Effects of transcranial alternating current stimulation on cognitive function in people with multiple sclerosis: A randomized controlled trial

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ABSTRACT

Background: Cognitive impairment is a core symptom that profoundly impacts the lives of people with multiple sclerosis (PwMS). Since the existing disease modifying therapies can only stabilize, but not actively treat, cognition in PwMS, there is an unmet need to expand approaches to treat these cognitive symptoms. Transcranial alternating current stimulation (tACS) permits frequency-specific entrainment of neural oscillations intrinsic to cognitive activity. However, the effects of the tACS on cognitive function in PwMS have not yet been assessed. We aimed to evaluate the potential efficacy of applying frontal theta-tACS to improve information processing speed in PwMS.

Methods: 60 PwMS with cognitive complaints were enrolled in a double-blinded, randomized, controlled trial with three stimulation groups: 2 mA, 1 mA, or sham control. A single session of theta-tACS was applied while participants were engaged in a cognitive program which has shown to improve processing speed in PwMS. tACS effects were examined by the Symbol Digit Modalities Test (SDMT). Tolerability, side effects and acceptability were measured.

Results: 1 mA groups had a significantly higher SDMT score after stimulation compared to their pre-stimulation score, 2 mA group showed a marginally significant improvement of their SDMT score, while the SDMT score in the sham group did not change. Overall, 49% of the stimulation group participants showed a clinically meaningful SDMT improvement (4+–point increase).

Conclusion: tACS is a well-tolerated, non-pharmacological intervention. Based on the positive effects observed in the current study of a single session of tACS applied during cognitive engagement, the effects of repeated tACS on cognitive function in PwMS merit further research.

Trial Registration: ClinicalTrials.gov NCT04466228.

1. Introduction

Multiple sclerosis (MS) is a neurological disorder characterized by a wide variety of disabling symptoms. Among these, cognitive impairment occurs in up to 70 % of people with MS (PwMS) (Benedict et al., 2020) and has a profound influence on a patient’s personal functioning, social interaction, vocational status and overall quality of life. The most commonly affected cognitive domains are speed of information processing, executive function and memory (Achiron and Barak, 2003; Rogers and Panegyres, 2007). Although disease modifying therapies (DMTs) that target primarily the inflammatory immunopathology of MS (Birnbaum, 2010; Lopez-Diego and Weiner, 2008) can slow progression of impairments including cognitive decline, these do not specifically target improving cognition (Geisler et al., 1996; Lovera et al., 2010; Shaygannejad et al., 2008). Therefore, it is of great importance to develop alternative therapeutic approaches to alleviate cognitive symptoms in MS.

Recently, different forms of non-invasive transcranial electrical stimulation (tES) have been evaluated for their potential to serve as non-pharmacological treatments for neurological and psychiatric disorders (Elyamany et al., 2021; Fregni et al., 2021). These have added safety and portability benefits, which could support at-home application. The two main forms of non-invasive tES are: transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS).
Preliminary studies suggest that tDCS may ameliorate cognition (Mat-
tioli et al., 2016), pain (Ayache et al., 2016; Mori et al., 2010), fatigue (Ferrucci et al., 2014; Hanken et al., 2016) and sensory deficits (Mori et al., 2013) in PwMS. While these studies provide intriguing support for tES as a novel therapeutic strategy for MS (Hsu et al., 2021), tES research in MS remains in its infancy and there are no consensus recommendations for its use in MS. Furthermore, to our knowledge, the effects of the tACS form of tES on cognitive function in PwMS have not yet been assessed. tACS applies weak sinusoidal currents to the brain through the scalp in a frequency-specific manner and is capable of entraining endogenous brain oscillations and enhancing cognitive function including attention (Hsu et al., 2019; Hsu et al., 2017) and working memory (Neiron and Lavdor, 2014; Polania et al., 2012; Vosskuhl et al., 2015). tACS capitalizes on the fact that a wide range of cognitive capabilities are mediated by the dynamic modulation of rhythmic oscillatory activity. Therefore, tACS could provide the advantage of a more principled approach by specifically targeting oscillatory neural activity. Theta oscillations in the prefrontal cortex (PFC) are related to information processing speed (Gevins et al., 1997; Klimesch, 1999; Mizuhara et al., 2004), and abnormal theta oscillatory brain dynamics have been described in PwMS compared to individuals without MS, as well as in PwMS with cognitive impairment relative to those without (Kiiski et al., 2012; Van der Meer et al., 2013). A collective interpretation of these findings is that theta power reduction in the PFC is a feature of more advanced cognitive decline in MS. Consequently, applying theta-tACS over the PFC can be hypothesized to improve information processing speed in MS.

