DOI 10.1007/s00702-005-0346-9
J Neural Transm (2006) 113: 609–623

Journal of Neural Transmission
Printed in Austria

Kinematic analysis of dopaminergic effects on skilled handwriting movements in Parkinson's disease

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Received May 10, 2005; accepted June 18, 2005
Published online August 5, 2005;

Summary. Patients with Parkinson's disease (PD) exhibit impairments in the execution of highly practiced and skilled motor actions such as handwriting. The analysis of kinematic aspects of handwriting movements has demonstrated that size, speed, acceleration and stroke duration are affected in PD. Although beneficial effects of dopaminergic therapy in regard to execution of movements have been reported, the effects of pharmacological therapy on these measures have not been examined in detail. The present study has compared kinematic aspects of handwriting movements of 27 healthy subjects and 27 patients with PD both on their usual dopaminergic treatment and following withdrawal of dopaminergic medication. Healthy subjects were matched with PD patients according to age, sex, handedness and education level. A digitising tablet was used for the assessment of handwriting movements. Subjects were asked to perform a simple writing task. Movement time, distance, velocity, acceleration and measures of fluency of handwriting movements were measured. Compared with healthy subjects, the kinematics of handwriting movements in PD patients were markedly disturbed following withdrawal of dopaminergic medication. Although dopaminergic treatment in PD patients resulted in marked improvements in the kinematics of handwriting movements, PD patients did not reach an undisturbed level of performance. The results suggest that dopamine medication results in partial restoration of automatic movement execution.

Keywords: Handwriting, kinematics, Parkinson's disease.

Introduction

Idiopathic Parkinson's disease (PD) is a motor disorder which is characterized by tremor, rigidity and slowness of movement (bradykinesia). It is well established that disturbances of motor control in PD are caused by depletion of dopamine due to a decrease in the dopaminergic projection from the substantia nigra to the striatum. These disturbances involve processing of motor planning, motor programming, motor sequencing, movement initiation and movement execution (Contreras-Vidal and Stelmach, 1996).

Hypometric movements, denoting movements with smaller than normal movement amplitudes, have frequently been found in PD patients (Oliveira et al., 1997, 1998; Konczak et al., 1997; Swinnen et al., 1997; Vinter and Gras, 1998). Furthermore, clinical studies on PD patients have reported a slowing of ballistic movements, in particular movement sequences (Flowers, 1976; Hallett and Khoshbin, 1980; Benecke et al., 1987; Georgiou et al., 1993). Movement slowing is associated with dysfunction of the supplementary motor area which constitutes the major cortical projection area of the putamen. This projection is mediated by the motor circuit which, originating in the supplementary motor area, premotor cortex, motor cortex, somatosensory cortex and the superior parietal lobule, passes through the putamen and projects via the ventrolateral thalamic nuclei to the supplementary motor area and premotor cortex (Alexander et al., 1986; DeLong, 1993; Bradshaw and Mattingley, 1995; Samuel et al., 1997). The supplementary motor area has been found to be especially activated when prelearned motor sequences are performed from memory (Jenkins et al., 1994; Jueptner et al., 1997). It is assumed that the basal ganglia provide an internal motor cue to terminate the tonic premotor activity of the supplementary motor area which is necessary for the execution of a subsequent movement in an automatic movement sequence (Georgiou et al., 1993; Bradshaw and Mattingley, 1995).

Although voluntary movements in general are affected in PD, handwriting movements seem to be particularly vulnerable (Margolin and Wing, 1983; Lewitt, 1983; Phillips et al., 1991). Handwriting is a highly skilled and complex, coordinated motor activity which has been described as the most demanding and complex fine motor function besides drawing (Gross, 1975; Blank et al., 1999). Handwriting constitutes a dynamic interplay of horizontal movements of the lower arm, wrist movements and finger movements (Thomassen and Teulings, 1983). The writing process comprises rapid, sequential and ballistic movements. In healthy subjects, these movements are automated (open loop) and do not require attentional resources (Meulenbroek and Van Galen, 1988; Longstaff and Heath, 1997; Tucha et al., 2001).

The handwriting of patients with PD is often characterized by hypometric movements which result in micrographia, a diminution of letter size which becomes more pronounced with continued writing (Teulings and Stelmach, 1991). Severe micrographia may occur at various stages during the progression of the disease (McLennan et al., 1972; Margolin and Wing, 1983). While PD patients with micrographia are unable to sustain letter size during the writing process, the former individual characteristics of handwriting are preserved (McLennan et al., 1972). Handwriting samples of patients with PD showing micrographia are published elsewhere (McLennan et al., 1972; Sandyk and Iacono, 1994; Walton, 1997; Anderson and Fisher, 1999). Furthermore, more recent experimental studies using advanced techniques in the assessment of handwriting and drawing movements have reported that not only the size of writing but also kinematic aspects of movements including speed, acceleration, force amplitude and stroke duration are affected in PD (Teulings and Stelmach, 1991; Muller and Stelmach, 1992; Flash et al., 1997; Longstaff et al., 2001; Van Gemmert et al., 2001).

