

A randomized clinical trial examined the impact of cerebellar stimulation on Alzheimer's patients' ability to regain their cognitive abilities

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ABSTRACT

The cerebellum is thought to play a role in cognitive processing, according to evidence. Uncertainty exists regarding the precise processes by which cerebellar repetitive Transcranial Magnetic Stimulation (rTMS) affects cognitive status.

Methods: 27 Alzheimer's Disease (AD) patients were randomly assigned to one of the two groups in the current randomized, double-blind, sham-controlled trial: rTMS real or rTMS-sham. We looked at how well bilateral cerebellar rTMS therapy administered over four weeks promoted cognitive recovery and changed certain cerebello-cerebral functional connections.

Keywords: Cerebellum; Alzheimer's disease; rTMS; Functional connectivity

INTRODUCTION

The most prevalent form of dementia, Alzheimer's Disease (AD), is characterized by a gradual decline in cognitive abilities as well as behavioral and personality abnormalities. In the past 30 years, the only clinically effective therapies for AD have been cholinesterase inhibitors and NMDA receptor antagonists. In 2021, the US FDA granted conditional approval to a human immunoglobulin gamma 1 monoclonal antibody that targets aggregated Ab fibrils. However, there are still a lot of questions about its efficacy and safety in clinical settings. The urgent need for novel therapeutic strategies for enhancing cognition in AD patients is highlighted by a number of phase III studies that failed. A novel method for treating AD called repetitive Transcranial Magnetic Stimulation (rTMS) has promising early outcomes. Depending on the stimulation parameters, it either reduces (1 Hz) or increases (5 Hz) excitability in the targeted brain region and modifies the activity of a particular neural network. The precise neurobiological workings of rTMS remain a mystery. However, they might entail altering neuroplasticity or rebuilding neural networks. Significant interest in cognitive neuroscience has been sparked by the cerebellum's function in cognitive processing. The most unexpected finding is that about 80% of the neocortex connects the cerebral cortex to the cerebellum, which is folded more tightly than the cerebral cortex. The cerebellum plays a crucial role in the processing of a variety of cognitive functions, including emotion, language working memory and other executive functions. This is likely because of the extensive connections it has with the cortical and subcortical regions, particularly the prefrontal cortices. Our earlier studies showed that several cognitive domains were affected by the cognitive impairment following cerebellar damage. Using the low-frequency fluctuations of blood oxygen level dependent signals inside the brain, resting-state functional Magnetic Resonance Imaging (rs-fMRI) depicts the synchronization between the disconnected brain regions or nodes. It has made it possible to separate cerebellar areas into separate motor and cognitive brain networks based on functional synchronization. The idea of adopting non-invasive brain stimulation (rTMS) for target specific manipulation of the functional connections is raised by the fact that various cerebellar lobules make up nodes of various brain networks. In the present work, we investigated whether 5Hz rTMS was applied to the bilateral cerebellum Crus II for four weeks to enhance memory and other cognitive functions and modify cognitive cerebello-cerebral connection [1].

LITERATURE REVIEW

Participant

The medical research ethical committee of the Nanjing brain hospital in Nanjing, China gave its approval to the current study.

Between June 2019 and October 2021, 27 right handed AD subjects 14 men and 13 women were recruited. Before registering for the study, each participant gave their written, informed consent. According to the most recent diagnostic standards released by the National Institute on Aging and the Alzheimer's Association working group (NIA-AA) in 2018, the patients were recruited. The evidence provided by Cerebrospinal Fluid (CSF) and imaging biomarkers and the guidelines are backed by episodic memory loss in AD pathogenesis. Age 60 to 80 years, no vision or hearing impairments, at least an eighth-grade education, a trustworthy informant caregiver, a Mini-Mental State Examination (MMSE) score of 16 or higher, and for patients taking medication, stable doses of ChEI or memantine for a period of time longer than 90 days were inclusion criteria. Patients with epilepsy or a history of using barbiturates or benzodiazepines within two weeks of enrolment, bipolar disorder, depression, psychotic disorders, or any other neurological or psychiatric disease that would have interfered with the trial were also excluded. Additionally, using any investigational medication in a clinical trial within six months of enrollment; contraindications for MRI or TMS; brain implantation with metal; immunosuppression; heavy alcohol or drug use; severe sleep disturbances; unstable medical conditions; or any other neurological or psychiatric disorder. All of the patients underwent a thorough clinical investigation, a thorough neuropsychological evaluation that examined all cognitive domains, a brain MRI scan, and a CSF study. An expert field investigator validated that the patients met the requirements to take part in the trial [2].

