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RESEARCH ARTICLE

Transcranial pulse stimulation in the treatment of mild neurocognitive disorders

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Abstract

Objective: There are limited effectiveness and potential side effects of existing pharmacological approach in treating mild neurocognitive disorder (NCD). Transcranial pulse stimulation (TPS) applies repetitive single high-pressure ultrashort shockwave pulses to stimulate the brain, which has been shown to effectively improve cognition in major NCD. However, the effectiveness of TPS in mild NCD patients remained unknown. This study aims to assess the effectiveness and tolerability of TPS with neuro-navigation in old-age adults with mild NCD by both clinical and biochemical assessments. **Methods**: An open-label study recruited older adults with mild NCD to receive neuro-navigated TPS intervention for two weeks with three sessions per week. Assessments included detailed cognitive assessments, APOE genotype, and brain-derived neurotrophic factor (BDNF). **Results**: Nineteen participants (12 females and 7 males) completed the whole TPS interventions with no serious adverse effects reported. Repeated measures ANOVA showed statistically significant effects of time on HK-MoCA (F (3, 54) = 4.99, P = 0.004), 30-sec interval of Verbal Fluency Test (F (3, 54) = 2.94, P = 0.041), Stroop interference (F (3, 54) = 3.46, P = 0.023), and Chinese IADL (F (3, 54) = 2.78, P = 0.050) after receiving the intervention. Bonferroni post hoc comparisons on HK-MoCA showed a significant improvement after intervention. There was no significant change in serum BDNF level. **Interpretation**: TPS has brought significant improvement in cognition of elderly with mild NCD. It has a great potential to delay the deterioration of cognition in older adults. The long-term effect of TPS in cognition would benefit from further large-scale, randomized, sham-controlled trials.

Introduction

Dementia is an age-related disease, currently known as a major neurocognitive disorder (NCD), is a worldwide health burden. Interventions that aim to ameliorate cognitive decline or to prevent the development of dementia offer a compelling alternative paradigm in reducing the impact of the disease, that not only benefit the individual but also the quality of lives of their families and society. Despite the dominance and popularity of pharmacological treatment, evidence that supports the pharmacological approach in preventing, redacting, or postponing cognitive decline during the stage of mild NCD showed limited effectiveness and potentially alarming side effects.[1] Given the limitations of the pharmacological approach, noninvasive brain stimulation (NIBS) is increasingly recognized as a potential alternative to tackle this problem.

Transcranial pulse stimulation (TPS) is regarded as one of the latest NIBS technology that applies repetitive single high-pressure ultrashort shockwave pulses within the ultrasound frequency range to stimulate the brain.[2] With a neuro-navigation device, TPS modulates the brain in a highly focal and precisely targeted manner.[3] The ultrasound stimulation of TPS differs from transcranial direct-

current stimulation (tDCS) and transcranial magnetic stimulation (TMS) from using direct or induced electric current. The limitation of direct electric current to stimulate the brain may include the problem of conductivity and failure to reach deep brain regions.[4,5] While ultrasound stimulation may come with the problem of skull attenuation, low-intensity focused ultrasound provides good spatial precision and resolution to modulate subcortical areas noninvasively.[6] The basic mechanism of TPS is mechanotransduction. It is a biological process where the cells convert the mechanical TPS stimulus into biochemical responses, thus modulating some fundamental cell functions such as migration, proliferation, differentiation, and apoptosis.[7,8]

Existing studies have provided supportive evidence for the effectiveness of TPS. A study with five patients who suffered from unresponsive wakefulness syndrome has shown improved vigilance and oropharyngeal motor function after TPS intervention.[9] Furthermore, a recent study has found beneficial and lasting effects of TPS to cognitive function.[3] TPS was applied to 35 old-age adults with Alzheimer's disease (AD) with a significant improvement in the cognition immediately, as well as one and three months after stimulation. Functional magnetic resonance imaging (fMRI) also showed markedly increased connectivity within the memory network including the hippocampus, parahippocampal cortex, parietal cortex, and precuneus.[3]

