Impact of twice-a-day transcranial direct current stimulation intervention on cognitive function and motor cortex plasticity in patients with Alzheimer's disease

Xingxing Li [1,2] Lei Chen,[3] Kunqiang Yu,[4] Wenhao Zhuang,[1,2] Hui Zhu,[3] Wenqiang Xu,[4] Hui Yan,[5] Gangqiao Qi,[5] Dongsheng Zhou,[1,2] Shaochang Wu[4]

ABSTRACT

Background Non-invasive brain stimulation has improved cognitive functions in patients with Alzheimer's disease (AD), and some studies suggest a close relationship between cognition and plasticity. However, the clinical benefits of transcranial direct current stimulation (tDCS) in patients still need to be evaluated.

Aims This study examined the role of tDCS in improving cognition and whether the improved cognition is related to altered cortical plasticity.

Methods 124 patients with AD were randomly assigned to active tDCS (n=63) or sham tDCS (n=61). The tDCS was applied at the dorsolateral prefrontal cortex for 30 treatment sessions across 6 weeks (5 days per week, 2 days off). The Mini-Mental State Examination and the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) were used for cognition evaluation at baseline, week 2 and week 6. The cortical plasticity was represented by motor-evoked potential (MEP) measured with an electromyogram.

Results The results showed that multiple courses of active tDCS can improve the cognitive functions of patients with AD, especially in the memory domain (word recall, recall of test instructions and word recognition). In addition, the damaged MEP level was enhanced following active treatment. In the active tDCS group, the improvements in ADAS-Cog total and subitem (word recall and word recognition) scores were negatively correlated with the enhancement of MEP.

Conclusions Our research indicates for the first time that twice-a-day tDCS may improve the cognitive function of patients with AD. This study also suggests that cognitive dysfunction may be related to impaired cortical plasticity, which warrants mechanistic investigations of the relationship between cognition and plasticity in the future.

Trial registration number ChiCTR1900021067.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ At present, the treatment for Alzheimer's disease (AD) is mainly based on drugs; however, the efficacy remains limited.

⇒ Non-invasive brain stimulation technology has gradually been applied in clinical practice.

⇒ Transcranial direct current stimulation (tDCS) is a non-invasive technique, and the clinical benefits in patients with AD still need to be evaluated.

WHAT THIS STUDY ADDS

⇒ This study is the first to examine the improvement in cognitive function of patients with AD receiving tDCS twice daily; we aimed to elucidate the relationship between cognitive improvement and plasticity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results can demonstrate the effectiveness of tDCS treatment and the importance of cortical plasticity as an electrophysiological indicator in clinical practice.

⇒ The relationship between plasticity and cognition will also be studied in other cognitive impairments to demonstrate the importance and uniqueness of plasticity in cognition.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with an insidious onset and a chronic progressive course, resulting in persistent global cognitive decline in the consciousness state, and seriously affecting patients' quality of life.[1–3] Presently, the treatment for AD is mainly based on drugs. However, the efficacy remains limited. When considering the pharmacological treatment of older adults, we need to recognise that they generally have comorbidities and chronic diseases, each requiring one or more medications. The decline of all physiological functions in older people, their reduced metabolic capacity for drugs and their higher sensitivity to drugs predispose them to increased risk of adverse drug reactions.[4] In recent years, with advancements

in international electromagnetic physiology technology, non-invasive brain stimulation technology has gradually been applied in clinical practice. The observability and safety of its therapeutic effects have made this type of technology a research hotspot in the field of clinical neuropsychology.

Transcranial direct current stimulation (tDCS) is a non-invasive technique that regulates cortical neural activity by applying a constant, low-intensity (1–2 mA) direct current outside the skull. tDCS can affect cortical excitability in brain regions and trigger polarity-related changes in neuronal excitability.[5] A recent meta-analysis showed that tDCS could improve cognitive abilities, including behavioural performance and cognitive control in healthy people and those with mental illnesses such as depression, schizophrenia, etc.[6] Other studies on the impact of tDCS on patients with AD or mild cognitive impairment support the efficacy of tDCS in improving cognitive ability.[7 8]

Many studies have shown that in addition to the hippocampus and left inferior frontal gyrus, the frontal lobe also plays an important role in cognitive function in patients with AD. For example, its size shrinks, showing abnormal brain activity patterns or functional connectivity networks. This leads to internal neurotransmitter level disorder, thus presenting complex clinical symptoms such as abnormal emotional regulation and cognitive function decline.[9] In addition, studies of older patients have found that they rely more on the dorsolateral prefrontal cortex (DLPFC) in associative memory than the hippocampus. Ageing in patients with AD will also lead to cortical plasticity disorder of the DLPFC.[10] Therefore, stimulating the DLPFC and changing its excitability may reverse the plasticity of older patients, thereby improving their cognitive function.

