Title

Relearning of writing skills in Parkinson's disease after intensive amplitude training

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Abstract

Background: Micrographia occurs in approximately 60% of people with Parkinson's disease (PD). Although handwriting is an important task in daily life, it is not clear whether relearning and consolidation, or the solid storage in motor memory, of this skill is possible in PD.

Objectives: To conduct for the first time a controlled study into the effects of intensive motor learning to improve micrographia in PD.

Methods: In this placebo-controlled study, 38 right-handed people with PD were randomized into two groups, receiving one of two equally time-intensive training programs (30min/day, 5 days/week for 6 weeks). The experimental group (N=18) performed amplitude training focused at improving writing size. The placebo group (N=20) received stretch and relaxation exercises. Participant's writing skills were assessed using a touch-sensitive writing tablet and a pen-and-paper test, pre- and post-training and after a 6-week retention period. The primary outcome was change in amplitude during several tests of consolidation: 1) transfer, using trained and untrained sequences performed with and without target zones; and 2) automatization, using single- and dual-task sequences.

Results: The group receiving amplitude training significantly improved in amplitude and variability of amplitude on the transfer and automatization task. Effect sizes varied between 7 and 17% and these benefits were maintained after the 6-week retention period. Moreover, there was transfer to daily life writing.

Conclusions: These results show automatization, transfer and retention of increased writing size (diminished micrographia) after intensive amplitude training, indicating that consolidation of motor learning is possible in PD.

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder primarily affecting dopaminergic neurons in the basal ganglia, predominantly in the posterior putamen.[1, 2] As the posterior putamen has been associated with control of habitual behavior, it has been put forward that automatically controlled movements in PD are affected leading to an increased reliance on goal-directed control of movements.[3, 4] Handwriting is a complex functional activity incorporating both automated and controlled processes.[5] Micrographia, defined as an impairment of a fine motor skill manifesting mainly as a progressive or stable reduction in amplitude during a writing task,[6] is often one of the first signs of PD. Recent research revealed a strong correlation between activity in the posterior putamen and writing size in PD, suggesting that impaired habitual control likely contributes to micrographia.[7] Although writing problems seem to respond well to dopaminergic medication, improvements resulting from medication are mainly found for movement speed and, often to a lesser extent, for writing size.[8, 9] In addition to dopaminergic medication, rehabilitation was found to improve motor function in the short term in PD patients.[10] This entails relearning of a known motor skill through intensive practice. However, as the basal ganglia are a key hub in the motor learning network,[11] it was suggested that consolidation of learning, often hallmarked by automatization, transfer and retention, may be affected in PD.[12] Nonetheless, for gait there is strong evidence that training with techniques that circumvent the impaired basal ganglia, such as cueing and feedback, thereby relying on a more goal-directed control of movement, can improve performance in PD with a certain degree of automaticity and retention.[13-15] However, other work showed greater dependence on the learning context and difficulties to switch to the automatic stage of consolidation in PD.[16, 17] This leaves the central question unanswered, namely whether consolidation of motor learning can be achieved in the face of basal ganglia dysfunction.

Motor learning can be defined as practice-dependent performance improvement, characterized by a reduction of motor variability and a degree of automatization that persist over time.[18] Models on how to distinguish true motor learning from mere short-term motor performance increments incorporate three crucial components: (i) transfer to untrained tasks; (ii) automatization so that performance becomes resistant to distraction; and (iii) retention as indicated by sustained improvements over time without practice.[11] Several short-term studies showed positive effects of visual cueing to improve writing, which may consolidate with prolonged practice similar to gait.[19-21] However, other work has shown inconsistent effects or worsening of performance after cue-withdrawal, suggesting limited learning.[22, 23]

As recent research in PD animal models showed that practice-related neuroplasticity was possible, we wanted to investigate whether consolidation of learning using a goal-directed approach can be expected in humans and whether it can overcome micrographia.[24] Therefore, the efficacy of highly intensive and focused task-oriented training was tested in people in the early to mid-stages of PD, when the likelihood of neuroplastic changes is still the greatest.[25] We hypothesized that writing amplitude would only improve and be retained in patients who received intensive amplitude training.[26] In addition, we hypothesized that patients in the motor learning group would show transfer of learning to different tasks and that learning effects would be resistant to distraction, unlike in the placebo group.

MATERIALS & METHODS

Participants

Thirty eight right-handed PD patients, as determined by the Edinburgh handedness scale[27], were included. Other inclusion criteria were: (i) diagnosis of PD according to the United Kingdom PD Society Brain Bank criteria;[28] (ii) Hoehn and Yahr (H&Y) stage I to III in the on-phase of the medication cycle;[29] (iii) a score of 1 or more on item II.7 of the Movement Disorder Society Unified Parkinson's Disease Rating

Scale (MDS-UPDRS) regarding handwriting;[30] and (iv) Mini-Mental State Examination (MMSE) ≥ 24.[31] Exclusion criteria were: (i) visual impairments, including color blindness; (ii) upper limb medical problems which would impede handwriting, such as arthritis or recent fractures of the hand and fingers; and (iii) deep brain stimulation.

Study design

Patients were assigned to one of two training programs using a stratified randomization procedure based on H&Y stage (I-III) and age (≤65 or >65 years). The researcher who performed randomization also carried out the testing. Eighteen patients were assigned to an intensive writing amplitude training (=EXP) and 20 to a placebo group (=PLB) (**Figure 1**). PLB consisted of a generic stretch and relaxation program designed not to influence amplitude.[32] Participants were tested during the on-phase of the medication cycle, i.e. approximately one hour after medication intake. Tests took place at baseline, after six weeks of training (post) and after six weeks without training (retention). Training started within one week of baseline-testing and the post-test was performed within one week of completing the training. There was one drop-out (PLB-group) due to increased dyskinesia interfering with writing. Medication intake was kept constant throughout the study.

