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The Cognitive Remediation of Attention in HIV Associated Disorders (HAND): A Meta-Analysis and Systematic Review

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Abstract

Objective: Despite medical advances in Highly Active Antiretroviral Therapy (HAART), patients living with HIV continue to be at risk for developing HIV-associated neurocognitive disorders (HAND) due to the virus' effect on neuronal function. The optimization of non-HAART interventions, including cognitive rehabilitation therapy (CRT), shows promise in reversing the impact of HAND. However, no data indicate CRT's efficacy in remediating attention skills following HIV infection.This paper presents a meta-analysis of randomised and non-randomised controlled trials (RCTs) to remediate attention skills following HIV cognitive rehabilitation therapy.

Method: Pre- and post-intervention data based on standardised mean differences (SMD) was calculated using a random effects model. Subgroup analyses of relevant moderator variables associated with outcomes in CRT were conducted, and publication bias was assessed. The study followed the PRISMA reporting guidelines for meta-analyses and was registered on Protocols.io.

Results: Fourteen studies met the inclusion criteria (n = 532). There were significant pre- to post-intervention between-group benefits due to CRT in the experimental group relative to control conditions for the remediation of attention skills following HIV infection (Hedges g = 0.251, 95% CI = 0.005 to 0.497; $p < 0.05$). No significant effects ($p > 0.05$) were demonstrated for subgroup analysis.

Conclusions: To the author's knowledge, this is the first meta-analysis that exclusively analyses the remediation of attention skills in the era of HAART and neuroHIV, where all studies included participants diagnosed with HIV. The overall meta-analysis effect indicates the efficacy of CRT in remediating attention skills in HIV and HAND. It is recommended that future cognitive rehabilitation protocols to remediate attention skills should be context and population-specific and that they be supplemented by objective biomarkers indicating the efficacy of the CRT.

Guidelines

1. This protocol followed the Prisma Guidelines for conducting meta-analysis and systematic reviews.

KEYWORDS

1 HIV, HAND, Attention Rehabilitation, Neuroplasticity, meta-analysis, meta-regression

BACKGROUND

2 Through pathobiology yet to be understood, after infecting its host, the Human Immunodeficiency Virus (HIV) permeates the blood-brain barrier (BBB), where it leads to the differentiation of monocytes into macrophages. This differentiation leads to the infection of cells in the CNS, namely microglia and astrocytes (Filipowicz et al., 2016; Sillman et al., 2018). In breaching the BBB, HIV is thought to dysregulate the brain's intrinsic nerve cell architecture, leading to aberrant neural transmission, including excess glutamate levels and decreased dopaminergic transmission (Elbirt et al., 2015; Nolan & Gaskill, 2019). Markedly, HIV's viral penetrance and persistence in the CNS is implicated in neuronal apoptosis, leading to a milieu of neurocognitive impairments associated with HIV (Das et al., 2016; Smail & Brew, 2018).

To date, pharmacological interventions, namely Highly Active Antiretrovirals (HAART), have been ineffective in treating HIV-associated cognitive disorder (HAND) resulting from the virus breaching the BBB (Benki-Nugent & Boivin, 2019; Jantarabenjakul et al., 2019). Based on the principles of brain plasticity, this study investigated the efficacy of cognitive rehabilitation therapy and brain plasticity measures to reverse HAND.

Summarily, the aim of this study was to conduct a meta-analysis investigating the efficacy of cognitive rehabilitation therapy to remediate attention skills following HIV infection.

METHODS

3 This systematic review and meta-analysis followed the PRISMA guidelines (Moher et al., 2009) for conducting summative research.

3.1 **Eligibility criteria**

Studies were selected based on the following criteria:

1) **Sample sizes**: All studies should have reported sample sizes to enabling effect size weightings.

2**. Population**: Studies should have included participants diagnosed with HIV.

3) **Intervention**: The experimental group should have undergone attention remediation (selective, sustained, divided).

4) **Outcome** : All studies should have reported pre and post attention scores, using recognised neuropsychological measures for attention as identified in Lezak, et al.. 2004).

5) **Languages**: Studies were included if they reported findings in English.

6) **Study designs:** Randomized, and non-randomized clinical trials (RCT) were included in the meta-analysis.

