Impairment of complex upper limb motor function in de novo Parkinson’s disease

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Abstract

The aim of the present study was to evaluate complex upper limb motor function in newly diagnosed, untreated Parkinson’s disease (PD) patients.

Four different unimanual upper limb motor tasks were applied to 13 newly diagnosed, untreated PD patients and 13 age- and sex-matched controls.

In a handwriting task, PD patients had significantly reduced sentence length and writing velocity, and decreasing letter height in the course of writing. Furthermore, PD patients performed an aiming task slower with than without target, and showed increased transposition in a pointing task.

The results of this study extend previous observations of impaired complex upper limb movements to newly diagnosed, untreated PD patients.
INTRODUCTION

Patients with Parkinson’s disease (PD) show clear disorders in the organization and control of movement. Deficits in movement initiation and movement speed are observed during the execution of simple movements. These problems become even more pronounced when complex sequential and bimanual movements of the upper limb have to be performed.

A well-practiced complex motor skill requiring a sequence of movements of the upper limb is handwriting. Handwriting involves extensive cognitive processing because each individual stroke has to be planned and executed. Therefore, as the number of words to be written in a sequence increases, on-line concurrent processing demands are also augmented. PD patients often produce writing patterns of smaller size than prior to their disease, or fail to maintain stroke size of the characters as writing progresses: this phenomenon is known as micrographia. In a series of studies, Van Gemmert et al. have shown that in mildly to moderately affected PD patients (Hoehn and Yahr stages 1-3) stroke duration is normal, whereas stroke size is reduced only in tasks involving increased processing demands or a stroke size of more than 1.5 cm. Since all patients in these studies were using dopaminergic medication, changes in handwriting may have been at least partly masked by the effect of dopaminergic treatment. It therefore remains unclear to what extent micrographia is a characteristic of early stage, untreated PD patients or, alternatively, develops fully only in moderately advanced stages of disease.

In his studies of rapidly alternating movements of the upper limb in normal subjects, Fitts noted that movement time varied systematically with changes in movement amplitude and target width, provided that accuracy was held constant (a relationship that later became known as ‘Fitts law’). Movements that are easier to perform, because they are smaller or directed to a larger target, are performed more rapidly. Sanes extended these observations on movement accuracy by assessing whether PD patients adapt to Fitts’ law and found that mildly to moderately affected PD patients (Hoehn and Yahr stages 1-3), all but one of whom were using dopaminergic drugs, had difficulty in producing larger movements (target size held constant) and movements to smaller target sizes (target separation held constant). In another study, involving aiming movements with and without an accuracy constraint, slowing of movement in the condition with the accuracy constraint was much more pronounced in medicated PD patients (average disease duration 6.4 years) than in controls.

In a previous study, we were able to demonstrate an impairment in complex bimanual movements in newly diagnosed, untreated PD patients. The aim of the present study was to evaluate complex sequential unimanual movements in the
same group of PD patients. Performance on a number of complex upper limb motor tasks of 13 newly diagnosed, untreated PD patients was compared with that of 13 age- and sex-matched healthy subjects.

**Materials and Methods**

*Subjects*
Thirteen non-demented PD patients (mean age 60.2 years) and thirteen age- and sex-matched healthy subjects (mean age 58.6 years) participated in the experiment. All patients were recruited from the outpatient clinic for movement disorders of the VU University Medical Center and fulfilled the United Kingdom Parkinson’s Disease Society Brain Bank (UK-PDSBB) clinical diagnostic criteria. The healthy subjects were recruited from the general population. All PD patients were newly diagnosed on average of two months prior to participation in this study, drug naïve and in Hoehn and Yahr stages 1-2.5. At the time of testing, the average disease duration as determined by the onset of subjective symptoms was 17.5 months (table 1). Subjects were excluded if they were < 40 or > 70 years of age, when they had a history of another neurodegenerative disease or a functional disability of the upper limbs from any other cause, and when they were using centrally active medications such as anticonvulsants, sympatheticomimetics, neuroleptics, antidepressants, benzodiazepines, lithium, antihistamines and methylphenidate. Motor function of PD patients was assessed using the Unified Parkinson Disease Rating Scale (UPDRS), section III (table 1). All healthy subjects had a UPDRS motor score of < 3. All subjects were self-proclaimed right-handed. The protocol of the study was approved by the local medical ethical committee of the VU University Medical Center, and all subjects gave their written informed consent prior to participating in the experiment.