Although a number of studies have been performed assessing kinematic aspects of movement execution during handwriting in PD, the effects of pharmacological therapy using dopaminergic medication on these variables have not been examined in detail. Margolin and Wing (1983) have observed a relationship between the level of antiparkinsonian medication and size, duration and velocity of movements during the execution of repetitive handwriting-like tasks (i.e. repetitive writing of the letter e) in five patients with PD. Eichhorn and colleagues

(1996) examined the effect of apomorphine in small samples of patients with untreated PD, patients with long-standing PD with L-Dopa related motor fluctuations and patients exhibiting L-Dopa unresponsive parkinsonism. They demonstrated that the kinematic analysis of movements during a repetitive handwriting-like task (i.e. repetitive generation of concentric circles) may be a helpful procedure in the prediction of responsiveness to L-Dopa treatment in parkinsonian syndromes.

The aim of the present study was to examine the effect of dopaminergic medication on kinematic aspects of handwriting in PD patients at different stages of disability according to Hoehn and Yahr (2001) using a digitising tablet.

Methods

Subjects

Twenty-seven right-handed patients with a diagnosis of idiopathic PD (11 female, 16 male; mean age = 64.8 years, S.E.M. = 1.4 years; mean education = 9.0 years; S.E.M. = 0.3 years) were assessed in the present study. Probable PD was diagnosed according to the UK brain bank criteria (Hughes et al., 1992). In all cases, PD was diagnosed by experienced consultant neurologists who also assessed the severity of clinical symptoms according to the modified Hoehn and Yahr rating scale (Hoehn and Yahr, 2001) while the patients were off treatment. The rating was I for 5 patients, II for 12 patients, III for 6 patients and IV for 4 patients. Mean duration of disease at the time of study was 5.7 years (S.E.M. = 0.8 years).

Exclusion criteria included a Hoehn and Yahr stage greater than IV, major depression according to DSM IV criteria, dementia, as assessed clinically by a neurologist, and any further neurological or psychiatric disease. All patients were receiving dopaminergic medication (levodopa or dopamine agonists) to which they had responded, either alone or in combination with other medication (amantadine: n = 5, MAO-B inhibitors: n = 7, COMT inhibitors: n = 2).

Furthermore, 27 right-handed healthy adult subjects (11 female, 16 male; mean age = 66.7 years, S.E.M. = 1.7 years; mean education = 9.1 years; S.E.M. = 0.4 years) drawn from the local community were assessed. None of the healthy participants had any history of neurological or psychiatric disease. Healthy subjects were matched with PD patients according to age, sex, handedness and education level since these variables may have been shown to affect handwriting performance (Slavin et al., 1996; Contreras-Vidal et al., 1998; Mergl et al., 1999; Tucha et al., 2000). Prior to their inclusion in the study, all subjects gave informed consent to participate in the study.

Procedure

PD patients were tested in two sessions separated by approximately one week. The order of testing on or off dopaminergic medication was counterbalanced across the group. In the first test session 14 patients were tested on dopaminergic medication and 13 patients off dopaminergic medication. The assessment off medication was conducted at least 15 hours after the withdrawal of dopaminergic medication. All examinations were performed in the morning in order to exclude fluctuations of psychomotor functioning caused by circadian patterns of motor activity (Raoux et al., 1994). Healthy subjects were tested only once.

Apparatus and task

A digitising tablet (WACOM IV) with a special pen containing a normal ink refill was used for the registration of handwriting movements. The position of the pen on the tablet, velocity and acceleration were measured continuously during writing. The digitising tablet used in this study had a maximum sampling rate of 200 Hz. Data processing was performed with a computational program for the analysis of handwriting movements (Mai and Marquardt, 1992; Marquardt and Mai, 1994).

The subjects were asked to write the sentence ''Ein helles grelles Licht'' (a bright and glaring light). This task was repeated four times so that the sentence was written a total of five times by each subject. Before the start of these writing tasks, several practice trials were undertaken in order to allow the subjects to become accustomed to the writing tablet. All writing tasks were performed on unruled paper. No restrictions of posture, speed or size of writing were imposed. Since PD patients have repeatedly been found to be impaired in problem solving (Lange et al., 1992, 1993, 1995), in particular in processes of planning and decision making, cognitive efforts during handwriting should be minimized. Therefore, as suggested by Siebner et al. (1999), a test sentence with an easy orthography and syntax was chosen for assessment.

Analysis of handwriting

For the assessment of kinematic aspects of handwriting, the letter combination ''ll'' of the German words ''helles'' (bright) and ''grelles'' (glaring) were taken.

The letter combination "ll" was chosen since these letters represent a simple letter combination which is usually executed in script type. Furthermore, the examination of the dynamic and static writing trace may often require its segmentation into meaningful units. From a motor viewpoint, single letters and in particular single strokes represent the smallest relevant units of the handwriting movement (Thomassen and Van Galen, 1992). In the evaluation of kinematic data, the total writing time (movement time in ms) and the distance of the writing trace (in mm) of the letter combination "ll" and of both the ascending and descending strokes was recorded per trial. Furthermore, the maximum and minimum absolute (tangential) velocities and both the maximum positive and negative absolute acceleration (slowing down) of ascending and descending strokes were measured. In addition, the number of inversions of the direction of the absolute velocity and acceleration profiles of the letter combination "ll" were calculated. The number of inversions in velocity represents a measure of the degree of movement automatisation. More fluent handwriting movements are reflected in a smaller number of inversions in velocity (Meulenbroek and Van Galen, 1988; Tucha et al., 2001). For further analysis, mean scores were calculated for each subject. The motion variables were chosen, since these parameters have been shown to be sensitive measures for alterations of handwriting movements (Eichhorn et al., 1996; Slavin et al., 1999; Tucha et al., 2002). Statistical analysis was performed using nonparametric tests. Furthermore, effect sizes for differences between paired observations were computed (Cohen, 1988). While the significance criterion represents the standard measure for analysing whether a phenomenon exists, the effect size refers to the magnitude or the importance of effects (Pedhazur and Pedhazur Schmelkin, 1991).

