Cueing training in the home improves gait-related mobility in Parkinson’s disease: the RESCUE trial

A Nieuwboer, G Kwakkel, L Rochester, D Jones, E van Wegen, A M Willems, F Chavret, V Hetherington, K Baker, I Lim

Objective: Gait and mobility problems are difficult to treat in people with Parkinson’s disease. The Rehabilitation in Parkinson’s Disease: Strategies for Cueing (RESCUE) trial investigated the effects of a home physiotherapy programme based on rhythmical cueing on gait and gait-related activity.

Methods: A single-blind randomised crossover trial was set up, including 153 patients with Parkinson’s disease aged between 41 and 80 years and in Hoehn and Yahr stage II–IV. Subjects allocated to early intervention (n = 76) received a 3-week home cueing programme using a prototype cueing device, followed by 3 weeks without training. Patients allocated to late intervention (n = 77) underwent the same intervention and control period in reverse order. After the initial 6 weeks, both groups had a 6-week follow-up without training. Posture and gait scores (PG scores) measured at 3, 6 and 12 weeks by blinded testers were the primary outcome measure. Secondary outcomes included specific measures on gait, freezing and balance, functional activities, quality of life and carer strain.

Results: Small but significant improvements were found after intervention of 4.2% on the PG scores (p = 0.005). Severity of freezing was reduced by 5.5% in freezers only (p = 0.007). Gait speed (p = 0.005), step length (p < 0.001) and timed balance tests (p = 0.003) improved in the full cohort. Other than a greater confidence to carry out functional activities (Falls Efficacy Scale, p = 0.04), no carry-over effects were observed in functional and quality of life domains. Effects of intervention had reduced considerably at 6-week follow-up.

Conclusions: Cueing training in the home has specific effects on gait, freezing and balance. The decline in effectiveness of intervention effects underscores the need for permanent cueing devices and follow-up treatment. Cueing training may be a useful therapeutic adjunct to the overall management of gait disturbance in Parkinson’s disease.
Design and procedures

The present study was a single-blind, randomised, clinical trial with a crossover design with no wash-out period. The choice of design was based on previous evidence of the short-lasting effects of cueing, the advantage of providing treatment for all patients, and increasing the statistical power within the constraints of research funding. In each centre, patients were randomly allocated in permuted blocks of six to an early or late intervention group by an independent investigator not involved in data analysis. Allocation was concealed by the use of opaque sealed envelopes. The early group received a cueing programme delivered in nine treatment sessions for 30 min over 3 weeks, immediately followed by 3 weeks in which no training was received. Subjects in the late group were put on a 3-week waiting list immediately followed by 3 weeks of cueing training. Both treatment arms underwent a follow-up period of 6 weeks without training. Medical treatment continued unchanged throughout the study. Before the Rehabilitation in Parkinson's Disease: Strategies for Cueing (RESCUE) trial, therapists and testers underwent separate training sessions lasting a full week to standardise the procedures in all centres.

Intervention

Cueing training was delivered in the home by one therapist at each location. A prototype cueing device, specifically developed for the study, provided three rhythmical cueing modalities: (1) auditory (a beep delivered through an earpiece); (2) visual (light flashes delivered through a light-emitting diode attached to a pair of glasses); and (3) somatosensory (pulsed vibrations delivered by a miniature cylinder worn under a wristband). Patients tried all cueing modalities in the first week, but trained with their preferred modality. By correcting the temporal aspects of gait, cueing modalities in the first week, but trained with their preferred modality. By correcting the temporal aspects of gait, cueing training aimed to improve step length and walking speed, prevent freezing episodes and improve balance.

Cued practice was applied during a variety of tasks and environmental situations and consisted of the following components: gait initiation and termination, heel strike and push-off, sideways and backwards stepping, walking while closing doors, and walking over various surfaces and long distances. For “freezers”, cues were applied to facilitate continuation of gait during turns and manoeuvres in tight places and doorways. On the basis of previous experiments undertaken by the RESCUE consortium and the literature, evidence-based cueing guidelines were drawn up, specifying the cueing parameters and instructions for different profiles of patients (available on CD-Rom at http://www.rescueproject.org/).

Outcome measures

As this study wanted to measure the training effects and not the immediate effects of cueing, outcome measures were tested without the cueing device. Most outcomes described below were tested for reliability and validity at home before the trial by three testers and during two consecutive visits. Part of this study, including the full method, was published elsewhere.

1. The primary outcome measure was the posture and gait (PG) score, a composite score of gait and balance UPDRS items (13–15 and 29–30), reflecting the main aims of cueing training (ICC = 0.79).
2. To explore the specific effects of cueing training, secondary outcome measures consisted of the following:
   a. Gait and balance measures: 10-m test of walking at the person’s preferred walking speed, using a stopwatch to calculate gait speed (m/s; ICC = 0.81), step length (m) and step frequency (steps/min); functional reach (ICC = 0.74); timed single leg and tandem stance until subjects reached a maximum of 30 s; Freezing of Gait Questionnaire (ICC = 0.84); and Timed Get Up and Go Test (ICC = 0.88). Timed walking and Get Up and Go tests were standardised for each patient’s home.
   b. Activity measures: Nottingham Extended Activities of Daily Living Index (ICC = 0.93) and Falls Efficacy Scale (ICC = 0.88).
   c. Participation measures: Parkinson’s Disease Questionnaire-39 (ICC = 0.79) and Carer Strain Index (ICC = 0.85).