The latest research shows that the therapeutic effect is enhanced when a physical intervention technique is implemented multiple times daily. For example, researchers have used intermittent theta burst stimulation (iTBS) 10 times daily for 5 consecutive days to respond to refractory depression.[11] In addition, a meta-analysis found that increasing the current density and treatment time of tDCS appropriately during the treatment of schizophrenia may produce better results, with twice a day being better than once a day.[12] Studies have shown that a single tDCS of 20 min has been shown to maintain a 70 min after-effect. Regarding electrophysiology, existing research suggests that this can selectively regulate synapses through spike-time-dependent plasticity (STDP), thereby affecting sustained oscillatory activity in the human cortex for a long time.[13] Therefore, when using electrophysiology to stimulate the cerebral cortex, better immediate effects (generated during the stimulation) and delayed effects (maintained after the stimulation period) are directly explored in AD.

Not only can repetitive transcranial magnetic stimulation (rTMS) be used as a therapeutic tool, but, combined with electromyography (EMG), it can also be used to measure many key neurophysiological cortical indices, such as motor threshold, cortical latency, central conduction time, wave amplitude, central resting period, and so on. We can also use single-pulse transcranial magnetic stimulation (TMS) to assess cortical excitatory/inhibitory deficits.[14] For example, some studies have found significant differences in the resting motor threshold (RMT) in patients with AD compared with other dementias, suggesting some connection between RMT and impairment of cognitive function.[15 16] Some studies have also shown that abnormalities in the RMT of the primary motor cortex (M1) can be observed in early AD even before it shows apparent problems, which may reflect changes in the underlying pathological M1.[17] In addition, it has also been found that improved cognitive function and changes in the motor evoked potential (MEP) values after treatment with high-frequency rTMS are positively correlated.[18] In other psychiatric disorders, a link between cognitive function and cortical plasticity has also been found by TMS-MEP in psychiatric disorders.[19] In summary, the present study also proposes to measure whether there is an association between cognitive function improvement and plasticity changes by transcranial magnetic stimulation-induced motor evoked potentials (TME-MEP) technology.

This study is the first to examine cognitive function improvement in patients with AD with tDCS twice daily. Through a randomised, double-blind and placebo-controlled clinical trial, we hypothesised that tDCS would improve cognitive function in patients with AD. We further hypothesised that treated patients with AD would show signs of normalisation of cortical plasticity compared with the sham group. Finally, we aimed to elucidate the relationship between cognitive improvement and plasticity. While these results can demonstrate the efficacy of tDCS, they are expected to demonstrate the importance of cortical plasticity as an electrophysiological indicator in clinical practice.

MATERIALS AND METHODS
Standard protocol approvals, registrations and patient consent
All patients or their guardians signed informed consent before enrolment. The first patient was enrolled on 1 January 2020. The study was registered with the Chinese Clinical Trial Registry (ChiCTR1900021067) at http://www.chictr.org.cn.