Results

Comparison between patients with PD and healthy subjects

Movement time and movement distance

Comparison between healthy subjects and patients with PD on dopaminergic medica-

Table 1. Handwriting performance of patients with PD and healthy subjects (means ± S.E.M.)

Variable	Healthy subjects	Patients with PD	
		On medication	Off medication
Analysis of the total letter combination "ll"			
Distance of the writing trace (in mm)	38.6 ± 2.1	32.1 ± 1.7^{A}	31.5 ± 1.9^{A}
Movement time (in ms)	503.7 ± 16.2	735.8 ± 50.7^{A}	991.1 ± 91.5$^{A, B}$
Number of inversions in velocity	8.1 ± 0.1	11.3 ± 0.9^{A}	17.4 ± 1.8$^{A, B}$
Number of inversions in acceleration	8.7 ± 0.2	13.4 ± 1.2^{A}	20.5 ± 1.9$^{A, B}$
Analysis of ascending strokes			
Distance of the writing trace (in mm)	10.4 ± 0.6	8.8 ± 0.5^{A}	8.6 ± 0.5^{a}
Movement time (in ms)	131.4 ± 4.7	188.5 ± 14.3^{A}	255.4 ± 25.8$^{A, B}$
Maximum velocity (in mm/s)	129.6 ± 7.6	89.9 ± 6.8^{A}	65.4 ± 5.9$^{A, B}$
Minimum velocity (in mm/s)	24.3 ± 2.4	12.9 ± 1.3^{A}	9.9 ± 1.7$^{A, b}$
Maximum positive acceleration (in mm/s^2)	2005.9 ± 181.2	1321.1 ± 114.3^{A}	889.2 ± 79.8$^{A, B}$
Maximum negative acceleration (in mm/s^2)	−2502.2 ± 174.3	−1606.5 ± 197.9^{A}	−995.3 ± 148.7$^{A, B}$
Analysis of descending strokes			
Distance of the writing trace (in mm)	9.0 ± 0.5	7.6 ± 0.6^{a}	7.2 ± 0.4^{A}
Movement time (in ms)	121.4 ± 4.5	180.7 ± 11.8^{A}	240.3 ± 21.4$^{A, B}$
Maximum velocity (in mm/s)	118.2 ± 6.8	76.6 ± 5.6^{A}	59.6 ± 5.6$^{A, B}$
Minimum velocity (in mm/s)	38.4 ± 3.4	19.4 ± 2.1^{A}	15.3 ± 1.6$^{A, B}$
Maximum positive acceleration (in mm/s^2)	2316.2 ± 163.0	1489.3 ± 133.6^{A}	1130.9 ± 106.3$^{A, B}$
Maximum negative acceleration (in mm/s^2)	−1951.7 ± 208.5	−1197.2 ± 124.5 ^{A}	−890.5 ± 128.3$^{A, b}$

$^{A}p \leq 0.01$ compared with healthy subjects (Wilcoxon test). $^{a}p \leq 0.05$ compared with healthy subjects (Wilcoxon test). $^{B}p \leq 0.01$ compared with PD patients on dopaminergic medication (Wilcoxon test). $^{b}p \leq 0.05$ compared with PD patients on dopaminergic medication (Wilcoxon test)

tion and following withdrawal of dopaminergic medication using the Friedman test revealed significant differences in regard to movement distance ($\chi^2 = 11.83$; $df = 2$; $p = 0.003$) and movement time ($\chi^2 = 43.98$; $df = 2$; $p < 0.001$) of the total letter combination (Table 1). Subsequent post hoc analysis using the Wilcoxon test indicated that patients, independent of their current state of medication, displayed longer movement times but shorter movement distances than healthy subjects ($p \leq 0.009$). While statistical comparison between PD patients on and off dopaminergic medication revealed that withdrawal of the drug resulted in prolonged movement times ($p \leq 0.001$), the movement distance of the total letter combination was not affected ($p > 0.05$).

The examination of movement time and movement distance of ascending and descending strokes accorded with the former findings. Statistical analysis using the Friedman test showed significant differences between healthy subjects and patients on and off dopaminergic medication regarding movement distance (ascending strokes: $\chi^2 = 9.55$; $df = 2$; $p = 0.008$/descending strokes: $\chi^2 = 7.19$; $df = 2$; $p = 0.028$) and movement time (ascending strokes: $\chi^2 = 35.85$; $df = 2$; $p \leq 0.001$/descending strokes: $\chi^2 = 38.82$; $df = 2$; $p \leq 0.001$). Further analysis using the Wilcoxon test demonstrated that while withdrawal of dopaminergic medication in PD patients did not affect movement distance (ascending strokes: $p = 0.454$/descending strokes: $p = 0.597$) the time of movement execution was significantly increased (ascending strokes: $p \leq 0.001$/descending strokes: $p \leq 0.001$) following withdrawal of dopaminergic medication. The remaining comparisons revealed significant differences between healthy subjects and PD patients on and off dopaminergic medication, indicating shorter stroke sizes (ascending strokes:

