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The reach-to-grasp movement in Parkinson's disease before and after dopaminergic medication

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Abstract

The aim of the present study was to assess the effects of dopaminergic medication on the organisation of the reach-to-grasp movement in Parkinson's disease. A three-dimensional kinematic system (ELITE, B|T|S| Italy) was used to record reach-to-grasp movements to objects of either small (0.7 cm) or large (8 cm) diameter placed at a reaching distance of either 20 or 30 cm. Vision of the reaching limb and target was also manipulated. Parkinson's disease participants ($N = 14$) were assessed in 'OFF' (12 h without medication) and 'ON' (1–2 h post-administration of medication) states. In the 'ON' state, movement duration and the time spent in arm deceleration were significantly less than in the 'OFF' state. The amplitudes of peak reaching velocity, acceleration and deceleration were all higher in the 'ON' than in the 'OFF' state. Further, in the 'ON' state, the acceleration profile no longer exhibited small irregular adjustments, the number of significant correlations between parameters measured from the transport and manipulation components was greater, and the movement was more direct in both the mediolateral horizontal and vertical planes. These results indicate that dopaminergic medication is of benefit in reducing bradykinesia and in fine-tuning kinematic parameterisation of a selected reach-to-grasp action.

Keywords: Parkinson's disease; Dopamine; Reach-to-grasp; Human; Motor control; Basal ganglia

1. Introduction

Despite an obvious need to ensure that therapeutic assessment is precise and objective [12,24,56], few studies have addressed the efficacy of dopaminergic medication in Parkinson's disease using reliable quantitative measurement instruments. Thus far, the results give a mixed picture of the effectiveness of therapy in improving the motor symptoms of Parkinson's disease (PD).

Blin et al. [8] identified what have been termed 'dopa-sensitive' and 'dopa-resistant' parameters. Using a quantitative system for the recording of gait kinematics, they demonstrated that rhythm-related gait measures, such as stride duration and swing duration, showed no change following administration of L-dopa, while other parameters, such as stride length and swing velocity, were clearly affected. Johnels et al. ([39], see also [40,52]) found that certain measures were less dopa-sensitive than others. In their whole body Posturo-Locomotor-Manual (PLM) task participants pick up an object from the floor and walk forward to place it on a high shelf. Following an oral single-dose of levodopa in combination with a decarboxylase inhibitor, the total time for performance of this action by PD participants decreased. However, a breakdown of the inherent movement components showed that the improvement in performance speed was decidedly more pronounced for the locomotion and arm elevation phases of the task than for the postural phase in which the participant straightened the body after bending down to pick up the object.

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Other researchers have also demonstrated medication effects on some but not all measured parameters. Using a combination of physiological (surface EMG) and kinetic/kinematic measures in a corrective balance task, Bloem et al. [9] reported that the increased backward sway of PD participants to toe-up rotational perturbations was not reduced with dopaminergic medication. However, low-amplitude late-latency responses in tibialis anterior in the 'OFF' state showed increases in amplitude in the 'ON' state. Caligiuri et al. [11] tested the ability of eight PD participants to perform simultaneous actions before and after a single dose of carbidopa/levodopa. The task required maintenance of a steady-state finger flexion force with one hand while exerting rapid response finger flexion pulses with the contralateral index finger. Stability of the steady-state task showed no change with medication; however, the degree of interference from the ballistic task upon the steady-state task was reduced for 87% of the PD participants. From these results the researchers suggested that Sinemet had acted upon a dysfunction in the ability to keep simultaneously activated motor programs from interfering with each other.

In the current study, a three-dimensional kinematic system was used to assess the effectiveness of dopaminergic therapy upon the organisation of the reach-to-grasp movement. This is a movement performed normally and routinely within the familiar context of living activities. It was chosen primarily because it was likely to recruit a well-used internal model within the central nervous system. Experimental learning effects would thus be largely avoided. It is also a movement that has been well characterised experimentally. The reach-to-grasp action is commonly described in terms of a proximo-distal distinction. The reaching and positioning actions, effected by upper arm and forearm musculature, are subserved by central nervous system visuomotor mechanisms that are largely independent from those mechanisms subserving the hand and digit action of opening and closing upon the object for its grasp. The two neural channels, transport and manipulation, are said to be activated simultaneously, in parallel [36,37] and to be coupled functionally for goal-directed actions by a higher-order coordinative structure [37]. The 'transport' channel extracts information about the spatial location of the object for transformation into motor patterns that bring the hand appropriately towards the object. The 'manipulation' channel extracts information about the intrinsic properties of the object (such as size and shape) for the determination of a suitable grasping pattern.

Apart from generalised slowing, the only abnormality demonstrated by PD participants compared with healthy control participants for reach-to-grasp, and one which appears to vary according to the level of task predictability, is a delayed onset of the grasp component. This suggests that the reported dysfunction for the sequential/simultaneous management of different motor programs in PD [14] also applies to the initiation of the components of a coordinated action [16,17]. That is, the ability to activate the reach and grasp components may almost simultaneously be disrupted.

To date, all PD participants of reach-to-grasp experiments were tested after having taken their morning dose of carbidopa/levodopa. Thus, it is not known whether the delayed activation dysfunction is a medication effect. Further, it is unclear whether the normal patterning of the reach-to-grasp movement seen in medicated PD participants according to object size and distance would also be evident in the non-medicated state.

The aim of the present study was to determine the effects of carbidopa/levodopa medication upon the kinematic parameterisation of the reach-to-grasp action of PD participants. The task was to reach to grasp a small or a large cylinder positioned at one of two distances. This was performed before and after the PD participants had taken the morning dose of carbidopa/levodopa. Two visual conditions were implemented. In one the participant could see the target and their limb during the movement, while in the other condition neither the target nor their limb was viewed.

The choice of two cylinder diameters enables the manipulation of accuracy, the small cylinder requiring a more precise grasp (precision grip) than the large cylinder (whole hand prehension). Medicated PD participants typically show a normal patterning according to object size, with, for example, movement duration and reaching arm deceleration being greater for actions to the small than to the large object [16]. The choice of two distances enables assessment of the ability to scale appropriately reaching velocity and acceleration. Again, medicated PD participants typically demonstrate appropriate scaling [16]. The choice of two different visual feedback conditions enables assessment of the reported greater reliance on visual feedback for movement in Parkinson's disease [31].