Mild NCD is a golden period for intervention before further progression of cognitive degradation that may lead to irreversible impairment. Up to date, there was no TPS trials targeting older adults with mild NCD. Besides, most of the neuromodulation studies, including previous TPS studies, have not been examined the impact of some important confounding factors such as APOE genotype and Brain-derived neurotrophic factor (BDNF). APOE-ε4 gene is the best known risk factor for developing dementia. APOE associates with the cognition of both dementia and nondementia persons.[10] BDNF level associated with worse cognitive impairment in multiple studies.[11,12]

The aim of this study was to perform an open-label study to assess the effectiveness and tolerability of TPS with neuro-navigation on cognition and functioning in old-age adults with mild NCD through the detail cognitive assessments and with the consideration of APOE gene and BDNF.

Materials and Methods

This study was a 2-week open-label interventional trial of TPS guided by neuro-navigation. All participants underwent the treatment-as-usual (TAU) period for 12 weeks. The intervention lasted for two weeks with three sessions per week. A total of six sessions TPS (6000 pulses each) were delivered. Cognitive status was assessed at baseline, after TAU periods, immediately after the intervention, and 12 weeks after the intervention.

Patients were referred by psychiatrists from the specialist outpatient clinic in the public sector. The clinician investigators assessed the potential participants based on the following inclusion and exclusion criteria. Inclusion criteria: (a) 60 years of age or above; (b) Chinese ethnicity; (c) Mild neurocognitive disorder (NCD) meeting the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria; (d) At least three months of stable antidementia therapy prior to enrolment (unchanged medication, if applicable).

Exclusion criteria: (a) A HK-MoCA score below the second percentile (adjusted to the subject's age and education level); (b) Alcohol or substance dependence; (c) Concomitant unstable major medical conditions or major neurological conditions (brain tumor, brain aneurysm, etc.); (d) Hemophilia or other blood clotting disorders or thrombosis; (e) Significant communicative impairments; (f) Participants with any metal implant in brain or treated area of the head.

Ethics approval was obtained at the institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (UW20-024). The study is also registered with the ClinicalTrials.gov (ClinicalTrials.gov identifier NCT05331560). The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants.

The intervention was performed at the University of Hong Kong. Trained healthcare personnel delivered the intervention. The TPS system consisted of a mobile single transducer and an infrared camera system for Magnetic Resonance Imaging (MRI) based neuro-navigation (NEUROLITH, Storz Medical AG, Tägerwilen, Switzerland). TPS generates single ultrashort (3 μs) ultrasound pulses with typical energy levels at 0.2–0.25 mJ/mm^2 and pulse frequencies at 4–5 Hz (pulses per second). A global brain stimulation approach was adopted where the total energy of 6000 TPS pulses per session was distributed homogenously over all accessible brain areas (frontal, parietal, temporal, and occipital lobes). Stimulation was applied with variable stand-offs at the handpiece for depth regulation and, manual movement of the handpiece over the skull with real-time visualization of the individual pulses on the patients' MRI brain images. The whole treatment session was recorded for post hoc evaluation of the individual intracerebral pulse localizations.

The participants were diagnosed with semistructured psychiatric diagnostic assessment using the validated

Chinese-bilingual version of the Structured Clinical Interview for DSM Mental Disorders. The participants' basic demographic data, including age, gender, years of education, place of birth, marital status, number of children, financial condition, family history of affective disorder, and household income were collected. Medical comorbidities were assessed with the Cumulative Illness Rating Scale (CIRS). The handedness of the participants was evaluated using the Edinburgh Handedness Inventory – Short Form. Details of the participants' psychiatric history, including the age of onset of the cognitive symptoms and current medication and dosage were recorded at baseline. The medical health history and treatment were obtained from the patients and confirmed with their electronic health records. APOE gene status and BDNF serum concentration were obtained through blood sample from participants. Structural MRI brain performed before the intervention.