Design overview: sample size, randomisation and masking
In order to detect changes in the differences between two groups with sufficient statistical ability (the active stimulus group and the sham group), G*Power V.3.1 was used for calculation (moderate effects F=0.25, α=0.05, power=0.80). It was found that at least 34 participants were required for each group. Considering the loss of participants, this study sets a loss rate of 35%, so each group will eventually include at least 53 participants.
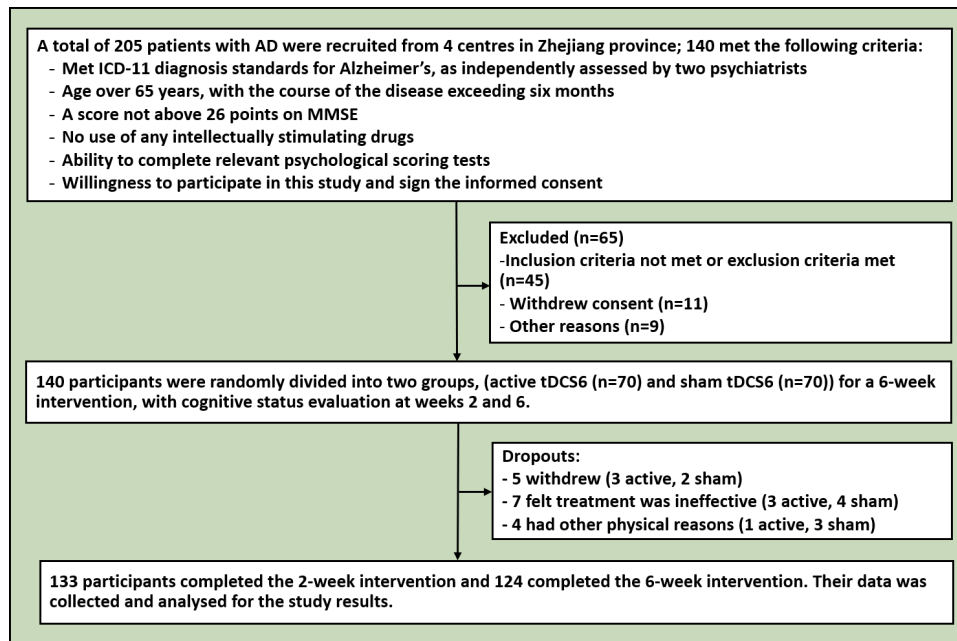
Figure 1 The CONSORT diagram of the primary phases of the clinical trial. AD, Alzheimer's disease; CONSORT, Consolidated Standards of Reporting Trials; ICD-11, International Classification of Diseases, 11 Edition; MMSE, the Mini-Mental State Examination; tDCS, transcranial direct current stimulation.

The Consolidated Standards of Reporting Trials chart for this clinical trial is shown in figure 1. A random list was generated through a computer simulator (number 1 or 2), and the patients were randomly divided into two groups (the tDCS active stimulation group and the sham group) based on the number (1 or 2).

All doctors and researchers were randomly divided into groups without patient contact. The patients received numbered stimulators and the machine was fixed during subsequent treatment. The operating nurse only provides stimulation to the corresponding numbered tDCS device based on the number extracted by the patient. All machines had the same appearance and size.

Study participants

All hospitalised AD patients came from four units in Zhejiang Province (Ningbo Kanging Hospital, the Second People's Hospital of Lishui, Taizhou Second People's Hospital and Yu Yao Third People's Hospital) from January 2020 to July 2022. They had to meet the following inclusion criteria: (1) Alzheimer's diagnosis according to the standards of the International Classification of Diseases-11th Edition, made independently by two psychiatrists; (2) age over 65 years, with the course of the disease exceeding 6 months; (3) a score not above 26 points on the Mini-Mental State Examination (MMSE); (4) no use of any intellectually stimulating drugs; (5) ability to complete relevant psychological scoring tests; and (6) willingness to participate in this study and sign informed consent.

The exclusion criteria included the following: (1) participation in previous or other current research projects, such as TMS, tDCS, transcranial alternating current stimulation (tACS) or other physical therapies; (2) the

placement of deep brain stimulation (DBS) electrodes in their brain; (3) other types of dementia, including vascular dementia and frontotemporal dementia; and (4) other accompanying mental illnesses, such as depression, schizophrenia, and so on.

Study intervention: tDCS

The stimulator model is TDCS-20A (Keyue, Xi'an, China). It provides 2 mA of stable direct current (DC) power through a battery and is used by placing two sponges ($5 \times 5\,cm^2$) on the rubber electrodes. The stimulation onset current rises from 0 mA to 2 mA within 3 s and drops from 2 mA to 0 mA at the end. The device has a pseudo-stimulation mode that maintains the stimulation for 10 s only at the beginning and then drops to 0 mA, after which no stimulation effect is produced. The equipment was operated by a uniformly trained research nurse, with the anode placed on the left DLPFC and the cathode on the right DLPFC and stimulated twice a day (once in the morning and once in the afternoon) for 20 min each time. Stimulation was performed for 5 consecutive days per week with 2 days off for 6 continuous weeks (a total of 30 sessions).

Primary outcome and secondary outcomes

Two trained neuropsychologists blinded to the group assignment performed the cognition assessments for the subjects at baseline, 2 weeks and 6 weeks. Trained neuropsychologists conducted all the cognitive assessments and did not know the interventions the patients received. The neuropsychologists' consistency training before the start of the study enabled them to score the scales reliably and ensured that their correlation coefficient remained above 0.8.

