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Original Research

Repetitive Transcranial Magnetic Stimulation Decreases Serum Amyloid-β and Increases Ectodomain of p75 Neurotrophin Receptor in Patients with Alzheimer's Disease

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Abstract

Background: This study investigated the impact of repetitive transcranial magnetic stimulation (rTMS) on serum levels of Amyloid-β (Aβ) as well as the ectodomain of p75 neurotrophin receptor (p75ECD) in patients with Alzheimer's disease (AD). **Methods**: A total of 46 patients diagnosed with AD between June 1, 2020 and December 31, 2021 were randomized to undergo either 20 Hz rTMS treatment of the left dorsolateral prefrontal cortex (DLPFC) or sham procedure. Cognitive function and activity of daily living were evaluated. Neuropsychological tests and blood samples were gathered at baseline and at 2, 3, 4, and 6 weeks after rTMS therapy. **Results**: There were no evident differences between rTMS group and sham group in serum Aβ40, Aβ42, total Aβ, ApoE, and p75ECD standards at baseline ($p > 0.05$). Serum levels of Aβ40, Aβ42, as well as total Aβ, were significantly lower in the rTMS group at 3, 4 and 6 weeks relative to the sham group ($p < 0.05$). Serum p75ECD levels in the rTMS group were significantly higher than those of the sham group at 3, 4 and 6 weeks ($p < 0.05$). Levels of serum Aβ40 (r: –0.78, –0.83, –0.68, respectively), Aβ42 (r: –0.76, –0.76, –0.61, respectively) and total Aβ (r: –0.74, –0.81, –0.66, respectively) were negatively correlated with MoCA, MMSE and MBI scores, while serum p75ECD levels (r: 0.84, 0.90, 0.72, respectively) were positively correlated ($p < 0.01$). The level of serum Aβ40 (r = 0.77), Aβ42 (r = 0.69) as well as total Aβ (r = 0.73) were positively correlated with ADAS-cog score, while p75ECD levels (r = –0.86) were negatively correlated ($p < 0.01$). **Conclusions**: The results of this study suggest that rTMS may decrease serum Aβ levels and increase serum p75ECD levels in patients with AD, offering insight into a potential underpinning mechanism of rTMS.

Keywords: Alzheimer's disease; repetitive transcranial magnetic stimulation; Amyloid-β; ectodomain of p75 neurotrophin receptor

1. Background

Alzheimer's disease (AD) is the most common form of dementia, affecting over fifty million people worldwide and making up 50%–75% of all dementias with an incidence roughly doubling every five years after 65 years of age [1]. The disease deprives people of their independence, and is estimated to be a main leading cause of death globally [2,3]. A number of risk factors, including older age, diabetes, hypertension and apolipoprotein E (ApoE) genotype are associated with an increased risk of developing AD [4–6]. Despite keen interest in the development of disease-modifying drugs for AD, treatments available are largely palliative in nature. The commonly used pharmacological treatments improve cognitive function in AD in only a limited fashion [7].

Noninvasive brain stimulation interventions have demonstrated satisfactory outcomes in clinical trials of AD. Ahmed *et al*. [8] showed that repetitive transcranial magnetic stimulation (rTMS) could improve cognitive function in patients with AD. More recent research showed that rTMS (20 Hz) at the left dorsolateral prefrontal cortex (DLPFC) could improve cognitive function in patients with AD [9,10]. These findings suggest rTMS as a potentially beneficial intervention for cognitive rehabilitation in AD with a good safety profile. However, the mechanism by which rTMS improves cognitive functions is at present poorly understood. Animal experiment has indicated that rTMS can reverse abnormal levels of Aβ1–42 in rats with memory impairment [11]. Amyloid-β (Aβ) peptides are known to play a vital role in the pathogenesis of AD. We previously found that the soluble ectodomain of p75 neurotrophin receptor (p75ECD) can inhibit the aggregation of Aβ and block Aβ induced neurotoxicity [12,13]. These studies suggest that p75ECD release is an essential neuroprotective factor in AD. Therefore, regulating the level of Aβ and p75ECD in the brain has significant therapeutic value, particularly through noninvasive and safe methods.