*Procedures*
Subjects were instructed to perform a number of upper limb motor function tasks on a graphics tablet (Wacom Ultrapad 1825) with matching electronic pencils. Movements were recorded at a sampling rate of 205 Hz and a spatial resolution of 0.02 cm. The control and collection program for the experiments was written in OASIS. Four different tasks were used in a single session. The first and second task were repeated at the end of the session to evaluate the influence of fatigue.

1. Handwriting task
The first and sixth (last) test was a handwriting task. The subjects were asked to write the sentence ‘en liesje leerde loesje lopen’ at a self-determined comfortable size and
speed. No capitals were allowed. The same sentence had to be written six times. Recording of each sentence started after an auditory signal caused by the pen touching a circle on the paper at the beginning of the sentence. Each sentence had to be concluded with a second auditory signal that could be evoked by touching the circle at the end of the sentence before starting with the next sentence. Variables included sentence length (defined as the vector between the beginning and end of each sentence), letter height (defined as the vector between the most upper part and lower part of the letter ‘l’) and the writing speed of the word ‘lopen’.

2. Pointing task
The second and fifth task was a pointing task. The subjects were asked to steadily hold a pen for 30 seconds with each hand. They were asked to fully extend their arm. The pen had to be maintained in a vertical position, about 1 cm above the digitizer (no target). Variables registered were transposition (defined as the movement in X direction and Y direction of the pen above the digitizer) and velocity of transposition (defined as the velocity of movement in X direction and Y direction of the pen above the digitizer).

3. Aiming task
The third task was an aiming task with two movement conditions, one with target constraint (i.e. landing on the target) and the other without target constraint (i.e. aiming beyond the target). The subjects were seated comfortably in a chair in front of the digitizer. The height of the chair was adjusted such that the forearm could be

Table 1 Clinical characteristics of the Parkinson’s disease patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Disease duration (months)</th>
<th>Hoehn and Yahr stage</th>
<th>UPDRS motor score</th>
<th>Most affected side</th>
</tr>
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<tr>
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<td>M / 70</td>
<td>24</td>
<td>2</td>
<td>18</td>
<td>R</td>
</tr>
<tr>
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<td>F / 67</td>
<td>23</td>
<td>2.5</td>
<td>20</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>F / 52</td>
<td>24</td>
<td>1.5</td>
<td>15</td>
<td>L</td>
</tr>
<tr>
<td>4</td>
<td>M / 63</td>
<td>25</td>
<td>1.5</td>
<td>12</td>
<td>R</td>
</tr>
<tr>
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<td>M / 60</td>
<td>18</td>
<td>2</td>
<td>13</td>
<td>L</td>
</tr>
<tr>
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<td>18</td>
<td>2</td>
<td>13</td>
<td>L</td>
</tr>
<tr>
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<td>M / 62</td>
<td>10</td>
<td>1.5</td>
<td>14</td>
<td>R</td>
</tr>
<tr>
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<td>M / 50</td>
<td>24</td>
<td>1</td>
<td>13</td>
<td>R</td>
</tr>
<tr>
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<td>M / 57</td>
<td>20</td>
<td>2</td>
<td>15</td>
<td>L</td>
</tr>
<tr>
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<td>18</td>
<td>2</td>
<td>11</td>
<td>R</td>
</tr>
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<td>1.5</td>
<td>12</td>
<td>L</td>
</tr>
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<td>M / 76</td>
<td>13</td>
<td>2.5</td>
<td>26</td>
<td>R</td>
</tr>
<tr>
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<td>F / 69</td>
<td>3</td>
<td>1.5</td>
<td>14</td>
<td>R</td>
</tr>
</tbody>
</table>
placed on the table in a horizontal position. The subjects made a linear movement away from the body that consisted of an elbow extension. In the on-the-target condition, the subjects attempted to move from the home position to a 3 x 3 cm target at a distance of 25 cm. In the beyond-the-target condition, the subjects were instructed to move in the direction of the target but not to stop on the target. Instead, they were instructed that movements should pass through the target until the subject’s arm was fully extended. All subjects were instructed to execute both versions of the task as fast and accurately as possible in response to an auditory go-signal. Subjects were allowed to first familiarize themselves with the task and performed 2 trials before each condition was run. In the experiment proper, 10 trials were executed and recorded per condition. Variables recorded were movement time and latency.

