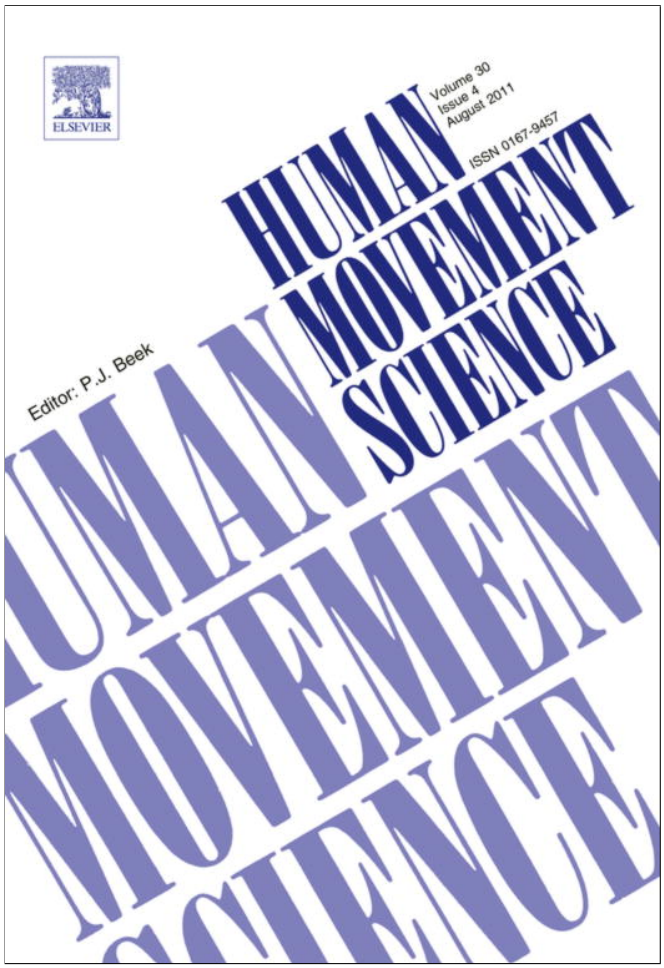

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Handwriting in patients with Parkinson disease: Effect of L-dopa and stimulation of the sub-thalamic nucleus on motor anticipation

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ABSTRACT

The present research focused on how patients with Parkinson's disease (PD) produce handwriting sequences. PD patients who were on/off medication or deep brain stimulation treatments had to write *lll* and *lln* trigrams. We evaluated their ability to anticipate on-line the last letter in the trigram. The results revealed that in PD patients, contrary to healthy participants, the percentage of time taken by the down-stroke of the second *l* did not vary as a function of the spatial constraints of the following letter (*l* or *n*). In other words, the handwriting of the PD patients did not exhibit any sign of motor anticipation. However, under treatment, PD patients exhibited similar results to healthy participants despite no improvement in movement variability. Taken together these results do not seem consistent with the hypothesis that PD patients do not anticipate future movements because of their movement variability. They are more in agreement with theories that postulate that PD patients have a general deficit in the parallel processing of the components of a motor sequence.

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1. Introduction

A striking characteristic of the human motor system is the ability to produce motor sequences in a smooth and continuous way without pauses between the successive components of the motor sequence. Several studies have shown that this ability was partly due to the capacity of the motor system to plan forthcoming components of the sequence during movement execution. This has been demonstrated in speech production (Benguerel & Cowan, 1974), in handwriting (Kandel, Orliaguet, & Boe, 2000; Kandel, Orliaguet, & Viviani, 2000; Orliaguet, Kandel, & Boe, 1997) and manual reaching movements (Gentilucci & Negrotti, 1999; Gentilucci, Negrotti, & Gangitano, 1997; Marteniuk, MacKenzie, Jeannerod, Athènes, & Dugas, 1987; Rand & Stelmach, 1999). For instance, the grasping of an object is performed faster when the goal of the action is to throw the object rather than to put it down on a small target (Marteniuk et al., 1987). Similarly, Gentilucci and Negrotti (1999) showed that a grasping movement was also executed faster if the object was put down on a large target than a small one. These results indicate that the spatial constraints of the upcoming motor components are anticipated during the execution of the previous components of the motor sequence. The present study examined motor anticipation in Parkinson's disease patients, who exhibit severe difficulties in coordinating the different components of motor sequences. More precisely, we investigated the effects of L-dopa or bilateral stimulation of the sub-thalamic nucleus on their ability to anticipate forthcoming motor sequences in handwriting movements.

