Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 487-497

Alzheimer's & Dementia

Featured Article

Gamma rhythm low field magnetic stimulation alleviates neuropathologic changes and rescues memory and cognitive impairments in a mouse model of Alzheimer's disease

Junli Zhen[a,b,c,d,1], Yanjing Qian[a,b,c,1], Xiechuan Weng[e,1], Wenting Su[c], Jianliang Zhang[a], Lihui Cai[f], Lin Dong[a,b,c], Haiting An[a,b,c], Ruijun Su[a,b,c], Jiang Wang[f], Yan Zheng[b,c,g,*], Xiaomin Wang[a,b,c,**]

[a]*Department of Neurobiology, Capital Medical University, Beijing, China*
[b]*Key Laboratory for Neurodegenerative Disorders of the Ministry of Education, Capital Medical University, Beijing, China*
[c]*Beijing Institute for Brain Disorders, Beijing, China*
[d]*The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China*
[e]*Department of Neurobiology and State Key Laboratory of Proteomics, Beijing Institute of Basic Medical Sciences, Beijing, China*
[f]*School of Electrical Engineering and Automation, Tianjin University, Tianjin, China*
[g]*Department of Physiology, Capital Medical University, Beijing, China*

Abstract

Introduction: The abnormal amyloid β (Aβ) accumulation and Aβ-related neural network dysfunction are considered central to the pathogenesis of Alzheimer's disease (AD) at the early stage. Deep-brain reachable low field magnetic stimulation (DMS), a novel noninvasive approach that was designed to intervene the network activity in brains, has been found to alleviate stress-related cognitive impairments.

Methods: Amyloid precursor protein/presenilin-1 transgenic mice (5XFAD) were treated with DMS, and cognitive behavior and AD-like pathologic changes in the neurochemical and electrophysiological properties in 5XFAD mice were assessed.

Results: We demonstrate that DMS treatment enhances cognitive performances, attenuates Aβ load, upregulates postsynaptic density protein 95 level, and promotes hippocampal long-term potentiation in 5XFAD mouse brain. Intriguingly, the gamma burst magnetic stimulation reverses the aberrant gamma oscillations in the transgenic hippocampal network.

Discussion: This work establishes a solid foundation for the effectiveness of DMS in treating AD and proposes a future study of gamma rhythm stimulation on reorganizing rhythmic neural activity in AD brain.

Keywords: Alzheimer's disease; Deep-brain reachable low field magnetic stimulation; Treatment; Aβ; Gamma oscillations; Animal model

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder in elderly people and is the main cause of approximately two of three cases of dementia [1]. Extracellular amyloid β (Aβ) assemblies, which result in senile plaques, are considered to be the pathologic hallmark of AD [2]. Because the neuronal hyperactivity and aberrant

Conflict of interest: The authors declare no competing interests.

[1]These authors contributed equally to this work.

*Corresponding author. Tel.: +86-10-83911829; Fax: +86-10-83911494.

**Corresponding author. Tel.: +86-10-83911707; Fax: +86-10-63291984.

E-mail address: zhengyan@ccmu.edu.cn (Y.Z.), xmwang@ccmu.edu.cn (X.W.)

http://dx.doi.org/10.1016/j.trci.2017.07.002

network function occur at an early stage of pathologic alterations even before the formation of Aβ positive plaques, they are thought to be crucial events leading to mild cognitive impairment or AD [3–12]. As such, noninvasive methods aimed to restore both integrity and function of specific neural network are emerging as a useful new therapeutic tool to supplement or replace most drugs that were designed to clear Aβ deposits from brains of patients with AD, but failed in clinical trials because of toxicity and/or limited efficacy [13,14].

