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**Title**: Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment: A randomized controlled trial

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**Title**: ~~Is one plus one always more than one?~~ Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment: A randomized controlled trial.

**Abstract**

***Background:*** Cognitive training (CT) for persons with mild cognitive impairment (MCI) may not be optimal for enhancing cognitive functioning. Coupling CT with transcranial direct current stimulation (tDCS) may maximize the strength of transmission across synaptic circuits in pathways that are stimulated by CT. The synergistic effects arising from this combination could be superior to those of the administration of CT alone.

***Objectives:*** To investigate whether the receiving tDCS combined with CT would be superior to receiving CT alone on domain-specific and task-specific cognitive outcomes in older adults with MCI.

***Methods:*** This double-blind, sham-controlled randomized trial included 67 older adults with MCI assigned to three groups: 1) tDCS combined with CT (tDCS+CT), 2) sham tDCS combined with CT (sham tDCS+CT) and 3) CT alone. Nine sessions of computerized CT were administered to the three groups for three weeks. In addition, tDCS and sham tDCS was delivered to the left dorsolateral prefrontal cortex to the tDCS+CT and sham tDCS+CT groups respectively, simultaneously with CT. Standardized cognitive assessments were carried out at baseline, post-intervention, and at six-week follow-up. Participants' performance in the CT tasks was rated every session.

***Results:*** Improvements in global cognition and everyday memory ($p < 0.017$) were found within the three groups after the intervention and at follow-up with larger effect sizes noted in the tDCS+CT group ($d > 0.94$). However, there were no significant differences between groups. Regarding the CT outcomes, significant differences among groups were observed in favour of the tDCS+CT group in decreasing the completion and reaction times of working memory and attention activities ($p < 0.017$).

***Conclusions:*** tDCS combined with CT was not superior to sham tDCS with CT and CT alone in its effects on domain-specific cognitive outcomes, but it did provide comparatively larger effect sizes and improve the processing speed of task-specific outcomes.

The study was registered at www.clinicaltrials.gov (Ref. No.: NCT03441152). There was no funding support from funding agencies in the public, commercial, or not-for-profit sectors.

**Keywords:** Mild Cognitive Impairment, Cognitive Rehabilitation, Cognitive Training, Non-invasive Brain Stimulation, Transcranial Direct Current Stimulation.

## Introduction

Mild cognitive impairment (MCI) is considered the frontier between the natural cognitive decline from ageing and the very early stages of dementia [1]. Although MCI can be classified as a cognitive disorder in non-demented persons, it is indeed an age-related condition with a probable degenerative aetiology associated with the onset of Alzheimer's disease (AD) [1, 2]. Cognitive compensatory mechanisms may activate in the ageing brain. For instance, when healthy older adults face difficulties in executive tasks, there is an over-activation of bilateral prefrontal cortex areas, whereas non-impaired young adults display this over-activation in one hemisphere [3]. This brain response might be explained in terms of cognitive restructuring in older adults because they are likely having a lower level of attention and WM capacity [3, 4]. The decline of executive functioning is exacerbated during MCI, which has been shown to cause deficits in working memory and attention [5, 6]. There is evidence that one or more cognitive domains can be impaired in people with MCI without affecting their preservation of independence in functional abilities or causing their activities of daily living to be performed in a less efficient manner [7]. Furthermore, people with MCI often report cognitive subjective complaints [7, 8].

Cognitive Rehabilitation (CR) is described as 'the therapeutic process of increasing or improving an individual's capacity to process and use incoming information so as to allow increased functioning in everyday life.' This includes methods to train and restore cognitive functioning [9] such as computerized cognitive training (CT). Changes in neural activity in persons with MCI suggest that CT can have restorative effects, improving the impaired brain area or function, as well as compensatory effects, engaging other intact neural networks [10]. In point of fact, memory training increased activation in areas associated with memory encoding before CT and also generated new activations in areas that were not active before the administration of CT [10, 11]. CT improved cognitive performance in the domains trained in healthy older adults. However, there is insufficient evidence regarding the effects of CT on populations with MCI reporting gains in training performance [12]. Similar conclusions were drawn in a systematic review when appraising the therapeutic benefits of CT in randomized control trials (RCT), which showed positive effects on various domains of cognitive functioning in healthy older adults, but

not in persons with MCI [13]. It appears that CT induces changes in neural activity that may not be translated into cognitive gains in individuals with known MCI.

The application of CT itself as an intervention for persons with MCI may not always be sufficient to produce tangible benefits to cognitive functioning [13]. A complementary solution would involve pairing CT with another intervention, thus creating synergistic effects [14, 15] . Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation (NIBS) technique that modulates brain excitability. tDCS delivers direct current to the brain cortex, travelling from the anode to the cathode electrode. The former has depolarizing properties that excite neural activity, whereas the latter has hyperpolarizing effects that inhibit neural activity [16, 17]. As a result, 'tDCS causes a shift in the membrane potential threshold which is likely to change the probability that an incoming action potential will result in post-synaptic firing during and after its administration' [18, 19]. According to a recent systematic review, the application of tDCS alone has exhibited promising improvements in various cognitive domains for different types of dementia and MCI, however, whether tDCS combined with CT concurrently might produce optimal therapeutic outcomes than when administered alone remains unclear yet [18].

Based on this background, we hypothesize that tDCS may augment the strength of transmission across synaptic circuits in pathways that are stimulated by CT. Hence using tDCS to target a brain region or function that could be impaired in persons with MCI during a CT may be more efficient than not using tDCS [20]. Consequently, it could produce more tangible benefits in cognitive functioning outcomes. The aim of the present study was to investigate whether the application of tDCS combined with CT would lead to superior domain-specific outcomes – both standardized cognitive outcomes and task-specific outcomes – of CT tasks in older adults with MCI compared to the application of sham tDCS and CT or of CT alone.

## 2. Material and Methods

### 2.1 Participants

Participants were older adults presenting with suspected MCI recruited by convenience sampling from community centre groups and by research recruitment posters in Hong Kong. The enrolment started in July 2017 and ended in July 2019. All included participants met the modified Petersen's criteria [21] (given by the MCI Working Group of the European Consortium on Alzheimer's Disease, Brescia Meeting, Italy, June 2005) and were required to: (a) be aged between 60 and 85 years old; (b) obtain a score on the Montreal Cognitive Assessment Test (MoCA) [22] between 19 and 26; (c) achieve a score on the Clinical Dementia Rating (CDR) of 0.5 or below [23]; (d) self-report cognitive decline; (e) self-report independence in daily living activities; and (f) have completed at least three years of primary education. Participants were excluded if they presented any of the following conditions: (a) individuals presenting with any neurological disease, except for suspected MCI; (b) individuals with suspected depression determined by a score on the Geriatric Depression Scale > 4 [24]; and (c) history of drug abuse. All participants were screened to detect any contraindications to tDCS (metallic implants, epilepsy, etc.).

