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RESEARCH ARTICLE

# Randomized controlled trial of TDCS on cognition in 201 seniors with mild neurocognitive disorder

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## Abstract

**Objective**: To examine the efficacy and safety of combined transcranial direct current stimulation (tDCS) and working memory training (WMT) in enhancing the cognitive functions for individuals with mild neurocognitive disorder due to AD (NCD-AD). **Methods**: In this double-blind, sham-controlled randomized clinical trial (RCT), 201 patients with NCD-AD were randomly assigned for a 4-week intervention of either a combination of tDCS and WMT, sham tDCS and WMT, or tDCS and control cognitive training (CCT). Global cognition and domain-specific cognitive function were assessed before and after the intervention with Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog), category verbal fluency test, logical memory, digit, and visual span tests. **Results**: Study participants did not show intervention group differences in baseline demographics, or cognitive characteristics (ANOVA). Cognitive enhancement was found across three groups after 4 weeks intervention. Combined tDCS-WMT group showed significantly greater improvement compared with single-modality groups in delayed recall ($P = 0.043$, $\eta^2 = 0.036$) and working memory capacity ($P = 0.04$, $\eta^2 = 0.038$) at 4th week, and logical memory at 12th week ($P = 0.042$, $\eta^2 = 0.037$). Adverse events, including skin lesions (2.2%), were similar between groups. **Interpretation**: tDCS or WMT could be a safe, feasible, and effective intervention for individuals with NCD-AD. A combination of tDCS and WMT presents greater cognitive enhancement, which may highlight the potential synergistic effects of combined modality intervention on cognition.

## Introduction

With rapid population aging in China and globally, Alzheimer's disease (AD) is expected to have profound impacts on individuals and society.[1,2] At present, there are no effective pharmacological treatments to halt or slow down cognitive decline in AD.[3–5] Thus, developing the strategies that may attenuate the cognitive decline in people at high risks of developing AD, or maintain the cognitive function is of great pragmatic value.

Of these, cognitive training, working memory training (WMT) in particular, presents modest but positive enhancing effects on cognition in preclinical AD, either in the cognitive domain being trained (i.e., working memory)[6,7] or across the other cognitive functions.[8,9] A noninvasive brain stimulation (NIBS), transcranial direct current stimulation (tDCS), also presents a promising efficacy. TDCS facilitates neural plasticity by delivering weak electric currents (usually ranging from 1 to 2 milliamps) to the scalp to modulating excitability of the underlying brain regions.[10–12] There are reports to suggest that tDCS over frontal and temporal cortex are associated with the improvements in memory performance in mild cognitive impairment (MCI)[13] and AD patients.[14,15]

Despite considerable efforts have been directed to investigate the therapeutic effects of WMT or tDCS as single modality, most previous studies were using a small sample size or absence of sham controls, thus lead to

controversial results of intervention-induced effects.[6–16] Recently, encouraging results from tDCS-augmented cognitive training in normal young adults,[17] highlight the possibility to develop the augmentation strategies that will consolidate the benefits of WMT. As working memory impairment is also a core and early symptom of AD,[18] it is of clinical interests to explore whether active tDCS have additional benefits on WMT, either in terms of synergistic effects of combined intervention, or sustainability of changes after intervention in individuals at risk for developing AD.

To contribute to the empirical evidence of tDCS in neurorehabilitation and overcome some limitations of previous studies, we aimed to investigate the effects of combined tDCS and WMT on global cognition, memory attention, and executive function in a relatively large sample of older adults with mild neurocognitive disorder due to Alzheimer's disease (NCD-AD). In our paradigm, we also build in a long postintervention observation period to examine the safety, efficacy, and potential enduring effects of these modality-driven interventions.

We hypothesized that (1) the intervention of WMT with/or without tDCS over left temporal cortex (with control cognitive training) would enhance the performance in memory and other core cognitive function; and (2) a combination of tDCS and WMT would be associated with greater and more sustained improvement in cognitive performance over single-modality intervention by either WMT or tDCS.

## Patients and Methods

### Study design

A full protocol has been published previously.[19] This study was a double-blind (participant and assessor), sham-controlled randomized clinical trial conducted at an academic cognitive training center from May 2015 to November 2017. As shown in Figure 1, eligible participants were randomly assigned to a 4-week intervention of either tDCS-working memory training (tDCS-WMT), sham tDCS-working memory training (sham tDCS-WMT), or tDCS-control cognitive training (tDCS-CCT). After intervention, participants were followed for 8 weeks. No changes to methods were made after the trial started. This study is reported in accordance to the Consolidated Standards for Reporting Trials (CONSORT) statement for nonpharmacological treatments.

### Patients

Participants were recruited from elderly social centers in Hong Kong. Interested participants would first undergo a screening assessment for cognitive deficits before recruitment for intervention. Potential participants with positive screen of impaired memory function as evaluated by the Chinese abbreviated MCI test would be invited to undergo further examination for eligibility.[20]

Two hundred and one right-handed Chinese adults (aged from 60 to 90 years) who met the criteria for mild neurocognitive disorder due to Alzheimer's disease (NCD-AD) in accordance with the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) were recruited in this study.

