Dissociable processing of temporal structure in repetitive eye–hand movements in Parkinson's disease

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Abstract

Movement takes place in multiple dimensions, including the temporal dimension, which itself may be made up of dissociable aspects. From this perspective, the present research tests three hypotheses: first, that the generation of regular, repetitive movement frequency is neurophysiologically dissociable from the generation of appropriate phase relations, or latencies, of such movements with respect to external stimuli; second, that the frontostriatal system is critically involved in the control of latency and not frequency and third that while the control of latency is closely linked to the effector motor system (e.g. eye, hand, etc.) the control of movement frequency is a more centralized function.

These three hypotheses were investigated in nine Parkinson's disease (PD) patients with asymmetric akinetic-rigid syndrome and in nine age-matched control subjects in the context of repetitive eye–hand movements generated in response to regularly displaced visual stimuli and then the continuation of these movements in the immediate absence of the stimuli. PD patients demonstrated increased latencies for pointing movements, particularly with the affected hand, while their ability to follow and then reproduce the movement frequency remained largely intact. Interestingly, saccade latency was improved for controls and PD patients when pointing with the Less-affected hand and impaired with the More-affected hand. In contrast, saccade frequency was unaffected in these pointing conditions. These results support the hypothesis that movement frequency and latency controls are dissociable, with the frontostriatal system playing an important role in latency but not frequency control. The fact that pointing and saccade latency displayed a hand-effect, while movement frequency did not, also tends to support the hypothesis that latency control is linked to specific motor systems, including their interaction, whereas frequency control is more centralized. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Parkinson's disease; Eye–hand movements; Temporal dimension

1. Introduction

Essentially all behavior takes place in the temporal dimension. For the specific behavior of goal directed movement we can consider this temporal dimension to include aspects such as movement latency, velocity and duration. While it appears evident that the temporal dimension is of central importance to movement, it is also quite likely that this dimension is not treated in a unitary fashion by the nervous system. Taking an analogy from studies of human memory, while we may have the perception of a unitary memory system, abundant neuropsychological studies delimit rather distinct and separable systems for the management of memory on different time-scales and for different types of content. It is likely that the representation of time, or the temporal structure of behavior, is similarly fractionated. As previously suggested by Gibbon et al. [17], Ivry and Keele [18] and Ivry [19] two candidate axes along which this separation might occur are related to the control of frequency versus latency for repetitive movements generated in response to a regularly displaced alternating stimulus.

One way to address this separation would be to demonstrate a dissociation (or correlation) between dysfunction of these temporal processing functions due to neurological disorders. Parkinson's disease (PD) provides an interesting model for this type of analysis as there are specific temporal processing deficits associated with this disorder. The PD pathology is characterized by a degeneration of mesencephalic dopaminergic neurons that leads to a perturbation of striatal function. The resulting basal ganglia dysfunction induces disruption of perceptual and motor control processing involving the complex striato-thalamo-cortical loop. From a purely perceptual perspective of temporal processing, it has been documented that the ability to estimate,

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reproduce and discriminate time intervals is abnormal in PD [1,25].

Corresponding to these more perceptual temporal processing anomalies, the resulting motor deficits of PD patients include delayed movement initiation, slowing (bradykinesia) or even a lack (akinesia) of movements, especially for sequential or internally generated motor acts [9]. An additional cognitive-motor deficit characteristic of PD is the difficulty in generating movements in the absence of external cueing or guidance [4,10,14,15,24,28]. In these studies the execution of sensorimotor sequences is significantly slowed when visual feedback, that could be used to trigger successive movements in a sequence, is removed. Thus, while PD patients may display overall increased visuomotor reaction times (RTs) with respect to control subjects, they also show clear improvement in RTs when provided with an external source of advanced cueing [28]. Likewise, patients display significant RT improvements in generating arm movements to random target locations when vision of the hand is provided [22]. This reliance on external cues is also seen in temporal movement sequences that are similarly impaired in their absence [11,15].

The dysfunction in PD patients of movement in the absence of external guidance has been further studied in tasks that require repetitive self-generated movement sequences [18,21,23,25,26]. These studies examined repetitive tapping movements that were guided by a regular external auditory stimulus and/or repetitive movements that were internally guided. While there are some discrepancies between these studies, it appears to be accepted that in internally guided conditions, PD patients showed a greater variability in movement frequency than control subjects. This is emphasized in patients with asymmetrical neurological signs by their display of a "hand-effect" such that the response variance was significantly greater in the worse hand than in both the better hand or in the control group [23]. A number of similar studies have investigated oculomotor saccades to an alternating target in PD patients. Such studies indicate that PD patients displayed abnormalities in saccade variability in a visually guided repetitive task and a reduced tendency to make anticipatory saccades [3,5,6,29].

The comparison of pointing (with the more- and less-affected hand) and saccadic eye movement motivates the consideration of dissociable processes for the control of movement latency, versus a more centralized control of regular movement frequency. The eye and the hand have different mechanic and dynamic properties and are in this sense distinct systems with respect to their control. It would thus, make sense that the control of their separate timing relations with respect to external stimuli should be system dependent. This does not exclude however, the possible interaction between different motor systems. In contrast, control of the frequency of repetitive movements would more logically be based on a more centralized function relatively independent of the motor system. Based on the observation of the role of the frontostriatal system described above and

these theoretical considerations, we can propose the following hypotheses: (a) that the generation of regular, repetitive movement frequency is neurophysiologically dissociable from the generation of appropriate phase relations, or latencies, of such movements with respect to external stimuli; (b) that the frontostriatal system is critically involved in the control of latency and less so in the control of frequency and (c) that while the control of latency is closely linked to the effector motor system (e.g. eye, hand, etc.) the control of movement frequency is a more centralized function.

