KU LEUVEN

GROEP BIOMEDISCHE WETENSCHAPPEN

FACULTEIT BEWEGINGS- EN REVALIDATIEWETENSCHAPPEN

Assessment of writing deficits in Parkinson's disease with a writing tablet: a pilot study

door Sanne Broeder

masterproef aangeboden tot het behalen van de graad van Master of Science in de revalidatiewetenschappen en kinesitherapie

o.l.v.
prof. dr. A. Nieuwboer, promotor

m.m.v. E. Nackaerts

LEUVEN, 2013

KU LEUVEN

GROEP BIOMEDISCHE WETENSCHAPPEN

FACULTEIT BEWEGINGS- EN REVALIDATIEWETENSCHAPPEN

Assessment of writing deficits in Parkinson's disease with a writing tablet: a pilot study

door Sanne Broeder

masterproef aangeboden tot het behalen van de graad van Master of Science in de revalidatiewetenschappen en kinesitherapie

o.l.v.
prof. dr. A. Nieuwboer, promotor

m.m.v. E. Nackaerts

LEUVEN, 2013

Opgesteld volgens de richtlijnen van *Movement Disorders*

WOORD VOORAF

Deze masterproef kwam tot stand in het kader van het behalen van het diploma Master in de Revalidatiewetenschappen en Kinesitherapie aan de KU Leuven. Graag wil ik in dit voorwoord mijn oprechte dank betuigen aan alle mensen die een bijdrage geleverd hebben tot de verwezenlijking van deze masterproef.

In de eerste plaats gaat mijn dank uit naar mijn promotor prof. dr. Alice Nieuwboer die mij de kans heeft geboden om mij in dit onderwerp te verdiepen. Haar vakkundige begeleiding, motivatie en opbouwende feedback hebben een belangrijke bijdrage geleverd aan de realisatie van mijn masterproef. Tevens wil ik mijn co-promotor, dra. Evelien Nackaerts, bedanken voor de aangename samenwerking en steun. Zij was nauw betrokken bij mijn onderzoek en heeft mij de nodige feedback en inzichten gegeven. Graag wil ik ook alle participanten die deelnamen aan deze pilootstudie bedanken voor hun inzet en bereidwillige medewerking.

In het bijzonder wil ik mijn vriend en mijn moeder bedanken voor hun steun, zowel tijdens mijn studie als tijdens het schrijven van deze masterproef. Hugo, bedankt dat je altijd voor me klaarstond. Mama, bedankt voor het onvoorwaardelijke vertrouwen in mij.

Ik wil mijn vrienden bedanken die er altijd voor me waren en die mij op de nodige momenten ontspanning bezorgd hebben. Ten slotte gaat mijn dank uit naar Tine, Bram en Myrthe voor het nalezen van mijn masterproef en het geven van commentaar.

’s-Hertogenbosch, 18 mei 2013 S.B.

SITUERING

Deze masterproef is gekaderd in het doctoraatsproject 'Neuroplasticiteit in de ziekte van Parkinson: consolidatie van motorisch leren en de gerelateerde veranderingen in hersenactiviteit', wat een deelproject is binnen het lopende onderzoek van de Onderzoeksgroep Neuromotorische Revalidatie van de Faculteit Bewegings- en Revalidatiewetenschappen aan de KU Leuven. Binnen deze groep is er een onderverdeling in pelvische reëducatie en in neuromotorische revalidatie bij volwassenen en kinderen. Deze masterproef valt specifiek in het domein van de neuromotorische revalidatie dat de nadruk legt op onderzoek naar patiënten met de ziekte van Parkinson.

De ziekte van Parkinson is wereldwijd een veelvoorkomende neurologische aandoening bij ouderen die wordt gekenmerkt door typische motorische en niet-motorische symptomen.[1,2] In een recente systematische review werd, op basis van wereldwijde epidemiologische studies, de incidentie van de ziekte van Parkinson op 10 tot 13 per 100.000 personen per jaar geschat.[1] In diezelfde studie werd geconcludeerd dat de gemiddelde leeftijd waarop de symptomen beginnen tussen de 62 en 70 jaar is, met een piekincidentie tussen de 70 en 79 jaar. Aangezien de ouderenpopulatie wereldwijd blijft toenemen, is er een stijging in het aantal patiënten met de ziekte van Parkinson te verwachten en is het dan ook van belang om extra aandacht te hebben voor deze patiëntenpopulatie.

De voornaamste klinische karakteristieken van de ziekte van Parkinson (i.c. tremor, rigiditeit, akinesie en posturale instabiliteit) leiden tot beperkingen in het verrichten van algemene dagelijkse activiteiten en een verminderde levenskwaliteit.[2,3] Meer specifiek, veel patiënten ervaren vaak al in een vroeg stadium problemen in fijn motorische taken en sequentiële taken, zoals schrijven.[4,5] Tot op heden is de ziekte van Parkinson echter een ongeneeslijke aandoening met een progressief karakter en bestaat de behandeling voornamelijk uit het verlichten van symptomen. Desalniettemin, is uit onderzoek gebleken dat patiënten met de ziekte van Parkinson het vermogen tot normaal bewegen niet verloren zijn, maar dat zij met behulp van therapie en oefening hun bewegingsbeperkingen kunnen verminderen.[6-10] Bovendien werd aangetoond dat patiënten met de ziekte van Parkinson nog steeds in staat zijn om nieuwe motorische taken te leren.[11]

In de literatuur is echter nog geen consensus over de oorzaak en specifieke triggers van de problemen die patiënten met de ziekte van Parkinson tijdens fijn motorische taken ervaren. Bovendien werd er tot nu toe weinig onderzoek verricht naar het opnieuw aanleren van een gekende motorische taak die wordt aangetast door de ziekte van Parkinson, zoals schrijven. Aangezien schrijven een belangrijke dagelijkse activiteit is, is het van belang om meer inzicht te verwerven in schrijfproblemen bij patiënten met de ziekte van Parkinson.

In de pilootstudie, die in het kader van mijn masterproef werd uitgevoerd, wordt een analyse gemaakt van schrijfproblemen bij patiënten met de ziekte van Parkinson in vergelijking met gezonde volwassenen. Hiervoor wordt er gebruik gemaakt van schrijfoefeningen op een digitaal schrijftablet en verschillende schrijftesten op papier. Daarnaast wordt er in een klinische testbatterij gepeild naar de emotionele, cognitieve en motorische eigenschappen van de deelnemers. De resultaten van dit onderzoek kunnen mogelijk bijdragen tot het opstellen van een optimaal trainingsprogramma voor het verbeteren van schrijfvaardigheden bij patiënten met de ziekte van Parkinson.

REFERENTIES

1. Muangpaisan W, Mathews A, Hori H, Seidel D. A Systematic review of the worldwide prevalence and incidence of Parkinson's disease. Journal of the Medical Association of Thailand. 2011; 94: 749–755.

2. Jankovic J. Parkinson's disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery & Psychiatry. 2008; 79: 368–376.

3. Hariz G-M, Forsgren L. Activities of daily living and quality of life in persons with newly diagnosed Parkinson's disease according to subtype of disease, and in comparison to healthy controls. Acta Neurologica Scandinavica. 2011; 123: 20–27.

4. Lees AJ, Hardy J, Revesz T. Parkinson's disease. The Lancet. 2009; 373: 2055–2066.

5. Elias de Oliveira M, Menegaldo LL, Lucarelli P, Andrade BLB, Büchler P. On the use of information theory for detecting upper limb motor dysfunction: An application to Parkinson's disease. Physica A. 2011; 390: 4451–4458.

6. Morris ME, Martin CL, Schenkman ML. Striding out with Parkinson disease: evidence-based Physical therapy for gait disorders. Physical Therapy. 2010; 90: 280–288.

7. Morris ME. Movement disorders in People with Parkinson disease: a model for physical therapy. Physical Therapy. 2000; 80: 578–597.

8. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Movement Disorders. 2008; 23: 631–640.

9. Allen NE, Sherrington C, Suriyarachchi GD, Paul SS, Song J, Canning CG. Exercise and motor training in people with Parkinson's disease: a systematic review of participant characteristics, intervention delivery, retention rates, adherence, and adverse events in clinical trials. Parkinson's Disease. 2012; 2012: 1–15.

10. Speelman AD, Van de Warrenburg BP, Van Nimwegen M, Petzinger GM, Munneke M, Bloem BR. How might physical activity benefit patients with Parkinson disease? Nature Reviews Neurology. 2011; 7 :528–534.

11. Nieuwboer A, Rochester L, Müncks L, Swinnen SP. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. Parkinsonism and Related Disorders. 2009; 15 Suppl 3: S53–S58

Assessment of writing deficits in Parkinson's disease with a writing tablet: a pilot study

ABSTRACT

Background: Patients with Parkinson's disease (PD) often show deficits in fine manipulative activities. Abnormalities in writing, a commonly used skill, are an early motor symptom of PD and may even be present before diagnosis. The purpose of this cross-sectional pilot study was to evaluate the sensitivity of specific writing tasks to assess writing deficits in PD.

Methods: 5 PD patients in the 'on'-phase of the medication cycle and 5 healthy age-matched control subjects performed different writing tasks in two sizes on a writing tablet. Writing amplitude and velocity were measured and the impact of writing pattern and visual cues were determined. An additional correlation analysis examined the relationship of writing performance with tasks on paper and manual dexterity measurements.

Results: PD patients showed deficits in writing performance compared to healthy controls. Significant pattern effects on amplitude of the sequential and varied writing tasks of both 0.6 cm and 1.0 cm letter sizes were found (resp. $p = 0.035$ and $p = 0.038$). In contrast, there was no apparent effect of visual cues on writing performance. Overall, scores of the '*Systematic Screening of Handwriting Difficulties'* and manual dexterity tests were correlated to writing amplitude.

Conclusion: The present study demonstrated that the writing tasks and the '*Systematic Screening of Handwriting Difficulties'* were capable of detecting writing deficiencies in PD. In addition, writing amplitude was influenced by the type of writing pattern. The results of this study will aid the development of target interventions to improve writing skills in PD patients.

Keywords*:* Parkinson's Disease, handwriting, visual cues, micrographia

1. INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta.[1] It causes typical motor symptoms including bradykinesia, tremor, rigidity and postural instability, as well as non-motor symptoms.[2] Motor dysfunctions in PD are known to occur in the axial part of the body. Less often it has been acknowledged that impairment of manual dexterity is common and frequently an early symptom of PD.[3,4] Moreover, patients with PD show such deficits in the execution of fine manipulative hand activities, e.g. writing. Despite the importance of manual skills in activities of daily living, upper limb motor performance and fine motor skills in PD have not been examined thoroughly.

Studies which have tried to characterize writing deficits in PD have demonstrated impairments in kinematic features of writing such as amplitude, variability, velocity, acceleration and movement duration.[5–13] In addition, patients with PD tend to drift in an upward direction and write progressively smaller and more cramped during writing tasks.[3] This phenomenon of progressively smaller writing and the use of hypometric movements during fine motor skills is defined as micrographia.[14,15] Recently, it was shown that micrographia occurs in approximately 63% of patients with PD.[15] Moreover, several studies described writing changes as an early motor symptom of PD that can be present and detected even before diagnosis.[3,5,16] For instance, using a graphics tablet, Ponsen *et al.* (2008) compared handwriting performance of newly diagnosed PD patients with healthy controls. *De novo* PD patients showed reduced sentence length and slower writing velocities as well as a progressive reduction in letter amplitude. Interestingly, in the same study, healthy controls showed an increase in sentence length and velocity in the course of writing.[5] Other studies have shown that normal writing size is typically kept constant within a range of 0.5 to 1.0 cm.[8,17] Patients with PD are able to write within this range, but are not able to double their stroke size when required.[13] Furthermore, in completing a drawing task in which target size and frequency were manipulated, significantly slower movements, less acceleration and smaller stroke sizes were produced by PD patients compared to healthy subjects.[18]

Whereas several studies showed deficits in writing in PD, inconsistencies can also be found in the literature. A recent study from Bidet-Ildei *et al.* (2011) did not observe micrographia in PD patients.[19] Moreover, when patients executed a free writing task in the Korean language, no difference in letter size was found compared to healthy subjects.[20] Similarly, other studies found no significant difference in stroke duration between PD patients and healthy subjects.[18,21] Although it remains unclear which hallmark mechanisms contribute to writing performance in PD patients, Contreras-Vidal *et al.* (1995) suggested the following neural network model. Due to dopamine depletion in the basal ganglia, less pallidothalamic gating signals are produced. This reduction affects the ability to control variable

movement speed which leads to the production of smaller-than-normal movement amplitudes in PD patients.[22,23] The irregular and reduced thalamic signals are projected to motor and premotor areas that are involved in the execution of handwriting. Therefore, deficits in speed and size during writing, as seen in patients with PD, might be caused by specific disruptions and neurochemical imbalances in basal ganglia output signals.[23]

Only a few studies have investigated the effect of interventions to improve writing abnormalities in patients with PD. Some studies examined the influence of dopaminergic medication and deep brain stimulation on handwriting performance in PD patients. However, these interventions only resulted in improvements in writing duration while no improvements in writing size were found.[19,24] Moreover, when compared with healthy subjects, PD patients in the 'on'-phase of the medication cycle did not reach the same level of writing performance.[25,26] It has also been suggested that writing deficits in PD can be reduced by the use of cues.[6,27–29] According to a definition provided by Nieuwboer *et al.* (2007), cues are 'external temporal or spatial stimuli which facilitate movement initiation and continuation'.[30] It was shown that PD patients write with a more normal amplitude when visual cues or auditory reminders are present in contrast to when they are not.[6] Bryant *et al.* (2010) also demonstrated an increase in the length of words and letter size after practicing with visual cues.[28] More recently, the influence of different cueing types on drawing was examined. Both patients with PD as well as healthy controls benefited more from auditory and verbal cues than from visual cues to reduce variability of amplitude and coordination in a drawing task. However, since this study did not include a non-cued condition, no conclusions could be drawn about the benefit of visual cues compared to no cues.[27] Taken together, these results give evidence for the effectiveness of providing external cues to improve handwriting in patients with PD. Though, as these studies only examined the short-term effects of external cues, it remains unclear whether there are any prolonged effects of external cues on fine motor skill performance in PD patients. The clinical benefit of such external cues may be related to the existence of different pathways in the brain for internally and externally generated sequential movements such as writing. When performing internally generated motor sequences, the basal ganglia and supplementary motor areas play an important role.[31,32] When sequential movements are externally, generated the cerebellum and parietal-premotor networks, and not the basal ganglia, are more involved.[31,33] Therefore, external stimuli or cues might be useful as compensatory mechanisms for bypassing the deficient brain structures in PD patients and improving sequential and continuous movement performance.[31,34]

