The Efficacy of Circuits-based Neuromodulation on Long-term Delayed Recall in Amnestic Mild Cognitive Impairment: A Pilot, Randomized, Controlled Clinical Trial

Study Protocol

Background

With the global population entering an aging phase, Alzheimer's Disease (AD), a neurodegenerative disease closely associated with age, has gained increasing attention from scholars. Due to the unsatisfactory efficacy of current AD treatments, early detection and diagnosis have become a focus of medical researchers, in addition to treatment-related studies. Against this background, amnestic Mild Cognitive Impairment (aMCI), which is considered to be an intermediate stage between normal cognitive aging and early AD, has received growing attention and research.

Transcranial magnetic stimulation (TMS) is a non-invasive and minimally side-effect neural modulation technique that plays a significant role in cognitive neuroscience and clinical neural functional regulation. TMS utilizes the induction of electric fields generated by pulsed currents to modulate neuronal excitability within brain tissue, allowing for targeted stimulation of specific cortical brain regions and improving cognitive functions in humans and animals. In recent years, using TMS for neural modulation to improve cognitive functions has become a hotspot of interest among researchers in neurorehabilitation. However, current research and clinical applications mostly focus on single-target treatments, which have shown limited effectiveness. Therefore, there is an urgent need to explore novel TMS-based rehabilitation strategies.

With the emergence of the concept of the "human connectome", people have gradually realized that different brain regions leading to similar symptoms may be part of a common network with interconnections. Fox et al. [1], in their publication in The New England Journal of Medicine, argued that lesion-based localization

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sometimes has limitations because damage to different brain locations may result in similar symptoms. For example, most language impairment is located outside the left frontal cortex, most memory impairment is located outside the hippocampus, and impairment of social behavior is typically located outside the frontal cortex. Even among patients with similar symptoms, lesion overlap and the overlapping locations may not align with traditional understanding of the corresponding brain functions. For instance, brainstem lesions causing visual hallucinations overlap in the midbrain and thalamus, but these locations do not have a clear role in vision or visual imagery. Therefore, the relationship between symptoms and lesion location is not direct. Another limitation of lesion-based localization is that many complex symptoms occur in patients without obvious brain damage. Common neurological and psychiatric disorders, such as delirium, amnesia, autism, and schizophrenia, often occur in patients without apparent brain damage. Complex symptoms may not be limited to a single brain region but can map to larger distributed brain networks. Damage to any region within these networks may disrupt behavior and lead to similar symptoms. For example, solving complex problems requires the coordinated function of frontal and parietal regions, and impairment in any of these areas would diminish performance. Similarly, damage to interregional connections can result in complex "disconnection" syndromes while the cortical areas necessary for the behavior remain intact. This article proposes a new approach based on identifying treatment targets within the damaged brain network.

Hebbian plasticity is an excitatory synaptic plasticity learning rule that activates when presynaptic and postsynaptic neurons are active simultaneously, resulting in the strengthening of functional connections between neurons (i.e., "fire together, wire together"). If this mechanism is repeatedly activated, the plasticity can shift from a functional level to a structural level, leading to the induction of new synaptic connections and long-term maintenance of functionality. Therefore, Hebbian plasticity is a crucial mechanism for brain circuit reconstruction and can establish new compensatory neural circuits in the brain after circuit damage by activating appropriate presynaptic and postsynaptic neurons, thereby restoring impaired

functionality [2].

Cortico-cortical paired associative stimulation (ccPAS), based on Hebbian theory, enhances or weakens synaptic transmission efficiency based on the timing interval (inter-stimulus interval, ISI) between two different sources of stimulation that converge on the postsynaptic neurons of cortical pyramidal cells. If a weak input signal is reinforced before activating the postsynaptic neurons, synaptic transmission efficiency is enhanced, resulting in long-term potentiation (LTP). Conversely, if the input signal follows the activation of postsynaptic neurons, synaptic transmission efficiency is weakened, leading to long-term depression (LTD). By adjusting the ISI, ccPAS can produce different effects on cortical excitability [3].

In summary, we believe that the use of ccPAS to modulate neural circuits based on the Hebbian model can improve cognitive function. In this study, we propose to conduct a randomized controlled trial with aMCI patients as the research subjects. By using behavioral measures (neuropsychological tests, activities of daily living, depression and anxiety scales) and multimodal magnetic resonance imaging, we aim to objectively evaluate the effects of TMS on memory function and central reorganization patterns, thereby developing an optimized cognitive rehabilitation program and suitable techniques. This research will establish an optimized cognitive rehabilitation program and suitable techniques, providing not only objective theoretical and practical foundations for clinical treatment but also contributing to the popularization and promotion of aMCI rehabilitation programs and appropriate techniques.

