Group cognitive rehabilitation to reduce the psychological impact of multiple sclerosis on quality of life: the CRAMMS RCT

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Scientific summary

The CRAMMS RCT

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Scientific summary

Background

Cognitive problems are common in people with multiple sclerosis, and include impairments of attention, information processing, executive function and memory. Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual's cognitive functions and to teach strategies to cope with these problems in daily life. Cognitive rehabilitation often distinguishes between 'restoration' or 'restitution' (whereby domain-specific and task-focused activities are repeated a number of times to improve specific functions, e.g. improved attention) and 'compensation' or 'adaptation' (whereby people are taught to use strategies to overcome their cognitive limitations, e.g. setting reminders on mobile phones). There are recommendations for the management of cognitive problems for people with multiple sclerosis in *The National Service Framework for Long-term Conditions* (Department of Health and Social Care. *The National Service Framework for Long-term Conditions*. London: DHSC; 2005) and the National Institute for Health and Care Excellence clinical guidelines [National Institute for Health and Care Excellence. *Multiple Sclerosis in Adults: Management*. Clinical Guideline 186 (CG186). London: NICE; 2014] for the management of adults with multiple sclerosis. However, the guidelines are based partly on expert opinions and make recommendations that further evidence is needed for the provision of cognitive rehabilitation.

Some randomised controlled trials have evaluated the effectiveness of cognitive rehabilitation for people with multiple sclerosis. Studies of computerised cognitive rehabilitation have demonstrated that it is possible to improve cognitive abilities with retraining, but there remains uncertainty about whether or not the gains made persist over time and whether or not there are beneficial effects on people's daily lives. Studies of compensatory strategy training have suggested that they may lead to greater use of strategies and fewer reports of cognitive problems in daily life, but it is unclear whether or not these benefits persist over time. Cochrane systematic reviews have not found overall evidence to support or refute the effectiveness of cognitive rehabilitation for people with multiple sclerosis (das Nair R, Martin KJ, Lincoln NB. Memory rehabilitation for people with multiple sclerosis. *Cochrane Database Syst Rev* 2016;**3**:CD008754 and Rosti-Otajärvi EM, Hämäläinen PI. Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database Syst Rev* 2014;**2**:CD009131). However, these reviews suggested that more high-quality trials were needed.

Two small-scale pilot randomised controlled trials used two cognitive rehabilitation programmes that were similar to each other, and their results suggested that this programme may help reduce cognitive problems in people with multiple sclerosis [das Nair R, Lincoln NB. Evaluation of Rehabilitation of Memory in Neurological Disabilities (ReMiND): a randomized controlled trial. *Clin Rehabil* 2012;**26**:894–903, and Carr SE, das Nair R, Schwartz AF, Lincoln NB. Group memory rehabilitation for people with multiple sclerosis: a feasibility randomized controlled trial. *Clin Rehabil* 2014;**28**:552–61]. The ReMiND trial (das Nair and Lincoln, 2012) was conducted in people with a range of neurological disabilities, including many who had multiple sclerosis. This trial evaluated the effectiveness of group memory rehabilitation programmes in participants with memory problems by comparing compensation strategy training, restitution strategies and a self-help control. Both quantitative and qualitative data from the study indicated that the interventions were worthy of further evaluation. The ReMiND-MS trial (Carr *et al.* 2014) was a modified version of the intervention in the ReMiND trial (das Nair and Lincoln, 2012), combining restitution and compensation strategies compared with a usual-care control of people with multiple sclerosis (total participants, $n = 48$). The results showed a significant effect on mood, favouring the intervention group. These two pilot randomised controlled trials suggested that the intervention required further evaluation.

This trial was designed to assess the clinical effectiveness and cost-effectiveness of a group cognitive rehabilitation programme.

Objectives

The primary objective was to determine whether or not attending a group cognitive rehabilitation programme (the intervention) in addition to usual care was associated with reduced psychological impact of multiple sclerosis on quality of life, as measured on the Multiple Sclerosis Impact Scale – Psychological subscale, compared with usual care alone (control). The secondary objectives were to assess the cost-effectiveness of the intervention and whether or not the intervention was associated with improvements in participants' attention and memory abilities, self-reported cognitive problems in daily life, mood, fatigue, employment status and carer strain.