Given reports of a decrease in the time taken to perform an action following dopaminergic medication [8,39,40,52], together with the common clinical finding of faster movements, it is hypothesised that the movement will be faster following medication. Based on several reports that PD participants in 'ON' show difficulty in the activation of movement components [16,17] it was hypothesised secondly that the activation delay of the manipulation component would increase prior medication. Finally, and in accordance with the stance that the basal ganglia are not responsible for the programming of actions [16,42,43], it is hypoth-

Table 1
Characteristics of the Parkinson's disease (PD) and control subjects

Parkinson's disease													Control	
Subject	Age	Gender	UPDRS						Hoehm & Yahr [33]	MMSE	Length of diagnosis	Medication dosage (Levodopa)	Age	Gender
			Limb-right	Limb-left	Alt. Mov.[a]	Duration[b]	Disability[b]	Painful Dyskinesias[b]						
1	37	f	3	5	1	0	0	0	1	29	5	Sinemet CR 200 × 3	37	f
2	66	f	4	3	1	0	0	0	1	29	1.5	Sinemet CR 200 × 1	66	f
3	71	m	8	8	2	0	0	0	2	28.5	5	Sinemet CR 200 × 3	71	m
4	57	m	5	5	1	0	0	0	2	28	7	Sinemet CR 100 × 3	57	m
5	66	m	5	4	1	0	0	0	2	30	1.5	Sinemet CR 200 × 1	68	m
6	65	m	8	6	2	0	0	0	3	28.5	3.5	Sinemet CR 100 × 3	65	m
7	68	m	4	10	2	0	0	0	1	30	3	Sinemet CR 200 × 1	68	m
8	75	f	8.5	7.5	2	1	1	0	2	28	13	Sinemet CR 200 × 4	75	f
9	63	m	3.5	3.5	1	0	0	0	2	28	6	Sinemet CR 200 × 3	63	m
10	76	f	5	4	2	1	2	0	2	28.5	16	Sinemet CR 100 × 3	77	f
11	73	m	3	2.5	1	0	0	0	2	28	4	Madopar CR 100 × 3	73	m
12	69	m	3	4.5	2	0	0	0	1	28.5	2	Sinemet CR 100 × 1/2	69	m
13	73	f	5	1.5	0.5	1	1	0	1	30	10	Madopar CR 100 × 3	73	f
14	79	m	3.5	3.5	1	0	0	0	2	28.5	7	Sinemet 100 × 2	80	m

[a] Rapid Alternating Movements.
[b] These three refer to the Dyskinesias items of the UPDRS.

esised that kinematic parameterisation according to manipulations of object size, distance and visual feedback will not show medication effects.

2. Methods

2.1. Subjects

The characteristics of the 14 (out of an original volunteer group of 15) PD participants are shown in Table 1. Each PD participant was initially tested before the first morning dose of carbidopa-levodopa, after not having taken medication for at least 12 h ('OFF' state), and then retested 1–2 h after medication, at a time when the participant reported being in the best 'ON' state. The results of clinical disability testing with the Unified Parkinson's Disease Rating Scale (UPDRS; [25]) are shown in Table 1. However, this was done only in the 'ON' state to minimise time in the 'OFF' state. Dopaminergic medication was most commonly Sinemet or Madopar, with other medications including Artane, Eldepryl and Parlodel. Disease duration for the PD participants ranged from 1.5 to 16 years and no participant showed motor complications due to therapy that interfered with the task (please refer to the dyskinesia ratings on the UPDRS presented in Table 1). The 14 sex- and age-matched control participants reported no neurological or skeletomotor dysfunctions. All participants showed right-handed dominance [46], were naive as to the experimental design or purpose, and gave informed consent to participate. The Mini-Mental State Examination (MMSE) was used to provide an index of the current global cognitive state [27]. The scores of the PD participants ranged from 28–30, and those of the control participants from 29–30. With visual acuity testing, PD participants scored, on average, 18 out of 20 and control participants 20 out of 20.

2.2. Apparatus

The participant was seated in a height-adjustable chair so that the feet and the back were supported, and the right arm, dominant in all cases, rested on the table surface. The starting position of the arm and hand was with the shoulder slightly flexed and internally rotated (~45°), the elbow flexed (~90°), the forearm in mid-pronation and the ulnar border of the hand resting upon a pressure sensitive switch 20 cm anterior to the thorax. The thumb and index finger were held in a relaxed position of opposition. The object to be grasped was a 10 cm high translucent cylindrical dowel made of clear perspex. It was either of a small (0.7 cm) or large (8 cm) diameter [independent variable = Object Size], and was positioned vertically in the midline at 20 or 30 cm [independent variable = Object Distance], from the starting switch. Upon hearing an acoustic signal (800 Hz), the participant was required to reach towards and then grasp to lift the object. This action was performed under one of two visual feedback conditions [independent variable = Visual Feedback]. Under the full vision condition, no visual constraints were imposed. Under the non-vision condition, the participant wore a black mask and was unable to see the object or the arm. Movement speed was not stipulated, except to ask the participant to perform the movement as he/she would normally if reaching to grasp an object at home. For each target size/distance combination, the participants performed five practice trials and then a block of ten trials for each vision condition. To distribute practice effects across conditions (size, distance and vision), the order of blocks was counterbalanced across participants.

2.3. Recording techniques

Movements were recorded with the ELITE motion analysis system. This consisted of two infrared cameras (sampling rate 100 Hz), inclined at an angle of 30° to the vertical and placed 3 m in front of the table and 3 m apart, that recorded the reflections of passive markers (0.25 cm diameter) attached to the following points of the right upper limb: (a) the wrist—radial aspect of the distal styloid process of the radius; (b) the index finger—radial side of the nail; and (c) the thumb—ulnar side of the nail. The spatial error measured from stationary and moving stimuli in a calibrated working space (parallelepiped) was 0.4 mm. Coordinates of the markers were reconstructed and sent to a host computer (Pentium).