This paper aims to characterize serum levels of Aβ and p75ECD in gerontal patients with AD before and after rTMS treatment. The results of this study may provide deeper insights into the mechanisms underpinning rTMS treatment in patients with AD.

2. Methods

2.1 Subjects

From June 1, 2020, to December 31, 2021, patients diagnosed with AD at the rehabilitation department or neurology department of the Chongqing Daping Hospital were recruited to participate in our study. AD was diagnosed by a senior neurologist following a previously described protocol [14]. All patients participating in the study underwent MRI examination. Dementia was diagnosed according to criteria modified from the Diagnostic Statistical Manual IV (DSM-IV), and AD was diagnosed according to the standard of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association [15–18]. Exclusion criteria included, those who refuse to participate in the study, serious physical illness (such as liver or kidney dysfunction, or severe cardiovascular illness), history of neurological diseases (such as epileptic disorders, seizures, brain tumors or trauma), mental illnesses (such as depression, schizophrenia or delirium), Mini-Mental State Examination (MMSE) value of 0–10, and patients who were not suitable for rTMS treatment (such as those with cardiac pacemakers or other metallic bodily implants). Patients were randomized using a random table number and received either rTMS or sham treatment.

2.2 Standard Protocol Approval, Registration, and Patient Consent

The institutional reviewing committee of Chongqing Daping Hospital approved the research, and all patients and their caregivers provided written informed consent.

2.3 Baseline Screening

For clinical assessment, case histories were gathered from patient medical records, and data on current medication use was obtained via formal questionnaire. Collected patient information included age, gender, educational level, hypertension, hypercholesterolemia, coronary artery illness, history of stroke, diabetes mellitus, as well as osteoporosis. All comorbidities were diagnosed using the international classification of diseases, 10th revision (ICD-10-CM).

2.4 Cognitive Function Assessment

We used the mini-mental state examination (MMSE), Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), and the Montreal cognitive assessment (MoCA) as assessments of cognitive function. Activity of daily living was assessed by modified Barthel index (MBI). These scales were administered according to our previous protocol [14]. Cognitive function and activity of daily living were estimated at baseline and at 2, 3, 4, and 6 weeks after rTMS therapy. All cognitive assessments were conducted by a trained neuropsychologist who had no knowledge of participants' treatment assignment throughout the study course.

2.5 Administration of rTMS

Patients in the rTMS group received rTMS to the left DLPFC for an uninterrupted session of 20 minutes. The figure-of-eight coil was placed over the F3 point according to the International 10/20 EEG system to target the left DLPFC. Each patient underwent sessions of rTMS (20 Hz and pulses at 100% resting motor threshold intensity) five times a week for six weeks, using the rTMS system (Yiruide Medical Equipment New Technology Co., Ltd, Wuhan, China). Within each session, 2 s of stimulation was followed by a 25 s gap, with a total of 1760 pulses per session. In the sham group, an identical coil was placed on the patient, but no magnetic stimulation was administered, and the patients heard the same voice recordings as those used for patients receiving rTMS. All patients received donepezil treatment (5–10 mg/day depending on the severity of the disease).

2.6 ELISA Assays of Serum Aβ, ApoE and p75ECD

Levels of serum Aβ40, Aβ42, ApoE and p75ECD of both cohorts were tested by enzyme-linked immunosorbent assay (ELISA) at baseline and at 2, 3, 4, and 6 weeks after rTMS treatment. Serum Aβ40 and Aβ42 levels were determined using an ELISA kit (Covance, Emeryville, CA, USA). Serum levels of p75ECD were determined using a human nerve growth factor receptor ELISA kit (R&D, Minneapolis, MN, USA). Levels of ApoE were determined using a human ELISA kit (Invitrogen, Carlsbad, CA, USA). All ELISA assays were conducted according to manufacturers' instructions. The sample and standard were in duplicate, and the mean value was taken for data analysis.

