Cognition-enhancement effect of median nerve electrical stimulation in patients with cognitive impairment: A retrospective cohort study

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Research Article

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Abstract

Background

People with cognitive impairment often face quality of life problems and require ongoing support, which has profound consequences for caregivers and society. Non-invasive brain stimulation techniques, such as median nerve electrical stimulation (MNS), have shown promising potentials in improving cognitive ability in patients with cognitive impairment. Therefore, we aimed to investigate the efficacy and safety of MNS in cognitive impairment.

Methods

Patients diagnosed with cognitive impairment from the hospital record management system of the First Affiliated Hospital of Nanchang University from April 1, 2020 to December 31, 2022 were enrolled. Data on patients' basic characteristics, treatment records, and examination results such as the Mini-Mental State Examination (MMSE), activities of daily living (ADL), and P300 event-related potential before and after treatment were collected.

Results

Overall, 146 patients with cognitive impairment were enrolled, including 71 patients who underwent conventional therapy (standard treatment group) and 75 patients who underwent conventional therapy and MNS preformation (active MNS group). Before treatment, there were no differences between the standard treatment and active MNS groups in terms of age, sex, etiology, duration of symptoms before therapy, hospital stay, whether they had undergone surgery, MMSE score, ADL score, and amplitude and latency of the P300 event-related potential ($P > 0.05$). After treatment, we observed significant improvements in the MMSE score, ADL score, amplitude of P300, and decreased latency of P300 event-related potentials in both groups compared with before treatment ($P < 0.05$). In addition, we observed that the active MNS group showed higher MMSE and ADL scores, higher amplitude of P300 event-related potential, and lower latency of P300 event-related potential than the standard treatment group after treatment ($P < 0.05$). Furthermore, no side effects were associated with MNS preformation.

Conclusion

These preliminary data provide early evidence that MNS may be an effective and safe method for promoting the recovery of cognitive ability in patients with cognitive impairment.

INTRODUCTION

Cognitive impairment is a limitation in the ability to perform intellectual tasks and is often associated with deficits in executive function, problem solving, memory, and attention. It can be caused by various diseases such as stroke, traumatic brain injury (TBI), and carbon monoxide (CO) poisoning (1–3), which seriously affects the patient's quality of life and places a heavy burden on the country and family (4, 5). A cross-sectional study conducted in 10 countries revealed that approximately 30% of ischemic stroke survivors have cognitive impairment (6). TBI can also cause several cognitive impairments in problem solving, memory, executive function, and attention (7). Currently, the main therapeutic methods for cognitive impairment include cognitive training, drug therapy, hyperbaric oxygen therapy, and aerobic exercise therapy (8–11). However, to date, there is no unequivocally efficacious treatment for cognitive impairment; hence, there is a need for further studies.

Recently, noninvasive neuromodulation techniques, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation, have shown promising potentials in improving cognitive function in patients with cognitive impairment caused by stroke or TBI (12, 13). Median nerve electrical stimulation (MNS) is a simple, inexpensive, and non-invasive neuromodulation technique that has been shown to improve recovery from TBI, hasten awakening from coma (14, 15), and used for treating chronic refractory pain (16). Our previous study revealed that MNS improves cognition in TBI-induced comatose rats (17). Therefore, this retrospective study aimed to investigate the efficacy and safety of MNS in patients with cognitive impairment.

MATERIALS AND METHODS

Study design and participants

This is a retrospective cohort study of hospitalized patients with cognitive impairment from April 1, 2020, to December 31, 2022, diagnosed and treated in the Department of Rehabilitation Medicine, the First Affiliated Hospital of Nanchang University.

Patients with cognitive impairment were diagnosed according to Chinese guidelines (18). We excluded patients with incomplete medical records, such as lack of MMSE, ADL, and P300 examinations, patients with worsened condition during treatment, or interruption of MNS treatment, such as death or transfer to another department. The patients were classified into two groups: a standard treatment group and an active MNS group. Patients were informed of the reasonable therapeutic schedule and potential adverse effects only if they agreed to undergo treatment. Patients in the active MNS group underwent standard treatment and the right MNS (EMG-Bio-feedback stimulator, MyoNet-BOW, NCC Medical Co., Ltd., Shanghai, China) preformation. The parameters of the MNS were as follows: pulse width, 300 us; frequency, 50 Hz; 2 h daily during hospitalization in the right hand. Patients in the standard treatment group only underwent standard therapy based on the guidelines for cognitive impairment in China (18, 19). Based on these guidelines, standard treatment includes controlling blood pressure, blood glucose, blood lipids, and symptomatic treatment, drugs, acupuncture, and cognitive training such as memory

training, orientation training, calculation training, agnosia and apraxia training, logical thinking ability training, and visual-motor organization ability training.