2.4. Data processing and analysis

The ELIGRASP (B|T|S|, 1994) software package was used to assess the data. This gave a three-dimensional reconstruction of the marker positions. The data were then filtered using a finite impulse response linear filter (cut-off frequency 10 Hz; [20,21]). The reach component was assessed by analysing the trajectory, velocity, and acceleration profiles of the wrist marker. The grasp component was assessed by analysing the trajectory of the thumb and index finger markers, and the distance between these two markers. Movement initiation time was the time taken between the onset of the tone which acted as a "go" signal and the release of the starting switch. Onset of the grasp component was taken as the time at which the hand began to open; that is, when the distance between the index finger and thumb markers was no longer constant and showed increments >0.4 mm. The end of

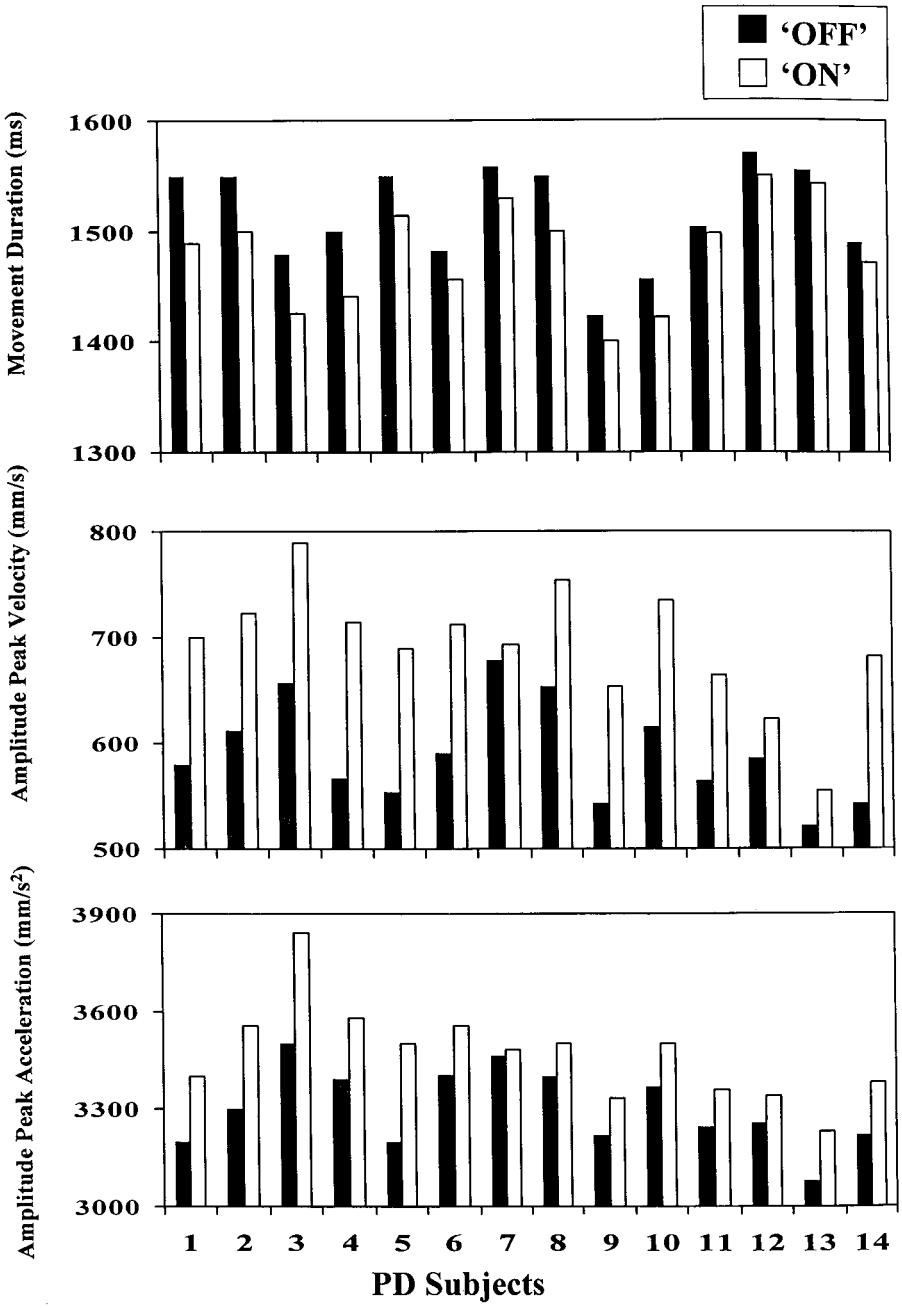

Fig. 1. Movement duration, amplitude of peak reach velocity and peak reach acceleration in 'OFF' and 'ON' states for each PD subject.

the movement was taken as the time when the fingers closed on the cylinder and there was no further change in the distance between the index finger and thumb. Movement duration was calculated as the time between movement onset and the end of the action. The period following this, in which the target was lifted, was not assessed. The dependent variables were (a) initiation time, (b) movement duration, (c) reach component parameters: times to peak velocity, peak acceleration and peak deceleration of the wrist marker, and the amplitudes of these peaks, and (d) grasp component parameters: time to maximum grip aperture, amplitude of maximum finger aperture and rate of finger aperture. The difference between the onset of the reach and the onset of the grasp components was also calculated ('delay'). Each temporal value of the reach and grasp component was also calculated as a percentage of movement duration (relative values).

3. Results

For each participant of the two groups, mean values for each of the dependent measures were calculated for

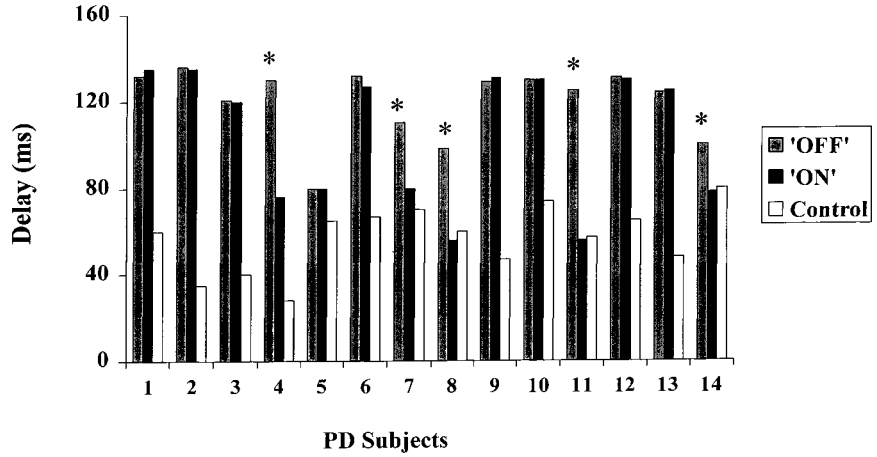

Fig. 2. The parameter 'delay' for PD and control subjects. This parameter refers to the time between onset of the transport component (release of starting switch) and onset of the manipulation component (initial opening of the hand). * = PD participants which show a significant difference (Ps < 0.01) for the parameter 'delay' between the 'OFF' and the 'ON' states.

