INPLASY PROTOCOL

Alterations in Corticomotor Excitability in Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis

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Review question / Objective: To systematically evaluate the utility of TMS to follow up on ALS patients using neurophysiological metrics and to quantify corticomotor excitability compared to sham controls or other neuromuscular diseases.

Condition being studied: Amyotrophic Lateral Sclerosis (ALS) is the third most common neurodegenerative disease (BRUNET et al., 2020). The condition is characterized by progressive muscle atrophy due to upper and lower motor neuron death (GOETZ, 2000).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 May 2023 and was last updated on 19 May 2023 (registration number INPLASY202350078).

INTRODUCTION

Review question / Objective: To systematically evaluate the utility of TMS to follow up on ALS patients using neurophysiological metrics and to quantify corticomotor excitability compared to sham controls or other neuromuscular diseases.

Rationale: The ALS pathophysiological process behind it has multiple dysfunctions including ribonucleic acid (RNA) processing, glial cell alterations, and glutamate accumulation at the synaptic gap, among many others (RIANCHO et al., 2019). Though the triggering factors for the beginning symptoms and progression are not clear, the scientific advancement for ALS treatment is promising. One of the emerging treatments, the ALS gene target

therapy, could potentially fix the genetic mutations that generate the disease even though most of these treatments are still developing and are restricted to specific mutations not common to most ALS cases currently known (AMADO; DAVIDSON, 2021). Furthermore, it is noticed that there is a heterogeneity in the treatment responses and many questions are still left to be answered.

Transcranial magnetic stimulation (TMS) has been pointed out as a possible diagnostic tool for ALS. The TMS is a neurophysiological non-invasive method for corticomotor excitability evaluation, this happens through a magnetic field generated at the scalp which induces an electric field at the corticospinal tract measured by the motor evoked potential (MEP). ALS patients with early-stage disease present cortical hyperexcitability, shown by the elevated MEP, central motor conduction time (CMTC), short-interval intracortical facilitation (SICF) and intracortical facilitation (ICF), as well as a reduction resting motor threshold (RMT), reduction or absence cortical silent period (CSP), short-interval intracortical inhibition (SICI) and (CIVARDI et al., 2020; GEEVASINGA et al., 2021; VAN DEN BOS et al., 2019; VUCIC et al., 2023). With disease progression, progressive increase in RMT occurs, leading to inexcitability of the motor cortex (GOUTMAN et al., 2022). The triple stimulation test enables precise neurological diagnoses in ALS that could detect loss of corticomotor neurons, even at a subclinical stage (GRAPPERON et al., 2021). All of the described alterations in the ALS patient's brain can be detected by the TMS, which makes it a good possible diagnostic device for the disease.

Condition being studied: Amyotrophic Lateral Sclerosis (ALS) is the third most common neurodegenerative disease (BRUNET et al., 2020). The condition is characterized by progressive muscle atrophy due to upper and lower motor neuron death (GOETZ, 2000).

METHODS

Search strategy: Database: MEDLINE, COCHRANE, LILACS, Scopus, Web of Science, EMBASE use the search strategy "Amyotrophic Lateral Sclerosis" or "ALS"[Mesh] or "Motor Neuron Disease"[Mesh] AND "Transcranial Magnetic Stimulation" or "TMS"[Mesh] AND "Cortical Excitability"[Mesh].
Database: EBSCO, CINAHL use the search strategy {Transcranial Magnetic Stimulation} AND Index Terms: {Transcranial Magnetic Stimulation} OR {Amyotrophic Lateral Sclerosis} AND Index Terms: {Transcranial Magnetic Stimulation} AND {Amyotrophic Lateral Sclerosis}
Database: APA PsycInfo use the search strategy Any Field: amyotrophic lateral sclerosis OR Any Field: ALS ANDAny Field: transcranial magnetic stimulation OR Any Field: TMS AND Any Field: cortical excitability.

Participant or population: Amyotrophic Lateral Sclerosis.

Intervention: Not applicable.

Comparator: Healthy people or other neuromuscular diseases.

Study designs to be included: Quantitative study, baseline from clinical trials.

Eligibility criteria: Make use of TMS and report quantitative data on the following outcomes: MEP, RMT, AMT, CMCT, CSP, SICI, SICF, ICF, LICI, SIHI, LIHI, SAI, LAI, CBI and TST.

Information sources: Additionally, the reference lists of systematic reviews about TMS and cortical excitability for ALS will be examined to propose or identify additional relevant articles and will retrieve papers, search conference abstracts, and grey literature (Google Scholar). Furthermore, clinical experts will be consulted. To check for unpublished trials, we will contact experts in the field and will consult the Clinical Trials database, and search for abstracts.

