of durations that were either shorter or longer than a standard duration of 400 milliseconds. The cerebellar subjects were the only group who showed standard deviations that were significantly different when compared to the elderly control subjects and the performance of the other neurologically impaired patient groups. As mentioned earlier the parkinsonian subjects were only tested on these tasks while they were medicated. The motor timing task used a standard finger tapping procedure of approximately 12-14 paced taps and 31 self paced taps and revealed similar findings to that of the discrimination task. The cerebellar and cortical subjects showed increased variability in their inter-response times on the tapping task when compared to parkinsonian patients or elderly controls whereas the parkinsonian patients did not show any difference in their performance in relation to the elderly controls.

On the basis of their findings, Ivry and Keele [1989] suggested that the cerebellum was crucial to the process of interval timing in the millisecond range because only the cerebellar subjects showed any impairment on both the temporal

discrimination and motor timing tasks. As noted earlier a problem with this conclusion does occur when comparing these results with those of other studies that have included parkinsonian patients. The parkinsonian patients in Ivry and Keele's [1989] study were tested when medicated whilst other studies with parkinsonian subjects have tested them off medication and subsequently found deficits in motor and perceptual timing [O'Boyle et al, 1996] and a dopaminergic influence on interval timing in the millisecond range [Rammsayer, 1993].

Temporal discrimination in cerebellar patients has also been investigated by Nichelli [1996]. The aim of this study was to specify the range of time intervals that the cerebellum may be involved in. Twelve subjects with cerebellar degeneration were tested using a standard bisection procedure across four time ranges [100-900ms,8-32sec, 100-600ms and 100-325ms]. For the first short range interval discrimination task [100ms-short and 900ms-long] cerebellar subjects showed a significantly shorter average bisection point but no actual impairment on the task. Their temporal discrimination abilities and precision however were impaired in the long interval task [8-32 seconds]. A further experiment that looked at discrimination in the two ranges of 100-600ms and 100-325ms revealed an impairment in the cerebellar subjects ability to discriminate in the range of 100-600ms. Several methodological difficulties in this research including the failure to counterbalance conditions and the use of different ratios between the short and long standards make it difficult to interpret the exact nature of those deficits reported.

Recent functional magnetic resonance imaging [fMRI] studies have revealed an increase in the activity level of the brain during tasks that involve temporal discrimination and motor timing. One study investigated changes to activity levels in the brain while subjects completed a standard finger tapping procedure, an increase in activity levels was evident in the cerebellum, the basal ganglia and frontal systems during the experimental portion of this task [Rao, Harrington, Haaland, Bobholz, Cox & Binder, 1997]. Another study used PET [positron emmission tomography] to test activity levels during temporal discrimination tasks [Jeuptner, Rijntjes, Weiller,

Faiss, Timmann, Mueller & Diener, 1995] and also revealed increased activity in the cerebellum on this task relative to a control task.

B: Empirical evidence from Animal studies:

Other than one early study by Kirk [1985], work on timing in animals with cerebellar damage has only recently begun to emerge. Kirk found that rats who were trained using DRL schedules and given lesions to the cerebellar vermis or fastigial nucleus exhibited pronounced deficits in their ability to time events post surgery, but this deficit was not discovered in rats with lesions to the dentate nucleus. Response distributions for the nucleus and vermal group showed a decrease in their peak time but conversely rats who received lesions to their cerebellum after some pre-training on these DRL schedules did not show any of these performance deficits.

Other evidence to suggest that cerebellar lesions disrupt timing comes from studies by Perret and Mauk [1995]. A previous study by Perret, Ruiz and Mauk [1993] found that rabbits who were trained to discriminate short and long durations using Pavlovian conditioning exhibited shorter onset to peak responses following hemispheric lesions. This finding was replicated and further evidence provided by Perret and Mauk that suggested the importance in particular of the anterior portion of the cerebellum in accurate timing.

Recent research by Breukelaar and Dalrymple-Alford [1998] has shown that rats that had been trained on a psychophysical choice procedure with stimuli between 2 and 8 seconds did not show any impairment after they had sustained lesions to the cerebellar vermis or cerebellar hemispheres. When trained using stimuli that ranged between 200ms and 800ms, however, a transient impairment in performance was discovered in the group with lesions to the cerebellar hemispheres.

Clarke, Ivry, Grinband, Roberts and Shimizu [1996] also carried out a study of temporal discrimination using a bisection procedure that looked at both the millisecond and seconds range. In the first of two experiments rats were trained to

discriminate between the ranges of 0.3-0.75s and 25-40s prior to being tested on a psychophysical choice procedure. The rats received bilateral lesions to the dentate nucleus or sham lesions before being retested. The rats that were lesioned did show temporary increases in performance measures [point of subjective equality [PSE], standard deviations [SD] and Weber fractions] for timing in the millisecond range relative to pre-surgery performance and in comparison to controls. For the seconds range, all performance measures between the lesion and sham group were the same for pre and post surgery conditions. A second experiment that gave rats training prior to surgery on a comparable discrimination task in the milliseconds range produced evidence to suggest that following lesions to the dentate nucleus performance was again impaired in comparison to those rats with sham lesions.

1.4. Theoretical Considerations:

One issue that has emerged from research on temporal information processing has been whether all timing related tasks involve the operation of a common timing mechanism or whether multiple interval timing mechanisms exist. A question that arises from this controversy has been whether a single model exists that can appropriately explain a single timing process or whether a model for multiple timing is required. Neuropsychological research has tended to agree more with the idea of multiple timing mechanisms because there is evidence to suggest that damage to a wide range of neural systems can affect performance on timing related tasks [Ivry, 1993]. However, evidence can also be provided to support the notion of a single internal timing system where temporal information can be represented explicitly [Ivry, 1996]. A number of different types of models have been put forward to try and account for temporal information processing. Pacemaker models [see Figure 2] focus on designating the origin of processing to a single timing mechanism whereas alternative timing models [neural network] concentrate on the idea of distributed representations of temporal information.

In their influential paper Ivry and Keele [1989] argued that their evidence supported the existence of a common timing mechanism that was used in both the perception and production functions of time-related decisions was restricted to the millisecond range. They originally suspected that the cerebellum could function as this timing mechanism because the two critical cerebellar signs, dysmetria and dysdiadochokinesia, were a result of a breakdown in the ability to time the onset and offset of antagonist muscles, because of some animal lesion work that revealed disruptions in timing responses, locomotion and rapid movement. Because their cerebellar patients were the only group to show impairment in making time related judgements in both of their perception and production tasks, Ivry and Keele concluded that a single clock mechanism based in the cerebellum was used for millisecond timing only.

Rammsayer [1993] also made a duration-dependent distinction, but this time on the basis of an assumption that there are different psychological and neurobiological processes for estimation [time interval of seconds to minutes] and perception [time interval of brief durations-milliseconds]. His reasoning was that processing in long ranges of seconds or more was dependent upon cognitive operations whereas temporal processing of brief duration ranges was suggested to be beyond cognitive control and in the domain of automatic processing at a subcortical level [Rammsayer, 1997]. Rammsayer [1993] suggested that the differential effect on time estimation and perception by haloperidol [both tasks] and remoxipride [estimation only] was due to the relative influence of D2 receptors on dopamine antagonistic effects in the basal ganglia [perception - milliseconds range] and the mesolimbic or mesocortical [estimation - seconds range] regions. A reason for this conclusion was that if mesolimbic or mesocortical activity was involved in the processing of brief durations in the millisecond range then performance on the time perception tasks should have been affected by both the typical [haloperidol] and the atypical [remoxipride] neuroleptic drug [Rammsayer, 1997]. Thus he concluded that this pharmacological evidence supported this dichotomy between millisecond

timing [basal ganglia-dependent] and seconds timing [limbic system-dependent]

Gibbon, Malapani, Dale and Gallistel [1997] discussed the importance of multiple interval timing systems in humans and animals but as evidence for multiple timing systems was weak they concentrated instead on a single model, a scalar timing model, to explain interval timing [see Figure 2]. Interval timing systems are known to be more flexible than other timing systems, for example circadian timing, but they noted the strong evidence that this flexibility is obtained at the expense of precision. A crucial feature of this view of interval timing is Weber's Law which suggests that the variability that underlies any timing accuracy distribution should show a constant coefficient of variation [SD / Mean]. If this law was true in the case of interval timing then it could be expected that time estimation distributions would superpose on a graph when the axis is normalized and thus reflect time scaling [see Figure 2]. This scalar property is a crucial feature of the information processing scalar timing model.

The scalar timing model consists of clock, memory and decision stages and successfully accounts for the evidence from a variety of timing tasks that are temporally controlled [see Figure 2]. The clock stage is made up of a pacemaker that generates pulses which are gated by a switch into an accumulator, effectively representing the total amount of time that has passed. This representation is kept temporarily in working memory and then fed into a store with a distribution of similar information that has been based on the previous outcomes [reference memory] so that values can be compared at a decision stage to influence current behavioural outcomes [Gibbon et al, 1997].

A problem that confronts a model such as the scalar timing model is the difficulty in suggesting plausible mechanisms for timing longer intervals especially when this procedure may involve different processing mechanisms at the neurobiological level. Research into the variability of interval timing in humans and animals spans a wide range of time orders and Gibbon and colleagues [1997] have suggested that one way to identify this notion of variability was to investigate coefficients of variation at different time ranges. They summarized a series of animal

and human data across different time ranges from a wide range of studies and paradigms and discovered that these coefficients tended to be high indicating other non-temporal sources of variability. The data did not give clear evidence as to whether coefficients of variation across different time ranges do in fact differ or not although this may have been due to the nature of the tasks used for different time ranges. They summarized previous work by extracting from the reported data the summary the coefficients of variations for patients with degenerative basal ganglia disease, frontal lobe lesions and cerebellar lesions relative to normal controls. In their view this evidence gave little indication of any differences when examining short and long time ranges. They state that this is an important point given that most of the research on dysfunction in the basal ganglia [presumed by some to be responsible for the seconds range] and cerebellum [milliseconds range] has been to propose a dichotomy between these neural structures in timing [Ivry, 1997]. Yet they have often come to this conclusion when comparing timing evaluated in different tasks in each case.

According to Gibbon et al [1997] what evidence exists on the effects of timing in different ranges suggests that subjects with basal ganglia deficits show an underestimation of time in the short ranges but overestimate time in a longer duration range, and that cerebellar subjects do not reveal a deficit in their accuracy relative to short or long time ranges. Ivry and Keele [1989], however, argued that cerebellar subjects were less accurate when making perceptual judgements in relation to small duration differences. Gibbon and colleagues [1997] concluded that it was unlikely that the basal ganglia and cerebellar systems were independent of each other in temporal information processing due to the fact that both neural structures produce variability in common tasks; they also argue that lesions in both the basal ganglia and the cerebellum result in disruptions to both long and short range timing tasks.

1.5. Some Procedural Issues:

A principal reason why evidence surrounding temporal information processing is mixed and unclear is that it is difficult to make comparisons between studies because of their procedural and methodological differences. One crucial issue that has not been conducive to comparative analysis relates to the way that subject characteristics are reported in the literature, the number of participants included in a study and the diversity in their neurological status. In some research case studies of a small sample of subjects have been used [Ivry, 1986] whereas other studies have gathered large numbers of subjects for research [Pastor et al, 1992]. Sometimes subject groups have been selected from a wide range of countries and their data has been pooled together to increase numbers [Ivry and Keele, 1989]. The reporting of the neurological status of participants in these timing studies has also been problematic. Many of the experimental studies have employed different criteria when choosing subjects to include or exclude. For instance participants across studies often differ in regard to their illness duration, disease severity or dementia scores, and a lack of standardized reporting procedures has resulted in problems when trying to compare and analyse data across them.

One important issue in the debate on temporal information processing has been whether or not parkinsonian subjects are receiving dopaminergic medication during testing on timing related tasks. Performance results of parkinsonian subjects on the estimation and the production of time have been mixed, some studies have tested their subjects while they are taking dopaminergic medication whilst others have tested them off medication. When parkinsonian patients have been tested on medication their timing performance has not been affected [Ivry and Keele, 1989] but other studies that have tested parkinsonian patients off dopaminergic medication have shown that over and underestimation of time can occur [Pastor et al, 1992]. A shortening in the inter-response intervals of tapping tasks [O'Boyle et al, 1996] has also been found in parkinsonian subjects and the effect of dopamine on timing

behaviour has been illustrated further by pharmacological manipulations of dopaminergic agonists and antagonists [Gibbon et al, 1997].

Another major concern is the fact that the experimental tasks employed in the literature vary significantly in their characteristics. Most of the human data comes predominantly from tapping research and a few discrimination studies [Ivry and Hazeltine, 1995; O'Boyle et al, 1996]. Results from tapping studies are often analyzed using the Wing and Kristofferson [1973] model of variability to extract separate but not independent measures of clock variance and motor variance and support for this model has been obtained from work with normal and neurologically impaired individuals. However a problem with the model occurs in that while the clock and implementation processes are thought to be independent their estimates are not obtained independently [Ivry and Hazeltine, 1995]. Thus the assumptions of the central timer and its relationship to motor timing that the model has been based remain dubious. Both cerebellar and parkinsonian subjects have been shown to violate some of the basic assumptions of the model particularly lag 1 covariance estimates. In the cerebellar group of Ivry and Keele's [1989] study an increase in the variability of their mean clock estimate and motor delay estimates was found in comparison to the elderly controls and parkinsonian subjects but this difference in the motor delay estimate was not reliable.