A description of the study was explained to all participants and informed written consent was obtained before the intervention began. The study was conducted in accordance with the Declaration of Helsinki and was approved by the human subject ethics committee of The Hong Kong Polytechnic University (ref. number: HSEARS20170526001) and registered at ClinicalTrials.gov (NCT03441152).

**2.2 Trial design**

The trial utilized a double-blinded sham-controlled design with 3 intervention groups. Interested participants underwent a screening assessment, after which all eligible participants were invited to receive a three-week computerized CT. Once recruited, the participants were randomly assigned to receive CT, either with tDCS (tDCS+CT group), with sham tDCS (sham tDCS+CT group), or only CT (CT group). Randomization was assigned following a random sequence generated by an online platform 'Qminim' (1:1:1 ratio) and the random allocation sequence was implemented based on the recruitment order by the therapist who administered the interventions and who did not get involved in the assessment of the participants. All groups

completed three sessions per week, undertaking a total of nine sessions in three weeks. Participants were assessed at baseline, post-treatment, and at six-weeks follow-up (FU). This study follows the non-pharmacological Consolidated Standards for Reporting Trials (CONSORT) [25] for RCT (Figure 1). The CONSORT checklist of information to include when reporting a randomized trial assessing non-pharmacologic treatments had been included in the additional material.

### 2.3 Intervention

The intervention sessions were carried out at the research facilities of the university. All participants were exposed to the same computerized CT content. Only the experimental group performed the CT with tDCS (tDCS+CT group). The participants in the sham tDCS+CT group served to provide a placebo effect, while the participants in the CT group served as the control for documenting differences among both tDCS modalities. Although the type of intervention was unknown to the assessors conducting the cognitive assessments as well as the participants (i.e. they were blind), the tDCS and CT administrator responsible for delivering the treatment remained unblinded.

#### 2.3.1 tDCS

Stimulation was delivered by the Soterix Medical 1 X 1 low-intensity tDCS stimulator. The electricity was conducted via two rubber electrodes inserted in saline-soaked sponges (5 X 3 cm, 15 $cm^2$). The anode electrode was placed over the left dorsolateral prefrontal cortex (LDPFC) corresponding to the F3 region based on the 10/20 EEG international system. The LDPFC was selected because it had been extensively used as a target in studies using tDCS in older adults with MCI and dementia [18]. In addition, the prefrontal cortex in older adults was selected for stimulation because it might influence the executive functional performance that are impaired in MCI [26, 27]. The cathode electrode was positioned, as an extra-cephalic reference, on the contralateral brachioradialis muscle in order to avoid the confounding effects of two electrodes with different polarities over the brain [16]. The sponges were attached to the abovementioned areas with a head and an arm elastic band, respectively. The application of tDCS for the tDCS+CT group included an initial ramp-up over 30 seconds, followed by a

constant current at 1.5 mA for 30 minutes, and ended with a ramp-down for other 30 seconds. In the sham condition, the whole process and parameters were mimicked excluding the delivery of constant current at 1.5 mA for 30 mins. However, the ramp-up and ramp-down procedures were maintained to replicate the physical sensations produced by tDCS. The CT was applied concurrently with the onset of tDCS and sham tDCS, respectively. The participants from the CT group did not receive any tDCS at all, so technically it was not possible to mask these participants to the type of intervention.

**2.3.2 Computerized CT**

The computerized CT used for the intervention was 'Neuron Up' [28], an online platform (https://www.neuronup.com/) which consists of customizable training materials to enable cognitive rehabilitation. This CT was selected because it has been shown to improve various cognitive outcomes in persons with MCI [29] and has been previously used for pairing with tDCS, showing mild cognitive gains [30].

The CT was administered for 30 mins to all groups and included the following content with a focus on executive function: one adaptive task associated with working memory delivered as a warm-up during the first five minutes, this activity consisted of remembering the order in which a set of buildings placed on different locations lighted up and later the participants were asked to reproduce that exact same order in reverse. The challenge of the task was that the more accurate the participants were, the more times the buildings lighted up in the following trials, hence, the difficulty of the task increased. The adaptive task was followed by the administration of six non-adaptive tasks related to arithmetic math (additions and subtractions) working memory, short-term memory, and attention, presented in counterbalanced order across nine sessions. The reason why the CT was based on working memory and attention was that both are components of executive functions [31]. The CT sessions were conducted individually and the participants were supervised by the investigator when performing the CT tasks to ensure that they understood how to realize the tasks and that they complied with the course of the intervention. The display format was a touchscreen 13.30-inch HP Spectre x360 laptop placed on a table approximately 35 cm in front of the participant.

### 2.4 Outcome measures

All primary outcome measures were conducted at baseline, post-assessment, and FU. They were domain-specific cognitive outcome measures, which included: MoCA (Hong Kong non-parallel version) to evaluate global cognitive functioning; the Digit Span Test (DST) for working memory, consisting of two parts in which sequences of digits are presented and must be verbally recalled in forward and reverse order (DST-f and DST-b), respectively [32]; and the Trail Making Test (TMT), encompassing attention skills, processing speed, and mental flexibility. In part A (TMT-a), a set of 25 numbered dots must be accurately connected in sequential order. The Chinese version was used in part B (TMT-b) [33], alternating dots with Chinese numerals. TMT is administrated with paper and pencil and performance time is measured as the main outcome.

The secondary outcome measures included: The Rivermead Behavioral Memory Test (3$^{rd}$ edition) (RBMT-3) – Hong Kong version [34], which assesses everyday memory skills and was administered following the same timeline as the primary outcome measures. Alternate forms of the parallel versions of the RBMT-3 were used in order to avoid any testing effect. Task-specific outcomes derived from the CT tasks were recorded for all non-adaptive tasks across time. Depending on the nature of the CT task, data such as the number of errors, completion time, and reaction time was collected.