The study was conducted from admission to discharge. The hospital's electronic medical records contained data on all patients from admission to discharge in the hospital, and data during treatment with MNS were also included from the doctor's advice on the HIS system. In addition, the examination data and complications were available from the medical record system.

Assessment method

The primary assessment methods were the MMSE, ADL, and P300 event-related potential at admission and discharge. The MMSE is a 30-point questionnaire widely used in clinical and research settings to measure cognitive impairment. It includes simple tasks in various areas: time and place tests, word repetition lists, arithmetic such as minus seven in a row, language use and comprehension, and basic motor skills (20, 21). ADL, with a total of 100 points, is closely related to cognitive function and comprises the following areas: grooming/personal hygiene, dressing, toileting/continence, transferring/ambulating, and eating (22, 23). The P300 event-related potential, which consists of both amplitude and latency, is a highly suitable measure for correlating neuronal function with cognitive processes such as executive function and working memory (24). The P300 event-related potential test was conducted in a quiet room without any interference. The evoked potential instrument used was an MEB-2306C electromyographic evoked potentiometer (Japan Opto-Electronics Industry Co., Ltd.). The electrode placement covered Fz, Cz, and Pz following the international 10–20 system and the bilateral mastoid process; the reference electrode was placed in the mastoid process, and the ground was in the center of the forehead. Using the Oddball auditory paradigm, the occurrence rate of the target stimulus was 20% and that of the non-target stimulus was 80%. The latency and amplitude of P300 event-related potentials induced by the target stimulus were recorded and analyzed.

Statistical analysis

Patient information, including clinical characteristics, MMSE and ADL scores, and amplitude and latency of the P300 event-related potential. Continuous variables following a normal distribution are described by means and standard deviations, using Student’s t-tests to compare differences. Non-normally distributed continuous variables are described by median (interquartile range [IQR]) using Mann—Whitney U tests to compare differences. Categorical variables are described as numbers and percentages using chi-squared or Fisher’s exact tests to compare differences. All data were analyzed using SPSS 26.0, if $P < 0.05$, data was considered statistically significant.

RESULTS

Participants

Six hundred and ninety-four patients were enrolled from the hospital record management system of the Department of Rehabilitation Medicine, the First Affiliated Hospital of Nanchang University. Moreover, 548

patients were excluded because of incomplete medical records or examination results, interruption of treatment, or aggravation of the patient's condition. Overall, 146 patients were included in the standard treatment (N = 71) and active MNS groups (N = 75) (Fig. 1).

Baseline characteristics

The baseline characteristics of the patients are presented in Table 1. Before treatment, there were no differences between the standard treatment and active MNS groups in terms of age, sex, etiology, duration of symptoms before treatment, hospital stay, whether they had undergone surgery, Mini-Mental State Examination (MMSE) score, activities of daily living (ADL) score, and amplitude and latency of the P300 event-related potential ($P > 0.05$).

Table 1
Clinical characteristics of patients at baseline.

Characteristic	Standard treatment group	Active- MNS group	P-value
Number	71	75	
Age (year)	53 (44, 63)	52 (39, 57)	0.196
Sex			0.323
Male	54 (76.06%)	62 (82.67%)	
Female	17 (23.94%)	13 (17.33%)	
Etiology			0.104
TBI	28 (39.43%)	40 (53.33%)	
Stroke	36 (50.70%)	25 (33.33%)	
CO	7 (9.86%)	10 (13.33%)	
Duration of symptoms before treatment (days)	35 (23,66)	36 (21,81)	0.908
Hospital day (days)	22 (16,29)	26 (19,30)	0.108
Surgery			0.576
Yes	43 (60.56%)	42 (56.00%)	
No	28 (39.43%)	33 (44.00%)	
MMSE scores	7 (0,17)	9 (0,17)	0.759
ADL scores	7 (0,32)	0 (0,37)	0.958
P300 latency (ms)	378 (329, 423)	376 (321, 434)	0.874
P300 amplitude (μv)	2.70 (1.50, 4.00)	2.70 (1.50, 5.00)	0.524

MNS, median nerve electrical stimulation; TBI, traumatic brain injury; CO, carbon monoxide; MMSE, Mini-Mental State Examination; ADL, activities of daily living; P300, P300 event-related potential.

Alteration of MMSE, ADL, and P300 after treatment

As shown in Fig. 2 and Fig. 3, the MMSE and ADL scores of the standard treatment and active MNS groups significantly improved after treatment ($P < 0.05$); however, the active MNS group showed higher MMSE and ADL scores than the standard treatment group after treatment ($P < 0.05$). As shown in Fig. 4, Fig. 5, **and** Fig. 6, we observed differences in P300 between the standard treatment and active MNS groups. The amplitude of P300 improved and the latency of P300 decreased after treatment ($P < 0.05$). In addition, the active MNS group showed higher amplitude and lower latency of P300 than the standard treatment group after treatment ($P < 0.05$).