The study was approved by the local Ethics Committee of the KU Leuven and was in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki, 1967). After explanation of the protocol, written informed consent was obtained prior to participation in the study. The trial was registered as ClinicalTrials.gov Protocol Record G.0906.11

(https://clinicaltrials.gov/ct2/show/NCT02288052?term=G.0906.11&rank=1)).

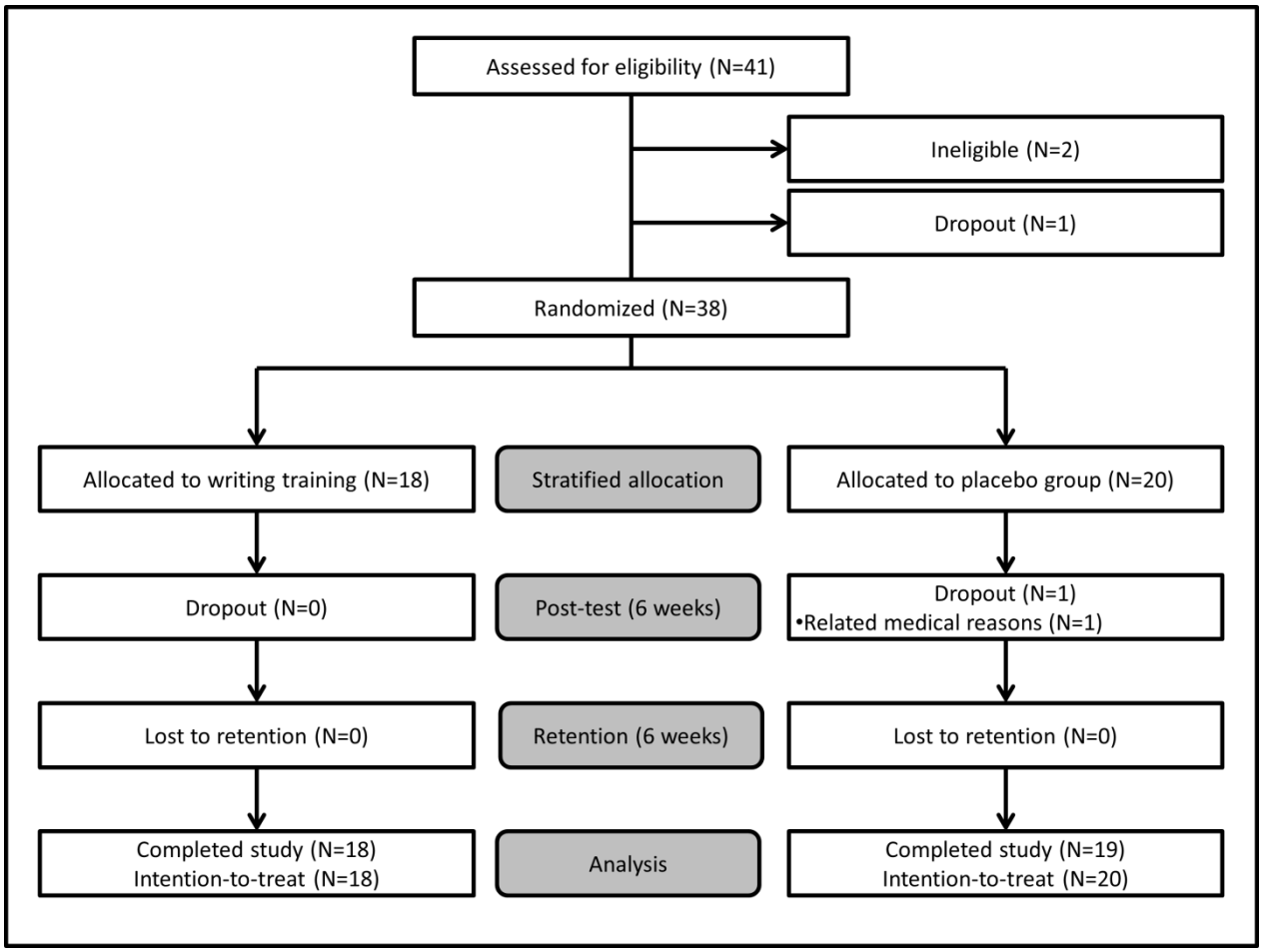

Figure 1: Flowchart of the study enrolment population. After assessment for eligibility, two participants were excluded due to the presence of other neurological disorders, one participant dropped out due to unrelated medical reasons.

Outcome measures

At each time point, patients' mood and sleep quality were assessed, as these can be affected by PD and influence motor learning and consolidation.[33, 34] Sleep problems were evaluated using item I.7 of the MDS-UPDRS-I.[30] The Hospital Anxiety and Depression Scale (HADS)[35] was used to assess anxiety and depression. The Manual Ability Measure (MAM-16)[36] captured the ability to perform fine motor skills.

Tests on a touch-sensitive tablet (sampling frequency=200 Hz; spatial resolution=32.5 µm) were performed in random order and were based on the hallmarks of consolidation, i.e. automatization, transfer and retention. They included simple repetitive pre-writing tasks, avoiding the involvement of language and higher order cognitive demands and allowing accurate measurement of pure motor

performance. Automatization of writing was measured with a dual task (DT) paradigm.[37] Patients were asked to write a three-loop sequence in the presence of visual target zones while counting high or low tones (**Supplementary Figure 1A**). Both tasks were also performed as single tasks (ST) and writing was performed at two sizes, 0.6 and 1.0 cm, considered within the normal range of writing sizes.[38] Each condition lasted 27 seconds and was preceded by a rest period of six seconds and instruction of three seconds. Tones were presented every three seconds and had a duration of 0.1 seconds. Each condition was performed once per run and three runs were completed.

Transfer was tested using a trained and an untrained sequence, both performed in the presence and absence of visual target zones (**Supplementary Figure 1B**).[39] The trained sequence consisted of the same continuous three-loop sequence and the untrained sequence of a figure of eight-like movement. For the latter patients were instructed to start in the yellow (middle) zone forming a loop till the top of the grey (top) zone and make a reversed loop till the bottom of the blue (bottom) zone. Three runs were performed. The setup of a run was identical to the automatization task.

