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Goal-orientated cognitive rehabilitation for dementias associated with Parkinson's disease- a pilot randomised controlled trial.

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Key Points:

1. Goal orientated cognitive rehabilitation uses goal setting and evidence-based strategies focussing on improving functioning in everyday activities in people with dementia.
2. There are no previous controlled studies of cognitive rehabilitation in dementias associated with Parkinson's.
3. This pilot randomised controlled trial showed that cognitive rehabilitation was superior to treatment-as-usual and relaxation therapy for primary outcomes in dementias associated with Parkinson's.
4. Cognitive Rehabilitation is feasible and potentially effective for dementias associated with Parkinson's but requires further study.

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JVH: None

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ABSTRACT

Objective

To examine the appropriateness and feasibility of cognitive rehabilitation for people with dementias associated with Parkinson's in a pilot randomised controlled study.

Methods

This was a single-blind pilot randomised controlled trial of goal-oriented cognitive rehabilitation for dementias associated with Parkinson's. After goal setting, participants were randomised to cognitive rehabilitation (n=10), relaxation therapy (n=10) or treatment-as-usual (n=9). Primary outcomes were ratings of goal attainment and satisfaction with goal attainment. Secondary outcomes included quality of life, mood, cognition, health status, everyday functioning and carers' ratings of goal attainment and their own quality of life and stress levels. Assessments were at two months and six months following randomisation.

Results

At two-months, cognitive rehabilitation was superior to treatment-as-usual and relaxation therapy for the primary outcomes of self-rated goal attainment ($d = 1.63$ and $d = 1.82$ respectively) and self-rated satisfaction with goal attainment ($d = 2.04$ and $d = 1.84$). At six-months, cognitive rehabilitation remained superior to treatment-as-usual ($d = 1.36$) and relaxation therapy ($d = 1.77$) for self-rated goal attainment.

Cognitive rehabilitation was superior to treatment as usual and/or relaxation therapy in a number of secondary outcomes at two-months (mood, self-efficacy, social domain of quality of life, carers' ratings of participants' goal attainment) and at six-months (delayed recall, health status, quality of life, carer ratings of participants' goal attainment). Carers receiving cognitive rehabilitation reported better quality of life, health status and lower stress than those allocated to treatment-as-usual.

Conclusions

Cognitive rehabilitation is feasible and potentially effective for dementias associated with Parkinson's disease.

INTRODUCTION

Neuropsychiatric symptoms including cognitive impairment and dementia are common features of Parkinson's disease (PD) ¹. Cognitive impairment and PD dementia (PDD) can occur at any stage of the disease course ² but become more prominent as the illness progresses, with more than 80% of people living with PD for longer than 20 years meeting criteria for dementia ³. Cognitive dysfunction precedes parkinsonian symptoms in Dementia with Lewy bodies (DLB) which shares common genetic, neuropathological and neuropsychological features with PDD ⁴ although relationship between the conditions is still subject to debate ⁵. People with PDD and DLB show impairments in various cognitive domains, notably memory, visuospatial abilities, attention, planning and reasoning. PDD is a major risk factor for care home placement ⁶ and poses considerable burden upon carers ⁷. Cognitive impairment in PD is associated with reduced functional status ⁸ and poorer quality of life, as well as poorer quality of life for relatives providing care ^{9, 10}. Current treatments for PDD and DLB focus on pharmacological interventions which may produce undesirable side-effects and have contra-indications ¹¹. Non-pharmacological approaches might offer complementary or alternative strategies, yet there remains limited research examining cognitive interventions in PD and no study has applied these approaches in PDD or DLB ¹². A previous systematic review raised concerns regarding the scientific rigour of existing studies, and highlighted the lack of randomised controlled designs ¹².

Cognitive intervention studies in PD without dementia have primarily used cognitive training (CT), the guided repeated practice of tasks to target specific cognitive functions. CT may provide some benefits to PD patients without dementia for domains of working memory, processing speed, and executive functioning, but negligible or no improvements in memory, attention, visuospatial abilities, depression, quality of life, and activities of daily living ¹³. Since these latter domains become increasingly impaired as dementia progresses, there is a need to develop treatments that can mitigate not only the effects of increasing cognitive decline, but also support quality of life and independence. Cognitive rehabilitation (CR) ¹⁴ supports people with dementia to develop and use evidence-based strategies that compensate for, or reduce the impact of, their cognitive and behavioural difficulties, focussing on improving functioning in everyday activities. It employs a person-centred approach with assistance from a trained therapist to devise and apply meaningful goals, commensurate to the individual's needs and abilities. The strategies employed may be compensatory (using reminders, calendars, alarms)

and/or restorative (spaced retrieval learning, mnemonics) depending on the goal selected. Similar to CR, cognitive strategy training (CST) also uses an individualised approach using strategies to achieve goals relating to daily function. A case-series study of CST for seven people with PD without dementia but reporting subjective cognitive decline and self-identified functional issues, reported that CST was feasible and potentially effective¹⁵. The study did not include people with dementia and thus the application of goal-focussed rehabilitation approaches have yet to be applied in PDD and DLB. The efficacy of CR for people with Alzheimer's disease (AD) has previously been indicated in a pilot study¹⁶ and a large multi-centre randomised controlled trial (RCT) of CR is currently underway to assess its effectiveness for people with AD and other dementias excluding PDD and DLB¹⁷. Recently, we showed that people with PDD and DLB were able to engage in goal setting for CR, with goals being selected most often in self-management and orientation, medication adherence, learning new skills and maintaining social and leisure activities¹⁸.