It can nevertheless be argued that far too little attention has been paid to optimal practice strategies to improve writing in PD patients. These patients do not lose their normal moving ability, but can obtain normal movements by specific physical therapy combined with optimal pharmacotherapy.[35,36] More specifically, existing evidence has suggested that exercise may improve movement impairments

and physical functioning in PD patients.[37–40] An important requirement for long-term effects of these practice strategies is the ability for motor learning. Motor learning has been studied from different perspectives and a distinction between motor sequence learning (i.e. acquisition of a new sequence of movements) and motor adaptation (i.e. adaptation to environmental changes) can be made.[41–43] Moreover, it has been shown that the basal ganglia play an important role in motor sequence learning, while the cerebellum and related structures are crucial in the consolidation of adapted movements.[43–48] It is therefore suggested that due to problems in the basal ganglia, PD patients may experience problems in the acquisition of new motor sequences.[49] Both behavioral and brain imaging studies have investigated whether motor sequence learning is possible in PD patients. Swinnen *et al.* (2000) found that they are able to improve their upper limb performance in a bilateral drawing task as a result of practice.[50] These results were confirmed by a recent meta-analysis which showed decreased movement times in upper extremity reaching tasks after practice.[51] Furthermore, it was demonstrated that PD patients and age-matched controls learn and retain a posture sequence task and a buttoning task in a similar way. However, patients needed more practice before obvious improvements were observed.[52] Corresponding results were obtained in a study from Stephan *et al.* (2011) where it was shown that patients with PD were capable of learning two consecutive motor sequences, but needed more time to learn than healthy subjects.[53] Interestingly, it was also observed that patients with PD recruited additional neural regions in the brain to reach similar levels of performance, including tissue of the cerebellum.[54] Moreover, conforming results were found in a functional magnetic resonance imaging (fMRI) study where PD patients, compared to healthy controls, showed more activity in the cerebellum and related areas after training in a sequential finger task.[55] These findings imply that, under some pathological conditions, the corticocerebellar system might have the ability to compensate for functional impairments of the corticostriatal system.[49,55] Motor sequence learning and re-learning of well-known tasks in patients with PD by repetitive practice might therefore still be possible.[29,56] Hence, it can be concluded that practice of motor skills provides valuable opportunities to learn new motor sequences and achieve motor refinement in PD patients. This statement is confirmed by a recent review on the topic of relearning of writing skills in PD.[29]

Writing is a commonly used skill and impairments in writing can lead to problems in daily life. Accordingly, it is important to search for strategies to tackle these problems. Since studies have shown that patients with PD are able to learn new motor skills, improve performance and benefit from practice, a specific training program could improve their writing skills. However, most of the available studies on writing are small-scale and only refer to a few aspects of writing in PD patients. Therefore, further knowledge about the characteristic deficits in writing and the effect of practice on writing performance in PD is required to be able to target training appropriately. The purpose of the present pilot study was to evaluate the sensitivity of specific writing tasks to assess writing deficits in patients with PD compared to age-matched controls. Accordingly, an experiment was designed in which

participants were required to write different figures and patterns on a writing tablet. These writing tasks were presented in two sizes (0.6 cm and 1.0 cm) and the influence of visual cues and type of writing pattern on writing performance was examined. Furthermore, to examine the relationship of subjects' writing performance with tasks on paper and dexterity measurements, a correlation analysis was conducted. It was hypothesized that PD patients would show more deficits in writing than healthy controls during these different tasks. Smaller writing amplitudes, lower writing velocities and more variability were expected in the PD patient group. It was also predicted that patients with PD would benefit more from external visual cues than the healthy controls. The outcomes of this study should provide useful information for further research, in order to develop an efficient training program to improve writing skills in PD patients.

2. MATERIALS AND METHODS

2.1 Subjects

In this cross-sectional study a total of ten right-handed subjects participated, five PD patients (1 woman, 4 men) and five age-matched control subjects (2 women, 3 men). Patients were recruited from the Movement Disorders Clinic of the University Hospital Leuven and they were included based on the following criteria: (i) idiopathic PD, diagnosed according to the United Kingdom PD Society Brain Bank criteria[57], (ii) right-handed and (iii) Hoehn and Yahr (H&Y)[58] stage I to III in the 'on'-phase of the medication cycle. The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[59] part III and the Montreal Cognitive assessment (MoCA)[60] were respectively used to assess patients' motor function and cognitive function. Exclusion criteria were an H&Y stage greater than III and daltonism. During the experiment all PD participants were on optimal medication therapy, i.e. approximately one hour after last drug intake. Five healthy age-matched control subjects were recruited by word of mouth. None of the healthy participants had a history of other neurological disorders. Study design and protocol were approved by the local Ethics Committee (KU Leuven) in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki, 1967). After full explanation of the procedures, a written informed consent was obtained from all participants prior to the experiment.

2.2 Procedure

Participants were tested once (± 3 hours) at the de Department of Rehabilitation Sciences of the KU Leuven. First, baseline demographics and current medication schemes were registered. To measure manual dexterity, the Purdue Pegboard Test[61] was used prior to the writing tasks. Participants were then instructed to perform different writing tasks on paper as well as on a writing tablet. The order of the writing tasks was randomized. Finally, both PD patients and healthy controls completed a clinical test-battery including MoCA, Manual Ability Measure (MAM-16)[62] and Hospital Anxiety and Depression Scale (HADS).[63,64] PD patients also completed the MDS UPDRS-III, the revised Freezing of Gait Questionnaire (NFOGQ)[65] and the H&Y staging scale.

2.3 Apparatus and tasks

Writing movements were registered using a newly developed writing tablet with a sampling frequency of 200 Hz. The writing tablet was composed of a touch screen (Fujitsu Components Europe) with a cross-section of 6.4 inches (131.20 x 100.10 mm) and a resolution of 32.5 micrometer (µm). Underneath this touch screen, a display (Flat Display Technology) was installed to provide

participants with online feedback of their movements. The writing tablet was driven by a laptop and incorporated into a frame to improve writing comfort. To avoid measurement errors, all subjects were instructed to touch the writing tablet with a matching pencil only and not with their hand or forearm. In addition, subjects also had to write several tasks on a blank paper with a regular ballpoint pen. Participants were seated in a chair at a desk during all tasks.

2.3.1 Writing tasks on the writing tablet

Participants were asked to write different tasks in a random order on the writing tablet. The writing tasks were devised so that various subcomponents of writing were tested (Figure 1). A-C included writing tasks which did not involve movement of the hand over the pad or paper and consisted of loops, reversed loops and a continuous-eight figure. D and E probed the ability to produce continued sequences while F and G tested the capacity to vary amplitude sizes. All these exercises signified pre-writing tasks reflecting components of writing per se. The different writing tasks were presented in separated blocks in a randomized order. Before each writing task, participants performed several practice trials both on paper and on the writing tablet to become familiar with the different figures. Each task started with a first beep that indicated the participant to move the pen towards the starting position of the task. A second beep stated the start of the task. The loop, reversed loop and continuous-eight figures were performed four times for 27 seconds with a short interval of rest (6 seconds) between each measurement and each figure was written in two sizes: 0.6 cm and 1.0 cm. Moreover, to establish the influence of an external visual cue on task performance, the tasks were presented in two conditions: with and without a cue. Visual cues consisted of differently colored target zones (grey, yellow and blue) with a band width of 2 mm. In the cued condition participants were instructed to target the middle of the colored zones. These targets disappeared after 2 seconds in the non-cued condition and participants were then instructed to maintain the indicated writing size. Furthermore, sequential and varied writing tasks were executed, only with cues. These writing tasks were also performed four times for 27 seconds and in two sizes (0.6 cm and 1.0 cm).

Figure 1. Writing tasks on the writing tablet: (A) loop figure, (B) reversed loop figure, (C) continuous-eight figure, (D) small sequence, (E) large sequence, (F) varied small-large and (G) varied large-small.

2.3.2 Writing tasks on paper

The tasks on the writing tablet were randomly alternated with tasks on paper. Two tests on paper were performed: the Alphabet-task, a subtest from the Process Assessment of the Learner test battery for reading and writing (as cited in Berninger *et al*. 2002)[66] and the '*Systematic Screening of Handwriting Difficulties (SOS)'*.[67] For the Alphabet-task, participants were instructed to write all letters of the alphabet in cursive writing. In addition, for the SOS-test, participants were asked to copy as much as possible of a text within 5 minutes, with the instruction to write as neatly and quickly as in daily life.

2.4 Data processing

Data processing was performed using Matlab R2011b with a Butterworth filter to extract and filter the dependent variables from the writing tasks on the tablet. Previous studies demonstrated clear impairments in amplitude and velocity during writing tasks in patients with PD.[5,6,25] Therefore, for each participant, writing amplitudes (in cm) and velocities (in cm/s) were determined as an average for the up and down strokes of the different writing figures. Writing amplitude was defined as the distance between the most upper and lower part of an individual stroke. And writing velocity was determined by calculating the time that was necessary to complete these individual strokes. For the writing tasks on paper, data processing was performed manually. The number of letters of the alphabet (in correct order) written within 15 seconds as well as the total amount of seconds necessary for completing the whole alphabet were calculated for the Alphabet task. All written texts of the SOS-test were assessed with the associated evaluation form. Writing velocity (i.e. number of letters written in 5 minutes), writing quality and mean writing size were determined. More specifically, for writing quality only the first five lines were evaluated by considering the following criteria: (i) fluency of letter formation, (ii) fluency in connections between letters, (iii) regularity of letter height, (iv) space between words and (v) straightness of the sentences.[67]

2.5 Statistical analysis

Statistical analysis was performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago IL, USA). Due to the small sample sizes, non-parametric statistics were used to compare the median scores between and within groups. The Mann-Whitney U test was used for comparing differences in subject characteristics between healthy controls and PD patients. To evaluate the effect of visual cues on writing performance for the loops, reversed loops and continuous-eight figure in both groups, a Kruskal-Wallis test was conducted followed by post-hoc testing (Wilcoxon signed-rank tests). Differences in the sequential and varied writing tasks were analyzed by the Kruskal-Wallis test and a post-hoc Mann-Withney U test. Finally, Spearman's rank correlations were computed to compare

subjects' performance on (i) the sequential and varied writing tasks on the tablet and the two tasks on paper (SOS-test and Alphabet-task) and (ii) the sequential and varied writing tasks on the tablet and the dexterity measurements (Purdue Pegboard, MAM-16 and MDS-UPDRS question 2.7). Unless otherwise indicated, two-sided significance levels for all tests were set at $p < 0.05$.

3. RESULTS

3.1 Subjects

Clinical characteristics of the participants are shown in Table 1. Differences between PD patients and healthy controls in demographic and clinical characteristics were compared using the Mann-Whitney U test. No significant differences were found for age, gender and cognitive function. However, manual dexterity measured by the MAM-16 and Purdue Pegboard Test was significantly worse in PD patients. Moreover, compared with healthy controls, PD patients showed significantly poorer results for the SOS-test and for question 2.7 of the MDS-UPDRS regarding the presence of writing difficulties. These results imply that PD patients experienced more problems with normal writing on paper than healthy controls. Finally, significant differences between PD patients and healthy controls were found for the HADS depression subscale, indicating that PD patients showed more depressed feelings than healthy controls.

Table 1. Subject characteristics; median and interquartile range (25%-75%).

Parameter	PD patients	Controls	P-value
Age (years)	61.0 (50.5-70.5)	62.0 (50.0-70.5)	0.917
Gender (M/F)†	3/2	4/1	0.490
MoCA (0-30)	26.0 (23.5-28.0)	26.0 (23.5-29.0)	0.916
HADS			
- Anxiety subscale (0-21)	6.0 (5.0-10.0)	6.0 (1.5-6.5)	0.395
- Depression subscale (0-21)	10.0 (4.0-12.5)	1.0 (0.5-4.5)	0.028*
MAM-16 (0-64)	60.0 (52.5-61.0)	64.0 (64.0-64.0)	0.005*
SOS-test			
- Writing fluency	1.0 (1.0-2.0)	0.0 (0.0-0.5)	0.014*
- Regularity in writing size	2.0 (1.5-2.0)	1.0 (0.0-1.0)	0.014*
- Total score	4.0 (3.5-6.0)	1.0 (0.5-2.5)	0.011*
Alphabet task			
- Letters within 15 seconds	18.0 (13.5-20.0)	19.0 (14.0-24.0)	0.530
- Number of seconds full task	23.0 (20.0-30.0)	20.0 (17.0-30.5)	0.530
Purdue Pegboard			
- right-hand	8.0 (8.0-10.0)	12 .0 (11.0-13.5)	0.013*
- left-hand	7.0 (5.5-9.5)	11.0 (9.5-12.5)	0.036*
- bimanual	12.0 (9.0-16.0)	20.0 (16.0-21.0)	0.027*
- combination	15.0 (12.5-20.5)	25.0 (17.5-30.5)	0.059
MDS-UPDRS question 2.7	2.0 (1.0-3.0)	0.0 (0.0-0.0)	0.017*
Disease duration (years)	11.0 (8.0-15.5)	-	-
MDS-UPDRS III (0-132)	32.0 (24.0-39.5)	-	-
H&Y (0-V)	3.0 (2.0-3.0)	-	-
FOGQ (0-24)	7.0 (2.5-12.5)	-	-

* Groups significantly different at $P \leq 0.05$ (Mann-Whitney U); † Pearson Chi-Square used; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; MAM, Manual Ability Measure; SOS, Systematic Screening for Handwriting Difficulties; MDS-UPDRS, Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr staging scale; FOGQ, Freezing of Gait Questionnaire.

3.2 Tasks on writing tablet

3.2.1 Loops, reversed loops and continuous-eight figure

3.2.1.1 Amplitude in 0.6 cm condition

A non-parametric analysis using a Kruskal-Wallis test showed no significant differences between the amplitudes of PD patients and healthy controls. This pertains to both the cued and the non-cued conditions for the loops, reversed loops and continuous-eight figures ($p \geq 0.05$). With regard to the reversed loops writing task, however, a within-group effect of cue-type was found using the Wilcoxon signed-rank test. Both PD patients and healthy controls showed a tendency to write bigger in the non-cued condition (resp. $p = 0.043$ and $p = 0.043$, Table 2). For the loop and continuous-eight figures, no significant within-group differences were found ($p \geq 0.05$).

3.2.1.2 Amplitude in 1.0 cm condition

In the larger writing size condition no overall significant differences for amplitude between PD patients and healthy controls in the cued and non-cued conditions were found ($p \geq 0.05$). A within-group analysis using the Wilcoxon signed-rank test did reveal a significant difference in the amplitude of the reversed loop figure in PD patients as well as a significant difference in the amplitude of the loop figure in the control group between the cued and non-cued conditions (resp. $p = 0.043$ and $p = 0.043$, Table 2). Interestingly, PD patients wrote the reversed loop figure bigger when cues were not present whereas healthy controls wrote the loop figure smaller in the non-cued condition compared to the cued condition. The box-plots in Figure 2 illustrate the amplitude of the reversed loop figure in the 1.0 cm condition. No significant within-group differences were found for amplitude in the loop and continuous-eight figures in PD patients ($p \geq 0.05$) and in the reversed loop and continuous-eight figures in the control group ($p \geq 0.05$).

Table 2. Differences in writing tasks on the writing tablet (loops, reversed loops and continuous-eight figure) between control subjects and PD patients in the cued and non-cued condition.[†]

Writing tasks	Patient group (N=5) With cue	Patient group (N=5) Without cue	Within-group p-value	Control group (N=5) With cue	Control group (N=5) Without cue	Within-group p-value	p-value
Small (0.6 cm)							
Loops							
Amplitude	0.566 (0.520-0.593)	0.559 (0.483-0.644)	0.686	0.603 (0.527-0.617)	0.579 (0.560-0.580)	0.500	0.917
Velocity	1.408 (0.759-1.867)	1.892 (0.644-1.992)	0.345	1.286 (1.217-1.568)	1.332 (1.230-1.620)	0.500	0.946
Reversed loops							
Amplitude	0.599 (0.552-0.622)	0.665 (0.588-0.703)	0.043*	0.609 (0.566-0.613)	0.624 (0.617-0.722)	0.043*	0.309
Velocity	1.068 (0.721-1.717)	1.648 (0.777-2.007)	0.043*	1.321 (1.282-1.345)	1.475 (1.412-1.520)	0.043*	0.684
Continuous-eight figure							
Amplitude	0.555 (0.554-0.590)	0.536 (0.487-0.574)	0.500	0.576 (0.571-0.606)	0.590 (0.543-0.602)	0.686	0.421
Velocity	1.543 (1.418-1.901)	1.549 (1.153-2.318)	0.500	1.713 (1.622-1.863)	1.804 (1.700-1.836)	0.686	0.983
Large (1.0 cm)							
Loops							
Amplitude	0.896 (0.790-0.957)	0.818 (0.702-0.870)	0.080	0.878 (0.853-0.956)	0.809 (0.766-0.859)	0.043*	0.635
Velocity	1.516 (1.050-2.989)	1.743 (1.082-3.241)	0.043*	2.114 (1.731-2.353)	1.956 (1.534-2.409)	0.225	0.927
Reversed loops							
Amplitude	0.995 (0.868-1.003)	1.003 (0.958-1.155)	0.043*	1.025 (0.889-1.031)	1.061 (0.915-1.066)	0.500	0.690
Velocity	1.640 (0.857-2.165)	2.544 (0.928-2.548)	0.043*	1.895 (1.763-1.953)	2.045 (1.875-2.058)	0.080	0.738
Continuous-eight figure							
Amplitude	0.931 (0.918-0.943)	0.910 (0.769-0.916)	0.225	0.938 (0.921-1.032)	0.904 (0.801-0.988)	0.080	0.428
Velocity	1.861 (1.859-2.540)	1.877 (1.719-2.994)	0.138	2.417 (2.241-2.550)	2.270 (2.265-2.337)	0.686	0.959

[†] Kruskal-Wallis test, median and Tukey's Hinges percentiles (25%-75test
%): * within-group significantly different at $P \leq 0.05$ by a post-hoc Wilcoxon signed-rank test.

