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Review article

Cognitive rehabilitation in multiple sclerosis: A systematic review

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ABSTRACT

Background: Cognitive impairment is a common clinical feature of multiple sclerosis (MS) at both the earlier and later stages of the disease, and has a significant impact on patients' functional status and quality of life. The need to address this deficit should be taken into account in clinical practice and research studies.
Objective: To conduct an updated systematic review of all published studies of cognitive rehabilitation interventions in people with MS, including studies with methodological shortcomings, to highlight major strengths and weaknesses in the field and to provide directions for future research.
Search methods: We searched electronic databases (PubMed and Web of Science) for articles published in English up until January 2014. The reference lists of all identified articles were also searched to complete the initial list of references.
Data extraction: Articles were categorized into outcome measures: cognition, imaging, mood, fatigue, quality of life and self-perceived cognitive deficits. All articles were reviewed independently and assessed according to predetermined criteria.
Results: A total of 33 studies met the inclusion criteria of which 4 were of Level II-1 and none was Level I. Although the majority of these studies reported some improvements in cognitive abilities (N = 31), the evidence which has been reported in the literature remains inconclusive and no definite conclusions can be drawn about the effect of different types of interventions on cognitive rehabilitation outcomes (recommendation C).
Conclusions: This review identified conflicting findings in the published literature about the effectiveness of various forms of cognitive rehabilitation techniques used in patients with MS. Studies with more rigorous methodology are therefore needed to clarify which form of cognitive rehabilitation may lead to greater clinical improvement.

Contents

1. Introduction

Multiple sclerosis (MS) is a chronic immune mediated disease of the central nervous system (CNS) which is characterized by the presence of

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widespread lesions affecting the brain, spinal cord and optic nerves. Inflammatory demyelination has traditionally been thought to be the main disease process in MS; however, axonal transection has been documented to occur early in the disease and to result in permanent disability [1]. Because of the widespread nature of the MS lesions within the CNS, this illness presents in a broad range of symptoms, which include visual, bulbar, sensory, motor, sphincter, cognitive, and neuropsychiatric [2,3], variable clinical presentations and disease courses [4].

Cognitive impairment is a common clinical feature of MS at both the earlier and later stages of the disease [5,6], with prevalence rates ranging from 43% to 70% [7,8]. MS has been shown to affect negatively various aspects of cognitive function including those associated with attention [9,10], efficiency of information processing [9,11], executive function [12], processing speed [13], and new learning and memory [8,13]. Cognitive dysfunction is closely associated with functional status in MS. Rao et al. [8] found that individuals with MS who were cognitively impaired participated in fewer social and vocational activities, were less likely to be employed, had greater difficulties in doing routine household tasks, and were more vulnerable to psychiatric illness than individuals with a purely physical disability. Functional impairments also include difficulty in shopping independently, completing housework, cooking, driving, and using public transport [14]. Such changes to patients' personal, occupational, and social lives have a deleterious impact on their quality of life (QoL). For this reason, developing therapeutic measures capable of alleviating such deficits should take precedence in MS research. So far, few studies have assessed the efficacy of interventions on cognitive deficits in MS, and many authors have highlighted the need for additional effective techniques [15].

Cognitive rehabilitation aims at reducing cognitive deficits, improving patients' awareness and ability to take their cognitive impairments into account in their daily living and promoting positive neurobiological changes. Although this research is still in its infancy, there have been some well-designed studies of cognitive rehabilitation in patients with MS that can provide a sound foundation from which to advance the field. Historically, most of the intervention implemented for use involved learning and memory-based interventions [15], but recently the focus has moved to other domains such as executive function and attention [21,23,30–32,47–49], since these are the cognitive functions that have been shown to be most affected by this illness. Interventions based on these functions appear to lead to more consistent results. This element of novelty, however, requires further investigations. In addition, a few recent studies have explored the subtle active processes of neuroplasticity that might be driven by these cognitive treatments. These new aspects have not been analyzed in previous published reviews [15–17]. This study had the aim to assemble a systematic review of the old and the more recent cognitive rehabilitation interventions in MS, including studies that have looked at neuroimaging as an outcome measure, to describe the current status of the field, and to provide directions for future research.