The aims of the current study were to examine the appropriateness and feasibility of CR for people with PDD and DLB, and explore indications of the treatment's efficacy relative to an active control condition or treatment as usual. Additional aims included assessing the usefulness of outcome measures and obtaining effect sizes to inform the development of future RCTs of CR in PDD and DLB.

METHODS

Design

The Cognitive Rehabilitation for Parkinson's disease dementia: a pilot randomised controlled trial (CORD-PD) was a three-arm, single-blind pilot randomised controlled trial. Ethical approval for the study was obtained from the Wales Research Ethics Committee 5 (13/WA/0340). The study complied fully with the Declaration of Helsinki. Informed written consent was obtained prior to participation.

Participants

Potential participants were recruited through Movement Disorder clinics and Memory clinics in Betsi Cadwaladr University Health Board (BCUHB), North Wales, UK. Potential participants were approached consecutively and invited to an initial screening interview with the researcher. Inclusion criteria were a diagnosis of PD according to UK PD Brain Bank Diagnostic Criteria¹⁹, a diagnosis of PDD according to Movement Disorder Society consensus

criteria^{20, 21} or a diagnosis of DLB according to consensus criteria²² and a score ≤ 82 on the Addenbrooke's Cognitive Examination-III (ACE-III)²³. Exclusion criteria were a lack of stability of prescribed PD medications, cognitive enhancers or psychotropic medication (such as substantial additions to medication in the four weeks before the trial or planned changes during the period of the trial), other major psychiatric disorder not related to PD, major depression, and other significant neurological disease.

Procedures

Participants completed baseline demographic, clinical and cognitive assessments and a goal-setting interview for CR was conducted, as described previously^{24, 25}. Following the baseline visits, participants were randomised to one of the three treatment arms: CR, relaxation therapy (RT) or treatment-as-usual (TAU). Post-intervention and follow-up assessments were conducted with the researcher two months and six months from randomisation, respectively.

Interventions

The CR treatment comprised eight weekly one-hour sessions with the therapist (JR)²⁵. The intervention included the use of evidence-based methods to assist the participant to pursue the agreed goals. These methods included compensatory strategies and/or restorative approaches to circumvent difficulties relating to orientation, planning, the retention of learned information and recall (for examples of goals and strategies used for CR see Supplementary Table 1a). Participants were encouraged to practice their strategies between therapy sessions, with the assistance of the carer (where available). Carers were invited to participate in the therapy sessions to support between-session implementation.

The RT intervention also comprised eight weekly one-hour sessions with the therapist (JR). Participants were taught progressive muscle relaxation and breathing exercises in accordance with the study's RT treatment protocol (see Supplementary Table 1b). Participants were encouraged to practice these techniques between sessions.

The TAU arm continued with the standard care available through their healthcare provider.

Randomisation and blinding

Following completion of the baseline assessment, participants were randomised to one of the CR, RT or TAU arms. Randomisation was conducted by a registered Clinical Trials Unit, the North Wales Organisation for Randomised Trials in Health (NWORTH), using a dynamic

adaptive sequential randomisation algorithm ²⁶. Allocation to the three groups was achieved through stratification on the following variables: diagnosis (PD/DLB), gender, and age (≤ 69 , 70+). The researcher who collected follow-up data (TJW) was blinded to all randomisation outcomes for the duration of the data collection period. After each follow-up assessment, TJW completed a form to indicate her beliefs regarding the participant's group allocation and rated her level of certainty regarding this allocation. The trial statistician (AB) and Chief Investigator (JVH) remained blind to participant allocations throughout the data collection and analysis phases.

Outcomes

Primary outcomes

Participants' ratings for goal attainment and satisfaction with goal attainment from the Bangor Goal-Setting Interview (BGSI) ²⁷ were measured at baseline, two-month and six-month follow-up assessments. Participants rated their current attainment and satisfaction with their attainment for these goals on a scale of 1 – 10, with 1 = unable to carry out or perform task/extremely dissatisfied with attainment and 10 = able to carry out or perform task without difficulty/extremely satisfied with attainment.

Secondary outcomes

Baseline and six-month assessments: Participant assessments comprised the Unified Parkinson's Disease Rating Scale (UPDRS) ²⁸ activities of daily living (ADL) and Motor domain scores; the modified 11-item Functional Activities Questionnaire (FAQ) ²⁹; the Hospital Anxiety and Depression Scale (HADS) ³⁰; Parkinson's Disease Questionnaire-8 (PDQ-8) ³¹; Euroqol Questionnaire-short version (ED5D3L) ³²; The World Health Organisation Quality of Life Scale – Brief version (WHOQOL-BREF) ³³; Generalised Self-Efficacy Scale (GSES) ³⁴; Delis-Kaplan Executive Function Scale (D-KEFS) Letter Fluency subtest ³⁵; D-KEFS Trail Making Test (TMT) ³⁵; Story Recall from the Rivermead Behavioural Memory Test-Second Edition (RBMT-II, version A&C) ³⁶; Test of Everyday Attention (TEA, version A&C) ³⁷ and the client services receipt inventory (CSRI) ³⁸ to monitor medication prescription. Levodopa-equivalent dose (LED) was computed according to standardised formulae ³⁹. The carer assessment included the carer ratings for participants' goal attainment

(BGSI); HADS, GSES, WHOQOL-BREF; EQ5D3L; the Neuropsychiatric Inventory Questionnaire (NPI-Q) ⁴⁰ and the Relatives' Stress Scale (RSS) ⁴¹.

Post-intervention assessment (two-month follow-up): Patient participant assessments comprised the HADS; GSES; PDQ-8; WHOQOL-BREF; D-KEFS letter fluency and TMT; TEA (version B); Story Recall (RBMT, version B). The carer assessment included the carers' ratings for patients' goal attainment (BGSI); HADS, GSES, WHOQOL-BREF and the RSS.