Methods

This was a multicentre, parallel-group, pragmatic randomised controlled trial with follow-up at 6 and 12 months after randomisation. A subset of participants took part in a qualitative study to assess the perceived effects of the intervention.

Participants were identified through NHS hospitals, charities (e.g. Multiple Sclerosis Society branches) and the UK multiple sclerosis register. Participants with multiple sclerosis were included if they were aged 18–69 years, reported having cognitive problems on the Multiple Sclerosis Neuropsychological Screening Questionnaire, had cognitive deficits on the Brief Repeatable Battery of Neuropsychological Tests, were able to travel to one of the centres to attend group sessions, were able to speak English and gave informed consent. Potential participants were excluded if they had vision or hearing problems, concurrent severe medical or psychiatric conditions, or were involved in other psychological intervention trials.

Once 9–11 participants, who could all attend the intervention sessions at the same time should they be randomised to receive it, had been recruited at a site, they were randomly allocated, to intervention or usual care on a 6 : 5 ratio. The randomisation was stratified by trial site and minimised by multiple sclerosis type (relapsing–remitting or progressive) and gender.

Those allocated to the intervention received 10 weekly sessions of a manualised group cognitive rehabilitation programme in addition to their usual care. Participants were taught restitution strategies to retrain impaired attention and memory functions and compensation strategies to enable them to cope with their memory problems. Some sessions were video-recorded in order to ascertain the fidelity of the intervention.

Outcomes were assessed 6 and 12 months after randomisation by using questionnaires and at visits. The primary outcome was the psychological impact of multiple sclerosis, measured using the Multiple Sclerosis Impact Scale – Psychological subscale at 12 months after randomisation. Secondary outcomes included measures of memory problems in everyday life from a subjective and relative's perspective, mood, fatigue, quality of life, attention and memory abilities, and cost-effectiveness as determined by the EuroQol-5 Dimensions, five-level version, and a service use questionnaire. The effect on carers was assessed on the Modified Carer Strain Index.

The sample size needed for the trial was 400 participants, to detect a minimum clinically relevant difference in the means of three points with a type I error of 0.05 and 80% power, assuming a standard deviation of 9 (Multiple Sclerosis Impact Scale version 1) and accounting for 15% lost to follow-up and the potential for clustering in the cognitive rehabilitation group because of the group intervention. The Multiple Sclerosis Impact Scale version 2 was used in the trial.

Analysis was according to randomised group, regardless of whether or not cognitive rehabilitation sessions were attended, without imputation for missing data (i.e. modified intention to treat). Outcomes were analysed using a multilevel linear model with site, gender, multiple sclerosis type and baseline score as

covariates, with a random effect for the cognitive rehabilitation group in the intervention group and allowing the participant-level variance to differ between the intervention and control groups.

A subset of participants was interviewed by a researcher or a patient and public involvement member who was a relative of a person with multiple sclerosis. Neither was involved with the participants' assessment or treatment.

Results

A total of 818 people with multiple sclerosis were screened for inclusion between 1 March 2015 and 31 March 2017. Of these, 579 (71%) gave consent and 449 (55%) were randomised: 245 to cognitive rehabilitation and 204 to usual care. A total of 173 (85%) participants in the usual-care group and 214 (87%) participants in the cognitive rehabilitation group were included in the primary analysis.

The mean age of participants was 49.4 years (standard deviation 9.9 years); 326 participants (73%) were women and 432 (96%) were white. About two-thirds (65%) reported having relapsing–remitting multiple sclerosis. The characteristics assessed at baseline were well balanced between the intervention and control groups.

Attendance at the cognitive rehabilitation groups was good. Participants attended a median of 10 sessions (interquartile range 7–10; range 0–10), with 208 (85%) participants attending at least three sessions. Fidelity analysis indicated that the intervention was delivered as intended.

At the 6-month follow-up, 405 participants (90%) returned the questionnaire booklet and 412 participants (92%) completed the assessment visit. Questionnaire booklet return and visit completion were similar in the two groups. At the 12-month follow-up, 392 participants (87%) returned the questionnaire booklet and 387 (86%) completed the assessment visit; and again, booklet return and visit completion were similar in the two groups.

