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COMMENTARY

Paired associative stimulation (PAS) and Alzheimer's disease (AD)

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Dementia is one of the most common neurodegenerative disorders in the world (Cao *et al.*, 2020). It is estimated that the global prevalence of dementia will increase from approximately 58 million cases currently to nearly 153 million cases by 2050 (GBD, 2022). Alzheimer's disease (AD) is the most common cause of dementia, and it accounts for nearly 60–80% of cases (2021 Alzheimer's disease facts and figures, 2021). In the United States alone, there are an estimated 6.2 million individuals with AD. It is projected that the number of individuals with AD will more than double to 13.8 million individuals by 2060. In the United States, AD is the sixth leading cause of death overall, and among individuals ≥ 65 year in age, it is the fifth leading cause of death. Between 2000 and 2019, the reported number of deaths in the United States due to AD increased by 145%. It is estimated that nearly $355 billion is spent each year in the United States alone for the care of individuals with AD and other dementias. By 2050, this cost is expected to rise to more than $1.1 trillion a year (2021 Alzheimer's disease facts and figures, 2021).

A recent retrospective cross-sectional study published in *International Psychogeriatrics* (IPG) found that the younger age at onset, dementia type other than AD and behavioral-variant frontotemporal dementia, and an increased number of services consulted often delayed the diagnosis of dementia by up to 6 months (Loi *et al.*, 2020). The use of a specialized service was found to reduce this time to diagnosis by up to 12 months, especially among individuals with young-onset dementia. In addition to the initial clinical assessment, the use of a standardized and validated screening tool like the Montreal Cognitive Assessment (MoCA) especially with a double threshold (i.e., double cutoff), ≥ 26 for normal and <21 for dementia, was found to increase specificity without decreasing sensitivity in identifying individuals with mild dementia who needed referral for neuropsychological assessment (Dautzenberg *et al.*, 2022). This use of double threshold for MoCA assists in reducing the oversubscription of essential services like the neuropsychological assessment that are often crucial in confirming the diagnosis of dementias.

The US Food and Drug Administration (FDA) had until recently only approved donepezil, galantamine, and rivastigmine (all cholinesterase inhibitors), memantine (N-methyl-D-aspartate receptor antagonist) and a combination of donepezil and rivastigmine for the treatment of neurocognitive symptoms of AD (Cummings *et al.*, 2019). The fixed-dose combination of donepezil and memantine is approved for the treatment of individuals with moderate to severe AD dementia who are stable on donepezil. In the European Union, donepezil, galantamine, rivastigmine, and memantine are licensed for the treatment of individuals with AD. Unfortunately, none of these are disease-modifying agents among individuals with AD. The only FDA-approved disease-modifying agent for use among individuals with AD is aducanumab (Tampi *et al.*, 2021). Aducanumab is a human IgG1 anti-Aβ monoclonal antibody that is selective for Aβ aggregates. The FDA has approved aducanumab for the treatment of mild cognitive impairment or mild dementia stage of AD (Tampi *et al.*, 2021). A recent systematic review published in IPG found that among individuals with dementia who exhibit disinhibited behaviors, data from good quality randomized controlled trials indicate that both nonpharmacological interventions (models of care, education and training, physical activity, and music-based interventions) and pharmacological agents (antidepressants and pain management) are effective in reducing these behaviors (Burley *et al.*, 2022). The investigators noted greater effect sizes for nonpharmacological interventions (mean Cohen's d = 0.49) when compared to pharmacological treatments (mean Cohen's d = 0.27). The data from this study emphasize the importance of not solely relying on one treatment modality alone to treat these complex and often distressing behaviors.

Transcranial magnetic stimulation (TMS) is a method of noninvasive brain stimulation (NIBS) that uses electromagnetic fields (Bashir *et al.*, 2022). The advantage of TMS is that it is a painless

procedure and does not require any type of skin preparation. Additionally, it does not require the use of anesthetic agents or intravenous drugs or any surgical procedure. The FDA has approved TMS for the treatment of major depressive disorder (MDD) among adults who have not responded adequately to previous antidepressant trials (Cohen *et al.*, 2022). Additional indications for TMS are for the treatment of refractory obsessive-compulsive disorder, for acute and prophylactic treatment of migraine headaches among adolescents and adults, as an adjunct in short-term smoking cessation among adults and for the treatment of comorbid anxiety symptoms among individuals with MDD who have not responded adequately to treatment with antidepressants (Cohen *et al.*, 2022).

The use of TMS among older adults has been gaining interest over the past two decades (Iriarte and George, 2018). The advantages of using TMS among the elderly are a focal electrical stimulation, minimal adverse effects, no harmful effects on cognition, and the absence of any drug interactions. There is growing evidence that TMS can improve cognition among individuals with mild cognitive impairment and mild AD dementia (Weiler *et al.*, 2020). Additionally, TMS has also been found to be useful in the treatment of behavioral and psychological symptoms of dementia (Vacas *et al.*, 2019). Although the definitive mechanisms by which TMS improves cognition among individuals with AD remains unclear, possible mechanisms include long-term potentiation (LTP) like changes in synaptic strength, increasing the level of the brain-derived neurotrophic factor, and the modulation of GABAergic synaptic activity that influences the overall inhibitory/excitatory balance (Somaa *et al.*, 2022).