The primary outcome is the cognitive function of the patients with AD using the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). The ADAS-Cog is the gold standard test for AD and has proven to be a clinical tool for evaluating the reliability and effectiveness of cognitive changes in AD. It includes the evaluation of four domains (language, memory, praxis and attention). The score ranges from 0 to 70, with a higher number indicating worse cognition.

Secondary outcomes are the MMSE measures and the MEP values of the electrophysiological indicators. The MMSE scale includes the following seven aspects: time orientation, place orientation, immediate memory, attention and calculation power, delayed memory, language, and visual space. A total of 30 questions were set: a correct answer received 1 point and a wrong answer received 0 points. The total score of the scale ranges from 0 to 30 points. A higher score indicates better cognitive performance.[20] We also used TMS connected to an EMG system to record the MEP values and induced plasticity using a high-frequency rTMS protocol. We measured MEP values (from peak to baseline) before and 15 min after the induction protocol to assess long-term plasticity (LTP)-like changes in cortical plasticity after rTMS stimulation.[18 21]

Statistical analyses

Statistical analyses were performed with SPSS V.23, and the data were expressed as mean (standard deviation, SD). χ^2 test and analysis of variance (ANOVA) were used to compare potential differences in baseline demographic data; repeated-measures (RM) multivariate analysis of variance (MANOVA) was used to compare cognitive function and MEP, including between-group factors (active, sham) and within-group time factors (baseline, 2 weeks, 6 weeks). If time and group interactions were significant, analysis of covariance (ANCOVA) was used to examine between-group differences by adjusting for age, sex,

education and disease duration. If the interaction was not significant, no further statistical analysis was performed. Bonferroni correction was used to make post-hoc comparisons between groups. The significance level of all statistical analyses was set at p<0.05.

RESULTS

A total of 205 patients were recruited but only 140 met the inclusion criteria; 133 completed the 2-week intervention and 124 completed the 6-week intervention (figure 1). Reasons for dropping out of the study included (1) the 6-week treatment duration was too long, (2) other physical reasons, (3) no reason given for discontinuation, (4) not receiving treatment for 2 consecutive days and (5) family members feeling that the treatment is ineffective. No one withdrew from the study due to discomfort during the treatment process.

Demographic and primary descriptive data

The demographic and neuropsychological characteristics of all 124 subjects (63 active and 61 sham) are shown in table 1. There were no significant differences between the two groups concerning sex, age, education level or disease duration (all p>0.05). The neuropsychological scale measures were also balanced between the active and sham groups.

Primary outcome

#### Total score and index scores on ADAS-Cog

We investigated whether tDCS treatment for 6 weeks improved cognitive functions among active and sham groups using the ADAS-Cog. There was no significant difference between the real and sham stimulation groups at baseline (F=0.077, p=0.782). After RM ANOVA, the outcomes revealed that the main effect of time ($F_{(1, 123)}$=22.58, p<0.001) and the interaction effect

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Table 1 Demographic and baseline clinical characteristics of patients with AD

	Active (n=63)	Sham (n=61)	F/χ^2	P value
Age (years)	76.71 (5.80)	75.57 (6.11)	1.136	0.289
Gender, n (%)			0.199	0.655
Male	22 (34.92)	19 (31.15)		
Female	41 (65.08)	42 (68.85)		
Disease duration (years)	3.83 (1.49)	3.90 (1.45)	0.084	0.773
Education, n (%)			2.053	0.358
Illiterate	17 (26.98)	23 (37.70)		
Junior level	15 (23.81)	15 (24.60)		
Senior level or above	31 (49.21)	23 (37.70)		
MMSE	16.33 (4.93)	16.54 (4.88)	0.056	0.814
ADAS-Cog	33.72 (9.20)	33.27 (8.87)	0.077	0.782