Unlike healthy people, patients with Parkinson's disease exhibit specific deficits in executing sequential movements such as handwriting (Jahanshahi & Frith, 1998; Lange et al., 2006; Smith & Fucetola, 1995; van Gemmert, Adler, & Stelmach, 2003), drawing (Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992) or reaching movements (Gentilucci & Negrotti, 1999; Smiley-Oyen, Lowry, & Kerr, 2007; Weiss, Stelmach, & Hefter, 1997). They have great difficulties in coordinating the different components of the motor sequence, irrespective of the motor task. They tend to perform sequential movements in a more segmented fashion. When the different components have to be produced in a motor sequence they are slower than when they are executed separately (Benecke, Rothwell, Dick, Day, & Marsden, 1986; Weiss et al., 1997). Hesitations and pauses are often observed between the components of the sequence (Agostino et al., 1992) and this arises even when the motor sequence is extremely simple. For example, when PD patients have to produce two reaching movements towards two successive targets under high-accuracy constraints (i.e., smaller target) on the second component of the motor sequence, they tend to execute the two reaching movements independently (Rand, van Gemmert, & Stelmach, 2002). A recent experiment has confirmed the difficulty in PD patients to anticipate the upcoming components in a motor sequence (Smiley-Oyen et al., 2007). It showed that PD patients could only anticipate up to one or two targets when they executed three-dimensional rapid aiming movements to 1, 3, 5, and 7 targets. Healthy participants, in contrast, used preplanning both for the shortest and the longest reaching sequences. According to the authors the difficulty of PD patients could be due to the variability of the initial force impulse of their reaching movement and this would render the planning and coordination of the components of the sequences extremely difficult.

There is scarce research on the way PD patients program the components of a handwriting sequence. Previous studies only mention that the writing of PD patients was characterized by a decrease in letter size (micrographia), a decrease in kinematic features such as speed, acceleration or stroke duration (Jahanshahi & Frith, 1998; Lange et al., 2006; van Gemmert et al., 2003), and an increase in the number of strokes (i.e., a decrease of motor fluency). The present research therefore focused on how PD patients produce handwriting sequences and, in particular, on their abilities to anticipate on-line the various components of forthcoming sequences. A series of experiments showed that when healthy participants have to write two letters, the motor system anticipates the execution of the second during the production of the first letter (Kandel, Orliaguet, & Boe, 2000; Kandel, Orliaguet, & Viviani, 2000; Orliaguet et al., 1997). The participants wrote cursive letters like digrams *ll* and *ln*. When producing the first *l* of *ll*, the motor system anticipated the execution of the other *l*. When producing the *l* of *ln*, the anticipation requires the processing of a change in letter size and rotation direc-

tion which implies a reduction of the force level and the use of a new coordination. These changes cause a modification in the tangential velocity profile of the first *l*. Furthermore, when examining movement time, the duration of the down-stroke of the *l* was shorter when it was followed by another *l* than by an *n*.

If PD patients produce sequential movements in a more segmented fashion they should have difficulties in the anticipation of handwriting sequences. In the present research PD patients wrote *lll* and *lln* sequences on a digitizer. We expected that during the production of the second *l* the motor system would not anticipate the forthcoming letter (*l* or *n*), resulting in equivalent durations for the down-strokes of the second *l*s of *lll* and *lln*. Then, we investigated the effects of dopaminergic medication or bilateral deep brain stimulation treatments on the PD patients' abilities to anticipate the same handwriting sequences. Some studies have shown that this kind of treatment had beneficial effects on the kinematics of handwriting in PD patients. In particular, they were observed in the regulation of letter size, movement duration, and fluency (Jahanshahi & Frith, 1998; Lange et al., 2006; Smith & Fucetola, 1995). We thus expected that under these treatments, the PD patients would write *lll* and *lln* in a similar fashion as healthy patients. They should anticipate the constraints to produce the third letter while writing the second *l*. We thus predicted that under dopaminergic medication or deep stimulation of the sub-thalamic nucleus the PD patients would produce longer down-strokes of the second *l* of *lln* than the second *l* of *lll*.