each size/distance/vision combination. Three ANOVAs have been conducted. In the first ANOVA the effects of 'ON' vs 'OFF' effects in PD are compared with Group as the between subjects factor (PD 'OFF' vs PD 'ON'). In the second ANOVA PD 'ON' medication were compared with control subjects (between factor Group: PD 'ON' vs controls). In the third ANOVA, PD 'OFF' were compared with control subjects (between factor Group: PD 'OFF' vs controls). For all the three analyses the within subjects factors were Object Size (small, large), Object Distance (20 cm, 30 cm) and Vision (Full vision, No vision). The means of the following parameters (chosen on the basis of having demonstrated vision, size and distance functions in previous research) were tested: movement duration, time to peak velocity, amplitude of peak velocity, amplitude of peak acceleration, time to peak deceleration, %deceleration time, time to peak grip aperture, and amplitude of peak grip aperture, %time of maximum grip aperture. A further ANOVA was conducted to determine group differences in the 'delay' parameter. Further, new parameters were calculated for a number of selected measures to give an index of: (a) the size function (small object reach-to-grasp minus large object reach-to-grasp), (b) the distance function (30 cm−20 cm) and (c) the vision function (non-vision minus vision). Given the number of dependent variables and analyses involved the significance level for the number of comparisons has been adjusted to $P < 0.01$.

3.1. Global effects of the dopaminergic medication

To address the hypothesis that the movement would be faster following medication, planned comparisons between the 'OFF' and 'ON' states were conducted upon the parameters of movement duration, and the amplitudes of peak acceleration, peak velocity and of peak deceleration. Not surprisingly, medication resulted in faster movements. Movement duration in the 'ON' state was, on average, 25 ms lower than movement duration in the 'OFF' state (1489 and 1514 ms, respectively; $F(1,13) = 25.02$, $P < 0.001$; see Fig. 1). Confirming this increase in speed, the peak of velocity was higher in the 'ON' (703 mm/s) than in the 'OFF' (678 mm/s) state ($F(1,13) = 10.56$, $P < 0.001$). Similarly, the peaks of reach acceleration and deceleration were greater in the 'ON' state (acceleration: 3426 vs 3209 mm/s^2, $F(1,13) = 22.15$, $P < 0.001$; deceleration: 2289 vs 2212 mm/s^2; $F(1,13) = 9.87$, $P < 0.001$; see Fig. 1).

The 'delay' parameter (onset of manipulation with respect to onset of transport) was assessed to determine if medication exerted an effect on the dysfunction in the simultaneous opening of both the transport and manipulation components. Unlike controls, PD participants showed a delayed onset of the grasp component that was not related to distance, size, visual condition or dopaminergic medication (main effect for Group. PD 'ON' vs PD 'OFF' $F(1,13) = 2.54$, $P < 0.001$; PD 'ON' vs controls: absolute value $F(1,13) = 22.33$, $P < 0.001$; relative value $F(1,13) = 31.62$, $P < 0.0001$; PD 'OFF' vs controls: absolute value $F(1,13) = 25.23$, $P < 0.0001$; relative value $F(1,13) = 29.72$, $P < 0.0001$). These results for the mean absolute and relative 'delay' parameters fail to reject the null hypothesis of no significant differences between the 'OFF' and 'ON' states (132 ms, 8% of MD and 136 ms, 9%, respectively). However, as shown in Fig. 2, 5/

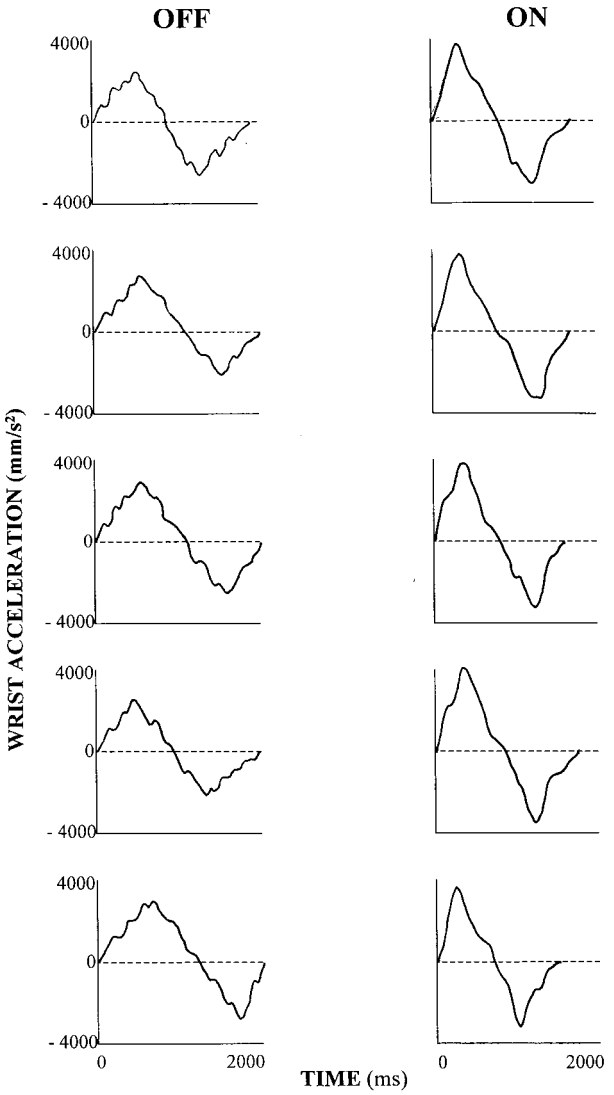

Fig. 3. Wrist acceleration profiles ($N = 5$) for PD1 in 'OFF' (left column) and 'ON' (right column) state. Small peaks and troughs in the 'OFF' state are much less evident in the 'ON' state.