2.7 Statistical Analysis

Student's T-test or one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to analyze the normally distributed baseline continuous data. Non-normally distributed data were represented as the median $\pm$ quartile and the Wilcoxon paired signed rank-sum test was used for intra-group comparison. Categorical data were analyzed using the χ^2 test or Fisher's exact test. Pearson or Spearman correlation analysis was performed on the correlation between Aβ level, P75ECD level and cognitive function scores. The differences were considered statistically significant at $p < 0.05$. Statistical analyses were carried out using SPSS 20.0 software (IBM Corp., Chicago, IL, USA).

3. Results

Initially, 50 patients were screened for eligibility. One refused to participate, and a further three were excluded due to severe physical disease, cardiac pacemaker or other metal implant. Of the 46 eligible AD patients, 23 were randomly assigned to the rTMS treatment group and the other 23 were randomly assigned to the sham (non-rTMS) group. Hereafter, no patients dropped out from the study for its 6-week duration. Thus, 46 patients were included in the final statistical analysis. A summary schematic of patients' participation is shown in Fig. 1.

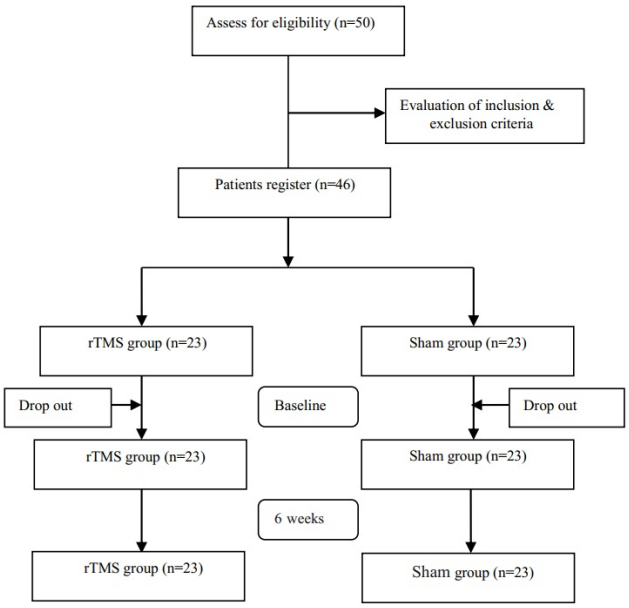

Fig. 1. A summary of the patients' participation in the study. rTMS, repetitive transcranial magnetic stimulation.

3.1 Baseline Patient Characteristics

The baseline clinic data of all patients are shown in Table 1. At baseline, there were no significant differences between the rTMS group and the sham group in terms of age, sex, body mass index, education level, comorbidities, drug treatment, and cognition assessment scores ($p > 0.05$) (Table 1).

3.2 Changes in Serum Levels of Aβ, ApoE and p75ECD

Differences in serum Aβ, ApoE, and p75ECD levels at 2, 3, 4 and 6 weeks from baseline are shown in Table 2. There were no statistically significant differences between the rTMS group and sham group at baseline in any serum levels measured ($p > 0.05$). No statistically significant differences were found in serum ApoE level between the two groups at any time point of the study ($p > 0.05$). One-way ANOVA revealed statistically significant differences between the two groups for serum levels of Aβ40, Aβ42, total Aβ and p75ECD at baseline and 2, 3, 4 and 6 weeks. The rTMS group showed significantly reduced levels of Aβ40, Aβ42 and total Aβ, as well as increased p75ECD levels, relative to sham at 3, 4 and 6 weeks ($p < 0.05$ throughout).

3.3 Changes in Cognitive Function Scores over Time

Differences in cognitive function scores at each measurement time point from baseline are shown in Fig. 2. At week 6, the rTMS group showed a statistically significant improvement in MoCA, MMSE and MBI scores relative to sham group ($p < 0.05$) (Fig. 2A,B,D). Meanwhile, ADAS-cog score was significantly lower in the rTMS group at week 6 relative to sham group ($p < 0.05$) (Fig. 2C).