### Inclusion criteria of NCD-AD

NCD-AD participants were defined by the following criteria:[21] (1) evidence of modest cognitive decline in one or more cognitive domains, identified with the Clinical Dementia Rating (CDR) subcategory box score $\leq$0.5 and Cantonese Mini Mental State Examination (CMMSE) score range from 22 to 27; (2) no interference with independence in everyday activities; (3) and no better explanation by other psychiatric disorders. NCD-AD patients fulfilled the criteria of NCD and demonstrated impaired episodic memory as assessed through delay recall in list learning and did not suffer from uncontrolled hypertension, diabetes, or hyperlipidemia.

The exclusion criteria were as follows: (1) previous diagnosis of dementia or other major neurocognitive disorders; (2) past history of bipolar affective disorder or psychosis; (3) history of major neurological deficit including stroke, transient ischemic attack or traumatic brain injury; (4) taking a psychotropic or other medication known to affect cognition (e.g., benzodiazepines, antidementia medication, etc.); (5) physically frail affecting attendance to training sessions; (6) already attending regular cognitive training; and (7) significant communication problems.

### Study Interventions

#### Transcranial direct current stimulation (tDCS)

Stimulation was delivered by a battery-driven constant current stimulator (NeuroConn, Ilmenau, Germany) through a pair of conductive-rubber electrodes. Two electrodes were fixed with conductive paste (Ten20®, Neurodiagnostic Electrode Paste, Weaver and Company, Aurora, CO, USA) and two elastic straps were used to affiliate the electrode placement. We positioned the anodal electrode (5 $\times$ 7 cm) over left lateral temporal cortex (LTC) (i.e., T3 in the international 10/20 EEG system) and the cathodal electrode (5 $\times$ 7 cm) over the contralateral upper limb.

The stimulation parameters were as follows: 20 min at 2 milliamps, 20 sec fade-in and 20 sec fade-out.[22] In the

 

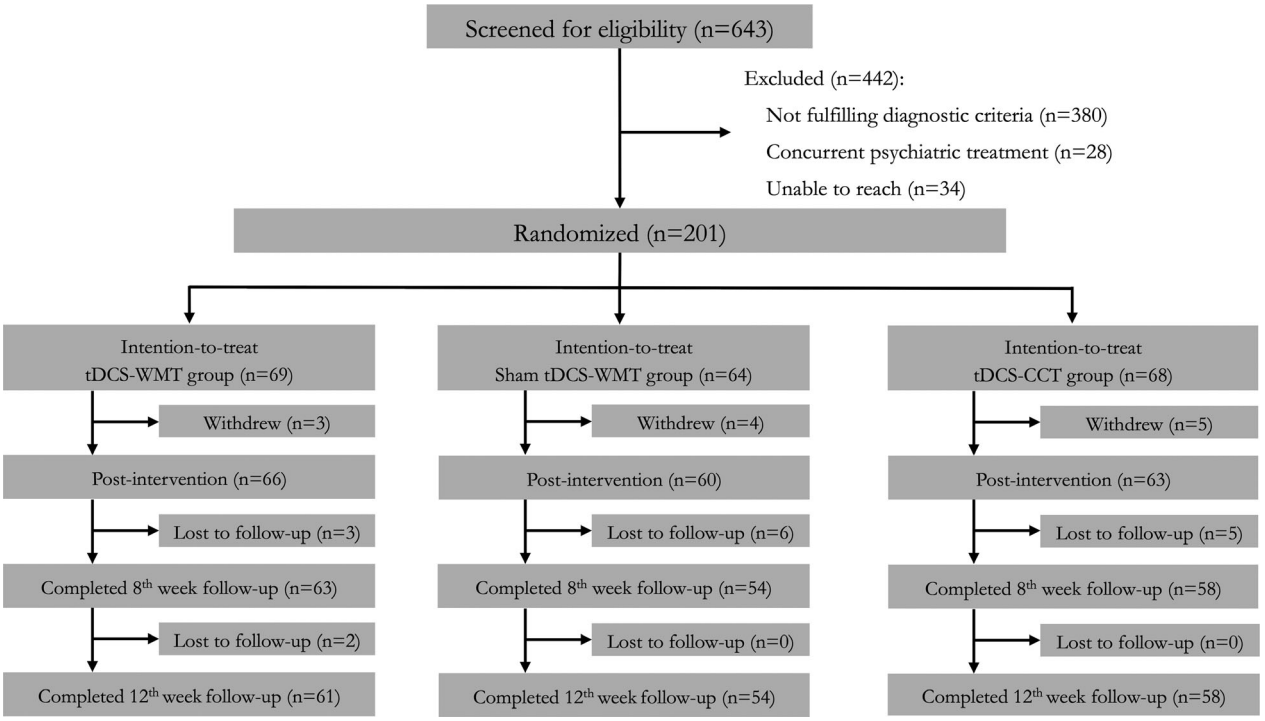


**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the transcranial direct current stimulation (tDCS) and working memory training (WMT) trial

sham condition, the stimulation parameters were the same as the ones used in active tDCS, but the stimulation only lasted for 30 sec with the electrodes left in place for a further 20 min. This procedure mimics the transient skin sensation of tingling and burning induced by real tDCS without producing any sustainable effects.