14 PD participants showed some reduction in the delay parameter (t-test, Ps < 0.01).

The acceleration profiles of 11/14 PD participants in the 'OFF' state were often characterised by a series of non-rhythmic adjustments (peaks and troughs) in both the accelerative and deceleration movement phases. The number of these adjustments diminished following administration of dopaminergic medication. The first column of Fig. 3 shows five examples of the irregular acceleration profile patterning in the 'OFF' state for PD participant 1. The second column shows the smoothing effect of medication in the 'ON' state. On average, in the 'OFF' state, PD participants showed four adjustments in the acceleration movement phase and three in the deceleration phase. In the 'ON' state these numbers decreased to one in each phase. The numbers of adjustments in each of the accelerative and deceleration phases for the 'OFF' and 'ON' phases are shown in Table 2. One (PD4) of the three PD participants who did not show adjustments in the 'OFF' state showed slight inflexions that were not clearly identifiable as peaks or troughs.

Table 2
Average number of identifiable adjustments (clear peak/trough) in the accelerative and decelerative phase of the acceleration profile of PD participants in the 'OFF' and 'ON' state. Data collapsed according to condition

	Accelerative phase		Deceleration phase	
	'OFF'	'ON'	'OFF'	'ON'
PD1	4	1	3	0
PD2	3	0	3	0
PD3	5	1	4	1
PD4	0	0	0	0
PD5	3	1	3	1
PD6	4	1	4	1
PD7	0	0	0	0
PD8	0	0	0	0
PD9	5	1	3	1
PD10	3	0	4	1
PD11	3	1	3	1
PD12	5	1	3	0
PD13	4	0	2	0
PD14	5	1	3	1

To test whether the movement showed a more direct trajectory to the object, planned comparisons were conducted upon the average maximum deviation along the mediolateral and antero-posterior horizontal axis, and along the vertical axis. The results showed that the trajectory of the wrist marker also showed differences with medication. As illustrated in the left column of Fig. 4, the extent of rightward deviation was lower in the 'ON' than in the 'OFF' state. The average maximum deviation of the marker from the starting sagittal axis in the 'ON' state, was significantly different from (in fact, almost half of) that in the 'OFF' state (21 mm vs 40 mm, $F(1,13) = 14.22$, $P < 0.01$). The right column of Fig. 4 shows the reduction of the height of the reaching arm trajectory with medication. The average peak of the deviation in the z direction from the starting horizontal axis in the 'ON' state (32 mm) was significantly less than that in the 'OFF' state (54 mm; $F(1,13) = 12.25$, $P < 0.01$).

Motivated by Jeannerod's [37] suggestion that grasp closure is synchronised with peak deceleration, the relationship between the time of peak deceleration and the time to peak hand opening aperture was explored with correlation analysis (Pearson product-moment correlation). Across all PD participants, the incidence of significant correlations was greater in the 'ON' than in the 'OFF' state. Out of the 168 analyses conducted (14 participants × six movement types × ON/OFF

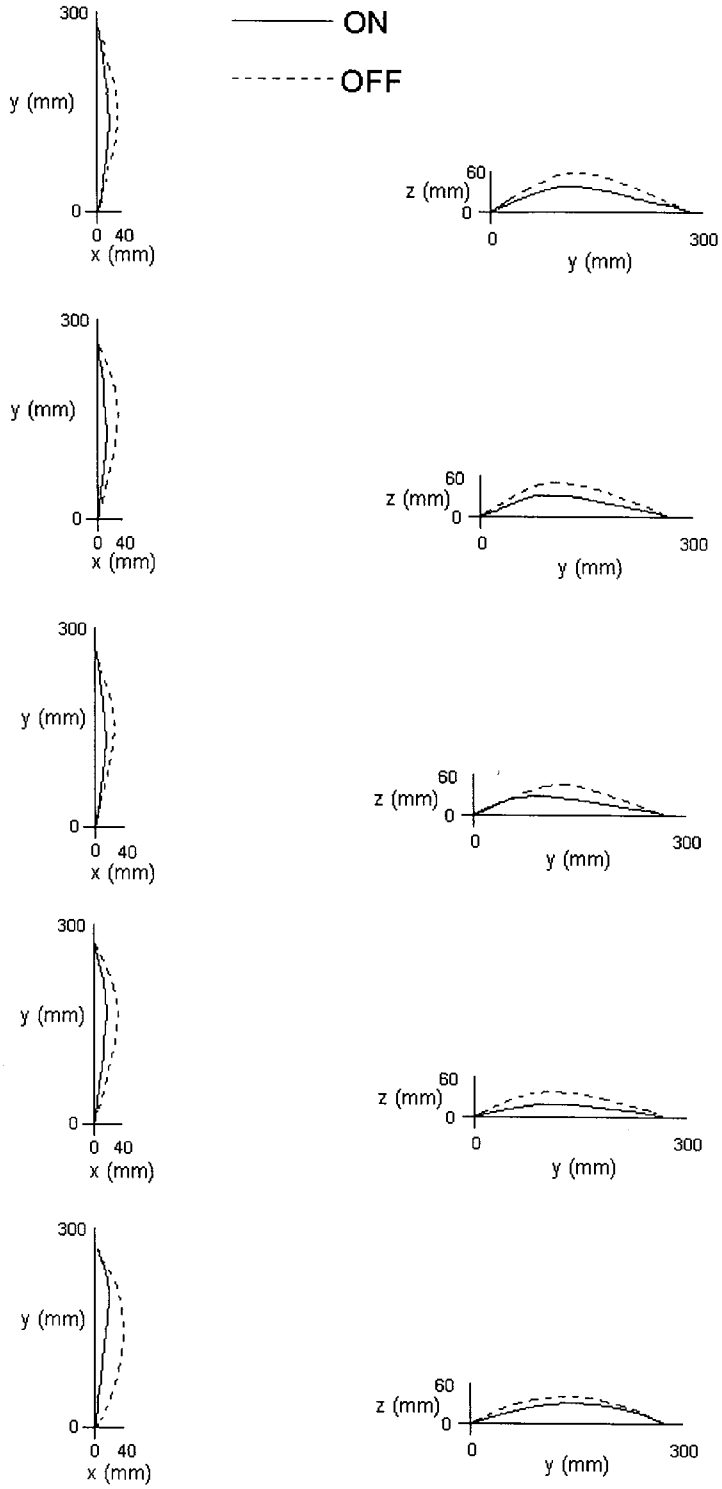

Fig. 4. Trajectories of the reaching limb of PD3 when reaching to grasp an object positioned at 30 cm from the starting switch. Dotted line: trajectory in the 'OFF' state; solid line: trajectory in the 'ON' state. The left column of graphs shows five examples of the reach trajectory as it deviates laterally (x coordinate) from the mid-saggital axis. The right column of graphs shows five examples of the reach trajectory as it deviates vertically (y coordinate) from the horizontal starting plane.