In order to evaluate these hypotheses, we studied PD patients with repetitive pointing and oculomotor movements during a series of regularly paced visually guided responses, immediately followed by a period during which subjects were asked to continue the ongoing movement at the same frequency in an internally guided condition. We selected PD patients with asymmetric motor impairments in order to compare the less- and more-affected hands. The experiment was conducted in two parts, using the same paradigm. In the first part, we investigated the predictive saccades without hand pointing. In the second part, predictive saccade and pointing performance was studied in an eye–hand coordination condition (oculomotor + less affected hand; oculomotor + more affected hand). Movement latencies and frequencies were analyzed in the initial externally guided phase and movement frequencies were analyzed in the immediately following internally guided phase. Our hypotheses predict: (1) that frequency and latency performance will be dissociated in PD patients; (2) that frequency control will be relatively spared in PD, while latency control will be relatively perturbed and (3) that different motor systems will display different latency profiles and possible interactions, but that the movement frequency profiles will be more uniform across the systems.

2. Materials and methods

2.1. Subjects

We investigated oculomotor and somatomotor performance independently, in nine right-handed patients with mild to moderate idiopathic PD of predominant akinetic-rigid type, fulfilling diagnosis criteria of the UK PD brain bank [16] (Table 1). There were six males and three females. The mean age and S.D. was 54.9 ± 10.5 years (range 38–69 years). The mean duration of disease was 4.1 ± 2.1 years (range 2–8 years). Among the nine PD patients, a sub-group of six patients (Table 1: case 4–9) were analyzed for both their separated and coupled eye and hand performance. They were three males and three females. The mean age of these patients was 55 ± 10 years (range 38–67 years) and their mean duration of the disease was 4.8 ± 2.1 years (range 2–8 years). All nine patients were chronically treated with levodopa plus a peripheral decarboxylase inhibitor (mean levodopa dosage was 322 ± 200.1 mg/day).

Table 1
Clinical description of the nine PD patients, R: right, L: left; motor score refers to items 18–31 of UPDRS and lateralized motor score to items 20–26 of UPDRS

	Patient no.								
	1	2	3	4	5	6	7	8	9
Age (years)	38	45	55	67	60	66	47	47	69
Duration of disease (years)	5	8	2	7	4	3	2	3	3
Hoehn and Yahr (0–5)	1.5	1.5	1.5	2	1.5	2	1.5	1	1.5
UPDRS motor score (maximum = 108)	10	28	6	14	16	18	0	8	11
UPDRS lateralized motor score (maximum per side = 36)	R: 2	R: 11	R: 1	R: 4	R: 7	R: 5	R: 2	R: 3	R: 6
	L: 6	L: 6	L: 4	L: 6	L: 2	L: 7	L: 5	L: 1	L: 1
Hemibody with predominant motor signs	L	R	L	L	R	L	L	R	R

Three patients had a dopaminergic agonist and three others each had either selegiline or tolcapone or an anticholinergic. Prior to the experiments, the PD patients' motor disability was assessed while "on" medication by using the Unified Parkinson's Disease Rating Scale (UPDRS) score [12] and the Hoehn and Yahr staging (Table 1). In the nine patients, the Parkinsonian syndrome was predominant on one side, in four patients on the right and in five patients on the left.

A control group of nine right-handed age-matched healthy subjects (five males and four females; mean age 53.5 ± 8.4 years, range 41–68 years) was studied in the same experimental conditions for statistical comparison with the PD group. The control subjects had no history of neurological nor ophthalmological disorders.

All subjects gave informed consent to participate in this research study, according to the local ethical committee.

2.2. Task and apparatus

The subject was seated in a dark room in front of a setup consisting of a computer screen, a mirror and a touch sensitive screen which were horizontally oriented and parallel to each other (Fig. 1). Visual targets were displayed on the computer screen and reflected in the mirror so that they
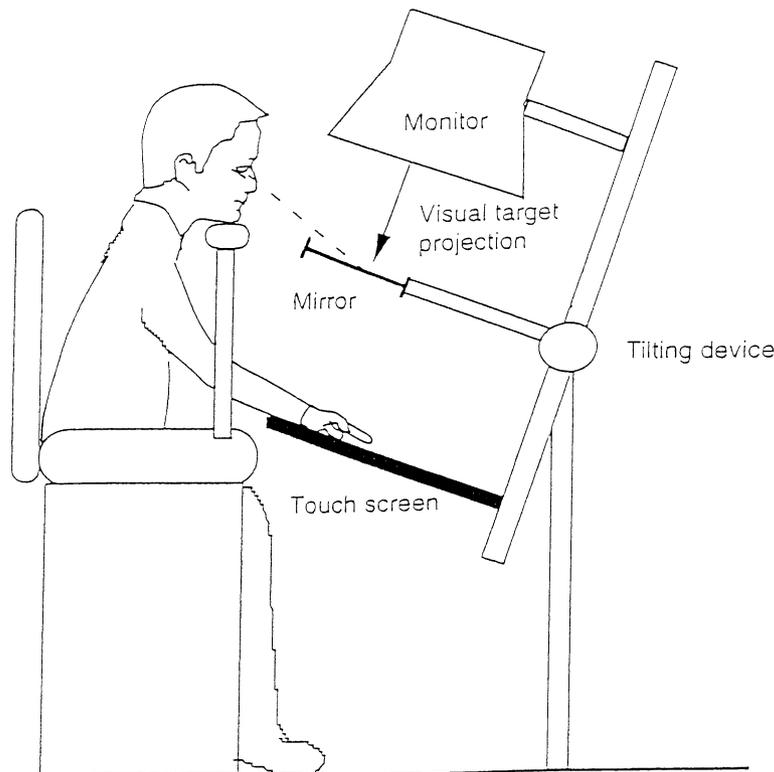

Fig. 1. Experimental setup: the subject is seated in front of a setup consisting of a computer screen, a semi-reflective mirror and a touch sensitive screen which are horizontally oriented and parallel to each other. Visual targets are displayed on the computer screen and projected on the mirror. The subject is looking at the mirror and pointing on the touch screen at the virtual images of the visual targets without seeing the hand (open-loop condition). Head movements are prevented by maintaining the subject's head on a chin rest.

appeared as virtual images on the surface of the touch screen. The subject was looking at the mirror and pointing on the touch screen to the virtual images of the visual targets. The visual target consisted of a small lighted square ($4\,cm^2$) subtending a $2.2°$ visual angle and stepping at $10°$ right and left. Head movements were prevented by maintaining the subject's head on a chin rest. The subject had to track the visual targets by hand pointing and ocular saccades. Pointing occurred in "open-loop" conditions, as the projection on the mirror provided subjects with vision of the target images, but not of their hand.