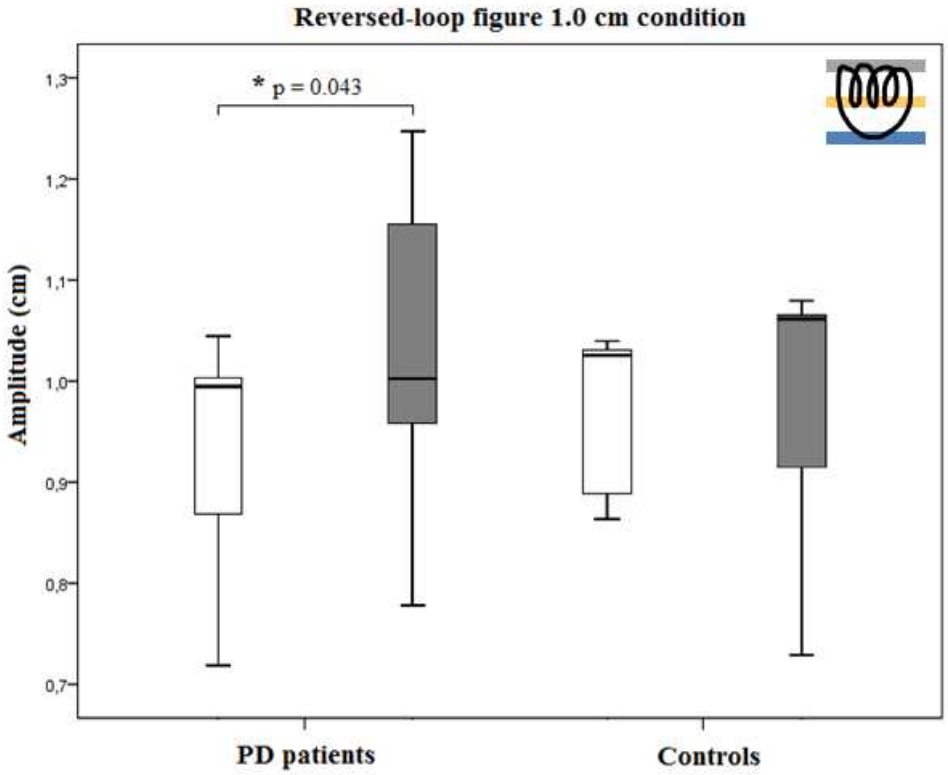

Figure 2. Box plot representation of the amplitudes of the reversed loop figure in the cued and non-cued conditions for PD patient and control groups. The white boxes represent the results for the cued condition and shaded boxes represent the results for the non-cued condition. The box plots illustrate the median value (horizontal center line), the 25th and 75th Tukey's Hinge percentiles (boxed area) and the maximum and minimum values (whiskers): * within-group significantly different at $p \leq 0.05$ by a Wilcoxon signed-rank test.

3.2.1.3 Velocity in 0.6 cm condition

Results of a Kruskal-Wallis test showed no statistically significant differences between the writing velocity of PD patients and healthy controls in the cued and non-cued condition of the loops, reversed loops and continuous-eight figures ($p \geq 0.05$). A within-group analysis rather revealed a significant effect of cue-type for both PD patients and healthy controls for the reversed loop figure (resp. $p = 0.043$ and $p = 0.043$, Table 2). When cues were present, both PD patients and healthy controls wrote slower compared to the non-cued condition. No significant within-group differences were found for the loop and continuous-eight figures ($p \geq 0.05$).

3.2.1.4 Velocity in 1.0 cm condition

In the larger writing size condition, non-parametric analysis using a Kruskal-Wallis test showed no overall statistically significant differences between the writing velocity of PD patients and healthy controls in the cued and non-cued condition ($p \geq 0.05$). However, in PD patients a within-group effect of cue-type for the loops and reversed loops was found using the Wilcoxon signed-rank test. PD patients wrote both the loop and reversed loop figures with a slower writing velocity when cues were present compared to the non-cued condition (resp. $p = 0.043$ and $p = 0.043$, Table 2). The box-plots in

Figure 3 illustrate this result for the velocity of the reversed loop figure in the 1.0 cm condition. In addition, Figure 3 shows a considerably higher variability in writing velocity in the PD patient group compared with healthy controls in both the cued and non-cued condition (Interquartile Ranges (IQR): IQR_{PDcued} = 2.439, $IQR_{PDnon\text{-}cued}$ = 2.789, $IQR_{CTRcued}$ = 0.402, $IQR_{CTRnon\text{-}cued}$ = 0.428). No significant within-group differences were found for the continuous-eight figure in the PD group ($p \geq 0.05$). Interestingly, in the control group, no significant within-group differences were found in writing velocity for all three figures ($p \geq 0.05$).

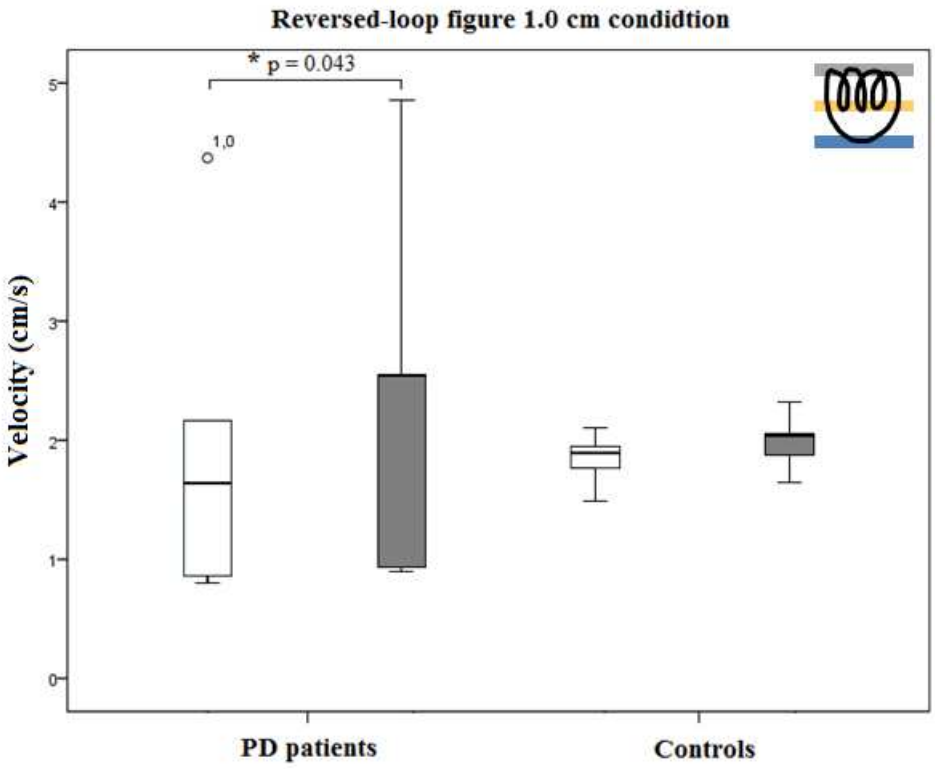

Figure 3. Box plot representation of the velocities of the reversed loop figure in the cued and non-cued conditions for PD patient and control groups. The white boxes represent the results for the cued condition and shaded boxes represent the results for the non-cued condition. The box plots illustrate the median value (horizontal center line), the 25th and 75th Tukey's Hinge percentiles (boxed area) and the maximum and minimum values (whiskers): * within-group significantly different at $p \leq 0.05$ by a Wilcoxon signed-rank test.

3.2.2 Sequential and varied writing tasks

3.2.2.1 Amplitude in 0.6 cm condition

There was a significant overall pattern effect on amplitude in the small writing size condition for the sequential and varied tasks on the writing tablet, indicating performance was different between groups ($p = 0.035$, Table 3a). As shown in Figure 4, the median amplitude for the sequence and both varied patterns was smaller for PD patients compared with healthy controls. Moreover, PD patients showed a

remarkable higher variability in writing amplitude than healthy controls in all three patterns (resp. $IQR_{PDsequence}$ = 0.141, $IQR_{PDsmall\text{-}large}$ = 0.239, $IQR_{PDlarge\text{-}small}$ = 0.171, $IQR_{CTRsequence}$ = 0.075, $IQR_{CTRsmall\text{-}large}$ = 0.104, $IQR_{CTRsmall\text{-}large}$ = 0.037). Furthermore, between-group analysis using a Mann-Whitney U test showed that PD patients wrote the 0.6 cm sequence with a significantly smaller amplitude than healthy controls (p = 0.028, Table 3a and Figure 4). No significant between-group differences were found in amplitude for the small-large and large-small patterns of the varied tasks between PD patients and healthy controls ($p \geq 0.05$).

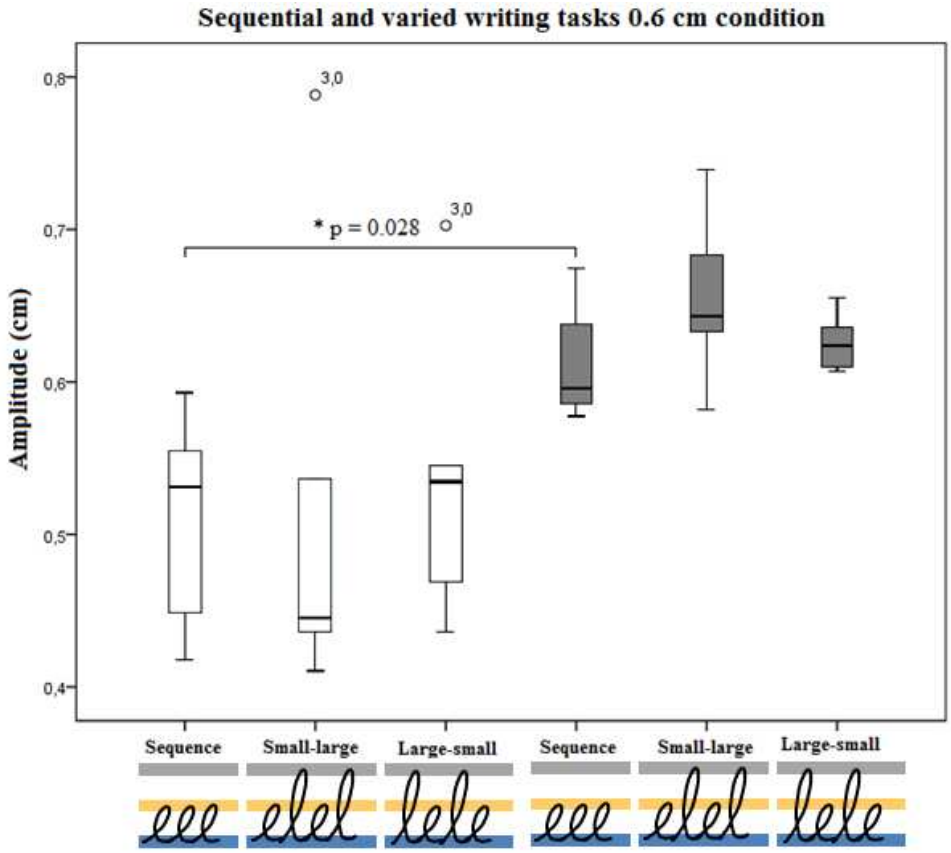

Figure 4. Box plot representation of the amplitude of the sequential and varied tasks on the writing tablet in the 0.6 cm condition for PD patient and control groups. The white boxes represent the results for the PD patient group and shaded boxes represent the results for the control group. The box plots illustrate the median value (horizontal center line), the 25th and 75th Tukey's Hinge percentiles (boxed area) and the maximum and minimum values (whiskers): * within-group significantly different at $p \leq 0.05$ by a Wilcoxon signed-rank test.

3.2.2.2 Amplitude in 1.0 cm condition

In the large writing size condition, non-parametric analysis using a Kruskal-Wallis test showed significant overall pattern effects for the amplitude of the sequential pattern as well as for the varied tasks (p = 0.038, Table 3a). As shown in Figure 5, the median amplitude for the sequential and both varied task patterns was smaller for PD patients compared with healthy controls. Moreover, PD patients showed a remarkably higher variability in writing amplitude than healthy controls for all three

patterns (resp. $IQR_{PDsequence}$ = 0.233, $IQR_{PDsmall\text{-}large}$ = 0.102, $IQR_{PDlarge\text{-}small}$ = 0.234, $IQR_{CTRsequence}$ = 0.104, $IQR_{CTRsmall\text{-}large}$ = 0.071, $IQR_{CTRsmall\text{-}large}$ = 0.098). However, a Mann-Whitney U between-group analysis revealed no significant differences in amplitude for the sequence pattern and large-small pattern of the varied task between PD patients and healthy controls ($p \geq 0.05$). Interestingly, significant between-group differences were found for the small-large pattern of the varied task. PD patients wrote the small-large pattern with a significantly smaller amplitude than healthy controls ($p = 0.016$, Table 3a and Figure 5).