Prior studies have shown that the effects of tES are more pronounced when it is applied while the participant is engaged in a cognitive task (Fertonani et al., 2014; Pozdniakov et al., 2021). Previously, we have shown that use of a tablet-based cognitive program, AKL-T03 (see below) over 4–6 weeks led to improved processing speed in PwMS (Bove et al., 2021; Bove et al., 2019). The current study evaluated whether a single session of frontal theta-tACS application, during this cognitive task (AKL-T03), improved information processing speed in MS. Information processing speed was targeted as a cognitive domain, as it is commonly impaired in MS (Achiron and Barak, 2003; Rogers and Panegyres, 2007). Since there are intensity-dependent effects of tES on cognitive function (Boggio et al., 2006; Iyer et al., 2005), the dose-response effects of different tACS intensities (2 mA vs. 1 mA) were further examined.

2. Methods

2.1. Study design

To evaluate the effects of frontal theta-tACS on information processing speed in PwMS during cognitive task engagement, a pre-registered, placebo controlled, double-blinded study was conducted randomizing individuals 1:1:1 to 2 mA tACS, 1 mA tACS, or Sham control.

2.2. Participants

A total of 60 participants with a diagnosis of MS by 2010 Revised McDonald criteria (McDonald et al., 2001) were recruited from the University of California, San Francisco Multiple Sclerosis and Neuro-inflammation Center between October 2020 and August 2022. Participants were either referred by their primary MS clinician or identified through review of their clinician’s notes for mention of patient subjective cognitive complaints. Inclusion criteria were: Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) ≤ 6.5, no paresis of the upper limbs (so participant could manipulate the tablet), a minimum of 3 months since the last relapse, and no changes in symptomatic medications in the past 2 months. Exclusion criteria were: prior history of brain surgery or seizure, clips in brain, inadequate visual, auditory, and motor capacity to operate tablet-based programs, other neurological or non-affective psychiatric disorders, and pregnancy. Participants’ clinical and demographic characteristics were collected from the electronic health record; handedness was self-reported at enrollment. The sample size was determined according to similar clinical trials of non-invasive tES in MS (Charvet et al., 2018; Ferrucci et al., 2014; Hanken et al., 2016).

Since the application of tACS in MS is still at a nascent stage, rather than include participants only if they met clear criteria for cognitive impairment (i.e. Symbol Digit Modalities Test (SDMT) z-scores ≤ −1.5 (Amato et al., 2018)), participants were also included if they had subjective complaints, despite z-scores > −1.5 (based on normative data (Kiely et al., 2014)), to allow for a broader range of cognitive functioning that might inform future study design. While not yet meeting formal criteria for cognitive impairment, the latter group’s subjective cognitive complaints might have been remediable to intervention.

2.3. Randomisation

Randomization to the active and sham control groups in a 1:1:1 ratio was performed by an independent researcher using a computer-generated list of random numbers. Those numbers were linked to the pre-programmed tACS stimulator that delivered the appropriate stimulation (2 mA vs. 1 mA vs. sham control) based on the randomization number. The relationship between the number coding and type of stimulation was unblinded only after all participants completed the study activities and the outcomes were fully scored.

2.4. Stimulation sessions

The study session began with standard assessment of information processing speed (SDMT (Benedict et al., 2017)). Then, the tACS apparatus was set up, and a 20-minute stimulation was performed. During the tACS stimulation, participants in all three groups completed a tablet-based cognitive program (AKL-T03, vide infra). After the 20-minute stimulation, a second SDMT assessment was performed using a different version. There was a 1-minute gap between the cessation of the stimulation and the start of the second SDMT assessment. During the 1-minute gap, the study staff removed the stimulation cap from the participants and help them clean up the conductive gel on the scalp. SDMTs were administered by trained study staff blinded to the randomization group. Both participants, and study staff administering the tACS and SDMT, were blinded to stimulation group assignment.