Data are presented as mean (SD) or n (%).
AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; MMSE, Mini-Mental State Examination; SD, standard deviation.
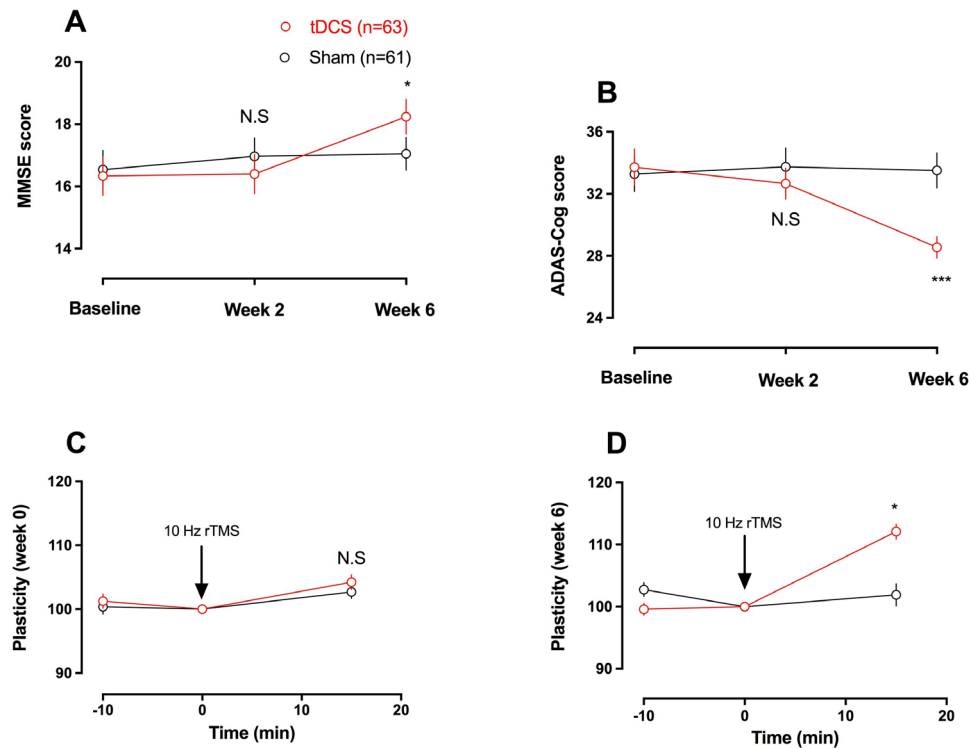
Figure 2 Enhanced cognitive and plasticity induced by tDCS in patients with AD. (A) Post-hoc tests revealed that there were no significant differences in the MMSE scores between the two groups at baseline (F=0.056, p=0.814), and the score significantly increased at week 6 compared with baseline (F=5.23, p=0.024) in the active group. In contrast, there was no significant difference in the sham group (F=0.39, p=0.534) over time. (B) Post-hoc tests revealed that there were no significant differences in the ADAS-Cog score between the two groups at baseline (F=0.077, p=0.782), and the scores were significantly reduced at week 6 (F=14.64, p<0.001) in the active group, indicating improved performance. (C, D) The post-hoc tests revealed no significant changes in the plasticity responses in the active and sham groups. Interestingly, there was a rapid significant difference in the enhancement of MEP at 15 min (F=4.87, p=0.029) following treatment. However, these failed to reach significance in the sham group (p>0.05). AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; MEP, motor evoked potential; MMSE, Mini-Mental State Examination; N.S, not significant; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation. *p<0.05, ***p<0.001.

(time×group) $(F_{(1, 123)}=24.10, p<0.001)$ reached significance. However, no significance was found in the group effect $(F_{(1, 123)}=1.68, p=0.198)$. Post-hoc tests revealed that the active stimulation group showed a significant statistical difference between the ADAS-Cog score at week 6 (p<0.001) but not at week 2 (p=0.442) after treatment, compared with the baseline value. Again, there was no significant difference in the sham group at any time point after treatment compared with the baseline (p>0.05) (online supplemental table 1, figure 2B).

Additionally, RM ANCOVA on 11 domains of the ADAS-Cog showed that there was a significant time effect on word recall, recall of test instructions and word recognition (word recall: $F_{(1, 123)}=28.10, p<0.001$; recall of test instructions: $F_{(1, 123)}=13.84, p<0.001$; word recognition: $F_{(1, 123)}=26.35, p<0.001$), together with a significant interaction of group-by-time effect on word recall, recall of test instructions and word recognition (word recall: $F_{(1, 123)}=23.69, p<0.01$; recall of test instructions: $F_{(1, 123)}=23.31, p<0.001$; word recognition: $F_{(1, 123)}=30.37, p<0.001$). The group's effect showed no difference in these three indexes (all p>0.05). The results of the RM ANCOVA of the other individual domains of the ADAS-Cog are provided in

online supplemental table 1. Covariates in RM MANOVA included sex, age, education level or disease duration.