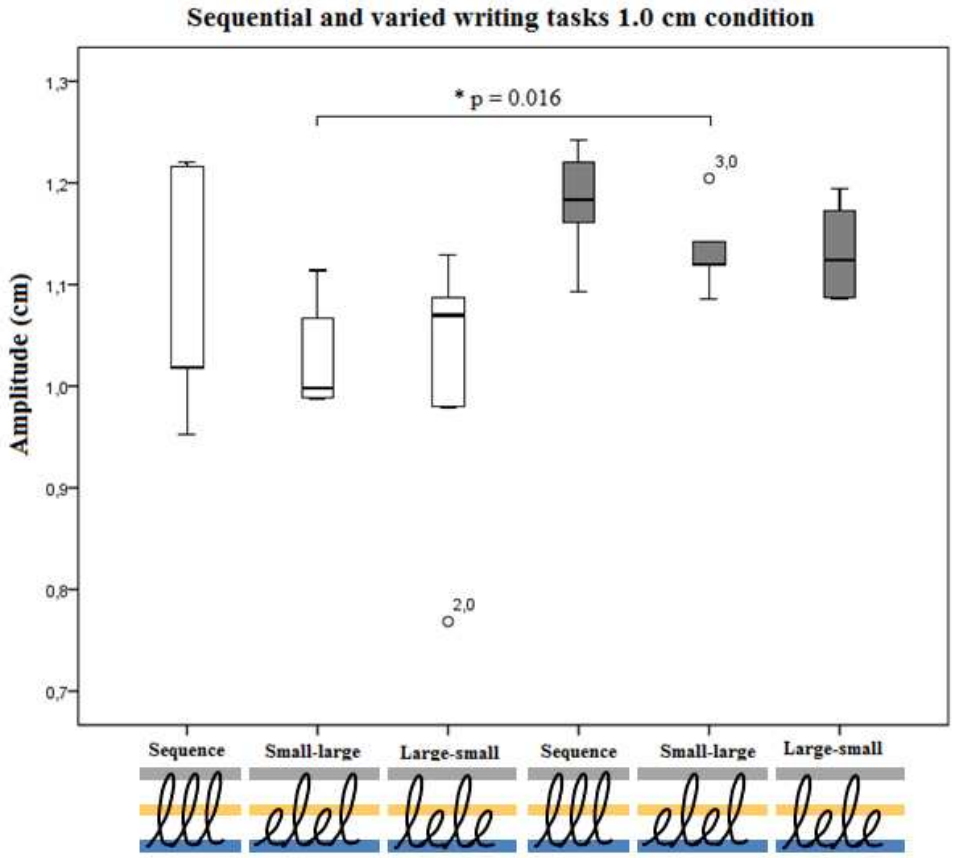

Figure 5. Box plot representation of the amplitude of the different sequential and varied tasks on the writing tablet in the 1.0 cm condition for PD patient and control groups. The white boxes represent the results for the PD patient group and shaded boxes represent the results for the control group. The box plots illustrate the median value (horizontal center line), the 25th and 75th Tukey's Hinge percentiles (boxed area) and the maximum and minimum values (whiskers): * within-group significantly different at $p \leq 0.05$ by a Wilcoxon signed-rank test.

3.2.2.3 Velocity in 0.6 cm condition

Results of a Kruskal-Wallis test showed no significant overall effect of pattern for the writing velocity during the sequential and varied tasks ($p \geq 0.05$, Table 3b). Moreover, a Mann-Whitney U between-group analysis revealed no significant writing velocity differences for all three patterns on the writing tablet between PD patients and healthy controls ($p \geq 0.05$, Table 3b).

3.2.2.4 Velocity in 1.0 cm condition

No overall statistically significant effects of pattern for writing velocity of the sequential and varied task in the large writing size conditions were found ($p \geq 0.05$, Table 3b). In addition, between-group analysis using a Mann-Whitney U test showed no significant differences in writing velocity for all three patterns between PD patients and healthy controls ($p \geq 0.05$, Table 3b).

Table 3a. Differences in amplitude for the sequential and varied writing tasks on the writing tablet between PD patients and control subjects.

Sequential and varied task amplitude	Patient group (N=5)	Control group (N=5)	Between-group p-value	Overall pattern effect p-value
Small 0.6 cm				
Sequence	0.532 (0.448-0.555)	0.596 (0.586-0.638)	0.028†	
Small-large	0.446 (0.436-0.536)	0.644 (0.633-0.684)	0.117	0.035*
Large-small	0.535 (0.469-0.545)	0.624 (0.610-0.636)	0.117	
Large 1.0 cm				
Sequence	1.019 (1.018-1.217)	1.183 (1.161-1.220)	0.175	
Small-large	0.998 (0.989-1.067)	1.120 (1.118-1.142)	0.016†	0.038*
Large-small	1.070 (0.980-1.087)	1.125 (1.087-1.172)	0.117	

* Groups significantly different at $P \leq 0.05$ by Kruskal-Wallis test, median and Tukey's Hinges percentiles (25%-75%); † significantly different at $P \leq 0.05$ by a post-hoc Mann-Whitney U Test.

Table 3b. Differences in velocity for the sequential and varied writing tasks on the writing tablet between PD patients and control subjects

Sequential and varied task velocity	Patient group (N=5)	Control group (N=5)	Between-group p-value	Overall pattern effect p-value
Small 0.6 cm				
Sequence	1.566 (0.933-1.582)	1.311 (1.187-1.425)	0.754	
Small-large	1.070 (0.970-1.266)	1.264 (1.220-1.327)	0.251	0.719
Large-small	0.960 (0.707-1.554)	1.294 (1.183-1.299)	0.347	
Large 1.0 cm				
Sequence	2.286 (1.260-2.669)	1.876 (1.812-1.896)	0.465	
Small-large	1.678 (1.259-2.287)	1.881 (1.707-1.916)	0.754	0.964
Large-small	1.569 (1.286-2.036)	1.872 (1.613-2.032)	0.465	

* Groups significantly different at $P \leq 0.05$ by Kruskal-Wallis test, median and Tukey's Hinges percentiles (25%-75%); † significantly different at $P \leq 0.05$ by a post-hoc Mann-Whitney U Test.

3.3 Correlation analysis

A correlation analysis was conducted to examine the relationships of subjects' performance between (i) the sequential and varied writing tasks on the tablet and the two tasks on paper (SOS-test and Alphabet-task) and (ii) the sequential and varied writing tasks on the tablet and the dexterity measurements (Purdue Pegboard, MAM-16 and MDS-UPDRS question 2.7).

3.3.1 Correlation between the computerized sequential and varied writing tasks and paper tasks

3.3.1.1 Amplitude

The correlations between the amplitude of the sequential and varied writing tasks on the writing tablet and the scores of the paper tasks are provided in Appendix 1a. Within the overall sample of PD patients and healthy controls, SOS-test total scores were significantly negatively correlated with the amplitude of the 0.6 cm sequence pattern (r_s = -0.673, p = 0.033) and the amplitude of the varied task 0.6 cm small-large pattern (r_s = -0.667, p = 0.035). Moreover, negative correlations were found between SOS fluency scores and the amplitude of the varied task 1.0 cm small-large pattern (r_s = -0.636, p = 0.048) as well as between SOS regularity in writing size and the amplitude of the varied task 1.0 cm small-large pattern (r_s = -0.701, p = 0.024). No other significant correlations were found between the amplitude of the different sequential and varied writing tasks on the writing tablet and scores of the paper tasks ($p \geq 0.05$).

3.3.1.2 Velocity

For the overall sample, the correlations between the velocity of the sequential and varied writing tasks and scores of the paper tasks are provided in Appendix 1b. No significant correlations between the scores on the SOS-test or the alphabet-task, and the writing velocity of the different patterns in both the 0.6 cm and the 1.0 cm conditions were found ($p \geq 0.05$).

3.3.2 Correlation between computerized sequential and varied writing tasks and dexterity measurements

3.3.2.1 Amplitude

The correlations between the amplitude of the sequential and varied writing tasks on the writing tablet and scores of the dexterity measurements for the total sample are presented in Appendix 2a. Within the total sample of PD patients and healthy controls, Purdue Pegboard right-handed scores were significantly correlated with the amplitude of the 0.6 cm sequence pattern (r_s = 0.667, p = 0.035), the varied task 0.6 cm small-large pattern (r_s = 0.667, p = 0.035), the varied task 0.6 cm large-small pattern (r_s = 0.654, p = 0.040) and the varied task 1.0 cm large-small pattern (r_s = 0.773, p = 0.009).

Significant Spearman's rank correlations were also found between Purdue Pegboard left-handed scores and the amplitude of the varied task 1.0 cm large-small pattern (r_s = 0.632, p = 0.050) as well as between Purdue Pegboard combination scores and the amplitude of the varied task 1.0 cm large-small pattern (r_s = 0.711, p = 0.021). Moreover, Purdue Pegboard right-and-left-handed scores were positively correlated with the amplitude of the varied task 0.6 cm large-small pattern (r_s = 0.640, p = 0.046) and the amplitude of the varied task 1.0 cm large-small pattern (r_s = 0.774, p = 0.009). Correlations among the amplitude of the sequential and varied tasks on the writing tablet and the MAM-16 scores were computed as well. The scores of the MAM-16 questionnaire were positively correlated with the amplitude of the 0.6 cm sequence pattern (r_s = 0.811, p = 0.004), the varied task 0.6 cm small-large pattern (r_s = 0.688, p = 0.028), the varied task 0.6 cm large-small pattern (r_s = 0.694, p = 0.026), the varied task 1.0 cm small-large pattern (r_s = 0.798, p = 0.006) and the varied task 1.0 cm large-small pattern (r_s = 0.701, p = 0.024). Furthermore, a significant negative correlation was found between the scores of MDS-UPDRS question 2.7 and the amplitude of the varied task 1.0 cm small-large pattern (r_s = -0.749, p = 0.013), indicating that amplitudes became smaller with greater writing deficits. No other significant correlations were found between the amplitude of the different sequential and varied writing tasks on the writing tablet and scores of the dexterity measurements ($p \geq 0.05$).

3.3.2.2 Velocity

For the overall sample, the correlations among the velocity of the sequential and varied writing tasks on the writing tablet and scores of the dexterity measurements are provided in Appendix 2b. Writing velocities of the different patterns in both the 0.6 cm and 1.0 cm conditions were not significantly correlated with the scores of the Purdue Pegboard, MAM-16 or MDS-UPDRS question 2.7 ($p \geq 0.05$).

4. DISCUSSION

The present cross-sectional pilot study was designed to evaluate the sensitivity of specific writing tasks to assess writing deficiencies in patients with PD compared to age-matched controls. This goal was operationalized by (i) requiring participants to write different figures and patterns on the writing tablet (i.e. loops, reversed loops, continuous-eight figures and a sequential and varied writing task), (ii) presenting these tasks in two sizes (0.6 cm and 1.0 cm) and (iii) presenting the loops, reversed loops and continuous-eight figures in both a cued and a non-cued condition.

As expected, PD patients showed typical deficits in writing during several writing tasks on the digital writing tablet when compared to healthy controls. However, patients with PD did not significantly benefit from visual cues during writing. An important and novel finding of this study was that the type of writing pattern plays an important role in amplitude scaling. Another remarkable and new finding was that scores of the SOS-test, an ecologically valid writing performance task, were correlated with the ability to scale a more normal writing amplitude. Significant correlations between writing amplitude and performance on manual dexterity tests were found as well.

4.1 Effects of visual cues on writing performance

Results of this study concerning the effect of external cues only partially confirmed the hypothesis that cues improve writing performance in patients with PD. When a visual cue was present, the PD patients wrote the loops and continuous-eight figures with a bigger amplitude and less variability in both writing sizes (0.6 cm and 1.0 cm). This advantage of cues in writing tasks for patients with PD is consistent with published literature.[6,14,27,28,68] However, the observed differences for amplitude between the cued and the non-cued condition for the loops and continuous-eight figures were not statistically significant. Contrary to expectations, it was found that PD patients wrote reversed loop figures significantly smaller in the cued condition, in both the small and large writing size. Moreover, healthy control subjects also showed significant smaller amplitudes for the reversed loops in the 0.6 cm condition when a cue was present.

A possible explanation for the lack of results for cue-effects on writing amplitude may be found in the instructions for the cued condition in this study. Participants were instructed to target the middle of the colored target zones, though several participants notably commented that they learned to write between the lines in school. Perhaps participants wrote more between lines instead of the instructed assignment, which might have resulted in the smaller amplitudes in the cued conditions compared to the non-cued conditions. This is important to take into consideration for future research since it indicates the necessity to include different instructions on how to use the visual cues (e.g. write from the top until the bottom of the colored target zones).

Another important within-group finding of cue-effect was that PD patients wrote all figures in both the 0.6 cm and 1.0 cm condition with a slower velocity when a cue was present. This finding was unexpected and suggests a negative influence of the visual cues on writing velocity. A possible explanation for this discrepancy between cued and non-cued conditions may be that participants tried to be more accurate in the cued-condition (i.e. they tried to write within the required target zones) at the expense of a reduction in writing velocity. Consistent with this suggestion, Mazzoni *et al.* (2007) found a normal speed-accuracy trade-off (i.e. higher accuracy at the cost of decreased speed, and vice versa) in PD patients during a reaching task.[69] Patients with PD were as accurate as healthy controls. However, when the accuracy requirement of the task increased, PD patients showed a higher probability of moving slowly compared to healthy controls. This could have been a manifestation of bradykinesia which is a cardinal feature of PD.

The results of the current study contradict previous gait studies where different external cue modalities (e.g. visual, auditory and attentional) increased walking velocity in PD patients.[30,70–74] This may be because gait does not require the same accuracy constraints as a fine motor task such as writing. Improvements in movement speed were not found for bimanual coordination tasks when an auditory cue was used.[50,75]

Overall, results of this pilot study showed no main effect of external visual cues on writing performance. This lack of cue-effect on writing amplitude and velocity may be explained by the impact of different cue modalities on writing. Previous work showed that patients with PD performed differently in sequential movements when different cue modalities were used. [27,76] Moreover, Bryant *et al.* (2010) found that adding extra visual cues to two parallel lines might increase the difficulty of a writing task and did not further improve writing performance.[28] Therefore, the three colored target zones used as visual cue in this study might not have been an optimal cue modality to improve writing performance in PD patients in terms of improving writing speed. In addition, the trade-off between amplitude accuracy and speed may point towards a need for an individualized cue-setting for each patient. This implies that the impact of different types of cue modalities on writing should be further investigated within a larger sample size with greater fine tuning of desired amplitude and speed to the writing deficit of the individual.

4.2 Effect of pattern-type and size on writing performance

The results of this study showed a significant overall pattern effect for amplitude of the sequential and varied tasks in both the 0.6 cm and 1.0 cm condition. Patients with PD wrote with a smaller amplitude and more variability during the sequential and varied writing tasks compared to healthy controls. The present findings seem to be consistent with other research assessing writing performance in PD patients. Both newly diagnosed and more advanced patients with PD demonstrated increasingly smaller amplitudes and more variability during different writing tasks.[5,6,8,14,15,18,25,77] However, in this

pilot study, the Wilcoxon signed-rank test showed that the results were only significantly different between PD patients and healthy controls for the amplitude of the 0.6 cm sequence pattern and the 1.0 cm small-large pattern of the varied writing task. No significant differences in amplitude were found for the other patterns. It is therefore possible that the pattern of writing tasks and order of figures within these patterns may influence writing performance of PD patients.

Since PD is a hypokinetic movement disorder, it could be expected that patients would perform better in the small writing size conditions compared to the large writing size conditions. Additionally, it was shown previously that kinematic features of writing were more affected when PD patients were required to produce larger stroke sizes.[8,13] Interestingly and in contradiction to these studies, results of the current study indicate that patients with PD found it more difficult to write the sequential pattern in the small (0.6 cm) rather than in the large (1.0 cm) writing size. This finding seems to be consistent with earlier studies in manual dexterity that observed more abnormalities in PD patients performance during small-amplitude movements.[68,78] Moreover, progressive slowing in velocity and a progressive decrease in amplitude in sequential movements (e.g. writing, speech and gait) appear to be characteristic for PD patients and have been described as the sequence effect.[79–81] The observed smaller writing amplitudes in the 0.6 cm sequential pattern in patients with PD compared to healthy controls may be explained by this sequence effect. Another possible explanation for this finding could be that PD patients experienced more fatigue during the sequence writing task than healthy controls. Since fatigue is a common symptom in PD.[82] However, Kang *et al.* (2010) found no significant correlations between the sequence effect and clinical fatigue in patients with PD.[79] More research on this topic needs to be undertaken to gain a more clear understanding of the associations between the sequence effect and writing deficits in PD patients.