2. Methods

2.1. Participants

Seven right-handed patients with a diagnosis of idiopathic Parkinson disease (PD) (3 female, 4 male, mean age = 50 ± 9 years, *M* ± *SD*) participated in the experiment, which was approved by the local Ethics Committee of the University Hospital Center of Grenoble. Diagnosis of PD was established by experienced neurologists who assessed the severity of clinical symptoms. All patients had a score higher than 130 in the Mattis Dementia Rating Scale (Mattis, 1988) and a score lower than 24 in the Beck Depression Inventory (Beck & Steer, 1987). Other clinical data concerning disease duration at the time of the study and the first symptoms are reported in Table 1. The patients showed no manifestation of cognitive and affective impairment. They presented motor fluctuations and inclusive criteria for a neurosurgical treatment by electrical stimulation of the sub-thalamic nucleus (STN) (Lozano, 2003). All PD patients gave informed consent to participate in the study.

Seven right-handed healthy adults (3 female, 4 male, mean age = 50 ± 9 years, *M* ± *SD*) without previous history of neurological disorders constituted the control group. They were matched with PD patients according to age and educational level. As for PD patients, they had a score higher than 130 in the Mattis Dementia Rating Scale and lower than 24 in the Beck Depression Inventory.

Table 1
Clinical characteristics of the group of patients with Parkinson's disease. The score of Part III of UPDRS contained several items concerning hand motions (rest and action tremor, rigidity, tapping, hand motions and rapid alternative motion). The handwriting's scores in each session were in brackets.

Patients	Age (years)	Sex	Duration of disease (years)	First symptom	Motor score of the UPDRS (part III) Handwriting scores are indicated in brackets			
					Off-Dopa	On-Dopa	On-Stim	Off-Stim
Patient 1	43	M	7	Hypokinesia	15 (3)	4 (0)	6 (1)	20 (0)
Patient 2	64	M	9	Rigidity and hypokinesia	52 (1)	6 (1)	11 (1)	43 (1)
Patient 3	58	F	8	Tremor	66 (4)	17 (3)	25 (1)	53 (1)
Patient 4	45	M	13	Tremor	36 (2)	7 (1)	12 (1)	30 (1)
Patient 5	53	F	10	Tremor	32 (3)	5 (1)	20 (2)	34 (1)
Patient 6	38	F	6	Tremor	32 (3)	8 (1)	6 (1)	27 (4)
Patient 7	49	M	15	Hypokinesia	50 (3)	13 (0)	7 (1)	23 (1)

2.2. Procedure

The participants were tested individually in a dimly illuminated and quiet room. They had to write the cursive trigrams *lll* and *lln*. They wrote on templates of *lll* and *lln* that were drawn on a sheet of paper. The *l*s and the *n* were 8 and 4 cm on the vertical axis, respectively. These sizes were chosen to avoid micrographia as much as possible. The participants were told that these templates were just an indicator of the letter size and that the task was not a copying task but consisted in producing natural movements at a self-paced rate. Each sequence was repeated 10 times. The trajectory of the movements (*xy* coordinates) was recorded on a digitizer (Wacom GD.1218R, frequency 200 Hz, spatial precision 0.2 mm) with an electronic stylus. It is noteworthy that the stylus did not leave any visual trace. The idea was to facilitate the planning of the movement and therefore limit the visual on-line motor control.