The estimation tasks are also problematic. Conflicting evidence has been provided that indicates the presence of overestimation and underestimation in bisection tasks. Some of the procedures used to assess temporal estimation do not actually focus on timing per se because they have used a counting based paradigm [verbal estimations] which may depend on an entirely different set of processes [Pastor et al, 1992]. It would thus be informative to have data from individuals who have parkinson's disease from a simple bisection procedure like those that have been successfully used with animal studies [eg. Breukelaar and Dalrymple-Alford, 1998] and with neurologically intact people [eg. Wearden, 1996].

A central issue in the timing literature concerns the fact that many studies have

investigated timing in only one time range, that is the long range or short range. It would thus be valuable to look at the performance of parkinsonian subjects in the same pair of tasks over different time ranges. Scant evidence has been revealed about the cerebellum and the basal ganglia and timing of different durations. The study by Nichelli and colleagues [1996] with cerebellar patients revealed a problem with temporal discriminations in the millisecond and seconds range but this study had several methodological problems such as not counterbalancing the time ranges used and using different ratios for the short and long standard as well as using articulatory suppression in the seconds range only [to prevent chronometric counting].

1.6. The Current Study :

The aim of the current study was to address some of these methodological issues that have appeared in the literature and to revisit some of the issues raised about temporal information processing in humans. The present study investigated the performance of people with Parkinson's disease on a production and an estimation task using two time ranges. Two types of timing task, an estimation and an interval production task were used. The estimation task was an external perception task that employed a psychophysical choice procedure [bisection task] in which a subject was trained to classify examples of a short and long duration stimuli and was then required to judge intermediate durations as more like the short or the long example. Three performance measures were obtained from this procedure, the PSE [point of subjective equality], the difference limen [DL], a measure of variability and the Weber fraction [DL / PSE] which is a measure of relative sensitivity. The interval production task was a finger tapping task [Ivry and Keele, 1989] which required a subject to tap their finger along in time with approximately twelve regularly spaced tones. They were then asked to continue tapping their finger at this rhythm until 31 self paced taps had been recorded. The finger tapping data were analyzed using the Wing and Kristofferson [1973] model of variability which decomposes performance

into separate clock and motor implementation variability.

Two experimental conditions were included in each of these timing tasks, the first manipulation aimed to look at timing of different durations. The reason for doing this was to explore the suggestion that the underlying neurobiology of timing differs in the range of seconds and milliseconds and to test the notion that parkinsonian individuals might be impaired on both the estimation and production task in the seconds range. The short range estimation task varied between 200-800ms and the long range condition varied between 1 and 4 seconds. The tapping task contained target rates of 550ms [short], and 2.25 seconds [long]. An experimental condition of secondary concern involved the use of or absence of articulatory suppression to control for non-vocal timing strategies like counting. Suppression tasks are known to affect attentional processes which may be deficient in parkinsonian individuals and it is because of this reason that it was considered necessary to control for this possibility in both time ranges even though it should not prove a difficulty in short range tasks. The suppression task should indicate whether there is an attentional deficit present or not. A frequency estimation task was also included to act as a control task for any deficit that may arise from the discrimination of short stimuli or for potential effects related to the suppression task.

The parkinsonian subjects in the current study were only tested off their dopaminergic medication. That is, they completed all of the tasks, short and long durations and with or without suppression, when their antiparkinsonian medication had been withdrawn for a period of approximately 12-15 hours prior to testing [they were tested in the morning before taking their morning medication]. The reason for choosing to do this is that evidence in the literature has suggested that with the removal of dopaminergic medication parkinsonian patients experience deficits in timing abilities. Given the number of experimental conditions and the fact that the suppression and non-suppression was viewed as the more important manipulation parkinsonian patients were not tested on medication.

2. Method:

2.1. Subjects:

The main experimental group consisted of 9 patients with neurologically confirmed idiopathic Parkinson's disease [7 men and 2 women with a mean illness duration of 6.3 years]. All of these subjects showed a premorbid preference for their right hand. The mean age was 65 years [+ or - 5 years] and the mean education level for this group was 3.5 years of secondary school [see Table 1]. These parkinsonian subjects were compared with a control group comprising of 6 healthy subjects, matched to 6 of the parkinsonian subjects on the basis of age [mean age was 64.6 years + or - 5 years], gender, premorbid hand preference and educational background [3.5 years secondary school + or - 2 years]. This control group consisted of 4 men and 2 women [see Table 1; unforseen delays meant that additional controls were not tested at this stage]. Also due to time restrictions, only 2 people could be tested who showed signs of lesions to the cerebellum of the brain [data not reported], but additional subjects are planned for testing in the immediate future. Both cerebellar subjects were female [age: 27 and 31 years, education: 5 years tertiary and 3 years secondary -see Table 1] and were tested with their left non-preferred hand because it was the more impaired in each case [lesions to the cerebellum result in disruptions to the hand ipsilateral to the lesion site]. One healthy female subject, 34 years of age and 3 years secondary education [see Table 1] provided control data for the cerebellar patients, and was also tested using their left hand to provide a comparable condition to that of the cerebellar subjects. Neurological patients were recruited through the Neurology Department at Christchurch Public Hospital. The control subjects were volunteers from local service groups and friends or family members. Participants in the study were subject to the following inclusion and exclusion criteria.

Table 1. Summary of subject details from neuropsychological assessments of the PD and Control subjects.

Participants	Gender	Age	Education	Hand used R / L	Vision left	Vision right	Hearing at .5k dB	Hearing at 1 k dB	Hearing at 2k dB	MMS Max 30	Hoehn/Yahr	UPDRS Total Score
PD1	Female	75 years	5 years sec	R	6/3	6/3	32.5	27.5	22.5	29	3	26
PD2	Male	56 years	4 years sec	R	6/5	6/5	37.5	40	22.5	28	2	33
PD3	Male	65 years	2 years sec	R	6/5-2	6/9-1	35	32.5	22.5	29	2	25
PD4	Male	57 years	5 years sec	R	6/6-1	6/6-3	25	15	17.5	29	2	37
PD5	Male	66 years	5 years sec	R	6/6	6/4	25	20	32.5	29	2	19.5
PD6	Female	66 years	3 years sec	R	6/9-1	6/6	27.5	20	17.5	29	2	29
PD7	Male	57 years	2 years sec	R	6/6-4	6/9-3	25	15	12.5	30	2	41
PD8	Male	71 years	4 years sec	R	6/6-4	6/5-2	37.5	30	40	27	2	55
PD9	Male	72 years	2 years sec	R	6/6	6/6	27.5	25	22.5	29	2	42
Mean (+/- SE)		65 (5 yrs)	3.5 (2 yrs)									
PD Control 1	Female	75 years	5 years sec	R	6/6-1	6/6-1	22.5	17.5	15	30		
PD Control 2	Male	53 years	3 years sec	R	6/5	6/5	25	17.5	15	28		
PD Control 3	Male	64 years	2 years sec	R	6/5-2	6/5-2	32.5	25	22.5	29		
PD Control 4	Male	62 years	5 years sec	R	6/5	6/5	15	12.5	15	30		
PD Control 5	Male	69 years	4 years sec	R	6/3	6/3	22.5	12.5	15	30		
PD Control 6	Female	65 years	2 years sec	R	6/5	6/5	30	20	25	29		
Mean (+/- SE)		64.6 (5yrs)	3.5 (2 yrs)									
CL 1	Female	31 years	5 years tert	L	6/6-1	6/6-1	27.5	27.5	25	30		
CL 2	Female	27 years	3 years sec	L	6/4	6/4	40	32.5	30	29		
CL Control	Female	34 years	3 years sec	L	6/4	6/4	27.5	25	15	30		
Mean (+/- SE)		30.6 (5 yrs)	5 (2 yrs)									

2.2. Inclusion Criteria:

The subjects in the Parkinson's disease [PD] group were rated at least a Stage 2 on the Hoehn and Yahr scale. They were tested off medication in the morning after their medication had been delayed for approximately 12-15 hours. The Cerebellar lesion [CL] group were included in the study on the basis of clinical assessments that showed that lesions were clearly restricted to the cerebellum and did not include other brain structures, in particular the adjacent brain stem. Two neurologists Professor Ivan Donaldson [PD group] and Doctor Tim Anderson [CL patients] evaluated each neurological patient prior to the beginning of testing.

2.3. Exclusion Criteria:

All participants in the study were subject to a number of basic exclusion criteria:

- not older than 75 years of age
- no impaired vision or hearing, ie; they satisfy the minimum vision requirement for driving using the Snellen chart with no less than 6/12 in both eyes [with glasses if required], or that they do not exceed the mild to moderate category of hearing impairment [using headphones] of 30-50dB over the range of 500Hz, 1K and 2K using an audiometer.
- no evidence of possible dementia, with at least 27/30 as assessed by the Mini Mental Status Examination.
- no history of any other neurological disorder or premorbid psychiatric illness other than Parkinson's disease in the PD group or lesions to the cerebellum in the CL group.
- A subject would also be excluded from the study if there was any clinical evidence to suggest that brain damage might extend to the brain stem or spinal structures in the CL group or if they may be receiving any medication known to affect the CNS other than anti parkinsonian medication in the PD group.

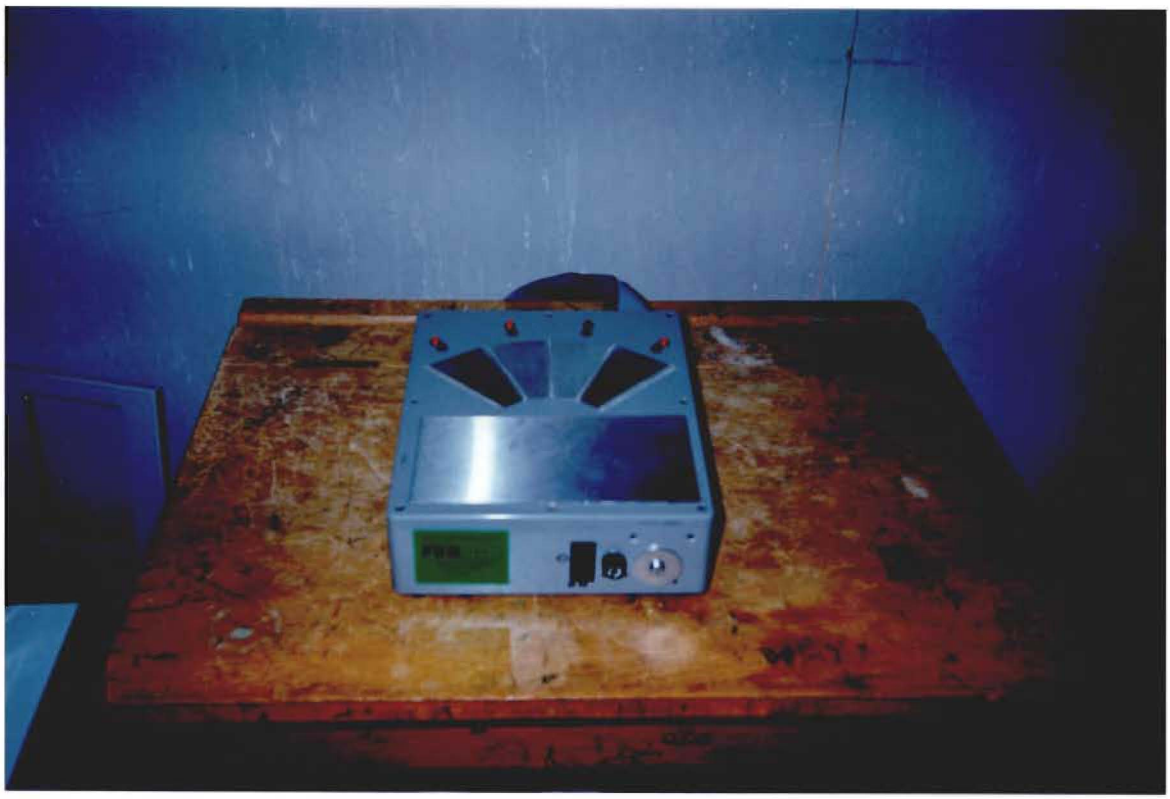
- Parkinsonian subjects would also be excluded if they exhibited signs of overt dyskinesia, if they were on / off type patients and if they satisfied only Stage 1 criteria of the Hoehn and Yahr rating scale.

2.4. Apparatus:

Presentation of stimuli and recording of data were controlled by a PC. One monitor presented the stimuli while a second monitor enabled the experimenter to control the parameters of any given experimental task and to provide feedback to the experimenter and subject as required.