medication) nine were found to be significant in the 'OFF' state (with Rs ranging from 0.71 to 0.88, Ps < 0.01), with all nine examples being from 2/14 PD participants. In the 'ON' state, 50 comparisons showed significant correlations (Rs = 0.77–0.92, Ps < 0.01), an incidence that was less than, but approaching, that of

Table 3
Effects of manipulating visual feedback

	PD 'off'		PD 'on'		Control	
	Vision	Non-vision	Vision	Non-vision	Vision	Non-vision
Movement duration (ms)	1313 (193)[a]	1714 (351)	1278 (180)	1701 (350)	1137 (180)	1664 (349)
Transport component						
Time to peak velocity (ms)	584 (101)	643 (125)	562 (100)	652 (97)	522 (89)	630 (131)
Time to peak velocity (%)	39 (6)	45 (5)	40 (5)	45 (5)	39 (5)	47 (3)
Amplitude peak velocity (mm/s)	768 (185)	587 (116)	774 (149)	631 (146)	891 (174)	690 (149)
Amplitude peak acceleration (mm/s^2)	3759 (1515)	2659 (696)	3833 (1169)	3019 (926)	5094 (1751)	3700 (1294)
Amplitude peak deceleration (mm/s^2)	2540 (977)	1883 (485)	2542 (736)	2036 (660)	3389 (997)	2276 (766)
Manipulation component						
Time to max. grip aperture (ms)	839 (136)	1106 (253)	802 (129)	1081 (215)	725 (108)	1004 (234)
Time to max. grip aperture (%)	64 (6)	64 (5)	62 (5)	64 (5)	64 (4)	61 (6)
Amplitude of grip aperture (mm)	100 (2)	106 (3)	98 (3)	107 (5)	99 (2)	105 (3)

[a] (SD).

the control participants (110/168 correlations; Rs = 0.69–0.90, Ps < 0.01).

3.2. Effects of medication upon the vision function

The vision function is defined as any difference in parameterisation between non-vision and vision conditions. For both participant groups, the ANOVAs confirmed that a number of parameters showed differences according to the degree of visual feedback. As revealed by the significant main effect of vision few of the dependent measures differ in the non-vision as opposed to the vision condition. Movement duration was longer (PD 'OFF' vs PD 'ON': $F(1,13) = 75.36$,

Table 4
Effects of manipulating object size

	PD 'off'		PD 'on'		Control	
Target size	Small	Large	Small	Large	Small	Large
Transport component						
Amplitude peak velocity (mm/s)	668 (137)[a]	687 (138)	675 (116)	730 (142)	764 (155)	817 (121)
Amplitude peak acceleration (mm/s^2)	3134 (1059)	3283 (1068)	3242 (873)	3610 (1084)	4243 (1353)	4551 (1340)
Amplitude peak deceleration (mm/s^2)	2087 (673)	2336 (702)	2074 (542)	2503 (802)	2689 (746)	2976 (692)
Manipulation component						
Time to max. grip aperture (ms)	880 (173)	1066 (206)	855 (132)	1029 (224)	796 (174)	933 (151)
Time to max. grip aperture (%)	59 (4)	69 (5)	58 (5)	68 (6)	57 (6)	67 (4)
Amplitude of grip aperture (mm)	53 (1)	102 (3)	55 (3)	103 (3)	52 (5)	102 (5)

[a] (SD).

Table 5
Effects of manipulating distance

	PD 'off'		PD 'on'		Control	
Distance (cm)	20	30	20	30	20	30
Transport component						
Time to peak deceleration	62	57	61	57	62	56
(%)	(6)[a]	(7)	(5)	(6)	(7)	(5)
Amplitude peak acceleration	2733	3684	2945	3907	3731	5063
(mm/s^2)	(1093)	(1054)	(910)	(1029)	(1195)	(1503)
Amplitude peak deceleration	1912	2511	1943	2634	2357	3308
(mm/s^2)	(651)	(740)	(523)	(816)	(502)	(963)
Manipulation component						
Time to max. grip aperture	894	1052	878	1005	775	953
(ms)	(165)	(215)	(159)	(169)	(134)	(188)
Time to max. grip aperture	63	65	62	64	61	63
(%)	(4)	(4)	(5)	(5)	(5)	(5)
Amplitude of grip aperture	78	82	77	85	77	84
(mm)	(6)	(7)	(6)	(4)	(24)	(4)

[a] (SD).

$P < 0.0001$; PD 'OFF' vs controls: $F(1,13) = 85.46$, $P < 0.0001$; PD 'ON' vs controls: $F(1,13) = 90.34$, $P < 0.0001$; see Table 3), the time to peak reach velocity was greater (PD 'OFF' vs PD 'ON': $F(1,13) = 25.17$, $P < 0.001$; PD 'OFF' vs controls: $F(1,13) = 17.32$, $P < 0.001$; PD 'ON' vs controls: $F(1,13) = 20.36$, $P < 0.001$; see Table 3) and maximum grip aperture was larger (PD 'OFF' vs PD 'ON': $F(1,13) = 82.16$, $P < 0.0001$; PD 'OFF' vs controls: $F(1,13) = 91.08$, $P < 0.0001$; PD 'ON' vs controls: $F(1,13) = 80.21$, $P < 0.0001$; see Table 3) for the non-vision than the vision condition. The mean differences between the vision and non-vision conditions for PD participants in both 'OFF' and 'ON' states were calculated for the parameters movement duration, deceleration time, the amplitudes of peak acceleration, velocity and deceleration, and the amplitude of maximum grip aperture. Two of these selected parameters showed medication effects. The Vision/Non-vision differences in the amplitudes of peak acceleration and peak deceleration were less in the 'ON' (814 mm/s^2 and 506 mm/s^2, respectively; see Table 3) than in the 'OFF' state (1101 mm/s^2 and 657 mm/s^2, $F(1,13) = 20.02$, $P < 0.0001$ and $F(1,13) = 15.02$, $P < 0.001$; see Table 3).

