

# Is Repetitive Transcranial Magnetic Stimulation a Safe and Effective Method of Improving Cognition in Patients with Alzheimer's Disease and Mild Cognitive Impairment - A Systematic Review and Meta-Analysis

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## Introduction

**Alzheimer's disease (AD)** is the leading cause of dementia worldwide, however, current drug treatments available offer only modest symptomatic benefit and do not alter disease progression.

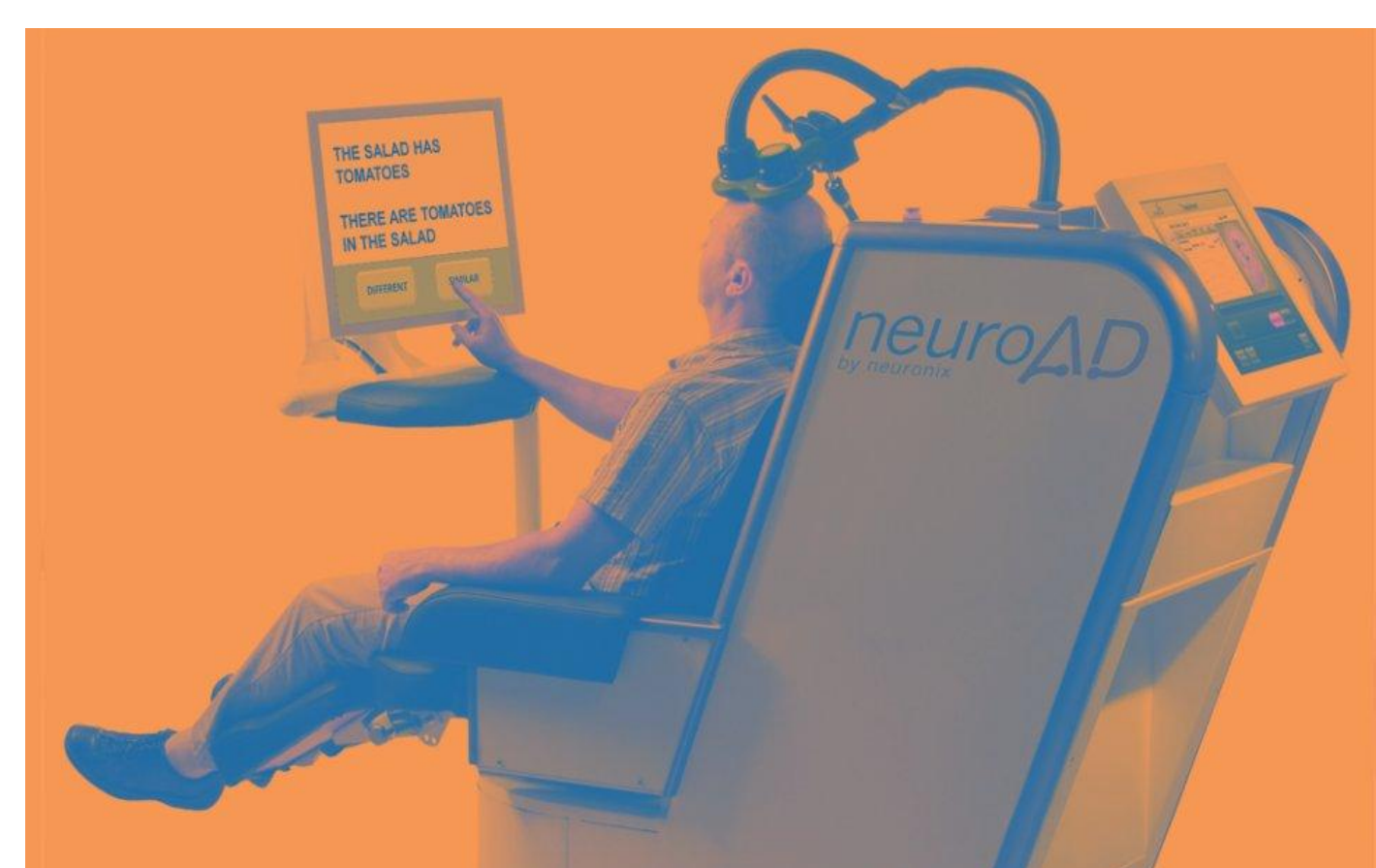
**Mild cognitive impairment (MCI)** represents a prodromal stage between normal ageing and dementia, with many individuals progressing to AD over time. Despite the high prevalence of both conditions, effective treatments to improve cognition remain limited.