2.4.1. Transcranial alternating current stimulation (tACS)

TACS was applied at 6 Hz via a pair of Ag/AgCl electrodes (3.14 cm²) through a Starstim device (Neuroelectrics, Spain). The intensity of the stimulations was 2 mA (peak-to-peak) and 1 mA (peak-to-peak) for high-dose and low-dose groups, respectively. Participants received 20 min of stimulation with a 15-s ramp up and 15-s ramp down. The stimulation was performed by an independent researcher using a computer-generated list of random numbers. Those numbers were linked to the pre-programmed tACS stimulator that delivered the appropriate stimulation (2 mA vs. 1 mA vs. sham control) based on the randomization number. The relationship between the number coding and type of stimulation was unblinded only after all participants completed the study activities and the outcomes were fully scored.

Fig. 1. Current modeling of electric field distribution of 2 mA (peak-to-peak) tACS. Red-yellow colors represent increased magnitude of the total electric field caused by tACS. Left panel depicts frontal regions, and the right panel shows top view of both hemispheres.
electrodes were located over the bilateral FPC centered at F3 and F4 of the 10–20 electrode coordinate system (above PFC). Fig. 1 shows the electric field distribution for the used tACS montage (modelled with the NIC software (Neuroelectrics, Spain)). Impedance was kept below 10 kΩ. For the control group, the 15-s ramp up period was immediately followed by a 15-s ramp down period and the stimulation was turned off for the remainder of the 19.5 min of the stimulation run. During this ramp up and ramp down periods in the control group, the current intensity increased to 2 mA (peak-to-peak) for half the participants and to 1 mA (peak-to-peak) for the other half. In order to validate the blinding procedure and evaluate tolerability of the tACS, at the end of the study all participants were asked to complete a survey rating their perception of stimulation (headache, neck pain, scalp pain, tingling, itching, burning sensation, sleepiness, trouble concentrating, and acute mood change, phosphene) on a Likert scale from 0 (none) to 10 (not tolerable).

2.4.2. Cognitive program (AKL-T03)

The 20-minute stimulation was applied while the participants were engaged in a tablet-based cognitive program, AKL-T03 (Akili Labs, Boston), an investigational digital therapeutic (Bove et al., 2021; Bove et al., 2019). It was developed based on the principles of NeuroRacer, an innovative cognitive intervention designed to engage frontal neural networks (Anguera et al., 2013). Previously, AKL-T03 was shown to improve SDMT scores in PwMS after 30 treatment sessions over 6 weeks, and the improvement was sustained for at least two months: 70 % of participants maintained a clinically meaningful SDMT improvement (4+ point increase) (Bove et al., 2021).

2.4.3. Symbol digit modalities test (SDMT)

This was the pre-specified primary outcome measure. The SDMT is widely used to measure speed of information processing in MS (Benedict et al., 2017). The number of correct written responses made within ninety seconds was recorded. Changes in absolute score were the primary outcome; the percentage of participants in each group achieving a 4-point clinically meaningful improvement in SDMT scores was also compared.

2.4.4. Tolerability, side effects and acceptability

Participants answered 10 questions assessing their perception of the stimulation, relating to: headache, neck pain, scalp pain, tingling, itching, burning sensation, sleepiness, trouble concentrating, acute mood change, and phosphene. Tolerability was defined as: fewer than 5 % of participants rate a score of 7 or higher (0–none to 10—not tolerable) in any of the 10 domains. Acceptability was defined as: more than 90 % of participants adhere to the study (i.e. complete the stimulation session).

2.5. Standard approval, registration, and consent

All study procedures were approved and in accordance with the ethical standards of the Committee for Human Research at the University of California at San Francisco (IRB No.20–30220). Written informed consent was obtained from all participants. The trial was registered with clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04466228).

2.6. Statistical analysis

All numerical data are presented as the mean ± standard error of the mean (SEM). The difference in baseline (pre-stim) SDMT score across the three groups (2 mA, 1 mA, control) was examined using one-way analysis of variance (ANOVA). To discern the effect of tACS on information processing speed, performance in SDMT was submitted to two-way repeated measures ANOVA with group (2 mA, 1 mA, control) as a between-subject factor and time (pre, post) as a within-subject factor. The Greenhouse-Geisser correction was applied when appropriate. Paired t-tests were carried out for within-group post-hoc comparisons to detect changes in SDMT score from pre- to post- stimulation. The Benjamini-Hochberg procedure (Benjamini, 1995) that controls for false discovery rate (FDR) was applied for multiple comparisons. Group differences in terms of changes in SDMT score from pre- to post-stimulation were examined by one-way ANOVA. The difference between stimulation and control groups in terms of the perception of tACS sensation (scaled from 0 to 10) was analyzed with one-way ANOVA. The statistical significance threshold was set as p ≤ 0.05. All statistical analyses were conducted using SPSS 22.0 (IBM Corp, Armonk, New York).