### Working memory training

Adaptive N-back test is a computerized working memory training (WMT) paradigm proposed by Kirschner for measuring working memory and processing speed.[23] During the test, participants were presented with a sequence of stimuli and required to indicate if the stimulus matched the one from $n$ steps earlier in the sequence. Adaptive N-back task refers to the adjustment of the level of difficulty of the task according to the accuracy. The N-back task starts from $n = 1$. The cases with a high degree of accuracy (i.e., greater than 70%) would be advanced to a higher level of difficulty. The WMT paradigm was programmed and performed by E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA).

### Controlled cognitive training

Continuous performance test is employed as a controlled experiment to working memory training. During the test, participants were presented with a sequence of stimuli and required to click the mouse when they detected the stimuli. The test was performed by E-Prime 2.0.

## Procedures

### Intervention schedule

This trial was a 4-week intervention with three sessions per week, 45 min per session. All participants received a total of 12 sessions of interventions. The schedule for intervention was the same in three randomized groups.

### Assessments schedule

Eligible participants were scheduled for comprehensive cognitive assessments.[19] Same assessments were conducted at baseline (T0), 4th week (T1, postintervention), 8th week (T2, 4 weeks postintervention) and 12th week (T3, 8 weeks postintervention).

## Outcome measures

### Primary cognitive outcomes

1. Working memory test: the N-back task performance in terms of reaction time (RT) at baseline, 4th, 8th, and 12th weeks were adopted as a direct measure of improvement in task performance.

 

2. Global Cognitive function would be measured by the Chinese version of the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog). It is a standard global cognitive assessment for clinical intervention of AD. The scale score ranges from 0 to 70, with increasing scores indicating higher severity of global cognitive impairment.

### Secondary outcomes

1. Memory and language tests: Logical memory, 10 min word list learning test, category verbal fluency test (CVFT) and trail making tests (TMT). During logical memory test, participants read a logically organized story, and approximately 20 min later are asked to recall the story. Word list learning test, consisting of 10 semantically nonassociated words that is presented consecutively over three free trials of immediate recall and a 20-min delayed recall (DR). DR performance, as the number of correct words recalled on DR trial in word list learning test, was used to evaluate the episodic memory performance. The score range of DR trial and logical memory is 0–10, with increasing scores indicating better performance. Working memory capacity refers to the maximum number of word recalled in word list learning test.[24]
2. The Chinese Neuropsychiatric Inventory (NPI) was used to assess the changes in neuropsychiatric symptoms across different 12 domains. In this study, NPI would evaluate potential mood and behavioral change, especially mood and euphoria that may theoretically be affected by tDCS administration.
3. A checklist of potential adverse effects associated with computer based cognitive training and tDCS administration were used to monitor tolerability and adverse events throughout intervention. The Adverse Event Checklist (AEC) covers the symptoms from eight systems, including body as whole, cardiovascular, digestive, circulatory, metabolic, musculoskeletal, nervous, and urogenital systems.[19] AEC were checked in each assessment points through the study.

We conducted randomization via Randomization.com (http://randomization.com/). Participants were unware of the type of intervention they received. Assessors conducting cognitive assessment and the researchers performing data analysis were blinded to the intervention type. Informed consent was obtained from all participants. This study was approved by the Joint Chinese University of Hong Kong-New territories East Cluster Clinical Research Ethics Committee. The study was registered with the Centre for Clinical Research and Biostatistics and Clinical Trials Registry of the Chinese University of Hong Kong (ChiCTR-TRC-14005036).

### Calculation of sample size

Based on the cognitive measures across time and intervention groups, the potential effect size of cognitive enhancement of cognitive training and tDCS is estimated from the findings from our recent study.[25] In a sample size calculation, $N = 51$ would yield a power of 80% to detect a statistically significant difference between the groups with modality-driven interventions. Taking into account of the dropout rate of 25%, 64 participants per arm (192 for three study arms) would be recruited.

### Statistical analysis

Multilevel generalized linear modeling was employed to account for the correlations from within participants and different time points of measurements. Demographics and cognitive characteristics at baseline were compared between tDCS-WMT, sham tDCS-WMT, and tDCS-CCT groups. Score changes in cognitive function from baseline to each follow-up point and intervention group were tested with occasions (time points) at level one and participants at level two. Secondary analyses of domain-specific cognitive function were performed to compute for group differences in outcome measures. Incidence of adverse events was recorded. Statistical significance was set at $P < 0.05$. Cohen's d was used to assess the effect size for the outcome measures within group (i.e., between time points). Cohen's $d = 0.2$ was considered a small effect size, 0.5 represents a medium effect size, and 0.8 a large effect size. Eta-squared ($\eta^2$) was calculated as a measure of intervention effect size for the outcome measures between groups, of which $\eta^2 > 0.36$ refers to a strong effect, $0.04 < \eta^2 \leq 0.36$ refers to a moderate effect, $\eta^2 \leq 0.04$ means the effect is statistically significant but weak. All analyses were performed using SPSS Statistics 24.0 (IBM, Armonk, NY).