A falls diary was left in the patient’s home during the trial period to indicate the number of falls as a measure of possible adverse cueing effects. A dichotomised score was derived (falls = 1 or no falls = 0) at crossover and at the end of therapy from the recorded number of falls during the previous 3-week periods and at follow-up for the previous 6 weeks. At test 1, the dichotomised score was calculated from the number of falls during the previous 3 months.

Descriptive measures included the Mini Mental State Examination, the Brixton Test for executive function, and the Hospital Anxiety and Depression Scale.

Assessment protocol

All outcome measures were assessed immediately before randomisation (test 1) and at 3 (test 2), 6 (test 3), and 12 weeks (test 4). One trained tester at each centre, not involved in training and blinded to group allocation, performed all assessments in the patient’s home. Each patient was assessed at the same time of day in the on phase, approximately 1 h after drug intake, to control for variations due to the drug cycle. The order of tests was randomised for each patient. Testers verified that patients had taken their drugs, and the efficacy of drugs was checked at each assessment.

Statistical analysis

Power analysis before the trial indicated that 150 patients were required for a 10% change relative to baseline values on the PG score (0.6 points) with a power of 80% and a critical value of 5% for statistical significance, allowing a drop-out of 10%.

The RESCUE trial

The present study was a single-blind, randomised, clinical trial with a crossover design with no wash-out period. The choice of design was based on previous evidence of the short-lasting effects of cueing, the advantage of providing treatment for all patients, and increasing the statistical power within the constraints of research funding. In each centre, patients were randomly allocated in permuted blocks of six to an early or late intervention group by an independent investigator not involved in data analysis. Allocation was concealed by the use of opaque sealed envelopes. The early group received a cueing programme delivered in nine treatment sessions for 30 min over 3 weeks, immediately followed by 3 weeks in which no training was received. Subjects in the late group were put on a 3-week waiting list immediately followed by 3 weeks of cueing training. Both treatment arms underwent a follow-up period of 6 weeks without training. Medical treatment continued unchanged throughout the study. Before the Rehabilitation in Parkinson’s Disease: Strategies for Cueing (RESCUE) trial, therapists and testers underwent separate training sessions lasting a full week to standardise the procedures in all centres.

Intervention

Cueing training was delivered in the home by one therapist at each location. A prototype cueing device, specifically developed for the study, provided three rhythmical cueing modalities: (1) auditory (a beep delivered through an earpiece); (2) visual (light flashes delivered through a light-emitting diode attached to a pair of glasses); and (3) somatosensory (pulsed vibrations delivered by a miniature cylinder worn under a wristband). Patients tried all cueing modalities in the first week, but trained with their preferred modality. By correcting the temporal aspects of gait, cueing training aimed to improve step length and walking speed, prevent freezing episodes and improve balance.

Cued practice was applied during a variety of tasks and environmental situations and consisted of the following components: gait initiation and termination, heel strike and push-off, sideways and backwards stepping, walking while closing doors, and walking over various surfaces and long distances. For “freezers”, cues were applied to facilitate continuation of gait during turns and manoeuvres in tight places and doorways. On the basis of previous experiments undertaken by the RESCUE consortium and the literature, evidence-based cueing guidelines were drawn up, specifying the cueing parameters and instructions for different profiles of patients (available on CD-Rom at http://www.rescueproject.org/).

Outcome measures

As this study wanted to measure the training effects and not the immediate effects of cueing, outcome measures were tested without the cueing device. Most outcomes described below were tested for reliability and validity at home before the trial by three testers and during two consecutive visits. Part of this study, including the full method, was published elsewhere.

1. The primary outcome measure was the posture and gait (PG) score, a composite score of gait and balance UPDRS items (13–15 and 29–30), reflecting the main aims of cueing training (ICC = 0.79).
2. To explore the specific effects of cueing training, secondary outcome measures consisted of the following:
   a. Gait and balance measures: 10-m test of walking at the person’s preferred walking speed, using a stopwatch to calculate gait speed (m/s; ICC = 0.81), step length (m) and step frequency (steps/min); functional reach (ICC = 0.74); timed single leg and tandem stance until subjects reached a maximum of 30 s; Freezing of Gait Questionnaire (ICC = 0.84); and Timed Get Up and Go Test (ICC = 0.88). Timed walking and Get Up and Go tests were standardised for each patient’s home.
   b. Activity measures: Nottingham Extended Activities of Daily Living Index (ICC = 0.93) and Falls Efficacy Scale (ICC = 0.88).
   c. Participation measures: Parkinson’s Disease Questionnaire-39 (ICC = 0.79) and Carer Strain Index (ICC = 0.85).

A falls diary was left in the patient’s home during the trial period to indicate the number of falls as a measure of possible adverse cueing effects. A dichotomised score was derived (falls = 1 or no falls = 0) at crossover and at the end of therapy from the recorded number of falls during the previous 3-week periods and at follow-up for the previous 6 weeks. At test 1, the dichotomised score was calculated from the number of falls during the previous 3 months.

Descriptive measures included the Mini Mental State Examination, the Brixton Test for executive function, and the Hospital Anxiety and Depression Scale.

Assessment protocol

All outcome measures were assessed immediately before randomisation (test 1) and at 3 (test 2), 6 (test 3), and 12 weeks (test 4). One trained tester at each centre, not involved in training and blinded to group allocation, performed all assessments in the patient’s home. Each patient was assessed at the same time of day in the on phase, approximately 1 h after drug intake, to control for variations due to the drug cycle. The order of tests was randomised for each patient. Testers verified that patients had taken their drugs, and the efficacy of drugs was checked at each assessment.