Table 2. Effect sizes for group differences

Variable	Healthy subjects vs. patients with PD on medication	Healthy subjects vs. patients with PD off medication	Patients with PD on medication vs. patients with PD off medication
Analysis of the total letter combination "ll"			
Distance of the writing trace	0.90	0.75	0.08
Movement time	3.76	8.19	6.63
Number of inversions in velocity	5.08	14.76	21.79
Number of inversions in acceleration	5.00	13.88	12.68
Analysis of ascending strokes			
Distance of the writing trace	0.95	0.69	0.12
Movement time	2.97	7.34	4.96
Maximum velocity	1.33	1.92	1.18
Minimum velocity	1.25	1.43	0.34
Maximum positive acceleration	0.83	1.58	0.64
Maximum negative acceleration	1.35	2.29	0.94
Analysis of descending strokes			
Distance of the writing trace	0.70	0.76	0.25
Movement time	3.21	6.23	6.20
Maximum velocity	1.48	1.85	1.02
Minimum velocity	1.39	1.71	0.37
Maximum positive acceleration	1.25	1.57	0.83
Maximum negative acceleration	0.80	1.08	0.47

$p \leq 0.015$/descending strokes: $p \leq 0.018$) and longer movement times (ascending strokes: $p \leq 0.001$/descending strokes: $p \leq 0.001$) in parkinsonian patients.

The analysis of effect sizes revealed medium to large differences between healthy subjects and PD patients concerning the distance of the writing trace of the total letter combination and both ascending and descending strokes ($d > 0.5$). Negligible to small effects ($d < 0.5$) were observed between the patients' performance on and off dopaminergic medication. With regard to movement time large differences ($d > 0.8$) were observed (Table 2).

Velocity and acceleration

Healthy subjects and patients with PD differed significantly concerning the maximum and minimum velocity and the maximum positive and negative acceleration of both ascending strokes (Friedman test; maximum velocity: $\chi^2 = 34.30$; $df = 2$; $p < 0.001$/ minimum velocity: $\chi^2 = 24.89$; $df = 2$; $p < 0.001$/positive acceleration: $\chi^2 = 33.56$; $df = 2$; $p < 0.001$/negative acceleration: $\chi^2 = 29.85$; $df = 2$; $p < 0.001$) and descending strokes (Friedman test: maximum velocity: $\chi^2 = 31.19$; $df = 2$; $p < 0.001$/minimum velocity: $\chi^2 = 36.74$; $df = 2$; $p < 0.001$/positive acceleration: $\chi^2 = 28.22$; $df = 2$; $p < 0.001$/ negative acceleration: $\chi^2 = 19.19$; $df = 2$; $p < 0.001$). Regardless of the direction of strokes, subsequent analysis (Wilcoxon test) revealed that healthy subjects performed the strokes significantly faster and with higher positive and negative accelerations than PD patients on both their usual dopaminergic treatment and following withdrawal of dopaminergic medication ($p \leq 0.006$). Withdrawal of dopaminergic medication in PD patients resulted in a significant reduction of maximum and minimum velocity and maximum positive and negative acceleration of movement execution ($p \leq 0.034$).

The analysis of effect sizes showed that all differences between healthy subjects and PD patients were large ($d \geq 0.8$). The differences between PD patients on dopaminergic medication and following withdrawal of dopaminergic medication were large ($d \geq 0.8$) in regard to the maximum velocity of ascending and descending strokes, the maximum negative acceleration of ascending strokes and the maximum positive acceleration of descending strokes. The remaining effect sizes indicated small to medium differences between parkinsonian patients on and off dopaminergic medication ($0.2 < d < 0.8$).

Number of inversions in velocity and acceleration

Furthermore, significant differences between healthy subjects and patients with PD were observed in the number of inversions in velocity (Friedman test: $\chi^2 = 29.34$; $df = 2$; $p < 0.001$) and acceleration profiles (Friedman test: $\chi^2 = 42.79$; $df = 2$; $p < 0.001$; Fig. 1). In comparison to healthy subjects, PD patients on and off dopaminergic medication produced significantly more inversions in velocity and acceleration profiles, indicating less fluent handwriting movements in PD (Wilcoxon test: $p \leq 0.002$; Fig. 2). Following withdrawal of dopaminergic medication, PD patients displayed a more severe dysfluency of handwriting than on their usual dopaminergic treatment (Wilcoxon test: $p \leq 0.001$).

The differences concerning the number of inversions in both velocity and acceleration profiles between healthy subjects and PD patients and between PD patients on and off dopaminergic medication represent large effects ($d > 0.8$).

Comparison between PD patients at different stages of disability according to Hoehn and Yahr (2001)

Statistical comparison between PD patients on dopaminergic medication at different stages of disability using the Kruskal-Wallis test showed no significant differences in kinematics of handwriting movements (movement