## Results

Six hundred and forty-three participants underwent screening and 201 of them were recruited in this study. As depicted in the CONSORT diagram (Fig. 1), 69 cases were assigned to tDCS-WMT group, 64 cases to sham tDCS-WMT group, and 68 cases to tDCS-CCT group. Twenty-eight participants dropped out from this study (total dropout rate: 13.9%), including eight cases from tDCS-WMT group, 10 cases from sham tDCS-WMT group, and 10 cases from tDCS-CCT group. The main reasons of withdrawn include physical condition (7/28),

 

uncomfortable feeling (6/28), lack of time (10/28), and personal reasons (5/28). There were no differences in demographic data and baseline cognitive characteristics between different intervention groups (Table 1).

As to adverse events, three cases had skin lesions under the cathodal electrode during the repeated sessions of tDCS.[26] There were no differences between tDCS-WMT group (2/69) and tDCS-CCT group (1/68).

## Outcome measures

### Primary outcomes

Global cognition measured by ADAS-Cog improved significantly from baseline to postintervention (T1) evaluation within three groups (tDCS-WMT group: $P < 0.001$, Cohen'd = −0.571; sham tDCS-WMT group: $P = 0.002$, Cohen'd = −0.333; tDCS-CCT group: $P < 0.001$, Cohen'd = −0.527) (Table 2). At T2 and T3, ADAS-Cog showed a trend for reverting toward the baseline, but the performance was still significantly better than baseline (T3: tDCS-WMT group: $P = 0.047$, Cohen'd = −0.212; sham tDCS-WMT group: $P = 0.045$, Cohen'd = −0.239; tDCS-CCT group: $P = 0.021$, Cohen'd = −0.328). However, comparing the magnitude of improvement between groups, no statistically significant differences were observed through the study period (Fig. 2A).

As for performance of N-back task, all randomized groups showed improvement in RT after intervention (T1: tDCS-WMT group: $P < 0.001$, Cohen'd = 0.902; sham tDCS-WMT group: $P < 0.001$, Cohen'd = 0.706; tDCS-CCT group: $P < 0.001$, Cohen'd = 0.884) (Table 2). Improvement persisted at T3 with no group differences at postintervention assessments (T1, T2, and T3) (Fig. 2B).

### Secondary outcomes – changes in other cognitive function

All randomized groups showed improvement in delayed recall after intervention (T1: tDCS-WMT group: $P < 0.001$, Cohen'd = 0.959; sham tDCS-WMT group: $P < 0.001$, Cohen'd = 0.633; tDCS-CCT group: $P < 0.001$, Cohen'd = 0.538). The tDCS-WMT group had greater improvement over single-modality intervention (Group effect: $P = 0.043$, $\eta^2 = 0.036$). The performance of delayed recall showed a trend for reverting toward the baseline at postintervention assessments. At T3, only tDCS-WMT group still showed significant enhancement on delayed recall performance over baseline ($P = 0.007$, Cohen'd = 0.296) (Fig. 3A). Similarly, all randomized groups showed improvement in working memory capacity after intervention (T1) (Fig. 3B). The tDCS-WMT group showed higher WM capacity compared with either sham tDCS-WMT or tDCS-CCT at T1 ($P = 0.04$, $\eta^2 = 0.038$).

Compared with either sham tDCS-WMT or tDCS-CCT group, the tDCS-WMT group showed better performance of logical memory at 12$^{th}$ week (Group effect, $P = 0.042$, $\eta^2 = 0.037$, Fig. 3C). The improvement on FDS after intervention (T2) were observed in all groups (tDCS-WMT group: $P = 0.029$, Cohen'd = 0.314; sham tDCS-WMT group: $P = 0.038$, Cohen'd = 0.307; tDCS-CCT group: $P = 0.013$, Cohen'd = 0.316). At T3, tDCS-WMT group still had improved performance on FDS ($P = 0.024$, Cohen'd = 0.292). There were no group