Statistical analysis

Power analysis before the trial indicated that 150 patients were required for a 10% change relative to baseline values on the PG score (0.6 points) with a power of 80% and a critical value of 5% for statistical significance, allowing a drop-out of 10%.

www.jnnp.com
The success of blinding and randomisation procedures was explored by comparing early and late groups using Wilcoxon tests Mann–Whitney U tests, χ² tests and unpaired t tests.

Exploratory analysis showed carry-over effects of treatment in the control period (test 3–test 2) in the early group. Hence, intervention effects were estimated using the first three assessments (tests 1–3), with multiple linear regression models accounting for repeated measures. Where appropriate, a linear, logistic or Cox regression model was fitted for each outcome with PROC MIXED and PROC GENMOD in SAS (V 8.2). In each model the same predictors were adopted, including indicators to represent time, intervention and carry-over. A logistic regression model with generalised estimating equations evaluated the effect of intervention on the risk of falling. A Cox regression model with frailty term verified the effect of intervention on the hazard of failing the timed balance tests (inability to remain standing for a maximum of 30 s), using the coxph function in Splus 2000. To explore whether cueing had an effect on movements that were not targeted by training, upper limb repetitive movement scores (UPDRS items 23–25) were analysed. Intervention effects are reported as log odds and hazard ratios (OR and HR; = exp(β)) with 95% confidence intervals are presented for the logistic and Cox regression models.

The statistical models adopted in this study were based on the assumption that missing values occur randomly and used the remaining information even if missing values were occasionally present. Missing values occurred in 1.7% of all outcomes over the four time points and 1.3% over the three time points. As all patients received treatment and only one drop-out occurred, an “intention-to-treat” analysis was not carried out.

RESULTS

Trial profile

The trial flow chart (fig 1) shows that of 289 potential candidates, 153 patients (53%) were eligible for inclusion into the study. Patients were mostly excluded because of insufficient impairment of gait (n = 44), comorbidity (n = 25), deep brain stimulation (n = 15) and an inability to commit the time needed (n = 15). Suitable patients were randomly allocated to the early (n = 76) or late intervention group (n = 77). One patient dropped out 3 weeks after randomisation, owing to a necessary change of drug. In total, 605 (99%) of the planned 612 measurements were performed. Drug intake remained necessary change of drug. In total, 605 (99%) of the planned 612 measurements were performed. Drug intake remained.

Comparison of early and late intervention

Patients received equal amounts of therapy in the early (271.8 min) and late groups (270.4 min) (t statistic = 0.27; p = 0.79).

No important differences were found between the clinical profiles of the two intervention groups (table 1). Most patients had mild to moderate disease severity as 46.4% of patients (n = 71) were in Hoehn and Yahr stage II, 41.8% (n = 64) in stage III and 11.8% (n = 18) in stage IV. Both early and late groups included similar numbers of freezers defined as having at least weekly freezing episodes (n = 31, 20.3% in early; and n = 32, 20.9% in late), as defined by a score >1 on item 3 of the Freezing of Gait Questionnaire. Table 2 shows the median and interquartile ranges of all outcomes at tests 1–4. No significant group differences were found for primary and secondary outcomes at test 1, confirming the success of the randomisation procedure. Table 2 shows that 41% in the early and 39% in the late group reported at least one episode of falling in the 3 months before the onset of trial.

Treatment effects

Table 3 shows the estimated intervention effects corrected for time and carry-over. The primary outcome, the PG score, improved by 4.2% after intervention (p = 0.005). As for the secondary outcomes, gait speed (p = 0.005) and step length (p = 0.001) improved by 5 cm/s and 4 cm, respectively. No significant change in step frequency was observed (p = 0.08). The Functional Reach test did not show an intervention effect (p = 0.18). However, the clustered tandem and one leg standing tests showed that the chance of failing these tests was decreased by 36% after intervention (HR 0.64; 95% confidence interval (CI) 0.48 to 0.87; p = 0.003). The Timed Get Up and Go test did not show improvement after intervention. As for the severity of freezing, the Freezing of Gait Questionnaire scores were not significantly affected by cueing therapy (p = 0.25) after transformation. Data showed a bimodal distribution indicating a group with low scores (non-freezers) and a group with high scores (freezers). When the Freezing of Gait Questionnaire scores were re-analysed on freezers only (n = 63), defined as having at least a weekly freezing frequency, a significant reduction of 5.5% of freezing severity was found (mean (SE) β estimate = −1.33 (0.48), p = 0.007).

Table 3 presents intervention effects that are smaller compared with the change in median values before and after intervention for the early and late groups in table 2 as a result of the statistical control for time and carry-over effects—for example, the PG score improved from a median of 6 to 4 after treatment, suggesting a 10% rather than a 4.2% change of the scoring range. Overall, carry-over effects were only significant for step length in the early group at test 3 (p = 0.014). Time effects showed significant improvements for the PG score (p = 0.03), gait speed (p = 0.04) and the TGUG (p = 0.004).

For the secondary outcomes in the activity domain, improvements were found on the Falls Efficacy Scale (p = 0.03), indicating that patients felt more confident during gait-related activities. ADL function as measured by the Nottingham Extended Activities of Daily Living Index was not significantly altered (p = 0.07). The Parkinson’s Disease Questionnaire-39 scores (p = 0.23) and the Carer Strain Index were not significantly changed after intervention (p = 0.14). The generalised estimating equations model showed no significant increase or decrease in the probability of falling as a result of treatment (OR 1.4; 95% CI 0.63 to 3.1; p = 0.4). Separate analysis of the upper limb repetitive movement scores of the UPDRS (III) showed no significant treatment effect (β = −1.1 (0.62), p = 0.08). Most patients (n = 95, 67%) chose auditory cueing as their preferred cueing modality, whereas 57 patients (n = 58, 33%) favoured somatosensory cueing.