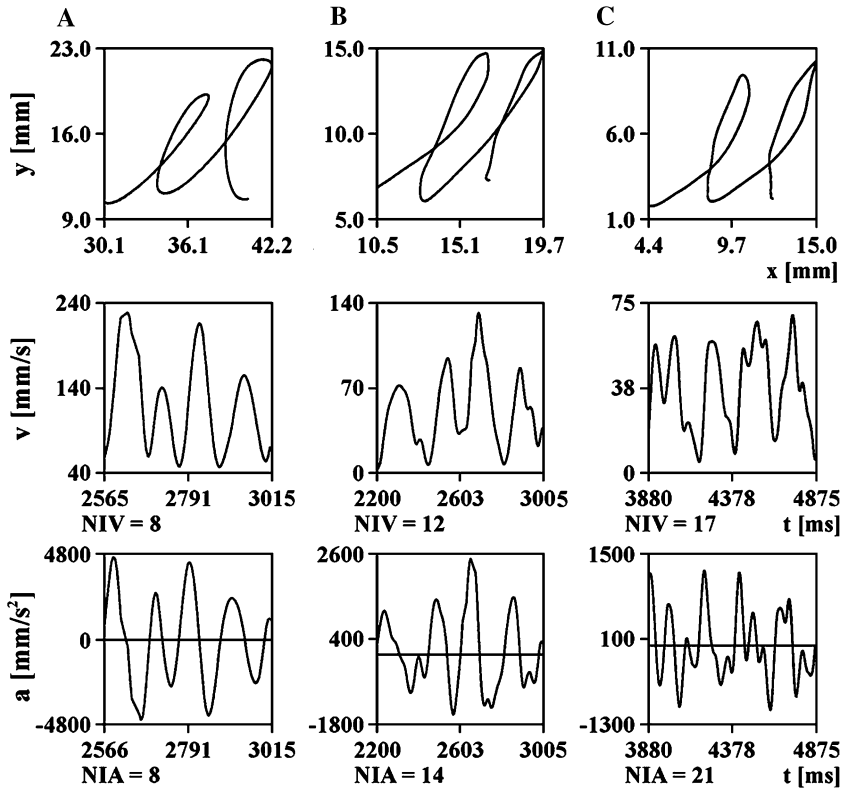

Fig. 1. Handwriting specimens of the letter combination "ll" with corresponding velocity and acceleration profiles of **A** a healthy subject, **B** a PD patient on dopaminergic medication and **C** the same PD patient following withdrawal of dopaminergic medication. The subjects differed in the number of inversions of the direction of their velocity profiles (NIV) and acceleration profiles (NIA)

distance of the total letter combination: $\chi^2 = 5.86$; df = 3; p = 0.119/movement distance of ascending strokes: $\chi^2 = 5.49$; df = 3; p = 0.139/movement distance of descending strokes: $\chi^2 = 4.35$; df = 3; p = 0.226/movement time of the total letter combina-

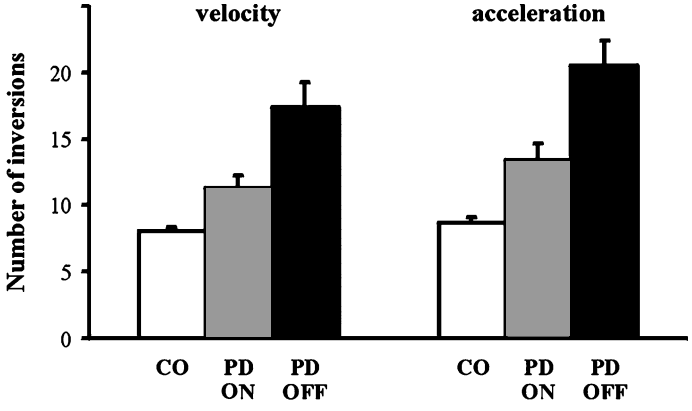

Fig. 2. Number of inversions of the direction of velocity profiles and acceleration profiles (Mean ± S.E.M.) of healthy subjects (CO), PD patients on dopaminergic medication (PD ON) and PD patients following withdrawal of dopaminergic medication (PD OFF)

Table 3. Handwriting performance of patient groups and healthy subjects (means ± S.E.M.)