From our results it also appeared that patients found it easier to produce a small movement after a large one, whereas the opposite was true for the reversed pattern (i.e. small-large pattern). This would suggest that energizing and scaling amplitude from large to small is easier. Although this pattern of results seems to be consistent with bradykinesia, the exact mechanism of why this occurs is not known. Furthermore, this suggestion is not supported by work from Van Gemmert *et al.* (2003). They observed that target size was undershot more when PD patients were required to write a large-small pattern compared to a sequence writing pattern.[8] The same authors also examined the influence of different writing patterns of varying complexity on the performance of patients with PD and found a significant main effect for writing pattern.[13] Moreover, differences in writing performance of patients with PD compared to healthy controls were observed for several types of required stroke sizes and various locations of a target pattern within a sentence.[8,21] These results should nevertheless be interpreted with caution since the used patterns in these studies were not comparable to the present study and pattern-effect was not a main outcome. Hence, an issue that emerged from this pilot study was that the type of writing pattern was an important factor in writing performance and the re-training

of writing skills. Future research with a more specific focus on the influence of specific patterns on writing performance in PD patients is therefore recommended.

Surprisingly, patients with PD did not write significantly slower than healthy control subjects for all sequential and varied patterns in both writing size conditions on the writing pad. This contradicts with their performance on the paper tasks (SOS-test) and with results from previous studies which found significant slower writing velocities in PD patients compared to controls. [5,6,18,25,77] A potential explanation for the discrepancy between the results of this study and previous research could be that PD patients did not reduce writing velocity at the expense of a reduction in writing amplitude during the sequential and varied writing tasks. This suggestion is supported by other writing experiments, which found that patients with PD tend to decrease writing amplitude to maintain a normal writing velocity.[8,13,18] Moreover, it has been observed that PD patients are able to show high amplitude accuracy at the cost of a decreased speed (i.e. speed-accuracy trade-off),[69] as previously discussed. Another possible explanation for the observed performances of PD patients and healthy controls could be that patients with PD were more motivated to perform well on the computerized writing tasks and were therefore more focused on maintaining an appropriate velocity than healthy controls. This is in accordance with observations of Nieuwboer *et al.* (2009), who reported a decreased concern with regard to accuracy during a bimanual coordination task of healthy controls compared to PD patients.[68]

4.3 Correlations with tasks on paper and dexterity measurements

This pilot study examined writing task performance on a digital tablet between patients with PD and healthy controls. An additional correlation analysis was conducted to examine the relationship of subjects' writing performance with two tasks on paper (SOS-test and Alphabet-task) and three dexterity measurements (Purdue Pegboard, MAM-16 and MDS-UPDRS question 2.7). More evidence of slowness and amplitude decline, as well as irregularity in writing size and writing fluency were found in PD patients during the writing tasks on paper, in contrast to the computerized tasks. Since in daily life writing occurs on paper, it seems possible that PD patients wrote more spontaneous when performing the writing tasks on paper. Consequently, these tasks may be more automatic and internally generated than the computerized tasks. As previously mentioned, the basal ganglia and supplementary motor areas play an important role during internally generated motor sequences.[31,32] Whereas the cerebellum and parietal-premotor networks are more involved in externally generated movements.[31,33] PD patients can therefore use external stimuli as compensatory mechanisms for bypassing deficient brain structures.[31,34] In this study the digital writing tablet may have acted as an external stimulus for the patients with PD which resulted in better writing performances on the computerized tasks compared to the tasks on paper.

Using the Spearman's rank test, considerable and novel correlations were found between writing amplitude of several sequential and varied patterns and total scores on the SOS- test on paper in the

overall sample. These correlations were negative, which indicates that higher scores on the SOS-test (i.e. more severe handwriting deficits) were associated with smaller writing amplitudes. A high total SOS-score corresponds to poor writing quality and is the sum of different sub-scores such as writing fluency and regularity in writing size.[67] It can thus be concluded that the tasks on the writing tablet, developed for this study, are capable of detecting characteristic writing deficits that PD patients experience on paper. Moreover, it can be suggested that the SOS-test may be a useful tool to detect differences in writing amplitude between patients with PD and healthy controls. It is interesting to observe that significant associations were also found between writing amplitude and SOS writing fluency on the one hand and SOS regularity in writing size on the other hand. Therefore, these sub-scores could be the most important factors in the total SOS-score to assess difficulties in writing amplitude of patients with PD. To the best of our knowledge, this pilot study is the first in which the SOS-test was used to asses writing differences between PD patients and healthy controls. Currently, the SOS-test is validated for children between 7 and 12 years of age.[67] Further research should be done in a larger sample size to validate the SOS-test for adults and patients with PD. Additional research is also necessary to gain a better understanding of the association between writing amplitude in computerized tests and SOS-scores.

In this study, other significant correlations were found between writing amplitudes of several sequential and varied writing patterns and all three dexterity measurements. Both Purdue Pegboard-scores and MAM-16-scores showed a positive association with writing amplitudes, whereas a negative correlation was found with question 2.7 of the MDS-UPDRS. These results suggest that deficits in writing amplitudes increase with decreased performances of manual dexterity. Moreover, current findings are consistent with previous research in skilled hand dexterity, which demonstrated decreased performance on skilled hand tasks in PD patients compared to age-matched controls as measured by the MAM-16 and Purdue Pegboard tests.[83] However, the correlations with the MAM-16-scores in the current study should be interpreted with caution since a sub-item analysis revealed that the significance of the correlations were driven by question 16 regarding the ability to write 3 to 4 sentences legibly.

4.4 Limitations of this study

Some limitations need to be considered regarding the present study. First, the sample size used in this pilot study was small. This may have limited the statistical power of the study. Moreover, caution must be applied with a small sample size and a small variability in PD disease severity, as the findings may not be transferable to the general population of PD patients. Patients with PD were furthermore only tested when they were ‘on’-medication which might have improved their performance during testing. For instance, it has been shown that dopaminergic medication and deep brain stimulation partially improve handwriting kinematics of PD patients.[19,24] All of the above factors, however, make

the results of this study more poignant and show that despite these factors differences between controls and PD were found.

Second, participants and researchers were not blinded to the writing assignments and writing performances of the tasks on paper were not analyzed blind either. This could have introduced bias into the analysis of results.

Third, the presence of significantly more depressed feelings in patients with PD compared to healthy controls might have influenced their writing performance. A relatively strong correlation was found between writing amplitude of the sequential and varied writing tasks and the depression subscale of the HADS. Although we do not believe that this detracts from our findings regarding writing performance, this may require further investigation.

Fourth, since participants were only tested once during a 3-hour experiment, this study only showed the immediate and short-term effects of visual cues on writing performance. Moreover, regarding cue-effect, the results of this study are limited to the visual cues investigated. In addition, participants did not write long texts with cues on the digital tablet, such as they might do in daily writing. Future studies with PD patients should assess the duration of cue-effect on writing performance and the influence of cues when writing longer passages.

4.5 Clinical implications and conclusions

This pilot study provides additional insight into the mechanisms that might contribute to writing performance in patients with PD. Several specific writing tasks on a digital tablet demonstrated typical writing deficiencies in PD patients compared to age-matched controls. Moreover, these writing deficits in PD patients were confirmed by correlations with writing tasks on paper and manual dexterity measurements. The most obvious finding that emerges from this study is that writing amplitude may be influenced by the type of writing pattern. PD patients showed significantly smaller amplitudes in the 0.6 cm sequence pattern and the 1.0 cm small-large pattern of the varied writing task, though no significant differences in amplitude were found for the other patterns. Future research regarding the role of writing patterns on writing performance in patients with PD is recommended to establish a better understanding of causal relationships. These insights may give information as to how training progressions need to be pursued and which exercises need to be included in a training program. Furthermore, this study failed to find significant benefits of visual cues on writing performance of PD patients. This contradicts the aforementioned hypothesis. Therefore, more studies should be conducted to assess the influence of different cue-modalities on writing performance in patients with PD and how these can be optimized to serve the clinical needs of each individual patient. Finally, the observations and limitations mentioned in this study can be used to develop target interventions aimed at improving writing skills in PD patients.

REFERENCES

1. Purves D, Augustine GJ, Fitzpatrick D, et al. Modulation of movement by the Basal Ganglia. In: Purves D, Augustine GJ, Fitzpatrick D, et al., eds. Neuroscience 4th edition.; 2008:453–474.

2. Jankovic J. Parkinson's disease: clinical features and diagnosis. Journal of neurology, neurosurgery & psychiatry. 2008;79:368–376.

3. Lees AJ, Hardy J, Revesz T. Parkinson's disease. The Lancet. 2009;373:2055–2066.

4. Elias de Oliveira M, Menegaldo LL, Lucarelli P, Andrade BLB, Büchler P. On the use of information theory for detecting upper limb motor dysfunction: An application to Parkinson's disease. Physica A. 2011;390:4451–4458.

5. Ponsen MM, Daffertshofer A, Wolters EC, Beek PJ, Berendse HW. Impairment of complex upper limb motor function in de novo Parkinson's disease. Parkinsonism & Related Disorders. 2008;14:199–204.

6. Oliveira RM, Gurd JM, Nixon P, Marshall JC, Passingham RE. Micrographia in Parkinson's disease: the effect of providing external cues. Journal of Neurology, Neurosurgery & Psychiatry. 1997;63:429–433.

7. Van Gemmert AWA, Teulings H-L, Stelmach GE. The influence of mental and motor load on handwriting movements in parkinsonian patients. Acta Psychologica. 1998;100:161–175.

8. Van Gemmert AWA, Adler CH, Stelmach GE. Parkinson's disease patients undershoot target size in handwriting and similar tasks. Journal of Neurology, Neurosurgery & Psychiatry. 2003;74:1502–1508.

9. Fucetola R, Smith MC. Distorted visual feedback effects on drawing in Parkinson's disease. Acta Psychologica. 1997;95:255–266.

10. Ondo WG, Satija P. Withdrawal of visual feedback improves micrographia in Parkinson's disease. Movement disorders. 2007;22:2130–2131.

11. Teulings H-L, Contreras-Vidal JL, Stelmach GE, Adler CH. Parkinsonism reduces coordination of fingers, wrist, and arm in fine motor control. Experimental neurology. 1997;146:159–170.

12. Teulings H-L, Contreras-Vidal JL, Stelmach GE, Adler CH. Adaptation of handwriting size under distorted visual feedback in patients with Parkinson's disease and elderly and young controls. Journal of Neurology, Neurosurgery & Psychiatry. 2002;72:315–324.

13. Van Gemmert AWA, Teulings H-L, Contreras-vidal JL, Stelmach GE. Parkinson's disease and the control of size and speed in handwriting. Neuropsychologia. 1999;37:685–694.

14. McLennan JE, Nakano K, Tyler HR, Schwab RS. Micrographia in Parkinson's disease. Journal of the Neurological Sciences. 1972;15:141–152.

15. Wagle Shukla A, Ounpraseuth S, Okun MS, Gray V, Schwankhaus J, Metzer WS. Micrographia and related deficits in Parkinson's disease: a cross-sectional study. BMJ open. 2012;2:1–7.

16. Hariz G-M, Forsgren L. Activities of daily living and quality of life in persons with newly diagnosed Parkinson's disease according to subtype of disease, and in comparison to healthy controls. Acta Neurologica Scandinavica. 2011;123:20–27.

17. Thomassen AJWM, Teulings H-L. Time, size, and shape in handwriting: exploring spatio-temporal relationships at different levels. In: Michon JA, Jackson JB, eds. Time, mind and behaviour.; 1985:253–263.

18. Broderick MP, Van Gemmert AWA, Shill HA, Stelmach GE. Hypometria and bradykinesia during drawing movements in individuals with Parkinson's disease. Experimental Brain Research. 2009;197:223–233.

19. Bidet-Ildei C, Pollak P, Kandel S, Fraix V, Orliaguet J-P. Handwriting in patients with Parkinson disease: Effect of L-dopa and stimulation of the sub-thalamic nucleus on motor anticipation. Human Movement Science. 2011;30:783–791.

20. Kim E-J, Lee BH, Park KC, Lee WY, Na DL. Micrographia on free writing versus copying tasks in idiopathic Parkinson's disease. Parkinsonism and Related Disorders. 2005;11:57–63.

21. Van Gemmert AWA, Teulings H-L, Stelmach GE. Parkinsonian patients reduce their stroke size with increased processing demands. Brain and Cognition. 2001;47:504–512.

22. Contreras-Vidal JL, Teulings H-L, Stelmach GE. Micrographia in Parkinson's disease. NeuroReport. 1995;6:2089–2092.

23. Contreras-Vidal JL, Stelmach GE. A neural model of basal ganlia-thalamocortical relations in normal and parkinsonian movement. Biological Cybernetics. 1995;73:467–476.

24. Poluha PC, Teulings H-L, Brookshire RH. Handwriting and speech changes across the levodopa cycle in Parkinson's disease. Acta Psychologica. 1998;100:71–84.

25. Lange KW, Mecklinger L, Walitza S, et al. Brain dopamine and kinematics of graphomotor functions. Human Movement Science. 2006;25:492–509.

26. Tucha O, Mecklinger L, Thome J, et al. Kinematic analysis of dopaminergic effects on skilled handwriting movements in Parkinson's disease. Journal of Neural Transmission. 2006;113:609–623.

27. Ringenbach SDR, Van Gemmert AWA, Shill HA, Stelmach GE. Auditory instructional cues benefit unimanual and bimanual drawing in Parkinson's disease patients. Human Movement Science. 2011;30:770–782.

28. Bryant MS, Rintala DH, Lai EC, Protas EJ. An investigation of two interventions for micrographia in individuals with Parkinson's disease. Clinical Rehabilitation. 2010;24:1021–1026.

29. Nackaerts E, Vervoort G, Heremans E, Smits-Engelsman BCM, Swinnen SP, Nieuwboer A. Relearning of writing skills in Parkinson's disease: a literature review on influential factors and optimal strategies. Neuroscience and Biobehavioral Reviews. 2013;37:349–357.

30. Nieuwboer A, Kwakkel G, Rochester L, et al. Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. Journal of Neurology, Neurosurgery, and Psychiatry. 2007;78:134–140.

31. Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Internal vs external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. NeuroImage. 2003;19:764–776.

32. Jenkins IH, Jahanshahi M, Jueptner M, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. Brain. 2000;123:1216–1228.

33. Jueptner M, Weiller C. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. Brain. 1998;121:1437–1449.

34. Cunnington R, Iansek R, Bradshaw JL. Movement-Related Potentials in Parkinson's Disease: External Cues and Attentional Strategies. Movement Disorders. 1999;14:63–68.

35. Morris ME. Movement disorders in People with Parkinson disease: a model for physical therapy. Physical Therapy. 2000;80:578–597.

36. Morris ME, Martin CL, Schenkman ML. Striding out with Parkinson disease: evidence-based Physical therapy for gait disorders. Physical Therapy. 2010;90:280–288.

37. Allen NE, Sherrington C, Suriyarachchi GD, Paul SS, Song J, Canning CG. Exercise and motor training in people with Parkinson's disease: a systematic review of participant characteristics, intervention delivery, retention rates, adherence, and adverse events in clinical trials. Parkinson's Disease. 2012;2012:1–15.

38. Petzinger GM, Fisher BE, Van Leeuwen J-E, et al. Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. Movement Disorders. 2010;25 Suppl 1:S141–S145.

39. Speelman AD, Van de Warrenburg BP, Van Nimwegen M, Petzinger GM, Munneke M, Bloem BR. How might physical activity benefit patients with Parkinson disease? Nature Reviews Neurology. 2011;7:528–534.

40. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Movement Disorders. 2008;23:631–640.

41. Doyon J, Penhune V, Ungerleider LG. Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. Neuropsychologia. 2003;41:252–262.

42. Doyon J, Benali H. Reorganization and plasticity in the adult brain during learning of motor skills. Current Opinion in Neurobiology. 2005;15:161–167.

43. Doyon J, Ungerleider LG. Functional anatomy of motor skill learning. In: Squire LR, Schacter DL, eds. Neuropsychology of memory 3th edition.; 2002:225–238.