7) **Publication dates**: There were no specific dates included for the meta-analysis.

Excluded: Studies were excluded if they were literature reviews, observational studies, case studies, or studies using qualitative design. Relevant, but excluded studies will be found in the Supplementary Materials section of the original research article.

Note

Studies in the RCT and non-RCT should have included at least an experimental and a control group (either active or passive control group). All studies should have reported pre and post rehabilitation attention scores.

3.2 Search strategy

Searches will be carried out in the following digital databases: PUBMED, PsycINFO, Web of Science, as well on key references related to HIV/AIDS. The authors of particular studies were contacted to request data on certain aspects of their research study.

The search for research articles used medical subject headings (MeSH) and text words including: 'HIV and attention rehabilitation' or 'HIV and cognitive rehabilitation', and 'HIV and/or attention', 'HIV and attention remediation'.

All terms that were added to the search are shown in Table 1.

Table 1 Full Search Strategy

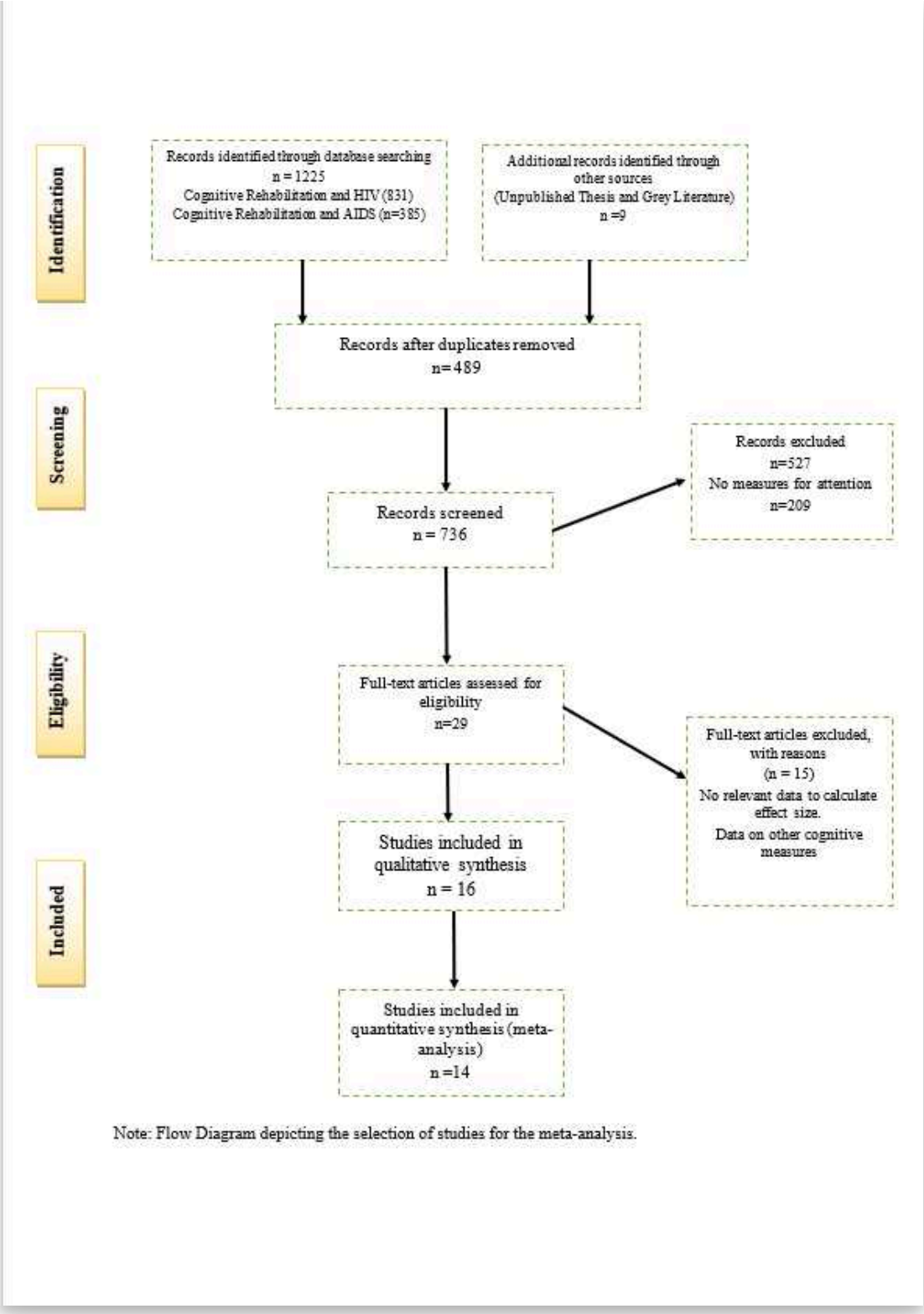
Database	Time	Strategy	Outcome
PubMed	2022.04.12	('HIV and attention rehabilitation' OR 'cognitive rehabilitation', OR 'cognitive training', OR cognitive remediation' OR 'HIV and attention remediation') AND ('PLWH' OR 'HIV' OR 'AIDS') AND 'effect', 'outcome', 'efficacy' of 'rehabilitation'	146
PsycINFO	2022.04.12	('HIV and attention rehabilitation' OR 'cognitive rehabilitation', OR 'cognitive training', OR cognitive remediation' OR 'HIV and attention remediation') AND ('PLWH' OR 'HIV' OR 'AIDS') AND 'effect', 'outcome', 'efficacy' of 'rehabilitation'	127
ISI Web of Knowledge	2022.06.12	('HIV and attention rehabilitation' OR 'cognitive rehabilitation', OR 'cognitive training', OR cognitive remediation' OR 'HIV and attention remediation') AND ('PLWH' OR 'HIV' OR 'AIDS') AND 'effect', 'outcome', 'efficacy' of 'rehabilitation'	287
Cochrane	2022.06.12	('HIV and attention rehabilitation' OR 'cognitive rehabilitation', OR 'cognitive training', OR cognitive remediation' OR 'HIV and attention remediation') AND ('PLWH' OR 'HIV' OR 'AIDS') AND 'effect', 'outcome', 'efficacy' of 'rehabilitation'	312