Variable	PD patients (H & Y I), n = 5		PD patients (H & Y II), n = 12		PD patients (H & Y III), n = 6		PD patients (H & Y IV), n = 4	
	on medication	off medication	on medication	off medication	on medication	off medication	on medication	off medication
Analysis of the total letter combination "ll"								
Distance of the writing trace (in mm)	27.7 ± 5.3	29.3 ± 5.5	31.2 ± 2.8	31.3 ± 2.9	37.1 ± 1.7	35.0 ± 3.3	33.2 ± 1.3	29.5 ± 4.3
Movement time (in ms)	577.6 ± 59.2	677.0 ± 76.2	687.3 ± 62.7	974.9 ± 173.9	787.5 ± 130.3	1024.3 ± 115.9[a]	1001.5 ± 145.5	1382.3 ± 145.0[a, b]
Number of inversions in velocity	9.2 ± 1.2	10.2 ± 2.0	10.8 ± 1.2	16.3 ± 3.1	12.3 ± 2.9	18.5 ± 3.0[a]	14.0 ± 2.9	28.1 ± 1.2[a, b, c]
Number of inversions in acceleration	10.4 ± 1.4	13.2 ± 2.1	12.4 ± 1.5	19.4 ± 3.4	14.3 ± 3.4	22.8 ± 3.2[a]	18.5 ± 3.6	29.5 ± 2.1[a, b]
Analysis of ascending strokes								
Distance of the writing trace (in mm)	7.6 ± 1.4	8.1 ± 1.6	8.5 ± 0.8	8.5 ± 0.8	10.1 ± 0.4	9.4 ± 0.9	9.2 ± 0.4	8.2 ± 1.4
Movement time (in ms)	146.8 ± 18.2	178.4 ± 28.9	176.6 ± 17.8	253.3 ± 50.3	194.1 ± 32.3	254.9 ± 27.0	268.0 ± 48.3	358.5 ± 44.3[a, b]
Maximum velocity (in mm/s)	94.4 ± 26.3	82.1 ± 21.1	87.3 ± 8.4	64.7 ± 8.4	102.0 ± 12.8	66.3 ± 8.5	74.0 ± 14.7	45.4 ± 7.5
Minimum velocity (in mm/s)	10.8 ± 2.7	9.3 ± 2.7	12.9 ± 1.9	11.9 ± 3.2	15.0 ± 3.7	11.6 ± 2.6	12.6 ± 3.8	2.1 ± 0.6[a, B, c]
Maximum positive acceleration (in mm/s^2)	1502.3 ± 433.3	1088.0 ± 309.2	1240.6 ± 137.0	936.5 ± 89.3	1482.3 ± 232.9	809.9 ± 128.4	1094.1 ± 241.4	617.9 ± 194.0
Maximum negative acceleration (in mm/s^2)	−1921.9 ± 720.8	−1573.0 ± 520.7	−1563.4 ± 247.4	−971.5 ± 210.3	−1908.9 ± 395.7	−862.1 ± 231.0	−887.6 ± 315.8	−544.6 ± 80.3
Analysis of descending strokes								
Distance of the writing trace (in mm)	6.2 ± 1.2	6.6 ± 1.2	7.9 ± 1.2	7.2 ± 0.7	8.4 ± 0.5	8.1 ± 0.7	7.4 ± 0.3	6.6 ± 0.8
Movement time (in ms)	142.0 ± 12.3	160.1 ± 12.7	167.0 ± 14.1	234.4 ± 37.4	199.7 ± 33.6	257.3 ± 40.9[a]	242.0 ± 24.8	332.6 ± 34.3[a, b]
Maximum velocity (in mm/s)	76.5 ± 18.5	74.2 ± 18.9	76.2 ± 8.1	57.0 ± 8.2	86.1 ± 11.5	64.9 ± 10.5	63.3 ± 11.2	41.8 ± 5.4
Minimum velocity (in mm/s)	23.4 ± 7.3	19.6 ± 3.9	21.8 ± 3.2	15.8 ± 2.2	15.8 ± 2.8	15.8 ± 3.8	13.0 ± 2.6	7.6 ± 2.6
Maximum positive acceleration (in mm/s^2)	1656.9 ± 460.9	1466.6 ± 340.5	1492.6 ± 194.5	1123.0 ± 170.7	1536.9 ± 256.4	1160.1 ± 111.1	1198.3 ± 260.6	691.0 ± 70.5
Maximum negative acceleration (in mm/s^2)	−1079.5 ± 344.3	−1254.1 ± 409.3	−1171.9 ± 181.0	−866.8 ± 168.5	−1487.2 ± 266.2	−957.3 ± 304.5	−985.4 ± 328.3	−407.4 ± 65.2

[a] $p \leq 0.05$ compared with PD patients (H & Y I) off dopaminergic medication (Mann-Whitney-U test). [B] $p \leq 0.01$ compared with PD patients (H & Y II) off dopaminergic medication (Mann-Whitney-U test). [b] $p \leq 0.05$ compared with PD patients (H & Y II) off dopaminergic medication (Mann-Whitney-U test). [c] $p \leq 0.05$ compared with PD patients (H & Y III) off dopaminergic medication (Mann-Whitney-U test)

tion: $\chi^2 = 6.92$; df = 3; $p = 0.074$/movement time of ascending strokes: $\chi^2 = 5.24$; df = 3; $p = 0.155$/movement time of descending strokes: $\chi^2 = 7.44$; df = 3; $p = 0.059$/maximum velocity of ascending strokes: $\chi^2 = 1.78$; df = 3; $p = 0.620$/minimum velocity of ascending strokes: $\chi^2 = 0.88$; df = 3; $p = 0.831$/positive acceleration of ascending strokes: $\chi^2 = 1.56$; df = 3; $p = 0.668$/negative acceleration of ascending strokes: $\chi^2 = 3.32$; df = 3; $p = 0.345$/maximum velocity of descending strokes: $\chi^2 = 1.67$; df = 3; $p = 0.643$/minimum velocity of descending strokes: $\chi^2 = 3.54$; df = 3; $p = 0.316$/positive acceleration of descending strokes: $\chi^2 = 0.89$; df = 3; $p = 0.827$/negative acceleration of descending strokes: $\chi^2 = 1.33$; df = 3; $p = 0.723$/number of inversions in velocity: $\chi^2 = 3.11$; df = 3; $p = 0.376$/number of inversions in acceleration: $\chi^2 = 3.45$; df = 3; $p = 0.327$; Table 3).