To study retention, all writing tests were performed after six weeks without practice. Patients were allowed to apply the learned techniques during daily life throughout the follow-up period. The 'Systematic Screening of Handwriting Difficulties (SOS)' test[40] was used to assess daily life writing. It involved writing a text for five minutes continuously and was previously used in PD.[37, 39]

Interventions

Training programs were developed so that patients could perform them independently at home. Both programs were equally time-intensive and included 30 minutes of practice, five days per week for six weeks. Patients were requested to keep a diary of all the dates and times of day at which exercises were performed. Compliance rates were calculated for each individual by dividing the number of days the patient reported to have actually practiced by the number that was required (i.e. 30 days) and were

95.8% for the EXP and 94.5% for the PLB group. Patients in each arm were supervised weekly by one of the researchers.

The amplitude training (EXP) consisted of pen-and-paper writing and exercises on a touch-sensitive tablet. Training was based on the Neuromotor Task Training shown to be effective in children.[41, 42] The exercises aimed to increase writing amplitude with the help of the same colored target zones as during testing. After three weeks of practice the accuracy requirement for amplitude was increased by decreasing the thickness of the target zones. **Supplementary table 1** illustrates the gradual build-up in difficulty at different levels: (i) from pre-letters to letters to words; (ii) from one sized letters to alternating between different sizes; and (iii) from ST- to DT-writing. In addition, the three-loop sequence was practiced on a daily basis both on paper and on the tablet.

The PLB group received a stretch and relaxation program provided on a DVD, teaching patients how to relax generally and alleviate tension in the upper limbs. Exercises were performed while lying down or sitting and consisted of breathing exercises, progressive relaxation and yoga. Each week a new technique was introduced to ensure that no effect of the intervention could be expected.

Data processing and statistical analysis

Data from the tablet were filtered at 7 Hz with a 4^{th}-order Butterworth filter and processed using Matlab R2011b. Writing amplitude (% of target size) and the within-patient coefficient of variation of amplitude (COV_{ampl}) were determined by calculating the differences between the local minima and maxima of individual strokes.[37, 39] The target size was determined as the distance between the bottom of the blue and top of the yellow target zone for the loop sequence and between the bottom of the blue and top of the grey target zone for the figure of eight-like movement. Improvement percentages (IP) were calculated relative to baseline amplitude. Accuracy on the secondary tone-counting task was determined as a percentage of correct answers (%).

Data processing of the paper-and-pencil test, i.e. the SOS-test, was performed manually by a blinded researcher. Mean writing size (mm) and writing velocity (letters written in five minutes) were determined manually. The total SOS-score was composed of: (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.[40] A higher total SOS-score indicated worse quality of handwriting (0-10).

Statistical analysis was performed using SPSS software (version 22). Demographic characteristics between patient groups were compared using independent t-tests or Mann-Whitney U (MWU) tests depending on the normality and equality of variance of the variables. As the dataset included missing values, a linear mixed model approach was chosen to analyze the tasks on the tablet and the SOS-test. Assumptions of linearity, homoskedasticity and normality of the residuals were checked before further analysis. To study automatization, Group (EXP or PLB), Time (pre, post or retention) and Task (single or dual) were included as fixed factors for writing amplitude, COV_{Ampl} and performance on the secondary task. To investigate transfer, Group, Time, Task (trained or untrained) and Cue (with or without target zones) were incorporated as fixed factors for writing amplitude and COV_{Ampl} on the tablet. Transfer to daily life was analyzed using Group and Time as fixed factors on the performance on the SOS-test. All analyses included MAM-16 as a covariate, as this differed between patient groups, and all models controlled for the within-subject differences by including participants as random effects. If assumptions for parametrical testing were not met, a non-parametric Friedman ANOVA and MWU tests were used, without MAM-16 as a covariate.

As learning effects may only become noticeable with greater intensity of practice, an additional analysis was performed including only patients with compliance rates ≥ 80% based on the diaries (N=17 in EXP, N=19 in PLB). The threshold of 80% was chosen based on studies showing average adherence rates of 80% for home-based training studies in PD.[43, 44] A repeated measures ANCOVA procedure was performed, as no missing values were present. To test for transfer, Time, Task and Cue were included as

within-subject and Group as a between-subject factor. To study automatization, Time and Task were included as within-subject and Group as a between-subject factor. MAM-16 was added as a covariate in all analyses. Significance levels for all tests were set at $p<.05$. Post hoc analyses were carried out using Bonferroni tests.

RESULTS

Subjects

Demographics and clinical characteristics of the patients are specified in **Table 1**. Groups were similar at baseline, except for MAM-16 which was lower in the EXP group, indicating greater fine motor skill problems.

Table 1: Patient characteristics.

	EXPERIMENTAL (N=18)	PLACEBO (N=20)	p-value
Age (years)	62.6 (±8.4)	63.6 (±10.9)	.756
Sex (♂/♀)	10/8	13/7	.633
Edinburg Handedness Inventory (%)	100 (90,100)	95 (90, 100)	.762
MMSE (0-30)	29 (29, 30)	28 (28, 29)	.251
HADS			
Anxiety (0-21)	6.6 (±4.3)	4.8 (±3.9)	.197
Depression (0-21)	5 (2, 7)	3 (1, 6)	.176
Disease duration (years)	7 (3, 8)	4.5 (3, 6)	.264
LED (mg/24h)	607.5 (337.5, 719)	310 (150, 615)	.112
H&Y (1-5)	2 (2, 2)	2 (2, 2)	.806
MDS-UPDRS on medication			
I.7 (0-4)	2 (1, 3)	1.5 (1, 3)	.534
II.7 (0-4)	2 (1, 3)	2 (1, 2)	.276
III (0-132)	27.3 (±12.5)	23.4 (±11.1)	.311
MAM-16 (0-64)	55.5 (50, 58)	59.5 (57, 62)	.009
Writing item (0-4)	3 (2, 4)	3 (3, 4)	.426
SOS-test			
Total SOS score (0-10)	3.5 (±1.9)	3.4 (±2.0)	.813
SOS size (mm)	2.1 (±0.4)	3.0 (±2.9)	.192
SOS speed (letters/5min)	364.8 (±126.7)	395.7 (±112.4)	.431