The PD patients were tested in four sessions. The first two sessions were conducted before the surgical treatment in off L-dopa condition after an overnight fasting condition (Session 1) and an on L-dopa condition after having taken 120% of the usual morning L-dopa dose (Session 2). Approximately 1 year after surgery, they were tested off-L-dopa, and on (Session 3) and off (Session 4) bilateral STN stimulation. The patients remained at least 30 min under stimulation before the beginning of tests. The idea underlying this procedure was to limit the overactivation of the globus pallidus which is supposed to be responsible for the inhibition of motor activity (bradykinesia and akinesia). The surgery consisted in positioning electrodes in the STN which projects to the globus pallidus. The electrodes were connected to a subcutaneous pulse generator that provided chronic high frequency stimulation. Healthy participants performed the writing tasks four times at approximately the same periods as the PD patients in order to control the influence of repetition.

Before each session, the motor level was assessed using Part III (motor score) of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987). The scores off and on-treatment are reported in Table 1. They showed that the score decreased by at least 30%, for both kinds of treatments (on-Dopa or on-Stim). We reported also the score obtained in handwriting's UPDRS task. Patient 4 presented micrographia without treatment.

2.3. Data analysis

After filtering the *xy* coordinates (Butterworth cut-off frequency 12 Hz) we calculated for each trial the trajectory of the writing trace and the tangential velocity of the handwriting movement. As in our previous experiments (Kandel et al., 2000), we isolated the middle *l* of the trigrams *lll* and *lln* (see

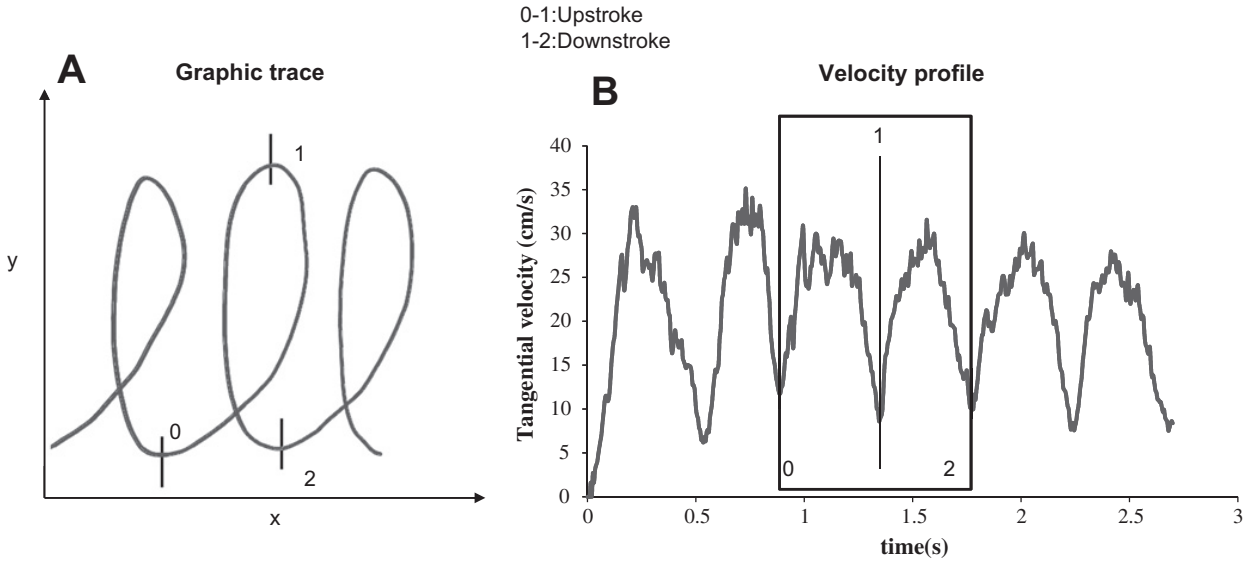

Fig. 1. Example of the graphic trace and the velocity profile for one PD patient.

