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Evaluation of a group-based memory rehabilitation for people with Multiple Sclerosis: a sub-group analysis of the ReMiND Randomised Controlled Trial

Research Article

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Abstract

Background: Memory problems are frequently reported in people with multiple sclerosis (MS). These can be debilitating and affect individuals, and their families. This sub-group analysis focused on the effectiveness of memory rehabilitation in patients with MS.

Patients and Methods: Data were extracted from a single blind randomised controlled trial, which also included participants with traumatic brain injury and stroke (the ReMiND trial). Participants were randomly allocated to compensation or restitution treatment programmes or a self-help control. The programmes were manual-based and comprised two individual and ten group sessions. Outcome measures included assessments of memory, mood and activities of daily living. There were 39 participants with MS, mean age 48.3 (SD = 10.8) and 29 (74%) were women.

Results: Comparison of groups showed no significant effect of treatment on memory, but there were significant differences between compensation and restitution on self-report symptoms of emotional distress at both 5 month ($p=0.04$) and 7 month ($p=0.05$) follow-ups. The compensation group showed less distress than the restitution group.

Conclusions: Individuals with MS who received compensation memory rehabilitation reported significantly less emotional distress than those who received restitution. Further research is needed to explore why self-reported memory problems did not differ between groups.

Introduction

Memory impairment is one of the most common neuropsychological deficits associated with MS, affecting 40%-65% (Rao et al., 1993). Memory impairments can affect all aspects of a persons' life: work, social and family. These memory impairments can also affect the emotional wellbeing of people with MS and have been associated with depression (Chiaravalloti, 2008).

Cognitive rehabilitation is a specific type of neuropsychological intervention designed to target cognitive deficits. This includes memory rehabilitation, which focuses on ameliorating memory deficits. Memory rehabilitation is a structured set of therapeutic activities, designed to improve memory by teaching patients about memory impairments, the use of compensatory strategies to manage these deficits better, and teaching the use of internal strategies to improve the coding, organisation and retrieval of information (Robertson, 2008).

Research on the effectiveness of memory rehabilitation for people with MS has produced inconsistent results. Lincoln et al (Lincoln, 2002) carried out a randomised control trial (RCT) with three groups: control (usual care), cognitive assessment only, and cognitive assessment and rehabilitation. The cognitive rehabilitation was individualised, and included training in a range of strategies and compensatory methods. No evidence was found to support or refute the effectiveness of cognitive rehabilitation for memory in people with MS. On the other hand, Stuifbergen et al. (Stuifbergen et al., 2012) conducted a RCT of a computer-based group rehabilitation programme for memory deficits in people with MS compared to a waiting list control. Results showed a larger increase in performance over time on memory assessments for the treatment group compared to the control group. Reviews have highlighted the need for more research into cognitive interventions for people with MS (O'Brien et al., 2008)(das Nair et al., 2012) as it is possible the lack of evidence for the effectiveness of memory rehabilitation for MS is a result of a lack of well-designed and suitably powered RCTs. However, a recent Cochrane review has shown evidence for the use of neuropsychological rehabilitation programmes in improving cognitive

deficits. This review showed the use of neuropsychological rehabilitation improves various types of memory as well as other cognitive deficits associated with MS (Rosti-Otajärvi EM, 2014).

The specific functions that lead to 'effective' memory rehabilitation are also disputed. Studies into memory rehabilitation across a number of neurological disorders have found evidence for a variety of strategies for improvement in memory. Hildebrandt, Bussmann-Mork & Swendemann compared strategy training with process-oriented treatment(Hildebrandt et al., 2006). Strategy training is the use of compensatory methods (e.g. external memory aids) designed to overcome memory problems, whereas process-oriented treatment is the use of internal strategies (e.g. chunking) to adapt the coding, organisation and retrieval of information (also called restoration or restitution). The results favoured the process-oriented treatment compared with the strategy training, however, this was not supported by Evans's (Evans, 2006) commentary on the study. This commentary stated there was no evidence of significant improvement of memory through restitution-oriented therapies. Evans used this, alongside the lack of well-controlled conclusive RCT's, to justify the use of compensatory methods as the treatment of choice. A review by Cicerone et al. (Cicerone et al., 2000) supported Evans's (Evans, 2006) comments, showing wider spread use of compensatory strategies over restitution, whilst highlighting the need for more research. It is also important to note that neither the original study (Stuifbergen et al., 2012) nor the review (Cicerone et al., 2000) had an MS focus and therefore it is hard to generalise these findings.