3.4 Correlation of Cognitive Function Score with Serum Aβ and P75ECD

Serum Aβ40, Aβ42 and total Aβ were found to be strongly negatively correlated with serum p75ECD ($r = -0.67$, $p < 0.01$; $r = -0.74$, $p < 0.01$; $r = -0.72$, $p < 0.01$; respectively). Furthermore, serum levels of Aβ40, Aβ42 and total Aβ were negatively correlated with MoCA, MMSE and MBI scores, while correlating positively with ADAS-cog score ($p < 0.01$ throughout; Table 3). In contrast, serum levels of p75ECD were positively correlated with MoCA, MMSE and MBI scores, while correlating negatively with ADAS-cog score ($p < 0.01$ throughout; Table 3).

4. Discussion

In studying the impact of rTMS on cognitive function in patients with AD, we measured serum levels of Aβ40, Aβ42, ApoE and p75ECD, as well as conducting neuropsychological evaluations, in all patients at each measurement time point from baseline. It was shown that serum levels of Aβ40, Aβ42 and total Aβ were significantly lower in the rTMS group compared to the sham group at 3, 4 and 6 weeks. In contrast, serum p75ECD levels in the rTMS group increased over the treatment period, and were significantly higher compared to the sham group at 3, 4 and 6 weeks. In addition, we found that serum levels of Aβ40, Aβ42 and total Aβ were significantly negatively correlated with MoCA, MMSE and MBI scores, while the serum level of p75ECD correlated positively. The levels of serum Aβ40, Aβ42 and total Aβ were positively correlated with ADAS-cog score, while the serum level of p75ECD correlated negatively. These findings suggest that rTMS may improve neuropsychological functioning in patients with AD, as well as supporting the notion that the associated mechanism may involve the modulations of levels of both serum Aβ and p75ECD. This paper offers new hypotheses for furthering the understanding of the mechanism underpinning rTMS, as a tool with potential applications for the clinical treatment of AD as well as for the identification of novel therapeutic targets.

There remains a lack of effective pharmacological or psychosocial interventions for AD and related dementias.

Table 1. Baseline patient characteristics.

Characteristics	rTMS group (n = 23)	Sham group (n = 23)	*p*
Demographics			
Age, years ± SD	67.8 ± 5.4	68.9 ± 4.9	0.473
Female, n (%)	12 (52.2)	13 (56.5)	0.767
BMI, kg/m^2 ± SD	23.9 ± 3.8	24.0 ± 3.1	0.922
Educational level, years ± SD	4.7 ± 2.1	4.6 ± 3.4	0.905
Comorbidities			
Hypertension, n (%)	8 (34.8)	7 (30.4)	0.753
Hyperlipidemia, n (%)	5 (21.7)	3 (13.0)	0.436
Diabetes, n (%)	6 (26.1)	2 (8.7)	0.119
Coronary artery disease, n (%)	3 (13.0)	2 (8.7)	0.520
History of stroke, n (%)	3 (13.0)	7 (30.4)	0.108
Osteoporosis, n (%)	6 (26.1)	8 (34.8)	0.521
Drug treatment			
Donepezil, mg ± SD	8.3 ± 2.9	8.2 ± 2.4	0.899
Cognition assessment			
MoCA score ± SD	16.0 ± 2.1	15.9 ± 2.3	0.878
MMSE score ± SD	13.8 ± 1.9	14.0 ± 1.8	0.715
ADAS-cog score ± SD	28.0 ± 3.2	27.4 ± 3.5	0.547
MBI score ± SD	80.0 ± 4.1	78.9 ± 5.9	0.467

Abbreviations: BMI, body mass index; SD, standard deviation; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; ADAS-cog, Alzheimer's disease assessment scale–cognitive subscale; MBI, modified Barthel index; rTMS, repetitive transcranial magnetic stimulation.