Follow-up (test 4 – test 3)

Table 3 also shows the change at follow-up. Most intervention effects in the gait and balance domains declined significantly from 6 to 12 weeks. Secondary outcomes at activity and
participation levels also tended to decline at test 4, a pattern that was significant for the Falls Efficacy Scale. The chance of failing the balance tests at test 4 was increased as compared with test 3 (HR 1.12; 95% CI 0.96 to 1.32), but this difference was not significant (p = 0.15). Table 2 shows that more patients reported a fall at test 4 compared with test 3 but this may reflect the fact that at test 4 a period of 6 weeks was assessed, as opposed to 3 weeks at test 3.

**DISCUSSION**

This is the first large-scale randomised clinical trial investigating the effects of a cueing training programme delivered at home using a multimodality cueing device. The main findings indicate that nine sessions of cueing training demonstrated considerable improvement in gait and gait-related mobility in people with Parkinson's disease, but that these effects were small and specific. The cueing method was widely accepted and well tolerated in a wide range of patients, ranging from Hoehn and Yahr stages II to IV, as evidenced by only one drop-out.

The present findings showed that a period of training with cues in the homes of people with Parkinson's disease resulted in improvement of gait immediately after intervention. We found a significant increase in walking speed and step amplitude accompanied by a tendency to reduce step frequency. This finding is in agreement with earlier work, showing that the potential to generate a more normal gait pattern can be tapped in Parkinson's disease. When looking at freezers participation levels also tended to decline at test 4, a pattern that was significant for the Falls Efficacy Scale. The chance of failing the balance tests at test 4 was increased as compared with test 3 (HR 1.12; 95% CI 0.96 to 1.32), but this difference was not significant (p = 0.15). Table 2 shows that more patients reported a fall at test 4 compared with test 3 but this may reflect the fact that at test 4 a period of 6 weeks was assessed, as opposed to 3 weeks at test 3.

**DISCUSSION**

This is the first large-scale randomised clinical trial investigating the effects of a cueing training programme delivered at home using a multimodality cueing device. The main findings indicate that nine sessions of cueing training demonstrated considerable improvement in gait and gait-related mobility in people with Parkinson's disease, but that these effects were small and specific. The cueing method was widely accepted and well tolerated in a wide range of patients, ranging from Hoehn and Yahr stages II to IV, as evidenced by only one drop-out.

The present findings showed that a period of training with cues in the homes of people with Parkinson's disease resulted in improvement of gait immediately after intervention. We found a significant increase in walking speed and step amplitude accompanied by a tendency to reduce step frequency. This finding is in agreement with earlier work, showing that the potential to generate a more normal gait pattern can be tapped in Parkinson's disease. When looking at freezers participation levels also tended to decline at test 4, a pattern that was significant for the Falls Efficacy Scale. The chance of failing the balance tests at test 4 was increased as compared with test 3 (HR 1.12; 95% CI 0.96 to 1.32), but this difference was not significant (p = 0.15). Table 2 shows that more patients reported a fall at test 4 compared with test 3 but this may reflect the fact that at test 4 a period of 6 weeks was assessed, as opposed to 3 weeks at test 3.

**DISCUSSION**

This is the first large-scale randomised clinical trial investigating the effects of a cueing training programme delivered at home using a multimodality cueing device. The main findings indicate that nine sessions of cueing training demonstrated considerable improvement in gait and gait-related mobility in people with Parkinson's disease, but that these effects were small and specific. The cueing method was widely accepted and well tolerated in a wide range of patients, ranging from Hoehn and Yahr stages II to IV, as evidenced by only one drop-out.

The present findings showed that a period of training with cues in the homes of people with Parkinson's disease resulted in improvement of gait immediately after intervention. We found a significant increase in walking speed and step amplitude accompanied by a tendency to reduce step frequency. This finding is in agreement with earlier work, showing that the potential to generate a more normal gait pattern can be tapped in Parkinson's disease. When looking at freezers participation levels also tended to decline at test 4, a pattern that was significant for the Falls Efficacy Scale. The chance of failing the balance tests at test 4 was increased as compared with test 3 (HR 1.12; 95% CI 0.96 to 1.32), but this difference was not significant (p = 0.15). Table 2 shows that more patients reported a fall at test 4 compared with test 3 but this may reflect the fact that at test 4 a period of 6 weeks was assessed, as opposed to 3 weeks at test 3.
period.22

Overcome freezing in their daily environment for a 3-week period.22 Freezers, and instructed patients on how to prevent and overcome freezing in their daily environment for a 3-week period.22 Specific guidelines to set the cueing frequency to the needs of the present results need cautious interpretation.