2.2.1. Hand pointing recording

As soon as the subject pointed to the visual target, the analogue signal of the touch was recorded by the touch sensitive screen (MicroTouch TM) and digitized at a sampling rate of 1 kHz. The time and position of the touch and the associated target were analyzed off-line on PC computer by an interactive software (Cortex, NIH, Bethesda, MD, USA).

2.2.2. Eye movement recording

Eye movements were recorded by DC electro-oculography (EOG). Cutaneous electrodes were placed on the outer canthi for horizontal eye movement recording and on the upper and lower ridges of the right eye for vertical eye movement recording. Vertical eye movements were recorded for blink rejection. The EOG signals were amplified and filtered with a low pass analogue filter (40 Hz). The filtered EOG signals were then digitized at a sampling rate of 250 Hz and stored for off-line analysis on PC computer by an interactive software [8].

The horizontal EOG signal was calibrated on reflexive saccades to visual targets (10, 20 and $30°$ in the right and left visual hemifields) that were elicited in two independent sessions at the beginning and at the end of the predictive saccade session.

In case of EOG drift, this drift was corrected either on-line during eye movement recording or during the data analysis, based on the subject's fixation of a central point before and after each session.

2.3. Behavioral paradigm

The predictive motor responses (saccades and pointing) were elicited by a visual target stepping at a predictable location ($10°$ right and left from the center) and at a predictable frequency (0.25, 0.5 or 1 Hz). For each frequency, 45 cycles of motor responses were tested in two different phases:

1. A first externally guided phase with visual stimulus, where the subject had to produce hand and/ or eye responses in time with the movement of the visual target, for 30 cycles.
2. A second internally guided phase without visual stimulus, in continuation with the first phase, where the visual stimulus was extinguished and the subject, in the dark,

had to continue moving the hand and/or the eyes at the same rhythm and location as during the visual phase, for 15 additional cycles of motor responses.

Each subject had to perform this predictive paradigm at different fixed frequencies (0.25, 1.0 and 0.5 Hz in this order) in two sessions: (1) a session where only the saccades were tested with no pointing and (2) another session where manual pointing was tested one hand after the other. This pointing session always started with the right hand for the control group and with the most affected hand for the PD group. The subject was asked to produce a motor response (eye and/or hand) at the same speed as the visual target in order to synchronize his/her movement to the target movement.

2.4. Data analysis

In order to study the steady-state performance, the first five movements in the externally guided phase were eliminated from analysis. For hand pointing and saccades, at each stimulus frequency (FS), the following parameters were extracted.

1. The amplitude, measured at the endpoint of the first saccade as reflecting the motor program.
2. The latency, determined by the time elapsed between the target displacement and the motor response. The initiation and the end of a saccade was automatically detected by the software as a function of the saccade acceleration with respect to a calculated threshold value.
3. The frequency of responses, measured as the reciprocal of the duration of one complete cycle at the left–right alternation, during the visually guided phase (frequency of response with stimulus (FRS)) and during the internally guided phase (frequency of response with no stimulus (FRN)).
4. The ratio FRS:FS, provides an estimation of the frequency matching ability during the externally guided movement phase.
5. The ratio FRN:FRS, provides an estimation of the ability to maintain the movement frequency during the internally guided phase, based on the subject's own response frequency.
6. The pointing effect (PE) on saccadic performance was calculated, for each parameter, as the difference between saccadic performance in the condition of manual pointing (PS: pointing + saccade) versus the condition without manual pointing (S: saccade).

PE = PS performance − S performance

For each parameter, the within-subject variability (the S.D.) was calculated over the 60 trials (30 cycles) during the visually guided condition and over the 30 trials (15 cycles) during the internally guided condition, at each frequency.

Statistical comparison was realized by repeated measures ANOVA and by post-hoc planned comparisons. The

dependent variables were: the five parameters identified above and their S.D. The between subject factors was the group (control, PD). The within-subject factors were the target frequency (0.25, 0.5, 1) and the hand (right hand versus left hand in the control group and affected hand (AH) versus non-affected hand (NAH) in the PD group). The significance level was established at a 95% confidence interval. Statistical analysis was performed with the Statistica[TM] software package.

3. Results

The results are presented in three sub-divisions corresponding to movement latency, frequency and eye–hand coordination. Certain results related to the eye–hand coupling described in a previous paper [30] are summarized in the present report.

3.1. Movement accuracy

A normal accuracy of predictive saccades (main group effect: $F(1, 16) = 2.9$, $P > 0.05$) and manual pointing, with either hand (main group effect: $F(1, 16) = 0.35$, $P > 0.05$; group × hand interaction: $F(1, 16) = 1.18$, $P > 0.05$) was found in PD group as compared to normal group.

3.2. Movement latency

In PD patients, the adjustment of the latency of movements with respect to the regularly alternating external stimulus is impaired for saccades and for pointing responses, particularly with the affected hand.