The protocol of NIBS is called paired associative stimulation (PAS) when a sensory peripheral stimulus is repeatedly paired with a TMS pulse over a cortical area that is known to be activated by the TMS pulse (Guidali *et al.*, 2021; Wischnewski and Schutter, 2016). PAS has been identified as causing synaptic plasticity and inducing both LTP-like and long-term depression (LTD)-like after-effects on cortical excitability.

Kumar *et al.* (2022) in their new paper that is being published in IPG conducted a pilot-randomized double-blind controlled trial of repetitive PAS (rPAS) that evaluated its effect on the plasticity of dorsolateral prefrontal cortex and working memory performance among 32 individuals (age = 76.4 ± 6.3 years) with AD. These individuals were randomized in a 1:1 ratio to receive a 2-week (5 days per week) course of active or control rPAS.

The investigators evaluated DLPFC plasticity at baseline and on days 1, 7, and 14 post rPAS using a single-session PAS which was combined with electroencephalography (EEG). In this study, the active rPAS consisted of repetitive pairing of electrical stimulation of the median nerve at the right wrist with TMS of the contralateral left DLPFC. The median nerve stimulation was 180 pulses at 0.1 Hz, and the TMS had the inter-stimulus interval of 25 ms. The control rPAS was similar to the active rPAS except that the inter-stimulus interval was 100 ms. All the participants who were randomized successfully completed the rPAS course without any serious adverse events.

Although the study was negative on primary outcome measures in terms of detecting differences between active and control rPAS groups, there was no significant group × time interaction for DLPFC plasticity (PASLTP, $P = 0.14$) or working memory on 2 back ($P = 0.444$) or 1 back ($P = 0.824$) tasks, the investigators noted that right after the intervention (post day 1), the active rPAS enhanced DLPFC plasticity ($P = 0.038$, Cohen's $d = 0.7$), working memory performance on 2-back task ($P = 0.043$, Cohen's $d = 0.7$), and theta–gamma coupling (modulation of gamma amplitude by theta phase noted on EEG) during 2-back performance ($P = 0.02$, Cohen's $d = 0.9$). This positive effect was not noted in the control rPAS group, DLPFC plasticity ($P = 0.954$, Cohen's $d = 0.027$), working memory performance on 2-back ($P = 0.7$, Cohen's $d = 0.2$), and theta–gamma coupling during 2-back performance ($P = 0.4$, Cohen's $d = 0.3$). However, the investigators also noted that without any booster rPAS sessions, the improvement in DLPFC plasticity did not persist. The improvements in working memory and theta–gamma coupling also became variable.

In the post hoc analyses, the investigators noted a correlation between working memory performance and theta–gamma coupling during the working memory task at all time points for both groups. Limitations of the study include a small sample size, short study duration, the use of a clinical diagnosis of AD in participant selection, not including pathologic markers of AD in the selection of participants, the use of unilateral rPAS delivery to the left DLPFC rather than bilateral delivery of rPAS, the lack of booster or continuation rPAS sessions, more than half of the participants continuing on cognitive enhancers during the study period, not correcting for coil-to-cortex distance as a factor for cortical atrophy in determining the intensity of DLPFC stimulation, and the exclusion of individuals with mild cognitive impairment.

Despite the limitations, the findings of this small pilot study add to the growing body of literature on the possible benefits of using NIBS techniques like

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TMS or rPAS for the assessment and management of individuals AD (Menardi *et al.*, 2022). Although these NIBS techniques are still not ready for use in the clinical management of individuals with AD, they provide exciting possible alternatives to currently available treatments for AD (Doroszkiewicz and Mroczko, 2022). When using NIBS techniques like TMS or rPAS, there should be further investigation into which combinations of protocol characteristics and parameters are most efficient in improving cognition, function, and behaviors among individuals with AD (Menardi *et al.*, 2022). Additionally, the use of biomarker-guided diagnostic framework, patient selection that takes into account individual differences in the underlying anatomical, structural, and functional connectivity of the individual's brain, and the consistent use of standardized neuropsychological testing to measure and monitoring of patient's cognitive functioning will improve treatment outcomes (Menardi *et al.*, 2022).

Finally, the use of precision medicine paradigm that involves the implementation of technological and scientific advances to determine which therapeutic approach will be most effective in a particular person at a specific disease stage must be adapted for the management of individuals with AD (Hampel *et al.*, 2019). This paradigm shift will assist in overcoming the limitations of the traditional symptom- and sign-based phenotypic diagnoses and clinical management of a largely heterogeneous disease like the AD.

Conflict of interest

None.

Description of author's roles

Rajesh Tampi conceptualized and wrote the commentary.

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