Safety and adverse effect

All patients in the active MNS group showed good tolerance to transdermal electrical stimulation. There were no significant changes in heart rate, breathing, or blood pressure during the electrotherapy. Possible complications, such as seizures, gastrointestinal bleeding, documented pneumonia, and increased sympathetic nerve activity during treatment, are presented in Table 2. These effects were not specific to the active MNS group, as the proportions were similar in both groups.

Table 2
Complications during the treatment period.

	Standard treatment group	Active- MNS group	p value
Seizures	3 (4.23%)	2 (2.67%)	0.950
Gastrointestinal bleeding	5 (7.04%)	6 (8.00%)	0.827
Pneumonia	9 (12.68%)	12 (16.00%)	0.567
Increased sympathetic activity	6 (8.45%)	8 (10.67%)	0.649
MNS, median nerve electrical stimulation.			

DISCUSSION

To our knowledge, this is the first retrospective cohort study to investigate the efficacy and safety of MNS in patients with cognitive impairment. The results showed that MNS improved cognitive function in patients with cognitive impairment, and no adverse effects were observed with the MNS preformation.

Cognitive impairment is caused by stroke, TBI, and CO poisoning. It affects patient's quality of life and poses a major burden to caregivers and healthcare systems. Cognitive impairment often manifests as memory loss, impaired orientation, and computational dysfunction. However, its underlying mechanism is uncertain. Many factors such as lesions on neuroanatomical structures, neuronal apoptosis, synaptic dysfunction, brain volume, and myelinated neuron reduction may cause cognitive dysfunction (10, 25). Some antidementia drugs have been shown to have positive effects on cognitive impairment (26). Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine have been approved for clinical use to treat cognitive dysfunction caused by Alzheimer's disease (27). Following clinical trials, cholinesterase inhibitors have proven to be promising agents for treating cognitive impairment after stroke, with donepezil being the most effective. A double-blind, placebo-controlled, randomized clinical trial showed that donepezil improved cognitive function in post-stroke patients; however, the improvement in overall cognitive function was inconsistent (28). Additionally, more randomized clinical trials have shown that memantine improves cognitive function (29, 30). Studies have shown that these drugs

significantly improve some cognitive domains, such as executive function; however, the uncertainty of global and daily function makes it difficult to evaluate the value of the drugs in the clinic.

Neuromodulation, both invasive and noninvasive, has been the most rapidly developed neuroscience technology in recent years. A randomized, double-blind, parallel-group study revealed that anodal transcranial direct current stimulation is a promising therapeutic option which can significantly improve cognitive performance, such as episodic memory, attention, working memory, and visuospatial skills, in patients with multiple sclerosis (31). Another controlled trial found that deep brain stimulation of the anterior thalamic nucleus may positively influence executive function, leading to better performance in verbal learning (32). Additionally, a clinical trial showed that auricular vagus nerve stimulation can improve cognitive performance and increase the overall Montreal cognitive assessment-basic (MOCA-B), N5, and N7 scores in patients with mild cognitive impairment (33). Cognitive function is an important part of consciousness, and our previous study demonstrated that vagus nerve stimulation may be an effective and safe method for promoting the recovery of consciousness (34, 35) and MNS can promote awareness recovery in TBI-induced comatose rats (17). This study revealed that MNS may be a safe and effective approach to improve the MMSE scores, ADL scores, and amplitude of P300 event-related potential, and decrease the latency of P300 event-related potential in patients with cognitive impairment. However, the mechanism of MNS-induced cognitive enhancement effect is still not fully understood.

A possible mechanism by which MNS improves cognitive function is as follows. First, the modulation of related neuroendocrine activity and neurotransmitters, such as orexin-A, norepinephrine, and glutamic acid, may be key factors in behavioral changes and abnormalities in cognition. According to our previous studies, MNS increases the expression levels of excitatory orexin-A and its receptor OX1R in the hypothalamic region of TBI rats (36), which can promote cognitive recovery (37, 38). Second, boosting cerebral blood flow may be another potential mechanism. Following MNS preformation, regional cerebral perfusion in the contralateral motor and somatosensory areas improved, and enhanced blood flow improved neural survival and promoted cognitive recovery (39). Changes in cortical excitability after stimulation may also be key factors. MNS can enhance low motor cortex excitability in patients with spinocerebellar ataxia (40).

The common complications of MNS include seizures, gastrointestinal bleeding, and increased sympathetic activity (41). In this study, we observed that the incidence of side effects in the standard treatment group was similar, and no new adverse effects were observed during the MNS period, suggesting that MNS may be a safe approach for patients with cognitive impairment.