4. Fitts’ task
The fourth task was an aiming task of the kind used by Fitts in establishing his lawful relationship between movement time and the difficulty of the task as determined by movement amplitude and target width. The trials were presented on A4 sheets of white paper in landscape orientation and comprised 32 rapid movements in four different conditions; short distance (4.5 cm)/ large target (Ø1 cm), short distance/ small target (Ø 0.3 cm), long distance (7 cm) /large target, long distance/ small target. Each condition consisted of 8 trials. Variables recorded were movement time and latency.

Data analysis
All movement parameters were compared (see below) between PD patients (n = 13) and healthy subjects (n = 13). Data of the handwriting task were analyzed in OASIS. Data of the pointing task, aiming task, and Fitts’ task were analyzed in Matlab. The latter data were high-pass filtered to eliminate low-frequency drift (second-order bi-directional Butterworth filter with a cut-off at 0.005 Hz). Trials were excluded when the subject did not respond to the starting signal (incorrect latency) or did not reach the end target (incorrect movement time). In the PD group, 7 trials of the accuracy task and 1 trial of the Fitts’ task were excluded on the basis of an incorrect latency, while 15 trials of the accuracy tasks and 4 trials of the Fitts’ task were discarded because of an incorrect movement time. In the group of healthy subjects, 6 trials of the accuracy task and 3 trials of the Fitts’ task were excluded on the basis of an incorrect latency and 11 of the accuracy trials, while 6 trials of the Fitts’ task were discarded because of an incorrect movement time.

Statistical Methods
Sentence length and writing velocity in the handwriting task were analyzed according to a 2 x 2 repeated measures ANOVA with a mixed factorial design involving the
between-subjects factor Group (PD, healthy subjects) and the within-subjects factors Task (1: first task, 2: last task) and Sentence (total of six). Letter height in the handwriting task was analyzed according to a 2 x 2 x 2 repeated measures ANOVA with a mixed factorial design involving the between-subjects factor Group (PD, healthy subjects) and the within-subjects factors Task (1: first task, 2: last task), Sentence (total of six), and L-number (total of 4 in each sentence).

Movement time and latency in the aiming task were analyzed according to a repeated measures ANOVA with a mixed factorial design consisting of the between-subjects factor Group (PD, healthy subjects) and the within-subjects factor Target (with target / without target). Movement time and latency in the Fitts’ task were analyzed according to a 2 x 2 repeated measures ANOVA with a mixed factorial design involving the between-subjects factor Group (PD, healthy subjects) and the within-subjects factors Target (small target / large target) and Distance (long / short). We recognized the possibility that movement time could have been affected by the distance between the starting point of the trial and target. We therefore performed an additional analysis for the long distance trials only.

The transposition and velocity of transposition in the pointing task were analyzed according to a 2 x 2 x 2 repeated measures ANOVA with a mixed factorial design involving the between-subjects factor Group (PD, healthy subjects) and the within-subjects factors Side (left hand / right hand), Direction (X, Y), and Period (begin, end).

Results

Handwriting task
Sentence length
Sentence length was significantly shorter in the PD (11.01 cm) group than in the healthy controls (14.05 cm) \([F(1, 24) = 7.99, p = 0.009]\) (figure 1a). Sentence length was also significantly shorter in the first task (12.12 cm) than in the second task (12.94 cm) \([F(1, 24) = 10.09, p = 0.004]\). In addition, a significant group by sentence interaction was found \([F(1, 24) = 5.44, p < 0.001]\): the PD patients showed a tendency to write progressively smaller (first sentence 11.21 cm, last sentence 10.89 cm), whereas in the healthy subjects sentence length slightly increased with the number of sentences written (first sentence 13.38 cm, last sentence 14.44 cm) (figure 2a). No significant effect of sentence was found, nor a significant task by group interaction.

Letter height
Letter height did not differ significantly between the PD group and healthy controls, but did differ significantly between the first task (0.63 cm) and the second task
Figure 1. Plots of the mean sentence length (1a) and the mean writing velocity (1b) in the handwriting task. Healthy subjects (filled squares); PD patients (filled triangles). Bars represent standard deviations.