Subjects' responses were recorded from a touch sensitive sensor [see Figure 3] interfaced to the PC. A green light would show up on the sensor to indicate to the subject when a response had been registered.

Figure 3: Tapping Sensor.



All auditory stimuli provided during the trial were relayed through the computer speakers and were generated from a voltage controlled tone generator. These tones were used for the frequency estimation task, the tapping tasks and the time estimation tasks.

2.5. Neurological assessment and evaluation:

The study employed a number of standardized tests as part of the evaluation procedure. The parkinsonian subjects were assessed using the UPDRS [Lang, 1990], and Hoehn and Yahr scales [Hoehn and Yahr, 1967]. The cerebellar subjects however were evaluated using detailed descriptions of the cerebellar signs exhibited by each subject. As indicated each patient was evaluated by a consultant neurologist prior to testing. All participants were assessed using the Mini Mental Status [Folstein, Folstein and Mchugh, 1975] examination. The subjects' vision was tested using the Snellen chart and by presenting a brief series of words on the computer monitor to ascertain that the subject could complete the suppression task and read the computer graphics. Hearing was tested using a calibrated audiometer using frequencies of 500Hz, 1K and 2K, which encompassed all of the frequencies to be used during the estimation task. All subjects had their finger tapping ability tested by means of a single trial of tapping that was extended from 31 to 62 self produced taps to ensure that the task could be sustained for longer than would be actually required during the experimental trials.

2.6. Design:

The experimental design for this study involved evaluating timing in production tasks [finger tapping] and timing in estimation tasks [bisection procedure]. Each of these tasks consisted of an experimental condition of short versus long durations [milliseconds and seconds range respectively]. The production and estimation tasks were also subjected to experimental manipulations where articulatory suppression or non-suppression was employed. Hence a set of 8 different

experimental conditions constituted the main experimental part of the study.

Testing always commenced however, with a frequency estimation [bisection] task at the beginning of each session. Testing took place over two experimental sessions that continued for about two hours in duration each. The following order of testing was used in each session: the first production task, first estimation task, second production task and finally the last estimation task. The order in which each time range was tested on both sessions and whether suppression or non-suppression sessions were used first was counterbalanced across subjects and for each of the two experimental sessions using a latin square design [see appendix A for a complete description of the latin square design for this study].

The suppression condition involved the subject reading out aloud a series of randomly spaced, one syllable words [see appendix B] to minimize any subvocal counting during the timing related trials. Each subject was tested at approximately the same time of day for each session and each of those sessions involved the same order of timing tasks. For example, **Mr X** underwent the following order of testing:

Session 1: [suppression]. Frequency, production short, estimation long, production long, estimation short

Session 2: [non-suppression]. Frequency, production short, estimation long, production long, estimation short

2.7. Frequency Estimation Task:

The frequency estimation task occurred at the beginning of each of the two testing sessions and was designed to function as a control task for any general deficit that may occur in the discrimination of stimuli of short duration and for any potential effects that may result from the use of an articulatory suppression task. The frequency task involved the presentation of 50ms tones. The subject was first trained to discriminate between two standard tones, one that was high in frequency and one that was low in frequency. Once the subject was able to make these judgements they were presented with tones of intermediate frequencies and were asked to estimate whether

they sound more like the high or the low standards.

The subject was seated facing the computer monitor that had been designated to supply any necessary visual stimuli to them during the course of the experimental session and they placed their hands either side of the tapping sensor so that their index finger could be used to make a response by touching either the further most right or left plate of the sensor and the subjects elbow and forearm was supported if necessary [see Figure 3].

A single tone set at approximately 73dB [A] with a duration of 50 milliseconds served as the stimulus for the subject. The subject was presented with a standard low frequency of 700Hz and a standard high frequency of 1600Hz, followed by five logarithmically spaced intermediate frequencies of 776Hz, 875Hz, 1000Hz, 1156Hz and 1352Hz.

This task consisted of a demonstration block, a warm up block and 10 test trial blocks. The demonstration block consisted of 5 random presentations of each of the two standard frequencies and was immediately followed by seven frequencies, the two standard high and low frequencies and five intermediate frequencies. The correct sensor was indicated on the computer monitor in front of the subject after each presentation of the frequencies directing the subject to choose the sensor which might be most appropriate and reminding them to make a response. The subject received prompting during the presentation of the ten examples at the beginning of this demonstration trial but was not given any prompting during the presentation of the seven test frequencies where the subject was expected to estimate whether they sounded more like the high or the low examples.

The warm up block began with only two presentations of the high and the low example frequencies and was then followed by a test trial where the seven frequencies in a different and random arrangement were produced for the subject to estimate as high or low. The subject was then required to complete ten test trial blocks; each trial block was made up of 2 presentations of the high and low standards, followed by the presentation of seven randomly ordered frequencies that contained both the standard

high and low frequencies and the five intermediate frequency tones.

In each of the demonstration portions for every test trial the subject was given prompting to respond to the presentation of the frequency tone, for example, this is high or this is low, and once the subject had responded by tapping one of the sensors, feedback was provided to them indicating whether their response was correct or incorrect. However during the actual experimental part of the test trials the subject was not provided with any prompting or any feedback apart from the appearance of two small computer graphics that reminded the subject which sensor should be tapped if they wished to choose high or low as their response. At the end of each test trial the subject was provided with a verbal explanation of their responses describing whether they made any incorrect estimates about the presented frequencies. The presentation order for the test frequencies was randomly determined at the beginning of each test trial by the experimenter who entered a word list number in the computer menu before starting. [see appendix C for an example of the sequence of events].

During the suppression condition the subject was required to read aloud a series of words that were displayed on the computer monitor facing them. The eye to monitor distance was approximately 123 centimetres and the words were presented in lowercase with a word size of 2.5 centimetres The words were displayed at irregular intervals with a mean rate of one word / 3 seconds, presented to the subject only after the demonstration portion at the beginning of a test trial. This suppression condition was the same across all of the bisection tasks.

After each trial the subjects' response was recorded and a summary of the responses corresponding to each frequency presentation was displayed on the computer screen in front of the experimenter who gave brief verbal feedback.

2.8. Interval production task - Finger tapping:

For the duration of this task the subject was required to use their most preferred hand, although the cerebellar subjects were instructed to use their opposite hand for this task if it appeared to be more impaired, because damage to the

cerebellum manifests itself by producing deficits in the hand ipsilateral to the lesion. The task began with a verbal explanation of the procedure [see appendix D], and was then followed by three practice trials. Each trial in this task began with a series of regularly spaced tones with a duration of 50 milliseconds [1000Hz @ approx 73dB [A]], which were synchronized with a small [5 cm] red flashing square which appeared on the computer monitor in front of the subject. For the short range tapping task [motor timing in the milliseconds range], the tone frequency or interval from onset to onset was designated to be 550 milliseconds. This interval was chosen because it had been reported in a number of studies [Ivry and Keele, 1989; O'Boyle, Freeman and Cody, 1996] that suggested that it was a rate that was significantly slower than the maximal tapping rate of parkinsonian subjects, making it likely that none of the subjects in the present study would have a problem maintaining this pace during the trials. For the long range tapping tasks an interval of 2.25 seconds [motor timing in the seconds range] was chosen because it provided a ratio of 1:5 relative to the millisecond condition, the same ratio as that used in the estimation [bisection] tasks.

Each trial was as follows. For either duration the subject was instructed to tap their finger in time with the tone and synchronized red flashing square. Once the subject had begun tapping they were paced until 12 responses had been made in this first synchronization phase. Once these 12 taps had been completed, the pacing stimuli [tone and square] would cease and the trial was completed by the subject continuing to tap their finger on the sensor plate at the same rate until 31 self-paced taps in this continuation phase had been completed.

Each of the interval production tasks consisted of a minimum of six successful or six unsuccessful trials with a maximum of 12 experimental trials in total. An unsuccessful trial was deemed to be any trial where the inter-response interval [ie: the rate of self-paced taps] was less than or greater than fifty per cent of the target duration. Thus for the short range the target duration was 550 milliseconds and the criterion was 225ms-775ms and the long range target duration was 2.25 seconds with

a criterion of 1.125-3.375s. A trial was also deemed unsuccessful should the subject fail to read aloud more than one of the words presented as part of the suppression condition [as described previously] that occurred during the continuation [self-paced] phase of each of the trials. Any unsuccessful trials were to be excluded from any subsequent analysis that separated clock and motor variance as per the Wing and Kristofferson model of clock variance.

2.9. Time Estimation Task: Bisection procedure.

The estimation tasks of this study follow essentially the same procedure as previously described for the frequency tasks. Each condition of short or long durations consisted of a demonstration block [5 presentations of each of the short and long standards plus seven test intervals that include the two extremes and five intermediate intervals], a warm up block [2 presentations of the short and long examples and seven test intervals] and 10 test trials that each consist of 2 presentations of the standard short and long intervals followed by the two extreme and five intermediate intervals. However, instead of employing a continuous tone of a set duration, the estimation task used an empty interval as the timing signal. An interval was denoted by two short tones of approximately 50 milliseconds in duration and it was this interval between the onset of the first tone to the onset of the second tone that the subject was required to time

Once the subject had heard the second tone denoting the end of the interval, graphics appeared on the computer screen in front of the subject directing them to choose whether the interval they had just heard was a short or long by using the sensor [See Figure 3]. The short range estimation task consisted of a short standard of 200ms and a long standard of 800ms with five intermediate intervals with durations of 251ms, 317ms, 400ms, 504ms, and 635ms. The long range estimation task had a short standard of 1 second and a long standard of 4 seconds with intermediate intervals of 1.26s, 1.587s, 2.000s , 2.520s and 3.175s. In both of these conditions the middle value chosen was the geometric mean which was expected to be the point of

subjective equality [PSE]. A suppression condition occurred for the estimation tasks on one of the testing sessions as described earlier in the paper.

2.10. Data Analysis:

Mean values and the standard error of the means are reported for all subjects in this experiment and the significance level for statistical tests was set at $p < 0.05$. Given the sample size used here, $p < 0.10$ was taken to represent a strong indication that significant differences would emerge with a larger sample size.

Time estimation task

The percent correct at each of the extremes provided the primary raw data for the estimation tasks. In addition to this, the bisection tasks required subjects to classify intermediate intervals as more alike to a short or long example interval which were expressed as the proportion of intervals judged to be long [Nichelli, Clark, Hollnagel and Grafman, 1995].The main dependent measure in the bisection tasks was the ratio of responses made on the right sensor plate (**P [R]**) for the extreme and intermediate signal values in each time range. The following equation was then fitted to the mean values of these data signals for each individual by using a weighted least squares procedure:

$$\mathbf{P(R) = p(A)\,p(R/A) + p(\sim A)\,p(R/\sim A)},$$

where **p (R / A)** was a logistic estimate of the cumulative normal distribution that provided the mean and standard deviation values. These data were used to generate psychophysical curves from the cumulative normal distribution to extract, the point of subjective equality (**PSE**) and the Weber fraction (**Difference Limen / PSE**). The point of subjective equality acts as a representation of the stimulus value where the individual is equally likely to choose the left or right sensor plate, that is the mean of the logistical function when normality is assumed. This DL can be defined as half of the range of values between the main signal value which has a probability of 0.25 or

0.75 of extracting a correct response or 0.675 of the standard deviation and the psychophysical function. The probability of attending to a stimulus is **p (A)** and it is assumed that when the individual does not concentrate on this stimulus then the probability of a right sensor plate response is a constant bias **p (R / ~ A)**.

Interval production tasks

The test data from the tapping procedure was analysed using the Wing and Kristofferson [1973] model. Mean and standard deviations for an individuals paced and unpaced tapping performance were generated and measures of inter-tap intervals were broken down into clock delay and motor delay variance scores. The primary measures of interest with regard to timing regularity derive from the inter-response intervals [IRIs; Duchek, Balota & Ferraro, 1994]. The clock delay variance can be seen as the period between the internal activation of a response [**i**] and the trigger for the next response [**i + 1**] [Duchek, Balota and Ferraro, 1994]. The motor delay variance, however, can be seen as the interim between the internal prompt for a response and the actual execution of that response after the signal to react has commenced. The model has then suggested that there were two processes involved in motor control, a time keeper system that determines when a response should be emitted [clock], and an implementation system that puts into effect a command to respond [motor] [Ivry, Keele & Diener, 1988].