Subjects were trained for 3 weeks with cues and were evaluated without wearing the device to see if the effects were maintained. The present results showed training effects in the absence of cues, indicating that some degree of motor learning is preserved in Parkinson’s disease. Whereas most studies investigated the immediate benefits of cued performance, our findings confirm the limited evidence available of improved ‘uncued’ performance after training with cues.22

The effects found in this study can be considered robust and not attributable to measurement error or learning effects. All but three outcome measures had established test–re-test reliability in the home situation23 and the order of testing was separated, a significant change on the Freezing of Gait Questionnaire after intervention was found, signifying a reduction of freezing severity. This is an important finding, as freezing is particularly resistant to drug treatment and often associated with falling.33 This result contradicts earlier work in which freezers were provided with a metronome for 1 week at home without clear benefits.34 In contrast, during the RESCUE trial, cueing therapy was provided by therapists, who used specific guidelines to set the cueing frequency to the needs of freezers, and instructed patients on how to prevent and overcome freezing in their daily environment for a 3-week period.22

Increased rates of falls in people with Parkinson’s disease are well documented and have been attributed to preserved mobility in this population.2,35 We were, therefore, concerned that any improvements in mobility due to therapeutic cueing could have resulted in an increased risk of falls. Our results, however, showed no evidence for this, but rather evidence of current effects sizes are in line with those observed in recent meta-analyses on physiotherapy in Parkinson’s disease34 and in other conditions such as stroke.26,27 The limited effects may also be explained by the relatively short training duration. Training

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Medians and interquartile ranges of the outcomes in early and late intervention groups at tests 1–4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td><strong>Secondary outcomes</strong></td>
</tr>
<tr>
<td><strong>PG score (0–20)</strong></td>
<td><strong>Walking speed (m/s)</strong></td>
</tr>
<tr>
<td>Early</td>
<td>6.0 (4.0–8.0)</td>
</tr>
<tr>
<td>Late</td>
<td>7.0 (5.0–8.5)</td>
</tr>
<tr>
<td><strong>Step length (m)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>0.50 (0.43–0.56)</td>
</tr>
<tr>
<td><strong>Step frequency (steps/min)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>99 (91.6–109.6)</td>
</tr>
<tr>
<td><strong>Functional reach (cm)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>25.2 (20.2–30.5)</td>
</tr>
<tr>
<td><strong>Single stance (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>9.1 (3.9–21)</td>
</tr>
<tr>
<td><strong>Tandem stance (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>23.1 (8.0–30)</td>
</tr>
<tr>
<td><strong>TGUG (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>13.9 (12.0–17.9)</td>
</tr>
<tr>
<td><strong>FOGQ (0–24)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>8 (4.5–12)</td>
</tr>
<tr>
<td><strong>NEADL (0–66)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>40 (35–51)</td>
</tr>
<tr>
<td><strong>FES (0–130)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>78 (57–99.5)</td>
</tr>
<tr>
<td><strong>PDQ-39 (total%)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>37.8 (27.6–45.9)</td>
</tr>
<tr>
<td><strong>CSI (0–13)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td><strong>Walking speed (m/s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>0.51 (0.44–0.58)</td>
</tr>
<tr>
<td><strong>Step length (m)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>102.5 (94.3–112.6)</td>
</tr>
<tr>
<td><strong>Step frequency (steps/min)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>102.2 (92.5–110.2)</td>
</tr>
<tr>
<td><strong>Functional reach (cm)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>25.5 (19.8–30.7)</td>
</tr>
<tr>
<td><strong>Single stance (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>9.5 (3.6–19.3)</td>
</tr>
<tr>
<td><strong>Tandem stance (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>20.7 (8.6–30)</td>
</tr>
<tr>
<td><strong>TGUG (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>12.7 (11.1–15.7)</td>
</tr>
<tr>
<td><strong>FOGQ (0–24)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>9 (4–12)</td>
</tr>
<tr>
<td><strong>NEADL (0–66)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>40 (35–51)</td>
</tr>
<tr>
<td><strong>FES (0–130)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>78 (57–99.5)</td>
</tr>
<tr>
<td><strong>PDQ-39 (total%)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>37.8 (27.6–45.9)</td>
</tr>
<tr>
<td><strong>CSI (0–13)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td><strong>Walking speed (m/s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>25.5 (19.8–30.7)</td>
</tr>
<tr>
<td><strong>Step length (m)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>9.5 (3.6–19.3)</td>
</tr>
<tr>
<td><strong>Step frequency (steps/min)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>20.7 (8.6–30)</td>
</tr>
<tr>
<td><strong>Functional reach (cm)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>12.7 (11.1–15.7)</td>
</tr>
<tr>
<td><strong>Single stance (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>14.2 (6.3–24)</td>
</tr>
<tr>
<td><strong>Tandem stance (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>24.6 (11.1–30)</td>
</tr>
<tr>
<td><strong>TGUG (s)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>12.2 (10.7–15.5)</td>
</tr>
<tr>
<td><strong>FOGQ (0–24)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>7 (3–11)</td>
</tr>
<tr>
<td><strong>NEADL (0–66)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>40 (35–51)</td>
</tr>
<tr>
<td><strong>FES (0–130)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>78 (57–99.5)</td>
</tr>
<tr>
<td><strong>PDQ-39 (total%)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>37.8 (27.6–45.9)</td>
</tr>
<tr>
<td><strong>CSI (0–13)</strong></td>
<td>Early</td>
</tr>
<tr>
<td>Late</td>
<td>2 (1–5)</td>
</tr>
</tbody>
</table>

CS1, Carer Strain Index; FES, Falls Efficacy Scale; FOGQ, Freezing Of Gait Questionnaire; NEADL, Nottingham Extended ADL Index; PDQ-39, Parkinson’s Disease Questionnaire; PG score, posture and gait score; TGUG, Timed Get Up and Go test.

*Falling: time periods of falls diary at each test period differ (test 1 = 3 months, test 2 = 3 weeks; test 3 = 3 weeks; test 4 = 6 weeks). Figures represent numbers of patients who fell. One missing value was obtained at test 1 in the early group and at tests 3 and 4 due to drop-out.