3.3 Study records

During the screening, eligibility, inclusion, and data extraction, were evaluated by 2 independent reviewers. After verifying the reviewers' responses, disagreements were resolved by a third reviewer. All studies were organized using Mendeley Reference Manager and later recorded in an excel spreadsheet for data organization.

Data summary data extraction included:

1) **General description** (identification code, author, year of publication, language, and study design);
2) **Description of participants** (pediatric or geriatric HIV, gender, sample size, age);
3) Description of the attention intervention (divided, sustained, selective);
4) **Screening** of studies (HIV and attention);
5) **Inclusion of studies** (pre and post-attention data, clear intervention, clear follow up).



Note: Flow Diagram depicting the selection of studies for the meta-analysis.

Figure: Prisma Flow Diagram for Meta Analysis

Note

Relevant but excluded studies are cited in the original article.

3.4 Risk of bias in individual studies

The risk of bias analysis was performed using study quality assessment ratings based on criteria established by the Cochrane Collaboration (Cumpston et al., 2019; Higgins & Green, 2008). These ratings can be found in the original publication.

For ease of reference, the below image indicates the Cochrane Collaboration criteria used for risk of bias.

Index[a]:

1	Randomization concealment
2	Blinding of subjects
3	Baseline comparability
4	Power analysis or N > 30
5	Completeness of follow up
6	Adequate handling of missing data through statistical applications

In addition, to the above, publication bias was assessed using a funnel plot.

3.5 Data synthesis and quantitative approaches

Data analysis was performed using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX. StataCorp, LLC).

Data was analyzed based on standardized mean differences (SMD). Kendall's tau and I^2 were used as measures of heterogeneity. The meta-analysis values were presented using “forest plots”. Subgroup analysis were conducted based on moderator variables related to cognitive intervention characteristics.

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SUPPLEMENTARY INFORMATION

5 The following supplementary details were added to the original research article submitted for publication.

Table 1: Full Search Strategy
Table 2: Prisma Checklist
Table 3: Relevant but excluded Studies
Table 4: Attention Outcome Measures
Table 5: Study Quality Assessment

Protocol references

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