Statistical methods

Analyses were completed for each outcome measure for the two-month and six-month follow-ups using an ANCOVA model, with baseline scores as covariates, group allocation and stratification variables as fixed factors. As this was a pilot study intended to provide information that will inform the sample size calculation for a full scale randomised trial no formal power calculation was undertaken. The original published trial design aimed to recruit 15 in each arm ^{24, 25}. One of the key objectives of this pilot study was to identify the most robust and sensitive outcome measures for development of a larger RCT and therefore due to the exploratory nature of this study, Bonferroni corrected *p* values and confidence intervals were deemed too stringent for the purposes of the current analyses. Missing data were imputed with mean substitution when a participant did not have a score on a measure but was still enrolled in the study for that time point. All statistical tests were two-tailed, and *p* values less than 0.05 were classified as statistically significant.

RESULTS

Recruitment and retention

The CORD-PD CONSORT diagram is shown in Figure 1. The recruitment rate was 38.8% (participants assessed at baseline /potential participants invited – participants not meeting inclusion criteria), with 31 participants recruited to the study. The attrition rate following randomisation (dropout/randomised) was 14% (4/29). One participant was included in the study due to a screening error but was later excluded at baseline. Reasons for withdrawal after randomisation were significant deterioration in cognition (n=1) or health-status (n=2) and a lack of motivation to continue participation (n=1). Treatment adherence for participants randomised to intervention conditions is shown in Supplementary Information Table 2.

“Insert figure 1 about here”

Participants

At the intervention time point, there were 29 participants with PDD or DLB and 26 carer participants. Table 1 shows participant and carer characteristics for the overall sample and across treatment groups. There were no significant differences between these groups on baseline measures.

“Insert table 1 about here”

Outcomes

Table 2 shows participants’ outcomes across treatment groups and time points. Mean LED estimates for antiparkinsonian medication are also shown.

At the two-month follow-up, analysis showed main effects for participants’ self-rated goal attainment ($F(1,19) = 8.24$, $P = 0.003$) and satisfaction with goal attainment ($F(1,19) = 10.42$, $P = 0.001$) on the BGSII.

At the six-month follow-up, there were main effects favouring CR for participants’ self-rated goal attainment on the BGSII ($F(1,18) = 6.39$, $P = 0.008$). Main effects were also found for participants’ general health (EQ5D3L, $F(1,18) = 5.23$, $P = 0.02$) and quality of life (PDQ8, $F(1,18) = 5.2$, $P = 0.02$).

There were no statistically significant differences in mean LED estimates between the baseline and six-month follow-up visits for any of the treatment arms (CR: $t(6) = 0.67$, $P = 0.53$; TAU: $t(8) = 0.0$, $P = 1.0$; RT: $t(8) = -1.7$, $P = 0.13$). Nine patients were prescribed cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists. Dosages for these drugs at baseline and follow-up are shown in Supplementary Information Table 3.

Table 3 shows standardised effect size estimates (d) and confidence intervals for statistically significant differences between groups on primary and secondary outcomes for participants.

“Insert tables 2&3 about here”

Carers

Table 4 shows carers' outcomes across treatment groups and time points.

Group differences favouring CR were found for carers ratings' of participants' goal attainment ($F(1,15) = 6.44, P = 0.01$), carers' self-ratings for the environmental domain of WHOQOL-BREF ($F(1,15) = 4.41, P = 0.03$) and carers' self-ratings for overall health using the ED5D3L visual analogue ($F(1,15) = 3.62, P = 0.05$). Table 3 shows standardised effect size estimates (d) and confidence intervals for statistically significant differences between groups on carers' outcomes.

“Insert table 4 about here”

Blinding

An exact binomial test performed on blinding control data revealed no indications that the researcher was able to correctly identify participants' treatment randomisation allocations at either the two-month (9 out of 26 participants correctly identified their group allocation, $P = 1$) and six-month (12 out of 25 participants correctly identified their group allocation, $P = 0.14$) assessments.

DISCUSSION

The CORD-PD pilot RCT is the first study to apply goal-oriented CR for dementias associated with PD, using an individualised intervention to address goals that are meaningful to the person and that take account of the person's cognitive and functional abilities. People with mild to moderate PDD and DLB are able to participate in goal-setting for CR using the BGSII²⁴ and the current results indicate that CR is a feasible and potentially effective intervention for individuals with PDD and DLB.

Relative to RT and TAU, participants receiving CR reported significant improvements in goal attainment at both the post-intervention and follow-up assessments. CR participants rated their satisfaction with their attainment more highly on average than those in either control condition at the post-intervention assessment. Analyses of secondary outcomes at two months also showed some positive effects for CR in ameliorating depression compared with TAU. Positive effects for CR were also found for the social aspects of quality of life when compared with TAU and RT, and for self-efficacy when compared with RT. At six months, improved health status (as measured by the ED5D3L Index and PDQ8), as well as better performance on a delayed recall task, were found for CR compared with TAU.

The CR group reported improvements on goals relating to medication management, planning and executing complex tasks (e.g. cooking), learning new skills (e.g. using email) and engagement in leisure activities. CR strategies focussing on improving disease management, such as medication or therapy adherence, could optimise symptom control in PDD or DLB possibly reducing morbidity and health-care costs. CR might enhance or support functioning required for everyday activities, reducing the need for institutionalisation and supporting community participation. This in turn might reduce isolation and maintain or improve well-being. Positive effects were obtained with only eight therapy sessions and some effects persisted four months after the end of treatment. A longer or more comprehensive treatment, perhaps with maintenance sessions in-between assessment visits, might render stronger benefits and is worthy of future exploration. One study has suggested that Memantine can lead to improvements in goal attainment in PDD⁴². It is possible; however, that CR combined with pharmacotherapy could provide enhanced benefits. However, prescriptions for anti-parkinsonian and dementia medications did not differ between groups at baseline or follow-up.