The Wing and Kristofferson model [1973] assumed that a central timing process generated pulses at intervals [**Cj**] which then initiated a motor response [**Rj**]. There are inherent latencies in enacting this motor response [**Rj**], such as a lag in neurotransmission and movement time so that the independent delay processes known as motor delay [**Dj**] have also been assumed so that **j** was greater than zero. The **j** response interval was described as;

$$Ij = Cj + Dj - D\,j - 1$$

If the assumption that **C** and **D** are independent and random variables was taken and that they had means $\mu_C + \mu_D$ and variance $\sigma^2_C + \sigma^2_D$

it was shown that $\sigma^2_I = \sigma^2_C + 2\sigma^2_D$

Consider now the special case where no central timer variability occurs [$\sigma^2_C = 0$] a randomly large motor delay [$D_{j-1} > \mu_D$] can produce an inter-response interval [**Ij - 1**], that was longer than the mean inter response interval, and given that the subsequent motor delay [**Dj**], has tended to be closer to the mean delay interval [μ_D], and when followed from the first equation where **Cj** is a constant, the next inter- response interval **Ij** would be shorter than the mean inter-response interval. The reverse holds when **Dj - 1** was a randomly shorter motor delay when $\sigma^2_C = 0$

In an alternative case where $\sigma^2_D = 0$, the inter-response interval equaled the pulse interval of the central timer, **Ij = Cj**.

The model predicts that as a consequence of random variation in motor delay adjacent response intervals [lag one] would tend to covary negatively. The notion being that when a motor delay began when a response interval is long, the subsequent interval would be shorter or vice versa [Duchek, Balota & Ferraro, 1994].

The calculation of autocovariance, **y at lag 1**, across a series of response intervals would then give estimates of the variance that can be attributed to motor delays.

[$\sigma^2_D = -\gamma(1)$]

Substitution into equation 2 would give an estimate of central timer variance;

$\sigma^2_C = \gamma(0) + 2\gamma(1)$

Estimates of autocovariance **y [k]** were given by **G [k]** where,

$$G(K) = \sum_{J=1}^{N-K} \frac{(I_J - \bar{I})(I_{J+K} - \bar{I})}{N-K}$$

and:

$$\bar{I} = \sum_{J=1}^{N} \frac{I_J}{N}$$

And furthermore given the assumptions of the model, autocorrelation at lag 1 should range between - 0.5 and 0 and for lags greater than 1 the autocovariance should be zero. $p(1) = y(1)/y(0) = -1(2+\sigma^2 c/\sigma^2 o)$

All of the trial runs that violate the prediction that $-0.5 < p[1] < 0$ would be eliminated from any further analysis. Otherwise using equations three and four total variance was to be partitioned into clock and motor delay variance and these values would be transformed into standard deviations. A subjects performance was summarized as the mean of these values across all runs within the millisecond range and separately across all runs in the seconds range. For lags that were greater than 1 the prediction that autocovariance equals zero was also assessed.

3. Results:

The main focus of the experiment was to investigate the performance of parkinsonian subjects off medication with controls on a range of tasks that involved time estimation [bisection procedure] and reproduction [tapping task].

3.1. Frequency Estimation Task.

In this task subjects were required to discriminate a range of high and low frequency stimuli against two standard frequencies. A group [PD = 9, Controls = 5] x suppression condition [no-suppression vs suppression] analysis of variance (ANOVA), with repeated measures on the last factor, revealed no significant effects or interactions on any measure [all F's < 1.0]; see Table 2. The PSE values were close to the geometric mean [1058 Hz] for this task.

Table 2: Mean values (+ or - SE) for the two frequency estimation tasks in the PD and Control groups.

Group	Measure	Non-Supp	Supp
PD	P (A)	0.858 (.045)	0.778 (.083)
Control	P (A)	0.897 (.061)	0.861 (.079)
PD	PSE	1038.803 (73.098)	1058.203 (82.378)
Control	PSE	1075.322 (64.973)	1010.758 (36.686)
PD	SD	153.632 (37.791)	159.03 (37.165)
Control	SD	124.51 (25.712)	171.618 (51.778)
PD	WF	0.1 (.030)	0.11 (.030)
Control	WF	0.08 (.020)	0.11 (.030)
PD	VEX	90.9 (3.065)	88.1 (5.416)
Control	VEX	95.6 (2.075)	90.8 (3.739)

P (A) = accuracy
PSE = point of subjective equality
SD = standard deviation
WF = Weber Fraction
VEX = variance explained
Non-Supp = non-suppression condition
Supp = suppression condition

3.2. Estimation Task

Mean performance on the psychophysical bisection tasks is shown in Table 3 and in figure 4a. Individual performance of the PD and control subjects is shown in Figure 4b. The principal measure of interest is the Weber fraction [figure 4a & b] which measures sensitivity to changes in the dimension of the stimulus independent of accuracy p (A). A group [PD = 9 and controls = 5] x range [milliseconds vs seconds] x suppression condition [no-suppression vs suppression] ANOVA [with repeated measures on the last two factors] confirmed a marked difference between the PD and control subjects across the two bisection tasks. While there was no overall group effect, $F (1, 12) = 1.78$, $p < .21$, there was a significant Group x Range interaction, $F (1, 12) = 7.03$, $p < .02$.

Analysis of the simple main effects of this interaction in the PD group showed that this group's Weber fraction increased markedly from the seconds to the milliseconds range, $F (1, 12) = 32.75$, $p < .001$, whereas there was no change across range for the control subjects, $F (1, 12) < 1.0$. Weber fractions for the PD group and the control group were the same for the seconds bisection task, $F (1, 12) < 1.0$, and approached a significant difference for the millisecond bisection task $F (1, 12) = 3.89$, $p < .07$. There was no evidence to suggest that the suppression conditions had any effect upon the Weber fraction $F (1, 12) = 1.99$, $p < .18$, irrespective of the range [milliseconds or seconds] tested [all interaction F's < 1.0], despite an indication in the mean data that suppression increased the Weber fraction disproportionately in the milliseconds condition for the PD group.

Table 3: Mean values (+ or - SE) for the four estimation tasks (Bisection) in the PD and control groups.

Group	Measure	Msecs		Seconds	
		Non-Supp	Supp	Non-Supp	Supp
PD (N = 9)	PSE	475.184 (35.402)	440.661 (28.926)	2090.206 (152.636)	2253.127 (262.655)
Control (N = 5)	PSE	442.107 (23.020)	428.592 (9.706)	1896.616 (119.425)	2037.551 (74.855)
PD	SD	109.684 (15.564)	150.737 (37.574)	243.249 (55.574)	255.261 (64.723)
Control	SD	73.581 (9.623)	68.245 (19.556)	206.648 (56.128)	298.05 (73.228)
PD	P (A)	0.947 (.015)	0.93 (.032)	0.925 (.037)	0.847 (.060)
Control	P (A)	0.967 (.016)	0.952 (.019)	0.959 (.020)	0.949 (.026)
PD	VEX	95.9 (1.315)	93.2 (2.762)	86.4 (10.782)	83.3 (10.938)
Control	VEX	98.3 (.752)	99.1 (.248)	99.2 (.487)	98.6 (.672)

P (A) = accuracy
PSE = point of subjective equality
SD = standard deviation
VEX = variance explained

Non-Supp = non-suppression condition
Supp = suppression condition

To re-assess this possibility that suppression may adversely affect PD performance in the milliseconds task, the statistical power of the analysis was improved by repeating the Weber fraction analysis after doubling the data set. An overall suppression main effect emerged with a small increase in the Weber fraction values resulting under the suppression condition, $F(1, 26) = 4.3$, $p < .05$. However, the finding of no significant three way interaction [Group x Range x Suppression condition] was maintained, $F(1, 12) = 1.9$, $p < .18$. Even a subsequent analysis of the PD and control subjects at the short range only, revealed no Group x Suppression interaction, $F(1, 26) = 2.5$, $p > .10$. There was however now a significant difference between the PD and control group on the Weber fractions in the milliseconds condition $F(1, 26) = 8.4$, $p < .001$. The PSE values for the PD and control subjects in the milliseconds range were at an intermediate level between the geometric [400 ms] and arithmetic mean [500ms]. The PSE values for the seconds range were either at or close to the geometric mean [2000ms]. There was no indication of any difference between the PD and control group with respect to the PSE values [see Table 3]. A three-way ANOVA on the PSE scores revealed the expected range main effect, $F(1, 12) = 1720.0$, $p < .001$, but there were no other effects or interactions [all F's < 1.13]. Because of the higher variance in the seconds range tasks, separate analyses were conducted on the milliseconds and seconds data; these analyses also revealed no main effects of group or interactions involving the group factor.

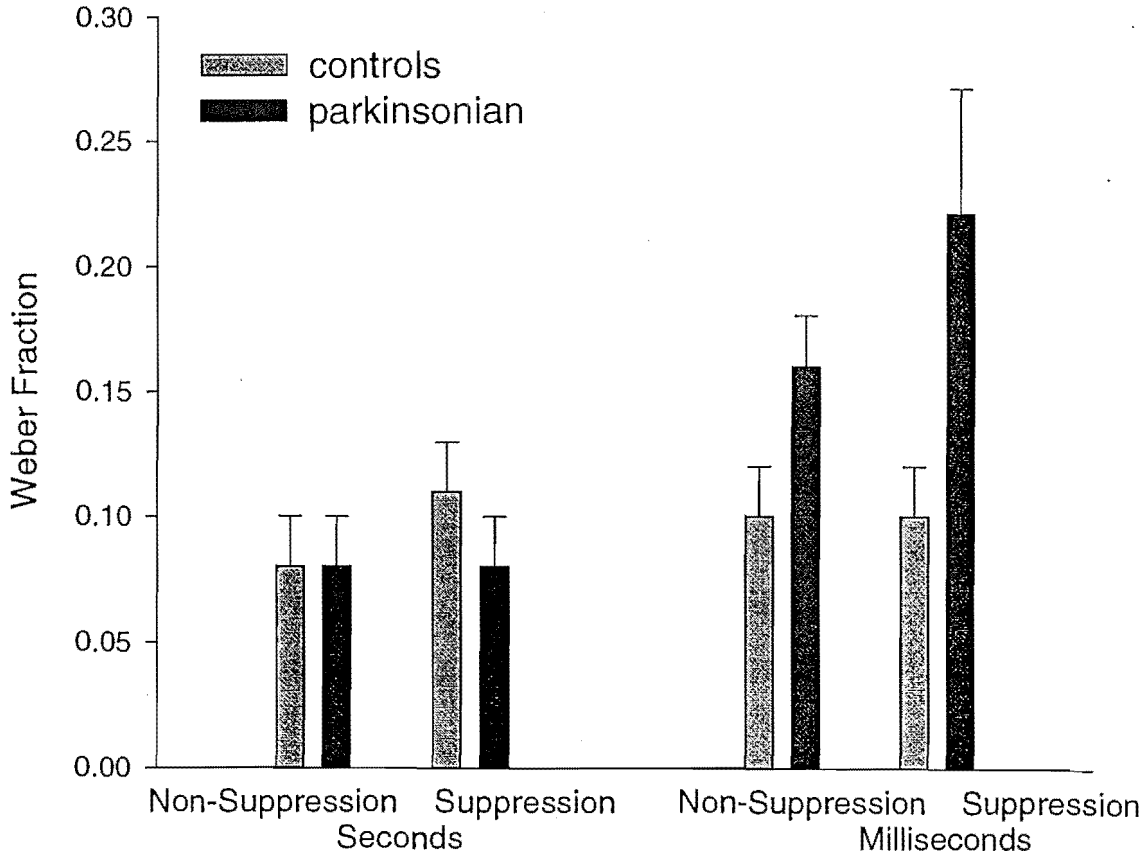
Standard deviation values [see Table 3] revealed no evidence of an overall difference between the PD and control subjects on the millisecond or seconds estimation tasks. A three-way ANOVA confirmed the expected effect across the PD and control subjects for the millisecond versus seconds tasks $F(1, 12) = 35.81$, $p < .001$, but no other significant interactions were found [all F's < 1.5] The same conclusions were obtained when these standard deviation values were analysed separately within the millisecond or seconds time range.

