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Evaluating cognitive rehabilitation in multiple sclerosis: on the bumpy road to establishing evidence

"Cognitive rehabilitation in multiple sclerosis is a steadily developing field of study. There is growing evidence for the effectiveness of cognitive rehabilitation in improving outcomes in people with multiple sclerosis."

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• **cognitive rehabilitation** • **disability** • **evidence-based practice** • **effectiveness** • **memory** • **multiple sclerosis**

"There is marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality," Charcot (1877) reportedly noted about people with multiple sclerosis (MS) [1]. Despite these early observations of what we now refer to as 'cognitive deficits' and 'mood disorders', the magnitude and severity of these problems in MS were not considered seriously until over 100 years later. By the early 1990s, studies had begun to consistently demonstrate that people with MS reported cognitive problems.

Cognitive problems in MS

The presence of cognitive problems in people with MS has been reported to be in the range of 40–60% [2]. These problems have been found in all MS disease subtypes [3], in the incipient phase of MS [4] and on long-term follow-up [5]. There are some aspects of cognition that appear to be more affected than others, with attention, memory and executive functions (information processing speed, problem solving) being most affected. Language ability appears to be largely left intact, although some may experience anomia. Overall, there is considerable difference in the expression of these problems with people having varied and idiosyncratic cognitive profiles.

There is growing consensus that cognitive problems, apart from affecting people's activities of daily living and quality of life, can also place a large economic burden on the individual, families and the state. Indeed, some researchers assert that cognitive problems are "probably the most important determinant of employment status and associated societal costs" [6]. It is therefore unsurprising that in 2013 the MS Society in the UK, along with the James Lind Alliance, identified treatments that are effective in improving cognition in people with MS, as one of their top ten research priorities.

To develop these treatments, we may need to establish what causes or maintains these problems. In most neurological conditions, examining pathophysiology might be the first port of call. However, in MS, the pathophysiological

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changes observed tend to be varied, and given their complexity, they are not fully understood [7]. Correlations between imaging and cognitive dysfunction have been variable and modest and only accounts for some of the variance. Researchers have, therefore, sought other explanations.

More recently, researchers have examined the role of 'cognitive reserve' as a variable that might explain the high interindividual variability in cognitive deficits in MS (i.e., people with similar lesions and illness profiles may have very different cognitive profiles), and the variable correlations between MRI findings and cognitive problems in people with MS. Cognitive reserve refers to the "ability to optimize or maximize performance through differential recruitment of brain networks, which perhaps reflects the use of alternative cognitive strategies" [8]. This model implies that in people with high reserve, cognitive tasks are processed using less resources and in a way that makes errors unlikely to occur, in other words, more effectively. Much of the research on cognitive reserve has been conducted in the area of dementia. Sumowski and Leavitt [9] note that cognitive reserve is a function of 'maximal lifetime brain growth' (biology) and 'intellectual enrichment' (environment), and these protect against disease-related cognitive decline. This is an interesting avenue for MS research to pursue, particularly in terms of how ideas related to cognitive reserve can be incorporated in interventions designed to address cognitive problems or help people to live "'brain healthy' lifestyles" [9].

"...double-blind, placebo controls, may not always be possible in randomized controlled trials of cognitive rehabilitation..."

Cognitive rehabilitation

One intervention to address cognitive dysfunction that has received much attention and has begun to attract research evidence is cognitive rehabilitation. Cognitive rehabilitation has been variously defined. My view is that it comprises therapeutic activities that are guided by theories and models of clinical and health psychology, and neuropsychology, that aims to reduce the impact of cognitive deficits, and to improve coping, function, psychological wellbeing, quality of life. While some interventions may strive to 'improve' cognitive performance, this is not seen as the primary goal of such rehabilitation [10].