At the post-intervention assessment, carer ratings for participants' attainment were significantly higher in the CR than in the RT group, but at follow-up, they were significantly higher in the CR than in both the RT and TAU groups. Additionally, carers in the CR group at follow-up, reported lower stress levels and higher ratings for overall health and an environmental component of quality of life relative to carers in the control groups. It is possible that improvements in participants' attainment are not immediately noticeable to third parties until they achieve significant progress with their goals with a reduction in care-related duties only at a certain level of independence.

A recent CT trial involving PD patients without dementia demonstrated that improvements to specific cognitive functions⁴³ were maintained one year following treatment and reduced the risk of developing cognitive impairment⁴⁴. The feasibility of CST for PD patients without dementia has also been demonstrated¹⁵. Following on from this work, our results show that the benefits of cognitive interventions might extend to patients with more severe cognitive impairments seen in PDD and DLB. While CT involves the practice of abstract exercises to train cognitive functions, our approach focuses on developing and practicing strategies to assist directly with actual daily activities which may be more relevant for people with mild to moderate dementia. There is increasing interest in combined treatments in non-pharmacological research in PD including exercise^{45, 46}. Avenues for future research could include investigating the impact of exercise, CT, and CR, in combination or in comparison with each other, on participant outcomes.

Limitations and Future Directions

One limitation of the current study is the small sample size, which might affect the generalisability of these results. Nonetheless, this sample size is typical of pilot psychosocial studies in PD^{47, 48, 49}. Medium to large effects were found in this study in favour of CR relative to the control conditions for primary and some secondary outcomes, suggesting that these results may be replicated in a larger study. The array of outcome measures is large, increasing the likelihood of type-one error inflation. However, a key objective of this study was to assess the usefulness of various outcome measures and calculate effect sizes to inform outcome selection for a fully-powered trial. DLB participant recruitment was disproportionately small, precluding subtype analyses. We did not use a clinical instrument to determine dementia stage and instead relied on the clinical judgement. Similarly, we used one measure, the ACE-III

global cut-off score, to guide participant selection. Due to the fluctuating nature of cognitive impairment apparent in PDD and DLB, such screening methods may have under- or overestimated cognitive impairment in some patients. We excluded patients without objective cognitive impairment but who may have shown other neuropsychiatric changes (e.g. apathy, depression) that could have benefited from this behavioural intervention. Since the emergence of neuropsychiatric symptoms is associated with increasing cognitive impairment in PD⁵⁰, these symptoms might represent prodromal stages of dementia. It would be interesting to examine whether CR provides benefits for patients experiencing only behavioural changes, such as apathy. Finally, while patients were encouraged to practice or implement strategies between CR sessions with carer help, we did not formally monitor practice and cannot assess whether the quality, frequency, duration of practice or involvement of a carer between-sessions influenced the intervention's efficacy.

Despite these caveats, the study has several strengths. It adopted the gold-standard RCT approach and included an active control condition that gave equal time and attention to participants to examine the role of possible placebo effects and other nonspecific variables. The study also ensured blinding of researchers to participants' treatment allocations. CR is individualised to the participants' abilities and priorities, consistent with the preference of people living with these conditions for receiving a personalised approach for their difficulties⁵¹. The results will inform the development of a larger RCT, powered to provide definitive evidence for the effectiveness of CR against standard or usual care. The next stages of the research will involve consolidating the therapeutic procedures and determining the assessment outcomes for a future larger trial which also examines cost-effectiveness alongside multi-disciplinary care for people with PDD or DLB.

Conclusions

Despite the negative impacts of PD-related dementia on individuals and their carers, the availability of tailored psychosocial treatments remains limited. The CORD-PD pilot study contributes to the development of non-pharmacological approaches for cognitive impairment in PD, and promotes scientific rigour in this area through the adoption of an RCT design. The current results provide primary evidence of the potential effectiveness of goal-oriented CR for promoting functional independence in people with PDD and DLB, and improving their well-

being and that of their carers. Further work is required to evaluate whether this intervention can produce benefits in larger cohorts.

Registration

ISRCTN16584442 (13 April 2015)

Protocol

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Authors' contributions

1. Research project: A. Conception, B. Organization, C. Execution, D. Clinical oversight, E. Research oversight.
2. Research funding A. Chief Investigator, B. Mentorship and support:
3. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
4. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

JVH: 1. A,B,C,D; 2. A; 3. C; 4. B.

TJW: 1. B,C; 3. B, C; 4. A

JR: 1. C; 4. B.

AB: 3. B ; 4. B.

ZH: 3. A, B, C; 4. B

AM: 1. A; 3. C. 4. B.

LC: 1. A, B, E; 2. B; 3. C; 4. B.