Figure 4:

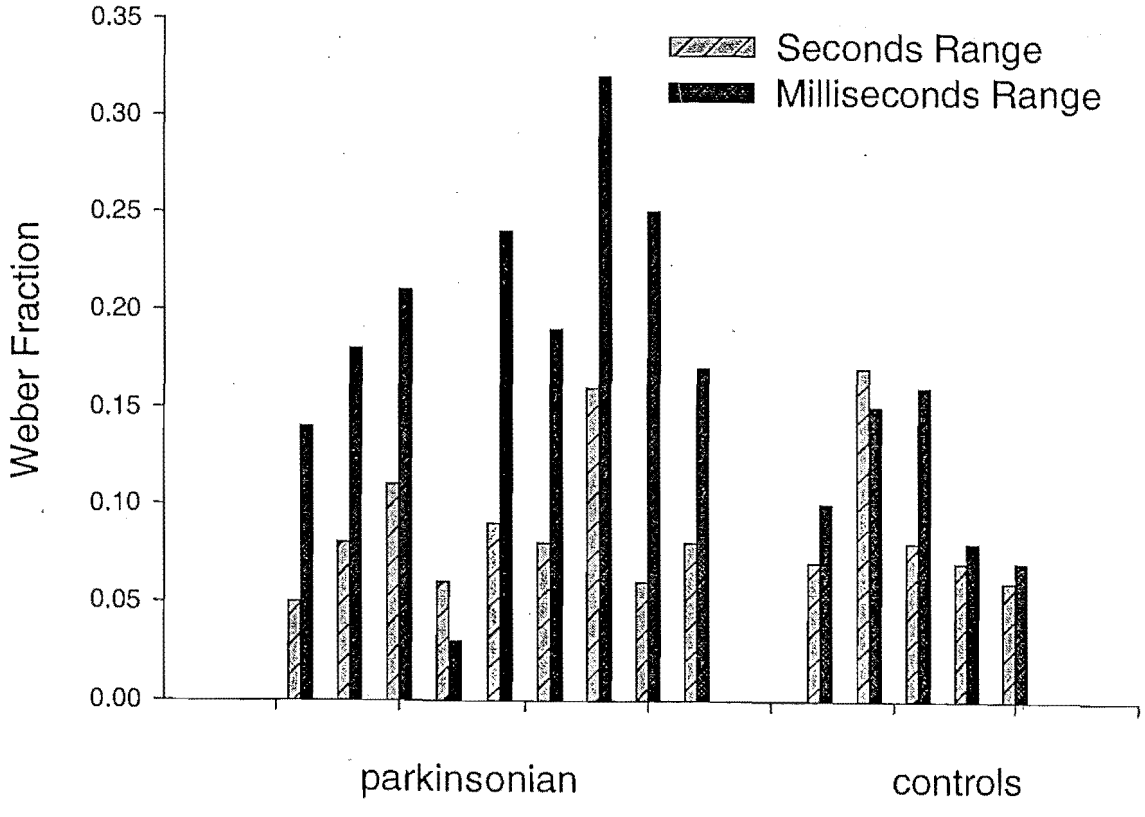
A: Mean Weber fraction scores (+ or - SE) for 9 PD and 5 control subjects for the Estimation task across the experimental conditions: milliseconds, seconds, no-suppression and suppression.

B: Individual Weber fraction scores (+ or - SE) for 9 PD and 5 control subjects for the Estimation task across the experimental conditions: milliseconds, seconds, no-suppression and suppression.

A: Mean Weber Fractions for the Four Estimation Tasks



B: Individual Weber Fractions
across Seconds and Milliseconds Estimation Tasks



Measures of accuracy p (A) are also shown in Table 3. A three-way ANOVA revealed no main effects or any interactions, all F's [1, 12] < 1.8. Doubling the data set to increase the statistical power just failed to produce a significant poorer performance overall in the PD group, $F(1, 26) = 3.85$, $p < .06$, and better overall performance across both groups on the millisecond task, $F(1, 26) = 3.88$, $p < .06$, but no other effects or interactions, all F's < 2.54.

There appeared to be some difference between the PD and control subjects on the measure of variance explained [see Table 3], that is the goodness of fit of the ogive psychophysical function relative to actual performance. Parkinsonian subjects showed more variation in their performance in comparison to the control subjects. A three-way ANOVA indicated evidence of an overall group effect $F(1, 12) = 4.39$, $p < .06$, but no other interactions were evident [all F's < 1.0].

3.3. Interval production Tasks.

Mean performance on the interval production tasks is shown in Table 4. The principal measure of interest here are the coefficient of variation [SD / Mean] values which are conceptually equivalent to the Weber fraction values of the bisection procedure. One PD subject was excluded from data analysis because his performance was, unlike that of the remaining PD subjects extremely poor in that his scores for the milliseconds and seconds unpaced tasks respectively were, 422ms and 1171 ms for the mean inter-tap intervals and 363ms and 838ms for the standard deviations.

Table 4: Mean values (+ or - SE) for the four interval production tasks [tapping] in the PD and control groups.

Group	Measure	Msecs Non-Supp	Msecs Supp	Seconds Non-Supp	Seconds Supp
PD (N = 8)	P Mean	535.4 (7.536)	540.7 (8.352)	2210 (28.18)	2179 (26.99)
Control (N = 5)	P Mean	556.6 (9.181)	532.1 (20.32)	2228 (7.112)	2179 (22.79)
PD	UP Mean	545.1 (15.56)	535.8 (13.96)	2314 139	2169 (98.44)
Control	UP Mean	548.9 (3.776)	549.7 (9.475)	2259 (90.64)	2264 (83.16)
PD	P SD	52.35 (11.83)	52.47 (8.809)	340.4 (77.91)	296.7 (45.12)
Control	P SD	64.7 (21.56)	72 (31.57)	203.3 (34.4)	279.2 (50.61)
PD	UP SD	52.6 (14.36)	43.28 (5.561)	285.3 (38.72)	397.4 (85.36)
Control	UP SD	21.72 (2.726)	29.25 (4.972)	167.1 (7.283)	245.7 (27.04)
PD (N = 5)	Clock SD	38.88 (11.61)	35.52 (5.253)	253.9 (52.93)	244.2 (43.27)
Control (N = 5)	Clock SD	17.22 (2.377)	23.79 (4.067)	182 (46.22)	226.9 (36.29)
PD (N = 5)	Motor SD	14.64 (2.878 0	16 3	88.78 (12.3)	75 14
Control (N = 5)	Motor SD	8.844 (1.721)	10 (1.7)	58.64 (4.135)	94 21

P Mean = paced mean, UP Mean = unpaced mean, P SD = paced standard deviation, UP SD = unpaced standard deviation, Clock & Motor SD = standard deviations

A: Paced Tapping

The paced coefficient of variation values are shown in Figure 5a. A group [PD = 9 and Controls = 5] x range [millisecond vs seconds] x suppression condition [no-suppression vs suppression] ANOVA on the coefficient of variation scores confirmed that there were no group or suppression effects [all F's < 1.0] on the paced portion of the tapping task. However there was some indication of a significant interaction between Group and Range [milliseconds vs seconds], $F(1, 11) = 3.65$, $p < .08$ because coefficient of variation scores decreased from seconds to milliseconds for the PD group whereas the reverse occurred for the control group [see figure 5a].

The inter-tap mean interval values [see Table 4] were at or close to the target interval for both the milliseconds [550 ms] and seconds range [2.25 secs]. A three-way ANOVA revealed no group effect $F(1, 11) < 1.0$ or interactions involving the group factor, [all F's < 1.0], other than the expected difference between the milliseconds versus seconds conditions, $F(1, 11) = 7352.2$, $p < .001$.

A Group x Suppression [no-suppression vs suppression] ANOVA on the standard deviation values of the paced inter-tap intervals [see Table 4] showed no evidence of any group effect or suppression effects or interactions [all F's < 1.0].

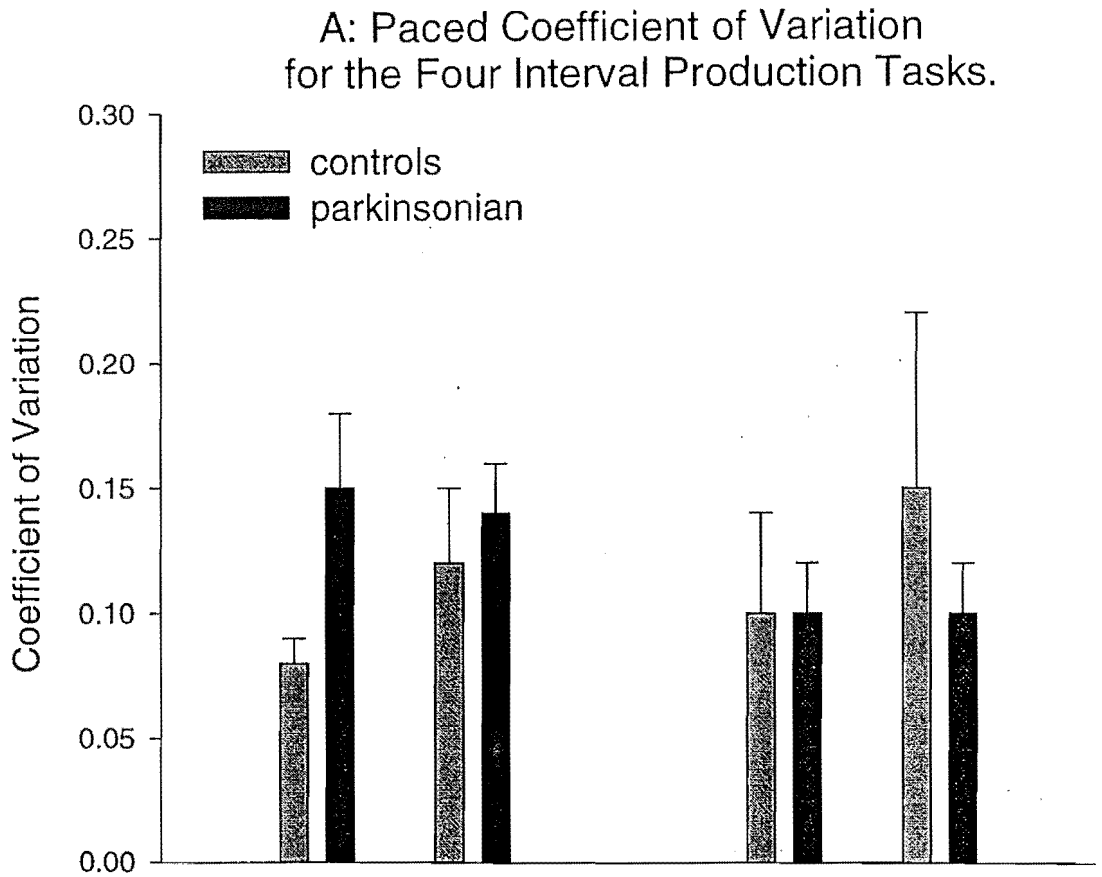
B : Unpaced Tapping

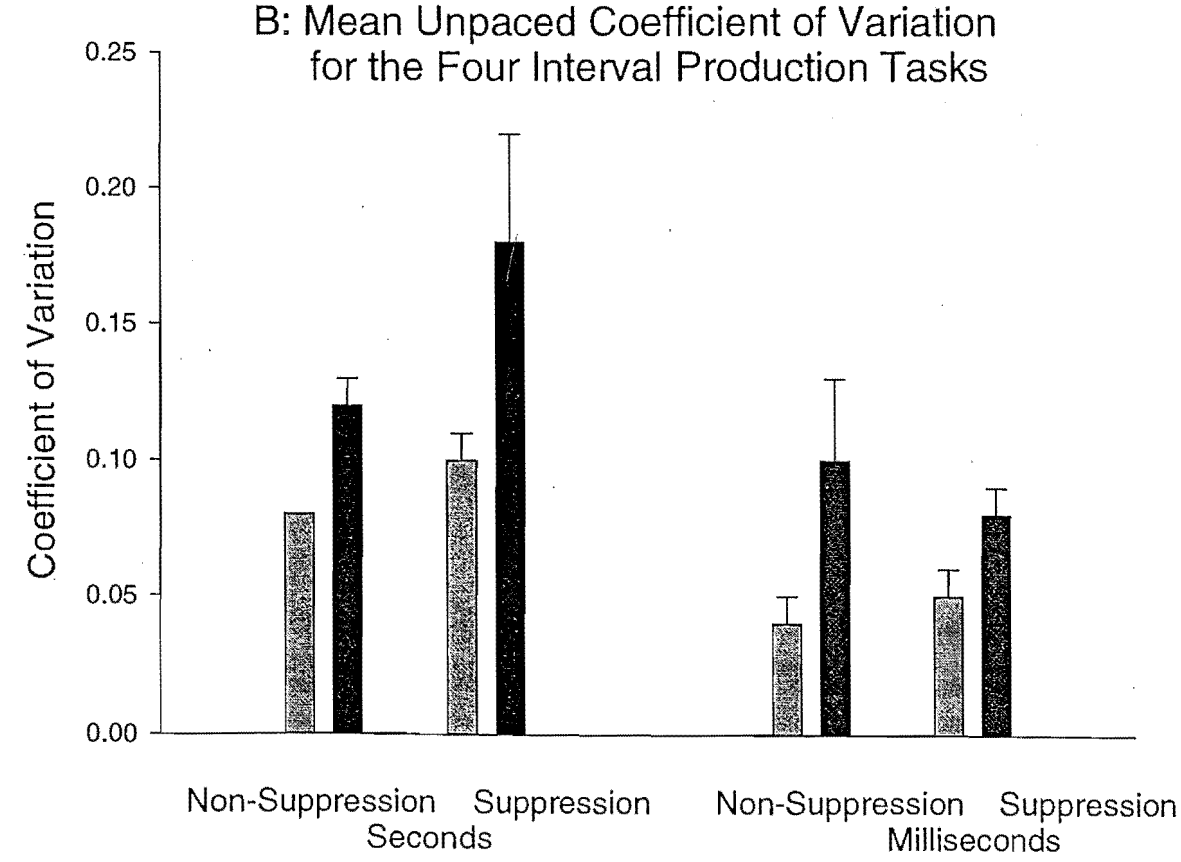
The unpaced coefficient of variation values are shown in Figure 5b. With respect to coefficient of variation scores derived from total variance, a three-way ANOVA showed that the PD group had higher coefficients than the control group, $F(1, 11) = 10.99$, $p < .01$, irrespective of range tested or suppression condition [interactions, F's $(1, 11) < 1.0$]. The Group x Range x Suppression condition was also not significant, $F(1, 11) = 2.13$, $p > .10$. The coefficients were however higher in the seconds condition than the milliseconds condition, $F(1, 11) = 6.73$, $p < .03$.