Clinical and neuropsychiatric evaluation

All of the individuals underwent thorough and typical neuropsychological evaluations. The MMSE Montreal Cognitive Assessment (MoCA). Clinical Dementia Rating Scale (CDR), and Alzheimer's disease were used to assess global cognition. ADAS-Cog, or Assessment Scale-Cognitive Section. The Rey Auditory-Verbal Learning Test (RAVLT) was used to evaluate episodic

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memory the visuospatial skills were evaluated using the Clock Drawing Test (CDT) [3].

Cerebrospinal fluid biomarker

A lumbar puncture was performed on each of the 27 patients to validate the characteristic CSF profile of AD pathology, which includes decreased amyloid b1-42 concentrations and elevated levels of total and phosphorylated-tau. The INNOBIA AlzBio3 immunoassay kit-based reagents (Innotest, Fujirebio, and Ghent, Belgium) were used to identify amyloid b1-42, p-tau, and t-tau [4].

Magnetic Resonance Imaging (MRI) data acquisition

A Siemens 3.0 T Singer scanner (Siemens, Verio, Germany) with an 8 channels radio frequency coil was used for all scans. Participants were instructed to remain motionless; close their eyes, stay awake, and refrain from thinking. The following parameters were used to create sagittal oriented three-dimensional T₁ weighted images: Time Repetition (TR) 14 1900 ms, Echo Time (TE) 14 2.48 ms, Inversion Time (TI) 14 900 ms, 176 sagittal slices, 1.0 mm slice thickness, gap 14 0.5 mm, matrix 14 256 256, Flip Angle (FA) 14 9°, Field of View (FOV) [5].

Procedure

Through the use of computer generated randomization software, patients who gave their assent were randomly assigned to receive actual or fake rTMS therapy. The grouping of individuals and one another were hidden from the neuropsychologists administering the scales. Up until the database was locked, all participants and researchers including the physiotherapists who administered the rTMS were kept in the dark. All patients had their experiences with administering actual or fake rTMS treatments counterbalanced [6].

The patients completed thorough clinical and neuropsychological evaluations at baseline (T₀), four weeks (T₄), and 12 weeks following the start of treatment (follow-up; T₁₂). Additionally, after four weeks of treatment and at baseline (T₀), the patients underwent brain MR scanning (T₄) [7].

Intervention-rTMS treatment

Using a Magventure Rapid stimulator and a figure of eight coil (cool-B65) with a diameter of 70 mm (MagPro X100, Denmark), TMS was performed at a maximum output of 6 T. Each participant's rTMS intensity was set to a maximum of 90% of their Resting Motor Threshold (RMT). Prior to beginning the course of treatment, it was calculated using the international federation of clinical neurophysiology. The patients were positioned with their hands relaxed and pronated in a comfy chair. The primary hand motor area on the scalp, which is contralateral to the target muscle, was then treated with a TMS coil held tangentially over it. The coil handle also pointed 45 degrees laterally and posteriorly to the sagittal plane. RMT was the lowest intensity that resulted in at least five out of ten trials with a motor evoked potential of at least 50 mV. The first muscle of the dorsal interosseum. The participants sat comfortably in a chair with a headrest to support the head during the rTMS therapy [8].