Reference

[1] Fox MD. Mapping symptoms to brain networks with the human connectome. The New England journal of medicine. 2018;379:2237-2245.

[2] Rowe JB, Chan V, Ingemanson ML, Cramer SC, Wolbrecht ET, Reinkensmeyer DJ. Robotic assistance for training finger movement using a hebbian model: A randomized controlled trial. Neurorehabilitation and neural repair. 2017;31:769-780.

[3] Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain : a journal of

neurology. 2000;123 Pt 3:572-584.

Objective

The aim of this study is to investigate the effects of cortico-cortical paired associative stimulation (ccPAS) on cognitive function and central reorganization patterns in individuals with amnestic mild cognitive impairment (aMCI) by comparing it to a sham stimulation group and assessing pre- and post-treatment outcomes.

Method

a parallel-group, randomized, controlled clinical trial.

Object

Source of cases

Participants were recruited from the rehabilitation center at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine.

Sample size calculation

Sample size calculation was calculated based on long delay recall score as the main observation index. As this study adopts a new treatment method, sample size was acquired from our preliminary study. As a result, the mean (5.1) and standard deviation (2.23) after treatment, as well as the mean (2.6) after false stimulation, a minimum total sample size of 33 treatment-completers was required to achieve 90% power at α=0·05. To account for attrition and ensure adequate power at 2 weeks after treatment, 42 participants need to be included, with 21 subjects in each group.

Diagnostic criteria

Referring to Jak/Bondi's relevant diagnostic criteria [4]:

Symptoms of cognitive impairment (found by patients/insiders/clinicians); 2) Objective evidence of impairment in at least one cognitive function domain (memory, language, executive function, etc.); The score below the mean of the age matched population at least 1.0 standard deviation (SD); 3) Complex instrumental daily ability

can be slightly impaired with no impairment in remaining activities of daily living; 4) No dementia.

[4] Bondi MW, Edmonds EC, Jak AJ, et al. Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. J Alzheimers Dis. 2014;42(1):275-89. doi:10.3233/jad-140276

Inclusion criteria

Case group: We will recruite adults aged 50–80 years who had a neuropsychological battery-confirmed initial diagnosis of aMCI. A patient meet inclusion criteria if he/she 1) having ≥ 6 years of education; 2) initial diagnosis of MCI and not having taken cognitive improvement medication; 3) complaining of memory loss with objective evidence (AVLT long delayed recall score at least 1.0 standard deviation lower than the mean of the age-matched population); 4) who understood and agreed to participate in this study and signed the informed consent form.

HC group: We will enroll adults aged 50–80 years who had a neuropsychological battery-confirmed normal cognition. A subject meet inclusion criteria if he/she 1) having ≥ 6 years of education; 2) No complaints of cognitive decompensation and which confirmed by objective evidence (a neuropsychological battery); 3) who understood and agreed to participate in this study and signed the informed consent form.

Exclusion criteria of all the subjects

1) Comorbid tumors, serious heart, liver, kidney, hematologic disorders or infectious diseases; 2) previous other neurological disorders such as cerebrovascular disease, Parkinson's syndrome, epilepsy, dementia from various causes; 3) previous psychiatric disorders such as anxiety, depression, schizophrenia, etc. 4) severe visual and hearing impairment; 5) a history of drug and alcohol abuse/addiction; 6) presence of contraindication to MRI and contraindication to TMS treatment (e.g., pacemaker, cardiac stent, artificial heart valve, fixed plate after fracture surgery, etc.

Exclusion, Withdrawal, and Dropout Criteria

(1) Exclusion Criteria

Misdiagnosis or inclusion of ineligible participants

Participants who deviate from the treatment protocol during the intervention

Participants who do not complete the entire course of the clinical trial, resulting in incomplete data that may affect efficacy or safety assessment.

(2) Dropout Criteria

Participants lost to follow-up during the course of the clinical trial

Participants who voluntarily withdraw from the study due to lack of efficacy, adverse reactions, or other reasons.

(3) Termination Criteria

Termination of the trial is decided by the participants and investigators when severe adverse reactions occur during the treatment process.

Significant protocol errors or deviations occur during the trial, making it difficult to evaluate clinical efficacy.

Participants develop other diseases or serious complications during the treatment period, requiring treatment or rescue measures that may affect the study protocol.

(4) Withdrawal Criteria:

Participants request to withdraw from the clinical research.

Inability to complete the required assessments, resulting in data collection being compromised.

Participants receive unauthorized additional treatment during the study period.

Participants develop other diseases or serious complications during the treatment period, requiring treatment or rescue measures that may affect the study protocol.

Test grouping

Patients with aMCI will be randomly allocated (1:1) to groups receiving either ccPAS or sham stimulation by personnel external to the clinical team using a computer-based algorithm.