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Table 1. Sample Characteristics at Baseline Assessment

Participants	Overall		Treatment Groups *			
Continuous variables (max score)	N=29		CR		RT	TAU
	Mean (SD) [Range]	N	Mean (SD)[Range]	N	Mean (SD)[Range]	N Mean (SD)[Range]
Age in years	76.34 (6.42) [61-85]	10	75.8 (6.61) [61-83]	10	74.9 (6.87) [61-85]	9 78.56 (5.77) [65-84]
Years of education	10.97 (1.55) [8-15]	10	10.9 (1.66) [8-13]	10	11 (1.41) [10-14]	9 11 (1.73) [9-15]
UPDRS Motor (92)	30.28 (9) [13-48]	10	27 (8.74) [13-41]	10	28.2 (7.86) [16-40]	9 36.22 (8.33) [24-48]
UPDRS ADL (52)	17.21 (6.23) [4-31]	10	15.2 (6.58) [4-25]	10	17.7 (5.96) [13-30]	9 18.89 (6.21) [13-31]
ACE-III (100)	71.3 (7.5) [52-81]	10	71.6 (6.74) [60-81]	10	71.9 (7.19) [60 - 81]	9 70.22 (9.38) [52-79]
NPI-Q Severity – carer rated (36)	N=26 10.96 (6.96) [1-27]	8	9 (4.34) [4 -17]	10	10.4 (8.91) [1-27]	8 13.62 (6.25) [8-25]
Categorical variables			CR (n=10)		RT (n=10)	TAU (n=9)
Diagnosis PDD/DLB	25/4		9/1		9/1	7/2
Gender M/F	23/6		8/2		7/3	8/1
H&Y (%)						
Stage 1	4 (13.8)		3 (30)		0 (0)	1 (11)
Stage 1.5	1 (3.4)		0 (0)		1 (10)	0 (0)
Stage 2	6 (20.7)		3 (30)		3 (30)	0 (0)
Stage 2.5	5 (17.2)		0 (0)		2 (20)	3 (33.3)
Stage 3	10 (34.5)		3 (30)		3 (30)	4 (44.4)
Stage 4	3 (10.3)		1 (10)		1 (10)	1 (11.1)
Carers	Overall		Treatment Groups			
Continuous variables	N=26		CR (n=8)		RT (n=10)	TAU (n=8)
	Mean (SD) [Range]		Mean (SD)[Range]		Mean (SD)[Range]	Mean (SD)[Range]
Age in years	70.5 (10.52) [44-85]	67	67 (9.47) [53-78]		70.5 (8.28) [58-80]	74 (13.75) [44-85]

Years of education	11.42 (1.63) [9-14]	11.62 (1.3) [10-14]	12 (1.83) [10-14]	10.5 (1.41) [9-12]
Categorical variables		CR (n=8)	RT (n=10)	TAU (n=8)
Gender				
M/F	5/21	1/7	3/7	1/7
Relationship				
Spouse/Child	23/3	7/1	9/1	7/1

Note: Higher scores indicate greater performance/higher ratings except for NPI Severity where higher scores indicate greater symptomatology. UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; ACE-III, Addenbrooke's Cognitive Examination – Third Edition; NPI-Q, Neuropsychiatric Inventory-Questionnaire; PDD, Parkinson's disease dementia; DLB, Dementia with Lewy bodies; H&Y, Hoehn & Yahr; M, Male; F, Female. CR, Cognitive rehabilitation; RT, relaxation therapy; TAU treatment as usual.

* There were no significant differences between these groups on baseline measures.

Table 2 Participant outcomes and mean LED estimates across assessment time points

Measures (max score)	Arm	Baseline		Post intervention		Follow-up	
		N	Mean (SD) [Range]	N	Mean (SD) [Range]	N	Mean (SD) [Range]
BGSI Attainment (10)	CR	10	3.08 (1.43) [1-5.33]	8	6.29 (1.44) [3-8]	7	6.6 (1.93) [4-9.5]
	RT	10	3.17 (1.3) [1-5]	9	3.64 (1.32) [2-6]	9	3.59 (1.93) [1-6.5]
	TAU	9	2.91 (1.27) [1.33-5]	9	3.69 (2.3) [1-8]	9	4.02 (2.38) [1-8]
BGSI Satisfaction (10)	CR	10	3.3 (1.36) [1-5]	8	6.54 (1.48) [4.3 – 9]	7	5.98 (1.7) [4.33-8.33]
	RT	10	4.13 (1.39) [2-6.67]	9	4.06 (0.8) [2.5-5]	9	4.57 (1.45) [2-7.5]
	TAU	9	2.69 (1.14) [1-4.5]	9	3.44 (1.9) [1-6.3]	9	4.31 (2.54) [1-8]
BGSI Attainment carer-rated (10)	CR	8	2.35 (0.99) [1-4]	6	4.89 (2.53) [2-8.33]	5	4.83 (2.44) [2.3-7.7]
	RT	8	2.35 (1.39) [1-5.33]	9	2.94 (1.46) [1-5.33]	9	2.59 (1.67) [0.7 - 5.3]
	TAU	8	2.04 (1.06) [1-4]	8	3.01 (2.59) [1-8.67]	8	2.10 (1.95) [1-6.67]
HADS Depression (21)	CR	10	9.13 (1) [2-16]	8	5.5 (3.5) [1-11]	7	6.14 (4.14) [1-12]
	RT	10	6.5 (3.54) [1-11]	9	6.22 (3.31) [1-10]	9	6.67 (3.67) [1-10]
	TAU	9	9.13 (4) [2-16]	9	10.22 (4.09) [3-17]	9	8.11 (4.01) [2-14]
HADS Anxiety (21)	CR	10	7.2 (3.8) [0-11]	8	6.38 (3.54) [0-10]	7	5.29 (2.69) [3-9]
	RT	10	5.8 (2.97) [0-8]	9	6.89 (3.55) [1-12]	9	6.56 (3.21) [1-10]
	TAU	9	10.7 (4.97) [2-19]	9	10.56 (5.08) [4-21]	9	10.33 (4.3) [3-17]
ED5D3L Index (1.0)	CR	10	0.65 (0.27) [0.06-1]			7	0.59 (0.31) [-0.16-1]
	RT	10	0.66 (0.18) [0.19-0.84]		Not measured	9	0.56 (0.31) [0.19-0.85]
	TAU	9	0.35 (0.31) [-0.02-0.71]			9	0.13 (0.26) [-0.07-0.64]
ED5D3L VAS (100)	CR	10	65 (15.09) [40-90]			7	67.86 (17.53) [50-90]
	RT	10	65.5 (14.99) [50-90]		Not Measured	9	57.22 (18.56) [30-80]
	TAU	9	56.1 (13.18) [35-70]			9	46.11 (17.82) [10-70]
PDQ8 (100)	CR	10	21.56 (15.27) [3.1-40.6]	8	29.3 (10.95) [9.38-40.63]	7	26.18 (16.1) [6.25-53.13]
	RT	10	30 (12.34) [9.4-46.9]	9	31.94 (10.34) [16.63-46.88]	9	26.39 (14.07) [9.38-53.13]
	TAU	9	40.28 (12.74) [18.8 - 52.5]	9	47.57 (16.3) [31.25-78.13]	9	54.51 (16.69) [31.25-81.25]
WHOQOL- BREF Physical (20)	CR	10	13.2 (2.57) [9-18]	8	12.5 (3.12) [7-18]	7	13.15 (2.1) [10-17]
	RT	10	12 (2.4) [9-16]	9	12.33 (1.87) [9-15]	9	13.33 (2.83) [8-17]
	TAU	7	10.29 (3.35) [6-15]	9	10.26 (2.69) [5-14]	9	11.67 (2.28) [8-16]
WHOQOL- BREF Psych. (20)	CR	10	14.5 (2.22) [13-20]	8	13.25 (2.82) [10-18]	7	14.49 (2.65) [11-19]
	RT	10	12.6 (1.96)[9-15]	9	12.44 (2.13) [10-16]	9	13.33 (2.5) [10-17]
	TAU	7	11.57 (2.07) [9-14]	9	10.44 (2.79) [5-15]	9	12.82 (1.1) [10-3.47]