The Rehabilitation of Memory in Neurological Disabilities (ReMiND) trial (das Nair and Lincoln, 2012) compared the effectiveness of two memory rehabilitation programmes; restitution and compensation interventions with a self-help control group, to improve memory, mood, independence in activities of daily living and adjustment. ReMiND included people with mixed aetiologies, including stroke, traumatic brain Injury (TBI), and MS. The aim of this analysis was to evaluate the effectiveness of these treatments in people with MS, with the primary outcome as self-

reported memory, and secondary outcomes including assessments of objective memory, mood, independence in activities of daily living and adjustment.

Methods

The ReMiND study was advertised through clinicians and charities, such as the Multiple Sclerosis Society. Participants were recruited if they were over 18 years old and reported memory problems, as well as being diagnosed with stroke, TBI or MS, which was verified by a clinician. Participants were excluded if they did not speak English, or did not live within 50 miles of Nottingham or Derby.

After informed consent was given, participants completed a baseline assessment. This included an a screening for acquired language disorders e.g. aphasia (Sheffield Screening Test for Acquired Language Disorders (Syder et al., 1993)); an estimate of pre-morbid IQ (National Adult Screening Test (Nelson and Willison, 1991)); objective assessment of memory (Rivermead Behavioural Memory Test Extended version (Wilson, 1999), Spatial and Digit Span subtests of the Weschler Memory Scale Third Edition (Wechsler, 1998)); executive abilities, such as attention, processing speed (Trail Making Test[*] (Reitan, 1958) and Stroop Neuropsychology Screening Test Victoria version (Regard, 1981)); and a screening assessment of psychological distress (General Health Questionnaire-12 (Goldberg and Williams, 1988)); and an assessment of independence in activities of daily living (Nottingham Extended Activities of Daily Living Scale (Nouri, 1987)). Participants were excluded if they had uncorrected visual or hearing impairments which prevented them from completing the assessments. Participants were also excluded if they had an overall profile score of >1 on the Rivermead

[*]We calculated the score of Test score B minus Test score A on the Trail Making Test

Behavioural Memory Test Extended; overall profile scores range from 0 to 4, and participants with a score <1 were deemed to not have a demonstrable memory deficit and therefore were not included.

Participants were randomised to one of the three groups: compensation, restitution, or self-help control. Participants who were randomly allocated to the self-help control were given the opportunity to attend one of the treatment groups (compensation or restitution) once they had completed the follow-up assessments. Randomisation was completed using cluster randomisation of four participants at once. This was completed by an independent randomisation centre, using a computer-generated random number sequence.

The intervention was carried out by research assistants who were trained by a Clinical Psychologist (RdN). All three of the programmes were manualised to ensure consistency. Each session lasted approximately 1.5 hours with a 10-15 minute break. All sessions began with a summary of the previous session and an outline of the current session, and finished with a review of the session, assignment of homework and a preview of the next session. Each programme contained 10 sessions, one per week for 10 weeks. The purpose of the homework was to give the participants an opportunity to practice strategies learned in the session in daily life. Travel expenses were offered to all participants.

The treatment manuals used in the programmes were developed on the basis of pre-existing programmes (Powell, 2003), as well from published articles and in consultation with practitioners. Participants in both of the intervention programmes (restitution and compensation) were taught the use of internal memory aids and errorless learning techniques. Participants in the compensation group were also taught how to use external memory aids (e.g. diaries). Those in the restitution group completed exercises to practice encoding and retrieval, and also included attention-retraining exercises, such as letter and number cancellation. Participants in the restitution group were also taught how to encode and retrieve specific information (e.g. remembering people's names by paying attention not only to the acoustic and orthographic presentation of the name but by creating a

visual image of the name). The self-help group were not taught any memory strategies, but were taught relaxation techniques and ways in which they could cope with their condition. To ensure there was no memory component to self-help group, and that the treatment groups were equal in terms of memory components, independent observational time-sampling was conducted (O'Brien et al., 2012).