Secondary outcomes
Mini-Mental State Examination
There was no significant difference between the tDCS (active) and sham stimulation groups at baseline (F=0.056, p=0.814). RM ANOVA revealed that there was a significant time effect on MMSE scores $(F_{(1, 123)}=18.52, p<0.001)$. The effect of the group failed to reach significance $(F_{(1, 123)}=0.03, p=0.865)$. The interaction effect (time×group) also had a significant effect $(F_{(1, 123)}=9.83, p<0.001)$. Post-hoc tests revealed that in the tDCS group, there was a significant statistical difference between the MMSE score at week 6 $(p_{6w}=0.024)$ but not at week 2 $(p_{2w}=0.941)$, compared with the baseline value. In contrast, there was no significant difference in the sham group at any time (p>0.05) (online supplemental table 1, figure 2A).

Motor evoked potential
We used the 10 Hz plasticity protocol to induce LTP, and no differences were found between the two groups before the intervention (all p>0.05). After 2 weeks of
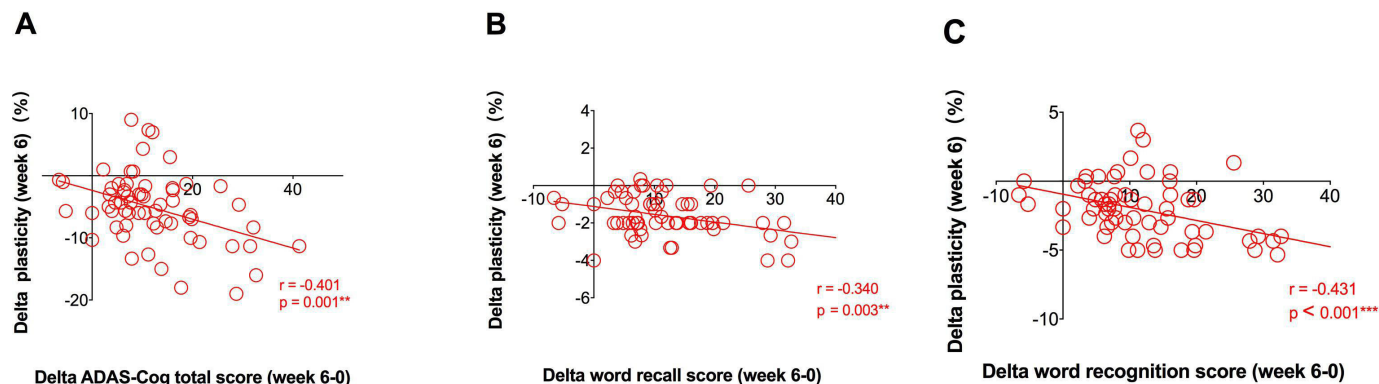
Figure 3 tDCS enhances cortical plasticity, and enhanced plasticity is associated with cognitive improvement. After 6 weeks of tDCS intervention, the potentiation of plasticity was significantly correlated with improvements in (A) total ADAS-Cog score (r=−0.401, p=0.001), (B) word recall score (r=−0.340, p=0.003) and (C) word recognition score (r=−0.431, p<0.001). ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; tDCS, transcranial direct current stimulation. **p< 0.01, ***p<0.001.

intervention, both groups had no change in MEP (all p>0.05). However, after 6 weeks of intervention, an increased plasticity response was demonstrated in the active stimulation group (F=4.87, p=0.029), but no changes were found in the sham group (F=0.05, p=0.819) (figure 2C,D).

Correlations between MEP changes and cognitive improvements

In the secondary outcome, the correlation analysis in the active tDCS group showed significant correlations between the reduction in the total ADAS-Cog score (from baseline to week 6) and the enhancement of MEP (r=−0.401, p=0.001) (figure 3A). Further analysis showed a significant association between the decrease in MEP and the change in word recall score (r=−0.340, p=0.003), as well as between the reduction in MEP and that of word recognition (r=−0.431, p<0.001) (figure 3B,C). However, no similar correlations were found in the sham group (all p>0.05), suggesting that the improvement in cortical plasticity may reflect the degree of cognitive improvement.

Adverse effects

No severe side effects were reported during the intervention, and no one withdrew from the group due to serious side effects. Five participants in the active stimulation group and three in the sham group experienced skin redness and swelling; however, they all recovered the following day without any treatment.