Figure 5:

A: Paced coefficient of variation scores (+ or - SE) for 8 PD and 5 control subjects for the Interval Production task across the experimental conditions: milliseconds, seconds, no-suppression and suppression.

B: Mean unpaced coefficient of variation scores (+ or - SE) for 8 PD and 5 control subjects for the Interval Production task across the experimental conditions: milliseconds, seconds, no-suppression and suppression.


A: Paced Coefficient of Variation
for the Four Interval Production Tasks.
controls
parkinsonian
Coefficient of Variation
0.30
0.25
0.20
0.15
0.10
0.05
0.00


B: Mean Unpaced Coefficient of Variation
for the Four Interval Production Tasks
Coefficient of Variation
0.25
0.20
0.15
0.10
0.05
0.00
Non-Suppression
Suppression
Seconds
Non-Suppression
Suppression
Milliseconds

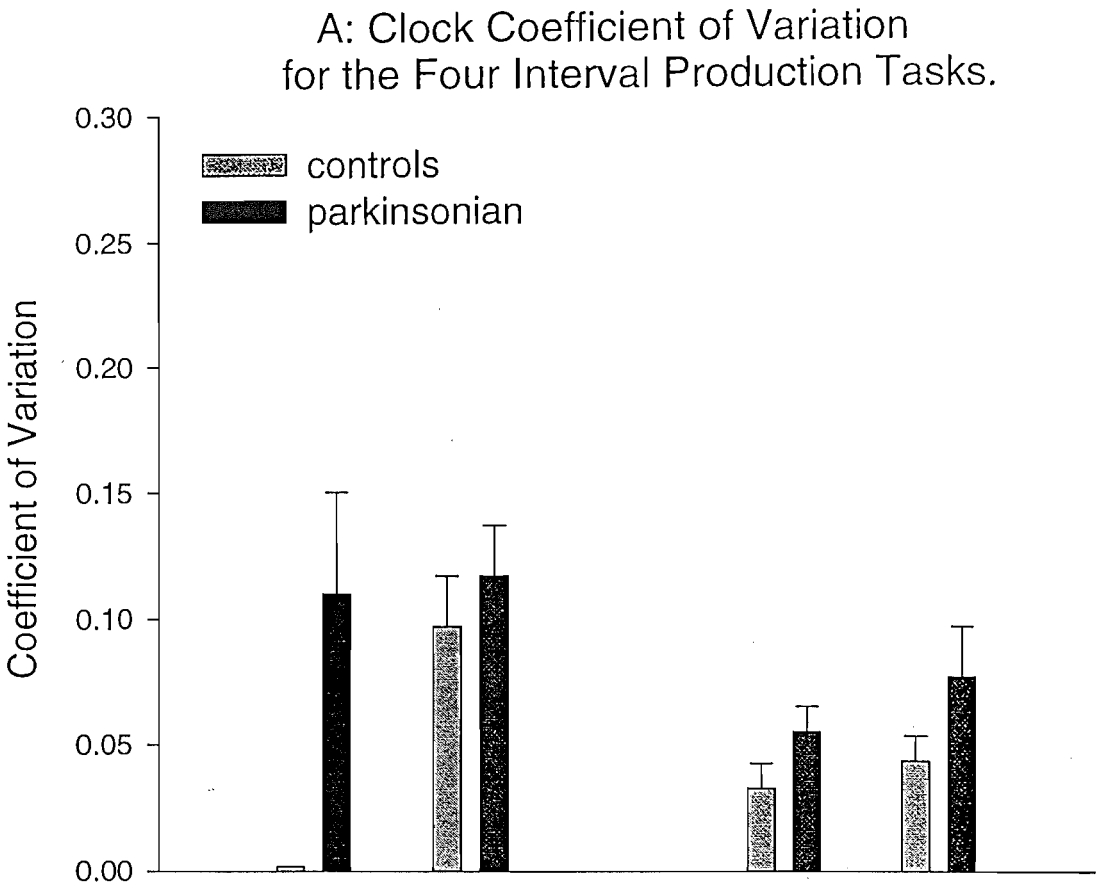
The suppression condition tended to increase coefficients in the milliseconds task only, $F(1, 11) = 3.80$, $p < .08$.

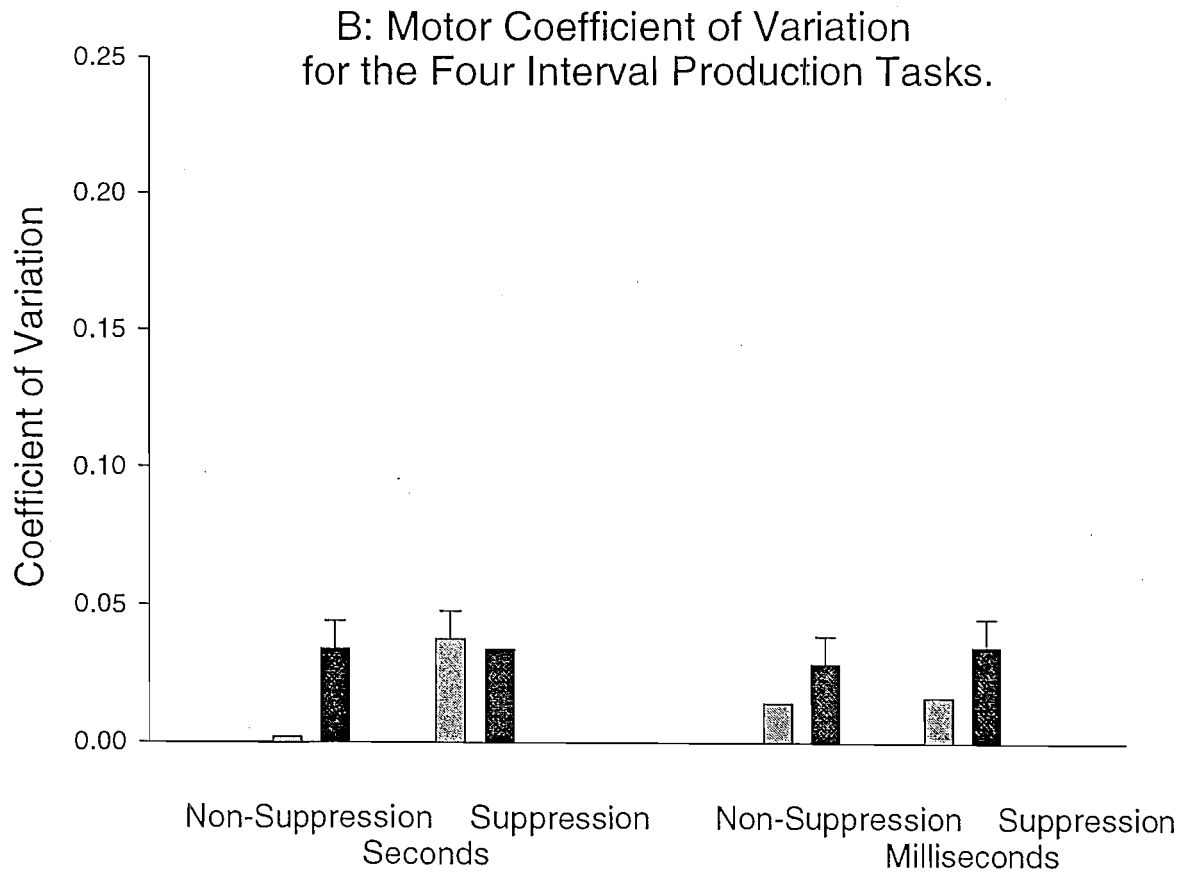
The coefficient of variation values were also decomposed into clock and motor components as per the Data Analysis Section [see Figure 6a & b]. This type of analysis was problematic in that these measures could not be extracted for some of the PD and control subjects. Overall, the data from only five PD subjects met the criteria for Wing and Kristofferson's model across all conditions. In the control group, the data could not be obtained from three subjects in the seconds no-suppression condition, but data could be extracted for all controls for the other conditions. A 2-way [Range x Suppression] ANOVA of clock coefficient scores restricted to the PD group [N = 5] confirmed that these scores were higher in the seconds condition than in the milliseconds condition $F(1, 4) = 10.99$, $p < .03$, irrespective of suppression [suppression effect, $F(1, 4) = 1.50$, $p > .10$; Group x Suppression, $F(1, 4) < 1.0$]. The data from the control subjects [N = 5] were analysed with a one-way ANOVA [three conditions excluding the seconds / no-suppression condition] and showed again that the coefficient of variation was higher in the seconds-suppression condition than in either millisecond condition, $F(2, 8) = 9.53$, $p < .001$. To compare PD and controls a Group [PD vs Controls] x Condition [again excluding the seconds / no-suppression condition] ANOVA was conducted which confirmed the higher coefficient of variation scores for the seconds task relative to the milliseconds tasks, $F(2, 16) = 18.84$, $p < .001$, but gave no evidence of higher scores overall for the PD group relative to the control group, $F(1, 9) = 2.94$, $p > .10$, irrespective of condition [Group x Condition, $F(2, 18) < 1.0$]. Doubling the latter data set to improve statistical power, however, resulted in a significant PD vs control group difference for the clock coefficient of variation scores, $F(1, 18) = 6.62$, $p < .02$, but still gave no Group x Condition interaction, $F(2, 36) < 1.0$.

Figure 6:

A: Clock coefficient of variation scores (+ or - SE) for 5 PD and 5 control subjects for the Interval Production tasks across the four experimental conditions: milliseconds, seconds, no-suppression and suppression.

B: Motor coefficient of variation scores (+ or - SE) for 5 PD and 5 control subjects for the Interval Production task across the four experimental conditions: milliseconds, seconds, no-suppression and suppression.


A: Clock Coefficient of Variation
for the Four Interval Production Tasks.
controls
parkinsonian
Coefficient of Variation
0.30
0.25
0.20
0.15
0.10
0.05
0.00


B: Motor Coefficient of Variation
for the Four Interval Production Tasks.
Coefficient of Variation
0.25
0.20
0.15
0.10
0.05
0.00
Non-Suppression
Suppression
Seconds
Non-Suppression
Suppression
Milliseconds

A 2-way [Range x Suppression] ANOVA of motor coefficient scores limited to the PD group [N = 5] confirmed that these scores were similar across the seconds and the milliseconds condition, irrespective of suppression, all F's (1, 4) < 1.15.

The data from the control subjects were examined with a one-way ANOVA [three conditions excluding seconds / no-suppression condition] which in contrast to the analysis for the PD group, showed that the coefficient of variation was higher in the seconds-suppression condition than in either millisecond condition on this motor component. A Group x Condition [excluding the seconds / no-suppression condition] ANOVA produced no group difference, $F (1, 8) = 2.42$, $p > 1.0$, condition effect, $F (2, 16) = 2.49$, $p > .10$ or Group x Condition interaction, $F (2, 16) = 1.51$, $p < .10$. Doubling the latter data set to increase the statistical power of the analysis resulted in a significant group effect, $F (1, 18) = 5.45$, $p < .05$, but there was now a Group x Condition interaction, $F (2, 36) = 3.4$, $p < .05$, reflecting the higher mean motor coefficient of variation in the PD group in the milliseconds condition only.

The inter-tap mean interval values for the unpaced tapping task, which was available for all 8 PD subjects and the 5 controls, [see Table 4] were either at or close to the target interval for both the milliseconds [550 ms] and seconds [2.25 sec] range. A three-way ANOVA revealed no group effect $F (1, 11) < 1.0$ or any other interactions involving the group factor, [all F's < 1.0] other than the effect between the milliseconds versus seconds conditions, $F (1, 11) = 610.73$, $p < .001$

A Group x Range x Suppression [milliseconds vs seconds and no-suppression vs suppression] ANOVA on the standard deviation values [see Table 4] for the unpaced portion of the tapping task produced the expected milliseconds vesus seconds difference, $F (1, 11) = 31.73$, $p < .001$, and indicated that the PD group showed more variation in their responding than the control subjects, $F (1,11) = 4.63$, $p < .06$. The only interaction effect that emerged was the Range x Suppression interaction, $F (1, 11) = 7.27$, $p < .02$ due to the fact that, in both the PD and controls, suppression had no effect in the milliseconds task but increased the standard deviation values in the

seconds task. The same conclusions were obtained when the standard deviation values were analysed separately within the millisecond and seconds time range.

4. Discussion

4.1. Summary of theoretical positions

Human and animal studies have implicated the mesotelencephalic dopamine system and the cerebellum in interval timing but the exact nature of their contribution to timing processes is unclear. Suggestions have been made that these neural structures are both involved in interval timing and that perhaps this involvement is of a duration- dependent nature. Three alternative positions have been offered in an attempt to explain the possible influence of the basal ganglia or cerebellar systems in temporal information processing.