3. Results

3.1. Participants

A total of 60 PwMS were recruited (Fig. 2). All participants completed the study. Table 1 summarizes their baseline demographic and clinical characteristics. Overall, the cohort mean age was 46.3 ± 1.1, education level was 17.3 ± 0.4 years (i.e. >college degree), MS duration was 10.5 ± 1.1 years, and median EDSS was 2.5 (interquartile range [2–3.75]); 58 % self-identified as White/non-Hispanic and 80 % were female. Overall, 18/60 participants had SDMT z-scores of –1.5 or lower; the distribution of z-scores is presented in Supplementary Figure 1. There were no significant differences between the 3 groups in terms of age (F(2,59)=2.61, p = 0.08), years of education (F(2,59)=0.63, p = 0.54), EDSS (F(2,59)=0.18, p = 0.83), disease duration (F(2,59)=1.75, p = 0.18), baseline SDMT score (F(2,59)=0.24, p = 0.78) and SDMT z-score (F(2,59)=2.00, p = 0.81). Three participants were excluded from SDMT data analyses: 2 due to poor performance at baseline (i.e. lower than 2 standard deviations from the mean of all 60 participants; n = 1 for 2 mA; n = 1 for 1 mA); and 1 (in the 1 mA group) for not following instructions properly during the post-tACS assessment; they still contributed to tolerability and acceptability analyses.

3.2. SDMT results

At baseline, there was no significant difference in SDMT score between the three groups (F(2,59)=0.36, p = 0.69). Overall, after the intervention, the mean increase in SDMT was 2.89 ± 1.31 for the 2 mA group, 5.05 ± 1.39 for the 1 mA group, and 0.40 ± 1.19 for the control group. When these differences were compared statistically using 2-way repeated measures ANOVA, there was a significant group x time interaction (F(2,59)=3.23, p = 0.04). A significant time main effect was discovered (F(1,54)=13.81, p<0.001). No significant group main effect was observed (F(2,59)=0.06, p = 0.93). Post-hoc paired t-tests showed that the 1 mA group had a significant increase in SDMT score after stimulation ((t(17)=3.63, p = 0.002); adjusted p-value with FDR correction = 0.006), the 2 mA group showed a marginal improvement in SDMT score ((t(18)=2.20, p = 0.04); adjusted p-value = 0.06), while there was no significant change in the control group (t(19)=0.33, p = 0.74; adjusted p-value = 0.74) (Fig. 3; Table 2). In line with this, one-way ANOVA revealed a significant difference in terms of changes in SDMT score from pre- to post-stimulation between the three groups (F(2,59)=3.23, p = 0.04). Post-hoc t tests with Bonferroni correction showed a greater change in SDMT in 1 mA group (5.05 ± 1.38) compared to the control group (0.40 ± 1.19) (p = 0.04). However, no significant differences were found for the comparison between 1 mA vs. 2 mA (p = 0.75) and control vs. 2 mA (p = 0.52). Including age, MS duration, baseline SDMT z-score as covariates did not change the results. Moreover, 36.8 % and 61.1 % of participants in the 2 mA and 1 mA groups, respectively, showed clinically meaningful improvement in SDMT (i.e. increase by 4+ points (Benedict et al., 2014) from baseline), compared with only 30 % in the control group.

To further compare the results of the three groups, effect sizes for SDMT were calculated based on the difference in performance between pre- and post-tACS assessment in each group using Cohen’s d. Absolute effect size values were considered as small (0.2 - 0.5), moderate (0.5 - 0.8) or large (>0.8) (Cohen, 1992). The effect size for the 2 mA group
was small (0.32), but it was moderate for the 1 mA group (0.51). The control group showed an effect size of 0.05 (Table 2). Overall, the 1 mA groups benefited from PFC theta-tACS, but the 2 mA group only showed a numerical improvement in SDMT after theta-tACS. The results suggest that PFC theta-tACS improves information processing speed in PwMS as measured by SDMT. Furthermore, higher stimulation intensity did not necessarily generate stronger effects.