2. Methods

We carried out a systematic review of research studies that have focused on cognitive rehabilitation interventions for people with MS. The aim was to offer an overview of all published cognitive rehabilitation studies and to provide the reader with an objective assessment of the strengths and limitations of the methods and approaches used in the rehabilitation of cognitive symptoms in MS. We elected not to follow the strict inclusion criteria adopted by the Cochrane Collaboration [16], because we wanted to provide a systematic and comprehensive overview of this research field, with a view of helping clinicians and researchers detect the strengths and weaknesses of different forms of intervention. For this reason we included pilot studies which do not meet the strict inclusion criteria of a Cochrane review, but may provide preliminary findings which could make a valuable contribution to this evolving field. In addition, unlike previous reviews [15–17] we also included studies that have looked at neuroimaging as an outcome measure to assess the neurobiological changes consequent to cognitive intervention.

An online literature search of PubMed and Web of Science using the terms cognitive rehabilitation, cognitive stimulation and cognitive training combined with multiple sclerosis and each of these cognitive domains attention, executive function, memory, learning, working memory, problem solving and language was undertaken for all articles published until January 2014 (see Appendix A). The reference lists from all identified articles were also searched to complete the initial list of articles. The abstracts or complete reports were reviewed to eliminate articles according to the following exclusion criteria: (1) not cognitive intervention, (2) theoretical article, (3) review articles, (4) studies that included people with other neurological conditions, (5) studies of pediatric participants, (6) non-peer reviewed articles, (7) non-English language articles, (8) case report, and (9) results of cognitive outcomes not reported. A total of 33 articles underwent a full review and classification with the aim of characterizing important elements of each study, identifying the cognitive domain(s) targeted, and describing the intervention, outcome measures, duration and frequency of the intervention and the results of the study. The quality of the scientific evidence provided by these articles was classified and an overall recommendation for the efficacy of this intervention was provided based on the US Preventive Service Task Force guidelines [18] (Table 1).

3. Results

The literature search process is described in Fig. 1. Overall, we reviewed 904 studies, including overlapping search results from the two different databases. Duplicate publications were excluded and 351 full copies were retrieved and assessed for eligibility. On initial review of the citations, 36 articles were identified as research intervention studies of cognitive rehabilitation in MS. A closer inspection of the full articles showed that 3 of them met some of the exclusion criteria and were therefore excluded. Of the 3 eliminated articles, 2 aimed to increase participants' knowledge of cognitive impairments and increase levels of self-efficacy to manage cognitive difficulties without any investigation of specific cognitive outcomes, and the third article described the increase of functional independence and QoL after a rehabilitation program that included physiotherapy, occupational therapy and social work (i.e., non cognitive intervention).

The 33 studies included in this review were published between 1993 and 2014. Cognitive tests, imaging techniques, self-perceived cognitive deficits, mood, quality of life and fatigue questionnaires were used as outcome measures. Detailed information is given in Table 1 and described below.

3.1. Cognition

All studies focused on cognitive outcomes. Although there was significant diversity in the cognitive domain targeted and the duration of each intervention, the majority of these studies reported some improvements (N = 31). Almost half of the studies were carried out on patients with mixed types of MS clinical courses (relapsing remitting, primary progressive and secondary progressive) (N = 15), fourteen studies included patients with relapsing remitting MS (N = 14), and four studies did not specify the clinical course of the illness that MS patients had (N = 4). Only seven studies, out of a total of 33 studies included in this review were properly designed randomized controlled trials. Regarding the type of intervention, 10 studies focused their intervention on the rehabilitation of non-specific multiple skills, 11 studies focused on the rehabilitation of learning and memory and the last 12 studies focused their intervention on the rehabilitation of attention, working memory and executive functions.