3.2.1. Saccade latency
Fig. 2A illustrates a non-significant increase of mean saccadic latency in the PD versus control group, independently
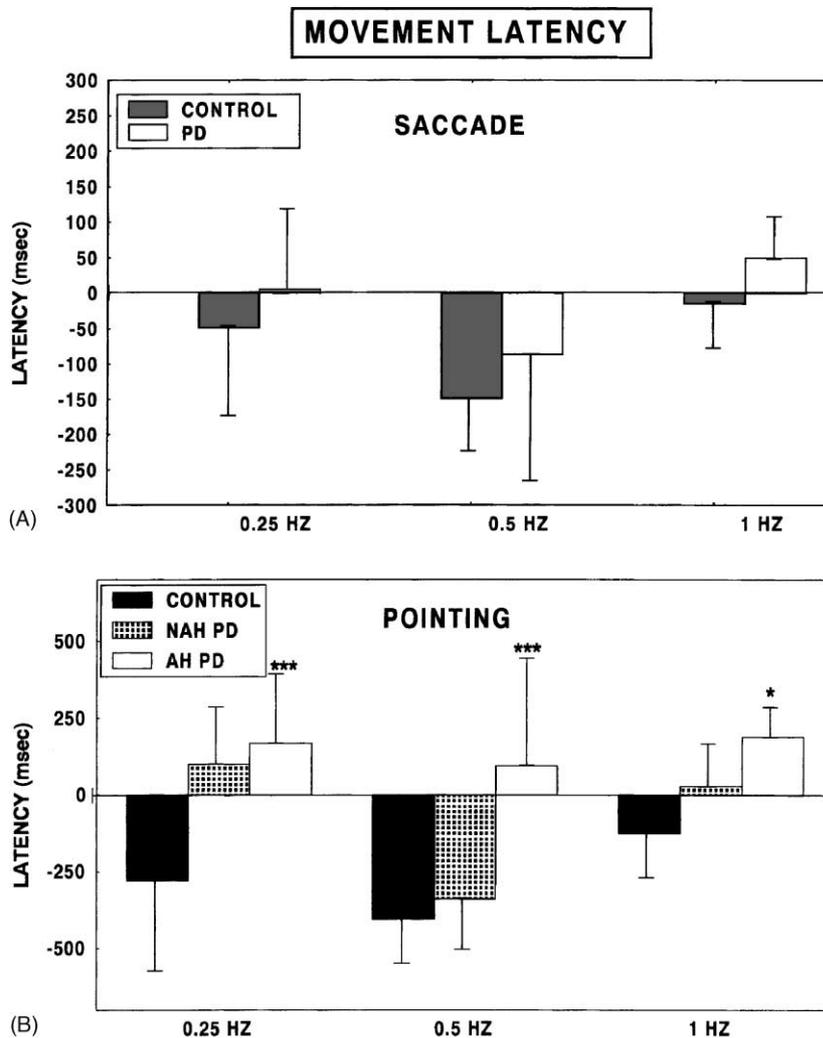

Fig. 2. Mean latency of predictive movements for saccades (A) and manual pointing (B) at three stimulus frequencies (0.25, 0.5 and 1 Hz) in the control group and in the PD group, with the NAH and with the AH. As the effect of hand laterality on movement latency was not significant in the control group, the latency in this group represents the average between the two hands. Bars: S.D. ($*** P < 0.001$, $* P < 0.05$).

of the FS (main group effect: $F(1, 16) = 2$, $P > 0.05$; group × FS interaction: $F(2, 32) = 0.1$, $P > 0.05$). The latency variability as measured by the S.D. was normal (main group effect: $F(1, 16) = 2.6$, $P > 0.05$).

3.2.2. Pointing latency

Mean latency of hand pointing was significantly increased in the PD versus control group, independently of the FS (main group effect: $F(1, 30) = 25.1$, $P < 0.001$; group × FS interaction: $F(2, 60) = 1.8$, $P > 0.05$). In Fig. 2B we see that for the PD group, this effect was highly depen-

dent on the pointing hand: affected or not (main hand-effect: $F(1, 5) = 16$, $P = 0.01$). This hand-effect on latency was dependent on the frequency, as it was more pronounced for the lower frequencies, especially at 0.5 Hz, as revealed by planned comparisons ($P < 0.05$). In the control group, the hand laterality (right hand versus left hand) had no effect on the pointing latency (main hand-effect in control group: $F(1, 7) = 0.2$, $P > 0.05$).

The pointing latency variability as measured by the S.D. was slightly increased in the PD group, independently of the pointing hand (main group effect: $F(1, 31) = 4.4$,
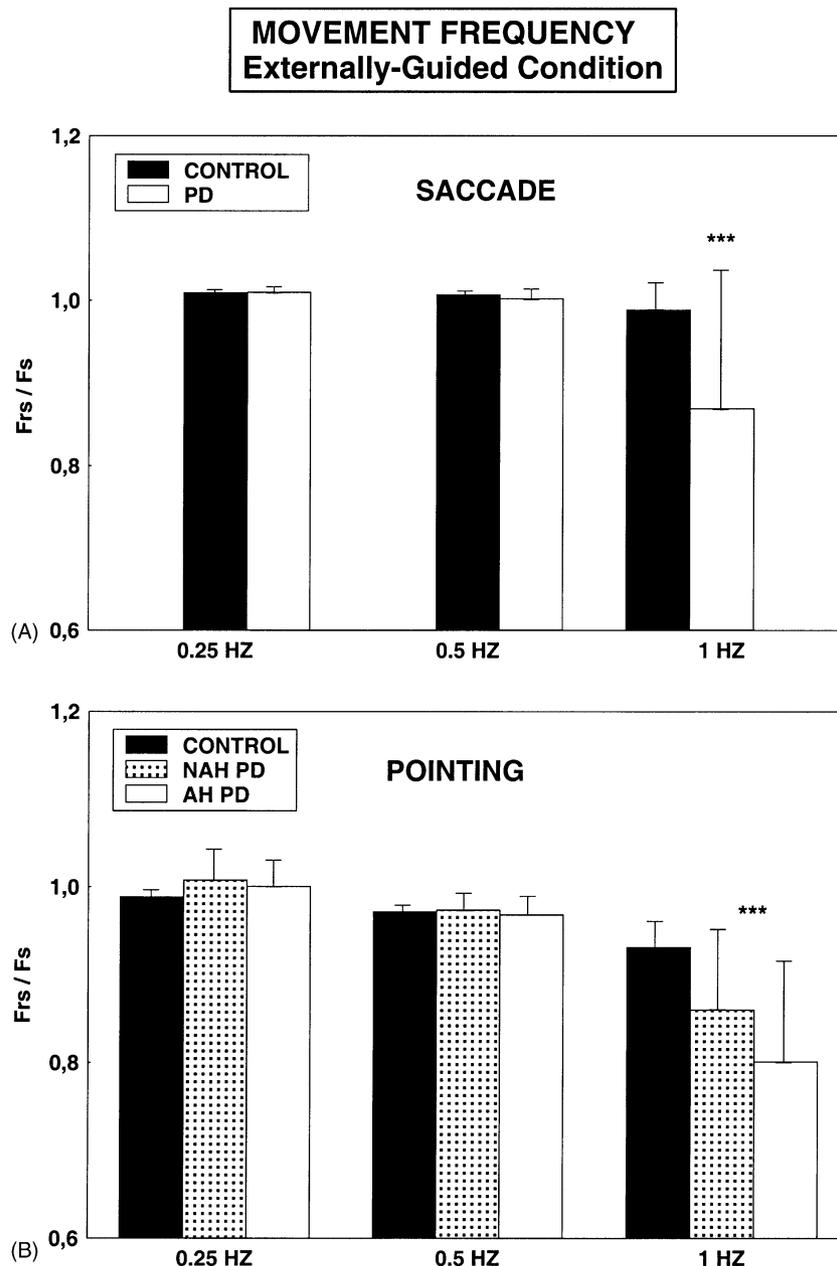