44. Grafton ST, Hazeltine E, Ivry R. Functional Mapping of Sequence Learning in Normal Humans. 1995;7:497–510.

45. Rauch SL, Whalen PJ, Savage CR, et al. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. Human Brain Mapping. 1997;5:124–132.

46. Diedrichsen J, Hashambhoy Y, Rane T, Shadmehr R. Neural correlates of reach errors. The Journal of Neuroscience. 2005;25:9919–9931.

47. Doyon J, Bellec P, Amsel R, et al. Contributions of the basal ganglia and functionally related brain structures to motor learning. Behavioural Brain Research. 2009;199:61–75.

48. Laforce R, Doyon J. Differential role for the striatum and cerebellum in response to novel movements using a motor learning paradigm. Neuropsychologia. 2002;40:512–517.

49. Doyon J. Motor sequence learning and movement disorders. Current Opinion in Neurology. 2008;21:478–483.

50. Swinnen SP, Steyvers M, Van Den Bergh L, Stelmach GE. Motor learning and Parkinson's disease: refinement of within-limb and between-limb coordination as a result of practice. Behavioural Brain Research. 2000;111:45–59.

51. Felix K, Gain K, Paiva E, Whitney K, Jenkins ME, Spaulding SJ. Upper extremity motor learning among individuals with Parkinson's disease: a meta-analysis evaluating movement time in simple tasks. Parkinson's Disease. 2012;2012:1–7.

52. Smiley-Oyen AL, Lowry KA, Emerson QR. Learning and retention of movement sequences in Parkinson's disease. Movement Disorders. 2006;21:1078–1087.

53. Stephan MA, Meier B, Weber Zaug S, Kaelin-lang A. Motor sequence learning performance in Parkinson's disease patients depends on the stage of disease. Brain and Cognition. 2011;75:135–140.

54. Mentis MJ, Dhawan V, Nakamura T, et al. Enhancement of brain activation during trial-and-error sequence learning in early PD. Neurology. 2003;60:612–619.

55. Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain. 2005;128:2250–2259.

56. Nieuwboer A, Rochester L, Müncks L, Swinnen SP. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. Parkinsonism and Related Disorders. 2009;15 Suppl 3:S53–S58.

57. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of Neurology, Neurosurgery & Psychiatry. 1992;55:181–184.

58. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology. 1967;17:427–442.

59. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. Movement disorders. 2008;23:2129–2170.

60. Nasreddine Z, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatric Society. 2005;53:695–699.

61. Tiffin J, Asher EJ. The Purdue pegboard: norms and studies of reliability and validity. The Journal of Applied Psychology. 1948;32:234–247.

62. Chen CC, Granger C V, Peimer CA, Moy OJ, Wald S. Manual Ability Measure (MAM-16): a preliminary report on a new patient-centred and task oriented outcome measure of hand function. The Journal of Hand Surgery. 2005;30B:207–216.

63. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavia. 1983;67:361–370.

64. Rodriguez-Blazquez C, Frades-Payo B, Forjaz MJ, De Pedro-Cuesta J, Martinez-Martin P. Psychometric attributes of the Hospital Anxiety and Depression Scale in Parkinson's Disease. Movement Disorders. 2009;24:519–525.

65. Nieuwboer A, Rochester L, Herman T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. Gait & Posture. 2009;30:459–563.

66. Berninger VW, Abbott RD, Abbott SP, Graham S, Richards T. Writing and reading: connections between language by hand and language by eye. Journal of Learning Disabilities. 2002;35:39–56.

67. Van Waelvelde H, Hellinckx T, Peersman W, Smits-Engelsman BCM. SOS: A Screening Instrument to Identify Children with Handwriting Impairments. Physical & Occupational Therapy in Pediatrics. 2012;32:306–319.

68. Nieuwboer A, Vercruysse S, Feys P, Levin O, Spildooren J, Swinnen S. Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease. The European Journal of Neuroscience. 2009;29:1422–1430.

69. Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. The Journal of Neuroscience. 2007;27:7105–7116.

70. Lohnes CA, Earhart GM. The impact of attentional, auditory, and combined cues on walking during single and cognitive dual tasks in Parkinson disease. Gait & Posture. 2011;33:478–483.

71. Rochester L, Hetherington V, Jones D, et al. The effect of external rhythmic cues (auditory and visual) on walking during a functional task in homes of people with Parkinson's disease. Archives of Physical Medicine and Rehabilitation. 2005;86:999–1006.

72. Howe TE, Lövgreen B, Cody FWJ, Ashton VJ, Oldham JA. Auditory cues can modify the gait of persons with early-stage Parkinson's disease: a method for enhancing parkinsonian walking performance? 2003;17:363–367.

73. Suteerawattananon M, Morris GS, Etnyre BR, Jankovic J, Protas EJ. Effects of visual and auditory cues on gait in individuals with Parkinson's disease. Journal of the Neurological Sciences. 2004;219:63–69.

74. Lim I, Van Wegen E, De Goede C, et al. Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. 2005;19:695–713.

75. Almeida QJ, Wishart LR, Lee TD. Bimanual coordination deficits with Parkinson's disease: the influence of movement speed and external Cueing. Movement Disorders. 2002;17:30–37.

76. Rochester L, Nieuwboer A, Baker K, et al. The attentional cost of external rhythmical cues and their impact on gait in Parkinson's disease: effect of cue modality and task complexity. Journal of Neural Transmission. 2007;114:1243–1248.

77. Oliveira RM, Gurd JM, Nixon P, Marshall JC, Passingham RE. Hypometria in Parkinson's disease: automatic versus controlled crocessing. Movement Disorders. 1998;13:422–427.

78. Vercruysse S, Spildooren J, Heremans E, et al. Freezing in Parkinson's disease: a spatiotemporal motor disorder beyond gait. Movement Disorders. 2012;27:254–263.

79. Kang SY, Wasaka T, Shamim EA, et al. Characteristics of the sequence effect in Parkinson's disease. Movement Disorders. 2010;25:2148–2155.

80. Kang SY, Wasaka T, Shamim EA, et al. The sequence effect in De Novo Parkinson's disease. Journal of Movement Disorders. 2011;4:38–40.

81. Iansek R, Huxham F, McGinley J. The sequence effect and gait festination in Parkinson disease: contributors to freezing of gait? Movement Disorders. 2006;21:1419–1424.

82. Karlsen K, Larsen JP, Tandberg E, Jørgensen K. Fatigue in patients with Parkinson's disease. Movement Disorders. 1999;14(2):237–241.

83. Proud EL, Morris ME. Skilled hand dexterity in Parkinson's disease: effects of adding a concurrent task. Archives of Physical Medicine and Rehabilitation. 2010;91:794–799.

APPENDIX 1

Appendix 1a. Spearman's rank correlation results comparing the amplitude of the sequential and varied writing tasks on the writing tablet and paper tasks**;** Spearman's rho correlation coefficient and p –value (r_s (p-value))

Variety task amplitude	SOS Fluency	SOS Regularity writing size	SOS Total score	Alphabet-task Letters within 15 seconds	Alphabet-task Total number of seconds
Small (0.6 cm)					
Sequence	-0.584 (0.076)	-0.623 (0.054)	-0.673 (0.033)*	0.000 (1.000)	0.006 (0.987)
Small-large	-0.493 (0.148)	-0.493 (0.148)	-0.667 (0.035)*	0.225 (0.532)	-0.152 (0.675)
Large-small	-0.480 (0.160)	-0.389 (0.266)	-0.563 (0.090)	0.170 (0.638)	-0.146 (0.688)
Large (1.0 cm)					
Sequence	-0.415 (0.233)	-0.415 (0.233)	-0.428 (0.217)	-0.152 (0.675)	0.164 (0.650)
Small-large	-0.636 (0.048)*	-0.701 (0.024)*	-0.544 (0.104)	-0.328 (0.354)	0.298 (0.403)
Large-small	-0.467 (0.173)	-0.519 (0.124)	-0.575 (0.124)	0.024 (0.947)	0.079 (0.828)

*Correlation is significant at the 0.05 level (2-tailed); SOS, Systematic Screening for Handwriting Difficulties

Appendix 1b. Spearman's rank correlation results comparing the velocity of the sequential and varied writing tasks on the writing tablet and paper tasks**;** Spearman's rho correlation coefficient and p –value (r_s (p-value))

Variety task velocity	SOS Fluency	SOS Regularity writing size	SOS Total score	Alphabet-task Letters within 15 seconds	Alphabet-task Total number of seconds
Small (0.6 cm)					
Sequence	0.337 (0.340)	0.117 (0.748)	0.281 (0.431)	-0.091 (0.802)	0.049 (0.894)
Small-Large	0.143 (0.694)	-0.519 (0.124)	-0.031 (0.933)	-0.085 (0.815)	0.055 (0.881)
Large-Small	-0.195 (0.590)	-0.091 (0.803)	-0.073 (0.840)	0.182 (0.614)	-0.231 (0.521)
Large (1.0 cm)					
Sequence	0.519 (0.124)	0.117 (0.748)	0.385 (0.271)	-0.073 (0.841)	0.073 (0.841)
Small-Large	0.363 (0.302)	-0.260 (0.469)	0.196 (0.588)	-0.103 (0.776)	0.073 (0.841)
Large-Small	-0.104 (0.775)	-0.052 (0.887)	0.012 (0.973)	0.134 (0.713)	-0.176 (0.626)

*Correlation is significant at the 0.05 level (2-tailed); SOS, Systematic Screening for Handwriting Difficulties

APPENDIX 2

Appendix 2a. Spearman's rank correlation results comparing amplitude of the sequential and varied writing tasks on the writing tablet and dexterity measurements**;** Spearman's rho correlation coefficient and p –value (r_s (p-value))

Variety task amplitude	Purdue Pegboard Right	Purdue Pegboard Left	Purdue Pegboard Right + Left	Purdue Pegboard Combination	MDS-UPDRS 2.7	MAM-16
Small (0.6 cm)						
Sequence	0.667 (0.035)*	0.432 (0.213)	0.549 (0.100)	0.389 (0.266)	-0.506 (0.135)	0.811 (0.004)**
Small-Large	0.667 (0.035)*	0.389 (0.266)	0.610 (0.061)	0.505 (0.137)	-0.284 (0.426)	0.688 (0.028)*
Large-Small	0.654 (0.040)*	0.401(0.250)	0.640 (0.046)*	0.456 (0.185)	-0.319 (0.369)	0.694 (0.026)*
Large (1.0 cm)						
Sequence	0.542 (0.105)	0.280 (0.434)	0.530 (0.115)	0.359 (0.309)	-0.347 (0.326)	0.629 (0.051)
Small-Large	0.561 (0.092)	0.401 (0.250)	0.604 (0.065)	0.413 (0.235)	-0.749 (0.013)*	0.798 (0.006)**
Large-Small	0.773 (0.008)**	0.632 (0.050)*	0.774 (0.009)**	0.711 (0.021)*	-0.624 (0.054)	0.701 (0.024)*

*Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); MDS-UPDRS 2.7, Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale question number 2. 7; MAM-16, Manual Ability Measure

Appendix 2b. Spearman's rank correlation results comparing velocity of the sequential and varied writing tasks on the writing tablet and dexterity measurements**;** Spearman's rho correlation coefficient and p –value (r_s (p-value))

Variety task velocity	Purdue Pegboard Right	Purdue Pegboard Left	Purdue Pegboard Right + Left	Purdue Pegboard Combination	MDS-UPDRS 2.7	MAM-16
Small (0.6 cm)						
Sequence	-0.349 (0.323)	-0.134 (0.713)	-0.439 (0.204)	-0.383 (0.275)	0.062 (0.864)	-0.311 (0.381)
Small-Large	0.093 (0.797)	0.030 (0.934)	0.018 (0.960)	-0.085 (0.815)	-0.028 (0.939)	0.130 (0.721)
Large-Small	0.287 (0.422)	0.474 (0.166)	0.341 (0.334)	0.261 (0.466)	-0.430 (0.215)	0.201 (0.577)
Large (1.0 cm)						
Sequence	-0.405 (0.245)	-0.188 (0.602)	-0.506 (0.136)	-0.371 (0.291)	0.187 (0.604)	-0.467 (0.173)
Small-Large	-0.218 (0.545)	-0.152 (0.675)	-0.323 (0.362)	-0.310 (0.383)	0.125 (0.731)	-0.195 (0.590)
Large-Small	0.206 (0.569)	0.438 (0.206)	0.244 (0.497)	0.219 (0.544)	-0.430 (0.215)	0.104 (0.775)

MDS-UPDRS 2.7, Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale question number 2.7; MAM-16, Manual Ability Measure

APPENDIX 3

POPULAIRE SAMENVATTING

De ziekte van Parkinson is een progressieve hersenaandoening die wordt gekenmerkt door motorische en niet-motorische klachten. Veel patiënten met de ziekte van Parkinson ervaren vaak al in een vroeg stadium problemen met de fijne motoriek, bijvoorbeeld tijdens het schrijven. Het doel van deze pilootstudie was om te onderzoeken wat de verschillen zijn bij het schrijven tussen patiënten met de ziekte van Parkinson en gezonde volwassenen. De deelnemers aan het onderzoek, 5 patiënten en 5 gezonde volwassenen, werden gevraagd om tijdens een sessie van circa 3 uur diverse schrijfoefeningen op een digitaal schrijftablet en op papier uit te voeren. Daarnaast werden er testen afgenomen om emotionele, cognitieve en motorische eigenschappen van de deelnemers te toetsen. Een belangrijk resultaat was, dat de ontwikkelde digitale schrijfoefeningen in staat waren om schrijfproblemen bij patiënten met de ziekte van Parkinson te ontdekken. Bovendien bleek de 'Systematische Opsporing van Schrijfmotorische problemen'-test, die oorspronkelijk ontwikkeld werd bij kinderen met schrijfproblemen, bruikbaar als meetinstrument bij de ziekte van Parkinson. Verder had het type van schrijfpatroon een invloed op de schrijfprestaties van de patiënten. Tenslotte, deze resultaten kunnen gebruikt worden om een optimaal trainingsprogramma op te stellen ter verbetering van de schrijfvaardigheid bij patiënten met de ziekte van Parkinson.

APPENDIX 4 (page 35-38)

Informatie- en toestemmingsformulier patiënten pilootstudie

KU Leuven
Biomedische Wetenschappen
Departement Revalidatiewetenschappen
Tervuursevest 101
B-3001 Heverlee
België

Vrijwillige en geïnformeerde toestemming tot deelname aan:

Schrijftaakonderzoek
Pilootstudie

Consolidatie van motorisch leren van schrijfvaardigheden en de gerelateerde veranderingen in hersenactiviteit bij de ziekte van Parkinson.

Promotor:
Prof. A. Nieuwboer
Co-promotoren:
Prof. Dr. B.C.M. Smits-Engelsman
Prof. S.P. Swinnen

Onderzoeker: Evelien Nackaerts
Studente: Sanne Broeder

Geachte heer/mevrouw,

U wordt uitgenodigd om deel te nemen aan een pilootonderzoek. De resultaten zullen worden gebruikt voor de masterproef van een studente Kinesitherapie en Revalidatiewetenschappen (Sanne Broeder) en nadien verder gebruikt in een grote studie naar het effect van schrijftraining. Het onderzoek wordt gesuperviseerd door Prof. Alice Nieuwboer van het Departement Revalidatiewetenschappen.

Doel van de studie

Aantasting van de grootte van het handschrift is vaak een eerste manifestatie van de ziekte van Parkinson. Op basis van onze ervaring denken wij dat bepaalde onderdelen van het schrijven vatbaar zijn voor training. In de voorgestelde studie zullen we daarom onderzoeken wat de verschillen zijn bij het schrijven tussen patiënten met de ziekte van Parkinson en gezonde volwassenen. Later willen we op basis van de informatie verworven via deze studie, een optimaal trainingsprogramma opstellen en nagaan of deze training een invloed heeft op het patroon van hersenactivatie. De resultaten van dit pilootproject kunnen mogelijk een bijdrage leveren tot het ontwikkelen van betere revalidatiemethodes voor schrijven.