Follow-up assessments were conducted at 5 and 7 months after randomisation. The outcomes assessor was blind to the group allocation. The primary outcome measure was the Everyday Memory Questionnaire (EMQ (Sunderland et al., 1983)) a, self-administered questionnaire of memory function in daily life. It has been shown to have good face and ecological validity (Royle and Lincoln, 2008) and is used in clinical practice. Secondary outcome measures included: the Rivermead Behavioural Memory Test Extended version (an objective assessment of memory ability), General Health Questionnaire-12, and Nottingham Extended Activities of Daily Living Scale. Internal and External Memory Aids Questionnaires, which were based on the Memory Aids Questionnaire (Wilson, 1984) were used to assess the frequency of use of memory aids. The Wimbledon Self Report Scale (Coughlan, 1988) was included as an assessment of emotional state and the Mental Adjustment to Brain Damage (modified from the Mental Adjustment to Cancer (Watson, 1988)) was included as an assessment of psychological adjustment.

The data on people with MS was extracted from the ReMiND data. Ethical approval was obtained from Nottingham Research Ethics Committee 1 in May 2004.

Results

Thirty nine participants in the ReMiND trial had a diagnosis of MS. Participant characteristics are shown in Table 1. The groups were well matched at baseline, with no significant differences between baseline variables (p values ranging from 0.13 to 0.82). Follow-ups were not compared against the

baseline data due to the potential of misleading results, as described in the previous literature (Bland and Altman, 2011).

Table 1 about here

An intention-to-treat analysis was used. The three groups were compared at 5 and 7-month follow-up.

As the data is ordinal, the non-parametric Kruskal-Wallis H Test was used. Table 2 shows a summary of the between-groups analyses. No significant differences were found between either of the treatment groups compared with the self-help control, significant between-groups differences were found for the Wimbledon Self Report Scale at both 5 month ($H(2)= 6.350$, $p=0.04$) and 7 month ($H(2)= 5.988$, $p=0.05$) follow-ups.

Table 2 about here.

Pairwise comparisons were used to determine where these significant differences lay. Adjusted p-values using the Dunn method for Kruskal Wallis(Dunn, 1964) were used to account for multiple comparisons. At 5-month follow-up, a significant difference was found between compensation and restitution [$H (1)= 4.955$, $p=0.04$] those in the restitution group scored significantly higher i.e. more distress, than those in the compensation group for the Wimbledon Self Report Scale. An estimate of effect size (eta^2) was calculated at 0.225, showing a small effect size. At 7-month follow-up, a significant difference was found between compensation and restitution [$H(1)= 5,709$, $p=0.04$] in the Wimbledon Self Report Scale. Those in the restitution group scored significantly higher than those in

the compensation group. An estimate of effect size (eta^2) was calculated at 0.238, showing a small effect size.

Discussion

There were no statistically significant differences between either of the treatment groups and the self-help group on self-reported memory problems at any time point. There were, however, statistically significant differences on emotional state between the two treatment groups at both 5 and 7-month follow-ups. This suggests those in the compensation group were less distressed by their memory problems (indicated by a higher score on the Wimbledon Self-Report Scale) than those in the restitution group at both these time points. Less distress in the compensation group could be attributed to the content of this group. From our time-sampling study (O'Brien et al., 2012), it was evident that although both intervention groups had equal amounts of memory content, the compensation group had more discussions regarding social activities, emotions and feelings, and coping with illness, compared to the restitution group. The social and emotional benefits of attending neuropsychological rehabilitation groups have been previously reported ((Evans, 1992), (Tate, 1997)), which could be attributed to these discussions outside of the intervention content. Carr et al (Carr, 2013) also found no significant differences between a memory rehabilitation group and a waiting list control on everyday memory problems, but reported differences in mood at 8 month follow-up. This supports the results found by this study, showing some evidence of compensatory strategies being related to a decrease in emotional distress in people with MS. However it could be a chance finding, due to the study being under-powered, therefore, this finding needs to be interpreted with caution.