Fig. 3. Ratio of FRS and FS at the three stimulus frequencies (0.25, 0.5 and 1 Hz) in the externally guided condition for saccades (A) and hand pointing (B), in the control group and in the PD group. For both saccades and hand pointing, the ability to match the FS is impaired only at high frequency (1 Hz) in PD group and independently of the AH or the NAH hand for pointing. As the effect of hand laterality on FRS:FS was not significant in the control group, the FRS: FS in this group represents the average between the two hands. Bars: S.D. (*** $P < 0.001$).

$P = 0.043$; main hand-effect in PD group: $F(1, 5) = 1$, $P > 0.05$).

3.3. Movement frequency

The ability to generate stable movement frequencies (pacing) was normal in PD patients (except at 1 Hz where a frequency ceiling appears to have been reached) for both saccades and pointing with the more- and less-affected hands. Interestingly, the movement frequency variability was more impaired in the visually guided condition than in the internally guided condition for both saccades and hand movements.

The ability in the visually guided condition to match the target frequency was evaluated as the ratio FRS:FS. The ability in the internally guided phase to store the movement frequency established during the externally guided phase was evaluated as the ratio FRN:FRS. Variability was evaluated as the S.D. of each of these ratios.

3.3.1. Saccade frequency

Saccade frequency matching (FRS:FS) was impaired in the PD group, depending on the FS (main group effect: $F(1, 16) = 7.2$, $P = 0.016$; group x FS interaction: $F(2, 32) = 5.9$, $P = 0.007$). Planned comparisons revealed however, that the PD and control subjects differed in this frequency matching performance only at the highest FS ($P < 0.01$) (Fig. 3A). At 1 Hz, mean FRS:FS was 0.87 in the PD group and 0.99 in the control group.

Interestingly, as shown in Fig. 4, the variability of predictive saccade frequency, as revealed by the S.D. of FRS:FS, depended on the stimulus condition: in the externally guided condition, it increased at nearly the significance level in the PD group (main group effect: $F(1, 16) = 3.8$, $P = 0.067$; group × FS interaction: $F(2, 32) = 2.5$, $P > 0.05$) while in the internally guided condition, the saccade latency variability (the S.D. of FRN:FRS) was not different between control and PD groups (main group effect: $F(1, 16) = 0.37$, $P > 0.05$; group × FS interaction: $F(2, 32) = 0.006$, $P > 0.05$).

As shown in Fig. 5A, the ability to maintain, in the internally guided condition, the established saccade frequency (FRN:FRS) was not affected in the PD group at any of the stimulus frequencies (main group effect: $F(1, 16) = 0.002$, $P > 0.05$; group × FS interaction: $F(2, 32) = 1.9$, $P > 0.05$).

3.3.2. Hand pointing frequency

In the externally guided condition, frequency matching (FRS:FS) performance in pointing was impaired in the PD group, depending on the FS (main group effect: $F(1, 31) = 7.6$, $P = 0.009$; group × FS interaction: $F(2, 62) = 21$, $P < 0.001$). This deficit in matching the FS was found only at 1 Hz ($P < 0.001$), for both hands (main hand-effect in the PD group: $F(1, 5) = 0.85$, $P > 0.05$) (Fig. 3B). In the control group, pointing frequency was independent of the pointing hand (main hand-effect in control group: $F(1, 7) = 4.1$, $P > 0.05$).

The variability in pointing frequency depended on stimulus condition as it was significantly increased in the
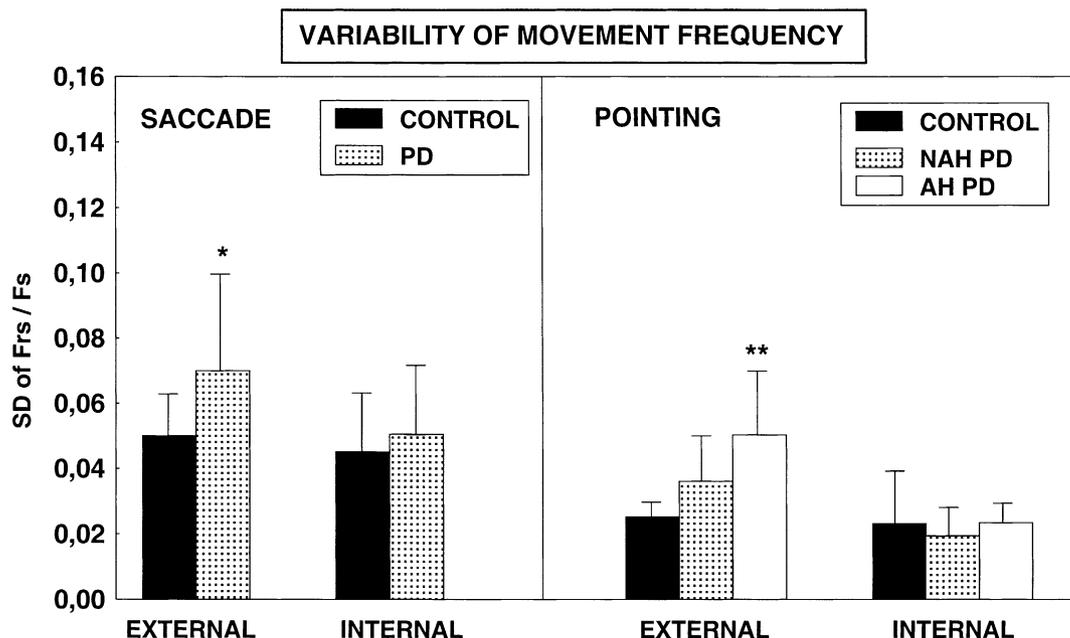