Fig. 1) using the geometrical parameters and the minima of the tangential velocity as segmentation criteria. Then we measured amplitude of movement (AM), duration of down-stroke (DDS) and total movement time (MT). In addition, for each parameter (duration and amplitude of movement) we calculated the coefficient of variation (*CV*) so that we could analyze the variability of performance. Given the great variability of movement duration in PD patients, we calculated the normalized jerk[1] (NJ) and the percentage of the time taken by the down-stroke (PTDS) so we could compare their movements to those of the healthy participants. The data were submitted to a series of Analyses of Variance (ANOVA's) and *t*-tests. Scheffé tests were used for post hoc analysis.

3. Results

3.1. General description of handwriting movements in PD patients

The kinematic analysis showed that all the patients produced handwriting without any pauses between the three successive letters of the sequence. No null velocity was observed at the end of the second stroke of the first and the second *l*.

In line with previous experiments, the comparison between the control group and PD patients without medication (off-Dopa and off-Stim) revealed significant differences. In PD patients we observed an increase of MT (M Patients = 1818 ms, SD = 382 ms; M Control = 1144 ms, SD = 187 ms; $F(1, 12) = 13.1$, $p < .01$) and higher duration *CV* (M Patients: 19%, M Control = 10%, $F(1, 12) = 5.5$, $p < .05$). In contrast, we did not observe significant differences between PD patients and the control group in AM (M Control = 18.4 cm; M Patients = 18.9 cm; $F(1, 12) < 1$) and trajectory *CV* (M Control = 4.7%, M Patients = 11.6%; $F(1, 12) = 2.49$, $p > .1$). Finally, in spite of PD patients presenting a tendency to have higher NJ (M Control = 25; M Patients = 39.5, $F(1, 12) = 3.6$, $p = .08$), we observed no significant difference between control and PD patients.

In patients, the treatments (on-Dopa and on-Stim) produced a decrease of MT (M without treatment = 1818 ms, SD = 382 ms; M with treatment = 1387 ms, SD = 255 ms, $t(6) = 2.7$, $p < .05$) and NJ (M without treatment = 52, SD = 21; M with treatment = 27, SD = 9.9, $t(6) = 3.12$, $p < .05$) but had no effect on duration *CV* (M without treatment = 19.9%, M with treatment = 15.5%, $t(6) = 1.22$, $p > .1$). Again, no differences were observed for AM (M without treatment = 18.9 cm, M with treatment = 18.5 cm, $t(6) = 0.86$, $p > .1$) and trajectory *CV* (M without treatment = 11.6%, M with treatment = 8.3%, $t(6) = 1.22$, $p > .1$).

3.2. Analysis of motor anticipation

We conducted an ANOVA for the control group with Session (1, 2, 3 and 4) × Letter (*lll*, *lln*) as repeated measures on the two factors. The results (see Fig. 2) were in agreement with the data of our previous experiments (Kandel, Orliaguet, & Boe, 2000; Kandel, Orliaguet, & Viviani, 2000; Orliaguet et al., 1997). We observed a significant effect of letter ($F(1, 6) = 6.3$, $p < .05$). The PTDS of the *l* was higher when followed by an *n* (M = 49.6%, SD = 0.9%) than by another *l* (M = 47.4%, SD = 2.5%). This pattern of results was replicated in each session, confirming that in the healthy group the timing of the *l* was regulated by the characteristics of the following letter (Kandel, Orliaguet, & Viviani, 2000). In addition, there was no effect of session ($F(3, 18) < 1$). This indicates that the repetition of the task did not influence the results. Motor anticipation was systematic in healthy participants. Since there was no significant session effect nor a significant interaction between letter and session ($F(3, 18) < 1$), the results of the four sessions were merged in the following analyses. Then, we conducted for each session a Group (healthy control, PD patients) × Letter (*lll*, *lln*) ANOVA with repeated measures on the last factor.

In the session without treatment (off-Dopa and off-Stim), we observed a significant interaction between group and the letter, ($F(1, 12) = 10.3$, $p < .01$, and $F(1, 12) = 6.9$, $p < .05$, respectively). In contrast to what we observed for the healthy participants, post hoc analysis did not reveal any difference

[1] Normalized jerk is a measure of motor fluency which is independent of size and duration variability (e.g., Contreras-Vidal, Teulings, & Stelmach, 1998).