The lack of significant differences in everyday memory could be attributed to the measure used (EMQ) or the scoring method. This EMQ is scored on frequencies of occurrences of forgetting and does not score the importance of these occurrences. It may be that the frequencies of forgetting are

not reduced *overall* but improvements on one or a few *personally important* items on the EMQ could result in reduced distress associated with forgetting these items. This is supported by participant feedback in the qualitative analysis of the ReMiND study (das Nair and Lincoln, 2013), where participants commented on the increased knowledge of their memory deficits and strategies taught, and improved mood. This suggests that the use of the strategies learnt in the compensation group may have reduced frustration/anger with forgetting, even if they did not always use their compensatory methods to overcome this. By adding in an 'impact scale' to the frequencies of forgetting on the EMQ), this effect could be analysed.

The persistence of the differences in emotional outcomes to the 7-month follow-up suggests that the benefits were maintained after the intervention stopped. Some studies have reported positive experiences of being in memory rehabilitation groups ((Spector et al., 2011), (Lexell et al., 2013), (Johansson and Tornmalm, 2012)) If, however, this improved emotional state was the result of being in a group setting, it is unlikely that this would be maintained beyond the end of the group sessions and would be likely to occur for all groups, irrespective of whether or not they included memory intervention. This points to the benefits of delivering compensatory strategy training in group settings. Mood-related improvements could have also been observed because the compensation group were taught to use more external memory aids, which could have placed less emotional strain on the individual themselves. In contrast, those in the restitution groups may have required more active attempts by participants to internally compensate for their memory problems and this may have been more emotionally demanding. However, if this were the case, greater reported use of external memory aids would be expected in the compensation group compared to the other groups. This was not the case.

Given that this was a sub-group analysis, there was a relatively small sample size. Therefore, the power was limited, and the results may be due to chance. Larger, fully powered RCTs are necessary to evaluate the effectiveness of memory rehabilitation for people with MS with memory problems.

Furthermore, although people with multiple aetiologies may be seen in rehabilitation settings, from a research perspective, there is a need to evaluate the efficacy of memory rehabilitation in people with MS. It could be that some of the intervention is not as applicable to those with MS compared to those with other aetiologies. This also applies to the selection of outcome measures. As MS is progressive, it may be beneficial to develop a specific intervention targeting people with progressive memory deficits. Again, as this was a sub-group analysis of a mixed aetiology study, there are other possible explanations for the memory deficits reported by those with MS. One possible explanation for the memory deficits could be attributed to attentional difficulties during learning tasks, due to fatigue. It would, therefore, be beneficial to assess fatigue if a further, fully powered RCT was completed. This sub-group analysis can provide some feasibility data to help with sample-size estimates for future trials of memory rehabilitation for people with MS.

Conclusions:

This sub-group analysis of data from people with MS- extracted from a, mixed-aetiology RCT of memory rehabilitation did not find any significant differences in memory between the groups at 5 or 7 month follow ups. However, at 5 and 7-month follow-up, the compensation group showed significantly less distress compared to the restitution or self-help groups. Further studies are needed to explore the mechanisms of such differences. This study provides preliminary data to help calculate sample-size parameters for a definitive trial of memory rehabilitation for people with MS.

Key Points:

- A large proportion of people with Multiple Sclerosis (MS) suffer cognitive difficulties, the most common being memory deficits.

- Currently, the evidence for the effectiveness of memory rehabilitation for people with MS is disputed, as is the mechanisms by which any change occurs.
- This article showed that patients with MS receiving compensatory memory training showed reduced emotional distress, which may contribute towards improved quality of life.
- This lowered emotional distress was maintained 7 months after randomisation, suggesting a lasting effect.
- Group-based rehabilitation programmes may have important therapeutic effects, which are wider than simply addressing memory problems, and may contribute to the overall management of people with MS.

Conflicts of Interest: No conflicts of interest to report.