**Repetitive Transcranial Magnetic Stimulation (rTMS)** is a **non-invasive brain stimulation (NIBS)** technique that uses electromagnetic fields to modulate cortical activity. High frequency stimulation is thought to enhance synaptic plasticity through mechanisms similar to long-term potentiation, strengthening neural networks involved in cognition. RTMS is already approved by NICE for the treatment of conditions such as depression and migraine, but its role in AD and MCI remains unclear.

## Aim

Our systematic review and meta-analysis aimed to:

- Determine whether rTMS improves cognition in individuals with AD and MCI
- Assess the safety and tolerability of rTMS in these populations
- Identify rTMS protocol-related factors that influence the efficacy of treatment.



NeuroAD system,  
Dual rTMS and  
Cognitive training  
system, Neuronix  
Ltd.

## Method

A systematic review was conducted as per the PRISMA 2020 guidelines. Databases searched included MEDLINE, Embase, Scopus, PsycINFO, ClinicalTrials.gov and the WHO trials registry.

We searched for randomised controlled trials published between 2018 and 2025 that compared active rTMS with sham stimulation in adults diagnosed with AD or amestic variant MCI. Response was measured by comparing changes in validated cognitive assessment tools such as the Mini Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA).

Studies that used participants with neurodegenerative pathologies other than AD or MCI, as well as those that utilised other NIBS methodologies than TMS were excluded from the review.

The Rayyan review screening software was used to organise, screen and remove duplicates from our search results. Data was then extracted from articles using a predesigned data extraction table. We focused data collection on coil shapes, stimulation frequency, target sites and severity of cognitive impairment at baseline to investigate if such factors affected the efficacy of treatment.

Risk of bias was assessed using the NIH quality assessment tool for controlled interventional studies. Meta-analyses were performed using a random-effects model, calculating standardised mean differences, allowing us to compare studies using different cognitive assessment tools. Cochrane's Q test was used to calculate between-group differences for subgroup analyses.

Subgroup analyses explored the following factors

- **Stimulation site**
- **Number of stimulation regions**
- **Combination with cognitive training (CT)**
- **Inclusion of neuronavigation protocols**
- **Diagnosis (AD v MCI)**

Safety analysis was assessed using a meta-analysis of proportions, using a random effects model and a Freeman-Tukey double arcsine transformation.