3.3. Effects of medication on the size function

The size function is defined as any differences in parameterisation between actions to the small object and those to the large object. For both groups, a number of parameters showed differences according to the size of the object (main effect of size). For movements involving the small than for those involving the large object lower peaks of acceleration (PD 'OFF' vs PD 'ON': $F(1,13) = 15.32$, $P < 0.001$; PD 'OFF' vs controls: $F(1,13) = 12.06$, $P < 0.001$; PD 'ON' vs controls: $F(1,13) = 10.14$, $P < 0.001$; see Table 4), velocity (PD 'OFF' vs PD 'ON': $F(1,13) = 21.03$, $P < 0.001$; PD 'OFF' vs controls: $F(1,13) = 17.76$, $P < 0.001$; PD 'ON' vs controls: $F(1,13) = 12.38$, $P < 0.001$; see Table 4) and deceleration (PD 'OFF' vs PD 'ON': $F(1,13) = 19.54$, $P < 0.0001$; PD 'OFF' vs controls: $F(1,13) = 15.56$, $P < 0.001$; PD 'ON' vs controls: $F(1,13) = 22.54$, $P < 0.001$; see Table 4) were found. For the manipulation component, maximum grip aperture was of lower amplitude (PD 'OFF' vs PD 'ON': $F(1,13) = 115.56$, $P < 0.0001$; PD 'OFF' vs controls: $F(1,13) = 175.16$, $P < 0.0001$; PD 'ON' vs controls: $F(1,13) = 99.14$, $P < 0.0001$; see Table 4) and occurred significantly earlier (PD 'OFF' vs PD 'ON' $F(1,13) = 43.18$, $P < 0.0001$; PD 'OFF' vs controls: $F(1,13) = 38.26$, $P < 0.0001$; PD 'ON' vs controls: $F(1,13) = 41.12$, $P < 0.0001$; see Table 4) for actions to the small than for those to the large object. The mean differences between the large and the small conditions in both 'OFF' and 'ON' states were calculated for movement duration, the amplitudes of peak acceleration, velocity and deceleration, deceleration time, and the time maximum grip aperture. Planned contrasts between the mean 'OFF' difference and the mean 'ON' difference were conducted. The only parameters to show medication effects were the amplitudes of the peaks of acceleration and deceleration. In both cases, the size difference was greater in the 'ON' (368 mm/s^2 and 429 mm/s^2, respectively) than in the 'OFF' state (149 mm/s^2 and 249 mm/s^2; $F(1,13) = 10.04$, $P < 0.001$ and $F(1,13) = 7.05$, $P < 0.05$).

3.4. Effects of medication on the distance function

The distance function is defined as any difference in parameterisation between actions to the object placed at 20 cm and those to the object at 30 cm. For both groups, the omnibus F tests confirmed that a number of parameters showed differences according to the distance of the object. In the transport component, for example, the peak of reach acceleration was of greater amplitude for 30 cm than for 20 cm reaches (PD 'OFF' vs PD 'ON': $F(1,13)=196.36$, $P < 0.0001$; PD 'OFF' vs controls: $F(1,13)=265.21$, $P < 0.0001$; PD 'ON' vs controls: $F(1,13)=190.21$, $P < 0.0001$; see Table 5). The peak of reach deceleration was earlier and of greater amplitude for 30 cm than for 20 cm reaches (PD 'OFF' vs PD 'ON': $F(1,13)=9.06$, $P < 0.01$; PD 'OFF' vs controls: $F(1,13)=10.36$, $P < 0.001$; PD 'ON' vs controls: $F(1,13)=10.14$, $P < 0.001$; see Table 5). In the manipulation component, the maximum grip aperture was of greater amplitude and later for 30 cm than for 20 cm reaches (PD 'OFF' vs PD 'ON': $F(1,13)=88.46$, $P < 0.0001$; PD 'OFF' vs controls: $F(1,13)=95.32$, $P < 0.0001$; PD 'ON' vs controls: $F(1,13)=95.11$, $P < 0.0001$; see Table 5). The mean differences between the 20 cm and 30 cm conditions in both 'OFF' and 'ON' states were calculated for movement duration, the amplitudes of peak acceleration, velocity, and deceleration, time to peak velocity, the relative time to peak reach acceleration, deceleration time. The mean 'OFF' difference and the mean 'ON' difference were not significant.

4. Discussion

In general, the therapeutic benefit of dopaminergic medication for PD participants is to the performance speed of the reach to grasp task. As shown in Fig. 1, all participants show some decrease in the time taken to complete this natural every-day action.

An explanation for this speed enhancement can be gained from the cortical-basal ganglia model of Alexander et al. [1] in which it is proposed that nigrostriatal dopamine deficiency results in decreased inhibitory activity from the putamen to the internal segment of the globus pallidus. This results in an unchecked pallidal inhibition of the ventrolateral thalamus and consequent lowering of activity in the supplementary motor (SMA), premotor and motor cortices. This model has received considerable support from single unit recordings in the human globus pallidus [53], from studies of non-human primates in which Parkinsonism has been induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [5,6,57] and from brain imaging studies [38,47]. Of particular relevance are the results from human positron emission tomography and single-photon emission computed tomographic studies showing that treatment with dopamine agonists increases movement-related activity in the supplementary motor area [38,47]. The reduction in movement duration with dopaminergic medication, observed in the current study, probably reflects the improved time efficiency of SMA and other motor cortical areas in reaching threshold for activation.

The results of this study also point to a more polished reach-to-grasp action with dopaminergic medication. In the 'OFF' state the movement of Parkinson's disease participants commonly shows small adjustments during both the accelerative and deceleration phases[1]. These adjustments were not apparent in the 'ON' state and do not appear to be in function of decreased movement speed. Though movement for PD subjects in 'ON' state are slower than those for the control subjects, they do not show adjustments.

The more direct trajectories of the reaching limb in the 'ON' than the 'OFF' state provide further evidence for medication acting to refine movement performance. In the 'ON' state, the extent of arm displacement laterally from the mid-sagittal starting plane and vertically from the horizontal starting plane was notably less than that during the 'OFF' state. In other words, the movement with medication did not skirt as widely nor with as much height as that without. The correlation results also add support to the idea of improvements to the fine-tuning of the action. In the 'ON' state the incidence of significant correlations between the transport and manipulation components is much greater than in the 'OFF' state. This suggests greater coordination between these parallel neural pathways in the 'ON' state.

