

CADTH RAPID RESPONSE REPORT: REFERENCE LIST

# Non-Invasive Brain Stimulation Techniques for the Treatment of the Behavioural and Psychological Symptoms of Severe Dementia: Clinical Effectiveness

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## Research Question

What is the clinical effectiveness of non-invasive brain stimulation techniques for the behavioural and psychological symptoms of dementia?

## Key Findings

Ten systematic reviews (seven with meta-analyses), eight randomized controlled trials, and five non-randomized studies were identified regarding non-invasive brain stimulation techniques for the treatment of the behavioural and psychological symptoms of severe dementia.

## Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 15, 2019. Internet links were provided, where available.

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

|                      |  |
|----------------------|--|
| <b>Population</b>    | Older adults with behavioural and psychological symptoms of dementia (all forms of dementia, including Alzheimer disease, Lewy body dementia, Parkinson's dementia, etc.)<br>Possible subgroups: 65 to 79; 80 years and older  |
| <b>Intervention</b>  | Emerging non-invasive brain stimulation techniques (such as repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST), theta burst stimulation (sometimes called intermittent transcranial brain stimulation (iTBS)), transcranial direct current stimulation, transcranial alternating current stimulation, non-invasive vagal nerve stimulation, cranial electrostimulation) |
| <b>Comparators</b>   | Usual Care<br>Any therapeutic intervention (e.g., antipsychotic drugs; physical restraints; environmental and behavioural therapies);<br>Sham stimulation<br>Before and after  |
| <b>Outcomes</b>      | Clinical effectiveness in reducing behavioural and psychological symptoms of dementia (e.g. agitation, aggression, confusion, insomnia, anxiety, psychomotor agitation, depression, cognitive function, mood);<br>Safety   |
| <b>Study Designs</b> | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies   |

## Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

Ten systematic reviews (seven with meta-analyses), eight randomized controlled trials, and five non-randomized studies were identified regarding non-invasive brain stimulation techniques for the treatment of the behavioural and psychological symptoms of severe dementia. No relevant health technology assessments were identified regarding non-invasive brain stimulation techniques for the treatment of the behavioural and psychological symptoms of severe dementia.

Additional references of potential interest are provided in the appendix.

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-analyses

1. Hauer L, Sellner J, Brigo F, et al. Effects of repetitive transcranial magnetic stimulation over prefrontal cortex on attention in psychiatric disorders: a systematic review. *J Clin Med*. 2019 Mar 27;8(4).  
[PubMed: PM30934685](#)
2. Iimori T, Nakajima S, Miyazaki T, et al. Effectiveness of the prefrontal repetitive transcranial magnetic stimulation on cognitive profiles in depression, schizophrenia, and Alzheimer's disease: a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019 Jan 10;88:31-40.  
[PubMed: PM29953934](#)
3. Lin Y, Jiang WJ, Shan PY, et al. The role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of cognitive impairment in patients with Alzheimer's disease: a systematic review and meta-analysis. *J Neurol Sci*. 2019 Mar 15;398:184-191.  
[PubMed: PM30735817](#)
4. Cheng CPW, Wong CSM, Lee KK, Chan APK, Yeung JWF, Chan WC. Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2018 Jan;33(1):e1-e13.  
[PubMed: PM28493371](#)
5. Dong X, Yan L, Huang L, et al. Repetitive transcranial magnetic stimulation for the treatment of Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2018;13(10):e0205704.  
[PubMed: PM30312319](#)

6. Inagawa T, Narita Z, Sugawara N, et al. A Meta-analysis of the effect of multisession transcranial direct current stimulation on cognition in dementia and mild cognitive impairment. *Clin EEG Neurosci*. 2018 Sep 19:1550059418800889.  
[PubMed: PM30229671](#)
7. Vacas SM, Stella F, Loureiro JC, do Couto FS, Oliveira-Maia AJ, Forlenza OV. Noninvasive brain stimulation for behavioural and psychological symptoms of dementia: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2018 Sep 24.  
[PubMed: PM30246461](#)
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[PubMed: PM28988547](#)
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[PubMed: PM26022770](#)
10. Liao X, Li G, Wang A, et al. Repetitive transcranial magnetic stimulation as an alternative therapy for cognitive impairment in Alzheimer's disease: a meta-analysis. *J Alzheimers Dis*. 2015;48(2):463-472.  
[PubMed: PM26402010](#)