Transcranial magnetic stimulation (TMS) has been introduced to study brain function several decades ago [15]. Recently, magnetic stimulation was applied in clinic to treat brain diseases, for example, depression, stress, AD, and other neurodegenerative diseases [16–18]. Although TMS demonstrated symptomatic improvement in patients with AD [19–23], the underlying mechanisms remain elusive. Moreover, there is an increasing need to develop more portable and safer alternative magnetic devices for AD and other neurodegenerative disorders. Deep-brain reachable low field magnetic stimulation (DMS) was therefore developed in response to this need. This method generates a magnetic field with output pulses of higher-frequency, lower-intensity, and wider scope. As a noninvasive approach, DMS affects brain structures in a deep layer, such as the hippocampus, an area critical for learning and memory and principally impaired at the very early stage of AD. In fact, DMS promoted hippocampal neurogenesis and neuroplasticity in a stress rodent model [24]. Together, increasing evidence implies that DMS has potential protective effects on AD brains. Therefore, in this study, we sought to investigate the possible impact of DMS on AD in a mouse model of the disease.

Aβ precursor protein/presenilin-1 double-transgenic mice (5XFAD), which can rapidly develop Aβ deposition and AD-like behaviors, were used in the present study to evaluate effects of DMS on AD. We found that DMS treatment for 8 weeks improved cognitive performances, reduced amyloid burden, and restored the loss of a prime synaptic protein, that is, postsynaptic density protein 95 (PSD95), in the cortex and hippocampus of the transgenic mice. Parallel with these results, DMS reinstated the long-term potentiation (LTP) in the hippocampus of 5XFAD mice. Remarkably, the AD-relevant neuronal gamma oscillations in the hippocampus of 5XFAD mice were reversed by gamma burst magnetic stimulation. These results indicate that DMS is effective in alleviating symptoms of a rodent model of AD and might be a novel noninvasive therapeutic strategy for AD.

2. Methods

2.1. Animals and equipment

Amyloid precursor protein/presenilin-1 double transgenic mice (5XFAD; 006554, Jackson Laboratory) aged 4 months were used in this study. The use and care of animals were in strict accordance with the Chinese regulations involving animal protection and were approved by the Animal Ethics Committee of the Capital Medical University. All mice used in the study were female because of more severe and early AD-like phenotypic changes in female than male mice.

The magnetic equipment (designed and made by Beijing Aldans Biotech Co, Ltd), including two 360 mm-diameter coils, was connected to a magnetic field generator and outputs a time-varying magnetic field. Every 2-second output was composed of several rhythmical trains spiking in intervals of 27, 25, 23, 21, or 19 ms and formed the intermittent gamma burst stimulation at 30 to 40 Hz. The train was composed of six pulses with 130 μs width and 1000 Hz frequency. These 2-second runs were separated by an 8-second resting interval. Moreover, the shape of magnetic fields was changed every 4 minutes (between linear gradient and approximate distribution), and the rhythm was gradually increased every 8 minutes (30, 32.25, 34.5, 37, and 40 Hz). Successive trains of DMS for 40 minutes were administered daily for continuous 8 weeks. Female 5XFAD mice and their littermates aged 4 months were randomly divided into four groups: wild-type (WT) and 5XFAD mice treated with sham magnetic field or DMS. The specific parameters were set up based on a previous study [24]. Mice in their cages without metal covers were placed between the DMS coil pairs (Fig. 1A).

2.2. Behavioral assessment

Behavioral tests were carried out 24 h after the last DMS treatment, when the mice were aged 6 months. The following behavioral tasks were sequentially performed: novel object recognition, open field tests, and morris water maze (MWM). There was a 1-day interval between tasks. All experiments were performed during a period from 9 AM to 5 PM. The experimenters were blinded to the treatment of animals. For novel object recognition test, mice were allowed to explore one familiar object and one novel object for 5 minutes. The number of novel object contacting and novel object recognition index (time for novel object/time for familiar object + time for novel object) was calculated. Animals were observed for 30 minutes to assess locomotor function in open field test.

In MWM test, mice were habituated in a circular swimming pool (1.2 m in diameter) containing a visible platform. The consecutive 5-day training was performed and the escape latency was recorded. A probe trial (60 second) with withdrawal of the platform 24 hour after the last training was applied, and the number of crossing the original platform and swimming time spent in the target quadrant were recorded by a video tracking system (for details, see Supplementary Materials and Methods).

2.3. Histology and staining

After completion of the behavioral tests, mice were anesthetized by an intraperitoneal injection of 6% chloral hydrate (400 mg/kg) and perfused transcardially with cold saline.