However, this study has some limitations. First, although we did not observe a difference between the two treatment groups at baseline, this retrospective cohort study has a potential bias. For example, the treatment for which patients received MNS and the specific regimen of standard treatment were not controlled. Second, the results are less persuasive because of the small sample size and lack of more accurate evaluation criteria, such as the MOCA and auditory verbal learning test. Third, additional factors affecting cognition, such as education level, sex, age and etiology, should be considered. Therefore, a

standard MNS intervention with an accurate assessment method and a larger sample size is required for future investigations.

CONCLUSION

In conclusion, MNS can promote cognitive recovery in patients with cognitive impairment, without significant adverse events. Therefore, MNS may be a safe, effective, and promising approach for treating patients with cognitive impairment.

Declarations

• Ethics approval and consent to participate

The study has been approved by the ethics committee of the First Affiliated Hospital of Nanchang University (protocol 2020-61-2) and the board waived the requirement for written informed consent because of the retrospective nature of the study. In addition, the study was performed in accordance with the Declaration of Helsinki.

• Consent for publication

Not Applicable

• Availability of data and materials

The data used in the present study can be seen in the supplementary file.

• Competing interests

The authors declare that they have no conflicts of interest.

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• Authors' contributions

Conceptualization, XYD; Data collection, YFZ, HHY and MYY; Methodology, ZF and XYD; Validation, YFZ and XYD; Data Analysis, YFZ and XYD; Data Curation, HHY and MYY; Writing – Original Draft Preparation, YFZ; Writing – Review and Editing, XYD; Supervision, ZF. All authors contributed to the article and approved the submitted version.