**Table 1.** Baseline demographics and cognitive characteristics across three randomized groups

| | tDCS-WMT ($n = 69$) | Sham tDCS-WMT ( $n = 64$) | tDCS-CCT ( $n = 68$) | *F* Value | *P* Value |
|---|---|---|---|---|---|
| Age | 74.2 ± 6.7 | 74.5 ± 6.6 | 73.4 ± 6.1 | 0.47 | 0.626 |
| Sex (F/M) | 42/21 | 36/17 | 30/27 | 2.35 | 0.098 |
| Education (years) | 7.3 ± 4.8 | 6.5 ± 4.3 | 7.5 ± 5.3 | 0.81 | 0.446 |
| ADAS-Cog | 9.4 ± 3.9 | 9.4 ± 4.0 | 9.7 ± 3.9 | 0.28 | 0.755 |
| Reaction time (msec) | 995.1 ± 237.9 | 963.2 ± 204.9 | 930.9 ± 238.2 | 1.87 | 0.201 |
| CIRS | 3.1 ± 1.9 | 3.3 ± 2.1 | 3.1 ± 2.1 | 0.27 | 0.764 |
| CNPI | 2.1 ± 3.4 | 2.9 ± 3.6 | 2.1 ± 3.2 | 1.14 | 0.321 |
| CDR-SOB | 1.1 ± 0.7 | 1.2 ± 1.0 | 1.2 ± 0.7 | 0.54 | 0.584 |
| CMMSE | 25.7 ± 2.6 | 25.6 ± 2.9 | 25.5 ± 2.5 | 0.10 | 0.907 |
| CVFT | 37.5 ± 10.6 | 38.8 ± 10.6 | 37.4 ± 8.4 | 0.39 | 0.676 |
| Forward digit span | 7.1 ± 1.5 | 7.3 ± 1.3 | 7.0 ± 1.3 | 0.85 | 0.427 |
| Logical memory | 3.5 ± 2.1 | 4.2 ± 2.1 | 3.9 ± 2.3 | 1.66 | 0.193 |

Data are raw scores and presented as mean ± SD.

Abbreviations: ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale; CDR-SOB, clinical dementia rating-sum of box; CIRS, cumulative illness rating scale; CMMSE, Cantonese Mini-Mental State Examination; CNPI, Chinese Neuropsychiatric Inventory; CVFT, category verbal fluency test.

 

**Table 2.** Primary and secondary cognitive outcomes across three randomized groups (Raw scores)

| | Performance at 4th week (T1) | | | Performance at 8th week (T2) | | | Performance at 12th week (T3) | | |
|---|---|---|---|---|---|---|---|---|---|
| Outcomes | tDCS-WMT | Sham tDCS + WMT | tDCS-CCT | tDCS-WMT | Sham tDCS + WMT | tDCS-CCT | tDCS-WMT | Sham tDCS + WMT | tDCS-CCT |
| Primary outcomes | | | | | | | | | |
| ADAS-Cog | 7.57 ± 3.16 | 8.14 ± 3.53 | 8.00 ± 3.25 | 8.36 ± 3.75 | 8.16 ± 3.64 | 8.45 ± 3.79 | 8.47 ± 3.62 | 8.53 ± 3.36 | 8.69 ± 3.41 |
| Reaction time (ms) | 816.87 ± 143.89 | 848.01 ± 210.09 | 771.94 ± 193.77 | 824.86 ± 214.76 | 882.04 ± 185.02 | 814.89 ± 228.96 | 867.09 ± 196.13 | 804.98 ± 286.27 | 834.24 ± 224.73 |
| Secondary outcomes | | | | | | | | | |
| CNPI | 0.84 ± 1.22 | 0.67 ± 0.86 | 0.94 ± 1.14 | 0.83 ± 1.13 | 0.71 ± 1.13 | 0.89 ± 0.93 | 0.82 ± 1.06 | 0.58 ± 0.72 | 1.11 ± 1.17 |
| CMMSE | 26.84 ± 2.49 | 26.26 ± 2.66 | 26.18 ± 2.73 | 26.27 ± 2.63 | 26.25 ± 2.81 | 26.02 ± 2.63 | 26.02 ± 2.75 | 25.74 ± 2.67 | 26.21 ± 2.67 |
| Delayed recall | 6.44 ± 2.05 | 5.75 ± 2.21 | 5.73 ± 2.23 | 4.59 ± 2.52 | 4.17 ± 2.34 | 4.21 ± 2.56 | 5.11 ± 2.51 | 4.85 ± 2.51 | 4.98 ± 2.45 |
| Logical memory | 3.65 ± 2.34 | 3.72 ± 2.43 | 3.93 ± 2.48 | 4.30 ± 2.23 | 3.96 ± 2.30 | 4.11 ± 2.12 | 5.15 ± 2.52 | 5.13 ± 2.56 | 5.02 ± 2.45 |
| CVFT | 39.67 ± 10.79 | 38.53 ± 11.12 | 38.07 ± 9.16 | 40.59 ± 11.22 | 41.60 ± 12.42 | 39.96 ± 8.96 | 41.79 ± 11.31 | 41.02 ± 12.23 | 40.82 ± 10.42 |
| FDS | 7.27 ± 1.32 | 7.43 ± 1.31 | 7.14 ± 1.29 | 7.44 ± 1.42 | 7.60 ± 1.32 | 7.30 ± 1.54 | 7.46 ± 1.36 | 7.55 ± 1.32 | 7.14 ± 1.29 |
| BDS | 2.94 ± 1.06 | 3.23 ± 1.40 | 3.20 ± 1.12 | 3.32 ± 1.25 | 3.17 ± 1.27 | 3.07 ± 1.01 | 3.15 ± 1.18 | 3.49 ± 1.60 | 3.13 ± 1.22 |
| TMT-A (s) | 18.48 ± 12.25 | 17.43 ± 13.24 | 16.78 ± 8.67 | 16.27 ± 11.11 | 16.17 ± 11.61 | 14.73 ± 7.95 | 14.64 ± 9.29 | 14.83 ± 12.09 | 15.01 ± 8.02 |
| TMT-B (s) | 76.62 ± 50.59 | 75.78 ± 58.01 | 93.11 ± 59.02 | 76.20 ± 61.89 | 77.23 ± 63.14 | 85.26 ± 59.19 | 78.16 ± 63.70 | 58.31 ± 32.65 | 84.21 ± 61.38 |

ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale; BDS, backward digit span; CMMSE, Cantonese Mini-Mental State Examination; CNPI, Chinese Neuropsychiatric Inventory; CVFT, category verbal fluency test; FDS, forward digit span; TMT-A, trail making test part A; TMT-B, TMT part B.

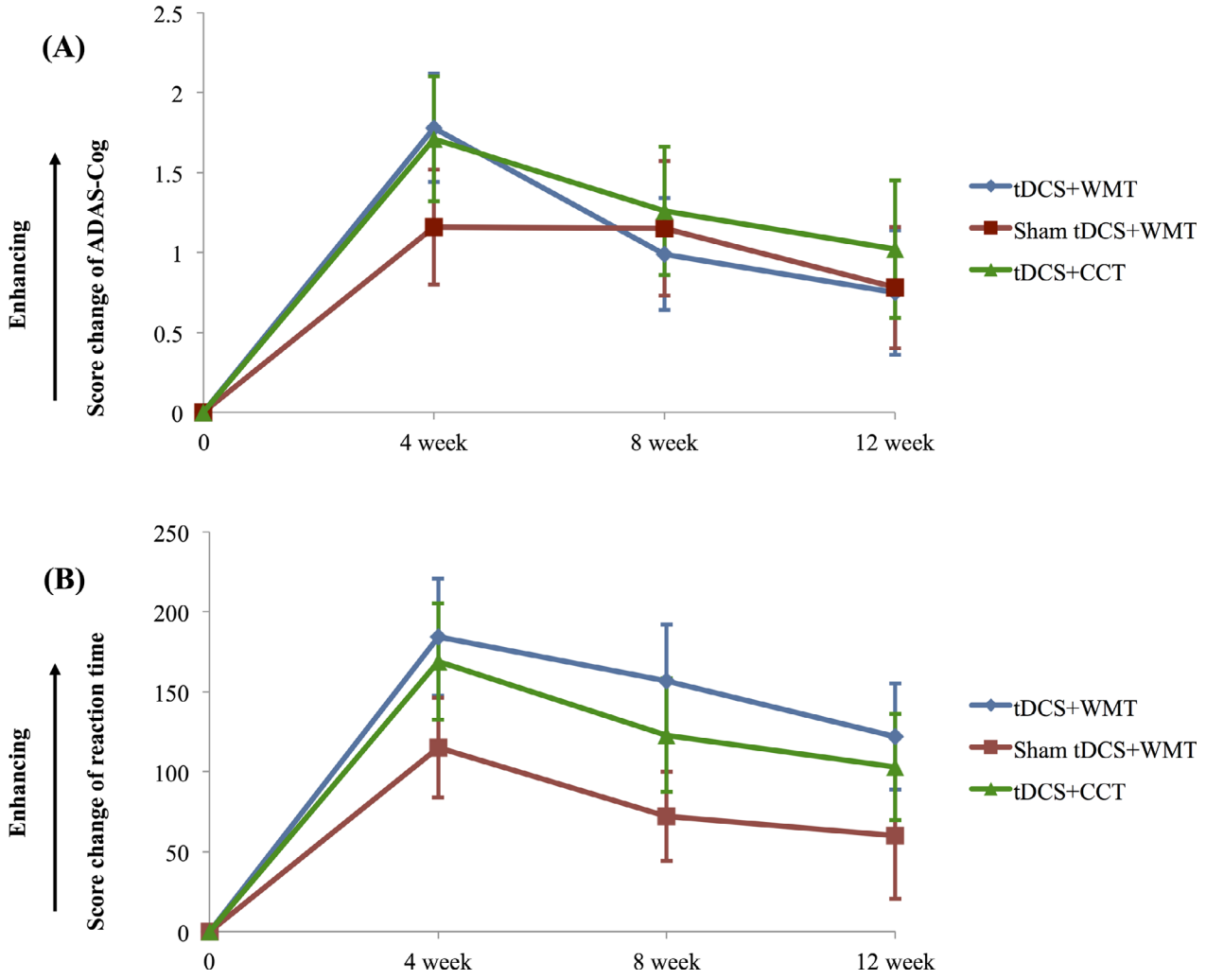


**Figure 2.** Primary outcome of the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and delayed recall. Panel A shows the results for the change from baseline in the score on ADAS-Cog (Higher score indicating greater enhancement). Panel B shows the results for the change from baseline in the score on mean reaction time (Higher score indicating great enhancement). Error bars represent the standard error (SEM)

differences in FDS at postintervention assessments (T1, T2, and T3).