Age, HADS-A, MDS-UPDRS-III and SOS measures were normally distributed and displayed as mean (±

standard deviation). Assumptions were not met for all other characteristics and are displayed as median (1^{st} quartile, 3^{rd} quartile).
Abbreviations: MMSE = Mini Mental State Examination; HADS-A/D = Hospital Anxiety and Depression Scale- Anxiety or Depression subscale; LED = L-dopa equivalent daily dose; H&Y stage = Hoehn and Yahr stage; MDS-UPDRS = Movement Disorders Society Unified Parkinson's disease rating scale; I.7 = night time sleeping pattern; II.7 = writing problems; III = motor examination; MAM = Manual Ability Measure; SOS-test = Systematic Screening of Handwriting Difficulties.

Automatization

For both the small- and large-amplitude condition, significant differences in writing amplitude were found between the two groups with time (small: F=10.33, p<.001; large: F=12.55, p<.001, **Figure 2A**). Both immediately after training (small: p=.001, IP=13.0%; large: p<.001, IP=17.4%) and at retention (small: p<.001, IP=13.4%; large: p<.001, IP=17.0 %) an increased amplitude was present in the EXP group, regardless of ST or DT condition. In addition, the EXP group wrote larger than the PLB group after training in the large-amplitude condition (p=.004). The COV_{ampl} analysis revealed no significant differences. Analysis including only participants with a compliance rate ≥ 80% confirmed these results. Results per condition can be found in **Supplementary table 2**.

For the secondary task of the DT paradigm, there was a greater accuracy in the EXP compared to PLB group (F=4.07, p=.047), in the ST- compared to DT-condition (F=152.65, p<.001) and an increase in accuracy from baseline to post-training (p=.018) and retention (p=.002) (F=6.89, p=.002). When only participants with a compliance rate ≥ 80% were included, additional differences between both groups during ST and DT with time were found (F=5.38, p=.010) (**Figure 2B**). A greater accuracy was present during ST compared to DT at all time points for both groups (all p<.01), but only the EXP group improved accuracy on the secondary task during DT-performance from baseline to post-training (p<.001) and to retention (p<.001). The EXP group also showed greater accuracy compared to the PLB group in the DT-condition post-training (p=.009) and at retention (p=.039).

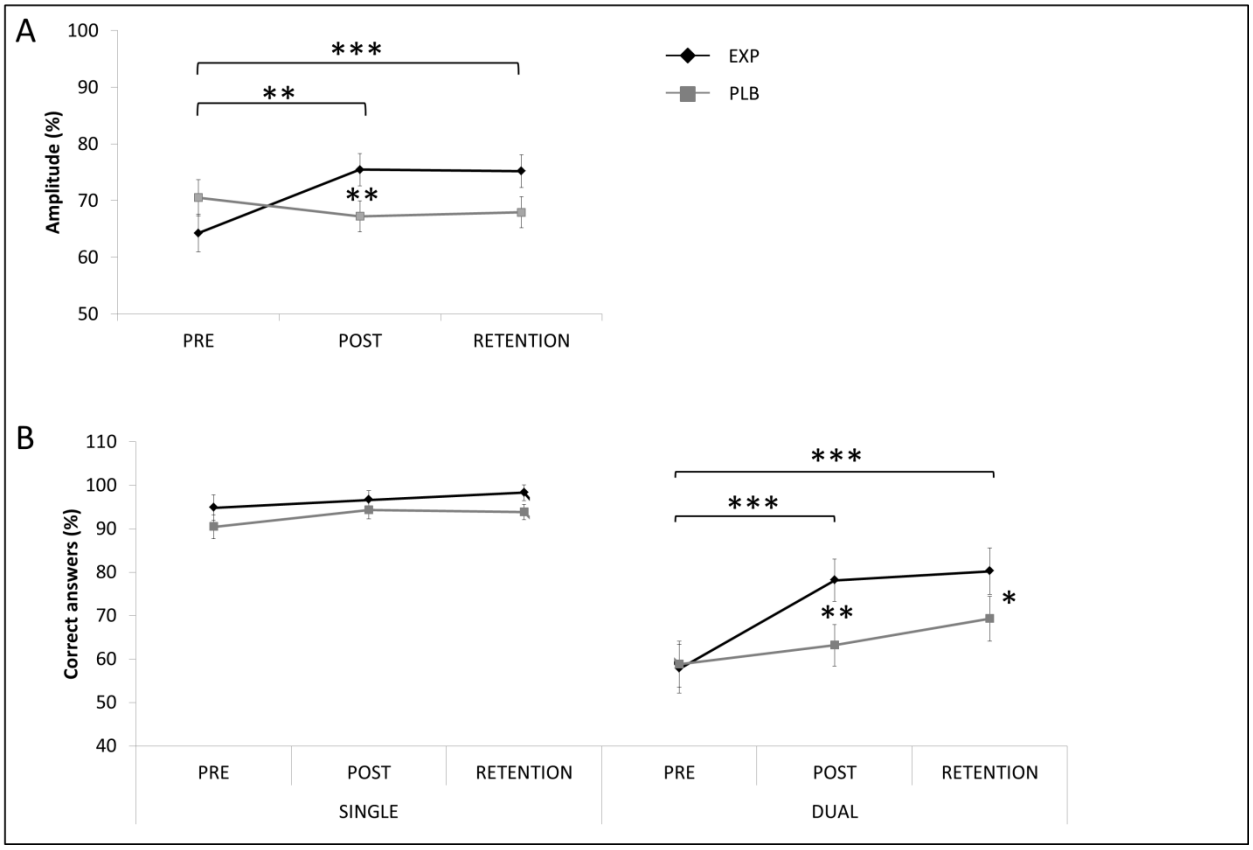

Figure 2: Performance during the automatization task. Mean and standard errors are presented. (A) Writing amplitude (% of target size) in the large-amplitude condition. (B) Performance on the secondary task (% correct answers) performed both as a single and dual task. * indicates p<.05, ** indicates p<.01 and *** indicates p<.001.