DISCUSSION
Main findings

The present study investigated the clinical safety and effects of twice-a-day tDCS on the cognitive function of patients with AD. The results showed the following: (1) 30 sessions of a daily 20 min tDCS session over 6 weeks significantly improved cognitive function in patients with mild to moderate AD, reflected by increased MMSE scores and decreased ADAS-Cog scores compared with the sham group; (2) patients with AD have impaired cortical plasticity, and 6-week tDCS can enhance the damaged cortical plasticity; and (3) after the intervention, there was a significant correlation between cortical plasticity changes and cognitive function improvements. Taken together, tDCS is a promising method for improving cognitive function with sufficient treatment. It is supported by electrophysiological evidence (MEP) in patients with AD, and these results support the potential role of cortical plasticity as a biomarker of treatment effect in patients with AD.

This 6-week, randomised, controlled, double-blind study found that twice-daily tDCS of the frontal lobe was necessary for cognitive improvement. This is consistent with previous research results. tDCS can significantly improve the working memory of older patients, and the stimulation changes the resting-state functional connectivity of the frontoparietal brain regions.[22] In a study of schizophrenia, we also found that tDCS of the prefrontal cortex (PFC) can improve patients' active cognitive control ability,[23] and in a study of depression, we found that tDCS not only improves depressive symptoms but also significantly improves patients' spatial memory ability.[24] A meta-analysis of AD has shown that tDCS significantly impacts the cognition of patients with AD, including their general cognitive state, memory and attention. However, some studies have not found any differences, which may be related to the number of treatments, current density and stimulation area.[25] This is consistent with our finding of no improvement in cognition after 10 interventions. The exact mechanism of tDCS for cognitive improvement in AD is still unknown. Research has shown that tDCS may impact ion activity, neurotransmitter release and brain oscillatory activity in various brain areas. tDCS can also change the release rate of neurotransmitters by influencing the propagation of action potential or the release of vesicles.[26] The latest nuclear magnetic resonance spectroscopy study shows that tDCS can alter the concentration of gamma-aminobutyric acid (GABA) and glutamate in the cortex, further supporting the regulatory effect of tDCS on neurotransmitters.[27] Other studies

show that individual sensitivity to tDCS is affected by the human brain-derived neurotrophic factor (BDNF) gene polymorphism, revealing the relationship between tDCS and BNDF.[28] In addition, many studies have reported changes in the theta frequency band of electroencephalography (EEG) signals in subjects receiving tDCS and that tDCS can effectively regulate gamma oscillations in the frontal lobe. Some studies have shown that after stimulating DLPFC with anode tDCS, the activity of the delta band in the left frontal lobe decreases, and the connection between the frontoparietal resting-state functional magnetic resonance imaging (MRI) network and the default network changes, with both important for cognitive functions.[29 30]

This study found impaired cortical plasticity in AD. In previous studies on cortical plasticity in mental disorders, it has been found that patients with schizophrenia, depression or addiction exhibit varying degrees of damage to cortical plasticity, and these suggest that there may be a specific connection between plasticity and the state of the disease.[21 31] In addition, a plasticity study on AD found that the plasticity of patients with AD was impaired and positively correlated with their cognitive function. After rTMS treatment, improved cognitive function and enhanced plasticity were also significantly correlated.[18] This is consistent with our results, which suggest that 6-week tDCS can reverse damaged cortical plasticity. Several factors may be responsible for these discrepancies regulating the thermoplastic effects of tDCS on symptoms of AD. Many studies have shown that tDCS does not directly induce changes similar to LTP or long-term depression (LTD) but regulates the strength and direction of synaptic plasticity by regulating intracellular homeostasis.[32] For example, tDCS can increase the concentration of Ca^{2+} in the cerebral cortex and hippocampal cells, and the increase in intracellular Ca^{2+} concentration will drive the production of short-term and long-term plasticity.[33 34] Research on cortical plasticity suggests that the key to the sustained effect of tDCS lies in the long-term enhancement and the long-term inhibition it triggers.[35] In the human motor cortex, it is found that tDCS promotes synaptic plasticity through a mechanism similar to LTP.[36] In addition, serotonin can regulate the plasticity induced by tDCS. The activity of the serotonin system induced by the reuptake inhibitor of serotonin increases and prolongs the LTP-like phenomenon caused by anode tDCS and reverses the LTD-like phenomenon induced by cathode tDCS.[37 38]