### 2.5 Sample size

The sample size of the study was not estimated according to our previous pilot study [30], as the parameters needed to determine the sample size were somewhat insufficient. Furthermore, no previous similar research was available on which to ground the sample size estimation. Therefore, we based the sample size estimation using a conservative approach [35], assuming 80% power at 5% Type I error, sample size estimates indicated that to detect a correlation among repeated measures of 0.325 with an effect size of 0.3, 54 participants (e.g., 3 groups x 18 participants) would be adequate to detect significance. By adding a 20% drop-out rate, a total of 65 participants were targeted to be recruited (G*power, Version 3.1.3, University of Kiel, Germany, 2010).

### 2.6 Statistical analysis

Differences at baseline among groups in demographics, primary outcome measures, and the total scores of RMBT-3 were tested employing Chi-square tests and One-way ANOVA, for categorical and continuous variables, respectively. A two-way repeated-measures ANOVA (time x intervention) was used to examine changes of the interventions applied in primary and secondary outcomes measures. If the time or interaction effect was significant in the primary outcomes and in the RBMT-3, post-hoc multiple comparisons were conducted to investigate the within-group differences for each group. Cohen's d was used to calculate the effect size [35] for the general outcome measures within groups. Multiple Independent t-tests were conducted for the grand average of the CT outcomes in every single session so that it could be explored at which endpoint the three groups started to show significant changes. Statistical significance was set at $p = 0.05$. Significance values for post-hoc tests were adjusted by the Bonferroni correction, $p = 0.017$. Data analyses were performed using IBM SPSS statistics 22.0. Last observation carried forward (LOCF) was the method chosen to deal with missing data for participants who dropped out.

## 3. Results

One hundred fifty participants were screened for eligibility and 67 of them were recruited to commence the study. Twenty-two participants were allocated to receive tDCS combined with CT, 24 participants to receive sham tDCS combined with CT, and 21 participants to receive CT alone. Two participants, 1 receiving tDCS+CT and 1 receiving sham tDCS+CT, dropped out during the intervention due to uncomfortable sensations with the current delivered (see Figure 1). There were no differences in demographic data and the baselines of outcomes across groups (see Table 1). None of the participants reported severe side effects.

### Primary outcomes

Significant main effects of time were found for all groups in MoCA after intervention with larger effect sizes in the tDCS+CT group (tDCS+CT group: $p = 0.001$, Cohen's d = 0.9; sham tDCS+CT

group: $p$ = 0.001, $d$ = 0.66; CT group: $p$ = 0.005, $d$ = 0.58). This improvement was also noted from baseline to six-weeks FU (tDCS+CT group: $p$ = 0.001, $d$ = 1.27; sham tDCS+CT group: $p$ = 0.001, $d$ = 0.9; CT group: $p$ = 0.001, $d$ = 1.16).

In the TMT-a, the tDCS+CT showed marginally significant improvement from baseline to 6-weeks FU ($p$ = 0.019, $d$ = -0.51). This gain was not evidenced in either the sham tDCS+CT group ($p$ = 0.640, $d$ = 0.06) or the CT group ($p$ = 0.267, $d$ = -0.23).

Regarding the DST-b, a better performance was observed in the CT group after the intervention (tDCS+CT group: $p$ = 0.297, $d$ = 0.16; sham tDCS+CT group: $p$ = 0.040, $d$ = 0.47; CT group: $p$ = 0.005, $d$ = 0.53), and six-weeks FU (tDCS+CT group: $p$ = 0.050, $d$ = 0.28; sham tDCS+CT group: $p$ = 0.159, $d$ = 0.22; CT group: $p$ = 0.005, $d$ = 0.58). However, no significant interactions (time x intervention) were found in any of the primary outcomes, as shown in Table 2.

**Secondary outcomes**

All groups showed significant improvements in RBMT-3 after the intervention (tDCS+CT group: $p$ = 0.001, $d$ = 0.95; sham tDCS+CT group: $p$ = 0.001, $d$ = 0.72; CT group: $p$ = 0.004, $d$ = 0.56) and at six-weeks FU relative to the baseline (tDCS+CT group: $p$ = 0.000, $d$ = 0.95; sham tDCS+CT group: $p$ = 0.000, $d$ = 0.89; CT group: $p$ = 0.005, $d$ = 0.67). Significant large effect sizes in everyday memory were evidenced, particularly in the tDCS+CT group. Nevertheless, two-way repeated-measures ANOVA showed no significant interaction effect in the total score (see Table 2). Regarding the subscores of RBMT-3, there was significant time vs intervention interaction in the orientation/date domain between post-intervention and baseline in favour of the sham tDCS+CT group ($p$ = 0.004). The improvement was significantly reversed between post-intervention and FU ($p$ = 0.016), there were also significant differences between groups at FU relative to the baseline in favour of the CT group ($p$ = 0.001). Regarding the CT outcomes, in the 'additions' task, all groups maintained an average of less than one error per operation. The tDCS+CT group committed fewer errors during the first four sessions and then the performance equalized across groups for the remaining sessions, reverting to the initial pattern in the last session. All these differences were minimal in terms of score and not statistically significant (see Figure 2a). However, the tDCS+CT group took less time to complete the operations in every

single session than the sham tDCS+CT and CT groups. In the first session, a marginally significant difference was found between the tDCS+CT group and the sham tDCS+CT group ($p = 0.037$). The difference between these groups was also significant ($p = 0.013$) in the last session (see Figure 2b).

Regarding the task-specific outcomes, two-way repeated-measures ANOVA showed no significant differences between groups in any of the tasks, although there were significant within-group changes in all the outcomes related to the completion time variable as shown in Table 3. Multiple independent t-test showed that in the working memory task, except for the first session, the tDCS+CT group completed the task successfully faster than the other two groups in all sessions. In sessions 4, 6, and 8, marginally significant performance differences were observed relative to the sham tDCS+CT group ($p = 0.041$, $p = 0.045$, $p = 0.029$). Furthermore, in session 9 the difference between these two groups was significant ($p = 0.007$) (see Figure 3a). In terms of reaction time, the tDCS+CT group showed significantly and marginally significantly faster scores than the CT group in sessions 2 and 3 respectively ($p = 0.013$, $p = 0.025$) (see Figure 3b).