Transfer

For writing amplitude, a significant difference between the two groups was found with time, regardless of task or cue in the small-amplitude condition (F=8.05, p<.001, **Figure 3A**). Amplitude increased from baseline to retention (p=.006, IP=6.9%) in the EXP group, while it decreased in the PLB group (p=.039, IP=-5.3%). In addition, there was a larger amplitude in the EXP compared to PLB group at retention (p=.001). Finally, writing was overall smaller while writing with target zones compared to without (F=16.38, p<.001). In the large-amplitude condition, a similar difference in amplitude was found between both groups with time, irrespective of task or cue (F=13.24, p<.001). Further analysis revealed an increased amplitude from baseline to post-training (p<.001, IP=9.8%) (**Supplementary video**) and to retention (p<.001, IP=8.4%) in the EXP group. In the PLB group on the other hand amplitude decreased

from baseline to retention (p=.041, IP=-4.7%). Also, the EXP group wrote larger than the PLB group at the post- (p=.001) and retention-test (p<.001). Moreover, differences were found between groups with respect to cueing (F=8.86, p=.003). While amplitudes were larger during writing with compared to without target zones in both groups (both p<.001), the EXP group wrote larger than the PLB group in both conditions (with: p=.052; without: p=.001). Finally, there was a larger amplitude in the untrained compared to trained sequence in general (F=91.85, p<.001). Results per condition can be found in **Supplementary table 2**.

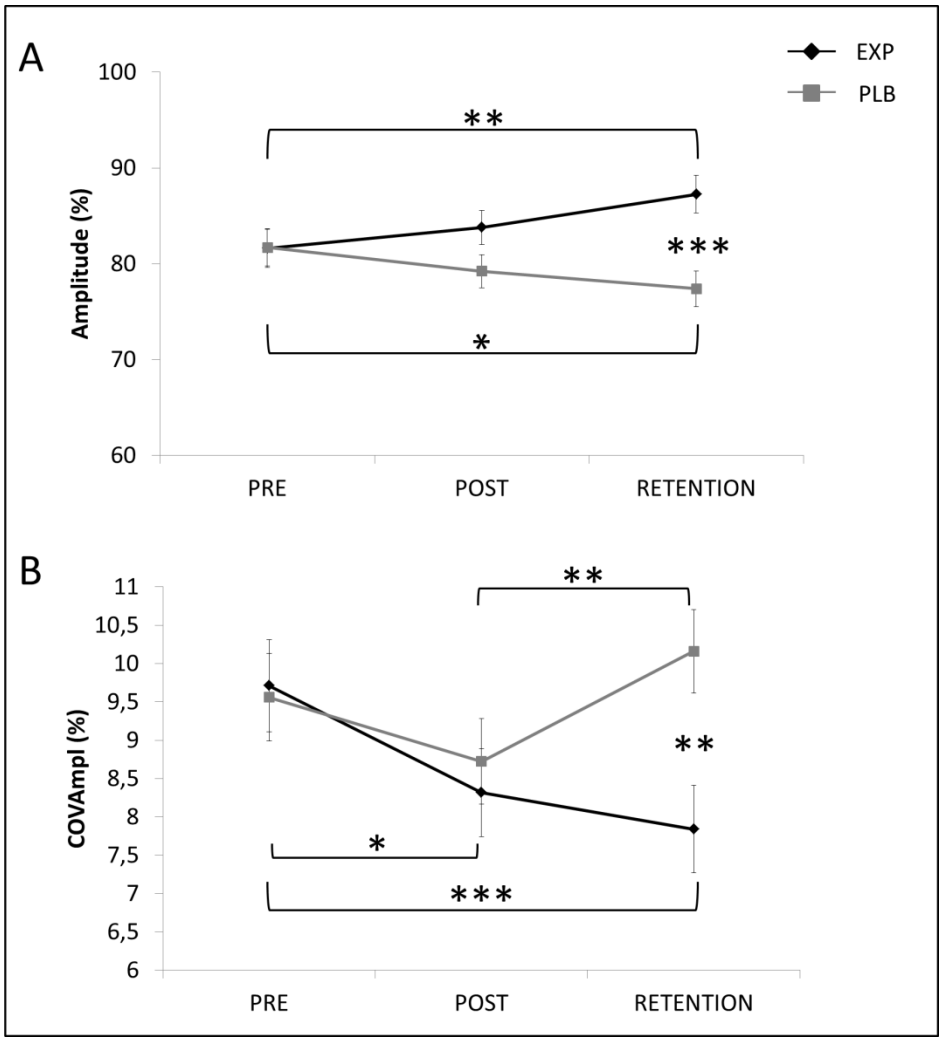

Figure 3: Performance during the transfer task. Mean and standard errors are presented. (A) Writing amplitude (% of target size) in the small-amplitude condition. (B) COVAmpl (%) in the small-amplitude condition. * indicates p<.05, ** indicates p<.01 and *** indicates p<.001.

The COV_{ampl} analysis revealed a significant difference between the two groups with time, regardless of task or cue in the small-amplitude condition (F=6.94, p<.001) (**Figure 3B**). More specifically, a decreased variability was found in the EXP group from baseline to post-training (p=.028) and retention (p=.001) and an increase in the PLB group from post-test to retention (p=.008). In addition, there was a lower variability at retention in the EXP compared to the PLB group (p=.006). Finally, there was a generally higher variability in the trained compared to the untrained task (F=19.52, p<.001) and during writing without compared to with target zones (F=10.43, p=.001). For the large-amplitude condition, the non-parametric Friedman ANOVA (χ^2=118.92, p<.001) showed a lower variability in all conditions with compared to without target zones (all p<.01). Analysis including only participants with a compliance rate ≥ 80% showed comparable results.