Patient groups off medication, however, differed significantly concerning the movement time of the total letter combination (Kruskal-Wallis test: $\chi^2 = 10.39$; df = 3; $p = 0.016$), of the ascending strokes (Kruskal-Wallis test: $\chi^2 = 8.65$; df = 3; $p = 0.034$) and of the descending strokes (Kruskal-Wallis test: $\chi^2 = 9.41$; df = 3; $p = 0.024$). Subsequent post hoc analysis using the Mann-Whitney-U test indicated that patients at Hoehn and Yahr stage III displayed a longer movement time of both the total letter combination and of the descending strokes than patients at Hoehn and Yahr stage I ($p \leq 0.045$). Furthermore, patients at Hoehn and Yahr stage IV displayed a longer movement time of the total letter combination, of the ascending strokes and of the descending strokes than both patients at Hoehn and Yahr stage I and patients at Hoehn and Yahr stage II ($p \leq 0.029$). Following the withdrawal of dopaminergic medication patient groups also differed with regard to the minimum velocity of ascending strokes (Kruskal-Wallis test: $\chi^2 = 8.72$; df = 3; $p = 0.033$). Post hoc analysis (Mann-Whitney-U test) revealed that patients at Hoehn and Yahr stage IV displayed a significantly slower minimum velocity when performing ascending strokes than the other patient groups ($p \leq 0.050$). Furthermore, significant differences between patient groups off medication were observed in the number of inversions in velocity (Kruskal-Wallis test: $\chi^2 = 11.03$; df = 3; $p = 0.012$) and acceleration profiles (Kruskal-Wallis test: $\chi^2 = 9.17$; df = 3; $p < 0.027$). In comparison to patients at Hoehn and Yahr stage I, patients at stage III produced significantly more inversions in velocity and acceleration profiles (Mann-Whitney-U test: $p \leq 0.035$). Patients at stage IV displayed a more severe dysfluency of handwriting than the other patient groups as indicated by an increased number of inversions in velocity (Mann-Whitney-U test: $p \leq 0.050$). In addition, patients at stage IV showed a significant increase of the number of inversions in acceleration than the patients groups at stages I or II (Mann-Whitney-U test: $p \leq 0.044$). Statistical analysis of the remaining kinematic measures of handwriting did not reach significance in patients groups following withdrawal of dopaminergic medication (movement distance of the total letter combination: $\chi^2 = 1.58$; df = 3; $p = 0.665$/movement distance of ascending strokes: $\chi^2 = 1.14$; df = 3; $p = 0.768$/movement distance of descending strokes: $\chi^2 = 2.13$; df = 3; $p = 0.547$/maximum velocity of ascending strokes: $\chi^2 = 3.18$; df = 3; $p = 0.365$/positive acceleration of ascending strokes: $\chi^2 = 2.55$; df = 3; $p = 0.466$/negative acceleration of ascending strokes: $\chi^2 = 2.86$; df = 3; $p = 0.414$/maximum velocity of descending strokes: $\chi^2 = 2.58$; df = 3; $p = 0.462$/minimum velocity of descending strokes: $\chi^2 = 5.37$; df = 3; $p = 0.147$/positive acceleration of descending strokes: $\chi^2 = 4.79$; df = 3; $p = 0.188$/negative acceleration of descending strokes: $\chi^2 = 3.05$; df = 3; $p = 0.384$).

Discussion

Clinical observations have shown that patients with PD have serious difficulties performing skilled motor actions of everyday

life such as walking or handwriting (Soliveri et al., 1992). It has been suggested that PD patients are impaired in the automatic execution of well-learned movements (Marsden, 1982). As stated by Soliveri et al. (1992) motor performance in skilled or even automated motor tasks of everyday life are difficult to quantify. One possible approach to the measurement of automatic motor processes is the kinematic analysis of handwriting movements which can easily be performed using digitising tablets (Teulings and Thomassen, 1979). Handwriting represents a well-habituated motor skill which has been exercised for many years (Gross, 1975). Furthermore, in healthy adults, handwriting movements represent automated movements which do not require conscious control and have no attentional requirements (Longstaff and Heath, 1997; Tucha et al., 2001). It has been shown that automated and non-automated handwriting movements can be distinguished from one another by profiles of velocity. Single strokes of automated movements lead to a smooth course and have only one peak (inversion of the direction) and a bell shaped course in their velocity profiles. A more severe dysfluency of handwriting is reflected in a higher number of inversions in velocity and acceleration (Meulenbroek and Van Galen, 1988, 1989; Mai and Marquardt, 1992; Tucha et al., 2001). Therefore, the number of inversions in velocity and acceleration profiles can provide information regarding the degree of automaticity of movement execution.

The present study has compared kinematic aspects of handwriting movements of healthy subjects and patients with PD on their usual dopaminergic treatment and following withdrawal of dopaminergic medication. Compared with healthy subjects, the kinematics of handwriting movements were markedly disturbed in PD patients following withdrawal of dopaminergic medication. PD patients off dopaminergic medication displayed a severe disturbance of automation, manifesting itself in an increased number of inversions of velocity and acceleration profiles. PD patients off medication produced slower velocities and accelerations during writing than healthy subjects. Furthermore, they showed an increased movement time, although the distance covered during writing was smaller than the distance of the writing trace of healthy subjects. Although dopaminergic treatment in PD patients resulted in marked improvements of the kinematics of handwriting movements, PD patients did not reach an undisturbed level of performance. In comparison to healthy subjects PD patients on dopaminergic medication nevertheless displayed non-automated handwriting movements with a reduced movement distance, an increased movement time and decreased velocities and accelerations.