Fig. 4. Variability of movements measured as the S.D. of movement frequency (FRS:FS), at the FS of 0.5 Hz. The S.D. of movement frequency is represented for saccades and manual pointing, in visually guided (external) and internally guided (internal) conditions, in the control group and in the PD group, NAH and AH. As the effect of hand laterality on S.D. of movement frequency was not significant in the control group, the S.D. in this group represents the average between the two hands. Bars: S.D. (∗∗ $P < 0.01$, ∗ $P < 0.05$).

**MOVEMENT FREQUENCY STORAGE
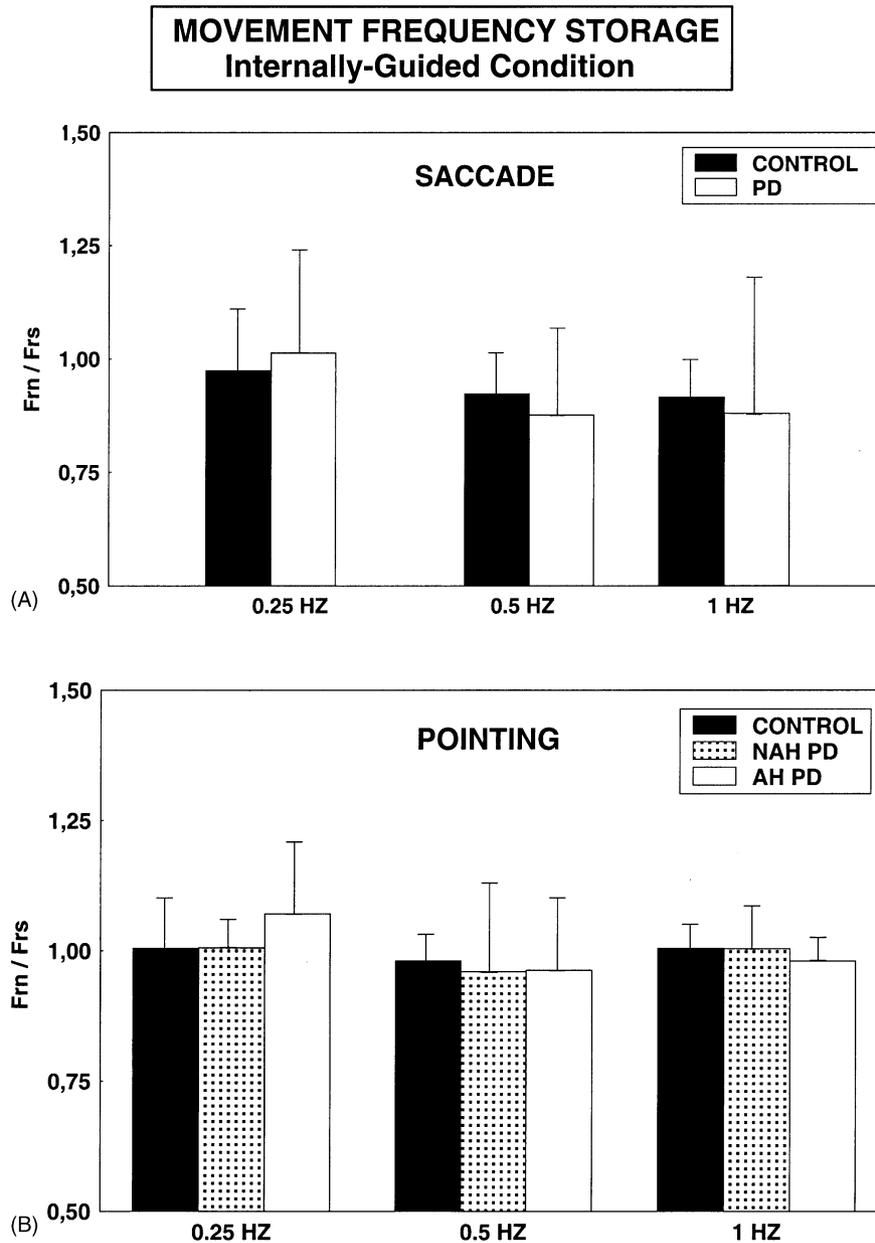Internally-Guided Condition**

Fig. 5. Ratio of movement frequencies (FRN: FRS) between the internally and the externally guided conditions, at the three stimulus frequencies (0.25, 0.5 and 1 Hz). A: saccades and B: manual pointing, in the control group and in the PD group, NAH and AH. As the effect of hand laterality on FRN:FRS was not significant in the control group, the FRN: FRS in this group represents the average between the two hands. The ability to store and maintain the movement frequency in the internally guided condition is normal in the PD group, for the ocular saccades and the pointing with either hand.

PD group in visually guided condition (group effect: $F(1, 31) = 5.6$, $P = 0.024$) independently of the hand (main hand-effect in the PD group: $F(1, 5) = 0.2$, $P > 0.05$) (Fig. 4) and not different between the control and PD groups in the internally guided condition (main group effect: $F(1, 31) = 2.3$, $P > 0.05$) independently of the hand (main hand-effect in the PD group: $F(1, 5) = 1.4$, $P > 0.05$) (Fig. 4).

As we see in Fig. 5B, the ability to maintain the point-ing frequency (FRN:FRS) in the internally guided condi-tion, did not differ between the control and the PD groups, independently of the FS (main group effect: $F(1, 31) = 0.003$; $P > 0.05$; group x FS interaction: $F(2, 62) = 0.92$, $P > 0.05$).