Subjects were trained for 3 weeks with cues and were evaluated without wearing the device to see if the effects were maintained. The present results showed training effects in the absence of cues, indicating that some degree of motor learning is preserved in Parkinson’s disease. Whereas most studies investigated the immediate benefits of cued performance, our findings confirm the limited evidence available of improved ‘uncued’ performance after training with cues.22

The effects found in this study can be considered robust and not attributable to measurement error or learning effects. All but three outcome measures had established test–re-test reliability in the home situation23 and the order of testing was randomised. To estimate the effects of intervention separately from carry-over and time effects, the statistical analysis controlled for these factors, providing a conservative estimation of treatment effects.

The fact that intervention effects were small could reflect a limitation of cueing training in the home setting. However, current effects sizes are in line with those observed in recent meta-analyses on physiotherapy in Parkinson’s disease4 and in other conditions such as stroke.26,27 The limited effects may also be explained by the relatively short training duration. Training
intensity rather than content was found to be a key factor in stroke research and may be equally crucial in Parkinson’s disease. In this study, training intensity was stipulated by the maximum number of physiotherapy sessions at home allowed for reimbursement according to existing healthcare policies. This raises the question of what the optimal duration and intensity of cueing training is and how this should be delivered over time.

What actually constitutes clinically relevant results in rehabilitation of a chronic degenerative disorder is still unclear at this point. Possibly, the improvements of gait and balance were too small to carry over to ADL and perceived quality of life. Additionally, the narrow focus of the intervention may have led to specific effects, as we showed that repetitive upper limb movements were not affected by cueing therapy. Equally, in other fields of rehabilitation lack of generalisation is a common feature.

Training effects were not sustained at 6-week follow-up as a considerable reduction in most outcomes was apparent. Similarly, Nieuwboer et al. showed a considerable deterioration at 12 weeks after training with cues and Thaut et al. found a declining slope from 4-week to 6-week follow-up. Other authors reported negligible reductions at 4–6 weeks after cueing training.

The effect of placebo as a result of increased attention during therapy was not controlled for, which is a limitation of this study. Although the specificity of the results argues against a general effect of increased attention, effects of gait-related attention rather than cueing cannot be ruled out. Previously, it was shown that gait training with auditory cues was more effective than training without cues and no training. Lack of Bonferroni correction and the fact that at tests 3 and 4 testers were aware of patients having received therapy, inherent to a repeated-measures design, warrant careful interpretation of the results. However, testers were not unblinded to treatment allocation at any time point. The findings of this study cannot be generalised to people with Parkinson’s disease who have significant cognitive decline and other comorbidities. Especially in the later disease stages, cues may overburden cognitive resources and increase fall risk. Future work should focus on determining such at-risk patients. Equally, the possibility that cues may actually reduce attentional cost in patients who are not at risk requires further investigation. Recently, we found that during cued performance of dual tasks, gait parameters improved rather than deteriorated. Future studies, assessing cueing effects over a longer period of time, will be able to determine whether habituation occurs to the stimulus of the cue and verify our findings on fall risk associated with cueing over longer periods. In addition, the cost effectiveness of an extended therapeutic cueing programme possibly supplemented with a permanent cueing device needs further investigation. Although most patients preferred the auditory cueing modality (67%), a large number of them (33%) perceived somatosensory cueing as a well-tolerated and discrete alternative. At present, auditory cueing alone can be provided at relatively low cost using metronomes with earphones or via digital music players.

We conclude that cueing training in the home situation has a small and specific benefit for managing gait and freezing in patients with Parkinson’s disease. In addition, this study has highlighted important questions on how to deliver cueing training in the most optimal way.

**ACKNOWLEDGEMENTS**

We thank the financial support from the European Commission Framework V funding, QLK6–2001–00120. We also thank the contribution of Professor Rowena Plant in gaining funding. Prof. ECH Wolters (MD, PhD), Dr HW Berends (MD, PhD), CM Jijlman (MD, PhD), Prof R Dom (MD, PhD), Dr D Burn (MD) and Dr R Walker (MD) are acknowledged for referral of patients. We also acknowledge help with data analysis from S Fieuw and K Desloovere, and, in particular, the patients with Parkinson’s disease and their carers who participated in this study.

**Authors’ affiliations**

A Nieuwboer*, A M Willems, F Chavret, Katholieke Universiteit, Leuven, Belgium

G Kwakkel*, E van Wegen, I Lim, Vrije Universiteit Medisch Centrum, Amsterdam, The Netherlands

L Rochester*, D Jones*, V Hetherington, K Baker, Northumbria University, Newcastle, UK

*These authors contributed equally to this work.