Writing velocity
Writing velocity was significantly lower in the PD group (3.37 cm/s) than in the healthy controls (4.46 cm/s) \([F(1, 24) = 6.99, p = 0.014]\) (figure 1b). Overall, writing velocity differed significantly between the first task (3.71 cm/sec) and the second task (4.13 cm/s) and \([F(1, 24) = 15.97, p = 0.001]\). In addition, a significant group by sentence interaction was found \([F(1, 24) = 3.28, p = 0.008]\): the PD patients wrote progressively slower (first sentence 3.46 cm/sec, last sentence 3.31 cm/sec), whereas the healthy subjects wrote progressively faster in the course of the task (first sentence 4.32 cm/s, last sentence 4.67 cm/s) (figure 2c). No significant effect of sentence was found, nor a significant task by group interaction.

Pointing task
The transposition in the PD patients was significantly larger than in the healthy sub-
Figure 2. Plots of the mean sentence length (2a), the mean letter height (2b) and the mean writing velocity (2c) of the six different sentences in the handwriting task. Healthy subjects (filled squares); PD patients (filled triangles). Bars represent standard deviations.
jects \([F(1, 23) = 6.64, p = 0.017]\). Across all subjects, including the PD patients, the transposition was larger for the right hand (0.03 cm) than for the left hand (0.02 cm) \([F(1, 23) = 6.43, p = 0.018]\) and higher in the X direction (0.04 cm) than in the Y direction (0.02 cm) \([F(1, 23) = 36.74, p < 0.001]\). A significant direction by group interaction was found \([F(1, 23) = 9.32, p = 0.006]\): in the X direction, the PD patients (0.05 cm) performed significantly worse compared to the healthy subjects (0.03 cm). No significant side by group and period by group interactions were found.

Repeated measures ANOVA for velocity of transposition did not reveal a significant group effect. Across all subjects, including the PD patients, velocity was significantly higher in the X direction \([F(1, 23) = 6.34, p = 0.019]\) than in the Y direction. No significant effect was found for side or period, nor any significant interactions.

**Aiming task**

Compared to the healthy subjects, the PD patients did not show a prolonged movement time for the aiming task as a whole. Across all subjects, i.e. including the PD patients, movement time in on-the-target condition (0.55 s) was significantly slower than in the beyond-the-target condition (0.40 s) \([F(1, 24) = 7.39, p = 0.012]\). In addition, there was a significant group by target interaction \([F(1, 24) = 4.88, p = 0.037]\): the PD patients performed the on-the-target version much slower than the beyond-the-target version (0.65 vs. 0.37 s), whereas in the controls movement time in the on-the-target version was similar to that in the beyond-the-target version (0.46 vs. 0.43 sec).

No significant differences in latency were found between the PD group and healthy subjects. Also no significant effect of target was found, nor a significant group by target interaction.

**Fitts’ task**

No significant difference in movement time was found between the PD group and the group of healthy controls. All subjects, including the PD patients, performed the Fitts’ task with long distance and large target significantly faster (0.53 cm/sec) than the Fitts’ task with long distance and small target (0.68 cm/sec) \([F(1, 24) = 70.97, p = 0.000]\). A similar result was found for the Fitts’ task with short distance: large target 0.70 cm/sec vs. small target 0.51 cm/sec \([F(1, 24) = 138.44, p < 0.001]\). No significant interaction effects were found.

With regard to latency, no significant effects of target, distance or group were found, nor any significant interactions. Similar results were obtained when analyzing the result of the long distance trials only.
DISCUSSION

The results of the present study show that newly diagnosed, untreated PD patients are impaired in performing complex unimanual upper limb motor tasks in comparison to healthy subjects. They appear to be particularly impaired in the handwriting task, exhibiting reduced sentence length and writing velocity, and a decrease in letter height in the course of writing. An aiming task with target was performed slower by the PD patients than the same task without target. In the pointing task, PD patients showed increased transposition of the pen above the digitizer.

