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Abstract

Objective: To report on the control group of a trial primarily designed to investigate exercise for improving mobility in people with Parkinson's Disease (pwP). The control group undertook a handwriting intervention to control for attention and time spent practising a specific activity.

Design: Secondary analysis of a two arm parallel phase II randomised controlled trial with blind assessment.

Setting: Community

Participants: PwP able to walk ≥ 100 meters and with no contraindication to exercise recruited from the Thames valley, UK and randomised (1:1) to exercise or handwriting, via a concealed computer-generated list.

Intervention: Handwriting was undertaken at home and exercise in community facilities, both were delivered through workbooks with monthly support visits and involved practice for one hour, twice weekly, over six months.

Main measures: Handwriting was assessed, at baseline, 3, 6 and 12 months, using a pangram giving writing speed, amplitude (area) and progressive reduction in amplitude (ratio). The MSD-UPDRS item 2.7 (UPDRS-2.7) measured self-reported handwriting deficits.

Results: 105 pwP were recruited (analysed: $n=51$ handwriting, $n=54$ exercise). Forty pwP adhered to the handwriting program most completing ≥ 1 session/week. Moderate effects were found for amplitude (total area: $d=0.32$ 95%CI $-0.11:0.7$, $p=0.13$) in favour of handwriting over 12 months, effects for writing speed and ratio parameters were small

≤0.11. Self-reported handwriting difficulties also favoured handwriting (UPDRS-2.7: OR= 0.55 95%CI 0.34:0.91, p=0.02). No adverse effects were reported

Conclusion PwP generally adhere to self-directed home handwriting which may provide benefit with minimal risk. Encouraging effects were found in writing amplitude and, moreover, perceived ability. (ClinicalTrials.Gov:NCT01439022).

Introduction

Problems with handwriting are frustrating and debilitating and affect the majority of people with Parkinson's Disease.¹ Manifest as micrographia it is a distinctive feature of the condition characterised by small handwriting and/or a progressive reduction in size character size through a sentence² coupled with a reduction in writing speed and legibility. Whilst, dopaminergic medication partially improves symptoms associated with writing speed and to an extent size of writing³ there is no specific treatment currently available, with current advice limited to strategies to reduce the impact of the symptom.^{4,5}

Handwriting is a co-ordinated highly automated motor skill that has been well-habituated by adulthood.⁶ In Parkinson's Disease impaired automaticity is thought to contribute to handwriting deficits^{2, 7} and attention has been shown to improve symptoms of both constantly small writing size (consistent micrographia) and progressive reduction in character size during a sentence (progressive micrographia).² External stimuli such as visual, auditory or verbal cues have been shown to increase writing size,⁸ with practise resulting in increased movement speed.⁹ However, the immediate effects of cueing and attentional control overcoming impaired automatic processes² may not be a good predictor for long-term retention of improvements.^{8, 10} Indeed the basal ganglia's role in motor learning is implicated in the impaired ability of people with Parkinson's to retain new motor skills¹¹ and until recently whether people with Parkinson's could acquire and retained improvements in handwriting remained equivocal.⁸ However, the results of a recent study are encouraging that people with Parkinson's are able to improve handwriting skills with intensive training.¹²

We conducted a phase II randomised control trial of an exercise intervention aimed at improving mobility and utilised handwriting practice as a control group.¹³ In developing the protocol we consulted people with Parkinson's who identified that handwriting an important issue and designed a handwriting programme for the control group in order to engage people through the study period. Here we report results specific to the handwriting, control group, of the phase II trial.

Methods

See Collett et al¹³ for a full trial reporting according to CONSORT guidelines.¹⁴ The trial received ethical approval (NRES: 11/SC/0267) and was registered with ClinicalTrials.Gov (NCT01439022).

Design

Secondary evaluation of handwriting from a two arm parallel single blind phase II randomised controlled trial of exercise. Participants recruited to the study were randomized individuals (1:1) into either exercise or handwriting groups via computer generated randomisation. Group allocation was concealed from assessors until after the end of the study.

