Review of: "Gamma connectivity predicts response to intermittent Theta Burst Stimulation in Alzheimer's disease: A randomised controlled trial"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

As the authors proposed, this manuscript is a pioneering study using intermittent theta burst stimulation (iTBS) in patients with Alzheimer's disease. Therefore, researchers in this field should pay close attention to the results for tailoring their future studies regarding relevant topics. The authors enrolled 58 randomly assigned participants to either active or sham condition. Participants in each condition received 21 sessions of iTBS targeting four brain regions (left dorsolateral prefrontal cortex (DLPFC), right DLPFC, left posterior parietal cortex (PPC), right PPC) over six weeks. Neurophysiological, cognitive, and functional assessments were conducted as outcome measures. Participants receiving active iTBS showed a significant and large increase in resting state gamma connectivity obtained from EEG and improved delayed episodic memory. In addition, baseline gamma connectivity and
the magnitude of gamma connectivity changes over the treatment period may predict improvement of delayed recall. Although the results undoubtedly guide future research in this field, I have several possibly helpful suggestions for the current manuscript.

Introduction

The authors justified the use of iTBS to modulate functional brain connectivity in patients with AD in this section. Given that the title of this manuscript begins with "gamma connectivity", it is expected to see texts to link iTBS with gamma connectivity. However, only studies concerning theta connectivity were presented. I was therefore confused with the exact neurophysiological outcome in the current study, particularly when the authors mentioned that the frequency band of interest consists of theta and gamma in the method section. I would recommend the authors spend several lines elaborating on the association between iTBS and gamma connectivity.

On page4, the authors addressed the limitations of previous TMS research to modulate cognition for AD. Precisely, it is suggested to use "rTMS" to denote the brain stimulation technique in these studies. Also, the authors highlighted that one of these limitations is "not full treatment doses given". The issue of the definition of "full" doses requires the authors' justification. Also, the description that iTBS can be done "within" 3 minutes is not accurate (also seen in the Materials and Methods). The time for a typical iTBS session (i.e., 600 pulses) should be 190 seconds (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) which is more than 3 minutes.

Materials and Methods

It would be appreciated if the authors could justify why they decided to give 21 iTBS sessions to their participants and why the stimulation intensity of 100% RMT was used instead of the conventional “80%” RMT.

I would also recommend replacing the current citation of ADASCog (Connor and Sabbagh., 2008) and GDS (Yesavage, 1988) with (Rosen, Mohs, & Davis, 1984) and (Yesavage et al., 1982), respectively.

Results

3.1 Resting State-EEG: Functional Connectivity

Considering the p-value (.055), it is suggested not to use “greater” to describe the gamma connectivity in the active group compared to the sham group at the end of treatment in the eye-closed condition. Also, the term “near significant” (P14, L2) is not favored.

In addition, the authors addressed that both theta and gamma were the frequency band of interest (P12, L1), but none of the results regarding theta frequency was reported.

Minor concerns

1. Abbreviations

The authors did not spell some terms in full at the first appearance in the abstract and main text, such as DLPFC, PPC, EEG, ADASCog, QoL-AD, and GDS.

2. citations and references

Some citations were not incongruent in the published year with those presented in the References section.

EXAMPLES:

(Folstein et al., 1978) on page 6, (Sabbagh et al., 2020) on page 23.

Some references were not presented in the correct format or lacked information regarding volumes or pages.

EXAMPLES (but not limited to):

No pages:

Alzheimer’s Association (2021) Alzheimer's disease facts and figures. Alzheimer's & Dementia, 17(3).

Sabbagh, M., Sadowsky, C., Tousi, B., Agronin, M. E., Alva, G., Armon, C., ... & Pascual-Leone, A. (2019). Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease. Alzheimer's & Dementia

Using abbreviated journal name:

Briels CT, Schoonhoven DN, Stam CJ, de Waal H, Scheltens P, Gouw AA (2020) Reproducibility of EEG functional connectivity in Alzheimer's disease. Alzheimers Res Ther 12, 68.

Connor DJ, Sabbagh MN (2008) Administration and scoring variance on the ADAS-Cog. J Alzheimer’s Dis 15, 461-464.

Incorrect format

Zhao, J.W. et al. Repetitive transcranial magnetic stimulation improves cognitive function of Alzheimer's disease patients.

Oncotarget 8, 33864–33871 (2017).

These issues should be appropriately fixed with any citation management software.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206. doi:10.1016/j.neuron.2004.12.033

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. *Am J Psychiatry, 141*(11), 1356-1364. doi:10.1176/ajp.141.11.1356

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of Psychiatric Research, 17*(1), 37-49. doi:10.1016/0022-3956(82)90033-4