Cognitive rehabilitation can also be defined based on content and mode of delivery. In terms of content, cognitive rehabilitation can involve direct retraining, which is normally cognitive domain-specific. Therefore, for instance, drill and practice exercises, repeated over several trials, are used to help people practice paying attention. For attention retraining this may include letter or number cancellation tasks, navigating through mazes, among others; or memory retraining may include tasks such as list-learning. Such training is linked to the theory of restitution or restoration of function, whereby through targeted and focused repeated stimulation, damaged neural networks are reactivated. Conversely, the content of cognitive rehabilitation could focus on teaching people to compensate for their difficulties using external and internal aids. For memory problems, for instance, people are taught to use visualization or generate acronyms to help remember things or activities (usually to be carried out at some point in the future). External aids, from 'low-tech' tools such as calendars, diaries and written lists, to more technological gadgets such as mobile phone and computers, can serve as useful memory aids. Mobile phone apps have also begun to be used to deal with certain problem solving issues.

Cognitive rehabilitation, irrespective of whether the focus is on restitution or compensation of lost function, most often begins with a comprehensive neuropsychological assessment. Such an assessment outlines the person's cognitive profile of strengths and weaknesses, and cognitive rehabilitation capitalizes on the strengths to deal with the weaknesses.

Finally, cognitive rehabilitation can be defined in terms of how it is delivered, in other words, whether in group settings or individually. Individually, this can include one-to-one therapy with a rehabilitation specialist, or it could be solely completed using computer software. These delivery formats are combined in some instances.

Effectiveness of cognitive rehabilitation in MS

These different approaches to cognitive rehabilitation content and delivery formats have been researched, and based on this literature, Amato *et al.* [7] produced a position paper on the treatment of cognitive impairments in MS. Based on their review of literature, they concluded that "behavioral techniques, designed to

improve information acquisition, have consistently resulted in significant improvements in learning and memory performance," and that "...targeted interventions can result in significant improvement in learning and memory, but the nature of the 'targeted' programme may be important." However, the authors acknowledge that this was not a systematic review, and they only sampled some of the literature. They also added a caveat to these findings related to the methodological problems they observed within studies e valuating cognitive rehabilitation.

The latest and most comprehensive systematic review and meta-analysis of neuropsychological rehabilitation in MS is the Cochrane Review by Otajärvi and Hämäläinen [10]. Their objective was to "assess the effects of neuropsy-chological/cognitive rehabilitation on health-related factors, such as cognitive performance and emotional well-being in patients with MS." In this review of 20 studies (n = 966 people with MS) from ten different countries, 18 of 20 trials found a positive effect of the intervention compared with a control. When the data were meta-analyzed, the authors found that: When comparing cognitive training with any control, there were improvements in memory span and working memory; and when cognitive training and compensatory strategies were combined, compared with any control group, they found improvements in attention, immediate verbal memory and delayed memory. However, for both these strategies, there was no effect on some of the other basic cognitive functions, or indeed patients' (or carers') self-reported everyday cognitive performance, depression, anxiety, fatigue or quality of life. The authors concluded that their review "found low-level evidence for positive effects of neuropsycho-logical rehabilitation in MS ... new trials may therefore change the strength and direction of the evidence." They too noted the methodological weakness of many of the studies included in their review.

Based on eight trials (n = 521), our 2012 Cochrane review [11] evaluating the effectiveness of memory rehabilitation on functional outcomes found no evidence to support the effectiveness of memory rehabilitation on memory function or functional abilities in people with MS. However, this conclusion was because of the limited number and quality of some of the primary studies reviewed. In our current update [12] that includes 13 trials (n = 786), we found that there is some evidence to support the effectiveness of memory rehabilitation on objectively measured memory function, as well as on quality of life. This is welcome news. However, the evidence is limited and effectiveness does not extend to subjective reports of memory functioning, activities of daily living or mood. Although compared with our previous review there was some improvement in the methodological quality of the studies, more work is required to raise the standard.

In summary, small individual trials tend to demonstrate effectiveness of cognitive rehabilitation, however, meta-analyses of randomized controlled trials (RCTs) are more cautious in their conclusions. However, perhaps RCTs of c ognitive rehabilitation only tell one part of the story.