There was no clinically important difference on the Multiple Sclerosis Impact Scale – Psychological subscale between the two groups at the 12-month follow-up [intervention group, mean 22.2 (standard deviation 6.1) and control group, mean 23.4 (standard deviation 6.0), adjusted difference in means –0.6, 95% confidence interval –1.5 to 0.3; $p = 0.20$], with lower scores indicating a lower impact of multiple sclerosis on quality of life. There was no evidence of a difference in the effect of cognitive rehabilitation across subgroups based on multiple sclerosis type, baseline Multiple Sclerosis Neuropsychological Screening Questionnaire score, the Doors and People test or the Symbol Digit Modalities test (p-value for interaction effect = 0.38 to 0.92). There were small differences between the groups in the Multiple Sclerosis Impact Scale – Psychological subscale score at 6 months (adjusted difference in means –0.9, 95% confidence interval –1.7 to –0.1; $p = 0.03$) in favour of the cognitive rehabilitation group.

There were differences between the groups in that the frequencies of participant-reported memory problems in everyday life on the Everyday Memory Questionnaire at 6 months (–5.3, 95% confidence interval –8.7 to –1.9) and 12 months (–4.4, 95% confidence interval –7.8 to –0.9) and in the relative-reported Everyday Memory Questionnaire at 6 months (–5.4, 95% confidence interval –9.1 to –1.7) and 12 months (–5.5, 95% confidence interval –9.6 to –1.5) were lower in the cognitive rehabilitation group. There were also differences in mood on the 30-Item General Health Questionnaire at 6 months (–3.4, 95% confidence interval –5.9 to –0.8) and 12 months (–3.4, 95% confidence interval –6.2 to –0.6), in that those in the intervention group reported fewer mood problems. There were no differences in fatigue, employment rate, level of physical disability or physical aspects of quality of life. Scores from the cognitive tests were similar in both groups at the 6- and 12-month follow-ups. No safety concerns were raised and no deaths reported.

The cost of the cognitive rehabilitation programme was estimated at £209 per participant. The primary cost–utility analysis indicated that cognitive rehabilitation was less expensive than usual care (–£574.93, 95% confidence interval –£1878.93 to £729.07) with negligible quality-adjusted life-year gain (0.00, 95% confidence interval –0.02 to 0.02), with no evidence of a difference between the groups. Similar conclusions were also reached for the cost-effectiveness analysis of the primary outcome and the cost–utility analysis of the Multiple Sclerosis Impact Scale – 8 Dimensions.

A total of 36 participants were interviewed: 18 from each group. The main findings were that usual care did not include cognitive rehabilitation; many people noticed changes in their cognitive abilities, particularly those in the intervention group; and these changes were attributed to increased strategy use, the educational aspects of the intervention and the support received through the group environment.

Conclusions

Implications for health care

- People with multiple sclerosis have problems with attention and memory and are seeking help for these problems.
- This trial has not shown any long-term effect of this cognitive rehabilitation programme on quality of life for people with multiple sclerosis, measured using the Multiple Sclerosis Impact Scale – Psychological subscale, but there was a short-term effect.
- There was some evidence that cognitive rehabilitation improved both memory problems in daily life and mood.
- Participant feedback was positive, with some participants reporting daily life benefits of attending the cognitive rehabilitation programme.
- There was no evidence of an effect on costs or quality-adjusted life-years.
- The results support the provision of this intervention in clinical practice, given the short-term clinical effects and the lack of alternative, more effective, treatments.
- However, further evaluation of those with multiple sclerosis who may benefit most is needed.

Recommendations for research

- There needs to be more small-scale efficacy studies to establish the appropriate selection criteria for cognitive rehabilitation programmes, so that the intervention is tailored to those who may benefit most.
- Future studies should attempt to control for the effects of the group environment, in order to ascertain whether it is the contact with others with similar problems or the content of the programme that is most important.
- Further research is needed to explore how the short-term benefits of cognitive rehabilitation can be maintained in the long term.

Trial registration

This trial is registered as ISRCTN09697576.

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This report

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