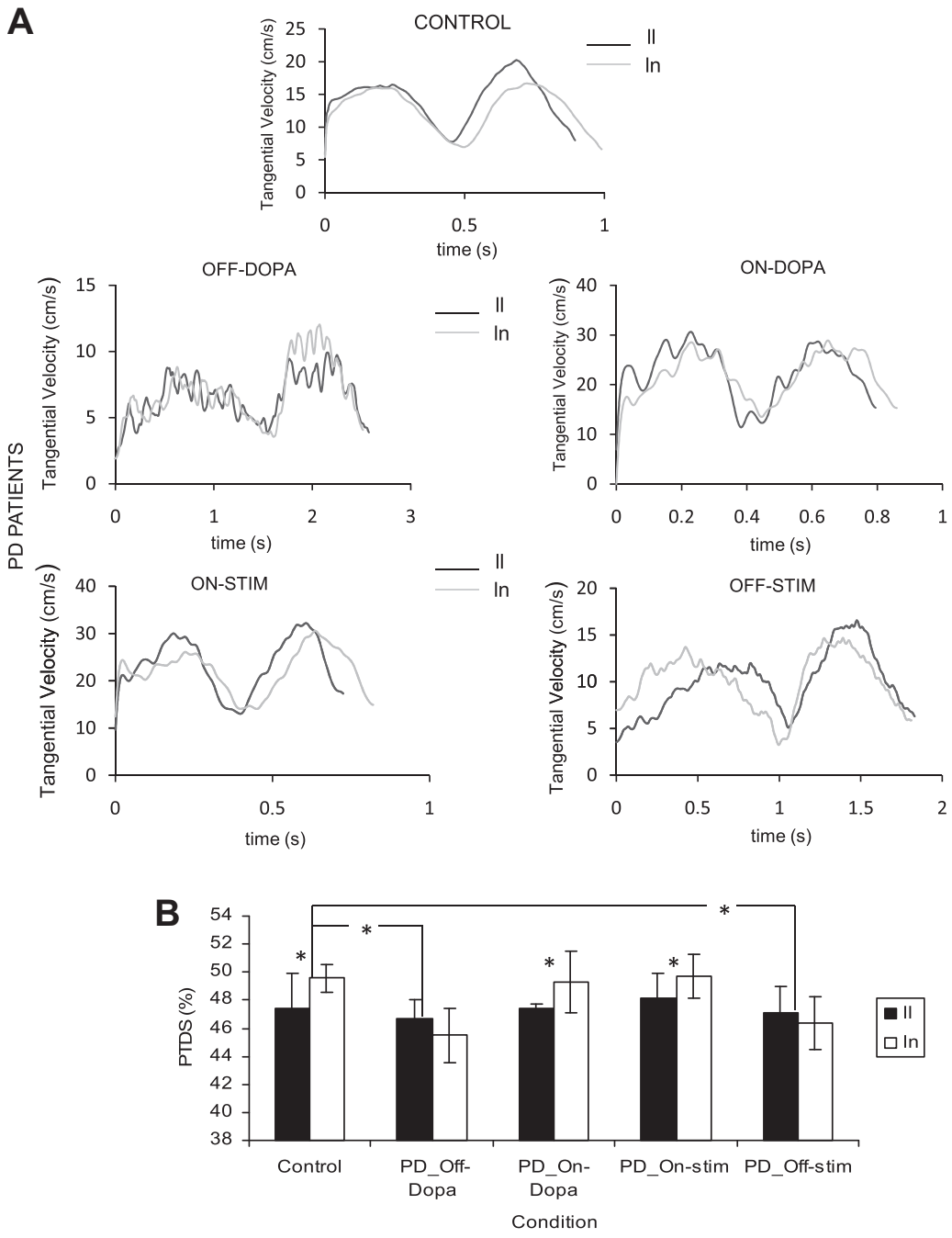

Fig. 2. Kinematic characteristics of handwriting for both PD and controls. (A) Representative tangential velocity profiles across all sessions. Given the absence of a difference in healthy participants, only one velocity profile was presented. (B) Mean and standard deviation of the percentage of time taken by the down-stroke of the second *l* (PTDS) as a function of condition (Control, PD_Off-Dopa, PD_On-Dopa, PD_On-Stim, and PD_Off-Stim) and letter (*l* of lll, *l* of lln).

between the PTDS of the *l*s of *lll* and *lln* in PD patients in off-Dopa as well as in off-Stim ($p = .90$ and .99, respectively), indicating that there was no anticipation of the following letter.