Participants

People were recruited from health services and local Parkinson's UK groups in the Thames valley region of the UK. Inclusion criteria (specifically aimed at the exercise and mobility component) were: (i) diagnosis of idiopathic Parkinson's Disease (as defined by the UK PD Society Brain Bank criteria); (ii) able to walk ≥ 100 meters (with or without walking aid).

Exclusion criteria were: (i) A diagnosis of dementia; (ii) history of additional prior neurological condition; (iii) severe depression or psychosis or a mental state that would preclude consistent active involvement with the study over its duration; (iv) cardiac precautions that would prevent the subject from participating in the intervention; (v) any known contraindication to exercise; (vi) reduced cognitive function of any cause (mini-mental state examination <23); (vii) an orthopaedic condition that limited independent walking. Participants' medication was continued as normal and was recorded.

Intervention

Both the exercise and handwriting groups were prescribed activity sessions lasting 60minutes twice a week over a period of six months.

Handwriting group

The handwriting program was developed considering the Parkinson's Disease Society guidance information sheet for handwriting¹⁵ and co-designed with people with Parkinson's. An iterative process was used to pilot and refine the content of the program. The handwriting intervention was developed as a printed workbook with each session clearly defined for each week. A clinical exercise professional went through the first workbook with the participant face-to-face at the participants' homes ensuring they knew how to complete the workbooks. The handwriting sessions took place in the participant's home supported by further monthly visits to review progress; additional equipment required for hand exercises were 'play dough' putty, clothes pegs, lolly sticks and a jar, and a soft tennis ball (provided by the study). Successive workbooks were delivered at monthly sessions.

The handwriting intervention totalled 48 sessions over a 24 week period (2x a week). The approximately 60minute session consisted of the following; warm up exercises for both hands (wriggling fingers, making a fist, touching fingers with thumb, circling wrists, shrugging shoulders and stretching hands) and then a variety of writing activities. Writing activities involved cued (in the form of printed lines that set target writing amplitude zones), free writing (no lines), copying shapes, writing pangrams, and activities such as writing a post card and filling in a form. The session finished with hand exercises (rolling putty, using pegs, placing sticks in a jar, and ball drop and catch). Writing activities varied from workbook to workbook in order to maintain interest. An example workbook can be found at [http://www.shs.brookes.ac.uk/images/pdfs/research/movement-science/example_handwriting_booklet.pdf]. There was no formal tailoring or progression, as all participants in the handwriting group followed the same workbooks. However, participants could monitor their own performance using the pangram 'The quick brown fox jumps over the lazy dog' which was performed every session and feedback was given by the clinical exercise professional at the monthly support sessions.

Exercise group

The exercise program was delivered through an exercise booklet and consisted of 30minutes of aerobic training (55-85% age predicted heart rate max (220-age)) followed by 30minutes of resistance training, at a local leisure centre. Further details can be found in Collett et al¹³.

Assessment

Demographic information was ascertained at the baseline assessment. All outcome measures were performed at baseline (entry), 3months (halfway intervention), 6months and (end intervention) and 12months (follow up). Measurements were made by the same assessor blind to intervention allocation. Participants followed their usual Parkinson's medication regime and if a patient had On and Off periods, assessments were carried out during ON state.

Handwriting Measures

Handwriting performance

Handwriting performance was evaluated in all patients using the pangram '*the quick brown fox jumps over the lazy dog*' pangram. Patients were instructed to copy the sentence on a blank piece of A4 paper (no lines) as fast as they could, and the time taken to complete the sentence was recorded. Another assessor blinded to group allocation analysed the writing. The area (height x width) of the first '*the*' in the sentence and the second '*the*' in the sentence was measured by hand using a ruler, to the nearest half a millimetre, to determine writing amplitude and the ratio between them to evaluate any progressive reduction in amplitude. The ratio is reported as a percentage of area of the second '*the*' in relation to the first '*the*', thus a percentage of less than 100% would represent a reduction in amplitude. Progressive micrographia was defined as a reduction of >30% and severe progressive micrographia as a reduction of >50%.¹