The primary and secondary outcomes were assessed by a trained clinical investigator at baseline, after 12 weeks of TAU periods, immediately after 2 weeks of intervention, and follow-up 12 weeks after the intervention. The Hong Kong Chinese version of the Montreal Cognitive Assessment (HK-MoCA) was the primary outcome of the study.[13] It was widely used to assess global cognition. The total score ranges from 0 to 30 with higher scores indicating better cognition. Secondary outcomes included specific areas of cognitive functions included attention, working memory, and executive functions measured by forward and backward digit span (DS), the Stroop test, the category Verbal Fluency Test (VFT) and the Trail Making Test (TMT) Parts A and B, respectively. Also, daily functioning was assessed by the Hong Kong Chinese version of the Lawton Instrumental Activities of Daily Living Scale (Chinese IADL). The presence of depressive symptoms was measured by the Hamilton Depressive Rating Scale (HAM-D-17), the Apathy Evaluation Scale (AES-C) for apathy symptoms. Blood samples were collected to measure the serum BDNF level and the APOE genotype of patients. The adverse effects of TPS were monitored in each session by using a checklist covering possible symptoms such as headache, pain or pressure, and mood deterioration.

Statistical analyses were performed using IBM SPSS Statistics Version 29.0 (SPSS Inc., Chicago, IL, USA). The normality of the data distributions was assessed by QQ plots. Descriptive analysis was used in depicting the sociodemographic characteristics of the participants by Chi-square tests and t-test. Repeated Measures ANOVA were used to compare the overall time effects on the cognitive and psychological instruments (HK-MoCA, VFT, Stroop, TMT, DS, HAM-D-17, AES-C, Chinese IADL) done by participants in four time points (Baseline, 12-week TAU, immediate post after 6-session TPS, 3-month follow-up). The level of significance was two-tailed and set at $p < 0.05$. Pearson's Correlation analysis was performed on the psychological measures (HAM-D-17, AES-C, Chinese IADL) and genetic results (baseline BDNF serum concentration, APOE gene type) with baseline HK-MoCA scores. Multiple linear regression analysis was further deployed to identify potential relationship between psychological measures with global cognition. A paired-sample t-test was used in comparing the BDNF serum concentration of participants before and after the TPS interventions. Missing data was handled by sample mean imputation.

Results

Twenty-seven participants were recruited for this study. 5 participants were excluded with history of heart or brain surgeries or body with metal insertion. Another three participants had other health concerns and refused to attend the TPS interventions. In total, 19 eligible participants completed the whole TPS interventions with 100% treatment adherence. All participants reported no severe side effects. Table 1 described the sociodemographic characteristics. There were 12 females and 7 males completed the interventions, with a mean age of 74.32. Slightly more than half of the participants were married (52.6%). The majority (89.5%) did not obtain a bachelor's degree.

Table 1. Sociodemographic characteristics.

	Overall (n = 19)		
	n	%	[a]χ^2
Gender			−0.52*
Male	7	36.8	
Female	12	63.2	
Age			−0.23
60–69	4	21.1	
70–79	10	52.6	
80 or above	5	26.3	
Marital status			−0.02
Married	10	52.6	
Single/Separated/Widowed	9	47.4	
Education level			0.38
Elementary or below	9	47.4	
High School/College	8	42.1	
University or higher	2	10.5	
Family history on mental disorders			−0.27
Yes	4	21.1	
No	15	78.9	

[a]Chi-squares comparing HK-MoCA baseline scores.
*$P < 0.05$.

Around one-fifth (21.1%) of participants had a family history of mental disorders. Except for one subject who failed to identify one of the APOE alleles, the APOE polymorphism showed that all participants had either ε2 or ε3 APOE genotype, but no ε4 APOE genotype was recorded. 4 participants (20.0%) had the ε2/ε2 genotype (i.e., T–T), with another three participants were found to have mutated APOE genotype ε2/ε3 (i.e., T–T/C).