## Randomized Controlled Trials

11. Elder GJ, Colloby SJ, Firbank MJ, McKeith IG, Taylor JP. Consecutive sessions of transcranial direct current stimulation do not remediate visual hallucinations in Lewy body dementia: a randomised controlled trial. *Alzheimers Res Ther*. 2019 Jan 18;11(1):9.  
[PubMed: PM30658705](#)
12. Koch G, Bonni S, Pellicciari MC, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. *Neuroimage*. 2018 Apr 1;169:302-311.  
[PubMed: PM29277405](#)
13. Zhao J, Li Z, Cong Y, et al. Repetitive transcranial magnetic stimulation improves cognitive function of Alzheimer's disease patients. *Oncotarget*. 2017 May 16;8(20):33864-33871.  
[PubMed: PM27823981](#)
14. Bystad M, Gronli O, Rasmussen ID, et al. Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial. *Alzheimers Res Ther*. 2016 Mar 23;8(1):13.  
[PubMed: PM27005937](#)

15. Lee J, Choi BH, Oh E, Sohn EH, Lee AY. Treatment of Alzheimer's disease with repetitive transcranial magnetic stimulation combined with cognitive training: a prospective, randomized, double-blind, placebo-controlled study. *J Clin Neurol*. 2016 Jan;12(1):57-64.  
[PubMed: PM26365021](#)
16. Wu Y, Xu W, Liu X, Xu Q, Tang L, Wu S. Adjunctive treatment with high frequency repetitive transcranial magnetic stimulation for the behavioral and psychological symptoms of patients with Alzheimer's disease: a randomized, double-blind, sham-controlled study. *Shanghai Arch Psychiatry*. 2015 Oct;27(5):280-288.  
[PubMed: PM26977125](#)
17. Khedr EM, Gamal NF, El-Fetoh NA, et al. A double-blind randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's disease. *Front Aging Neurosci*. 2014;6:275  
[PubMed: PM25346688](#)
18. Suemoto CK, Apolinario D, Nakamura-Palacios EM, et al. Effects of a non-focal plasticity protocol on apathy in moderate Alzheimer's disease: a randomized, double-blind, sham-controlled trial. *Brain Stimul*. 2014 Mar-Apr;7(2):308-313.  
[PubMed: PM24262299](#)

## Non-Randomized Studies

19. Antczak J, Kowalska K, Klimkowicz-Mrowiec A, et al. Repetitive transcranial magnetic stimulation for the treatment of cognitive impairment in frontotemporal dementia: an open-label pilot study. *Neuropsychiatr Dis Treat*. 2018;14:749-755.  
[PubMed: PM29559782](#)
20. Ferrucci R, Mrakic-Sposta S, Gardini S, et al. Behavioral and neurophysiological effects of transcranial direct current stimulation (tDCS) in fronto-temporal dementia. *Front Behav Neurosci*. 2018;12:235.  
[PubMed: PM30420799](#)
21. Nguyen JP, Suarez A, Kemoun G, et al. Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease. *Neurophysiol Clin*. 2017 Feb;47(1):47-53.  
[PubMed: PM28161090](#)
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[PubMed: PM26064066](#)

## Safety Studies

23. Elder GJ, Firbank MJ, Kumar H, et al. Effects of transcranial direct current stimulation upon attention and visuoperceptual function in Lewy body dementia: a preliminary study. *Int Psychogeriatr*. 2016 Feb;28(2):341-347.  
[PubMed: PM26250473](#)