Procedure

Indien u wilt meedoen aan de studie wordt u in 1 van de onderzoekslaboratoria, op de begane grond van Gebouw De Nayer van de Faculteit Bewegings- en Revalidatiewetenschappen, Tervuursevest 101 in Leuven, uitgenodigd. U zal een aantal schrijfoefening moeten uitvoeren, waarna we ook uw geheugen en de ernst van de ziekte van Parkinson aan de hand van een aantal vragenlijsten zullen testen. Op de dag van de tests mag u uw medicatie innemen zoals gewoonlijk. Er zijn pauzes voorzien tijdens de testafname, waarbij u kan rusten. We voeren de testen uit in de vroege voormiddag als de medicatie goed werkt. De duur van dit onderzoek bedraagt 2.5 à 3 uur.
Deelname aan deze studie brengt voor u geen bijkomende kosten met zich mee. Tevens zullen uw vervoersonkosten door ons worden vergoed en kunnen we een taxi voorzien indien nodig.

Voorzorgsmaatregelen

De testen zijn volstrekt ongevaarlijk en schadeloos.

Vertrouwelijkheid

Vertrouwelijkheid is verzekerd wat betreft uw identiteitsgegevens. De gegevens verzameld gedurende de testen zullen gecodeerd worden om associaties met een bepaald individu te voorkomen. U kan op elk ogenblik uw medewerking stopzetten zonder dat u daar een verklaring voor hoeft te geven en zonder consequenties voor uw toekomstige behandeling binnen de universitaire ziekenhuizen Leuven.

Verzekering

De opdrachtgever van deze studie (KU Leuven) heeft een verzekering afgesloten die de aansprakelijkheid voor alle schade die u eventueel zou oplopen dekt. Indien u schade zou oplopen, rechtstreeks of onrechtstreeks ten gevolge van uw deelname aan deze studie zal die schade bijgevolg worden vergoed conform de Belgische wet van 7 mei 2004.

Vrijwillige en geïnformeerde toestemming

Ik ben in de mogelijkheid gesteld om de informatie in dit formulier te lezen en vrij te kiezen om wel of niet mee te werken aan het project. Ik ben geïnformeerd dat ik vrij ben om mijn medewerking aan het project in te trekken op gelijk welk ogenblik, zonder consequenties voor mijn toekomstige behandeling binnen de universitaire ziekenhuizen.
Ik heb het bovenstaande gelezen en goedgekeurd. Ik ga akkoord met deelname aan deze studie.

Datum Datum

Proefpersoon Onderzoeksleider

Informatie- en toestemmingsformulier vrijwilligers pilootstudie

KU Leuven
Biomedische Wetenschappen
Departement Revalidatiewetenschappen
Tervuursevest 101
B-3001 Heverlee
België

Vrijwillige en geïnformeerde toestemming tot deelname aan:

Schrijftaakonderzoek
Pilootstudie

Consolidatie van motorisch leren van schrijfvaardigheden en de gerelateerde veranderingen in hersenactiviteit bij de ziekte van Parkinson.

Promotor:
Prof. A. Nieuwboer
Co-promotoren:
Prof. Dr. B.C.M. Smits-Engelsman
Prof. S.P. Swinnen

Onderzoeker: Evelien Nackaerts
Studente: Sanne Broeder

Geachte heer/mevrouw,

U wordt uitgenodigd om deel te nemen aan een pilootonderzoek. De resultaten zullen worden gebruikt voor de masterproef van een studente Kinesitherapie en Revalidatiewetenschappen (Sanne Broeder) en nadien verder gebruikt in een grote studie naar het effect van schrijftraining. Het onderzoek wordt gesuperviseerd door Prof. Alice Nieuwboer van het Departement Revalidatiewetenschappen.

Doel van de studie

Aantasting van de grootte van het handschrift is vaak een eerste manifestatie van de ziekte van Parkinson. Op basis van onze ervaring denken wij dat bepaalde onderdelen van het schrijven vatbaar zijn voor training. In de voorgestelde studie zullen we daarom onderzoeken wat de verschillen zijn bij het schrijven tussen patiënten met de ziekte van Parkinson en gezonde volwassenen. Later willen we op basis van de informatie verworven via deze studie, een optimaal trainingsprogramma opstellen en nagaan of deze training een invloed heeft op het patroon van hersenactivatie. De resultaten van dit pilootproject kunnen mogelijk een bijdrage leveren tot het ontwikkelen van betere revalidatiemethodes voor schrijven.

Procedure

Indien u wilt meedoen aan de studie wordt u in 1 van de onderzoekslaboratoria, op de begane grond van Gebouw De Nayer van de Faculteit Bewegings- en Revalidatiewetenschappen, Tervuursevest 101 in Leuven, uitgenodigd. U zal een aantal schrijfoefening moeten uitvoeren, waarna we ook uw geheugen zullen testen aan de hand van een aantal vragenlijsten. De duur van dit onderzoek bedraagt 2.5 à 3 uur.
Deelname aan deze studie brengt voor u geen bijkomende kosten met zich mee. Tevens zullen uw vervoersonkosten door ons worden vergoed.

Voorzorgsmaatregelen

De testen zijn volstrekt ongevaarlijk en schadeloos.

Vertrouwelijkheid

Vertrouwelijkheid is verzekerd wat betreft uw identiteitsgegevens. De gegevens verzameld gedurende de testen zullen gecodeerd worden om associaties met een bepaald individu te voorkomen. U kan op elk ogenblik uw medewerking stopzetten zonder dat u daar een verklaring voor hoeft te geven en zonder consequenties voor uw toekomstige behandeling binnen de universitaire ziekenhuizen Leuven.

Verzekering

De opdrachtgever van deze studie (KU Leuven) heeft een verzekering afgesloten die de aansprakelijkheid voor alle schade die u eventueel zou oplopen dekt. Indien u schade zou oplopen, rechtstreeks of onrechtstreeks ten gevolge van uw deelname aan deze studie zal die schade bijgevolg worden vergoed conform de Belgische wet van 7 mei 2004.

Vrijwillige en geïnformeerde toestemming

Ik ben in de mogelijkheid gesteld om de informatie in dit formulier te lezen en vrij te kiezen om wel of niet mee te werken aan het project. Ik ben geïnformeerd dat ik vrij ben om mijn medewerking aan het project in te trekken op gelijk welk ogenblik, zonder consequenties voor mijn toekomstige behandeling binnen de universitaire ziekenhuizen.
Ik heb het bovenstaande gelezen en goedgekeurd. Ik ga akkoord met deelname aan deze studie.

Datum Datum

Proefpersoon Onderzoeksleider

APPENDIX 5 (page 39 -45)

AUTHOR GUIDELINES (MOVEMENT DISORDERS)

MANUSCRIPT SUBMISSION INFORMATION

Movement Disorders is pleased to offer authors web-based manuscript submission and peer-review.

Authors are required to submit online at http://mc.manuscriptcentral.com/mds. All accompanying supplementary material (e.g., videos, appendices) should also be submitted online.

Policy Regarding Inappropriate Submissions and Publications

The editors, members of the editorial board, and publisher's staff at Movement Disorders take their responsibility seriously to assure that the highest ethical publishing standards are maintained by assisting in safeguarding the medical scientific literature against fraudulent publications. Please note manuscript submissions are now submitted for plagiarism detection through CrossCheck. Wiley-Blackwell policy is based on the 'Guidelines on Good Publication Practice' published by the Committee on Publication Ethics (COPE) and can be found at Author Services.

Examples of fraud in scientific research include (but are not limited to):

1) The submission of duplicate publications using similar data (i.e., attesting that work submitted is original when, in fact, it was submitted to or accepted by another journal);

2) Falsification of data, copyright, or information regarding conflict of interest;

3) Submission of work from other sources that was not done by the author and is presented as a new and original (plagiarism);

4) Authorship (allowing one's name to appear as an author or adding an author to a manuscript) without substantial input or without having agreed to submission of the manuscript.

The above examples are not meant to be a comprehensive list of fraudulent publication practices. Rather, it should provide adequate basis for careful consideration of avoidable conflicts and editorial scrutiny regarding inappropriate preparation and submission of manuscripts.

Manuscripts that have appeared in publications that are not peer-reviewed, are not registered in Pub Med, or are available only on the internet, will be considered for publication in MDS as long as the Editor is informed and grants approval prior to submission of the manuscript for review. If there are questions as to any issues regarding inappropriate submission, the Editor should be consulted prior to the submission. If a submitted or published manuscript is discovered or suspected to be inappropriate, the authors will be asked for a written explanation. If the rationale provided by the authors remains unsatisfactory in the judgment of the editors, the manuscript will be rejected or retracted. Retractions become a matter of public record and are registered in Pub Med. The provost (or equivalent) of the authors' academic institutions will be informed of inappropriate submissions or publications, and the authors will not be allowed to subsequently submit their research to MDS. The leadership of MDS will also inform the editors and publishers of other journals which have published manuscripts judged to be inappropriately submitted to MDS.

Editorial Office Information

Jose A. Obeso, MD, PhD
University of Navarra
Pamplona, Spain
Phone: 34-948-194700, ext. 2038
E-mail: movementdisorders.east@gmail.com

C. Warren Olanow, MD, FRCPC
Mount Sinai School of Medicine
New York, New York, USA
Phone: 1-212-241-8435
E-mail: cwolanow@gmail.com

Submit your manuscripts online at http://mc.manuscriptcentral.com/mds. Please note: Manuscripts submitted online are marked as received on the day of submission, evaluated by the Chief Editors, and assigned to associate editors to oversee the review process. Papers that are not determined to be of sufficient clinical/scientific interest, focus, or relevance by at least two senior editors may be rejected without review. Through your individual Author Center on this website, you can view the status of your manuscript as it progresses through the review process. Notification of the final disposition of each manuscript will be sent by E-mail to the corresponding author on the day of decision. To submit your manuscript online:

- Go to the submission website (http://mc.manuscriptcentral.com/mds)

- Click on the "Check for Existing Account" button at the bottom of the opening page. If you do not already have an account, then create one by clicking on the "Create an Account" button. You will then be able to submit your manuscript.
- Click on “Author Center.” Follow the on-screen instructions carefully. Tables and figures should be uploaded as individual files and not part of the manuscript text. (You do not need to mail hard copies of your manuscript).
- At the end of a successful submission, you will see a confirmation screen with your manuscript number, and you will receive a separate E-mail confirmation of manuscript reception by the journal. If these two messages do not appear, then go into your Author Center and make sure that you have clicked on the “Submit” button or contact technical support athttp://mchelp.manuscriptcentral.com/gethelpnow/question.htm.

Video Submission

File size limitations: **Files may be no larger than 50 MB.**

General Information: When submitting manuscripts online, authors must indicate whether the article has an accompanying video. Video must be submitted with manuscripts online in a digital format. If an article includes video, the upper right corner of the title page of the manuscript must be marked *“Video is part of ms.”* Video clips should be limited to 90 seconds unless formal approval is obtained from the editorial office. Authors must also supply, as part of the manuscript, a video legend for the video clip. If the author does not have the capacity to generate an electronic video, the author may contact the editorial office for assistance.

Content: Video content should be edited to illustrate the key findings in a concise and informative manner. They should be less than 90 seconds in duration, except for special instances, which must be cleared in advance with the appropriate chief editor. Legends for the video segments should be placed at the end of the article and should concisely and sequentially describe what is seen in the video so that it can be readily understood by the viewer. Do not repeat explanatory material that is already in text. The video should be of high quality (both in content and visibility). The video should be edited to ensure maximal efficiency and make the specific point; particularly, it should demonstrate the features described in the text of the manuscript. In addition, the video should be labelled and should directly follow the sequence and content of the video legend.

The use of text and/or special transition effects between the titles, subtitles and video segments is permitted. The video you submit should be the final product that will be published with the article. The Editors reserve the right to request additional video editing by the authors (which may delay publication).

Patient Consent: The corresponding author must confirm in the author copyright form (Article V) that he or she has received a signed release form from each patient videotaped authorizing the offline and/or online distribution of this video material. Manuscripts with videos will not be sent out for review until the signed copyright form (Article V) with appropriate documentation is received. The date of submission will be the date all components of the article arrive at the editorial office.

For tips on preparing your video for submission, see the Technical Note by Jog and Grantier on digital video preparation. This article appears in volume 16, issue 6, and is available to all readers.

Cover Letter, Author Copyright Form, and Legal Information

Cover Letter. The cover letter should briefly describe the scientific or clinical importance of the manuscript. It must confirm that all authors have read the manuscript, the paper has not been previously published, and it is not under simultaneous consideration by another journal. Also, a statement that no ghost writing by anyone not named on the author list must be included (see Editorial in *Movement* Disorders 2005;20:1536). Identify the corresponding author and provide a complete mailing address, telephone number, and email address for each author where possible.

Author Copyright Form. The author Copyright form includes (1) a statement on authorship responsibility, (2) a statement on financial disclosure, (3) one of two statements on copyright or federal employment, and (4) a statement of acknowledgment. Each of the first three statements must be read and signed by each co-author. The corresponding author must sign the acknowledgment statement (See the copyright form at the top of this page).:5) When there is accompanying video or photographs on which patients can be identified, the corresponding author must sign the video consent section (Article V).

*Group Authorship. The journal does not limit the number of authors for an individual manuscript providing that: a)*If there are multiple authors , all authors must meet the full criteria and requirements for authorship; b). If there is group, authorship, one or more individuals are designated as authors or members of a writing group who meet full authorship criteria and who take responsibility for the group. Other members of the group are not authors individually, but may be listed in the acknowledgment section (Flanagin A, Fontanarosa PB, DeAngelis CD. Authorship for research groups. JAMA 2002;288:3166-3168).

Documentation of Author Roles. At the end of the manuscript, all authors must be listed, along with their specific roles in the project and manuscript preparation. These should include but not be restricted to:

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

Data Access and Responsibility. For clinical trials sponsored by pharmaceutical companies, authors must state in their letter of submission that (1) they have had full access to the data, (2) they have the right to publish all the data, and (3) they have had the right to obtain independent statistical analyses of the data. For any report containing original data, at least one author should indicate that he or she "takes responsibility for the integrity of the data and the accuracy of the data analysis" (DeAngelis CD, Fontanarosa PB, Flanagan A. Reporting financial conflicts of interest and relationships between investigators and research sponsors. JAMA 2001;286:89-91).

Patient Consent. When submitting a patient video or photograph in which a patient can be identified, the corresponding author must provide the *Movement* Disorders journal with a written confirmation (author copyright form, Article V) that stipulates that authorization signed by the patient has been obtained in compliance with any laws regarding patient authorizations relating to the use or disclosure of protected health information of the jurisdiction(s) to which the patient and the physician are subject including, if applicable, the United States Health Insurance Portability and Accountability Act of 1996 ("HIPAA").[1] Manuscripts including, without limitation, a patient video or photograph will not be reviewed until a signed author's accompanying statement (see Item V) has been received.

Copyright. The *Movement* Disorder Society will hold copyright to all published articles and videos.

The copyright transfer agreement form can be downloaded from the top of this page. If you are a government employee, please check the "Government-Owned Work" checkbox.

Financial Disclosures. All submissions require two entries that cover financial disclosure of all authors:

- § Financial disclosure related to research covered in this article: A statement that documents all funding sources and potential conflicts of interest from each author that relate to the research covered in the article submitted must be included on the title page, regardless of date. This material will be printed with the published article.
- § Full financial disclosure for the previous 12 months: A statement that documents all funding sources, regardless of relationship to the current research in the article, from each author must be attached to the article at the end of the manuscript on the last page. This material will be posted on the journal website and may be printed at the Editors' discretion.