Qualitative studies evaluating patient experiences of such interventions have been positive. Our meta-synthesis [13] of five qualitative studies of memory rehabilitation (n = 87) found improvements in insight and acceptance of participants' neurological condition and taking control over their cognitive problems; the therapeutic effects of the groups, with social support and leisure activities, improvements in memory and other psychological effects (such as mood, fatigue and confidence), and a positive impact on personal, interpersonal and professional lives.

"...the goal of rehabilitation is to ultimately improve function."

Discrepancy between qualitative & quantitative study findings

The discrepancy in findings based on the methodology that studies use raises certain questions, highlight the challenges of conducting cognitive rehabilitation research in MS, but also suggests possible avenues for future research.

RCT methodology

Some researchers have suggested that perhaps the RCT methodology is not the best way to evaluate complex interventions such as cognitive rehabilitation. Walach *et al.* [14] challenged the 'hierarchical model' of evidence (with double blind, placebo controlled RCTs at the top of the hierarchy) to a 'circular model'. This model advocates a multiplicity of methods, with different designs, that balances the strengths and weaknesses of each, to arrive at synthesized, pragmatic evidence. However, this model also

advocates that each method is implemented with 'optimal scientific rigor'. This is not always the case with RCTs of cognitive rehabilitation.

Based on the above-mentioned literature reviews, some common problems with trials of cognitive rehabilitation in MS have been observed. It must, however, be noted that some of the studies included in all these reports are the same, so it is perhaps unsurprising, but also reassuring, that all authors have consistently picked up these problems. These include small sample sizes with studies not powered sufficiently to evaluate group differences, lack of or inadequate control groups, selection bias, inadequate randomization and blinding protocols, outcomes lacking relevance to daily life, lack of long-term follow-up and poor reporting of trials. These problems are not specific to cognitive rehabilitation studies in MS, and have been reported in cognitive rehabilitation studies in other neurological conditions, for example, stroke *[15]*. Some of these issues are further discussed below.

"...small individual trials tend to demonstrate effectiveness of cognitive rehabilitation, however, meta-analyses of randomized controlled trials are more cautious in their conclusions."

Sample size

Small sample sizes are common in cognitive rehabilitation trials of MS. In the Rosti-Otajärvi and Hämäläinen [10] review, samples sizes ranged from 15 to 240, with most trials having 20–30 participants. Because of a lack of sensitive outcome measures, sample sizes in such trials need to be large. To some extent not having fully powered studies is understandable, because some of these trials were conducted with little or no funding, over short periods of time. We are currently recruiting to an UK National Institute for Health Research (NIHR) funded trial CRAMMS *[16]*. This pragmatic RCT aims to randomize 400 people with MS to either a manualised cognitive rehabilitation training group intervention or usual care control. Further trials, evaluating other types of cognitive rehabilitation, should be of this magnitude; suitably powered to be c onfident of the statistical findings.

Control groups

Suitable control groups are essential for RCTs, and in complex interventions, such as cognitive rehabilitation, it is not always possible to have 'active' control groups. Most studies tend to use a 'treatment as usual' control, but some have tried delivering control activities with limited intervention content (e.g., use of a 'placebo' computerized program vs an active computerized memory retraining program). In one of our trials of memory rehabilitation *[17]*, we delivered an 'attention placebo' or 'self-help' control, wherein the control group spent the same amount of contact time with the facilitator as the intervention groups, but the participants only engaged in group discussions about their problems and learned relaxation techniques. Through time sampling, we were able to demonstrate that there was a significant difference in terms of the content of the intervention groups and the control group (i.e., control group had very little discussion around cognitive problems), so we were confident that only the intervention groups were receiving the active components of the intervention [18]. However, these groups were difficult to run and participants were aware that they were not getting the intervention. Despite this, they continued to attend the groups and participant feedback showed that even those in the control group benefited from the group activity *[19]*. This may therefore have dampened the possibility of finding significant differences between groups on quantitative outcome measures. Therefore, reviewers not familiar with cognitive rehabilitation should be mindful that double-blind, placebo controls, may not always be possible in RCTs of cognitive rehabilitation.