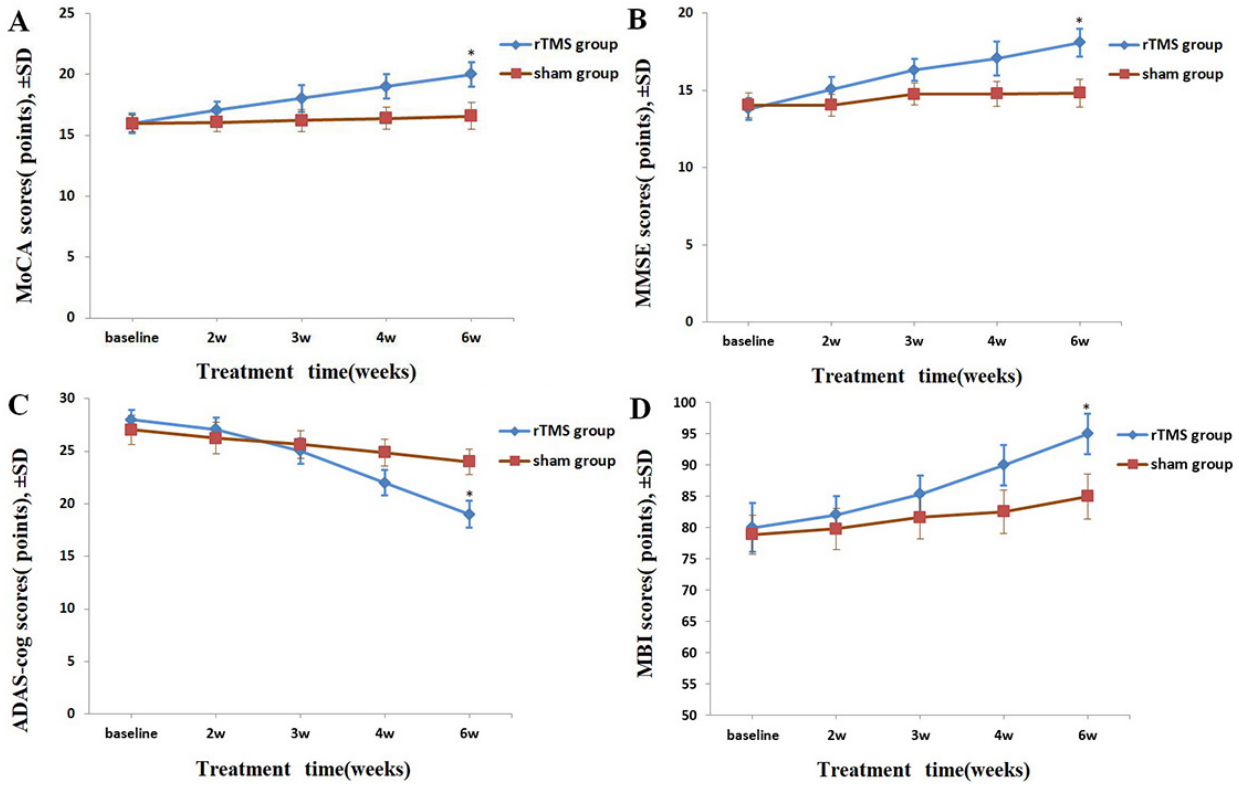

Fig. 2. Cognitive function and activity of daily living scores at baseline and study time points for the two groups. Cognitive function of patients with AD was assessed using MoCA, MMSE, ADAS-cog and MBI scores. (A) Changes in MoCA score. (B) Changes in MMSE score. (C) Changes in ADAS-cog score. (D) Changes in MBI score. *$p < 0.05$, rTMS group versus sham group. Abbreviations: MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; ADAS-cog, Alzheimer's disease assessment scale–cognitive subscale; MBI, modified Barthel index; SD, standard deviation.

Table 2. Changes of serum indexes at baseline, 2, 3, 4 and 6 weeks in the rTMS and sham groups.