Research process

This study is mainly divided into three parts. First, identify the stimulation

targets related to long-term delayed recall; Second, intervene the stimulation target and observe the effect in patients with aMCI; Third, explore the relationship between the clinical efficacy and function of the stimulated brain region. Specifically, it is divided into the following six points: 1. In 21 healthy controls, the "cortex-hippocampus" network with white matter fiber connection will be identified based on probabilistic fiber tracking and segmentation techniques; 2. In the white matter based "cortex-hippocampus" network, identify the long-term delayed recall related to "cortex-hippocampus" functional connectivity in 42 patients with aMCI, and select the most relevant functional connectivity that TMS can stimulate as the stimulation target. 3. 42 patients with aMCI will be randomly divided into two groups (treatment group and sham stimulation group), and the stimulation targets on individual space will be calculated in each subject. 4. The TMS protocol and the sham stimulation protocol will be implemented in patients with aMCI. 5. The changes of cognitive function between the sham stimulation group and the treatment group before and after intervention will be compared. 6. The changes of fMRI between the sham stimulation group and the treatment group before and after intervention will be compared, as well as the impact of the changes on cognitive function.

ccPAS Procedure

Treatment will be delivered with a MagPro X100 stimulator equipped with the B70 fluid-cooled coil (MagVenture). The maximum surface magnetic field intensity of the coil is 4.2T. All patients will receive 10 interventions (5 times a week for two weeks). Each patient's resting motor threshold (RMT) will be determined in accordance with standard clinical practice.

Treatment group: two B70 fluid-cooled coils will be needed for the ccPAS in left prefrontal lobe and left precuneus. The ccPAS consisted of 5-Hz stimulation and a total of 900 pairs pulses, the interval of each pair stimulation at two stimulation targets is 2ms. First, 80% RMT will be given to the left prefrontal lobe, and then 120% RMT will be given to the left precuneus. Five times a week for two consecutive weeks.

Sham stimulation group: the two coils will be placed vertically on the scalp of the patients, and the stimulation parameters will be the same as those in the treatment group. The sound generated by the coil simulating, and the method has virtually no effect on the cerebral cortex. Other parts are the same as the treatment group**.**

Outcome

1. The primary outcome is change from baseline in long-term delayed recall performance (Delta AVLT_N5) following the ccPAS intervention compared with the sham stimulation group.

2. Secondary outcome measures is also recorded as the primary outcome, included MMSE, other AVLT items, STT, SDMT, BNT, CFT. In exploratory analyses, we will assesse the relationship of changes in cognitive performance and FC.

Statistical analysis

SPSS 21.0 (SPSS Inc., Chicago, Illinois) software will be used for statistical analysis in clinical data. The statistical description of measurement data is expressed by mean ± standard deviation. The comparison of the two groups of mean: when it conforms to the normal distribution and homogeneity test of variance, the independent sample t test is used.

The stimulation targets related to long-term delayed recall will be identified by analyzing the relationship between FC of “cortex-hippocampus” circuit and AVLT long delayed memory performance in aMCI patients. Using the left hippocampus as the seed point, ROI based FC analysis to the cortical brain area of the “cortex-hippocampus” network will be calculated. A generalized linear model will be constructed with AVLT_N5 score as dependent variable and every FC value of left “hippocampus-cortex” network as independent variable.

The repeated measurement ANOVA will be performed in comparison between the treatment group and sham stimulation group before and after treatment, the test of intra subject effect will be corrected by Greenhouse-Geisser, and the post test will be performed by LSD method. Effect sizes (Cohen’s d) will be interpreted as small = 0.2, medium = 0.5, large = 0.8. Non parametric test shall be adopted when it does not

conform to normal distribution or homogeneity of variance. The counting data will be expressed by frequency/rate, and the comparison between the two groups will be made by chi square test or Fisher exact probability method. The $p < 0.05$ (two-sided) indicates significant statistical difference. GraphPad Prism 6 will be used for drawing.

The statistical analysis of magnetic resonance data will be carried out using Matlab2013b, SPM12, GRETNA and the Resting State fMRI Data Analysis Toolkit (REST version 1.8). The flexible factorial of the second order analysis will be used to design the statistical matrix, and the three factors of subjects, grouping and time are set, in which grouping and time are fixed factors, and the number of subjects is random factors, and then the main effect and grouping× the time interaction matrix are set respectively for statistical analysis, and then post hoc analysis will be done. The results will be reported using bspmview software, and the names of brain regions will be referred to AAL template. BrainNetView and GraphPad Prism 6 are used for drawing. For correlation analysis, a generalized linear model will be fitted with the delta AVLT_N5 as the dependent variable and the delta FC value between left hippocampus and left precuneus as independent variables, using age and years of education as covariates.