• Acknowledgements

Not Applicable

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Figures

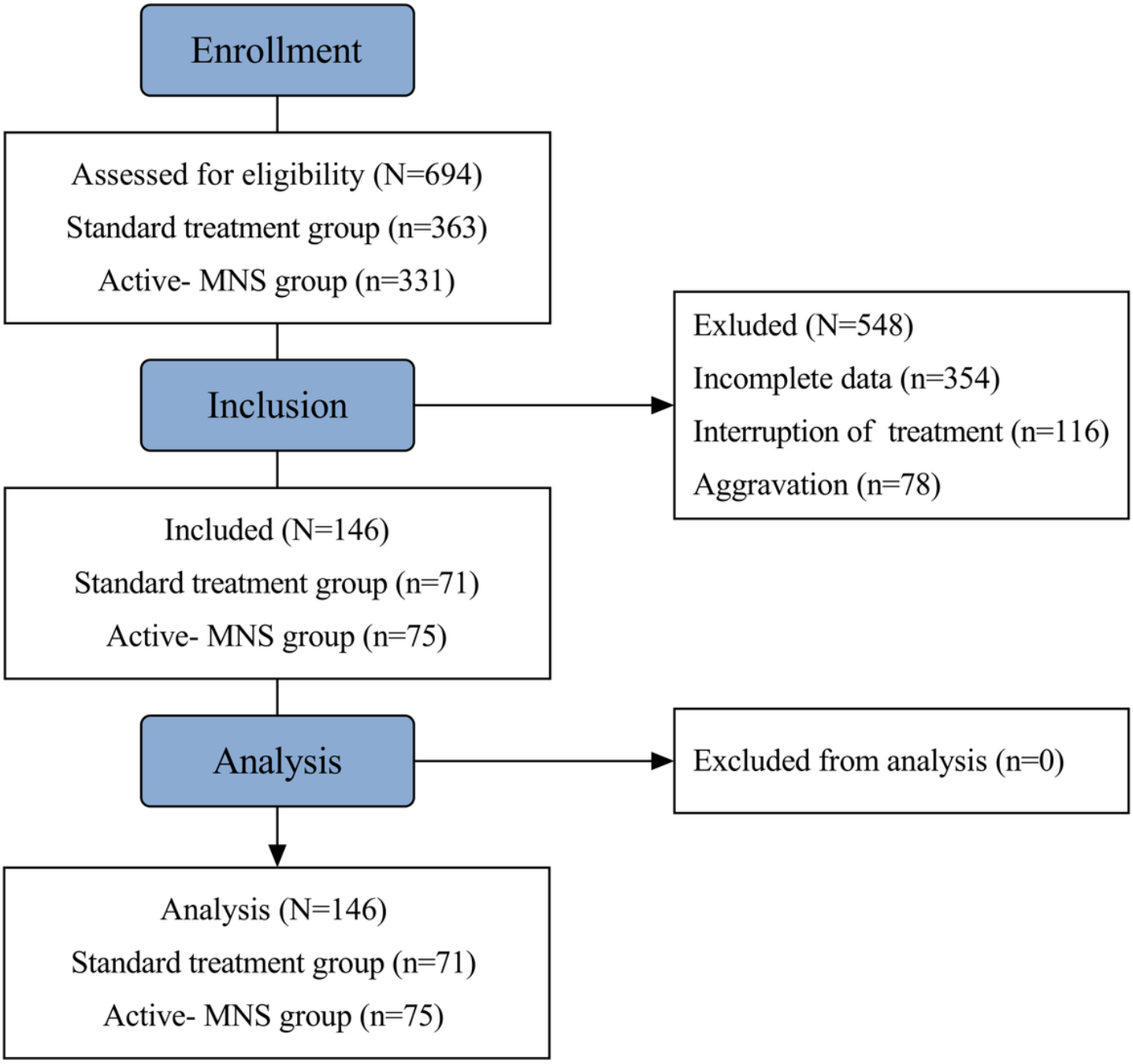

Figure 1

Flow diagram of participants. MNS: median nerve electrical stimulation.

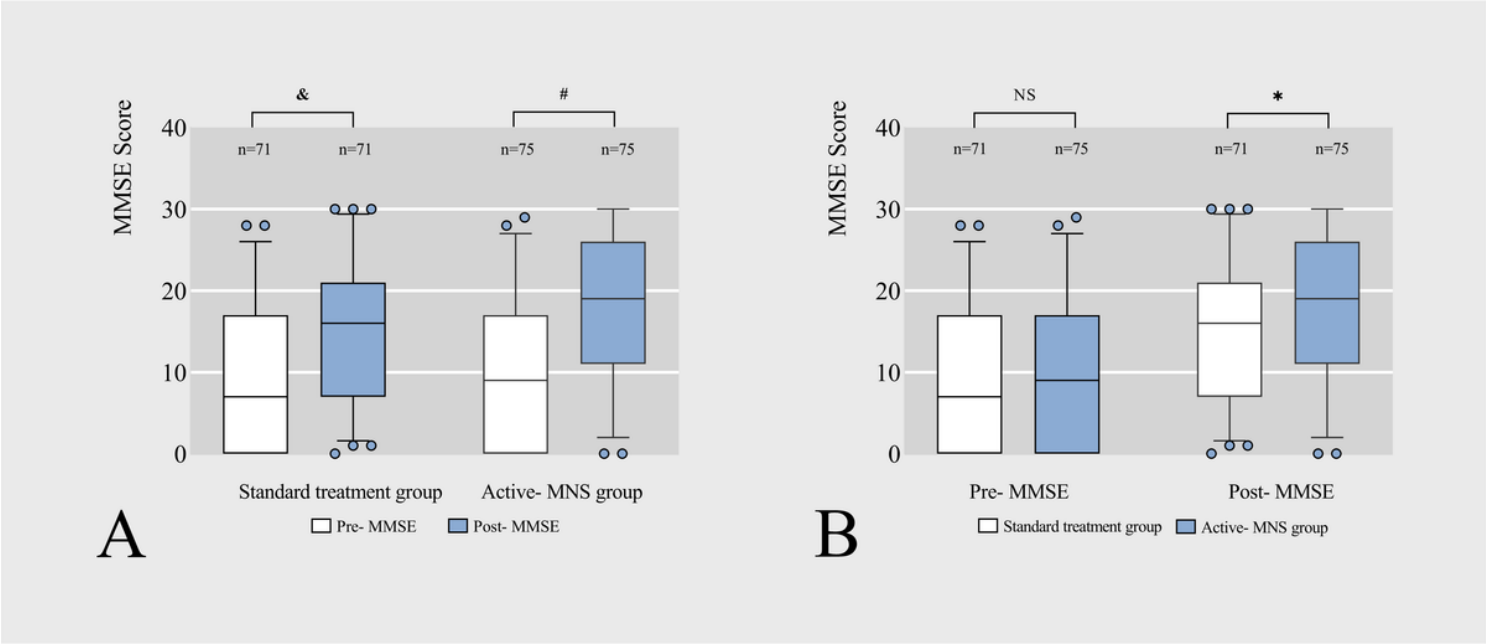

Figure 2

MMSE improvements in patients with cognitive impairment. (A) MMSE scores before and after treatment in two groups. $^{\&}P< 0.05$, $^{\#}P< 0.05$. (B) Comparison of MMSE improvement in two groups before and after treatment, NS indicates no statistically significant difference, $^{*}P< 0.05$. MMSE: Mini-Mental State Examination. MNS: median nerve electrical stimulation.