Compared to baseline, all three groups showed enhanced performance on CVFT (Table 2). There were no group differences at postintervention assessments (T1, T2, and T3), of which all groups showed similar improvements in CVFT performance (Fig. 3D). There were no group differences in CNPI at postintervention assessments (T1, T2, and T3).

## Discussion

Through scheduled tDCS and working memory training, individuals with NCD-AD appeared to have improvement in global cognition and domain-specific cognitive functions. As compared with single-modality intervention, a combination of tDCS and WMT showed greater improvement in memory performance after a 4-week intervention, and the cognitive benefits appeared to carry-over to 8 weeks after the intervention. Moreover, the enhancement induced by dual modality intervention also appeared to influence a broader spectrum of cognitive function including attention and language.

To our knowledge, this is one of largest sham stimulation-controlled randomized clinical trial on tDCS and WMT for individuals at risk for developing AD. Prior research has evaluated the cognitive effects of tDCS and WMT as single-modality intervention.[6–16] Our findings are consistent with the previous findings that tDCS- or WMT-induced cognitive benefits, and replicated the

 

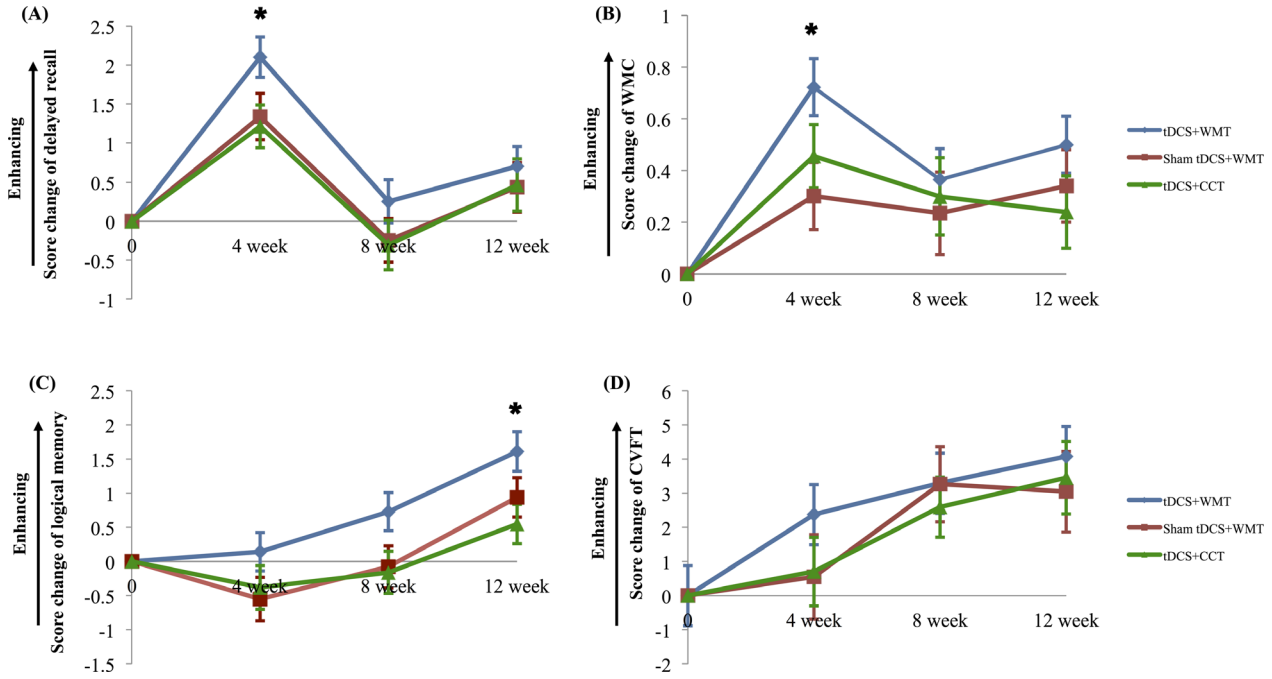


**Figure 3.** Secondary outcomes of other memory performance. Panel A shows the results for the change from baseline in the score on delayed recall performance (Higher score indicating greater enhancement). Panel B shows the results for the change from baseline in the score on working memory capacity (WMC) (Higher score indicating greater enhancement). Panel C shows the results for the change from baseline in the score on logical memory (Higher score indicating greater enhancement). Panel D shows the results for the change from baseline in the score on category verbal fluency test (CVFT) (Higher score indicating greater enhancement). Error bars represent the standard error (SEM). *Indicates significant between-group difference ($P < 0.05$)

observations in a relatively large and well-characterized population.

Stemming from diverse mechanisms, WMT through N-back task enables a purposeful training of speed-based working memory; active tDCS delivers weak electrical currents to possibly modulate the membrane potential of the neurons embedded in the targeted cortical region and consequently enhance the brain's capacity to adapt (i.e., neuroplasticity).[27] It is not surprising to detect the improvement in the domain being trained, such as memory.[28] When WMT with an add-on tDCS, the two modalities showed synergistic effects presenting with gains across the broader domains of cognitive functions over time.