Self-reported handwriting difficulties

Perceived handwriting difficulties were assessed using Item 2.7 on the MDS-UPDRS, which is a 0 to 4 scale (0: normal: no problems, 4: Severe: Most or all words cannot be read) asking *'Over the past week, have people usually had trouble reading your handwriting?'*

Data analysis

Whilst, this was a phase II trial and not designed to determine efficacy, sample size was based on the estimated effect on two minute walk distance and did not considered effects on handwriting outcomes. Descriptive statistics were calculated for demographic characteristics and compliance data. Independent samples T-test or χ^2 test was used to assess differences between group mean and frequencies at baseline. All outcome data were analysed based on the intention-to-treat principle. For handwriting performance outcome data the Linear Mixed Models (LMM) procedure of SAS 9.4 was used to determine the mean changes in measures, as response variables, according to two intervention regimes (exercise and handwriting) and three repeated measurements, using baseline as a covariate. Further and based on the differences of Least Squares (Marginal) means between two groups (exercise vs. handwriting) provided by LMM analysis, powers, effect sizes (Cohen's d) and their 95% non-central confidence limits were calculated.

Self-reported handwriting difficulties (Item 2.7 on the MDS-UPDRS) was considered ordinal data and, therefore, analysed by Generalised Mixed Model (Glimmix) procedure of SAS 9.4 with multinomial response and cumulative logit link-function to determine the odds ratios.

Results

Recruitment, randomisation and participant flow

Figure 1 shows participant flow, between December 2011 and August 2013 the trial recruited 105 participants from the Thames valley UK. One participant allocated to receive handwriting received exercise and was included in analysis as part of exercise group, resulting in 54 in the exercise and 51 in the handwriting groups.

Table 1 shows an imbalance after randomisation with the area of the second 'the' being significantly greater in the handwriting group at baseline. There was also a trend for the exercise group to have faster handwriting and nine hole peg test times. The statistical model account for these differences in outcome analysis by using baseline data as a covariate.

Attrition after randomisation was similar between groups (figure 1). In the handwriting group at the primary assessment (6months) point withdrawing without reason and unrelated medical reasons were the main cause of lost to follow-up at the primary (6month) assessment point equally accounting for all lost to follow ups.

Intervention fidelity.

Handwriting group: In total 11 individuals had discontinued intervention by the 6month follow-up, most did not give a reason (n=6), one person lost the handwriting booklets, one did not reply to further correspondence and three discontinued intervention due to unrelated medical reasons. Two serious adverse events were recorded that did not result in discontinue intervention (a fall that occurred during the intervention and a death which occurred after the intervention in the follow-up period). There were no related adverse

events in the handwriting group. The median number of handwriting sessions performed was 40 out of the 48 prescribed sessions and most people (n=36) did more than one session a week on average.

Exercise group: Figure 1 shows attrition in the exercise group was similar, further information can be found in Collett et al.¹³

Outcome

Handwriting performance data is reported in table 2, effect sizes are between group and considered all three follow-up assessments and used baseline measures as covariate to account for any differences. Moderate effect sizes [16] were found for writing amplitude outcomes in favour of the handwriting group, with the direction consistent across amplitude measures and assessments and the largest effect found for total area 0.32 (95%CI - 0.11:0.74). Effects for progressive reduction in writing size, although favouring the handwriting group, were small and inconsistent across assessments (ES 0.11 (-0.31:0.53)) and, whilst, there appeared little change in handwriting speed the overall direction of effect favoured the exercise group (0.10 (-0.33:0.52)).

Table 3 shows perceived handwriting difficulties and the results of the generalised mixed model analysis. Considering all assessments we found an overall significant difference (p=0.02) between groups. By 12 months (6months after the intervention) there was reduction in the proportion of people experiencing severe and moderate problems with handwriting in the handwriting group whereas there was an increase in the proportion of those in the exercise group experiencing severe problems.