---

**Table 3 Intervention effects and change at follow-up (test 4 – test 3)**

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Intervention β estimate (SE)</th>
<th>Change in units* (%) range†</th>
<th>p Value</th>
<th>Follow-up β estimate (SE) test 4-test 3</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG score (0–20)</td>
<td>↑ – 0.85 (0.3)</td>
<td>4.2%</td>
<td>0.005</td>
<td>↓ 0.582 (0.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gait and Balance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed (m/s)</td>
<td>↑ 0.05 (0.02)</td>
<td>5 cm/*</td>
<td>0.005</td>
<td>↓ 0.02 (0.007)</td>
<td>0.03</td>
</tr>
<tr>
<td>Step length (m)</td>
<td>↑ 0.04 (0.09)</td>
<td>4 cm</td>
<td>0.001</td>
<td>↓ 0.02 (0.004)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Step frequency (steps/min)</td>
<td>↑ – 2.1 (1.19)</td>
<td>–2.1 steps/min*</td>
<td>0.08</td>
<td>↓ 1.24 (0.56)</td>
<td>0.03</td>
</tr>
<tr>
<td>Functional reach (cm)</td>
<td>↑ 1.3 (0.97)</td>
<td>1.3 cm</td>
<td>0.18</td>
<td>↓ 1.08 (0.46)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tandem stance (s)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Single leg stance (s)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>↑ – 0.002 (0.73)</td>
<td>2 ms</td>
<td>0.6</td>
<td>↓ 0.14 (0.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>FOGQ (0–24)</td>
<td>↑ – 0.86 (0.44)</td>
<td>3.6%</td>
<td>0.25‡</td>
<td>↓ 0.8 (0.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEADL (0–66)</td>
<td>↑ 1.71 (0.94)</td>
<td>2.6%</td>
<td>0.07</td>
<td>↓ 0.65 (0.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>FES (0–130)</td>
<td>↑ 4.77 (2.29)</td>
<td>3.7%</td>
<td>0.04</td>
<td>↓ 2.92 (1.22)</td>
<td>0.02</td>
</tr>
<tr>
<td>Participation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDQ-39 (total%)</td>
<td>↑ – 1.36 (1.14)</td>
<td>1.4%</td>
<td>0.23</td>
<td>↓ 0.99 (0.52)</td>
<td>0.06</td>
</tr>
<tr>
<td>CSI (0–13)</td>
<td>↑ – 0.76 (0.32)</td>
<td>5.8%</td>
<td>0.14‡</td>
<td>↓ 0.15 (0.18)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

CSI, Carer Strain Index; FES, Falls Efficacy Scale; FOGQ, Freezing Of Gait Questionnaire; NEADL, Nottingham Extended ADL Index; PDQ-39, Parkinson’s Disease Questionnaire; PG score, posture and gait score; TUG, Timed Get Up and Go test.

* Estimate represents change in direction of improvement.

† Estimate represents change in direction of deterioration.

*Change expressed as measured units, positive figures represent an improvement.

†Change expressed as % of the scoring range, positive figures represent an improvement.

‡After transformation.
Competing interests: The proceeds of the sale of the CD-Rom will be used to fund completion of analysis of the full RESCUE dataset. We may be involved in this further work.

REFERENCES

REFERENCES

BOOK REVIEW
Vascular cognitive impairment in clinical practice

In 2006, the NIH convened a conference, which attempted to establish a new concept, vascular cognitive impairment (VCI). The resulting document has been published and now, 3 years later, several of the key participants, and others, have contributed to a new book on that topic. Edited by leading authorities and joined by several eminent experts, the book addresses clinicians dealing with demented individuals in order to distribute the concept of VCI which has not been accepted unopposed.

The term VCI is supposed to cover the whole spectrum of cognitive decline which occurs as a result of vascular changes to the brain. Because these changes result from a multitude of factors (haemorrhage, ischaemia, emboli, small vessel disease, etc), VCI cannot be considered a disease, but rather is a syndrome since there is very little in common between cognitive changes resulting from different processes (eg, leuкоaraiosis and those due to a single thalamic stroke).

In addition, the vascular lesions occurring mostly in elderly subjects rarely affect an otherwise normal brain. Alzheimer pathology is very common in the elderly, and even if changes fail to satisfy arbitrary pathological criteria of Alzheimer’s disease (AD), they cannot and should not be ignored. In fact, a growing body of evidence forces us to accept that most cases of dementia in the elderly are the result of combined lesions, and therefore the concept of (pure) VCI may be misleading. The authors of several chapters in the book acknowledge these issues, albeit in a soft voice. It seems that they try to simplify the question of the pathogenesis and manifestations of dementia in old age by resorting to a dualistic approach. Unfortunately, this entrenched position does not benefit scientific progress.

The authors do not even agree on the definition of VCI. Whereas the editors limit it to “from the earliest deficit” (p4), others ask whether VCI can be a prodrome to vascular dementia (p11). If vascular dementia is included in the spectrum of VCI, how can VCI be a prodrome to it? Still others claim that the “brain at risk stage” (ie, prior to cognitive changes) should be included (p54).

Particularly disappointing are the chapters on treatment where data from AD are used freely without mentioning that they do not necessarily apply to other dementia types, particularly vascular dementia. The chapter on “control of vascular risk factors” contains a well structured review of the role of dementia. However, if VCI has so many underlying pathologies, preventative treatments are hard to identify to any of its subtypes. A discussion as to why none of the anti-AD drugs has been accepted by authorities for treatment of vascular dementia is missing. Is rigid control of the risk factors useful in preventing, or at least slowing, the cognitive deterioration? This important clinical question is neglected. While there is some discussion of symptomatic therapies, this is directed at manifestations of dementia in general, perhaps because the authors believe that the clinical behavioural manifestations are similar, both in underlying mechanisms and in presentation, in VCI and in other dementia syndromes. Among atypical antipsychotic agent, the most atypical, clozapine, is not mentioned.

There are a few errors, for example, the claim that “the diagnosis of dementia can be done at the bedside using global cognitive measures (eg, Mini-Mental State Examination)”, p32. Sometimes statements are made without reference (eg, “The levels of Aβ may be reduced in the users of statin and Ginko biloba”, p85).

While the authors of the different chapters have generally completed well the missions assigned to them, the editors and publisher could have done more. Each chapter has its own structure. Summaries, which are so important in such a comprehensive work, are missing in some chapters and replaced by significance, conclusions, conclusions remarks, etc, in others. The reference list after each chapter is not made without reference (eg, “The levels of Aβ may be reduced in the users of statin and Ginko biloba”, p85).