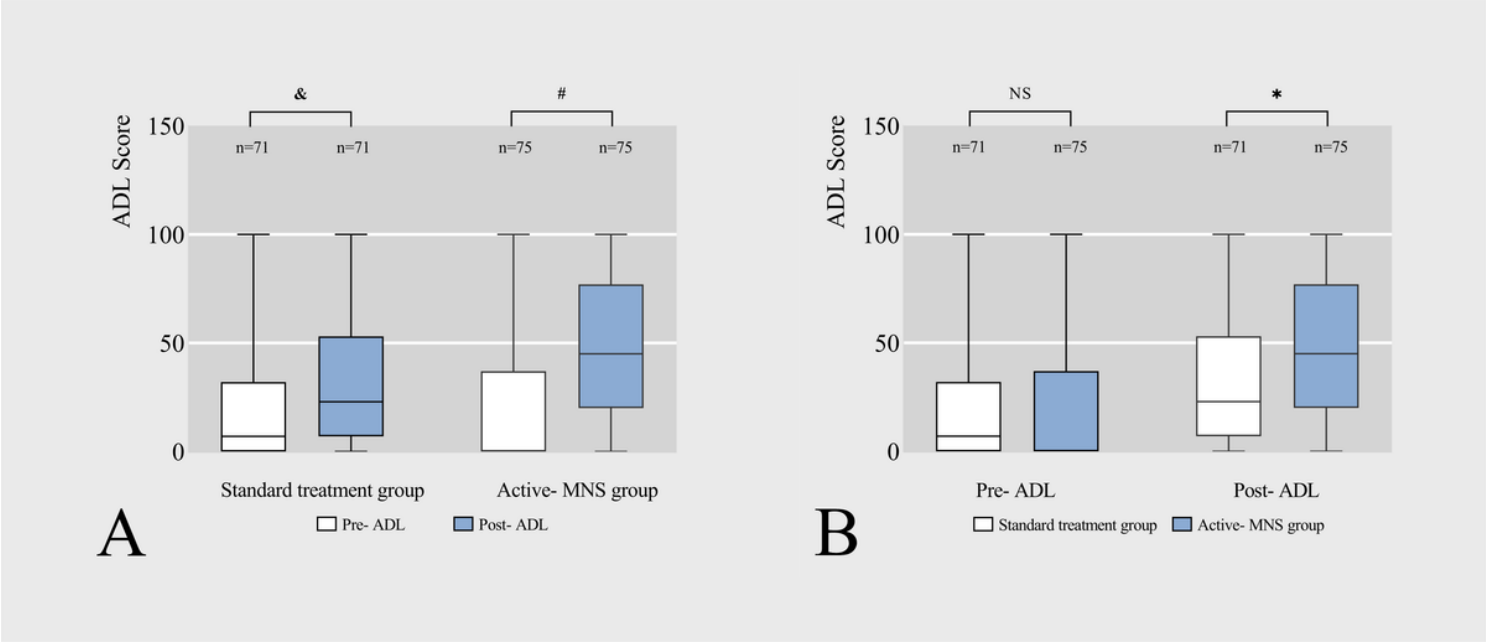

Figure 3

ADL improvements in patients with cognitive impairment. (A) ADL scores before and after treatment in two groups. $^{\&}P< 0.05$, $^{\#}P< 0.05$. (B) Comparison of ADL improvement in two groups before and after

treatment, NS indicates no statistically significant difference, $^{*}P< 0.05$. ADL: activities of daily living. MNS: median nerve electrical stimulation.