## Appendix — Further Information

### Randomized-Controlled Trials

#### *Alternative Population*

24. Padala PR, Padala KP, Lensing SY, et al. Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: a double-blind, randomized, sham-controlled, cross-over pilot study. *Psychiatry Res.* 2018 Mar;261:312-318.  
[PubMed: PM29331848](#)
25. Tsapkini K, Webster KT, Ficek BN, et al. Electrical brain stimulation in different variants of primary progressive aphasia: a randomized clinical trial. *Alzheimer's & dementia (New York, N Y).* 2018;4:461-472.  
[PubMed: PM30258975](#)
26. Drumond Marra HL, Myczkowski ML, Maia Memoria C, et al. Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: a randomized controlled study. *Behav Neurol.* 2015;2015:287843.  
[PubMed: PM26160997](#)
27. Meinzer M, Lindenberg R, Phan MT, Ulm L, Volk C, Floel A. Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms. *Alzheimers Dement.* 2015 Sep;11(9):1032-1040.  
[PubMed: PM25449530](#)

#### *Alternative Outcome*

28. Khedr EM, Salama RH, Abdel Hameed M, Abo Elfetoh N, Seif P. Therapeutic role of transcranial direct current stimulation in Alzheimer disease patients: double-blind, placebo-controlled clinical trial. *Neurorehabil Neural Repair.* 2019 Apr 3:1545968319840285.  
[PubMed: PM30940012](#)
29. Cotelli M, Adenzato M, Cantoni V, et al. Enhancing theory of mind in behavioural variant frontotemporal dementia with transcranial direct current stimulation. *Cogn Affect Behav Neurosci.* 2018 Dec;18(6):1065-1075.  
[PubMed: PM29995274](#)

#### *Protocol Papers*

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[PubMed: PM30450044](#)
31. Nguyen JP, Boutoleau-Bretonniere C, Lefaucheur JP, et al. Efficacy of transcranial direct current stimulation combined with cognitive training in the treatment of apathy in patients with Alzheimer's disease: study protocol for a randomized trial. *Rev Recent Clin Trials.* 2018;13(4):319-327.  
[PubMed: PM29658441](#)

32. Woods AJ, Cohen R, Marsiske M, Alexander GE, Czaja SJ, Wu S. Augmenting cognitive training in older adults (The ACT Study): design and Methods of a Phase III tDCS and cognitive training trial. *Contemp Clin Trials*. 2018 Feb;65:19-32.  
[PubMed: PM29313802](#)
33. Hampstead BM, Sathian K, Bikson M, Stringer AY. Combined mnemonic strategy training and high-definition transcranial direct current stimulation for memory deficits in mild cognitive impairment. *Alzheimers Dement*. 2017 Sep;3(3):459-470.  
[PubMed: PM29067352](#)
34. Narita Z, Yokoi Y. Transcranial direct current stimulation for depression in Alzheimer's disease: study protocol for a randomized controlled trial. *Trials*. 2017 Jun 19;18(1):285.  
[PubMed: PM28629447](#)

## Non-Randomized Studies - Alternative Population

35. Murugaraja V, Shivakumar V, Sivakumar PT, Sinha P, Venkatasubramanian G. Clinical utility and tolerability of transcranial direct current stimulation in mild cognitive impairment. *Asian J Psychiatr*. 2017 Dec;30:135-140.  
[PubMed: PM28934620](#)

## Review Articles

36. Buss SS, Fried PJ, Pascual-Leone A. Therapeutic noninvasive brain stimulation in Alzheimer's disease and related dementias. *Curr Opin Neurol*. 2019 Apr;32(2):292-304.  
[PubMed: PM30720478](#)
37. Liu CS, Rau A, Gallagher D, Rajji TK, Lanctot KL, Herrmann N. Using transcranial direct current stimulation to treat symptoms in mild cognitive impairment and Alzheimer's disease. *Neurodegener Dis Manag*. 2017 Oct;7(5):317-329.  
[PubMed: PM29043928](#)
38. Elder GJ, Taylor JP. Transcranial magnetic stimulation and transcranial direct current stimulation: treatments for cognitive and neuropsychiatric symptoms in the neurodegenerative dementias? *Alzheimers Res Ther*. 2014;6(9):74.  
[PubMed: PM25478032](#)