Figure 4a shows that the tDCS+CT group performed the visual attention task successfully and significantly faster than the CT group in session 4 ($p = 0.012$). Marginally significant differences were also found versus the CT group in session 3 ($p = 0.028$) and versus the sham tDCS+CT group in session 5 ($p = 0.021$). In terms of reaction time, the tDCS+CT group evidenced significantly faster responses than the CT group in session 4 ($p = 0.017$) and marginally significant differences relative to the sham tDCS+CT group in sessions 4, 5, and 6 ($p = 0.020$, $p = 0.039$, $p = 0.036$) (see Figure 4b). No significant differences were observed in the remaining CT tasks (subtractions, short-term memory tasks, and an additional attention task).

## 4. Discussion

The purpose of this study was to investigate whether a multisession intervention of anodal tDCS on the LDLPFC, combined with a computerized CT consisting of working memory and attention tasks, would improve cognitive functioning and whether the improvement would be

superior to that from computerized CT alone. To answer this question, we compared the effects of anodal tDCS+CT with both sham tDCS+CT and CT alone, thus rigorously eliminating bias. Our statistical analysis confirmed that tDCS+CT was not superior to sham tDCS+CT and CT alone as the cognitive domain outcomes failed to exhibit significant differences among groups after the intervention and at FU. There are few possible reasons for these disappointing results. First, both the experimental and comparison groups were effective in enhancing global cognition and everyday memory as indicated by the MoCA and RMBT-3 respectively. This finding is similar to that of a recent meta-analysis of the effects of computerized CT with 17 RCTs, that CT is a viable intervention for enhancing various cognitive domains including but not limited to global cognition and memory [36].

The results from the study we are presenting are in line with an RCT carried out by Martin et al. [37] in which participants with MCI received either CT with tDCS or sham tDCS on the LDLPFC as well. Both groups reported significant improvements at post-intervention in different domains of cognition, although there was no significant difference among groups. The largest RCT study to date on tDCS paired with working memory training for individuals with mild neurocognitive disorder due to AD [38] indicated that all participants regardless of group allocation (tDCS+working memory training, sham tDCS+working memory training, tDCS+CT) enhanced global cognition and memory function, which is consistent with our findings. On the other hand, Lu et al. [38] targeted the lateral temporal cortex whereas we selected the LDPFC as the area of stimulation for anodal tDCS. The DPFC plays a crucial role in functional connectivity and in high-order cognitive functions [39] such as attentional processes, decision making, and working memory. Moreover, several studies have reported deficits in working memory, irrespective of the MCI subtype [5], and in attention [6], as well as functional disconnection of the LDPFC [40].

Following this rationale, we prepared a specific CT based mainly on working memory and attention modules. Regarding this aspect, only the tDCS+CT group appeared to show significant within-group improvements in attention and processing speed as revealed by TMT-a score. However, this pattern was reversed for the DST-b score, since the greatest improvements were seen in the group that received CT alone. These mixed results are difficult to explain, given that it has been previously shown that tDCS combined with CT resulted in a greater subsequent

improvement in working memory outcomes in healthy adults [14, 41]. Interestingly, Park et al. targeted both the right and left DPFC, yielding significant improvements in the DST-f [36], although none of the cited studies reported significant improvements in DST-b.

It was unexpected to find the within group and interaction effects in the orientation/date subtest of the RMBT-3. Since the Orientation and Date subtest does not fit in the everyday memory construct of the RBMT-3 [34], the significant results were probably due to the testing effect or by chance.

In order to track the participants' performances in CT tasks simultaneously with tDCS, this study lacked the presence of a condition with the application of tDCS alone. The reason of applying tDCS with a CT task was that the efficacy of tDCS improves when applied with a cognitive task instead of rest [41], and the advantages of tDCS modulation could only be seen explicitly through a task-specific training. For this reason, our novel design allowed us to track the participants' performance on the computerized CT tasks in every single session across the whole intervention. It is noteworthy that these computerized CT task-specific scores have generated substantial valuable data, given the fact that the majority of the studies that combine NIBS with CT rely on scores of standardized cognitive domain outcomes acquired solely after the completion of interventions. The CT task results elucidated clearer performance during the training process in the tDCS+CT group. For example, when the participants realized additions, all groups had the tendency to make few errors each session. Moreover, in terms of completion time, the tDCS+CT group finished the operations much faster than the sham tDCS+CT and CT groups, particularly in the last session. This behaviour was repeated in the tasks related to working memory and attention (Figure 3 and Figure 4) in which the performance of the task was rated by the time it took to finish the task successfully. Faster responses in terms of reaction time were also evident for the tDCS+CT group. Processing speed is linked to the efficient use of other cognitive abilities [42] that affect the speed with which one processes information and completes tasks [43]. Processing speed deficits have been associated with ageing and are emphasized in pathological conditions such as dementia and MCI [44]. Following this line of thought, we can speculate that tDCS could enhance the efficacy of CT activities in terms of processing speed. Our hypothesis would be in consonance with previous research

studies that have shown that tDCS applied to the LDPFC as compared to sham tDCS enhanced processing speed as measured by the Paced Auditory Serial Addition Task in young adults [45]. The findings are consistent with our pilot study using a single subject-design for 5 older adults with MCI [30]. Our findings regarding processing speed could be explained by the mechanism of long-term potentiation, in which 'a brief episode of strong synaptic activation leads to a persistent strengthening of synaptic transmission'. Therefore, tDCS in combination with CT may boost the effects of training via LTP [14]. Another interesting observation when analysing the data of the CT task is that the tDCS+CT group yielded lower standard deviations as compared with the sham tDCS+CT and CT groups, which tended to exhibit greater variability. This suggests that the application of tDCS provides more stable and less variable responses to the performance of the CT task that could also be attributed to the constant strengthening of synaptic transmission. However, the interpretation of task-specific outcomes we are presenting must be taken with caution, because of the multiple statistical comparisons conducted for each CT task over 9 time points.

There are limitations to the current study. For instance, a question that remains unanswered in the literature is how many tDCS sessions are needed to induce behavioural changes. Some studies have stated that a single session is sufficient while other studies suggest various numbers of sessions, making it difficult to draw adequate conclusions [18]. In our study, significant differences were registered across sessions in different CT tasks, adding more uncertainty regarding the optimal frequency of tDCS application. It would be useful for future studies to focus on contributing to this area as it could have an impact on the length of interventions in clinical settings. Although the participants included in this study met the modified Petersen's criteria [21] with regards to the diagnosis of MCI and the neuropsychological tests were conducted by experienced researchers, we lacked confirmed diagnoses of MCI (e.g. the presence of a physician to confirm the suspected diagnosis of MCI as well as to determine the subtype of MCI). In addition, we did not control the use of medications by the participants, this might be a factor to be considered in future studies involving the application of tDCS since medications may alter the excitability effects of tDCS [46]. Despite one of the strengths of this study was having both the sham and control groups, participant blinding

was not assessed. We encourage researchers to control this variable after the end of the intervention as it could provide valuable information regarding participant blinding and tolerability [47].