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		Intervention					
		Compensation n= 12		Restitution n= 17		Self-help n= 10	
		n	%	n	%	n	%
Gender	Men	3	25	4	24	3	30
	Women	9	75	13	76	7	70
Employment	Full-time	3	25	6	35	3	30
	Part-time	3	25	1	6	1	10
	Unemployed	6	50	10	59	5	50
Living arrangements	With other/carer	8	67	13	76	6	60
	Alone	3	25	1	6	2	20
	With other as carer	0	0	2	12	0	0
	Other	1	8	1	6	1	10
		Mean	SD	Mean	SD	Mean	SD
Age (years)		48.3	10.8	45.2	7.5	47.7	10.9
Time since injury (months)		131.5	98.2	100.8	93.6	95.7	55.1
Education(years)		14.8	2.1	14.4	2.2	13.7	2.3
National Adult Reading Test- Pre-morbid IQ		109.1	7.5	106	10	109	8.2
Sheffield Screening test for Acquired Language Disorders		19.3	0.7	19.1	1	18.7	1.5
WAIS III Digit Span (Scaled Score)		9.8	1.7	9.2	2.3	8.1	2.9
WAIS III Spatial Span		9.7	2.0	8.9	3.9	9.3	2.4
Trail Making (B-A)		50.6	31.0	56.1	44.8	105.3	108.8
Stroop time (colour-word) (seconds)		36.8	12.1	43.8	25.5	42.2	17.4
Stroop error (colour-word)		0.3	0.9	1.6	2.6	0.6	1.1

Table 1: Demographic and baseline characteristics of study participants

National Adult Reading Test- Pre-morbid IQ: assessment for an estimate of pre-morbid intelligence. Sheffield Screening test for Acquired Language Disorders: assessment of language ability (screens for aphasia etc.) WAIS III: Wechsler Adult Intelligence Scale; sub-tests used to give an indication of working memory ability, including attention, concentration and mental control. Trail Making: test of visual attention and task switching. Stroop: measure of executive function (selective attention, processing speed)

Outcome Variable	Intervention	5 Months				7 Months			
		n	Median	SD	p	n	Median	SD	p
Everyday Memory Questionnaire	Compensation	11	43.0	18.7	0.99	11	39.0	19.2	0.78
	Restitution	16	36.0	25.3		16	30.0	25.2	
	Self-Help	10	38.0	18.9		10	41.0	20.6	
Rivermead Behavioural Memory Questionnaire- Extended	Compensation	12	27.0	7.7	0.35	12	26.5	6.1	0.26
	Restitution	17	26.0	7.6		17	29.0	7.9	
	Self-Help	10	24.5	9.8		10	22.5	9.3	
General Health Questionnaire	Compensation	12	2.0	3.8	0.96	12	2.5	3.6	0.30
	Restitution	17	4.0	3.8		17	7.0	4.4	
	Self-Help	10	3.0	4.0		10	2.0	3.8	
Extended Activities of Daily Living	Compensation	12	53.0	11.9	0.53	12	54.0	11.9	0.62
	Restitution	16	47.0	12.9		16	48.5	10.9	
	Self-Help	9	50.0	14.1		9	55.0	12.4	
Internal Memory Aids	Compensation	10	25.0	3.8	0.74	10	25.5	2.9	0.15
	Restitution	14	25.0	4.4		15	28.0	6.7	
	Self-Help	7	22.0	6.7		7	22.0	3.3	
External Memory Aids	Compensation	10	33.0	10.9	0.52	10	32.0	11.7	0.46
	Restitution	14	29.0	6.3		15	27.0	5.2	
	Self-Help	7	28.0	4.8		7	28.0	1.8	
Wimbledon Self Report Scale	Compensation	10	16.0	4.1	0.04*	10	16.5	3.9	0.05*
	Restitution	15	21.0	7.6		15	22.0	7.2	
	Self-Help	7	18.0	7.9		7	20.0	7.4	
Mental Adjustment to Brain Injury	Compensation	10	101.5	11.4	0.83	10	99.0	7.6	0.41
	Restitution	15	105.0	10.9		15	106.0	11.3	
	Self-Help	7	103.0	2.4		7	103.0	4.1	

Table 2: Between group analyses and descriptive statistics for each outcome measure.

*Significant at $p<0.05$

Everyday Memory Questionnaire: subjective assessment of memory. Rivermead Behavioural Memory Questionnaire- Extended: objective assessment of memory. General Health Questionnaire: assessment of mood and screening tool for psychological disorders. Extended Activities of Daily Living: and an assessment of disability and independence in activities of daily living. Internal Memory Aids: assessment of frequency of use of internal memory strategies. External Memory Aids: assessment of frequency of use of external memory aids (e.g. diaries). Wimbledon Self-Report Scale: assessment of emotional state. Mental Adjustment to Brain Injury: assessment of psychological adjustment