Previous studies have shown that in mildly to moderately affected, medicated PD patients (Hoehn and Yahr stages 1-3), stroke duration is normal, whereas stroke size is reduced only in tasks involving increased processing demands or a stroke size of more than 1.5 cm\(^8,9,15\). Contreras et al.\(^{16}\) found micrographia in only 5 out of 17 PD patients tested. The results of the present study show that in PD patients both size and speed of handwriting are reduced even without specific task demands. The differences between our observations and those in previous studies most likely reflect important differences in study population. In the present study, all PD patients were drug naïve, whereas in all previous studies PD patients were treated and tested either in the “on” phase of optimally balanced anti-parkinsonian medication or in a “practically defined off state”, i.e. not having used their usual medication for the last 12 hours prior to testing. The use of dopaminergic medication, even when tested in “practically defined off state”, may at least partly have masked changes in handwriting. Furthermore, we tested PD patients within a few weeks following the clinical diagnosis, whereas in previous studies disease duration was much longer and ranged between 0.5 and 22 years from the clinical diagnosis. The present study therefore provides a reliable view of upper limb motor function in the earliest clinical stages of PD, uninfluenced by any short- or long-term effects of dopaminergic medication.

The reduction in movement time in the aiming task with accuracy constraint compared to the aiming task without accuracy constraint can be interpreted as an early manifestation of bradykinesia. This corroborates previous results concerning PD patients in more advanced stages of the disease and on dopaminergic medication\(^{12}\).

The pointing task involves several aspects of motor function, including proprioception. Previous studies in medicated PD patients (Hoehn and Yahr 1-4) revealed impaired unilateral elbow-joint position sense\(^{17,18}\). Although the results of the pointing task in the present study may seem to confirm these observations and extend them to newly diagnosed, untreated PD patients, other aspects of motor function might be involved as well in the particular task used.

Surprisingly, the Fitts’ task, which involved similar terminal accuracy demands as the aiming task, did not reveal significant group differences. According to a previ-
ous report, parkinsonian patients in a more advanced stage of the disease have difficulty in executing larger movements (target size held constant) and movements to smaller target sizes (target separation held constant)\(^1\). The most likely explanation is a difference in average disease duration between our study and the study by Sanes and colleagues. Although disease duration is not specifically reported in the latter study, all but one of the PD patients were using dopaminergic medication, implying a longer disease duration than that of our newly diagnosed, drug-naive group of PD patients. An alternative explanation for the lack of impairments of the PD patients on the Fitts’ task we used is a methodological difference between the Fitts’ task used in this study and that used in the study by Sanes and colleagues. The Fitts’ task in the present study consisted of 32 rapid pen movements in four different conditions presented on paper. In contrast, Sanes and colleagues evaluated the movement of a hand-held stylus between two targets whose size and distance were systematically varied (size between 1.0 mm and 4.0 cm, distance between 4.0 mm and 32.0 cm). Possibly, longer trial distances are more sensitive to subtle motor dysfunction. This might also explain the discrepancy within the present study between the results of the Fitts’ task (trial distances 4.5 and 7 cm) and the aiming task (trial distance 25 cm). Obviously, the present results in a selected group of PD patients do not bring Fitts’ law in general into question.

Considering the differences in performing complex unimanual upper limb motor tasks between newly diagnosed, untreated PD patients and healthy subjects, the assumption can be made that subtle motor impairments may also be present in the preclinical phase of PD. This assumption is consistent with the results of a number of previous studies. Increased movement time and latency have been reported in early stage PD patients using a task that involved movement towards a designated target\(^1\). In addition, changes in handwriting and handgrip force have been noted in the subjectively unaffected arm of early stage PD patients\(^2\). Lastly, impairments of wrist flexion and extension were found in early stage PD patients (Hoehn and Yahr stages 2 or 2.5)\(^2\). Since they are easy to perform, tests of upper limb motor function might be considered as a potential component of early diagnostic test batteries for PD. In the present study, there was overlap at the individual level in performance of complex unimanual upper limb motor tasks between healthy subjects and PD patients. This would seem to limit the expected contributory value of upper limb motor tasks to early diagnostic test batteries for PD. Nevertheless, future studies in populations at increased risk for PD are necessary to fully resolve this issue.

In conclusion, the results of the present study in \textit{de novo}, untreated patients with PD, demonstrate that an impairment in performing tasks involving complex unimanual upper limb movements is a very early characteristic of PD.
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REFERENCES