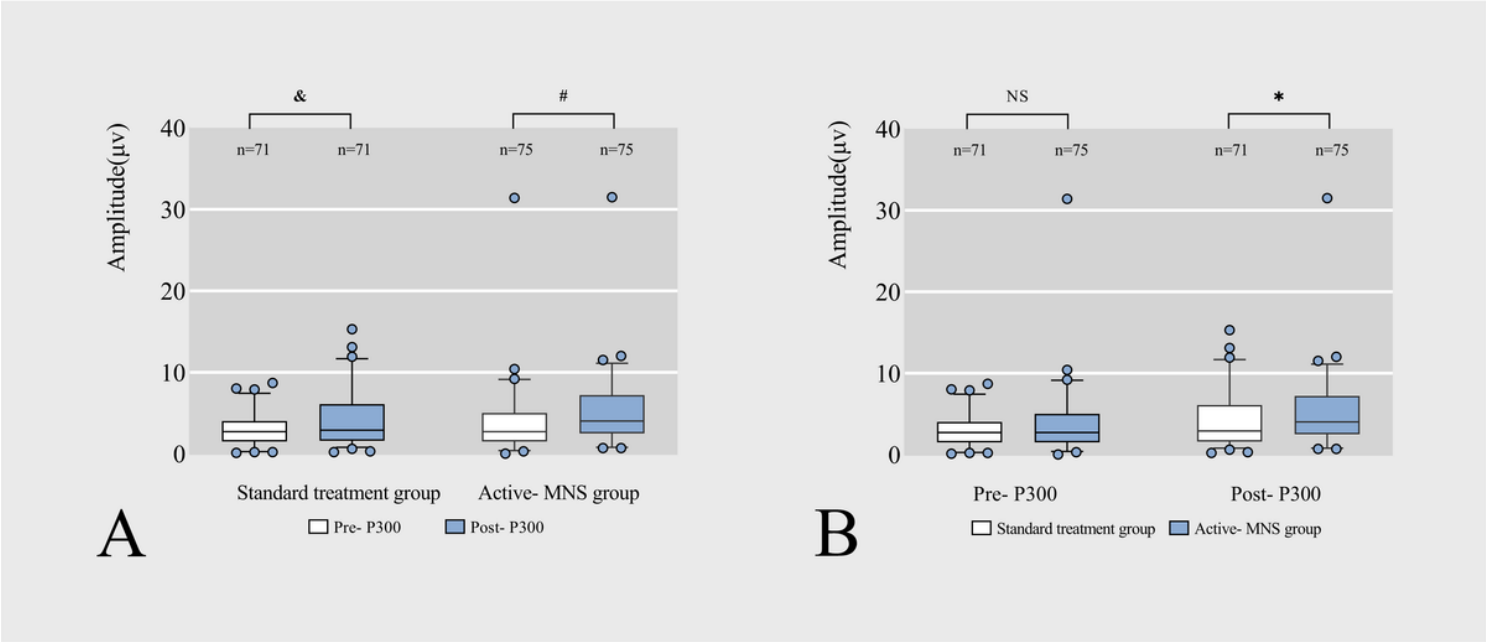

Figure 4

Amplitude of P300 event-related potential improvements in patients with cognitive impairment. (A) Amplitude of P300 event-related potential before and after treatment in two groups. $^{\&}P< 0.05$, $^{\#}P< 0.05$. (B) Comparison of the amplitude of P300 event-related potential improvement in two groups before and after treatment, NS indicates no statistically significant difference, $^{*}P< 0.05$. MNS: median nerve electrical stimulation.

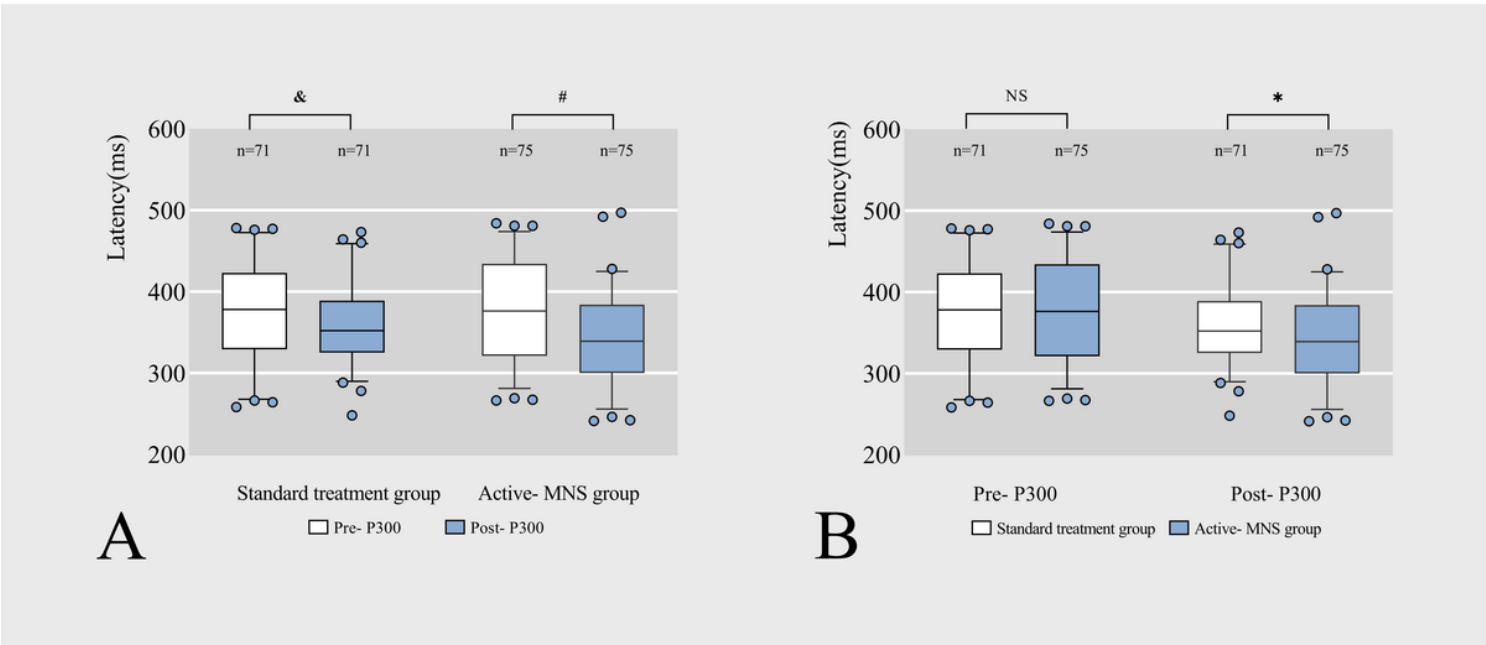

Figure 5

Latency of P300 event-related potential in patients with cognitive impairment. (A) Latency of P300 event-related potential before and after treatment in two groups. $^{\&}P< 0.05$, $^{\#}P< 0.05$. (B) Comparison of latency of P300 event-related potential in two groups before and after treatment, NS indicates no statistically significant difference, $^{*}P< 0.05$. MNS: median nerve electrical stimulation.