It is also important to note that the CT administered to the participants was non-tailored. In other words, the cognitive tasks were not customized to the individuals' cognitive deficits [48].However, as it was our interest to monitor the participants' daily performance between groups, it was essential for them to all be exposed to the same content to enable us to compare the responses in a standardized manner. The common factor for all groups in this study was CT. Looking at the results, it is evident that all groups therapeutically benefited from receiving this intervention. However, our study did not include a waitlist control group, which would have supported this statement. For this reason, it could be argued whether the existence of a learning effect has favoured all groups to improve their scores on the outcome measures. Another potential limitation was that the CT tasks that were recorded were non-adaptive, participants could have become unmotivated or performed at ceiling when proficient [49]. Finally, the fact that we did not have a robust reference on which to base our sample size estimation might have contributed to make our study underpowered.

## 5. Conclusions

CT with or without tDCS can enhance global cognitive functioning and everyday memory. The significance of this study was to determine if CT coupled with tDCS could be used as a non-pharmacological therapy more efficiently than CT in the absence of tDCS for older adults with MCI. Whereas the combination of tDCS with CT did not create a superior effect as compared with sham tDCS+CT or CT alone, the coupling improved the processing speed of CT tasks related to working memory and attention, in which tDCS appears to be a potential effective adjunct to CT exercises. Whether tDCS can be coupled with CT in clinical settings as a superior therapeutic intervention to CT alone warrants larger RCTs using persons with MCI.

## Disclosure of interest

The authors declare that preliminary data of this study with a lower sample size was presented at the 3rd International Brain Stimulation Conference: Vancouver, Canada; 2019 with the abstract of which has been published. The reference for this abstract is as follows:

Gonzalez PC, Fong K, Brown T. Is transcranial direct current stimulation (tDCS) an effective adjunct to cognitive training for older adults presenting with mild cognitive impairment (MCI)? Brain Stimul 2019; 12(2): 448-9. (Abstract)


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**Figures Captions**

**Figure 1. CONSORT flow diagram.**

tDCS, transcranial direct current stimulation; CT, cognitive training

**Figure 2. CT task, additions.**

tDCS, transcranial direct current stimulation; CT, cognitive training.

Figure 2A represents the mean performance of the three groups across nine sessions in terms of accuracy. Errors bars with plus caps represent the standard deviation. Figure 2B represents the mean performance of the three groups across nine sessions in terms of time. Errors bars with both caps represent the standard deviation. # shows marginal significant differences across groups $p < 0.050$.

**Figure 3. CT task, working memory.**

tDCS, transcranial direct current stimulation; CT, cognitive training.

Figure 3A represents the mean performance of the three groups across nine sessions in terms of time. Errors bars with both caps represent the standard deviation. Figure 3B represents the mean performance of the three groups across nine sessions in terms of reaction time. Errors bars with plus caps represent the standard deviation. # shows marginal significant differences across groups $p < 0.050$. * shows marginal significant differences across groups $p < 0.017$.

**Figure 4. CT task, attention.**

tDCS, transcranial direct current stimulation; CT, cognitive training.

Figure 4A represents the mean performance of the three groups across nine sessions in terms of time. Figure 4B represents the mean performance of the three groups across nine sessions in terms of reaction time. Errors bars with both caps represent the standard deviation. # shows marginal significant differences across groups $p < 0.050$. * shows marginal significant differences across groups $p < 0.017$.

**Table 1.** Demographic and clinical data at baseline.

| Variable | tDCS+CT group (n = 21) Mean (SD) | Sham tDCS+CT group (n = 24) Mean (SD) | CT group (n =21) Mean (SD) | $F/x^2$ | *p* |
|---|---|---|---|---|---|
| **Gender (Male/Female)** | 6/15 | 8/16 | 4/17 | 1.17 $x^2$ | 0.555 |
| **Age** | 69.8 (5.3) | 71.0 (6.2) | 70.6 (5.4) | 0.23 | 0.792 |
| **Years of education** | 9.7 (3.6) | 9.7 (3.6) | 11.9 (4.9) | 2.02 | 0.140 |
| **MoCA** | 23.7 (1.7) | 24.1 (2.4) | 24.3 (1.7) | 0.48 | 0.617 |
| **TMT-a** | 54.9 (17.9) | 50.1 (24.2) | 47.6 (16.7) | 0.69 | 0.505 |
| **TMT-b** | 77.7 (32.5) | 73.0 (24.2) | 76.2 (37.4) | 0.11 | 0.888 |
| **DST-f** | 13.6 (1.7) | 13.6 (2.0) | 13.6 (1.9) | 0.00 | 0.996 |
| **DST-b** | 6.6 (2.6) | 6.0 (2.4) | 6.1 (2.5) | 0.36 | 0.697 |
| **RBMT-3** | 123.4 (16.9) | 124.5 (14.1) | 126.8 (18.9) | 0.21 | 0.805 |

$X^2$, Chi-square; *p*-value was between groups. n, sample size; tDCS, transcranial direct current stimulation; CT, cognitive training; MoCA, Montreal Cognitive Assessment; TMT-a, Trail Making Test part A; TMT-b, Trail Making Test part B; DST-f, Digit Span Test forward; DST-b, Digit Span Test backwards; RBMT-3, Rivermead Behavioral Memory Test ($3^{rd}$ edition).