WHOQOL-BREF Social (20)	CR	10	14.4 (3.92) [8-20]	8 15.85 (2.31) [12-19]	7 15.47 (2.02) [14.4-20]
	RT	10	15.8 (3.49) [7-19]	9 14.78 (3.27) [9-20]	9 14.56 (4.12) [8-19]
	TAU	7	14.86 (4.06) [11-20]	9 14.06 (4.30) [7-20]	9 13.47 (3.5) [5-16]
WHOQOL-BREF Environ. (20)	CR	10	15.7 (2.54) [11-20]	8 16.13 (2.23) [13-19]	7 15.98 (1.49) [14-18]
	RT	10	15.9 (2.02) [13-19]	9 15.33 (1.22) [14-17]	9 15.67 (1.8) [13-18]
	TAU	7	15.43 (2.51) [12-19]	9 14.99 (2.38) [12-19]	9 15.32 (2.22) [12-19]
FAQ (33)	CR	10	9.5 (7.04) [2-24]	Not measured	7 13.57 (7.87) [0-25]
	RT	10	8.6 (6.57) [2-25]		9 13.44 (8.29) [3-28]
	TAU	9	15.33 (4.92) [8-24]		9 17 (8.59) [4-27]
GSES (40)	CR	9	31 (4.15) [25-38]	8 31.5 (4.24) [27-37]	7 31.83 (5.07) [26-39]
	RT	10	31.1 (5.43) [21-39]	9 28.22 (5.56) [18-39]	9 28.64 (4.87) [18-37]
	TAU	9	27.89 (4.46) [18-35]	9 28.86 (2.5) [25-32]	9 26.87 (2.4) [23-29]
D-KEFS Fluency (tot. corr. resp.)	CR	10	27.4 (11.83) [7-47]	8 30.13 (14.4) [7-54]	7 23.14 (7.58) [9-31]
	RT	10	29.1 (12.45) [11-51]	9 31.44 (10.4) [16-48]	9 31.44 (12.2) [17-54]
	TAU	9	23.89 (10.73) [7-46]	9 24.67 (13.82) [8-53]	9 24 (11.38) [7-43]
TEA No distraction (7)	CR	10	5.9 (1.29) [3-7]	8 6 (1.2) [4-7]	7 5.86 (0.9) [5-7]
	RT	10	6.4 (1.07) [4-7]	9 6.44 (0.53) [6-7]	9 6.33 (1) [4-7]
	TAU	9	5.56 (1.51) [3-7]	9 5.44 (2.56) [0-7]	9 4.33 (2.74) [0-7]
TEA Distraction (10)	CR	10	3.9 (1.79) [1-6]	8 4.64 (2.33) [2-9]	7 3.06 (1.82) [1-5.22]
	RT	10	7 (2.21) [3-9]	9 5.22 (3.8) [1-10]	9 7.22 (3.96) [0-10]
	TAU	8	6 (3.42) [1-9]	9 5.13 (2.89) [1-10]	9 4.8 (3.9) [0-10]
D-KEFS TMT Switching Scaled score (19)	CR	3	4.33 (3.21) [2-8]	3 4 (3.46) [2-8]	2 4.5 (2.1) [3-6]
	RT	6	4.83 (2.93) [2-9]	3 6.67 (4.04) [2-9]	4 2 (0.82) [1-3]
	TAU	5	4.2 (1.92) [2-7]	3 3.67 (1.12) [3-5]	3 4.67 (2.89) [3-8]
RBMT Immediate memory recall (21)	CR	10	3.45 (2.13) [1-8.5]	8 4.38 (1.58) [2.5-7.5]	7 3.43 (2.15) [0-7]
	RT	10	3.3 (2.32) [1.5-8.5]	9 3.72 (3.1) [0.5-10.5]	9 3.33 (0.97) [2-4.5]
	TAU	9	3.5 (2.14) [1-8]	9 3.94 (1.79) [1.5-7]	9 3.06 (1.63) [0.5-5]
RBMT Delayed memory recall (21)	CR	10	1.7 (2.46) [-1-6.5]	8 2.17 (1.36) [0-3.5]	7 3.06 (1.57) [1.5-5.5]
	RT	10	1.45 (1.5) [-0.5-3.5]	9 2.33 (2.45) [-1-6.5]	9 2 (1.85) [-1-4.5]
	TAU	9	1.33 (1.58) [1-3.5]	9 2.39 (1.85) [-1-4.5]	9 0.99 (1.27) [-1-2.5]
LED estimates					
LED estimate (mgs.)	CR	7	635 (62734) [150-1950]	Not Measured	7 503.4 (430.2) [150-1360]
	RT	9	533.3 (391.7) [0-1080]		9 600 (459.7) [0-1420]
	TAU	9	588.1 (679.4) [0-2273]		9 588.1 (671) [0-2273]