A good index is a very important tool in a book such as this but, unfortunately, it is rather incomplete. For example, “Binswanger’s disease” is mentioned in the text more frequently then four times, as suggested by the index. Abbreviations are used without spelling them out first. Table 14.1, among others, has not been proofread.

Surely, a distinguished publisher like Cambridge University Press could have done a better job.

A D Korczyn
Tel-Av University Medical School, Ramat Avar 69978, Israel; amoskor@post.tau.ac.il

REFERENCES

CORRECTIONS
doi:10.1136/jnnp.2005.086579 corrective1
J D Putzke, N R Whaley, Y Baba, et al. Essential tremor: predictors of disease progression in a clinical cohort. J Neurol Neurosurg Psychiatry 2006;77:1255–1257. This article was originally published with an incorrect digital object identifier (doi) of 10.1136/jnnp.2006.086579. It has been updated online with the correct doi: 10.1136/jnnp.2006.086579.
doi:10.1136/jnnp.2006.095547 corrective1
E J Thompson. Lock and key approach to “hidden” encephalitis. J Neurol Neurosurg Psychiatry 2006;77:901. This article was originally published with an incorrect digital object identifier (doi) of 10.1136/jnnp.2005.095547. It has been updated online with the correct doi: 10.1136/jnnp.2006.095547.
doi:10.1136/jnnp.2006.097923 corrective1
doi:10.1136/jnnp.2006.010315 corrective1
J L Dornhoffoer, M Menmeneimeier. Transcranial magnetic stimulation and tinnitus: implications for theory and practice. J Neurol Neurosurg Psychiatry 2007;78:113. This article was originally published with an incorrect digital object identifier (doi) of 10.1136/jnnp.2006.010315. It has been updated online with the correct doi: 10.1136/jnnp.2006.010315.

J Neurol Neurosurg Psychiatry January 2010 Vol 81 No 1

Downloaded from jnnp.bmj.com on May 17, 2013 - Published by group.bmj.com
Although it could be argued that this reduction may simply be the result of reduced life expectancy in MS patients, this is unlikely, as an age-specific Cox survival model also showed a significant reduction in the risk of cancer. Similarly, it is unlikely that this would represent under-reporting of cancer because patients are typically in closer contact with health practitioners than the normal population. Explanations could include lifestyle alterations following diagnosis, genetic factors or immunological changes due to MS. Further study of mechanisms is therefore warranted, but more immediately, the results of this meta-analysis will be of use for MS patients and their care givers.

Acknowledgements We would like to thank all members of the Ebers group for helpful discussion and frequent support.

Adam E Handel,1,2 Sreeram V Ramagopalan1,2
1Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK; 2Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Oxford, UK

Correspondence to Dr Sreeram V Ramagopalan, The Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK; sreeramr@well.ox.ac.uk

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Received 21 September 2009
Revised 11 November 2009
Accepted 16 November 2009
Published Online First 19 August 2010


REFERENCES


CORRECTIONS
doi:10.1136/jnnp.2008.169029corr1

J Pretnar-Oblak, M Zaletel, T M Hajnšek, et al. Isolated bulbar paralysis in a patient with medullar tau pathology: a case report (J Neurol Neurosurg Psychiatry 2010;81:847–849). The authors misplaced the label number (9) in Figure 1 of this paper and therefore this area indicated does not represent the nucleus ambiguous. The reprinted version of Figure 1 represents the correct area for nucleus ambiguous.

The authors would also like to explain further the labels in Figure 2C and 2D. 2C: Extensive tau pathology in DNVN composed of numerous neuropil threads and tau-positive neurons (arrows). 2D: Tau pathology of few neuropil threads in the SN (arrows).

Figure 1 The corrected version with previously misplaced number 9.

doi:10.1136/jnnp.2008.089540

Jes Olesen, Mary G Baker, Tamas Freund, et al. Consensus document on European brain research (J Neurol Neurosurg Psychiatry 2006;77:i1–i49). This paper was published in the journal without a doi. The doi is 10.1136/jnnp.2006.089540.

doi:10.1136/jnnp.2006.095547

E J Thompson. Lock and key approach to “hidden” encephalitis (J Neurol Neurosurg Psychiatry 2006;77:901). This paper was published in the journal with an incorrect doi of 10.1136/jnnp.2005.095547. The correct doi is 10.1136/jnnp.2006.095547.

doi:10.1136/jnnp.2006.097923


doi:10.1136/jnnp.2006.103135

J L Dornhoffer, M Mennemeier. Transcranial magnetic stimulation and tinnitus: implications for theory and practice (J Neurol Neurosurg Psychiatry 2007;78:113). This paper was published in the journal with an incorrect doi of 10.1136/jnnp.2006.0103135. The correct doi is 10.1136/jnnp.2006.103135.

doi:10.1136/jnnp.2008.146548

Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial

A Nieuwboer, G Kwakkel, L Rochester, et al.

*J Neurol Neurosurg Psychiatry* 2007 78: 134-140
doi: 10.1136/jnnp.200X.097923

Updated information and services can be found at:
http://jnnp.bmj.com/content/78/2/134.full.html

**References**

These include:

This article cites 35 articles, 11 of which can be accessed free at:
http://jnnp.bmj.com/content/78/2/134.full.html#ref-list-1

Article cited in:
http://jnnp.bmj.com/content/78/2/134.full.html#related-urls

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

Physiotherapy (46 articles)
JNPP Patients' choice (77 articles)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/