Parameter	Group (n)	Baseline visit	2 weeks	3 weeks	4 weeks	6 weeks
ApoE (mg/L), ±SD	rTMS (23)	35.41 ± 14.23	35.34 ± 13.79	34.28 ± 13.49	34.22 ± 13.65	33.49 ± 13.04
	Sham (23)	35.48 ± 14.21	35.51 ± 14.26	35.43 ± 14.08	35.49 ± 13.98	35.58 ± 13.99
Aβ 40 (pg/mL), ±SD	rTMS (23)	94.41 ± 43.92	93.99 ± 43.08	70.55 ± 29.99^{ab}	69.74 ± 29.04^{ab}	68.13 ± 28.13^{ab}
	Sham (23)	92.38 ± 41.72	92.11 ± 40.98	92.37 ± 41.38	91.23 ± 41.27	90.19 ± 40.98
Aβ 42 (pg/mL), ±SD	rTMS (23)	62.76 ± 36.26	60.85 ± 35.88	42.71 ± 20.99^{ab}	41.68 ± 21.83^{ab}	40.16 ± 21.44^{ab}
	Sham (23)	60.88 ± 35.46	60.01 ± 35.26	60.81 ± 35.49	59.94 ± 36.58	60.32 ± 34.88
Total Aβ (pg/mL), ±SD	rTMS (23)	157.17 ± 62.87	154.84 ± 61.92	113.26 ± 60.88^{ab}	111.42 ± 60.32^{ab}	108.29 ± 59.83^{ab}
	Sham (23)	153.26 ± 64.39	152.12 ± 64.75	153.18 ± 63.91	151.17 ± 65.32	150.51 ± 69.48
p75ECD (pg/mL), ±SD	rTMS (23)	50.12 ± 21.21	51.24 ± 22.26	68.18 ± 28.17^{ab}	70.26 ± 29.56^{ab}	73.88 ± 30.14^{ab}
	Sham (23)	52.33 ± 22.34	53.01 ± 21.35	53.28 ± 20.37	53.68 ± 23.45	53.36 ± 24.77

$^{a}p < 0.05$ in comparison to baseline measurements; ^{b} $p < 0.05$ in comparison to sham group; SD, standard deviation; rTMS, repetitive transcranial magnetic stimulation.

Table 3. The correlation of neuropsychological evaluation with serum Aβ and p75ECD.

	Aβ40		Aβ42		Total Aβ		p75ECD	
	r-value	*p*-value	r-value	*p*-value	r-value	*p*-value	r-value	*p*-value
MoCA	–0.78	<0.01	–0.76	<0.01	–0.74	<0.01	0.84	<0.01
MMSE	–0.83	<0.01	–0.76	<0.01	–0.81	<0.01	0.9	<0.01
ADAS-cog	0.77	<0.01	0.69	<0.01	0.73	<0.01	–0.86	<0.01
MBI	–0.68	<0.01	–0.61	<0.01	–0.66	<0.01	0.72	<0.01

Abbreviations: MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; ADAS-cog, Alzheimer's disease assessment scale–cognitive subscale; MBI, modified Barthel index.

Thus, there is an urgent need to investigate novel therapeutic approaches, one of which is neuromodulation. Current evidence suggests that rTMS is a non-invasive, safe and effective strategy for AD treatment [19,20]. Recent research has demonstrated the impact of inhibitory rTMS of the prefrontal cortex on memory in patients with AD. Turriziani *et al*. [21] found that inhibition of the right DLPFC by rTMS improved recognition as well as memory function in patients with AD. In a study of 131 AD patients between 60 and 90 years of age, Sabbagh *et al*. [22] showed that patients treated with rTMS showed improvements relative to those undergoing sham procedures. In a meta-analysis of randomized controlled trials of rTMS in AD, Wang *et al*. [23] found a treatment benefit for patients with mild-to-moderate AD. More recently, Li *et al*. [9] showed significant recovery of cortical plasticity in patients with AD receiving rTMS compared to a cohort receiving pseudo-stimulation, which not only supports the clinical use of rTMS for the treatment of AD, but also provides potential clinical biomarkers for the assessment of cognitive function changes. These studies suggest that rTMS holds important therapeutic benefits for patients with AD.

While rTMS has been applied in the treatment of AD, its mechanism remains unclear. Aβ is one of the main causes of cognitive impairments in AD patients. Soluble Aβ40 and 42 have been shown to be decreased in cerebrospinal fluid (CSF) [24] and increased in the peripheral blood [25,26] of patients with AD.Though rTMS has been acknowledged to alter cortical excitability as well as modulating cognitive activity, it remains unclear whether rTMS can reverse Aβ-mediated cognitive decline in AD patients. Few experimental animal studies focus on the potential effects of Aβ in AD after rTMS treatment [11,27]. In a recent study exploring the mechanism of high-frequency rTMS treatment on AD mice, it was found that rTMS could not only effectively improve memory, but also inhibit the production of Aβ [27]. Similar findings came from another study in rats, wherein rTMS reversed Aβ1–42 related memory impairment [11]. Such findings indicate that the underlying mechanisms may be related to rTMS-induced decrease in Aβ neuropathology. However, further study is necessary to further elucidate these mechanisms.