Discussion

We observed sustained participation in a 6 month home writing practice intervention and a consistent trend towards improvement in writing at 12 months, six months after the end of active practice. This supports the conclusions of the only previous randomised trial of writing practice, suggesting it is possible for people with Parkinson's to acquire and retained improvements in this debilitating aspect of the condition.¹²

We found handwriting amplitude may be maintained or improved through pragmatic intervention. These possible benefits are consistent with the results Nickaerts et al¹² who evaluated a more intensive intervention (30min a day x five days a week x 6 weeks), specifically targeting amplitude using spatial cues (target amplitude zones), finding improvements of between 7% and 17% in trained (3-loop sequence) and untrained writing tasks (figure of eight sequence) with and without target zones compared to a control group. They had excellent compliance with the intervention (95.8% of practice sessions) and found improvements were maintained at their 6 week follow up. Over our 6 month intervention period we found that, although 11 people discontinued intervention, most (71%) did more than one practice session a week. Taking this into account our results, using intention-to-treat analysis, are extremely encouraging that a less intensive, but pragmatic, intervention may lead to improvements in writing amplitude that are maintained 6 months post intervention. However, it is important to highlight that, due to a clerical error, not discovered until after the intervention, one individual allocated to handwriting received the exercise intervention. Although contrary to intention-to-treat it was deemed appropriate for this participant to be analysed according to the intervention received due to the exploratory nature of the study.

Nickaerts et al¹² also reported improvements from the writing tasks practiced, which did not involve writing letters and forming word and sentences, transferred to a paper and pencil 'free' writing test. Our intervention involved a variety of writing tasks but fundamentally involved writing words, sentences and included real world writing tasks (eg filling in forms). Whilst, the sizes of the effects in handwriting amplitude were not as large as that of Nickaerts et al,¹² in addition to being a less intensive intervention, our outcome was based on writing a pangram. This task may be less sensitive to change than reproducing a repetitive pattern sequence, but may be more reflective of handwriting ability. Indeed, we found significant improvements in self-reported handwriting difficulties. Although it might be expected that perceived writing problems may be improved when taking part in a handwriting intervention, importantly we found these benefits remained. Notably, at the 12month assessment 28% in the exercise group reported moderate and severe handwriting problems, whereas only 8% of handwriting group were in these categories. However, whilst similar between groups, it is important to consider numbers loss to follow up at 12 months when interpreting these results.

To date research has focused on measuring handwriting on an impairment level, though assessments such as writing repetitive pattern sequences ('elele' sequence), culminating in using electronic tablets to digitise the writing of the repetitive pattern sequences in order to obtain in depth temporal and spatial data¹⁷. Whilst, these measures have revealed extremely valuable insights into the underlying mechanisms of the symptom² they may not be optimal at assessing improvements in handwriting function. Naacherates et al¹² found improvement in a paper and pencil 'free' writing test (handwriting SOS) designed for children¹⁸ and our largest effects were seen in perceived handwriting benefits based on

legibility. In order to evaluate the benefits of handwriting interventions measures that have greater ecological relevance may be more appropriate than the current emphasis on writing repetitive pattern sequences and measuring at the impairment level.

The presence of micrographia has been shown to be correlated with Bradykinesia, with a reduction in writing speed a feature of the handwriting deficits found in Parkinson's.¹ Our intervention did not improve writing speed and the majority of research has investigated the effects of spatial (amplitude) rather than temporal aspects of the symptom.⁸ However, Swinnen et al⁹ found that auditory temporal cueing (metronome) lead to short term improvements in writing time. Temporal cueing may have particular benefit for those with *freezing of gait* as the greater impairments to rhythmical arm movements found in those with *freezing of gait*, compared to those without freezing of gait, are diminished in the presence of a temporal cue.¹⁹ Indeed people with Parkinson's with freezing of gait have shown to benefit less from the handwriting intervention of Nickaerts et al.^{12, 20} In addition there is emerging evidence that forcing movement speed, exercise at a great rate than voluntarily preferred, may improve global motor function.²¹ However, temporal cueing has yet to be tested in a handwriting trial but may be relevant for optimised or tailored interventions.