Outcomes

The desired primary outcome of cognitive rehabilitation has been debated [20,21], and studies have either chosen a 'neuropsychological' measure or a 'functional' measure. In our Cochrane review of memory rehabilitation [12], the objective measures used by most trials were list learning tasks (such as Hopkins Verbal Learning Test, Auditory Verbal Learning Test, and California Verbal Learning Test). While these tests have good diagnostic and predictive value, they have limited ecological validity as outcome measures of rehabilitation, thus potentially limiting the generalizability of findings into daily life.

Another point to consider is the psychometric properties of some of these measures. For instance, Rasch analysis of the Nottingham Extended Activities of Daily Living scale, a scale widely used in clinical practice and rehabilitation research, did not find support for the total scale as a unidimensional measure of activities of daily living. There were differential item functioning for age and for gender

on some items [22]. Rasch analysis has been recommended for the development of new, and evaluation of current scales used in rehabilitation, and more such research on commonly used scales is needed.

A systematic review [23] found that Goal Attainment Scaling (GAS) is a sound measure for physical, neurological and geriatric rehabilitation settings. However, our experience of applying it as an outcome measure in RCTs has been fraught with challenges. Challenges have included clients' goals not remaining static over time (sometimes outcomes are conducted 12–18 months after randomization to evaluate the longevity of intervention effectiveness); keeping outcome assessors blind to group allocation becomes difficult whereby the more time assessors spend with people with memory problems, the greater the chance that they will become unblinded; and Tennant [24] identified some scientific and measurement challenges posed by GAS, but also provided some helpful solutions.

I share Wilson's [25] assertion that standardized neuropsychological tests are not the best outcome measures for evaluations of cognitive rehabilitation, because the goal of rehabilitation is to ultimately improve function. Using the International Classification of Functioning, Disability and Health (ICF) [26], we can classify outcomes associated with impairments, activity limitations and participation restrictions, and the desired outcome of cognitive rehabilitation straddles the latter two categories.

● Reporting

Quality of reporting of trials of complex interventions has perhaps improved with the adoption of the CONSORT statement [27], but cognitive rehabilitation has been insufficiently described by trialists [28,29]. This makes it difficult for researchers to replicate studies and for clinicians to implement them in practice. The recently published Template for Intervention Description and Replication (TIDieR) checklist [30] and more cognitive rehabilitation-specific guidelines [28,29] may improve the quality of reporting such interventions, particularly if journal editors recommend that such guidance is followed.

● Effectiveness

Finally, we need to acknowledge that cognitive rehabilitation may not be effective for everyone with MS. Currently, we have limited knowledge about who benefits most from cognitive rehabilitation, when in the patient's journey it is best to offer such an intervention, and for how long. Indeed, without routine screening for cognitive problems in MS, it may be difficult to identify people early after diagnosis to provide them with rehabilitation if they experience cognitive problems. Langdon *et al.* recommend the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) as a suitable screening tool [6]. The value of this tool in effecting systemic changes in healthcare provision and ultimately improved patient outcomes is yet to be established, and such an assessment is urgently needed.

Conclusion

Cognitive rehabilitation in MS is a steadily developing field of study. There is growing evidence for the effectiveness of cognitive rehabilitation in improving outcomes in people with MS. Researchers are, however, still exploring what the focus and content of such rehabilitation should be, how and when the intervention can be delivered, how the intervention works (if it works), how change and effectiveness can be assessed using process and outcome measures, and whether or not cognitive rehabilitation in MS is clinically effective and cost effective. Large trials such as CRAMMS may provide the answers to the latter question on effectiveness, but the jury is still out on many of these issues. More well-conducted and reported trials are required, but equally, the 'black-box' of cognitive rehabilitation needs to be scrutinized and detailed analyses of the mechanisms of change need to be investigated. We have been on this road for some time and much has been learned, but in some respects, the journey has only just begun.

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