However, when PD patients were under treatment (on-Dopa and on-Stim), the pattern of results was different. There were no differences between the PD patients and healthy participants ($F(1, 12) < 1$, respectively for on-Dopa and on-Stim conditions). The interaction between group and letter was not significant ($F(1, 12) < 1$). The PTDS was higher in the *l* of *lln* than in the *l* of *lll* in both on-Dopa (49% vs 47%) and in on-Stim (50% vs 48%). Thus, we observed the same pattern of motor anticipation in the PD patients with treatment as healthy participants.

Finally, no difference appeared in PD patients between L-dopa and stimulation treatments both concerning Off and On conditions (in Off: $F(1, 6) = 1.3$, $p > .1$, in On: $F(1, 6) < 1$, respectively).

4. Discussion

Our study aimed at examining the deficits in the programming of cursive handwriting sequences in PD patients. We also examined the effects of L-dopa medication and the bilateral stimulation of the sub-thalamic nucleus by deep electrodes on the on-line coordination of the components of the motor sequence.

The results showed that PD patients were able to write the three letters in a continuous fashion, without pauses. This is in agreement with previous studies (Jahanshahi & Frith, 1998; Lange et al., 2006; Smith & Fucetola, 1995). When comparing the results with those of the healthy participants, the kinematic analysis revealed that PD patients' movements were slower and subject to a greater variability in total movement time. The data also indicate, as expected, that the treatments improved movement production, resulting in a decrease in movement time. However, the treatments did not have an effect on the variability of movement time. Regarding letter size, we did not observe the micrographia described in most studies on PD disease. There were no differences in size letter between PD patients and healthy participants, irrespective of the session analysis of size letter revealed no difference between PD patients and healthy participants. This could be due to the fact that in our experiment the participants had to write the letter sequences according to a template that pre-established the writing size. In addition, the participants were instructed to respect the size of the letters of the template as much as possible. This is in accordance with observations showing that in PD patients the motor function is improved by external visual cues, especially when they have to produce handwriting movements (Jahanshahi & Frith, 1998; Lange et al., 2006; Smith & Fucetola, 1995). Moreover, in our sample, only one patient complained of micrographia.

The results also revealed that when the PD patients were off medication the percentage of time taken by the down-stroke of the second *l* did not vary as a function of the constraints imposed by writing the following letter. In other words, the handwriting of the PD patients did not exhibit any sign of motor anticipation. Although they could write the three letters without pauses, the PD patients tended to produce each letter in a more independent manner. This confirms that continuous movements such as those required for handwriting production are also executed in a rather discrete fashion, as observed in reaching movements. The study with PD patients conducted by Smiley-Oyen et al. (2007) with aiming movements indicated that they could only anticipate one to two targets. This means that they could only plan one or two successive strokes, which corresponds to the up and down-strokes that are required to produce the writing of an *l*.

Several arguments could explain the lack of motor anticipation in PD patients. The segmentation of the motor sequence could be due to the high movement time variability observed in both our experiment and aiming movement studies (Desmurget et al., 2004; Gentilucci & Negrotti, 1999; Smiley-Oyen et al., 2007; Weiss et al., 1997). This variability of movement time is the consequence of the well-known difficulties of PD patients in the generation of force impulse and the modulation of the agonist-antagonist muscle groups (Kelly & Bastian, 2005; Smiley-Oyen et al., 2007). Smiley-Oyen et al. (2007) suggested that the variability in force generation makes the prediction of the outcome of the first stroke too difficult. Consequently, it would be less advantageous to plan the sequence too far in advance and therefore be more efficient to plan a movement sequence in a more segmented fashion, anticipating only one or two strokes in advance. This interpretation is not consistent with our results which showed that the movement variability did not prevent the PD patients from executing the handwriting movement in an integrated fashion when they were under treatment. The kinematics analysis revealed a marked sign of motor anticipation under treatment although the variability of movement time remained identical to that observed when PD patients were in off treatment.