Main outcome(s): Extracted data will include sample size, sample characteristics, TMS protocol, statistical data of motor evoked potential (MEP), resting motor threshold (RMT), active motor threshold (AMT), central motor conduction time (CMCT), cortical silent period (CSP), short-interval intracortical inhibition (SICI), short interval intracortical facilitation (SICF), intracortical facilitation (ICF), long-interval intracortical inhibition (LICI), short-latency interhemispheric inhibition (SIHI), long-latency interhemispheric inhibition (LIHI), short-latency afferent inhibition (SAI), long-latency afferent inhibition (LAI), cerebellum-to-motor cortex inhibition (CBI) and triple stimulation test (TST) for effect size estimation.

Additional outcome(s): Potential adverse response.

Data management: The analysis will be made in each of the outcomes separately MEP, RMT, AMT, CMCT, CSP, SICI, SICF, ICF, LICI, SIHI, LIHI, SAI, LAI, CBI and TST, searching for differences in these parameters in ALS patients, related to healthy controls or individuals with other neuromuscular diseases. Descriptive statistics will include mean and standard deviation (SD) from confidence interval data using the following formula: $SD = \sqrt{N} \times (upper\ limit - lower\ limit)/3.92$, as recommended by Chapter 7 of Cochrane Handbook (HIGGINS et al., 2011). If the means and SDs are not provided, median values will be considered to be equal to the mean values, and the interquartile range divided by 1.35 to be equal to the SD. If necessary, we will also calculate the SD from confidence interval data informed in the studies as recommended by Chapter 7 of Cochrane Handbook (HIGGINS et al., 2011).
Apart from the study design, the authors of the paper will be contacted to obtain the remaining data.

Quality assessment / Risk of bias analysis: Two different authors will use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the quality of evidence (ATKINS et al., 2004). Four levels of quality of evidence will be specified: high, moderate, low, and very low. An initially assumed a high level of evidence would be downgraded for meeting any of the following criteria: (1) risk of bias (downgrade once if less than 75% of the included studies are at low risk of bias across all risk of bias domains), (2) heterogeneity (downgrade once if heterogeneity between the included studies is significant and the I2 value is greater than 40%), (3) indirectness (downgrade once if more than 50% of the participants were outside the target group), (4) imprecision (downgrade once if a low number of participants) (GUYATT et al., 2011) and (5) publication/selection bias (downgrade once if the publication/selection bias is significant).
The risk of bias will be performed separately by two authors (ALYSS and DMRC). Any disagreement will be solved through discussion between the review authors (ALYSS, DMRC, and LSGN). It will assess the risk of bias using the criteria suggested in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The following criteria will be considered: blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias (HIGGINS et al., 2011). The risk of bias of each criterion will be classified as low, unclear, or high risk of bias. The results will be summarized in a table and a figure entitled "Risk of bias". The funnel plot will assess the potential role of publication bias.

Strategy of data synthesis: It is intended to perform a sensitivity analysis examining the influence of the risk of bias through the exclusion of high-risk of bias articles, or when the risk of bias is not clear, the influence of non-published papers, or excluding the studies with abstracts only. Data will be synthesised by the standardized mean differences, and 95% confidence intervals, and presented in

forest plot form. The I2 statistics will be used to assess the degree of heterogeneity between the included studies.

Subgroup analysis: Subgroup analysis will be performed if there is >50% of heterogeneity in the principal analysis, and will consider the following variables: disease onset time, ALS types, ALS staging, and use of medications, among other.

Sensitivity analysis: It is intended to perform a sensitivity analysis examining the influence of the risk of bias through the exclusion of high-risk of bias articles, or when the risk of bias is not clear, the influence of non-published papers, or excluding the studies with abstracts only.

Language restriction: There will be no restriction of language and year of publication.

Country(ies) involved: Brazil.

Other relevant information: Heterogeneity will be evaluated by visual inspection of the forest plot, with statistical analysis applying Cochran's Q test to determine if the evidence is strong enough to establish genuine heterogeneity, considering a p-value < 0.05 as an indicator of heterogeneity. The assessment will be through the statistics I2, characterized as followed: <25% (no heterogeneity); 25% to 49% (low heterogeneity); 50% to 74% (moderate heterogeneity); ≥ 75% (high heterogeneity) (DEEKS et al., 2019). When heterogeneity is greater than 25%, a random effect model will be used. And when the heterogeneity index is less or equal to 25%, the fixed effect model will be applied. Additional analysis (sensitivity) will also be performed to determine effect size when low-quality studies are excluded.

Keywords: Amyotrophic Lateral Sclerosis, Transcranial Magnetic Stimulation, Cortical Excitability.

Dissemination plans: The results of this study will be submitted to peer review analysis, to be published in a recognized journal in the area.

Contributions of each author:
Author 1 - Ana Lúcia Yaeko da Silva Santos - The author drafted the manuscript and will participate actively in the selection process, data extraction, risk of bias assessment, quality of evidence assessment.
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Author 2 - Deyse Mayara Rodrigues Caron - The author drafted the manuscript and will participate actively in the selection process, data extraction, risk of bias assessment, quality of evidence assessment.
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Author 3 - Livia Shirahige - The author will be resolve any disagreement in the selection process, data extraction, risk of bias assessment, quality of evidence assessment, and statistical expertise.
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