The copyright form that is signed by each author confirms that both of these entries are documented in the submitted material.

Expedited Publications (Fast Track)

Movement Disorders will attempt to accommodate authors of manuscripts dealing with extremely topical issues or with findings of great scientific or clinical importance by offering Expedited Review and Publication. Expedited papers will be rapidly reviewed and published within 8 weeks.

Scope

Movement Disorders publishes Full-length Articles, Reviews, Opinion papers/Viewpoints/Hypotheses/Editorials, Brief Reports, and Letters. Case reports in which a definitive pathological or genetic diagnosis has been made can be submitted for publication in the Clinico-Pathological Grand Rounds section of the journal. If the editor determines that the report is appropriate for the Clinico-Pathological Grand Rounds format two referees can be solicited to discuss the case and become co-authors of the report. All articles in *Movement* Disorders, including letters, can be accompanied by a video when appropriate.

Authors who are not perfectly fluent in English should have their manuscript professionally edited before submission. A list of independent suppliers of editing services can be found at www.blackwellpublishing.com/bauthor/english_language.asp. Japanese authors can also find a list of local English improvement services at http://www.wiley.co.jp/journals/editcontribute.html**.** All services must be arranged and paid for by the author, and use of one of these services does not guarantee acceptance for publication. In addition, the journal will edit accepted papers to ensure uniformity of language and style.

- **Full-Length Articles:** Full-length articles should present new clinical or scientific data in a field related to movement disorders. The format should include - Structured Abstract (up to 250 words with only essential abbreviations (e.g. DNA)). Text; (up to 3000 words exclusive of abstract, legends, and references) Minimize abbreviations. Tables and/or figures – up to 5.. Legends; should be concise and describe results without repeating data in text. Videos; see above. The word count must appear on the title page.

- **Reviews:** Clinical and basic science Reviews are generally published upon request or after agreement with the editors of *Movement* Disorders. Unsolicited Reviews will also be considered for publication. Reviews can be up to 3600 words. The word count must appear on the title page.
- **Viewpoints, Hypotheses, Editorials: Editorials are solicited by the editors. Hypotheses and viewpoints** related to any aspect of movement disorders may be submitted without solicitation. Viewpoints, Hypotheses/Editorials should be limited to 2000 words and 50 references. The word count must appear on the title page.
- **Brief Reports:** Brief reports are short original clinical or basic science reports related to any aspect of movement disorders. Structured Abstracts up to 150 words, text up to 1500 words, tables and figuresup to 2. References should be limited to 40. The word count must appear on the title page.
- Case reports are not normally recommended for consideration as a research article or brief report and should be submitted as a letter unless they make a scientifically important point.
- **Letters**: Letters to the Editors should have no more than five authors. Movement disorders permits publication of two types of letters to the editor with no abstract:
  -
  - **A)** Letters related to new observations. This section is appropriate for preliminary scientific observations and case presentations that raise a novel clinical or scientific issue. Letters on new observations may be up to 500 words and contain no more than 1 table/figure and 7 references.
  - **B)** A letter related to published articles. These may be submitted up to 8 weeks after the paper was published in print. Text length for both letters and replies may be up to 500 words and contain 1 table/figure and up to 5 references. Letters from original authors must be submitted within 4 weeks after request for response.
- **Articles reporting Clinical Trials:** Clinical Trial Reports must be written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher D et al., JAMA 2001;285:1987–1991; see also Moher D et al., Lancet 2001;357:1191–1194). Authors should ensure that information on all of the critical design features listed in the CONSORT checklist is reported in the manuscript. A CONSORT flow diagram should be included with the manuscript, clearly outlining the flow of patients through the trial. In addition, a statement is required in the cover letter specifically confirming that there has been no ghost writing by anyone not named on the author list (see Editorial in Movement Disorders 2005;20:1536). The precise financial relationship between a clinical trial sponsor and the authors must be delineated in the manuscript.
- **Medical Images –**Medical Images should have no more than three authors. High quality clinical or scientific photographs, drawings, scans, or other images may be submitted along with a title and a legend that describes what is observed in the image and its clinical, scientific or conceptual significance. One image (could have multiple parts) in color or in black and white may be submitted. The image may be based on an MRI, PET, pathologic specimen or clinical phenomenon, etc. Appropriate consent must be included. 200 words of text are permitted as a legend. The legend should begin with a description of what is in the image and then can go on to describe the clinical or pathologic circumstances relevant to the image. This is an imaging section and while we do want some clinical or pathological detail as appropriate, the focus of this section is on the image.

- **A New Section for Movement Disorders –** Most movement disorder specialists were initially attracted to the field by their experience with patients. With all of the advances that have been made in the basic sciences and treatment, clinical phenomenology and accurate diagnosis remain at the heart of the field. Starting with this issue of the journal, we will inaugurate a new section entitled “Clinical Vignettes”, under the direction of Dr. Steven Frucht. Each month we will feature one or two interesting cases that illustrate an important diagnostic, clinical or therapeutic point. These cases may illustrate novel clinical or scientific findings, but could also represent an unusual or informative case. In most instances this will include a video demonstration of the movement disorder. Clinical Vignettes should have no more than five authors. Each case can be accompanied by one figure illustrating a salient feature of the vignette (an image or pathologic slide, for example). Additional information can be added as supplementary material on the web site. Clinical vignettes will frequently be accompanied by a brief editorial commentary. Each case will be limited to 1000 words of text; no abstract; and 10 references. Submissions to this section should be labeled “Clinical Vignettes”. They will be published in the regular print issue and will also be available online. Any questions should be directed to Dr. Steven Frucht at steven.frucht@mssm.edu, or to the journal staff.

Form of Manuscripts.

The text of the manuscript should be in the following sequence: (1) Title page, (2) Abstract, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, (7) Acknowledgment, (8) Authors' Roles, (9) Financial Disclosures of all authors (for the preceding 12 months), (10) References, (11) Video Legend, (12) Figures, and (13) Tables. Pages should be numbered in succession, the title page being number one.

Title: Titles should be short, specific, and clear. They should not exceed 100 characters. Do not use abbreviations/acronyms in the title.

Title Page:The opening page of each manuscript should include: (1) article title (no abbreviations/acronyms); (2) authors' names and affiliations (indicate the specific affiliation of each author by superscript, Arabic numerals); (3) name, address, telephone and email address of the corresponding author; (4) word count; (5) a running title not exceeding 45 letters and spaces; (6) Key words – up to 5; (7) Financial Disclosure/Conflict of Interest concerning the research related to the manuscript: All information on support and financial issues from all authors relative to the research covered in the

submitted manuscript must be disclosed regardless of date. Other financial information unrelated to the current research covering the past year will be documented at the end of the manuscript (see below). (8) Funding sources for study.

Structured Abstract: We require that authors submit structured abstracts, but will consider unstructured abstracts if requested by the authors prior to submission. The page following the title page of Full-Length Articles, and Reviews, should include an abstract of up to 250 words. The abstract should be structured (background, methods, results, and conclusions) unless not appropriate for a specific article. The page following the title page of a Brief Report, should include a structured abstract of up to 150 words. Authors are required to spell out all abbreviations/acronyms in the structured abstract unless this has become accepted in the standard scientific literature (e,g, DNA, MPTP).
Introduction: Give a brief description of the background and relevance of the scientific contribution.

Methods: Describe the methodology of the study. For experimental investigation of human or animal subjects, please state in this section that an appropriate institutional review board approved the project. For those investigators who do not have formal ethics review committees, the principles outlined in the "Declaration of Helsinki" should be followed. For investigations in human subjects, state in this section the manner in which informed consent was obtained from the subjects. A letter of consent must accompany all photographs, patient descriptions, and pedigrees in which a possibility of identification exists. The authors are responsible for ensuring anonymity.
Results: No specific regulations.
Discussion: No specific regulations.
Acknowledgment: No specific regulations. These may be published on line at the discretion of the editor.
Author Roles: List all authors along with their specific roles in the project and preparation of the manuscript. These may include but are not restricted to: 1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Full Financial Disclosures of all Authors for the Past Year: Information concerning all sources of financial support and funding for the preceding twelve months, regardless of relationship to current manuscript, must be submitted with the following categories suggested. List sources or "none".

Stock Ownership in medically-related fields	Intellectual Property Rights
Consultancies	Expert Testimony
Advisory Boards	Employment
Partnerships	Contracts
Honoraria	Royalties
Grants	Other

References: See "Details of Style" below for the proper formatting of citations and References.

Video Legend: No specific regulations but should be concise and reflect the sequence of observations on the video

Tables and Figure Legends: Double-space legends of fewer than 40 words for tables and figures. For photomicrographs, include the type of specimen, original magnification, and stain type. Include internal scale-markers on photomicrographs when appropriate. Where applicable, indicate the method used to digitally enhance images.

Tables: Tables should be typed neatly, each on a separate page, with a title above and any notes below. Explain all abbreviations. Do not repeat the same information in tables and figures that is present in text.Tables and figures should be uploaded as individual files and not part of the manuscript text. (You do not need to mail hard copies of your manuscript).

Figures and Illustrations: Adapt any figures to an appropriate size of art and letters to make them readable in the printed version. Illustrations in full color are accepted at additional charge from the publisher. In the case of review articles or in special circumstances, color articles may be included at no charge with the permission of the Chief Editor. Any illustration or figure from another publication must be acknowledged in the figure legend, and the copyright holder's written permission to reprint in print and online edition of *Movement*Disorders must be submitted to the editors. In addition, figures to illustrate concepts are welcome particularly in review articles, and may be enhanced by a professional artists at no cost to author at the discretion of the Editors.

Copyright and Disclosure Forms The corresponding author should upload one PDF file that includes copyright and disclosure forms for all authors to the Movement Disorders submission site with the revised version of the paper. These forms also can be emailed to mdjedoffice@movementdisorders.org.

Digital Artwork Preparation

For best reproduction, electronic artwork files must be in TIFF or EPS format, at a resolution of 600 dpi or higher, sized to print. *Movement* Disorders offers Rapid Inspector™ to help ensure that your electronic graphics files are suitable for print purposes. This free, stand-alone software application will help you to inspect and verify illustrations right on your computer. Go tohttp://rapidinspector.cadmus.com/wi/index.jsp and create a new account.

Details of Style

No patient identifiers (e.g., patient initials) are to be included in the manuscript or video (e.g., case reports, tables, figures, etc.).
Units of measure: Conventional units of measure according to the *Systeme International* (SI) are preferred. The metric system is preferred for length, area, mass, and volume. Express temperature in degrees Celsius.

Drug Names: Use generic names only in referring to drugs, followed in parentheses after first mention by any commonly used generic variant.
Abbreviations: Follow the list of abbreviations given in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (see section on References). For additional abbreviations, consult the CBE Style Manual (available from the Council of Biology Editors, 9650 Rockville Pike, Bethesda, Maryland 20814, USA) or other standard sources. We encourage authors to minimize the use of abbreviations except where they are routinely employed and the full term would be cumbersome (eg MPTP).
Spelling: American spelling is used throughout the Journal.

References

Movement Disorders complies with the reference style given in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals". (See Annals of Internal Medicine 1982;96:766-771, or British Medical Journal 1982:284:1766-1770.)
References are to be cited in the text by number, and in the list of References they are to be numbered in the order in which they are cited. The reference section should be double-spaced at the end of the text, following the sample formats given below. Provide all authors' names when fewer than seven; when seven or more, list the first three and add et al. Provide article titles and inclusive pages. Accuracy of reference data is the responsibility of the author. For abbreviations of journal names, refer to List of Journals Indexed in Index Medicus (available from the Superintendent of Documents, U.S. Government Printing Office, Washington DC 20402, USA, DHEW Publication No. (NIH) 83-267; ISSN 0093-3821).

Sample References

- Journal article:

  1. Krack P, Benzzzouz A, Pollak P, et al. Treatment of tremor in Parkinson's disease by Subthalamic nucleus stiumulation. Mov Disord 1998; 13: 907-914.

- Book:

  2.Fahn S, Jankovic J, editors. Principles and Practice of Movement Disorders, Philadelphia, Churchill Livingstone, 2010, pp 96.

- Chapter in a book:

  3. Olanow CW. Hpyerkinetic Movement Disorders. In: Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson JL, Loscalzo J. Eds. Harrison's Textbook of Medicine 17th edition. 2008; p2560-2565.

Accepted Articles: Materials Required for Publication

After acceptance, please check to be sure that you have submitted your signed copyright transfer and author consent form as well as permissions forms (if applicable). Authors using images of their patients, whether in artwork or video format, must submit a copy (signed by the corresponding author) of the copyright transfer and author consent form. A sample form is available to authors on Manuscript Central.

Proofs

Proofs must be returned within 3 days of receipt; late return may cause a delay in publication of an article. Please check text, tables, legends, and references carefully. To expedite publication, page proofs rather than galleys will be sent electronically to the author, and it may be necessary to charge for alterations other than correction of printing errors.
E-mail proof pages to: MD Production Editor, *Movement* Disorders, John Wiley & Sons, Inc., Wiley-Blackwell, 111 River St., Mail Stop 8-02, Hoboken, NJ 07030-5774, USA. E-mail:mdsprod@wiley.com.

For Video Clips or Pictures of Patients (U.S. Contributors Only): The United States Health Insurance Portability and Accountability Act of 1996 ("HIPAA")

According to HIPAA, the following core elements must be included in the consent form:

1. A specific and meaningful description of the information to be used
2. The name of the Physician and/or Hospital allowed to disclose the information
3. That the video clip and/or photograph will be submitted for publication in a peer-reviewed medical journal
4. That the video clip and/or photograph will eventually be used by the readers of a peer-reviewed medical journal for educational purposes
5. An expiration date that relates to the individual or the purpose of the use or disclosure
6. The individual's signature and the date the authorization is signed.

In addition, the patient's consent form should include the following:

1. A statement that the Patient has the right to revoke his or her consent in writing
2. A statement regarding whether the Physician has the ability to condition medical treatment on the Patient's giving such consent
3. A statement that information, once disclosed, may be subject to further disclosure by the recipient journal, in which case confidentiality would no longer be assured. The consenting party must understand, additionally, that in some cases the video might be re-presented elsewhere because the journal has policies that allow permissions and/or use copyrighted materials with other educational organizations. The consenting party must understand that in such a case the signed author's consent form may be shared with this third party and the consenting party consents to this sharing of information for educational purposes.

OnlineOpen is available to authors of primary research articles who wish to make their article available to non-subscribers on publication, or whose funding agency requires grantees to archive the final version of their article. With OnlineOpen, the author, the author's funding agency, or the author's institution pays a fee to

ensure that the article is made available to non-subscribers upon publication via Wiley Online Library, as well as deposited in the funding agency's preferred archive. For the full list of terms and conditions, seehttp://wileyonlinelibrary.com/onlineopen#OnlineOpen_Terms.

Any authors wishing to send their paper OnlineOpen will be required to complete the payment form available from our website at: https://onlinelibrary.wiley.com/onlineOpenOrder.

Prior to acceptance there is no requirement to inform an Editorial Office that you intend to publish your paper OnlineOpen if you do not wish to. All OnlineOpen articles are treated in the same way as any other article. They go through the journal's standard peer-review process and will be accepted or rejected based on their own merit.

Color and Page Charges

All figures accepted in color will be reproduced in full color in the online edition of the journal at no cost to authors. Authors are required to pay the cost of reproducing color figures in print. The cost for the first page of color is $950. Color agreement forms will be sent in conjunction with the PDF proofs. Authors are not required to pay for printed pages, except in the cases of errata. For errata due to publisher error, there is no page charge. For errata due to author error, the charge to the author is $150 per printed page.