3.4. Effects of pointing on saccades

Manual pointing produced significant effects on saccadic eye movements (as measured by PE = saccade latency during pointing—saccade latency without pointing), mainly

on the latency and not on the latency variability [30]. Saccade latencies were significantly reduced in the control group (PE = −243) and in the PD group, when pointing with the less-affected hand (PE = −147) and in contrast, were increased when pointing with the more-affected hand (PE = 43). No effect of pointing with either hand was found in saccade frequency matching nor reproduction nor on their variability.

3.4.1. PE on saccade latency

In PD group, the PE on saccade latency was significant and independent of FS (main hand-effect: $F(1, 5) = 11$, $P = 0.02$; hand x FS interaction: $F(2, 10) = 2.4$, $P > 0.05$). In PD group, no significant difference in the variability of saccade latencies was found between the conditions with and without pointing with either hand (main group effect: $F(1, 5) = 0.09$, $P > 0.05$).

3.4.2. PE on saccade frequency

In PD group, no significant difference, as compared to control group, was found in saccade frequency with versus without pointing, as PE was close to 0 with either hand pointing, both in the externally guided (main group effect: $F(1, 9) = 1$, $P > 0.05$; main hand-effect in PD group: $F(1, 5) = 0.84$, $P > 0.05$) and in the internally guided conditions (main group effect: $F(1, 10) = 2$, $P > 0.05$; main hand-effect in PD group: $F(1, 5) = 0.2$, $P > 0.05$). Similarly, in PD group, the pacing variability measured by S.D. was not significantly different while pointing or not, in the visually guided condition (main group effect: $F(1, 9) = 0.07$, $P > 0.05$; main hand-effect in PD group: $F(1, 5) = 0.2$, $P > 0.05$) nor in the internally guided condition (main group effect: $F(1, 10) = 3$, $P > 0.05$; main hand-effect in PD group: $F(1, 5) = 0.6$, $P > 0.05$).

4. Discussion

The main finding of the present study supports the three components of our dissociation hypothesis. (1) PD patients displayed intact capabilities to store and reproduce regular movement frequencies but significantly increased movement latencies. This also argues for the hypothesis (2) that the frontostriatal system is implicated in the control of movement latency but less so in the control of frequency. The hypothesis (3) that latency is motor system dependent while frequency is independent and centralized, is supported by the observation of a hand-effect for latency but not for frequency; indeed, when movement frequency was impaired for one system, it was impaired for all at that frequency. We thus, provide support for the models suggested by Gibbon et al. [17], Ivry and Keele [18] and Ivry [19] concerning the separation of basal ganglia and cerebellar function in the control of movement latency and frequency, respectively.

4.1. Dissociation between frontostriatal roles in phase and frequency processing

Visually guided repetitive movement involves (a) the generation of repetitive movements with fixed frequency and (b) the adjustment of the phase or latency of these fixed frequency movements to coincide with or to anticipate the repetitive external stimulus. These two processes may be carried out either by a single or by dissociable mechanisms. Gibbon et al. [17] suggest a two process model in which the variability of movement timing relies on cerebellar function, while the accuracy of movement timing relies on the basal ganglia, compatible with the results of Ivry and Keele [18] in patients with PD or cerebellar lesions. If frequency and latency of repetitive movements are processed by a common timing system then we would expect to see a disruption in one to be correlated with a disruption in the other. In contrast, if frequency and latency of these movements are processed by dissociated mechanisms, then their disruptions should not be correlated.

4.1.1. Hand-effect in PD for latency but not frequency

In PD patients, hand movement latencies to predictable targets at either 0.25 or 0.5 Hz were significantly increased in the more-affected hand, while they were less or not significantly increased in the less-affected hand. We refer to this performance asymmetry as a "hand-effect". Moreover, there was a strong hand-effect on saccadic latency during pointing, independently of the movement frequency. In the control group, the saccadic latency was reduced when the subject was pointing. Interestingly, in the PD group, while the saccadic latency was reduced when pointing with the less-affected hand, it was increased when pointing with the more-affected hand. This hand-effect arises from the eye–hand coupling mechanism that is preserved in PD [30].

Given this hand-effect for latency in the externally guided condition, the existence of a common timing-related mechanism for movement latency and frequency would predict a hand-effect for movement frequency in pointing and in eye–hand coupling. In contrast to this prediction, we observed no hand-effect on movement frequency at any FS, neither in internally nor in externally guided conditions.

4.1.2. External cues induce interaction between latency and frequency

In our study, while the mean of movement frequency was normal at low frequencies in both externally and internally guided conditions, its variability was abnormally increased only in the presence of external stimuli. Indeed, an increased manual pointing latency Co-occured with an increase in frequency variability in externally guided conditions. This augmentation in pointing frequency variability was no longer observed in internally guided condition. In consequence, the frequency variability increase observed during externally guided conditions might result from the deficits in latency and not from an impaired frequency control. This effect was

likely due to interference between the impaired sensorimotor latency regulation (that would yield increased frequency variability) and the rather intact capability to generate a stable movement frequency (that would leave mean frequency intact). Despite such a latency–frequency interaction, the behavioral dissociation between the effects of external stimuli on mean latency versus mean frequency indicates that these two components of repetitive movements are controlled independently.

4.2. System-specific latency versus centralized frequency control

While saccadic latency was slightly though not significantly, perturbed over the whole range of stimulus frequencies, hand pointing latency was more perturbed at low frequencies and particularly for the more-affected hand. This view of the different effects of PD on latency in the oculomotor and somatomotor (less- and more-affected hands) clearly indicates that the neural control of the latency component of the temporal dimension is largely motor system-specific. On the opposite, for these motor systems, in the externally and internally guided conditions, movement pace (movement frequency and its S.D.) in PD patients was normal at low stimulus frequencies for which saccadic and pointing latencies were perturbed.