**Table 2.** Comparison of standardized cognitive outcome variables across and within groups (Raw means, SD)

| | tDCS+CT (n = 21) | | | Sham tDCS+CT (n = 24) | | | CT alone (n = 21) | | | Within group | | Time x Intervention | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Post | 6-week FU | Baseline | Post | 6-week FU | Baseline | Post | 6-week FU | F | *p* | F | *p* |
| MoCA | 23.7(1.7) | 25.7(2.4)** | 26.2(2)** | 24.1(2.4) | 25.8(2.5)** | 26.4(2.6)** | 24.3(1.7) | 25.7(2.8)** | 26.7(2.3)**/*** | 49.82 | 0.000 | 0.34 | 0.851 |
| TMT-a | 54.9(17.9) | 52.5(29.7) | 45.5(18.1)* | 50.1(24.2) | 50.5(25.3) | 48.4(26.0) | 47.6(16.7) | 48.3(16.8) | 44.0(14.2) | 3.39 | 0.037 | 0.64 | 0.628 |
| TMT-b | 77.7(32.5) | 79.8(41.2) | 72.5(34.1) | 73.0(24.2) | 73.0(23.4) | 66.0(24.5) | 76.2(37.4) | 73.8(35.5) | 68.5(26.3) | 2.67 | 0.073 | 0.08 | 0.988 |
| DST-f | 13.6(1.7) | 12.7(2.0) | 13.3(1.8) | 13.6(2.0) | 13.9(1.9) | 14.0(2.1) | 13.6(1.9) | 13.6(2.1) | 13.5(2.2) | 1.03 | 0.359 | 1.99 | 0.099 |
| DST-b | 6.1(2.5) | 6.6(2.7) | 6.9(2.8)* | 6.0(2.4) | 7.3(2.9)* | 6.8(2.9) | 6.6(2.6) | 8.1(2.7)** | 8.3(3.2)** | 10.52 | 0.000 | 1.15 | 0.333 |
| RBMT-3 | 123.4(16.9) | 137.1(10.9)** | 138.0 (13.2)** | 124.5(14.1) | 136.4(18.2)** | 137.7(15.4)** | 126.8(18.9) | 137.7(19.5)** | 140.8(22.5)** | 39.02 | 0.000 | 0.13 | 0.967 |
| Names-DR | 8.6(2.3) | 9.4(2.4) | 10.1(2.5)** | 8.5(2.1) | 9.7(2.5)* | 10.4(2.3)** | 7.8(2.7) | 9.3(3.0)* | 9.6(2.7)** | 15.36 | 0.000 | 0.17 | 0.951 |
| Belongings-DR | 8.0(2.6) | 9.2(2.3) | 9.0(2.2) | 9.3(2.4) | 10.4(2.7) | 9.6(2.8) | 7.9(3.1) | 10.1(2.8)** | 9.7(3.0)* | 7.44 | 0.001 | 0.70 | 0.593 |
| Appointments-DR | 8.4(2.5) | 10.2(1.9) | 9.4(1.8) | 8.0(2.2) | 9.4(2.4) | 9.9(1.9)* | 8.2(2.3) | 9.5(2.5)* | 9.9(2.1)** | 13.78 | 0.000 | 0.83 | 0.496 |
| Picture Recognition-DR | 10.0(2.1) | 9.7(2.3) | 9.7(2.1) | 8.8(2.6) | 9.4(2.3) | 9.2(2.9) | 9.8(2.3) | 9.7(2.3) | 10.3(2.2) | 0.11 | 0.892 | 0.51 | 0.724 |
| Story-IR | 9.8(2.4) | 10.0(2.2)* | 10.3(3.3) | 8.9(2.3) | 9.8(2.9) | 10.8(2.3)** | 9.5(3.1) | 11.7(1.9)** | 11.2(2.0)** | 9.36 | 0.000 | 2.02 | 0.095 |
| Story-DR | 8.8(2.8) | 9.6(2.8) | 9.7(3.0) | 9.0(2.5) | 9.3(3.1)** | 10.4(2.3) | 8.9(2.8) | 10.3(2.2)* | 10.4(2.9)* | 6.96 | 0.001 | 0.61 | 0.651 |
| Face Recognition-DR | 8.7(2.7) | 9.3(3.1) | 10.3(3.1)** | 7.3(2.5) | 9.7(3.1)** | 8.7(3.0)* | 8.7(2.9) | 8.9(1.7) | 9.7(3.3) | 6.60 | 0.002 | 2.14 | 0.079 |
| Route-IR | 8.8(3.1) | 10.9(1.9)* | 10.3(2.7)*** | 10.3(3.0) | 10.6(3.3) | 11.3(1.9) | 10.8(2.7) | 10.2(2.4) | 11.5(1.9) | 3.46 | 0.039 | 1.90 | 0.120 |
| Route-DR | 9.0(3.0) | 10.2(2.3) | 10.4(2.2) | 10.8(1.9) | 10.5(2.8) | 10.7(2.0) | 9.9(2.4) | 9.6(3.2) | 10.2(2.7) | 1.08 | 0.333 | 1.21 | 0.308 |
| Messages-IR | 9.8(1.9) | 10.4(1.4) | 10.5(1.0) | 9.5(2.6) | 9.9(2.1) | 9.5(2.3) | 10.1(1.7) | 9.8(2.0) | 9.2(2.6) | 0.25 | 0.773 | 0.92 | 0.452 |
| Messages- DR | 9.2(2.6) | 10.2(1.5) | 10.4(1.2) | 9.5(2.0) | 9.5(2.2) | 10.1(2.0) | 9.9(1.8) | 9.6(2.2) | 9.1(2.4) | 0.59 | 0.553 | 1.74 | 0.144 |
| Orientation and Date | 7.9(2.5) | 8.0(2.0) | 7.9(2.4) | 7.3(2.3) | 9.1(2.5)** | 7.9(2.2)*** | 7.6(2.0) | 7.8(2.9)* | 9.1(2.4)** | 4.03 | 0.020 | 4.28 | 0.003 |
| Novel Task-IR | 7.7(2.7) | 10.2(2.7)** | 9.5(2.5)** | 8.2(2.6) | 9.5(2.9) | 9.9(2.5) | 8.5(2.2) | 10.5(3.3)* | 10.3(2.8)* | 14.15 | 0.000 | 0.49 | 0.742 |
| Novel Task-DR | 8.2(2.7) | 9.2(2.3) | 9.8(2.1)** | 8.5(2.2) | 9.0(2.6) | 8.8(2.8) | 8.7(2.7) | 10.1(2.4) | 9.9(2.0) | 4.99 | 0.008 | 0.76 | 0.550 |

n, sample size; tDCS, transcranial direct current stimulation; CT, cognitive training; MoCA, Montreal Cognitive Assessment; Post, post-intervention FU, follow-up; TMT-a, Trail Making Test part A; TMT-b, Trail Making Test part B; DSTf, Digit Span Test forward; DST-b, Digit Span Test backwards; RBMT-3, Rivermead Behavioral Memory Test (3$^{rd}$ edition); DR, delayed recall; IR, immediate recall.