Ivry and Keele [1989] argued that a single timing mechanism existed for the production and perception of time in the milliseconds range. They proposed that the cerebellum rather than the dopaminergic forebrain system provided the neural basis for this timing mechanism on the evidence that cerebellar subjects were the only group to show an impairment in both perception and production tasks in the milliseconds range. Animal lesion work, which revealed that cerebellar lesions can cause disruptions to timing responses in the milliseconds range rather than the seconds range [Breukelaar and Dalrymple-Alford, 1998; Clarke et al, 1996] also provides evidence to support the role of the cerebellum in interval timing.

Rammsayer [1993] advocated a distinctive role for the basal ganglia in timing on the basis of duration-dependent processes. Estimation processes in the range of seconds or more were considered to depend on cognitive processes at the level of the cortex and the limbic system, whereas time perception [milliseconds] was defined in terms of the automatic processing of brief durations that were, in contrast to Ivry's hypothesis, dependent upon neural processes in the basal ganglia.

Rammsayer's [1993] view was consistent with information about pharmacologically induced changes in D2 receptor activity. The differential effect that haloperidol [estimation and perception tasks] and remoxipride [estimation tasks only] exhibited on timing in the milliseconds range was maintained to be a result of the influence of D2 receptors on dopamine antagonistic influences in the basal ganglia [milliseconds] and the mesolimbic and mesocortical [seconds] regions.

Gibbon and colleagues [1997] focused upon a single model [scalar timing] to explain interval timing. The central aspect of this model is the scalar property, a potent example of Webers's law. It suggests that problems in making accurate time estimations are proportional to the target time and that even though the precision of responding decreases with an increase in the target duration length, a rescaling of these estimates should result in a similar outcome. A direct result of this is that whole estimation distributions should become superposed when they are scaled in relation to a subjective average time [depending on the task, the PSE, mean inter-tap interval or median time]. Gibbon and colleagues have posed a question about whether a common neural system exists in the domain of perception and the production of time and have argued that there may not be a single, specific neural structure involved, instead proposing that both the basal ganglia and the cerebellum are unlikely to be independent of each other as there is evidence that both produce an increase in variability across common time-related tasks.

4.2. Relevance of current findings to previous research

One suggestion that has been made regarding the influence of the basal ganglia on interval timing is whether or not time-related processes normally exhibit scalar variability. If the basal ganglia was this source of variability and the scalar property [Weber's law] was true then it could be expected that timing processes would be disrupted in both the millisecond and seconds range within a task. In the present study the scalar property is clearly evident in the control subjects on the

bisection task. Their data provide a perfect example of the scalar process at work, because the Weber fractions for this group were effectively the same across the millisecond and seconds range [see Figure 4].The control subjects did not however appear to exhibit this same scalar property for the interval production task. The level of variability between the millisecond and seconds range of the tapping task was not constant indicating the presence of non-scalar sources of variability within this task, that is the controls produced markedly higher coeffcient of variation scores [comparable to the Weber fraction as a measure of sensitivity] for the overall variance for unpaced tapping for the seconds range task than the milliseconds range [see Figure 5 and 6].

The change in the tapping coefficient of variation scores across durations for the control data suggest that performance there may be different to that expected from scalar timing theory. Tapping has not been conducted in the seconds range before but the current millisecond data are equivalent to that reported elsewhere. The control subjects were able to maintain their tapping speed, unpaced mean scores were close to the target inter-tap interval for both the milliseconds [550 ms] and seconds [2250 ms] condition respectively [548.8, 549.7& 2259, 2264ms]. The inter-tap intervals and standard deviation values of Ivry and Keele's [1989] college-aged and elderly control subjects were [ITI = 535-550 and SD = 23.6-30.6 ms]. The control subjects in the present study produced similar mean inter-tap intervals and similar standard deviation values [22 and 29 ms for the non-suppression and suppression condition respectively]. Given the similarity between the millisecond data reported here and elsewhere, the change in coefficient of variation scores between the millisecond to second range in the present study is likely to be a robust one.

The data collected from the interval production task was decomposed into clock and motor-delay components as per the Wing and Kristofferson [1973] model. The control subjects again showed evidence of non-scalar variability by producing higher levels of coefficient of variation scores in the seconds range condition than the milliseconds range. It is again noteworthy that the clock variation scores for the

millisecond range [about 17 ms] were comparable to those control scores [about 16 ms] previously obtained by O'Boyle et al [1996].

In contrast to the control subjects, the parkinsonian subjects [who were tested off dopaminergic medication] did not exhibit scalar timing in the bisection task. Their Weber fraction scores in the seconds bisection tasks did not differ to those obtained for the controls but the PD groups Weber fraction increased markedly when judging time in the milliseconds range [see Figure 4] This finding is consistent with Rammsayer's [1993] assertion that the basal ganglia system is important in the processing of temporal information in the milliseconds range [time perception] and with other clinical investigations which have found that disorders of the basal ganglia do not exhibit the scalar property in the millisecond time range [Gibbon et al, 1997]. The parkinsonian subjects showed evidence of more variability in the bisection task across the millisecond and second time ranges, a finding that is in conflict with the notion [Ivry, 1996; gibbon et al, 1997] that the basal ganglia is involved in temporal information processing in the seconds range.

Gibbon and colleagues [1997] used a peak interval procedure to investigate scalar timing in cerebellar and parkinsonian subjects and they argued that the impaired interval timing processes in subjects with cerebellar lesion were scalar across different time durations. Their lateral cerebellar lesion subjects produced higher levels of variability in both time ranges than did subjects with mesial cerebellar or striatal lesions, but there was no evidence to suggest any changes in accuracy. Their parkinsonian subjects showed scalar variability when tested on medication but when tested off dopaminergic medication they violated the scalar rule. Although their PD group showed impaired timing in the 8 seconds condition and the 21 seconds condition, performance across the two conditions was not scalar, with the 8 second condition producing higher coefficient values overall. Gibbon et al [1997] suggested that these effects in the PD group were probably due to deficits in memory and decision processes.

While the bisection data for the PD subjects in the present study are not

consistent with Gibbon et al's peak interval findings, performance on the interval production task by the parkinsonian subjects here showed some indication that timing in the tapping task was poorer in both the seconds condition and the milliseconds condition. The PD group was like the controls in the tapping tasks, however, in that coefficient of variation scores were higher in the seconds condition suggesting the presence of other non-scalar sources of variability within this task for the PD group also [see Figure 5].

Although Ivry and Keele [1989] found that parkinsonian subjects underestimated the mean inter-tap interval for milliseconds tasks [524] and showed similar standard deviation values [32.2] to the control subjects, their cerebellar subjects revealed markedly different results. These cerebellar subjects were close to the target mean inter-tap interval [542] but had much larger standard deviation values in relation to the PD and control groups [46.8]. In contrast to this the parkinsonian subjects in the current study were found to be more like the cerebellar subjects in Ivry et al's study in the milliseconds task with the current PD group having a mean inter-tap interval of 545.1 and 535.8 ms and standard deviation scores of 52.6 and 43.28 ms [non-suppression and suppression, respectively].

Clock coefficient of variation scores for the parkinsonian group were higher in the seconds range condition, but there was no evidence to suggest that these scores were any higher in relation to those of the control subjects [only when the statistical power of the analysis was increased by doubling the data set]. Once again the parkinsonian group's performance in the milliseconds condition [38.88 & 35.52 ms] was more like the performance measures obtained by Ivry et al [1989] for their cerebellar lesion group [38.1] than their parkinsonian group [27.7]. Motor-delay variance scores for the parkinsonian subjects were higher than those obtained for the control subjects in the milliseconds condition [14.64, 16] and to those reported by Ivry et al [1989] (9.3).

In summary, the control subjects performance on the bisection task is a very good example of scalar timing, but other non-scalar processes enter into this equation

in the interval production task where the controls do not show constant variability across time ranges. In contrast to this the parkinsonian subjects showed no evidence of scalar processes in the bisection task especially in the milliseconds range or in the interval production task. Both the parkinsonian subjects and the controls produced higher coefficients of variation for the seconds range tapping relative to the milliseconds tapping. The performance of the parkinsonian group in the current study differed to the results obtained by Ivry and Keele [1989] for their PD subjects, and produced scores that were similar to those found in their cerebellar lesion group.

The suggestion that timing processes in different ranges are served by two separate neural systems [Ivry, 1996], the basal ganglia [seconds to minutes] and the cerebellum [milliseconds], has provided much debate. The present study has established that parkinsonian individuals are impaired in their ability to judge brief time intervals on a bisection procedure and provided evidence that they may show an additional impairment in their ability to reproduce time in the seconds range on an interval production task. This discrepancy in performance raises the important question about whether or not timing across ranges of different durations is task-dependent; the immediate response to this on the basis of the present study's findings is yes. Other studies have found conflicting evidence across tasks. For example, Gibbon and colleagues [1997] discovered that there was a clear effect of task upon coefficient of variation scores especially in ranges below 1 second. Synchronization tasks like interval production and discrimination tasks produced lower coefficient scores than tasks involving temporal generalization [bisection] indicating that the bisection tasks are better suited to specifically address internal timing independent of motor timing which has proven to be problematic in the current and previous studies.

4.3. Further Issues and Future studies.

The issue of articulatory suppression and whether it affected performance on timing tasks was also of interest to the present study, suppression tasks are known to affect attentional processes particularly in parkinsonian individuals. It was considered

important to control for this possibility in both the millisecond and seconds range although it was not expected to be a problem in the short range. The performance of the control subjects was not affected at all by the suppression condition across all measures of accuracy, standard deviations or means for the bisection task but did produce a weak overall suppression effect on coefficient values in the millisecond unpaced tapping task. The suppression task also had an effect on the standard deviations values in the seconds condition but no other interactions were present. The parkinsonian subjects, in their mean data on the bisection task showed an indication that the suppression condition was increasing the Weber fractions in the milliseconds range but this was statistically non-significant. Even increasing the statistical power of the analysis by doubling the data set did not reveal a significant suppression effect on this measure There was no other evidence that the suppression condition interfered with the performance of the parkinsonian subjects on any other measures [PSE, P (A), SD] in the bisection task. Suppression did not affect performance in the interval production task except to increase the standard deviation values in the seconds range in both PD and control subjects.

The clear deficit in timing performance on the millisecond bisection task shown in parkinsonian subjects in the present study is an interesting finding and provides a benchmark against which the argument about the task-dependent nature of timing can be assessed. The precise role of the basal ganglia in temporal information processing is still unclear, however, as the present study also indicated that parkinsonian subjects were impaired in their timing abilities across both the milliseconds and seconds range interval production tasks. Caution must be taken when making conclusions about timing performance in PD subjects in the present work and when comparing these findings to previous studies. This is because it is difficult to draw conclusions from such a small sample of PD and control subjects and make inferences about their timing performance without testing a larger number to increase the statistical power of the analyses. There were also some methodological and analytical problems in the data analysis of the current study especially in relation

to the decomposition of interval production data as per the Wing and Kristofferson [1973] model, with a number of subjects violating the assumptions of the model and subsequently producing no data for clock and motor-delay components.

Notwithstanding the above caveats, the results from the present study are important for a number of reasons. It is only the second study to look at the problem of assessing timing abilities across two separate time ranges within a single task in parkinsonian individuals, and the present work is the only one to assess the two important ranges, namely milliseconds versus seconds. Malapini, Rakitin, Meck, Deweer, Dubois and Gibbon [in press] looked at a peak procedure with 8s and 21s target times. Moreover, the current study is also the first to study PD subjects in a psychophysical choice procedure [bisection task], one that has been extremely effective in the study of timing in humans and animals [Wearden, 1991]. This bisection task has provided clear evidence about timing deficits within the millisecond time range in PD subjects. The bisection task is perhaps better suited to study central timing processes than are tapping tasks or other motor-dependent timing tasks. Further use of bisection procedures employing more varied time ranges would be beneficial to the study of interval timing and identifying its underlying neurobiological bases, as would testing parkinsonian patients both on and off medication. Further study of subjects with cerebellar lesions would also be of interest and is intended as part of a continuation of the present study.

To conclude, this study supports the suggestion made by Rammsayer [1993] that temporal information processing in the range of milliseconds is mediated by dopaminergic influences on the basal ganglia. Clearly, the validity of this conclusion is one that may vary according to the nature of the timing task under study which suggests that the component processes evaluated by different timing procedures deserve greater attention in the literature if we are to firmly establish the basis of the neurobiology of timing.

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Appendix A: Latin Square Design

PD/CB study: Experimental Design

Digram balanced design with suppression counterbalanced across sessions.