These findings accord with previous studies in which aspects of handwriting performance of PD patients were assessed. In PD patients following overnight withdrawal of dopaminergic medication and patients with newly diagnosed and untreated parkinsonism (de novo), kinematic analysis of handwriting movements revealed marked disturbances of handwriting (Eichhorn et al., 1996; Siebner et al., 1999). In addition, beneficial effects of L-Dopa therapy on movement size, movement duration and velocity have been reported (McLennan et al., 1972; Margolin and Wing, 1983; Klawans, 1986). However, the value of previous studies is limited in regard to the effects of dopaminergic medication since these studies focus primarily on handwriting size (McLennan et al., 1972; Klawans, 1986) or required PD patients to perform repetitive handwriting-like tasks such as the generation of concentric circles (Margolin and Wing, 1983; Eichhorn et al., 1996). The repetitive execution of a single movement pattern does not provide an adequate measure in the assessment of handwriting. The participants of the present study were asked to write a short sentence fives times at their own speed and handwriting size.

From a motor viewpoint, the writing of a sentence is more difficult and requires more complex motor coordination than the production of a single movement pattern. The writing of a sentence requires the dynamic interplay of several motor subsystems including the arm-elbow system, the wrist system and the finger system. While the arm-elbow system produces the large left-to-right progression, the wrist system produces the more local horizontal movement as in left-right strokes. The finger system generates the vertical movement (Thomassen and Teulings, 1983; Dooijes, 1983; Meulenbroek and Thomassen, 1991; Teulings et al., 1997; Blank et al., 1999). Furthermore, handwriting is a task that requires the accurate sequencing and online scaling of open loop movements and the programming of subsequent strokes during the execution of the current stroke (Thomassen and Teulings, 1985; Teulings, 1986; Longstaff et al., 2001). The writing of letters or words consisting of different strokes requires a high degree of simultaneous processing and may therefore have a higher programming load than the sequencing of identical strokes (Van Galen, 1991; Van Gemmert et al., 1999). This appears to be particularly important in the assessment of handwriting in PD since both sequencing of motor programs and concurrent processing have been shown to be disturbed in PD patients (Benecke et al., 1987; Malapani et al., 1994; Weiss et al., 1997).

In the present study, the velocity profiles of PD patients were characterised by multiple velocity peaks, indicating a non-automated execution of prelearned motor sequences. In comparison to the automatic processing of handwriting movements displayed by healthy subjects, PD patients appeared to shift from an automatic to a more controlled processing of movement execution. This assumption is supported by the findings of previous studies in which automaticity of handwriting was measured (Eichhorn et al., 1996; Siebner et al., 1999). Furthermore, experimental studies on healthy subjects demonstrated that these non-automated movements can easily be elicited in healthy writers by asking subjects to focus their attention on particular characteristics of handwriting such as neatness (Tucha et al., 2000, 2001). Impairments of automated movement execution in PD patients were related to disturbed activation of the supplementary motor cortex which constitutes the major cortical projection area of the putamen and which is in particular involved in the execution of open loop motor sequences (Oliveira et al., 1997; Samuel et al., 1997). In contrast, attention controlled movements (closed loop) are associated with the lateral premotor cortex. The lateral premotor cortex has been found to be activated when new motor sequences are learned (Jenkins et al., 1994; Jueptner et al., 1997), when externally guided movements are required (Goldberg, 1985; Passingham, 1988, 1993) and when subjects attend to the preparation of movements (Oliveira et al., 1997; Jueptner et al., 1997; Jenkins et al., 2000). Since previous studies measuring regional cerebral blood flow have demonstrated that ballistic movements in PD are related to an impaired activation of mesial frontal and dorsal prefrontal association areas but not of lateral premotor cortex or primary motor cortex (Playford et al., 1992; Jahanshahi et al., 1995), it is assumed that the function of the lateral premotor-parietal circuits are preserved in PD (Samuel et al., 1997). Furthermore, during the execution of a motor sequence consisting of automatic finger movements Samuel et al. (1997) observed that, in comparison to healthy subjects, PD patients displayed an increased activation of the lateral premotor cortex and the parietal circuits. It can therefore be assumed that PD patients shift from an automatic to a more controlled processing of movement execution by switching from impaired striato-mesial frontal projections to an alternate route via the use of the intact lateral premotor-parietal cortex circuits. This assumption may explain why PD patients are

able to partially overcome their motor disturbances with the support of external visual cues (Flowers, 1975; Brown and Marsden, 1988; Lueck et al., 1990; Jackson et al., 1995; Morris et al., 1996; Oliveira et al., 1997). Although the underactivity of the supplementary motor activity has been shown to be reversed by pharmacological treatment using L-Dopa (Haslinger et al., 2001) or apomorphine (Jenkins et al., 1992) the present findings indicate only a partial restoration of an automatic processing of movement execution.

In conclusion, kinematic analysis of handwriting movements in PD revealed that withdrawal of dopaminergic medication resulted in marked deterioration in the automatic execution of well-learned movements. Pharmacological therapy using dopaminergic medication resulted in improved kinematics of movement execution in PD patients. The performance of the patients, however, remained impaired when compared to healthy subjects. Kinematic profiles indicate that PD patients perform handwriting movements under conscious control. According to Samuel et al. (1997) it is assumed that in PD there is a shift from the striato-mesial frontal projections which are associated with the processing of automatic movement execution to the lateral premotor-parietal cortex circuits which have been shown to be associated with the controlled execution of motor sequences. The present study has demonstrated that the influence of dopaminergic medication on motor disturbances in PD can easily be quantified by the kinematic analysis of handwriting movements. This approach may provide a useful criterion in achieving the optimal dosage of pharmacological treatment. Furthermore, the present study has demonstrated that there are marked differences regarding the kinematics of handwriting movements between PD patients at different stages of disability. The kinematic analysis of movements may provide important information on the course of the disease of an individual patient.

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