Paper-and-pencil test

Writing size on the SOS test differed between both groups after training (F=3.69, p=.034), with an increased writing size in the EXP group from baseline to post-training (p=.037). This was confirmed when only patients with a compliance rate of ≥ 80% were included.

DISCUSSION

The results of this study show, for the first time, that intensive amplitude training supported by visual target zones can lead to consolidation of writing skills in PD. This was shown by significant improvements in amplitude and consistency in a variety of conditions. A previous study investigating amplitude training during gross motor tasks, such as the Berlin-Big study, also showed general performance improvements using strategies focusing on goal-directed control.[45] However, previous work did not specifically test for consolidation, i.e. transfer, automatization and retention of the learning effects.

We used a DT-paradigm for investigating the robustness of motor learning by adding a distracting task and found no differences between ST and DT amplitude at baseline. However, in line with a previous study, tone counting was performed less accurately in the DT-condition suggesting that patients prioritized writing performance at the expense of the secondary task.[37] This hypothesis is supported by a recent study looking into the effect of attention on writing size in PD. It was found that focusing attention on a larger writing size led to an increased activity in the dorsolateral prefrontal cortex and anterior putamen, which suggested an increased use of attentional processing to be able to maintain writing size.[7] Similarly, the presence of visual target zones in the current study could have triggered this attentional processing, resulting in similar writing performance in ST and DT, thereby neglecting the secondary attentional task. Remarkably, after 6 weeks of intensive amplitude training, both writing amplitude and secondary task performance improved, similar to what was found for gait, suggesting automatization of the motor learning process.[46, 47] Previous fMRI-based research showed that PD patients required increased activity in brain areas such as the cerebellum, premotor area and parietal cortex relative to healthy controls during the automatic performance of sequential tasks and that these networks were also less efficiently connected.[4] Interestingly, learning-related shifts towards increased striatal activation during DT motor execution were shown in PD after short-term motor learning.[48] However, PD patients and not controls showed decreased connectivity from the striatum to the motor execution networks when asked to re-attend to the learned task, indicating a shift back from automatic to controlled processing.[48] Further fMRI studies are therefore needed to address whether the effects of long-term and intensive training can be ascribed to altered, more efficiently used, compensatory brain activity patterns, thereby freeing attentional resources for performance of the secondary task.[49]

Importantly, we also found that transfer of learning took place after practice as training effects were similar in trained and untrained writing tasks and in the presence and absence of target zones, similar to gait.[15, 50, 51] In general, amplitudes of the untrained task were larger compared to the trained task, but

improvements of amplitude were similar. The different task demands of the untrained task, requiring a larger amplitude, may offer an explanation for this task-effect. A recent study suggested that writing at smaller amplitudes in the presence of visual cues added accuracy constraints and led to decreased writing performance.[39] Thus, as the untrained task required larger strokes, micrographia may have been less distinct. Nevertheless, the current study showed consistently that long-term training was beneficial for writing at both amplitudes. The fact that there was also transfer to the paper-and-pencil test, suggests that with prolonged practice transfer to daily life writing was possible.

Retention was studied by investigating the effects after 6 weeks without training and was found to be present in both automatization and transfer tasks. This is partially in line with previous non-writing studies, showing retention not only in the same conditions, but also during untrained conditions, albeit not consistently.[15, 26, 50, 51] These results support the storage of relearned writing skills in long-term memory and underscore the neurobiological evidence for neuroplasticity in PD, mostly based on animal models.[24]

Patients were extremely compliant during the writing program and effect sizes of up to 17% for amplitude were found. Hence, offering a varied program of amplitude training, with and without visual targets seemed to have tapped the learning reserve in PD.[15] Although the study was generally not blinded, highly objective and standardized measures of writing were used via a writing tablet with high measurement accuracy. A blinded tester evaluated the paper-and-pencil test and therefore detection bias was unlikely. In addition, it has to be noted that although the tests have been previously used in PD, they were not yet formally validated. The study was also placebo-controlled, and therefore effects are most probably training-related. Nevertheless, future studies are crucial to outline the optimal strategy for relearning of writing skills in PD. In this regard, the specific effects of using visual target zones should be explored and contrasted to practice of non-specific writing. Furthermore, the writing training should be expanded to writing longer sentences and texts to optimize transfer potential to real life writing.

Conclusion

Taken together, this is the first study to show that consolidation of relearning of writing skills, measured by automatization, transfer and retention, is possible in PD and ameliorates micrographia after intensive training using a goal-directed motor control. The results indicate that intensive training to optimize writing can be included as part of neurorehabilitation for PD, as well as performed independently at home with minimal supervision. Future work should include longer follow-up periods and address how the relearning potential and transfer to daily life writing can be further maximized in PD and what the underlying neural mechanisms are.