3.3. Tolerability, side effects and acceptability

Confirming that the control stimulation was an appropriately blinded manipulation, there were no statistical differences in the perception of stimulation among the three groups (p ≥ 0.09 for each of the 10 domains) (Supplementary Table 1). The mean scores of potential unpleasant tACS-induced sensations were below 2.5 (i.e. noticeable but does not interfere with activities) for each of the 10 sensations (scale range: 0 = none to 10 = not tolerable). None of the participants rated a score of 7 or higher for any of the 10 sensations, suggesting that tACS is a tolerable approach in this patient population. All participants tolerated the tACS well and completed the study, indicating strong acceptability.

To determine whether improvements in SDMT could have been attributed to side effects of the tACS, Pearson’s correlations were conducted between improvements in SDMT scores and tACS side effects for each group. No association was noted between the changes in SDMT and side effects (1 mA group: all p > 0.26; 2 mA group: all p > 0.26; control group: all p > 0.23).

4. Discussion

The present study evaluated frontal theta-tACS as a therapeutic approach to improve cognitive function in MS. There was significantly increased SDMT score after a single session of tACS, compared with no increase in SDMT after sham application. Further, in response to different tACS intensities, a more pronounced increase, stronger effect size, and greater proportion of individuals increasing SDMT by 4 points

Table 1
Baseline demographic and clinical characteristics of PwMS enrolled in the study.

<table>
<thead>
<tr>
<th></th>
<th>2 mA (N = 20)</th>
<th>1 mA (N = 20)</th>
<th>Control (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.7 (1.7)</td>
<td>42.8 (2.1)</td>
<td>47.4 (1.8)</td>
</tr>
<tr>
<td>Sex</td>
<td>17F, 3M</td>
<td>14F, 6M</td>
<td>17F, 3M</td>
</tr>
<tr>
<td>Education (years)</td>
<td>17.8 (0.6)</td>
<td>16.8 (0.6)</td>
<td>17.5 (0.8)</td>
</tr>
<tr>
<td>Right-handedness, n (%)</td>
<td>20 (100 %)</td>
<td>20 (100 %)</td>
<td>20 (100 %)</td>
</tr>
<tr>
<td>Part- or full-time employed, n (%)</td>
<td>12 (60 %)</td>
<td>14 (70 %)</td>
<td>14 (70 %)</td>
</tr>
<tr>
<td>Baseline SDMT score</td>
<td>43.05 (2.13)</td>
<td>42.35 (2.35)</td>
<td>44.40 (1.84)</td>
</tr>
<tr>
<td>Baseline SDMT z-score</td>
<td>−1.1 (0.2)</td>
<td>−1.3 (0.3)</td>
<td>−1.1 (0.2)</td>
</tr>
<tr>
<td>EDSS (median±IQR)</td>
<td>2.5 ± 1</td>
<td>2.5 ± 1.25</td>
<td>3 ± 1.25</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td>11.6 (1.9)</td>
<td>7.7 (1.4)</td>
<td>12.1 (2.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>14 (70 %)</td>
<td>11 (55 %)</td>
</tr>
<tr>
<td></td>
<td>Black/African American</td>
<td>1 (5 %)</td>
<td>1 (5 %)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>3 (15 %)</td>
<td>3 (15 %)</td>
</tr>
<tr>
<td></td>
<td>Other/Unknown</td>
<td>2 (10 %)</td>
<td>6 (30 %)</td>
</tr>
<tr>
<td></td>
<td>MS subtype, n (%)</td>
<td>19 (95 %)</td>
<td>18 (90 %)</td>
</tr>
<tr>
<td>Relapsing-Remitting</td>
<td>19 (95 %)</td>
<td>18 (90 %)</td>
<td>17 (85 %)</td>
</tr>
<tr>
<td>Primary Progressive</td>
<td>N/A</td>
<td>1 (5 %)</td>
<td>2 (10 %)</td>
</tr>
<tr>
<td>Secondary Progressive</td>
<td>1 (5 %)</td>
<td>1 (5 %)</td>
<td>1 (5 %)</td>
</tr>
<tr>
<td>Current DMT, n (%)</td>
<td>Oral</td>
<td>4 (20 %)</td>
<td>1 (5 %)</td>
</tr>
<tr>
<td></td>
<td>Self-injectable</td>
<td>2 (10 %)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Infused</td>
<td>9 (45 %)</td>
<td>15 (75 %)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>5 (25 %)</td>
<td>4 (20 %)</td>
</tr>
</tbody>
</table>