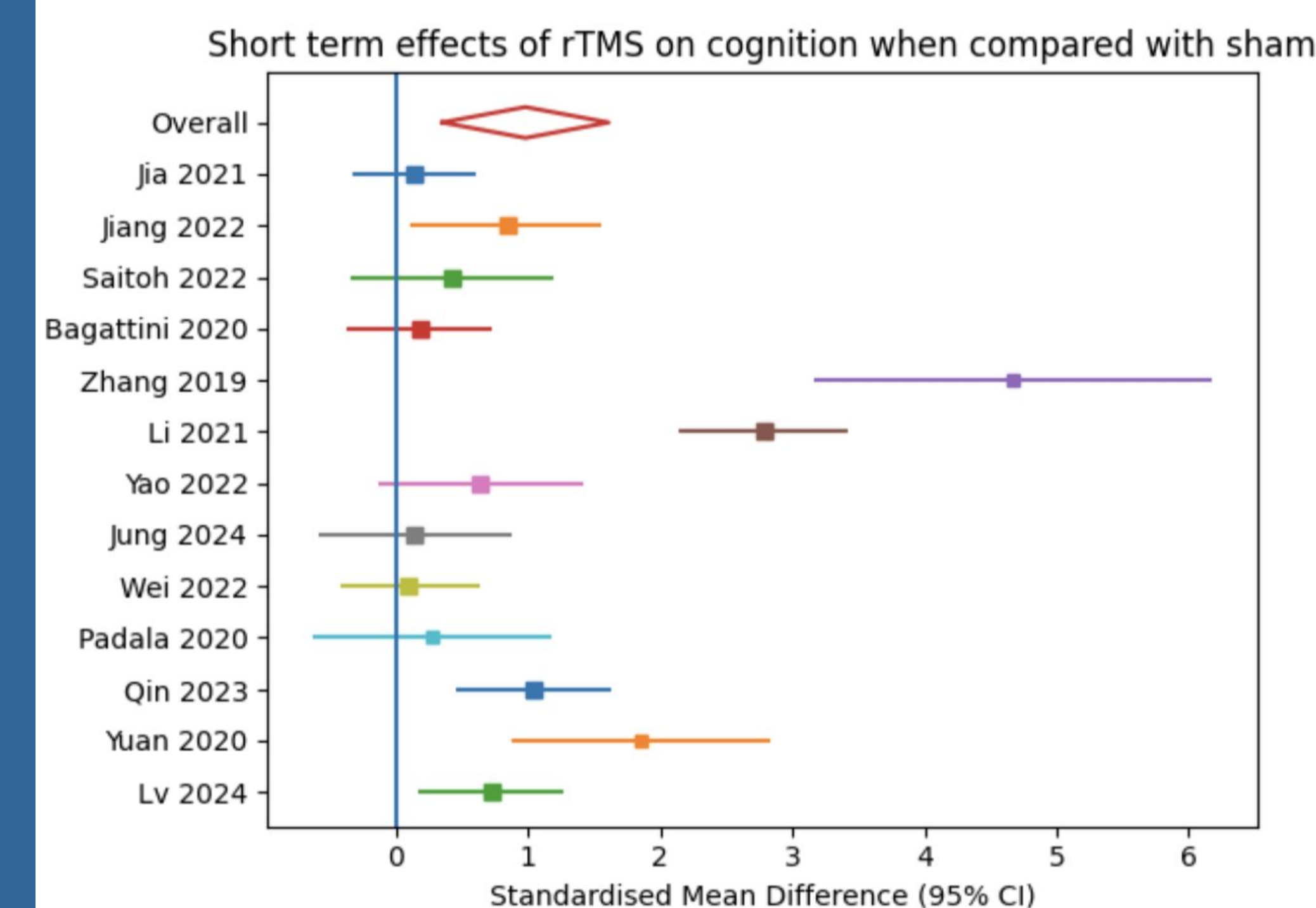
## Results

Thirty-one studies (n = 1,397) met our inclusion criteria. Thirteen studies were included in the meta-analysis for short-term outcomes (n = 548).

### Short term effects

TMS significantly improved cognition compared to sham:

- **SMD = 0.98 (95% CI 0.35-1.61, p < 0.01)**



Cognitive benefits of TMS appeared to be sustained at follow-up:

- **SMD = 0.77 (95% CI 0.16-1.37, p < 0.02)**

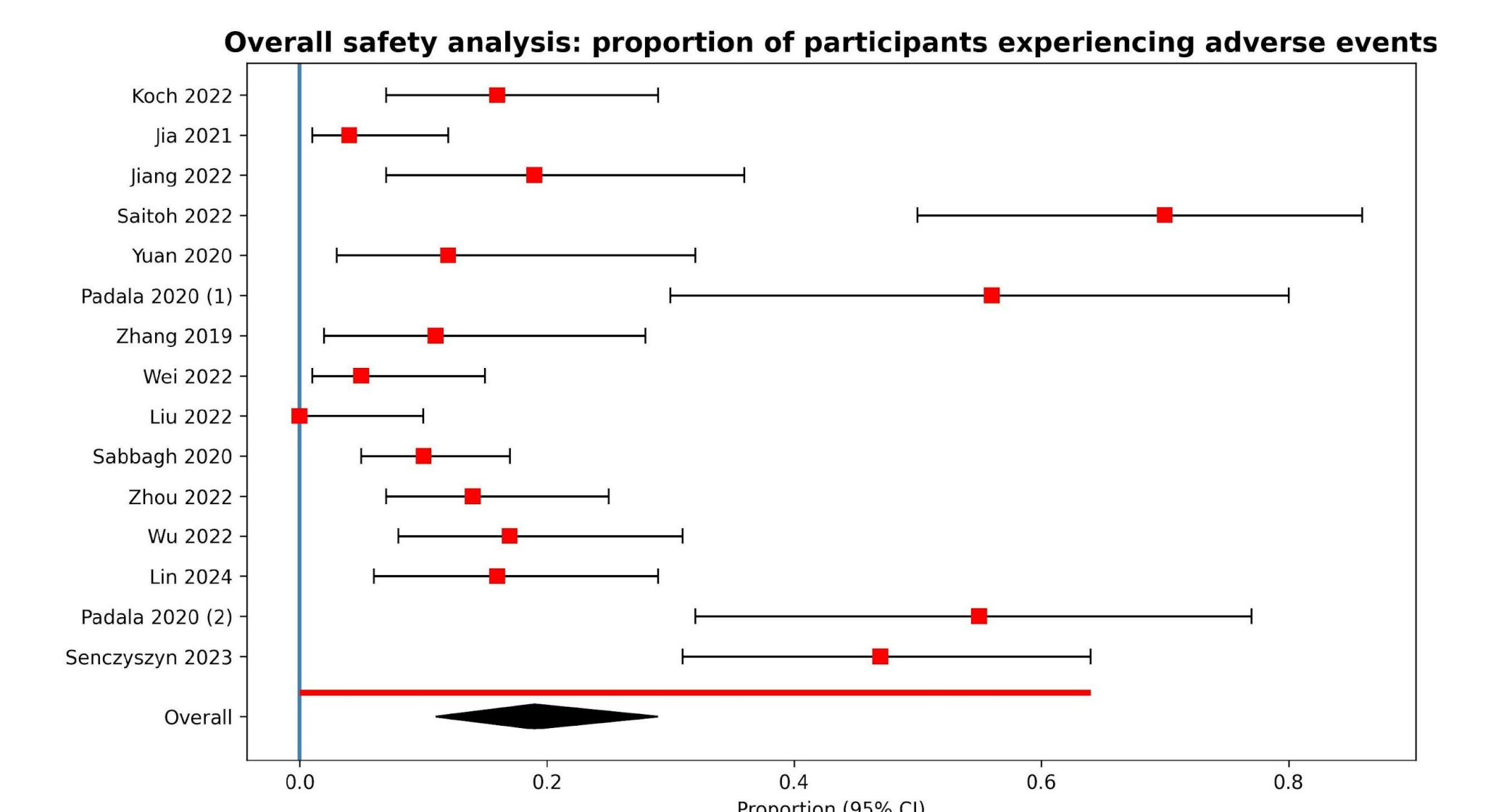
### Subgroup analyses

- **Multi-site stimulation** showed a greater effect size (SMD, 1.65; CI: 0.42-2.88; p = 0.0083) when compared to single-site stimulation (SMD, 0.40; CI 0.05-0.74; p = 0.0233). A statistically significant between-group difference was noted for these groups at both short-term (Q = 12.00, p = 0.00053) and long-term (Q = 4.19, p = 0.041) follow-up.
- The addition of **cognitive training** and **neuronavigational aids** failed to show any significant increase in the efficacy of rTMS.
- There was **no significant difference** between the effect size of participants with AD when compared with MCI groups.

## Safety analysis

Fifteen of the randomised control trials reported data regarding adverse events (n = 682).

- 17.6% experienced at least one adverse event
- Most side effects were mild and transient (scalp discomfort, headache).
- One seizure (0.1%) was reported.
- There was no significant difference in the rate of adverse events based on the number of stimulation sites or frequency of TMS.



## Conclusion

RTMS appears to significantly improve cognitive performance in individuals with AD and MCI, with benefits observed at both short and long-term follow ups.

Protocols targeting multiple brain regions appear superior to single-site stimulation. Treatment is generally well tolerated with mostly mild and transient side effects.

RTMS represents a promising non-invasive therapeutic option for future dementia care. However, large-scale, standardised clinical trials are needed to confirm optimal stimulation parameters and long-term efficacy.

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