Regarding the clinical outcomes of the TPS interventions, repeated measures ANOVA confirmed there were statistically significant main effects of time on HK-MoCA (F (3, 54) = 4.99, P = 0.004), 30-second interval of Verbal Fluency Test (F (3, 54) = 2.94, P = 0.041), Stroop interference (F (3, 54) = 3.46, P = 0.023), and Chinese IADL (F (3, 54) = 2.78, P = 0.050) over the study phase (shown in Table 2). Bonferroni post hoc comparisons on HK-MoCA showed that both scores from immediate post (Mean = 21.16, SD = 3.98) and 12-week follow-up (Mean = 20.58, SD = 4.29) were significantly higher than that of 12-week TAU (Mean = 18.74, SD = 3.87) ($P < 0.05$). Bonferroni post hoc comparisons on Stroop interference revealed that participants during postintervention (Mean = 15.96, SD = 11.41) did significantly faster than that of TAU (Mean = 28.81, SD = 23.60) ($P < 0.05$). Regarding the psychological effects, although only significant effects of time were found on the daily functioning domain, a trend of improvements were shown on both depressive symptoms and apathy after the participants finished the TPS intervention.

BDNF serum concentration was measured before and after the TPS interventions. Out of the 19 participants who have completed the interventions, two participants refused to provide blood sampling after TPS interventions. And thus, the BDNF serum levels of 17 participants were retrieved for analysis (shown in Fig. 1). The mean BDNF serum level collected after intervention (Mean = 13.79 ng/mL, SD = 11.80) was lower than that of preintervention (Mean = 21.00 ng/mL, SD = 14.30). However, a paired-sample t-test revealed that the difference was not statistically significant, t (16) = −1.57, P = .135.

Discussion

To the best of our knowledge, this is the first TPS study targeting older adults with mild NCD. The results showed that TPS has significantly improved the global cognition of patients and the effect maintained for at least three months postintervention. The improvement could not be explained by the change in mood symptoms measured by HAM-D-17. Besides the global cognition, executive function measured by the Stroop test also showed significant improvement immediately after the intervention. There were no major adverse effects reported during the whole study period.

The overall result is compatible with the previous TPS study.[3] TPS could bring a significant improvement in the cognition immediately after the intervention and the effect maintained for a period of time. It showed that TPS has beneficial effect not only in older adults with major NCD, but also in older adults with mild NCD.

BDNF was believed to be important for the brain development and maintenance of its function.[14] Low-serum BDNF was associated with lower cognitive test

Table 2. Clinical outcomes of the TPS interventions (n = 19).

		Baseline		12-Week treatment-as-usual		2-Week TPS immediate post		12-Week follow-up		One-way repeated ANOVA
										Effect of time
Domains	Measures	Mean	SD	Mean	SD	Mean	SD	Mean	SD	(n = 19)
Global cognition	HK-MoCA total	19.32	4.52	18.74	3.87	21.16	3.98	20.58	4.29	F (3, 54) = 4.99, P = 0.004**
Cognitive functioning	Verbal Fluency Test									
	30-sec interval	24.89	4.36	26.37	5.39	26.53	5.95	28.42	6.79	F (3, 54) = 2.94, P = 0.041*
	60-sec interval	33.58	5.08	34.58	7.91	34.84	8.60	36.74	9.72	F (3, 54) = 1.72, P = 0.173
	Stroop interference	26.14	21.86	28.81	23.60	15.96	11.41	19.46	13.64	F (3, 54) = 3.46, P = 0.023*
	TMT interference	94.56	96.53	78.29	81.01	85.13	57.61	84.10	69.98	F (3, 54) = 0.51, P = 0.487
	Forward DS total	9.26	2.16	10.26	2.49	9.89	2.62	9.79	2.78	F (3, 54) = 2.61, P = 0.061
	Backward DS total	4.58	2.22	4.58	2.04	4.89	2.40	4.84	2.34	F (3, 54) = 0.83, P = 0.484
Depressive symptoms	HAM-D total	6.63	4.55	6.79	4.16	5.26	4.42	6.05	4.80	F (3, 54) = 1.03, P = 0.388
Apathy	AES-C total	34.26	10.35	32.47	6.87	31.84	8.60	29.63	8.04	F (3, 54) = 2.76, P = 0.051
Daily functioning	Chinese IADL total	23.42	3.32	22.16	4.26	23.00	3.16	23.32	2.93	F (3, 54) = 2.78, P = 0.050*