Our other finding is that after 6 weeks of intervention, in the active stimulus group rather than in the sham group, there was a close correlation between the total improved ADAS-Cog score and changes in MEP. This is consistent with another study on the treatment of AD with rTMS, suggesting that improved cognitive function positively correlates with cortical plasticity.[18] In addition, Chou et al[39] found that in AD and mild cognitive impairment, patients' cognitive impairment was proportional to the degree of cortical damage. In

studies on depression, it has also been found that while patients had improved cognitive function, their cortical plasticity was also enhanced. These studies support the possible common-case mechanisms of cognitive performance and plasticity. This may be because when these treatments improve cognition, the level of neurotransmitters in the brain, especially those related to cognition (such as BDNF), is also changed to an extent. The level of these neurotransmitters will affect the activation of brain regions and thus change neuroplasticity.[40] In addition, long-term tDCS intervention will also regulate the changes in the volume and thickness of the hippocampus and amygdala cortex. However, whether the relationship between plasticity and cognition is direct or indirect requires more research in the future. Other physical therapies, including tACS, rTMS and light, can also improve the cognitive function of patients with AD, especially their working memory and instant memory in cognitive function.[6 41] This is consistent with our findings that in the active stimulus group, tDCS mainly changed patients' word recall, word recognition ability and recall of test instructions–three domains that are related to memory dimensions. This indicates that neuromodulation techniques have a significant effect on cognitive improvement. However, because memory involves much content, the exact mechanism of neuromodulation techniques improving cognitive function in patients with AD deserves further research and investigation.

Limitations

This study has several limitations. First, although it is a multicentre study, the sample size selected from each centre was insufficient and further expansion is needed. Second, this study did not conduct MRI or electroencephalography at enrolment to elucidate changes in the brain network and lacked exploration of the neurophysiological mechanisms of efficacy. Third, this study lacked biological research and did not collect blood samples or cerebrospinal fluid, making it impossible to investigate neurotransmitter changes such as BDNF, Aβ, and so on. Finally, this study did not follow up with the patients to measure effects over a longer period. Had we done so, we could have explored the duration of the effectiveness of tDCS. In the future, we will consider joint exploration with electrophysiology, MRI and blood indicators to combine these central biomarkers for early prediction and intervention.

Implications

In summary, the results of this study strongly indicate that tDCS treatment is a significant and promising intervention for improving cognitive function in AD. In addition, plasticity plays a vital role in cognitive change. Further research is needed to elucidate the relationship between plasticity and cognition. The relationship between plasticity and cognition will also be studied in other diseases with cognitive impairment

to demonstrate the importance and uniqueness of plasticity in cognition.

Author affiliations
[1]Department of Psychiatry, Ningbo Kangning Hospital & Affiliated Mental Health Centre, Ningbo University, Ningbo, Zhejiang, China
[2]Ningbo Key Laboratory for Physical Diagnosis and Treatment of Mental and Psychological Disorders, Ningbo University, Ningbo, Zhejiang, China
[3]Department of Psychiatry, Yu Yao Third People's Hospital, Ningbo, Zhejiang, China
[4]Department of Psychiatry, Second People's Hospital of Lishui, Lishui, Zhejiang, China
[5]Department of Psychiatry, Taizhou Second People's Hospital, Taizhou, Zhejiang, China

ORCID iD
Xingxing Li http://orcid.org/0000-0003-3929-7625

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Xingxing Li is presently a PhD student at the Institute of Psychology of the Chinese Academy of Sciences (enrolled in 2022). He received a Master of Science degree from the School of Medicine of Ningbo University, China, in 2016. Since then, Xingxing Li has been working at Kangning Hospital in Ningbo, currently in the Department of Physical Diagnosis and Treatment of Mental and Psychological Disorders. He is an assistant researcher and PhD student at the Secretary of the Physical Diagnosis and Treatment Center of Ningbo Kangning Hospital. He is also a member of the Physical Diagnosis and Treatment Group of the Elderly Mental Disorders Branch of Zhejiang Medical Association and a young member of the Precision Medical Special Committee of the Zhejiang Bioinformatics Society. Xingxing Li is mainly engaged in clinical research related to physical therapy for neurological and psychiatric diseases and basic research on brain plasticity. His main research interests include TMS-MEP, TMS-EEG synchronous detection, dual-pulse paired stimulation technology, resting-state fMRI EEG, tDCS/tACS-EEG synchronous stimulation EEG technology, near-infrared detection, and other clinical electrophysiological technologies. He has published ten articles related to physical therapy and brain plasticity. He has led a project funded by the Provincial Natural Science Foundation and has participated in more than ten national, provincial, and other research projects.