Significant results in bold- see table 3 for effect sizes.

Note: For all measures, higher scores indicate greater performance or higher ratings except for HADS Depression, HADS Anxiety, PDQ8 and FAQ where higher scores indicate lower performance or greater symptomatology. BGSi, Bangor Goal Setting Interview; HADS, Hospital Anxiety and Depression Scale; ED5D3L, Euroqol Questionnaire-short version; VAS, visual analogue scale; PDQ8, Parkinson's Disease Questionnaire-8; WHOQOL-BREF, World Health Organisation Quality of Life Scale – Brief version; Psych., Psychological; Environ., Environmental; FAQ, Functional Activity Questionnaire; GSES, Generalised Self-Efficacy Scale; TEA, Test of Everyday Attention; D-KEFS, Delis-Kaplan Executive Function Scale; tot., total; corr., correct; resp., responses; TMT, Trial Making Test; RBMT, Rivermead Behavioural Memory Test; LED, Levodopa-dose Equivalent; mgs., Milligrams. CR, Cognitive rehabilitation; RT, relaxation therapy; TAU treatment as usual.

Table 3 Standardised effect size estimates (*d*) and confidence intervals for statistically significant differences ($p < 0.05$) on primary and secondary outcomes

Measures	Post-intervention (two months)			Follow-up (six months)		
	Comparison	<i>d</i> (95% CI)	<i>P</i>	Comparison	<i>d</i> (95% CI)	<i>P</i>
Primary						
BGSI	CR vs. TAU	1.63 (0.53-2.73)	.004	CR vs. TAU	1.36 (0.27-2.46)	.015
Attainment	CR vs. RT	1.82 (0.69-2.95)	.002	CR vs. RT	1.77 (0.61-2.93)	.003
BGSI	CR vs. TAU	2.04 (0.87-3.22)	.001	No statistically significant differences		
Satisfaction	CR vs. RT	1.84 (0.7-2.97)	.002			
Secondary - Participants						
BGSI	CR vs. RT	1.19 (0.07-2.31)	.039	CR vs. TAU	1.89 (0.55-3.22)	.005
Attainment carer rated				CR vs. RT	1.77 (0.5-3.05)	.007
HADS Depression	CR vs. TAU	-1.22 (-2.26- -0.18)	.027	No statistically significant differences		
GSES	CR vs. RT	1.07 (0.06-2.09)	.041	No statistically significant differences		
WHOQOL- BREF Social	CR vs. TAU	1.11 (0.09-2.14)	.039	No statistically significant differences		
	CR vs. RT	1.13 (0.1-2.16)	.037			
ED5D3L Index	Not measured			CR vs. TAU	1.74 (0.59-2.9)	.007
				RT vs. TAU	1.53 (0.48-2.58)	.016
PDQ8	No statistically significant differences			CR vs. TAU	-1.43 (-2.53- -0.32)	.033
				RT vs. TAU	-1.65 (-2.72- -0.58)	.006
RBMT Delayed memory recall	No statistically significant differences			CR vs. TAU	1.26 (0.18-2.34)	.025
Secondary- Carers						
HADS Anxiety	RT vs. TAU	-1.12 (-2.14- -0.09)	.044	No statistically significant differences		
ED5D3L VAS	Not Measured			CR vs. TAU	1.41 (0.17-2.65)	.028
				CR vs. RT	1.33 (0.13-2.53)	.038
WHOQOL- BREF Psych.	No statistically significant differences			CR vs. RT	1.41 (0.2-2.63)	.029

WHOQOL- BREF Environ.	No statistically significant differences	CR vs. TAU	1.71 (0.41-3.01)	.01
		CR vs. RT	1.21 (0.02-2.39)	.053
RSS	No statistically significant differences	CR vs. TAU	-1.42 (-2.6 - -0.18)	.027

Note: A positive effect size indicates that the first group is greater/higher than second group; a negative effect sign indicates the second group is greater/higher than the first group (for HADS Depression and Anxiety, PDQ8 and the RSS, higher scores indicate lower well-being or greater symptomatology). BGSi, Bangor Goal Setting Interview; HADS, Hospital Anxiety and Depression Scale; GSES, Generalised Self-Efficacy Scale; WHOQOL-BREF, World Health Organisation Quality of Life Scale – Brief version; Psych., Psychological; Environ., Environmental ED5D3L, Euroqol Questionnaire-short version; PDQ8, Parkinson’s Disease Questionnaire–8; RBMT, Rivermead Behavioural Memory Test; ED5D3L, Euroqol Questionnaire-short version; VAS, visual analogue scale; RSS, Relative’s Stress Scale. CR, Cognitive rehabilitation; RT, relaxation therapy; TAU treatment as usual.