AES-C, Apathy Evaluation Scale-Clinician; DS, digit span; HAM-D, Hamilton Depression Rating Scale; IADL, Instrumental Activities of Daily Living; MoCA, Montreal Cognitive Assessment; SD, standard deviation.
*$P < 0.05$.
**$P < 0.01$.

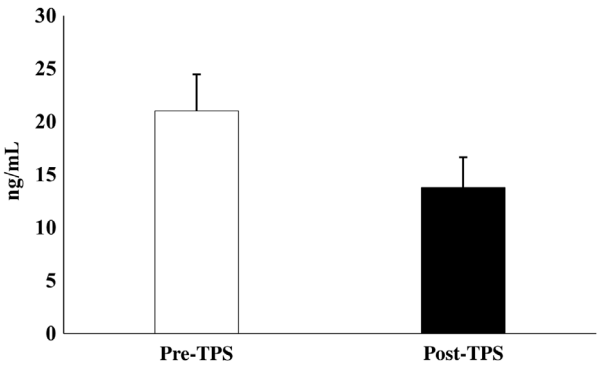

Figure 1. BDNF serum levels before and after TPS interventions ($N = 17$). Data are the mean ± standard error mean. Values are expressed in ng/mL.

scores and mild cognitive impairment (MCI).[15] Some of the previous interventional studies reviewed improved cognitive performance mediated by the BDNF.[16] We have also conducted the measurement of BDNF in this study. However, there was no significant change in the serum concentration and no correlation was found between the BDNF and the improvement of cognition. Despite the importance of BDNF, the correlation between BDNF serum level and cognitive performance was not always consistently reported.[12,17] In addition, the relatively small sample size of the current study may have contributed to the undetectable change of BDNF induced by the TPS.

It is worth noting that the strength of the current study included the comprehensive measurement of cognitive functions, the biomarkers including the APOE gene status and BDNF. However, the current study did not detect any significant effect of APOE gene polymorphism on the change of cognition, probably due to the majority of participants having same ε2 or ε3 allele instead of the high-risk ε4 allele. Also, the current study included a 12-week TAU period in this study to control the impact of practice effect of the repeated testing of the same cognitive assessment tools within a period of time. The limitations of this study include the open-label study design, which could introduce the bias. The relatively small sample size ($n = 19$) may result in the issue of underpower to detect the changes in other areas of cognitive function and BDNF. The short period of intervention (only six sessions within two weeks) may not be enough to induce significant long-lasting changes in the brain although the clinical effect was maintained at least 12 weeks in this study.

Conclusion

TPS is a safe and effective noninvasive neuromodulation intervention for the older adults with MCI. It has a great potential to delay the deterioration of cognition in older adults. The effectiveness and the long-term effect of TPS in cognition still require further large-scale, randomized, sham-controlled trial to support the findings.

Author Contributions

TF is responsible for conducting the study. TC, KT, JN and VL are responsible for the data organization and writing the manuscript. WCC and CC are responsible for the design and supervision of the whole study. CW is responsible for the data analysis.

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Conflict of Interest

The authors received the grant from the Associated Medical Supplies Co. Ltd.

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