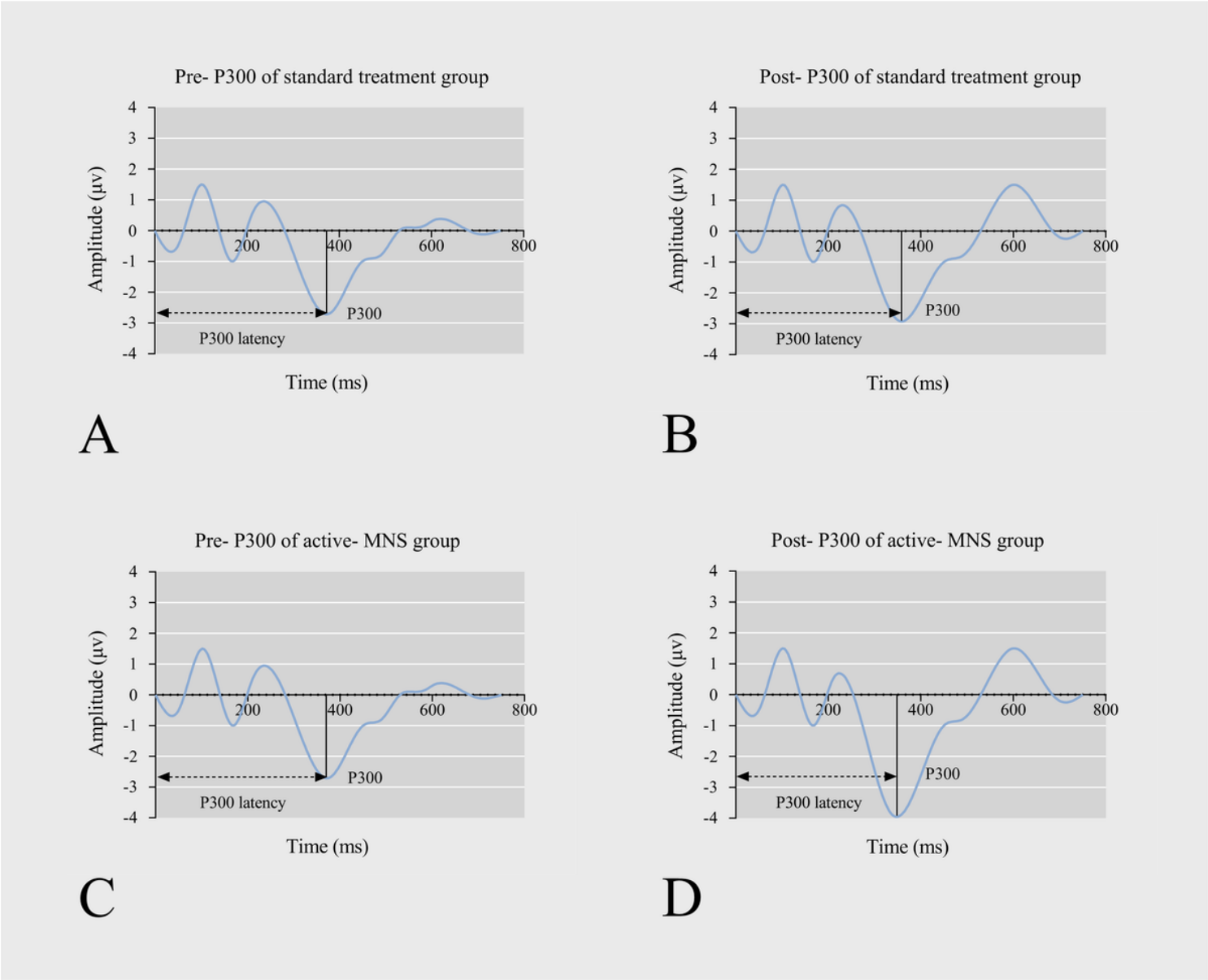

Figure 6

Representative graph of P300 event-related potential in two groups before and after treatment. (A) P300 before treatment in the standard treatment group. (B) P300 after treatment in the standard treatment group. (C) P300 before treatment in the active MNS group. (D) P300 after treatment in the active MNS group. MNS: median nerve electrical stimulation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Rawdata.xlsx