* $P < 0.05$; ** $P < 0.017$. The *P*-values were within-group comparisons versus baseline.

*** $P < 0.05$; The *P*-values were within-group comparisons, follow-up assessment versus post-intervention assessment. / represents the separation of results.

**Table 3.** Comparison of task-specific outcomes across and within groups

| CT task | Within group | | Time x Intervention | |
|---|---|---|---|---|
| | **F** | ***p*** | **F** | ***p*** |
| **Additions (errors)** | 0.31 | 0.940 | 0.55 | 0.888 |
| **Additions (completion time)** | 5.29 | 0.000 | 0.68 | 0.756 |
| **Working memory (completion time)** | 12.14 | 0.000 | 0.82 | 0.585 |
| **Working memory (reaction time)** | 2.37 | 0.032 | 0.62 | 0.814 |
| **Attention (completion time)** | 11.09 | 0.000 | 1.38 | 0.196 |
| **Attention (reaction time)** | 8.57 | 0.000 | 1.27 | 0.260 |

Figure 1

Click here to access/download;Figure;Figure 1. CONSORT flow diagram.jpg

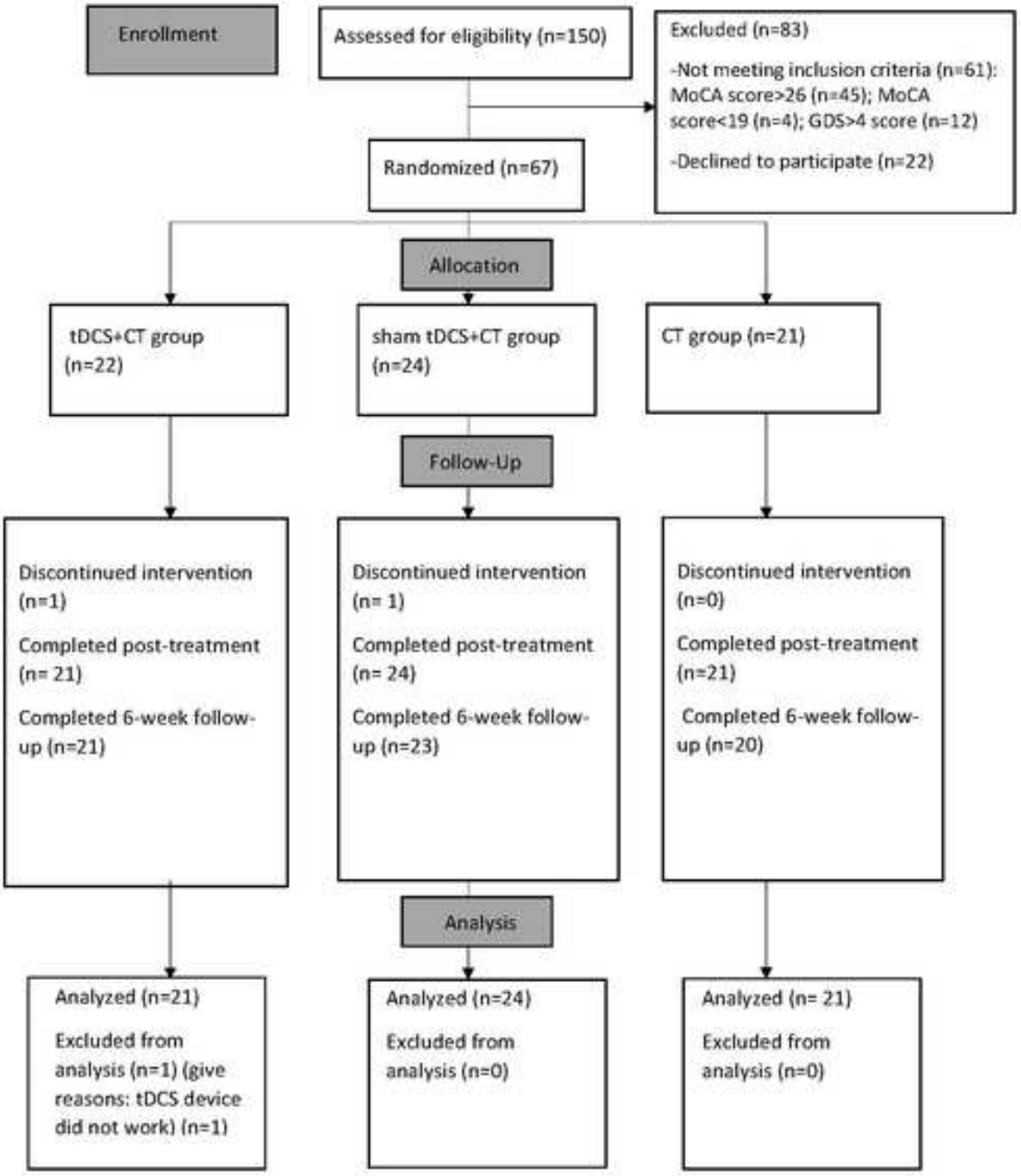

Figure 2

Click here to access/download;Figure;Figure 2. CT task, additions.jpg

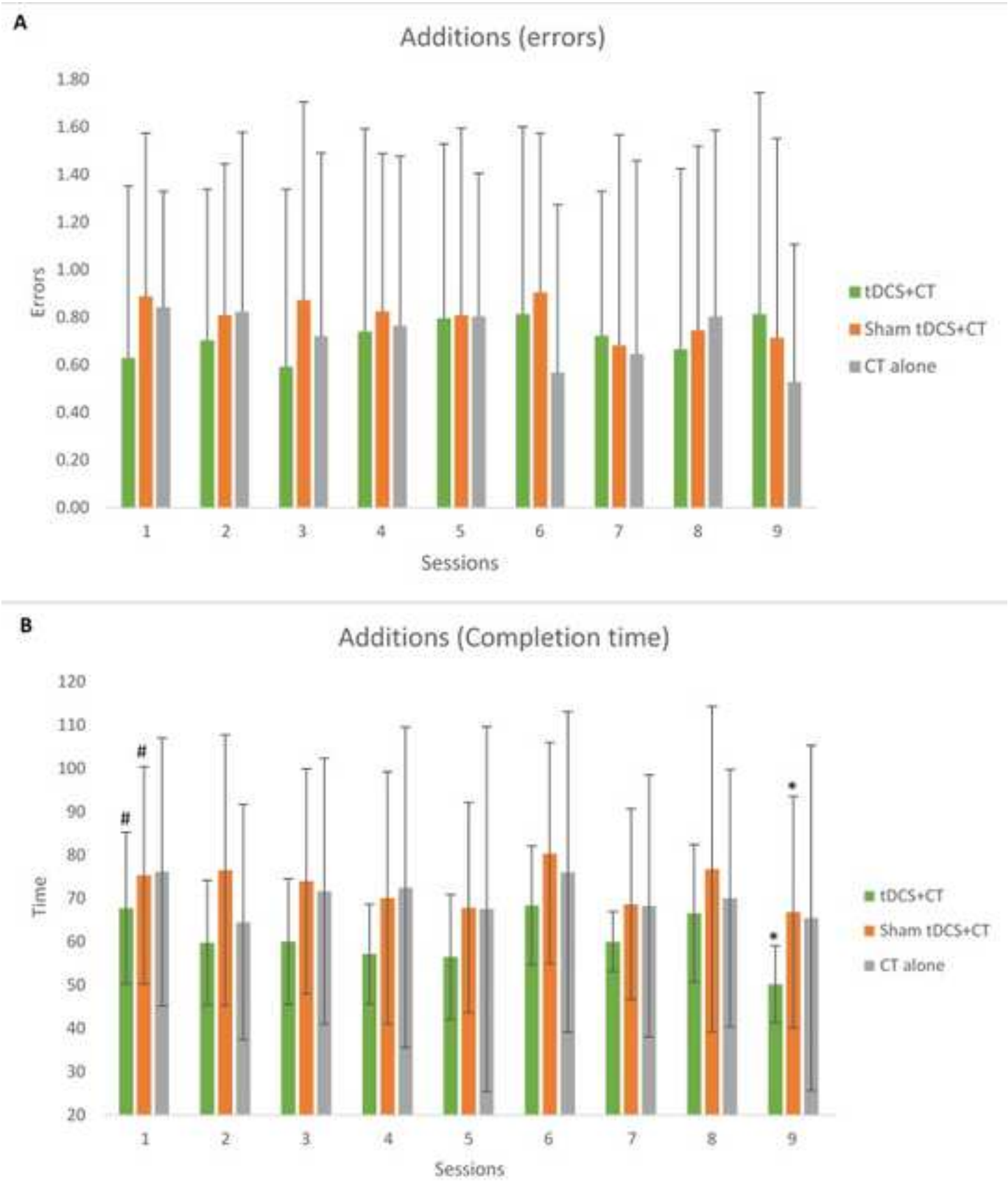

Figure 3

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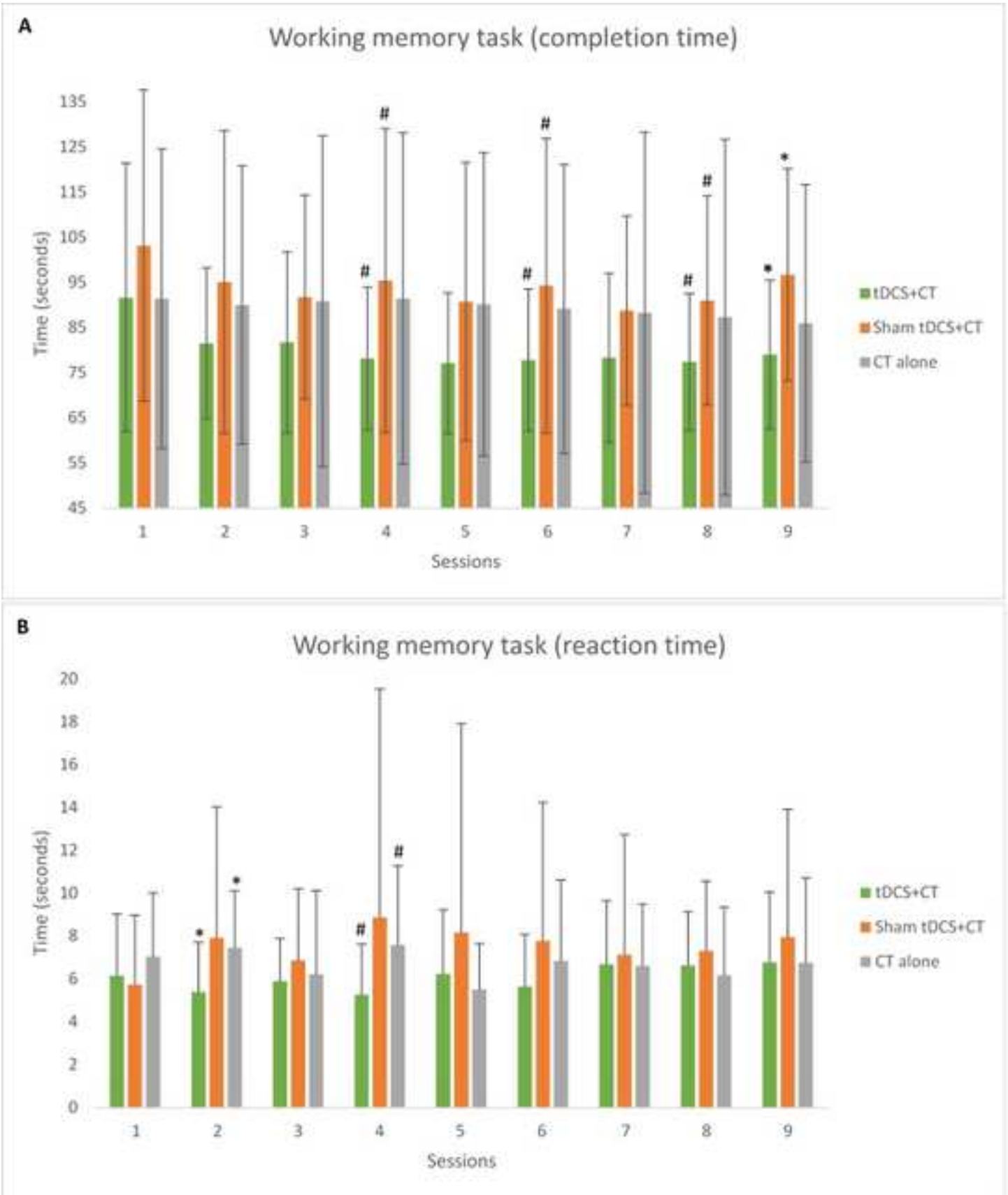

Figure 4

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