RESULTS

Clinical characteristics assessment

Gender, education, age, disease severity, or concurrent AD medication dose of several patients were not significantly different between the genuine and sham groups at baseline. More than 90% of participants completed at least 18 of the 20 scheduled therapy sessions (25 patients completed the experiment, while two were dropped due to an incomplete treatment course) (15 in the real and 10 in the sham group) [9].

Neuropsychological assessment

For each cognitive domain at baseline, there were no differences between the two groups that were statistically significant. Following the cerebellum rTMS treatment in the real group, overall cognitive levels, episodic memory ability, executive ability, verbal ability, and visuospatial functional scores were significantly higher within 12 weeks of treatment onset (follow-up; T₁₂) and four weeks of treatment (T₄) than baseline (T₀).

Functional connectivity changes of the left and right cerebellum crus I

Four weeks of Treatment (T₄) in the actual rTMS group showed improved functional connectivity between the left cerebellar Crus II and right DLPFC, the bilateral medial frontal cortex, and the bilateral cingulate cortex in comparison to the baseline (T₀) state. Additionally, there was increased connection between the bilateral medial frontal cortex, the bilateral DLPFC, and the right cerebellum Crus II. and the phoney rTMS group, however, showed no promising benefits [10].

Correlation analysis with neuropsychological scores

The DFC between the right cerebellar Crus II and the left DLPFC was favourably correlated with the improved MMSE score after four weeks of Treatment (T₄) relative to the baseline (T₀) (DMMSE), according to a correlation study. The DFC between the right DLPFC and the left Crus II of the cerebellum was related with the DRAVLT score. Between the right medial frontal cortex and the right cerebellar crus II, the DSDMT score and the DFC were connected. A correlation research found a positive link between the enhanced MMSE score following four weeks of Treatment (T₄) compared to the baseline (T₀) (DMMSE) and the DFC between the right cerebellar crus II and the left DLPFC [11].

DISCUSSION

Treatment for AD related dementia has a very low success rate. Only a small number of AD-related drugs have been licenced in the last 15 years to slow or change the course of the illness. This promising study showed that rTMS treatment over the bilateral cerebellum, which was randomised, sham-controlled, and blinded, had very high adherence rates, an outstanding safety profile, and greater efficacy on cognitive testing in AD patients. The evaluation scales used to evaluate both general cognitive performance and other cognitive domains showed a striking influence, according to this study [12].

As a result, rTMS directed at the bilateral cerebellum can enhance a variety of cognitive functions more so than rTMS directed at the DLPFC or the precuneus. Thus, the treatment's clinical importance was supported. However, the precise neurobiological processes of rTMS are yet unknown, notwithstanding the neuroplasticity modulation epidemic theory. The primary motor cortex's cortical LTP like plasticity is noticeably impaired in AD patients as determined by Theta-Burst Stimulation (TBS) procedures (M₁). It is regarded as the main reason why AD patients have cognitive impairment. In addition, a prior study reported that AD patients with the following cerebellar iTBS had impaired cerebellar cortical plasticity. The cerebello-thalamocortical circuits may be activated as a result of changes in excitability caused by rTMS. The findings suggest that the cerebellum, which has close physiological connections to multiple cognition-related brain areas, may provide a unique target for neuroregulation in AD patients. According to earlier neuroimaging results, AD is thought to be an illness that affects the mechanisms of synaptic plasticity of long-distance connections linking the various brain areas. This theory is compatible with the reduced functional connectivity between the cerebellum and cerebral cortex.

CONCLUSION

According to our findings, 5Hz rTMS over the bilateral cerebellum may be a useful treatment option for AD patients. There is no treatment readily available right now. Our results are consistent with an emerging theory that

identifies the cerebellum as a unique therapeutic target to considerably enhance cognitive performance in individuals with AD and views circuit based dysfunctions as a model for cognitive impairment.

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