Of these, our data provide evidence in support of the hypothesis that WMT with an add-on tDCS (i.e., combined modality) could enhance the efficacy of WMT. Different from previous tDCS studies, we selected left lateral temporal cortex (LTC) as the targeted cortical region for anodal tDCS, rather than the mostly used target as left dorsolateral prefrontal cortex (DLPFC).[29] The rationale for selecting LTC is that medial temporal lobe (MTL), including hippocampus, is the primary region affected in late onset AD[30] Deep-brain stimulation (DBS) on MTL has shown positive effects on visuospatial memory.[10,31] Because MTL is difficult to reach through noninvasive approach, LTC, as the "surface" part of MTL, engages a disease-specific spotlight here.[32] Our observations indicate that NCD-AD patients with memory impairment demonstrated improvements in global cognition and memory function. A combination of left LTC tDCS and WMT improved the memory function including episodic memory and logical memory. In addition, we also observed benefits in tDCS-WMT group in tasks related to attention, language, and possibly executive function as reflected by improvement in CVFT performance at T1. Therefore, the intervention is associated with cognitive benefits in both memory and non-memory functions, and our findings supports the quest for further research in optimizing cognitive compensatory reserve in individuals with high risks of developing clinical AD.

With recent intense interests in noninvasive brain stimulation, the sustainability of treatment effects also engages a growing concern. From our observations, while cognitive performance declined upon cessation of intervention, some carryover effects remained at 8 weeks. This stimulation-induced changes related to neuroplasticity

 

have been reported in animal models, of which the repeated sessions of tDCS displayed an increase in the long-term potentiation (LTP) accompanied by the enhancement in WM-related behavior.[33,34] Meanwhile, the plasticity in WM system has also been investigated across the lifespan. Capacity, as a fundamental element of Baddeley's WM model,[28,35] reflects the maximum amount of information that WM can handle, could be employed as an indicator of plasticity. Closely tied to this model, the prominent magnitude of the improvement in WM capacity in combined modality group appeared to suggest that some long-term changing in WM capacity had been induced by left LTC tDCS, a possible proxy marker for neuroplasticity response to the intervention.

## Conclusions

A 4-week of tDCS and/or WMT intervention, either single or combined modality, can enhance the global cognition and memory function in individuals with NCD-AD with relatively low incidence of adverse events. Compared to single modality, combined modality intervention has greater memory enhancement and longer sustainability. The paradigm could be adapted for further translation into clinical interventions for individuals at risk of cognitive decline.

## Clinical Significance of Observed Effects

For a novel intervention to be considered clinically useful, the extent of cognitive improvement has to be low risk, clinically meaningful and sustainable. As for the primary outcome, a combination of tDCS and WMT enhanced the delayed recall performance. Although $\eta^2 = 0.036$ is a statistically small to moderate effect size, in clinical terms, a 2-point increase in the 10-point scale makes the difference between groups, for instance, tDCS-WMT (2.1 point) versus sham tDCS-WMT (1.4 point) and tDCS-CCT (1.2 point). Regarding to the duration of the intervention effects, significantly greater enhancement occurs after the intervention. The longer lasting improvement found in tDCS-WMT group suggests that tDCS might modulate the effects of WMT by acting like an enhancer or primer for cognitive training.

## Limitations and Future Directions

Findings of this study have to be interpreted in the context of limitations. The diagnosis of NCD-AD was determined by neuropsychological tests and clinical evaluation without support by advanced neuroimaging (e.g., amyloid imaging). Even though this study recruited a relatively large sample size, the absence of a double-dummy control group (i.e., sham tDCS and control cognitive training) may limit interpretation of the treatment efficacy. Improvements in cognitive performance after intervention may be also related to practice effects or social interactions with tDCS, although the trend for decline in cognitive performance 8 weeks after intervention (T3 and T4) suggested that practice effects should not be the main confounders for our findings. Without neuronavigation may reduce the precision of localizing stimulation target. On the basis of the International 10-20 EEG system, we targeted the location of left LTC individually and completed the standardized placement of electrode. Considering the heterogeneity embedded in cortical morphometry in aging population, it would be imperative to develop electroencephalography-informed (i.e., closed-loop) transcranial electrical stimulation, which can localize the targeted region and collect the feedback individually in real time. Moreover, whether tDCS would modulate the neuroplasticity to achieve a longlasting cognitive optimization in early stages of cognitive decline deserves further investigation. It would be interesting to collect the neurophysiological biomarkers to monitor the neuroplasticity response in the long-term follow-ups.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

## Author Contributions

L. C. W. Lam was responsible for study design, clinical supervision, and preparation of manuscript. H. Lu was responsible for conducting the trial, performing data analysis, and preparing the manuscript. S. M. Chan, W. C.

 

Chan, and P. W. Cheng participated in conceptualizing the study and subject recruitment. C. Lin participated in conducting the intervention and assisted the data analysis. All authors contributed to reviewing the manuscript and approving the final version. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. All authors substantially contributed to the trial and its reporting, approved of the final version of this manuscript and agree to be accountable for all aspects of the work.

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