							Session 1				Session 2			
1	PD1	PDMC1	CB1	CBMC1		St	Lt	Le	Se	St	Lt	Le	Se
2	PD2	PDMC2	CB2	CBMC2		Lt	Se	St	Le	Lt	Se	St	Le
3	PD3	PDMC3	CB3	CBMC3		Se	Le	Lt	St	Se	Le	Lt	St
4	PD4	PDMC4	CB4	CBMC4		Le	St	Se	Lt	Le	St	Se	Lt
5	PD5	PDMC5	CB5	CBMC5		St	Lt	Le	Se	St	Lt	Le	Se
6	PD6	PDMC6	CB6	CBMC6		Lt	Se	St	Le	Lt	Se	St	Le
7	PD7	PDMC7	CB7	CBMC7		Se	Le	Lt	St	Se	Le	Lt	St
8	PD8	PDMC8	CB8	CBMC8		Le	St	Se	Lt	Le	St	Se	Lt
1	PD9	PDMC9	CB9	CBMC9		St	Lt	Le	Se	St	Lt	Le	Se
2	PD10	PDMC10	CB10	CBMC10		Lt	Se	St	Le	Lt	Se	St	Le
3	PD11	PDMC11	CB11	CBMC11		Se	Le	Lt	St	Se	Le	Lt	St
4	PD12	PDMC12	CB12	CBMC12		Le	St	Se	Lt	Le	St	Se	Lt
5	PD13	PDMC13	CB13	CBMC13		St	Lt	Le	Se	St	Lt	Le	Se
6	PD14	PDMC14	CB14	CBMC14		Lt	Se	St	Le	Lt	Se	St	Le
7	PD15	PDMC15	CB15	CBMC15		Se	Le	Lt	St	Se	Le	Lt	St
8	PD16	PDMC16	CB16	CBMC16		Le	St	Se	Lt	Le	St	Se	Lt
1	PD17	PDMC17	CB17	CBMC17		St	Lt	Le	Se	St	Lt	Le	Se
2	PD18	PDMC18	CB18	CBMC18		Lt	Se	St	Le	Lt	Se	St	Le
3	PD19	PDMC19	CB19	CBMC19		Se	Le	Lt	St	Se	Le	Lt	St
4	PD20	PDMC20	CB20	CBMC20		Le	St	Se	Lt	Le	St	Se	Lt
5	PD21	PDMC21	CB21	CBMC21		St	Lt	Le	Se	St	Lt	Le	Se
6	PD22	PDMC22	CB22	CBMC22		Lt	Se	St	Le	Lt	Se	St	Le
7	PD23	PDMC23	CB23	CBMC23		Se	Le	Lt	St	Se	Le	Lt	St
8	PD24	PDMC24	CB24	CBMC24		Le	St	Se	Lt	Le	St	Se	Lt

PD	Parkinson's patient
PDMC	Parkinson's patient matched control
CB	Cerebellar patient
CBMC	Cerebellar patient matched control

	Suppression
	No suppression

Word Lists: Suppression Task.

name laugh it oil salt day heart cut rest grow field cat free
moon wine clue pain man bill back rock earth dig box face

knee arm real win high late rice wall now air flour rag tin
chin war worm harp they ice grass with break bush eye go

save to cow been boy the dog good from kite way mud home
fair rose press spain what mouse all give firm bone back you

show ear flute of we bark green space axe pig top sing love
flow ball seen can bag rent run sword some hair tree part

heal film year gin wood pull roof key ring pant grow score tale
wrap lake brute peel rank lick car bare tap star beer still

front boat hill knock top class heart king old tear blue line
block my mad lost sky head wool hat chair hand fruit piece red

pin hope plane fire shoe art joy phone rise seat lost note desk
light tape new pill gun plant but rain nail book feel toy

Appendix C: Event Sequence for the Estimation Task

As a further example of this consider the following sequence of events;

A) The experimenter asks if the subject if they are ready

B) A one second interval occurs between the reply and the presentation or description of the signal. For the demonstration trial the word high or low would occur followed by the signal and for the test trial a blank screen occurs followed with the signal presentation.

C) Following the presentation of the signal a response interval occurs with the appearance of some screen graphics to remind the subject which sensor plate to tap to choose the high or low response.

D) There is then a one second interval where feedback occurs for the demonstration trial, for example, " correct ", or a blank screen for the test trial that contains no subject feedback.

E) A fixed inter-trial interval [ITI] of three seconds.

Instructions

General Instructions

The first thing I would like to do is welcome you to this study on the estimation and production of time, your participation is greatly appreciated.

My name is Talei and I am going to be the experimenter for this session of the study, if you have any questions or are unsure what to do, do not hesitate to ask me, I will be more than happy to help. The tasks involved in this experiment are related to timing and centre around you producing and estimating some time intervals in two ranges the millisecond and second range.

- During these trials I will tell you what you need to do and how you are to complete the task.
- At the end of each task your results will be shown to you so that you can see how well you are doing.
- It is very important that you do not attempt any counting during any of the following tasks as that would complicate the findings. In one set of conditions you will be asked to read aloud some words that will appear on the screen in front of you but you will not be required to recall these words at any later time. The words make it easier for you not to count but in another set of conditions it would be good if you tried not to count of your own accord. The most important thing is that you simply concentrate on the signals and the task at hand and if presented just read each of the words out aloud as they appear on the computer screen in front of you.
- Once again thank you very much for taking part in the study and do not hesitate to ask for help.

Hearing and Vision:

I am going to ask you to tell me whether or not you can hear each of these tones

from the computer. If you can hear it just reply yes after the tone. I would like you to face the screen that is in front of you. I am going to show you some words on this screen and I would like you to read each of them out aloud to me as they appear.

Frequency estimation:

In this task you will be asked to choose whether a tone you hear is high or low in frequency after hearing some examples of high and low frequencies. This is a frequency estimation task in which we test a range of frequencies between a high and a low tone. I would like you to place your arms on the books in front of you and rest them on the sensor plate. Place your hands either side of the tapping sensor and rest your index fingers so that they can reach the left and right sensor plates.

To make your choice of whether a tone you hear is high or low in relation to the examples of high and low that have been presented to you, press the **right** / left key when the tone you hear is most like the high tone and press the **left** / right key when the tone you hear is most like the low tone you have heard.

Suppression condition:

During this task words will appear on the screen in front of you. You should read each of these words out aloud as soon as they begin to appear and then make your choice of high or low by tapping the left or right sensor plate after the tone has finished. If you are unsure if the tone you hear is high or low then simply make the closest guess as to whether it was high or low.

Non suppression condition:

You should make your choice of high or low by tapping either the left or right sensor plate after the tone is finished. If you are unsure whether the tone is high or low then simply make the closest guess of high or low.

Do you understand what you need to do to complete this task?

Here are some examples for you of what a high and a low tone should sound like. The computer will tell you here what each of the frequencies are and all you need to do is to make a response by tapping the corresponding sensor plate.

Firstly here is a warmup trial for you, it will give you a few examples of high and low and then will present you with some frequencies that you will be required to decide whether they are high or low.

Are you ready to begin the proper trials? Remember if any words appear on the screen you simply need to read each of them aloud and then make your choice of high or low.

Finger Tapping:

This task is designed to test finger tapping at a short / long range. A short time range is one tested in milliseconds whereas a long time range tests the tasks in a seconds range. In this task you will need to tap your finger on your left / right hand in time with a tone generated by the computer. So I would like you to rest your arm on the books in front of you and rest your hand on the sensor plate in front of you. You will need only to use your index finger to make a response on the left / right plate of the tapping sensor.

When you tap the sensor with your finger a red flashing square will appear on the screen in front of you. This is designed to appear in sequence with the tone .

In this part of the experiment you need to tap the sensor with your finger in time with the tone however once you have begun tapping the tone and the red flashing square will only pace you for twelve taps and then it will be up to you to continue tapping for a little while without the help of the tone or the square until I tell you to stop.

Suppression condition:

Once the 12 paced taps are finished , words will begin to appear on the screen in front of you. You should simply read each of these words out aloud as they begin to appear

but remember the important task is to keep tapping your finger on the sensor plate and try to maintain the same rhythm.

Non suppression condition:

Once you have begun tapping , the tone and the square will pace you for 12 taps only and then it will be up to you to try and maintain your tapping until the trial is finished.

Do you have any questions before you begin?

You may start tapping as soon as you are ready.

Time Estimation:

This task is designed to test time estimation in a short / long range [millisecond and second]. For this task you are going to be asked to classify an interval that you will hear as short or long in relation to a short or long interval that we present to you. An interval can be described as the time between 2 brief tones [verbal demonstration].

Examples of what a short and a long interval sound like will be provided and your task will be to estimate whether other intervals you hear are short or long.

I would like you to place both of your arms on the books in front of you_and then rest your hands on either side of the tapping sensor and place your index fingers where they can reach the left and right sensor plates.

To make your choice of whether the interval you hear is most like the short or the long interval, press the **right** / left key when the interval you hear is most like the long interval and press the **left** / right key when the interval you her is most like the short interval you have heard.

Two boxes, one with an S and one with an L will appear on the bottom of the screen to remind you which of the sensors you should choose if your response is short or long.

Suppression condition:

During this task words will appear on the computer screen in front of you. You should simply read each of these words out aloud when they appear and then make your choice of short or long after you have heard the second tone. If you are unsure whether the interval you have heard is short or long then make the closest guess of short or long.

Non suppression condition:

If you are unsure whether the interval you have heard is short or long then it is important that you make a guess which you think it is closest too and then choose short or long.

Do you understand what you have to do to complete the task?
Here are some examples of what a short and a long interval sound like, the computer will tell you what they are and then you need to tap the corresponding sensor plate. This is a warmup trial for you, a few examples will be given to you and then you will hear some other intervals and you need to then make your choice of whether they are short or long.

Are you ready to begin ?, and remember to make a choice even if you are unsure.

APPENDIX

UNIFIED PD RATING SCALE, VERSION 3.0 (FEBRUARY 1987) DEFINITIONS OF 0-4 SCALE

I MENTATION, BEHAVIOUR, AND MOOD

1. Intellectual Impairment:

0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 =Severe memory loss with disorientation for time and often place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2 Thought Disorder (Due to dementia or drug intoxication):

0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3 Depression :

0 = Not present.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4 Motivation/Initiative :

0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (non-routine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (DETERMINE FOR "ON/OFF")

5. Speech:

0 = Normal.
1 = Mildly affected; no difficulty being understood.
2 = Moderately affected; sometimes asked to repeat statements.
3 = Severely affected; frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation:

0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have night-time drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing:

1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrostomy feeding.

8. Handwriting:

0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected ; not all words are legible.
4 = The majority of words are not legible.

9. Cutting Food and Handling Utensils:

0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone , but can still feed slowly.
4 = Needs to be fed.

10. Dressing :

0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene :

1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in Bed and Adjusting Bed Clothes:

0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (Unrelated to Freezing):

0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Fall more than once daily.

14. Freezing When Walking:

0 = None.
1 = Rare freezing when walking; may have start-hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing; occasionally, falls from freezing.
4 = Frequent falls from freezing.

15. Walking:

0 = Normal.
1 = Mild difficulty; may not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor:

0 = Absent.
1 = Slight and infrequently present.
2 = Moderate ; bothersome to patient.
3 = Severe ; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory Complaints Related to Parkinsonism:

0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech:

0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression:

0 = Normal.
1 = Minimal hypomimia, could be normal "poker face."
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed faces with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at Rest:

0 = Absent.
1 = Slight and infrequent)y present.
2 = Mild in amplitude and persistent. Or moderate in amplitude but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands:

0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude ; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored):

0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession\tab with widest amplitude possible, each hand separately):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands: (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 in.):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straight-backed wood or metal chair, with arms folded across chest):

0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to rise without help.

28. Posture:

0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait:

0 = Normal.
1 = Walks slowly, may shuffle with short steps, but not festination or propulsion.
2 = Walks with difficulty, but requires little or not assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared):

0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness hesitancy, decreased armswing, small amplitude, and poverty of movement in general):

0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

(Lang,1990 p 16-21).

APPENDIX 1.3

PARKINSON;S DISEASE: CLINICAL EXAMINATION

NAME: SEX: M F AGE:

ADDRESS: PH:

DRIVING LICENCE: Y N

HANDEDNESS: R L

DIAGNOSIS: PD NORMAL

TYPE OF PD:

DURATION OF DISEASE:

DDRUG THERAPY:

UPPER-LIME INVOLVEMENT: R-only R>L R=L L>R L-only

DEGREE OF DISABILITY (Hoehn-Yahr): I II III IV V

	R-ARM	L-ARM
TREMOR (0-3) :		
RIGIDITY (0-3) :		
BRADYKINESIA(0-3) :		

Visual Acuity (both eyes, corrected):

Mentation:

Other:

Examiner: Date:

KEY

Level of impairment scale:

Normal	=	0
Slight	=	1
Moderate	=	2
Severe	=	3

HOEHN-YAHR DEGREE OF DISABILITY (Neurology 17: 427-443,1967)

Stage I: Unilateral imvolvement only, usually with minimal or no functional impairment.

Stage II: Bilateral or midline involvement, without impairment of balance.

Stage III: First sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyes closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending upon the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.

Stage IV: Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

Stage V: Confinement to bed or wheelchair unless aided.