The PD patients display considerable difficulty in matching the target frequency of 1 Hz both for saccades and for pointing with either hand. This global deficit at 1 Hz suggests the existence of a more centralized clock function that contributes to multiple motor systems. Previous studies of repetitive movements have also documented this kind of frequency dependence in PD [13,25,26]. In an effort to understand this breakdown at higher frequencies, it is noteworthy that Cunnington et al. [7] have demonstrated that cortical processes in the supplementary motor area associated with the termination of an ongoing movement appear to have a prolonged duration in PD. At low movement frequencies, this prolonged movement termination duration might not be problematic, whereas at higher frequencies it could overlap with the preparation of the subsequent movement. Thus, the FS of 1 Hz might be considered as a ceiling frequency at which the disrupted SMA-striatum loop cannot operate for maintaining regular and alternating fast movement in PD. This could contribute to the frequency dependent impairments observed in the current and related studies.

Finally, we can consider that a possible attention effect in PD is not likely to account for our observed motor defects for at least two reasons. (1) Our elementary alternating task demands a low attentional load and the predictive responses elicited in this context usually become rapidly automatic with anticipatory movements that are rather independent of the stimulus and consequently of attention processing. (2) The asymmetrical effect of the hand on the saccade performance, with a beneficial and an adverse effect depending on the less-affected or the more-affected hand used by the

PD patient, respectively, is also suggestive of specific motor defects rather than attentional disorders which might occur symmetrically. Based on these two observations, it is reasonable to eliminate a purely attentional explanation for these motor defects even though we can assume that any behavioral task yields to some attentional demand.

4.3. Comparison with related studies

A number of previous studies have examined the ability of PD patients to maintain a previously established movement rhythm after the stimulus has been removed. As we observed, a dysfunction in this capability appears to increase with both the frequency of movement and with the degree of motor impairment [23,25,26]. In a group of asymmetrically affected PD patients, O'Boyle et al. [23] found that internally guided movement variance in the "worse" hand was significantly higher than that of the "better" hand, which did not differ from controls. Pastor et al. [26] found that for movement frequencies in excess of 1.5 Hz, PD patients movement timing accuracy declined and that at all frequencies, their variability was increased with respect to that of controls.

We were interested in the comparison between movement frequency and its variability in the externally versus internally guided conditions. We measured variability as the S.D. of the mean movement frequency and did not analyze its sub-components of motor-delay variance (MDV) and clock variance (CV), as in the Wing and Kristofferson [31] model. O'Boyle et al. [23] demonstrated that both the CV and the MDV were impaired in the affected hand in asymmetric PD patients. This is contrary to the results of Ivry and Keele [18], but in agreement with those of Pastor et al. [25,26]. As observed by Pastor et al. [26], the assumptions of the Wing and Kristofferson [31] model are often not met in the data in repetitive movement tasks with PD patients. They conclude that "the validity and utility of the model proposed by Wing and Kristofferson [31] for the study of repetitive rhythmic movements cannot be accepted as proven and require further assessment". Given this context, we directed our analysis at the mean movement frequency and the total variability in this measure under different conditions.

Taking this approach, we do not observe abnormal frequency variability in the PD patients during the internally guided movements, as did Pastor et al. [25,26] and O'Boyle et al. [23]. There are several factors contributing to this difference, all related to important experimental differences in the tasks used. With respect to somatomotor system results, we employed a pointing task that involved use of proximal and distal muscles to move the hand and forearm, in contrast to the single finger tapping tasks used in the related studies. Our task thus, involved the inertial damping effects of the forearm that were absent in the other studies. In addition, for both pointing and saccades, our protocol involved 30 cycles (with two "taps" or saccades per cycle, for a total of 60 synchronization trials) of visually guided performance to establish the movement frequency before removal of the

visual stimulus. O'Boyle et al. [23] used 15 tones and Pastor et al. [25,26] used 30 tones during the "synchronization" phase. Finally and perhaps the most importantly, our pointing and saccade movements were directed towards visible, spatial goals. In contrast to the auditory cues previously used [23,25,26], these visuospatial goals provided a sensorimotor coherence between the stimulus and the response that likely contributed to reduced movement variability. These differences in the experimental tasks likely explain the different results in the frequency variability.

The main point of the current study is the dissociation between movement latency and movement frequency, including their variability, in externally versus internally guided conditions. In our PD patients, for frequencies 0.25 and 0.5 Hz, movement frequency or pacing performance is normal while latency is perturbed. Based on this observation, we suppose that, while latency or phase processing relies on the frontostriatal system, pacing or frequency is likely provided by nervous structures other than frontostriatal system. Interestingly, several studies also report on the relative independence of the internal clock from the motor implementation mechanisms [2,17,19,20]. In particular, they suggested that the cerebellum, possibly the cerebellar hemisphere or the vermis, might be a good candidate for temporal information processing or time-keepers which might be triggered by repetitive external stimuli [19,20], consistent with the preservation of this function in PD. In our experimental conditions, the visual stimulus provides the temporal frequency which might thus, trigger and set the frequency of an internal clock in the cerebellum. The temporal information from the cerebellum might be provided to the SMA through thalamic relays, which constitute a major recipient for segregated pallidal and cerebellar inputs to different sectors of the SMA [27]. The cerebello-thalamic pathways could thus, supply the pacing information to the oculomotor and somatomotor areas to be used in repetitive movements either by the SMA itself or other striato-thalamo-cortical circuitries not impaired in PD.

5. Conclusions

The current study investigated the comparison between phase (latency) and pacing (frequency) performance, including their variability, in externally versus internally guided conditions. In our PD patients, for frequencies 0.25 and 0.5 Hz, pacing performance is normal while latency performance is perturbed, particularly for the more-affected hand. Our results thus, support the three hypotheses evoked at the outset, namely: that (a) the generation of regular, repetitive movement frequency is neurophysiologically dissociable from the generation of appropriate phase relations or latencies, sub-serving anticipation process, of such movements with respect to external stimuli; (b) that the frontostriatal system is critically involved in the later and less so in the former and (c) that while the control of latency is specific to the physical characteristics of the effector motor system (e.g. eye, hand, etc.) the control of movement frequency is a more centralized function.

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