One other factor contributing to the deficiency in motor anticipation could be the difficulty of PD patients to switch from one movement to another during the execution of a motor sequence. Several studies showed that in discrete sequencing movements like drawing (Agostino et al., 1992), finger movement (Benecke et al., 1986), hand postures (Harrington & Haaland, 1991) tapping (Stelmach, Worringham, & Strand, 1987) and reaching (Weiss et al., 1997) PD patients have a specific deficit in coordinating the different components of the motor sequence, particularly when the sequence is made up with different movements. These studies observed an increase of movement time but above all,

hesitations and pauses between the first and the second movement. Our data, in contrast, did not reveal such difficulties. If PD patients had difficulties in changing from one program to another they should more easily, and thus more quickly, execute the second *l* of *lll* than the second *l* of *lln* when they were off treatment. Our study did not yield such a pattern of results. We did not observe pauses between the two letters. Furthermore, there were no differences between the percentage of time taken by the down-strokes of the second *l* of *lll* and *lln*. Although the differences were not statistically significant, the time percentages were even higher for the second *l* of *lll* than *lln* in the two without treatment sessions.

As a consequence, it seems that the difficulty to anticipate the upcoming letters when writing a letter is rather the expression of a general difficulty to produce simultaneous actions in patients with basal ganglia disorders. For example patients with PD are less accurate than controls in tasks involving bi-manual co-ordinations (i.e., Johnson et al., 1998). They are able to produce bi-manual in-phase movements but have great difficulty to perform asymmetrical bi-manual anti-phase movements and they even tend to produce a symmetrical in-phase movement during the execution of the movement. In addition, Desmurget et al. (2004) showed that on-line control is severely impaired in PD patients when they have to correct the trajectory of aiming movements. Healthy participants are able to correct their movement very quickly (after only 220 ms) by iterative on-line motor control, whereas PD patients need more time to initiate corrective sub-movements. They tend to correct the trajectory after completion of the initial movement or show on-line corrections with abnormally slow corrective reaction times (above 700 ms). According to the authors these results show that PD patients' corrective sub-movements could not be implemented in parallel with the ongoing movement. The deficit exhibited by PD patients would rely on a forward control that is a predictive control. PD patients could not estimate the position and the movement speed in real time in order to add sub-movements or corrections. This deficit could explain the reason why PD patients tend to slow or stop their movement to use retroactively visual and/or proprioceptive feedback in aiming movements. This difficulty to produce simultaneous actions and use a feedforward control, could explain the lack of motor anticipation in the execution of letter sequences. Writing *lll* or *lln* involves the accurate sequencing of letters and the programming without pauses of subsequent letters during the execution of the current letter. Therefore, this requires feedforward control and a parallel processing (Thomassen & Teulings, 1985; van Galen, 1990) and a difficulty in this domain (Desmurget et al., 2004) would explain the reason why PD patients off treatment would be unable to anticipate the upcoming letters *l* or *n* while writing the middle *l*.

Finally, our study showed that the treatments had an effect on the way the sequential movements were executed. There were no differences between the percentages in the time taken by the down-stroke of PD patients and the healthy participants. What differed between the two groups was writing speed. PD patients' writing movements were slower than those produced by the healthy participants. Therefore both medical and surgical treatments lead to a partial restoration in the executing of sequential handwriting movements. Under treatment the PD patients were able to anticipate the upcoming letter of the sequence during the production of a current movement. This argues in favor of basal ganglia implication in parallel processing of motor control (Groenewegen, 2003) and suggest that automation of handwriting should be disturbed in PD patients (Jankowski, Scheef, Huppe, & Boecker, 2009). Further investigations are nevertheless necessary to confirm this point.

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