There are thought to be two, usually co-existing, manifestations of micrographia associated with distinct mechanisms.^{1, 2} Wu et al² found consistent micrographia was primarily related to basal ganglia motor circuit dysfunction and progressive micrographia related to basal ganglia motor circuit dysfunction and disconnection with the pre supplementary motor area, rostral cingulate motor area and cerebellum. Functional imaging revealed only consistent micrographia recruited the superior parental lobe. The superior parental lobe is

associated with representation, selection and production of shapes during writing.²² Our intervention involved copying shapes, words and sentences thus may have stimulated this pathway giving a possible explanation that, although our intervention appeared to have a moderate effect on writing amplitude, only a small effect was found on progressive reduction in amplitude. However it should also be considered that the majority of people in our study it not present with progressive micrographia.

This study has to be viewed within the limitation that it was not designed to evaluate the handwriting intervention, thus the sample size, eligibility criteria, intervention and outcome measures were primary chosen for the aims of the main study¹³ and this should be considered when interpreting results. Never-the-less the study produced important and relevant insights into treating mircographia that benefit from the rigor of a randomised controlled trial. This coupled with the pragmatic nature of the intervention delivery make the results highly relevant for Parkinson's rehabilitation. In addition this approach enabled a handwriting intervention to be evaluated which may have not have been a justified in its own right. Indeed control groups are often underutilised and potentially represent an efficient means of testing distinct or nascent interventions.^{23, 24.}

In summary people with Parkinson's will generally adhere to self-direct home handwriting practice over a 6-months period. We found no related adverse events and there is minimal conceivable risk associated with handwriting practice. Our positive results, and those of others, suggest that practice can lead to benefits to handwriting that are retained.¹² Therefore, current evidence suggests that people with Parkinson's wishing to practise handwriting should not be discouraged. However, there appears to be opportunity to refine

interventions and develop measures beyond the impairment the level, in order to inform optimal treatment content, dose and delivery. Thus more research is needed to support a substantive evaluation of efficacy.

Clinical Messages

- These results suggest people with Parkinson's will, for the most part, adhere to a largely self-managed home handwriting practice over 6months
- The results are encouraging that pragmatic intervention has the potential to lead to improvements in handwriting
- The study identifies the need for more ecologically valid outcome measures to assess handwriting function in Parkinson's Disease

Conflict of interest

The authors report no conflict of interest

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Table 1: Baseline characteristic and pre intervention assessment data

	Exercise	Handwriting	Delta (p)
<i>Demographics</i>	n=54	n=51	
Age (years)	66±9	67±7	-2±2 (0.307)
Gender (M:F)	31:23	30:21	X ² (0.883)
MMSE	29±1	29±1	0±0 (0.882)

Time since diagnosis	4.8±4.1	5.3±4.1	-0.5±0.8 (0.547)
UPDRS III	16.7±10.1	19.9±9.9	-2.4±2.0 (0.214)
9 hole peg test (sec)	24.9±5.4	26.8±5.9	-1.9±1.1 (0.089)
<i>On PD Medication (Y:N)</i>	52:2	47:4	
<i>Levodopa</i>	<i>n=39</i>	<i>n=30</i>	
<i>Dopamine agonists</i>	<i>n=25</i>	<i>n=29</i>	
<i>Anticholinergics</i>	<i>n=2</i>	<i>n=3</i>	
<i>MOA-B inhibitors</i>	<i>n=14</i>	<i>n=14</i>	
<i>COMT inhibitors</i>	<i>n=2</i>	<i>n=1</i>	
<i>Handwriting</i>			
UPDRS 2.7	1 (IR:1)	1(IR:2)	0 (0.154)
Progressive Micrographia (Y:N)	25:29	17:34	X ² (0.175)
<i>30-49% reduction</i>	<i>n=9</i>	<i>n=7</i>	
<i>>50% reduction</i>	<i>n=16</i>	<i>n=10</i>	
Time	18.7±5.2	21.3±7.6	-2.6±1.3 (0.051)
Area 1	24.3±12.6	27.8±12.7	-3.5±2.5 (0.19)
Area 2	18.7±13.5	25.2±18.0	-6.5±3.1 (0.037)
Total Area	43.1±23.8	52.3±29.4	-9.2±12.6 (0.079)
Ratio	78.4±40.7	89.0±39.2	-7.8±26.2 (0.178)

