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Effect of neuropsychological rehabilitation on executive functions, learning, and memory in adults with relapsing-remitting multiple sclerosis: A systematic review and meta-analysis protocol

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ADMINISTRATIVE INFORMATION**Support** - None. Unfunded study.**Review Stage at time of this submission** - Risk of bias assessment.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100134

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 October 2026 and was last updated on 31 October 2026.

INTRODUCTION

Review question / Objective Formulated using the PICO framework: (i) Population: Adults with relapsing-remitting multiple sclerosis (RRMS); (ii) Intervention: Neuropsychological rehabilitation programs; (iii) Comparison: Absence of neuropsychological rehabilitation programs; (iv) Outcome: Executive functions, learning, and memory performance.

Research Question: What is the effect of neuropsychological rehabilitation on executive functions, learning, and memory in adults with RRMS?

Objective: The objective of this systematic review and meta-analysis is to present a synthesis of current knowledge regarding the effect of neuropsychological rehabilitation on executive functions, learning, and memory in adults with RRMS compared to active and inactive control groups.

Rationale Multiple Sclerosis (MS) is an autoimmune demyelinating central nervous system disease characterized by the dissemination of lesions in time and space. The clinical spectrum typically begins with Relapsing-Remitting Multiple Sclerosis (RRMS), accounting for 85% to 90% of cases, followed by progressive forms. Other clinical categories include Clinically Isolated Syndrome (CIS), fulminant, and benign forms (Tafti et al., 2024). Cognitively, approximately one-third of adults with RRMS experience deterioration in at least two domains, primarily affecting attention, information processing speed (IPS), memory, and executive functions. Executive functions are closely tied to the structural integrity of fronto-subcortical circuits and frontoparietal networks (Belhaouchet, 2023; Jellinger, 2024). Given that previous literature frequently combines distinct MS phenotypes, this systematic review is necessary to rigorously evaluate the specific effect of neuropsychological rehabilitation on executive functions, learning, and memory exclusively in adults with RRMS.

Condition being studied Relapsing-Remitting Multiple Sclerosis (RRMS), an autoimmune demyelinating disease of the central nervous system characterized by clinical relapses followed by periods of remission. The specific factors and events of interest addressed by this systematic review are the associated cognitive impairment profile, focusing on objective performance, alterations, and response to neuropsychological rehabilitation in executive functions, learning, and memory domains in adult patients.

METHODS

Search strategy A comprehensive search will be conducted using keyword combinations and boolean operators across electronic scientific platforms: (i) PubMed: (Multiple Sclerosis[Title/Abstract]) AND (cognitive rehabilitation[Title/Abstract] OR neuropsychological rehabilitation[Title/Abstract] OR neuropsychological intervention[Title/Abstract]) AND (executive functions[Title/Abstract] OR memory[Title/Abstract] OR learning[Title/Abstract]) (Applied limits: Clinical Trial, Randomized Controlled Trial); (ii) Web of Science y Scopus: (Multiple Sclerosis) AND (cognitive rehabilitation OR neuropsychological rehabilitation OR neuropsychological intervention) AND (executive functions OR memory OR learning) AND (clinical trial OR randomized controlled trial OR randomized controlled trial); (iii) LILACS y SciELO: (Esclerosis Múltiple) AND (rehabilitación cognitiva OR rehabilitación neuropsicológica OR entrenamiento cognitivo OR intervención neuropsicológica) AND (funciones ejecutivas OR memoria OR aprendizaje). The literature search will be executed independently by two reviewers (G.E. V-G & P.A. A-J), and any discrepancies will be resolved through consultation with a third reviewer (V.M. M-N).

Participant or population Adults (≥ 18 years old) with a confirmed diagnosis of Multiple Sclerosis, exclusively with the Relapsing-Remitting phenotype (RRMS). Studies involving mixed or progressive phenotypes without disaggregated RRMS data will be excluded.

Intervention Neuropsychological rehabilitation, training, or cognitive stimulation programs focused primarily on executive functions, learning, or memory (delivered face-to-face, via telerehabilitation, or through computerized platforms).

Comparator Active control groups (e.g., psychoeducation, non-specific cognitive exercises)

or inactive control groups (e.g., waitlist, treatment-as-usual/standard care).

Study designs to be included Peer-reviewed Randomized Controlled Trials (RCTs) and quasi-experimental studies published in English, Portuguese, and Spanish.

Eligibility criteria Studies will be selected based on the PICOS components. Hierarchy of exclusion criteria: (A) Inappropriate or mixed phenotype without disaggregated RRMS data; (B) Unspecified MS phenotype; (C) Ineligible publication type.

Information sources An exhaustive search will be conducted across electronic databases: PubMed, Web of Science, Scopus, SciELO, and LILACS. Additionally, other sources will be searched, including Google Scholar, reference lists of other systematic reviews, ScienceDirect, and TESIUNAM.

Main outcome(s) Objective cognitive performance measured by standardized, quantitative neuropsychological test scores (evaluating executive functions, learning, and memory) pre- and post-intervention.

Additional outcome(s) None.

Data management Screening and study selection were conducted using Microsoft Excel. Data extraction will be carried out using a standardized matrix recording: author/year, study design, sample size, age, sex, education level, EDSS, detailed intervention parameters, comparators, neuropsychological instruments, and pre- and post-intervention quantitative outcomes (means, standard deviations, and effect sizes).

Quality assessment / Risk of bias analysis Methodological quality and risk of bias assessment for individual studies will be conducted using the Cochrane Risk of Bias 2 (RoB 2) tool for RCTs, and ROBINS-I for quasi-experimental studies, implemented and diagrammed using Review Manager (RevMan) software evaluating five standard domains.

Strategy of data synthesis A comprehensive and differentiated analysis of the studies will be performed, presenting a narrative synthesis of study characteristics, intervention parameters, and observed results. If statistical homogeneity permits, a random-effects meta-analysis will be conducted using RevMan to calculate pooled effect estimates (standardized mean differences) with 95% confidence intervals.

Subgroup analysis Subgroup analyses may be explored based on intervention delivery mode (computerized vs. face-to-face) or type of control group (active vs. inactive), if available data allow.

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness of pooled estimates according to methodological quality (excluding studies with high risk of bias).

Language restriction English, Portuguese, and Spanish.

Country(ies) involved Mexico.

Other relevant information Special acknowledgment to Dr. Victor Manuel Mendoza Nuñez for his support in the development of this protocol.

Keywords Multiple sclerosis; relapsing-remitting multiple sclerosis; neuropsychological rehabilitation; cognitive training; executive functions; memory; learning; systematic review protocol.

Dissemination plans Publication of the systematic review and meta-analysis in a peer-reviewed scientific journal and presentation at academic conferences or forums.

Contributions of each author

Author 1 - Gabriela Esther Villagómez-García - Lead author. Conception of the review, protocol design, search strategy definition, screening, data extraction, and protocol writing.

Author 2 - Pedro Alejandro Aguilar-Juárez - Corresponding author and supervisor. Critical methodological and clinical content review, and data synthesis strategy.

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