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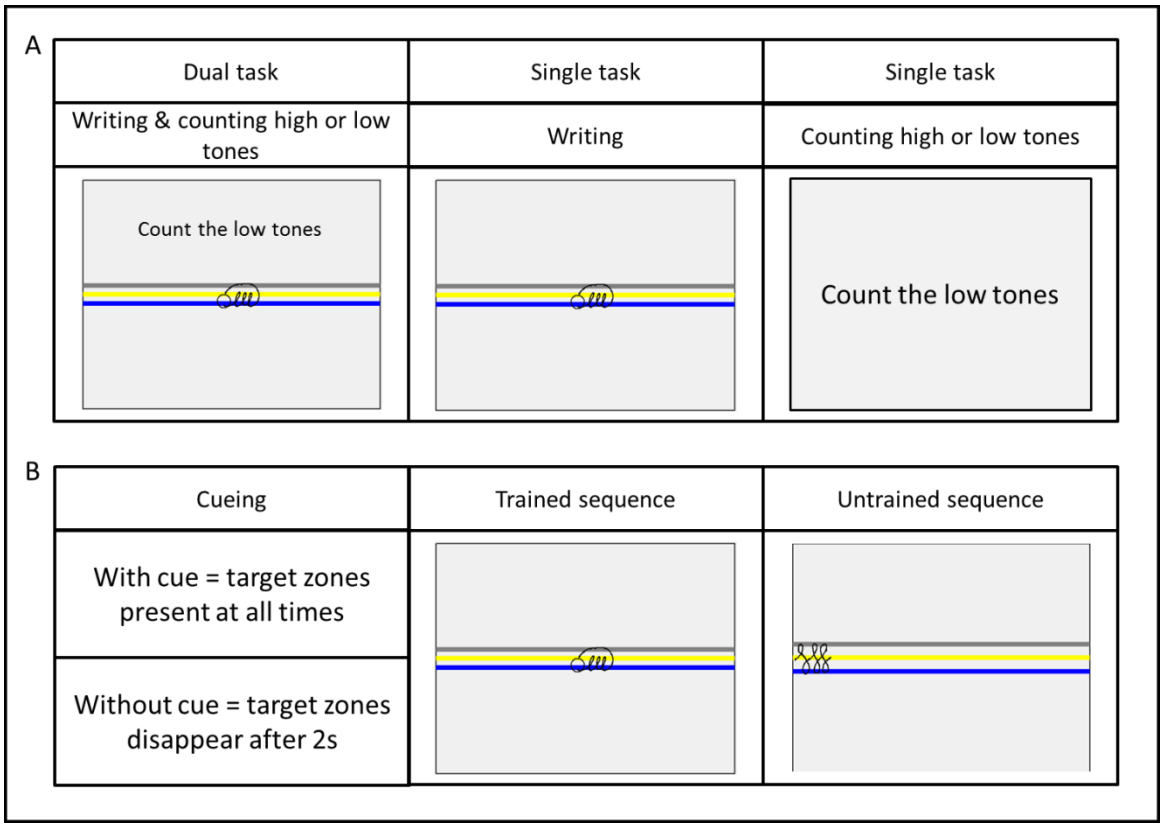
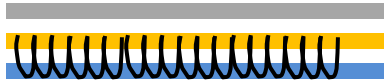
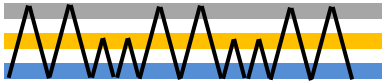
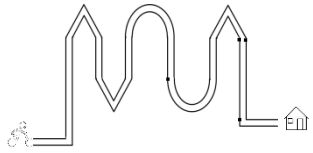
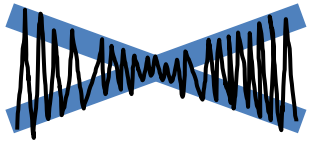
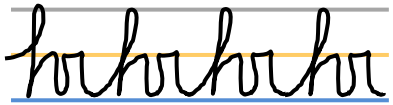


Supplementary Figure 1: Writing tasks on the touch sensitive tablet. (A) Set-up of the automatization task, displaying the different conditions. (B) Set-up of the transfer task, displaying the different conditions. The distance between the bottom of the blue (bottom) and top of the yellow (middle) target zone was either 0.6 or 1.0 cm.

<table>
<tr><th colspan="3">Supplementary table 1: Writing training program</th></tr>
<tr><td colspan="3">General set-up</td></tr>
<tr><td colspan="3">30 min / day</td></tr>
<tr><td colspan="2">Writing tablet
• 2 exercises, each consisting of 3 trials of 27s, with 6s rest in between
• Exercises performed one day at 0.6, the next at 1.0 cm</td><td>Paper
• Remaining time (± 20-25 min)
• All exercises performed at 2 sizes: 0.6 and 1.0cm
• Sufficient exercise sheets provided</td></tr>
<tr><td colspan="3">Week 1-3</td></tr>
<tr><td colspan="3">CUEING</td></tr>
<tr><td colspan="3">Broad target zones of 2 mm, with either 0.6 or 1.0 cm between the bottom of the blue and top of the yellow target zone</td></tr>
<tr><td colspan="2">○ 0.6 cm  </td><td>○ 1.0 cm  </td></tr>
<tr><td colspan="3">EXERCISES ON TABLET</td></tr>
<tr><td colspan="2">• Trained sequence  </td><td>• Writing of a pre-letter: continuous size  </td></tr>
<tr><td colspan="3">EXERCISES ON PAPER</td></tr>
<tr><td colspan="3">• Trained sequence: same as on tablet</td></tr>
<tr><td colspan="3">• Writing-related task: i.e. a different exercise each day, e.g. maze exercise, drawing exercise, etc. (for examples see week 4-6)</td></tr>
<tr><td colspan="3">• Free writing at day 5:
○ Writing a text of 5-10 lines on a blank page about a given topic (e.g. movies, news of the week, etc.)
○ Self-evaluation: highlight 2 positive aspects and 2 aspects to pay attention to the following weeks</td></tr>
<tr><td colspan="3">• Pre-letters: Two different types of pre-letters each day</td></tr>
<tr><td>Week 1</td><td>Week 2</td><td>Week 3</td></tr>
<tr><td>○ Continuously the same size
○ Gradual increase in amount of letters written jointly (1 to 6)  </td><td>○ Continuously the same size
○ Gradual increase in amount of letters written jointly (7 to entire line)  </td><td>○ Alternating between sizes
○ Gradual increase in amount of letters written jointly (2 to 6)  </td></tr>
</table>