Mean±SD, Delta = between group difference (Exercise – Handwriting) ± Standard error of difference reported with p value of independent samples T test, for nominal data p value for X² statistic reported. Abbreviations: MMSE = mini-mental State Examination; MOA-B = Monoamine oxidase type B; COMT = catechol-O-methyl transferase; MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale part III, UPDRS 2.7 = Movement Disorder Society Unified Parkinson's Disease Rating Scale part II, item 2.7 (reported as median with Interquartile range (IR))

Table 2: Handwriting Performance

	3month			6month			12month			Effect size
	Exercise	Handwriting	Delta	Exercise	Handwriting	Delta	Exercise	Handwriting	Delta	d (95%CI)
Time (sec)	19.5±0.6	20±0.6	-0.5±0.8	19.4±0.7	19.5±0.7	-0.2±0.9	18.8±0.6	19.1±0.6	-0.2±0.8	0.10 (-0.33:0.52)
Area 1 (mm ²)	29.4±2.1	31.7±2.0	-2.2±2.9	28.1±1.8	30.4±1.7	-2.3±2.4	27.9±1.8	31.1±1.9	-3.1±2.6	0.28 (-0.15:0.70)
Area 2 (mm ²)	19.9±1.6	23.7±1.6	-3.7±2.3	22.4±1.5	22.9±1.5	-0.5±2.2	23.3±1.7	25.6±1.8	-2.3±2.5	0.26 (-0.17:0.68)
Total Area (mm ²)	49.3±2.9	55.3±2.9	-6.0±4.1	50.5±2.6	53.0±2.7	-2.5±3.8	51.3±2.9	56.7±3.0	-5.5±4.2	0.32 (-0.11:0.74)
Ratio (%)	66.7±5.3	77.1±5.3	-10.4±7.5	81.2±5.0	75.2±5.1	6.0±7.1	78.9±6.1	86.3±6.4	-7.4±8.8	0.11 (-0.31:0.53)

Least squares means ± Standard error estimates, delta = between group difference (Exercise – Handwriting), Effect size = Cohen’s d based on least squares (marginal) means differences over all assessments with non-central 95% Confidence Intervals. Abbreviations: Timed =time to complete pangram, Area 1 = area of first ‘the’ in the pangram, Area 2 = area of second ‘the’ in the pangram, Total Area = Area 1+ Area 2, Ratio = percentage of area of the second ‘the’ in relation to the first ‘the’.

Table 3: Self-reported handwriting difficulties

UPDRS 2.7 category	3month (n= 43 exercise, n= 45 handwriting)					6month (n= 44 exercise, n= 45 handwriting)					12month (n= 36 exercise, n= 32 handwriting)					Odds Ratio
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	(95%CI)
Exercise (%)	20.0	35.6	20.0	20.0	4.4	21.7	26.1	30.4	17.4	4.3	18.6	23.3	30.2	16.3	11.6	0.55 (0.34:0.91)
Handwriting (%)	43.2	27.3	15.9	9.1	4.5	38.6	31.8	13.6	11.4	4.5	35.1	32.4	24.3	5.4	2.7	

Percentage of responses according to level on the MDS-UPDRS 2.7, (0: normal: no problems, 4: Severe: Most or all words cannot be read). Odds ratio based on

Generalised Mixed Model over all assessments with 95% confidence intervals. Abbreviations: UPDRS 2.7 = Movement Disorder Society Unified Parkinson’s Disease Rating

Scale part II, item 2.7