Table 4 Carers' outcomes across assessment time points

Measures (max score)	Arm	Baseline		Post intervention		Follow-up	
		N	Mean (SD) [Range]	N	Mean (SD) [Range]	N	Mean (SD) [Range]
HADS Depression (21)	CR	8	3.5 (2.78) [0-8]	6	3 (3.69) [0-9]	5	2.8 (3.03) [1-8]
	RT	10	4.4 (2.59) [0-8]	9	4.67 (2.78) [1-8]	9	5.89 (3.28) [1-12]
	TAU	8	8 (4) [1-9]	8	4.38 (3.02) [1-11]	8	5.38 (3.11) [2-10]
HADS Anxiety (21)	CR	8	8 (4.13) [0-8]	6 4.5 (2.17) [1-7]		5	5.8 (2.94) [3-9]
	RT	10	4.8 (3.01) [0-11]	9 4.44 (3.21) [0-10]		9	6.53 (4) [1-13]
	TAU	8	6.5 (2.98) [3-11]	8 7.57 (3.41) [5-15]		8	8.13 (4.76) [4-17]
ED5D3L Index (1.0)	CR	8	0.92 (0.11) [0.73-1]			5	0.75 (0.24) [0.36-1]
	RT	10	0.8 (0.19) [0.52-1]	Not Measured		9	0.77 (0.15) [0.62-1]
	TAU	8	0.69 (0.27) [0.09-1]			8	0.7 (0.69) [0.62-0.85]
ED5D3L VAS (100)	CR	8	76.9 (14.13) [50-90]			5 84 (8.94) [70-90]	
	RT	10	82 (12.29) [65-100]	Not Measured		9 71.1 (20.43) [45-100]	
	TAU	8	67.8 (14.31) [50-90]			8 54.13 (28.5) [3-90]	
WHOQOL- BREF Physical (20)	CR	8	16.75 (1.83) [13-18]	6	16.83 (1.17) [15-18]	5	16.6 (2.07) [14-19]
	RT	10	15.8 (3.61) [9-19]	9	14.7 (4.36) [8-19]	9	14.1 (3.66) [10-19]
	TAU	8	14.12 (2.53) [10-18]	8	14.25 (2.19) [10-17]	8	14.2 (2.3) [10-18]
WHOQOL- BREF Psych. (20)	CR	8	16.75 (1.39) [15-19]	6	16 (2.83) [11-19]	5 17 (1.58) [15-19]	
	RT	10	16 (2.75) [11-19]	9	15.89 (2.93) [10-19]	9 14.56 (1.81) [12-17]	
	TAU	8	14.5 (2) [11-17]	8	14.63 (1.6) [12-17]	8 14.37 (1.68) [11-16]	
WHOQOL- BREF Social (20)	CR	8	16 (2.51) [12-20]	6	14.33 (2.34) [12-17]	5	15.2 (5.22) [8-20]
	RT	10	14.9 (15) [12-19]	9	15.22 (3.46) [11-20]	9	15.3 (2.5) [11-20]
	TAU	8	15.12 (2.42) [11-19]	8	14.75 (1.83) [12-17]	8	14.6 (1.4) [13-16]
WHOQOL- BREF Environ. (20)	CR	8	17.12 (1.36) [15-18]	6	17.2 (2.99) [13-20]	5 18.4 (1.34) [17-20]	
	RT	10	16.7 (1.49) [14-19]	9	15.89 (2.09) [12-18]	9 16.2 (1.97) [14-20]	
	TAU	8	16.38 (2.88) [10-19]	8	15.75 (2.55) [10-18]	8 15.42 (2.34) [10-18]	
GSES (40)	CR	8	33.5 (4.31) [28-40]	6	33.5 (3.67) [30-38]	5	36 (4.3) [30-40]
	RT	10	33.6 (4.06) [27-38]	9	32.67 (5.34) [26-40]	9	32.33 (5.55) [26-40]
	TAU	8	31.12 (5.33) [24-39]	8	32.13 (4.42) [25-39]	8	31.88 (4.39) [56-38]
RSS (60)	CR	8	17.75 (11.16) [5-35]	6	19.83 (13.94) [4-41]	5 16.2 (10.89) [4-27]	
	RT	10	22.7 (8.93) [6-37]	9	21.44 (7.18) [10-30]	9 22.69 (10.5) [6-35]	
	TAU	8	22.12 (7.7) [8-34]	8	25 (8.91) [11-37]	8 9.68 (3.87) [5-16]	
NPI-Q Distress (60)	CR	8	6 (4.81) [0-16]			5	10.8 (14.79) [0-36]
	RT	10	9.4 (9.97) [0-29]	Not Measured		9	7.11 (5.42) [0-15]
	TAU	8	14 (9.9) [5-33]			8	10 (4.81) [1-16]

Significant results in Bold- see table 3 for effect sizes.

Note: For all measures, higher scores indicate greater performance or higher ratings except for HADS

Depression, HADS Anxiety, RSS and NPI Distress where higher scores indicate lower well-being or greater symptomatology. HADS, Hospital Anxiety and Depression Scale; ED5D3L, Euroqol Questionnaire-short version; VAS, visual analogue scale; WHOQOL-BREF, World Health Organisation Quality of Life Scale – Brief version; Psych., Psychological; Environ., Environmental; GSES, Generalised Self-Efficacy Scale; RSS, Relatives' Stress Scale; NPI-Q, Neuropsychiatric Inventory-Questionnaire. CR, Cognitive rehabilitation; RT, relaxation therapy; TAU treatment as usual.