Such findings may be interpreted with reference to a relatively old body of literature that speaks of the basal ganglia as a 'clearing house' [10,23,28] that facilitates desired neural activity in the thalamus and cortex while suppressing unwanted activity. The faster, more direct and more coordinated movement in the 'ON' state may reflect more precise filtering [44] of neural information so that unnecessary activation noise is reduced. This concept of delineating and refining a desired action resembles learning models [50,51] in which it is proposed that the basal ganglia play a role in establishing limits on available response options. The results of the current study suggest that dopaminergic medication acts in a similar manner, to facilitate fine-tuning of motor performance. 'Energisation' of the action [32], with correct movement coordination,

[1] The non-rhythmical nature of these adjustments, together with the inconsistency of manifestation, suggests that they are not related to parkinsonian tremor.

and optimal timing and sequencing of muscle activity, are thus promoted [8,17].

Given the premise that dopaminergic medication enhances cortical activation, it might also be expected that improvements to the activation of movement components simultaneously would be found following medication. Of note, however, is that the PD dysfunction of a delayed onset of the manipulation component was not affected by medication. As shown in Fig. 2, this parameter showed no change or a decrease from the 'OFF' to the 'ON' state. Theoretically, this absence of results is interesting as several researchers have attributed the deficit in the simultaneous processing of two different motor programs to the abnormality of striopallidal function, caused by nigrostriatal dopamine deficiency, and the consequent decrease in readiness levels of cortical areas for excitation [2–4]. Hence, the delay in activating the manipulation component has been thought to reflect the longer times taken to activate this component at the cortical level because of these lowered readiness levels. Acknowledging that dopaminergic medication does not mean complete replenishment of dopamine, the results of the current study suggest caution in adopting this theory as an explanation of the well-known dysfunction of PD patients in the initiation of movements, or movement components, in sequence or simultaneously.

A major aim in this research project was to ascertain whether or not dopaminergic medication acted upon movement patterning. For this purpose, several 'functions,' tested with previous research, were investigated. A global view of the results suggests that medication appears to have little effect on the size, distance or vision functions addressed in this study.

4.1. The vision function

The current investigation tested the hypothesis that the vision function (parameter measured under non-vision condition minus parameter measured under full-vision condition) in the 'OFF' state would not differ from that in the 'ON' state. This hypothesis was tested in lieu of reports that PD participants become more dependent upon visual feedback to guide movement [18,26,30,48,49,54]. The PD participants of the current study did show differences in movement patterning from controls although the vision function was largely preserved. Some planned comparisons showed differences for the function value when comparing the 'OFF' and 'ON' states indicating that the deficit exhibited by the PD participants on no-vision reaches is enhanced in absence of medication. These deficits were confined to those kinematic landmarks associated with the reach component alone [35]. The amplitudes of peak acceleration and deceleration were less in the 'ON' than in the 'OFF' state. These differences could be attributed to the fact that PD participants may be dependent upon visual feedback to scale movement appropriately [35]. This dependency becoming stronger in absence of dopaminergic medication.

Despite the above mentioned medication effects other results are consistent with previous studies of non-brain-damaged participants in which vision has been manipulated. The movement was longer in the absence of visual feedback, and the hand opened more widely as if to create a wider safety zone for object catchment [7,15,34,57]. The similarity of patterning for control and PD participants places some questions on the proposal that greater emphasis is placed upon the responsive lateral premotor feedback dependent systems in Parkinson's disease [31]. Undoubtedly the lack of findings can be attributed to the particular task that has been tested, that is, a functional upper limb action that is performed frequently and routinely. Further, the PD subjects did not show obvious errors of performance under non-vision conditions, theoretically reducing the need to revert to feedback pathways to avoid the errors associated with the non-feedback movement performance by PD participants [19,22]. The results of the current study would suggest that though dopaminergic medication acts to speed up neural processing within striato-thalamo-cortical processing systems, it exerts no clear effects upon a function that ensures appropriate movement patterning according to different feedback conditions. Even with the eyes closed and irrespective of medication state, Parkinson's disease participants seem able to place greater emphasis on endogenous mechanisms to recruit an appropriate motor program [41].

4.2. The size and distance functions

In general, the results obtained for PD participants and for control participants mirrored those from previous studies [7,13,29,35,45]. The accuracy requirements for the small object were reflected in a reaching action of lower velocity and a hand action of smaller and earlier maximal opening than that for movements to the large object. The scaling of object position was reflected in the longer, faster movement for the target placed at the greater reaching distance.

The patterning of movement according to the size of the object to be grasped showed some medication effects. The significant differences found for two kinematic landmarks relative to the reach component, that is, the amplitude of peaks acceleration and deceleration, for the size function indicate that the ability to change movement patterning according to the intrinsic characteristics of a target is partially affected by dopaminergic medication.

A possible confound in the present study is the time of release of the levodopa preparation. The PD partici-

pants were all taking Sinemet CR except for two participants on Madopar CR. It is believed that one problem with both these forms of dopaminergic medications is the long latency to the patients' turning 'ON' [54]. The lack of change to the 'delay' dysfunction together with the absence of effects on the patterning of the reach to grasp movement could thus reflect inadequate levels of dopamine release at the time of testing. However, we are reasonably confident that this is not the case. As shown in Figs. 1 and 2, the effects on movement duration and velocity and acceleration were evident 1–2 h following the first morning dose for all PD participants. In other words, we are sufficiently certain that our patients were in the 'ON' state during the period of the second testing session.

5. Conclusions

With dopamine replenishment, and the consequent changes to various features of an action performed under conditions of dopamine depletion, it is possible to infer certain roles for the basal ganglia. Not surprisingly, they serve to enhance processing speed, probably by increasing the signal-to-noise ratio at cortical levels. Further, they appear to fine-tune an action, probably by maximising activation in only the most appropriate neural channels [10,23,28]. Confirming reports from previous research [16,42], the basal ganglia appear to play a marginal role in specifying movement parameterisation. Further, there are remaining queries about the importance of the basal ganglia for the activation of movement components, or, at least, for the optimal preparation of cortical centres for activation.

Current research in our laboratories is being directed to two further medication-related factors. One is the effect of chronic levodopa exposure. It is known, for example, that dyskinesia is a common side effect in 80% of PD participants treated with levodopa for over five years [12]. The second medication-related factor is the difference between fast and slow release preparations of levodopa [55]. As explained previously, it is clear that effects were observable in all PD participants 1–2 h following medication. Nevertheless, research emphasis in future studies will be placed on the assessment of movement patterning at different stages post-medication to investigate this aspect more fully.

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