Whether and how the serum levels of p75ECD change in patients with AD after rTMS treatment is not well documented. Neurotrophin receptor p75 is an Aβ receptor that mediates Aβ-induced neurodegenerative signaling. p75ECD is a recombinant human protein recently developed as a new target for the treatment of AD [28]. Previous study has demonstrated that p75ECD is a physiological protective factor against Aβ in AD patients [29]. Jiao *et al*. [26] identified a distinct p75ECD profile in AD, characterized by a decreased CSF level and an increased serum level, when compared with subjects with Parkinson's disease, stroke, and with healthy elderly controls. Our present study suggests that rTMS can increase the level of serum p75ECD in patients with AD, but how rTMS regulates the level of p75ECD is unclear.

Whether rTMS regulates the core pathogenetic biomarkers in patients with AD, and what the potential mechanisms of that are, is still unclear. The extracellular signal-regulated kinase (ERK) 1/2 signaling pathway has been shown to be affected by rTMS. In a study of depression, it was found that rTMS promoted the proliferation of hippocampal neural stem cells by increasing the level of p-ERK1/2 [30]. In addition, magnetic stimulation promoted the proliferation of human amniotic membrane cells by activating the ERK1/2 pathway [31]. Tumor necrosis factor-convertase (TACE) is the key enzyme for p75ECD release, and its activation is achieved through phosphorylation modification. Moreover, ERK1/2 is considered a key upstream signal that regulates TACE phosphorylation [32]. Hence, we speculate that the ERK1/2 signal pathway is an important way by which rTMS regulates p75ECD release in AD.

In patients with AD, the ApoE polymorphism is the primary genetic factor related to a more aggressive clinical course. rTMS plays a potentially protective role in the prevention and treatment of AD by decreasing ApoE expression as well as promoting autophagic flux [33]. In clinical study of induced controlled brain disruption with rTMS as a model of brain injury and adaptation, ApoE polymorphism status was found to determine the effect of rTMS on distributed brain network performance [34]. In the present study, we found no distinctions in serum ApoE levels between the two study groups, however.

Our study had a number of limitations. First, the main limitation of the study is the lack of correction of multiple testing correction. Given this limitation, our results are probabilistic and these data require verification in further studies. Second, it has previously been reported that low versus high frequencies of rTMS differently impact cognitive function as well as cortical excitability in patients with AD [8]. This was not investigated in our study. Third, a recent study suggested that rTMS is related to clinical cognitive improvements in individuals with mild cognitive impairment (MCI) [35]. We did not evaluate the influence of rTMS on patients with MCI. In addition, we did not study the relationship between rTMS and different degrees of AD dementia. Fourth, it has been shown that rTMS mediates the secretion and expression of brain-derived neurotrophic factor (BDNF) as well as other proteins involved in the regulation of synaptic plasticity [36]. In addition, previous studies found that after rTMS APOE ε4-carriers showed significant changes in brain network activation [34]. The effect of rTMS on serum BDNF and APOE ε4-carriers were not investigated in our study. Finally, while additional valuable findings could come from the investigation of CSF levels of Aβ and P75ECD, we did not carry these tests out in our study.

5. Conclusions

Our results suggest that rTMS may decrease the serum levels of Aβ and increase the level of p75ECD in patients with AD, as well as improving cognitive function in AD. These findings offer insight into the mechanism of rTMS, as well as supporting the applications of rTMS for the clinical treatment of AD as well as for the identification of novel therapeutic targets.

Author Contributions

YT and BL—study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript; YZ, XF—study concept and design, acquisition of data; LL, DC—acquisition of data, analysis and interpretation of data; CG—study concept and design, study supervision, critical revision of manuscript for intellectual content.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Chongqing Daping Hospital, and all of the participants and their caregivers provided written informed consent. Ethical approval number of our study (Medical research ethics review (2018) No. 127).

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Conflict of Interest

The authors declare no conflict of interest.

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