<table>
<tr><th colspan="3">Week 4-6</th></tr>
<tr><td colspan="3">CUEING</td></tr>
<tr><td colspan="3">• Small target lines of 0.5 mm</td></tr>
<tr><td colspan="3">• 2 sizes: between the bottom of the blue and top of the yellow target zone</td></tr>
<tr><td colspan="2">○ 0.6 cm  </td><td>○ 1.0 cm  </td></tr>
<tr><td colspan="3">EXERCISES ON TABLET</td></tr>
<tr><td colspan="2">• Trained sequence in dual-task: count high or low tones while writing</td><td>  </td></tr>
<tr><td colspan="2">• Writing of a pre-letter: alternating between sizes</td><td>  </td></tr>
<tr><td colspan="3">EXERCISES ON PAPER</td></tr>
<tr><td colspan="2">• Trained sequence</td><td>  </td></tr>
<tr><td colspan="2">• Writing-related task: similar to week 1-3</td><td>   </td></tr>
<tr><td colspan="3">• Free writing at day 5: similar to week 1-3</td></tr>
<tr><td colspan="3">• Pre-letters, letters & words</td></tr>
<tr><td>Week 4</td><td>Week 5</td><td>Week 6</td></tr>
<tr><td>○ Pre-letters: similar to week 3 (entire line)
○ Letters: 2 letters each day  </td><td>○ Pre-letters: similar to week 3 (entire line)
○ Letters: 2 letters & 1 letter combination  </td><td>○ Pre-letters: similar to week 3 (entire line)
○ Words: 6 words  </td></tr>
</table>

Supplementary table 2: Amplitude (%), COV_{Ampl} (%) and correct answers on the secondary task (%) per condition and group.

	Pre		Post		Retention	
	EXP	**PLB**	**EXP**	**PLB**	**EXP**	**PLB**
			0.6 cm - Amplitude			
Single task	71.7 ± 4.2	80.0 ± 4.0	81.4 ± 3.1	73.9 ± 3.0	81.3 ± 2.9	75.1 ± 2.7
Dual task	71.4 ± 3.9	78.9 ± 3.7	80.6 ± 3.1	74.6 ± 3.0	81.4 ± 2.7	74.3 ± 2.5
Trained with cue	77.4 ± 3.1	80.3 ± 2.9	81.4 ± 2.4	77.5 ± 2.3	86.2 ± 3.0	76.5 ± 2.9
Trained without cue	82.9 ± 3.1	82.7 ± 2.9	86.8 ± 3.0	82.2 ± 2.9	90.3 ± 3.3	81.0 ± 3.2
Untrained with cue	80.7 ± 2.9	79.5 ± 2.7	84.0 ± 1.8	77.1 ± 1.8	85.5 ± 2.3	73.4 ± 2.2
Untrained without cue	85.5 ± 3.1	84.3 ± 3.0	83.1 ± 2.3	80.1 ± 2.3	87.0 ± 2.7	78.7 ± 2.6
			1.0 cm - Amplitude			
Single task	65.1 ± 3.8	70.6 ± 3.6	75.1 ± 3.0	67.8 ± 2.9	74.6 ±2.9	67.8 ±2.8
Dual task	63.4 ±3.9	70.5 ± 3.7	75.8 ± 2.9	66.6 ± 2.8	75.8 ± 3.1	68.1 ± 3.0
Trained with cue	68.9 ± 3.1	73.6 ± 3.0	77.8 ± 2.5	70.8 ± 2.4	78.1 ± 2.6	69.0 ± 2.5
Trained without cue	63.5 ± 2.6	61.1 ± 2.4	73.9 ± 2.9	62.5 ± 2.8	72.8 ± 2.8	59.0 ± 2.7
Untrained with cue	83.3 ± 2.5	80.3 ± 2.3	86.9 ± 2.0	78.2 ± 1.9	84.8 ± 2.0	76.3 ± 1.9
Untrained without cue	73.3 ± 2.7	67.1 ± 2.5	78.7 ± 2.3	67.1 ± 2.2	77.4 ± 2.6	64.4 ± 2.5
			0.6 cm - COV_{Ampl}			
Single task	9.5 ± 1.0	8.8 ± 0.9	9.3 ± 1.5	9.8 ± 1.4	8.7 ± 1.0	10.4 ± 0.9
Dual task	9.7 ± 1.1	10.6 ±1.0	10.0 ± 1.2	9.1 ± 1.2	9.1 ± 0.9	10.0 ± 0.8
Trained with cue	9.8 ± 0.9	9.4 ± 0.9	8.2 ± 0.8	8.2 ± 0.8	7.7 ± 0.8	10.5 ± 0.7
Trained without cue	10.4 ± 1.0	10.7 ± 1.0	10.7 ± 0.8	10.1 ± 0.8	9.1 ± 0.9	11.5 ± 0.9
Untrained with cue	9.5 ± 0.9	8.9 ± 0.9	5.8 ± 0.8	8.8 ± 0.7	7.1 ± 0.7	9.2 ± 0.7
Untrained without cue	9.1 ± 0.8	9.1 ± 0.8	8.6 ± 1.0	7.8 ± 1.0	7.5 ± 0.8	9.6 ± 0.8
			1.0 cm - COV_{Ampl}			
Single task	8.5 ± 1.3	8.2 ± 1.2	6.5 ± 1.1	9.2 ± 1.0	7.6 ± 1.4	9.2 ± 1.4
Dual task	9.3 ± 1.2	10.4 ± 1.2	7.7 ± 1.2	9.5 ± 1.1	6.9 ± 1.2	9.1 ± 1.1
Trained with cue	10.6 ± 1.6	10.3 ± 1.6	9.2 ± 1.7	9.0 ± 1.6	7.1 ± 1.6	11.6 ± 1.6
Trained without cue	14.2 ± 2.1	13.1 ± 2.0	11.3 ± 1.7	11.9 ± 1.7	10.5 ± 1.2	13.1 ± 1.2
Untrained with cue	7.7 ± 1.0	7.6 ± 0.9	5.6 ± 0.8	6.3 ± 0.8	7.3 ± 0.9	7.2 ± 0.8
Untrained without cue	11.3 ± 1.2	12.9 ± 1.1	7.8 ± 1.0	11.2 ± 1.0	8.7 ± 0.9	12.3 ± 0.9
			Secondary task			
Single task	94.8 ± 3.0	90.5 ± 2.8	96.7 ± 2.1	94.3 ± 2.1	98.3 ± 1.8	93.9 ± 1.8
Dual task	57.8 ± 5.6	58.8 ± 5.3	78.1 ± 4.9	63.2 ± 4.8	80.3 ± 5.3	69.3 ± 5.2

Presented values are means ± standard error, corrected for Manual Ability Measure (MAM-16).