PwMS, people with multiple sclerosis; F, female; M, male; IQR, interquartile range; SDMT, Symbol Digit Modalities Test; EDSS, Expanded Disability Status Scale; DMT, disease-modifying therapy.
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Entrainable by tACS. Low intensity tACS may decrease neural entrainment. Neurons with higher levels of baseline activity are less generally thought to be capable of entraining endogenous brain oscillations. For example, frontal theta activity (Keune et al., 2019). Furthermore, although tACS is effective in PwMS, whereby PwMS with low SDMT scores displayed an increased theta activity relative to baseline, while high stimulation intensities are needed to reinstate neural activity to an externally applied electric field (Krause et al., 2022). Based on these assumptions, an alternative explanation of the current finding is that 1 mA tACS may have induced a desynchronization of theta oscillations that resulted in improved processing speed, whereas 2 mA tACS may not have been strong enough to reinstate theta activities while the baseline desynchronization was already weak, and therefore the 2 mA stimulation did not lead to a pronounced change in processing speed.

Table 2

<table>
<thead>
<tr>
<th>Pre-tACS</th>
<th>Post-tACS</th>
<th>Cohen’s d</th>
<th>Proportion of participants showing a clinically meaningful 4-point increase in SDMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mA</td>
<td>44.05 (1.98)</td>
<td>46.94 (2.05)</td>
<td>0.32</td>
</tr>
<tr>
<td>1 mA</td>
<td>42.63 (2.33)</td>
<td>47.88 (2.30)</td>
<td>0.51</td>
</tr>
<tr>
<td>Control</td>
<td>44.40 (1.84)</td>
<td>44.80 (1.47)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

SDMT, Symbol Digit Modalities Test; tACS, transcranial alternating current stimulation.

* p < 0.05 for the comparison between pre- and post-tACS performance.

# p = 0.06 for the comparison between pre- and post-tACS performance.

was observed in the low (1 mA) than in the high (2 mA) intensity group. The findings suggest that theta-tACS can improve information processing speed in PwMS, and higher tACS intensity does not necessarily result in stronger effects. Moreover, based on participant responses, the intervention was acceptable and tolerable.

To our knowledge, the current study is the first to address the potential of the TACS form of tES to improve cognitive function in PwMS. Importantly, significant benefits on processing speed were observed. Theta oscillations are related to information processing tasks (Gevins et al., 1997; Mizuhara et al., 2004). Reduced PFC theta activity has been reported in PwMS relative to people without MS, as well as in PwMS with cognitive impairment relative to those who have no cognitive impairment (Kiiski et al., 2012). This suggests that reduced PFC theta activity may be an important feature that underlies cognitive dysfunction in MS. Application of theta stimulation over the frontal cortex was found to improve SDMT scores, a measure of information processing speed in MS. Nevertheless, it was also reported that frontal theta power could represent an inverse marker of information processing speed in MS, whereby PwMS with low SDMT scores displayed an increased frontal theta activity (Keune et al., 2019). Furthermore, although tACS is generally thought to be capable of entraining endogenous brain oscillations, it does not necessarily enhance the power of neural oscillatory activities at the stimulation frequency (Hsu et al., 2017). In a recent study, it was discovered that tACS competes with the ongoing brain oscillations. Neurons with higher levels of baseline activity are less entrainable by tACS. Low intensity tACS may decrease neural entrainment relative to baseline, while high stimulation intensities are needed to reinstate neural activity to an externally applied electric field (Krause et al., 2022).

Of note, it has been reported that tACS effects can be caused by transcutaneous stimulation of peripheral nerves (Azamoa et al., 2019). Frontal stimulation montage can also lead to rhythmic entrainment in visual cortex (Kar and Krekelberg, 2012; Laakso and Hirata, 2013). These co-stimulation sensory effects may potentially mediate behavioral responses by affecting arousal level or producing placebo effect. Thus, it is possible that the observed improvement in SDMT may be partly attributed to indirect stimulation effects. Yet, we did not identify any differences in side effects between the stimulation groups. Moreover, no correlation was observed between the side effects and the change in SDMT. Therefore, it is unlikely that the observed effects of tACS on processing speed were driven by perceived side effects.

The mechanisms underlying observed effects of tACS are uncertain. Previously, it was demonstrated that training with AKL-T03 in PwMS over the course of 6 weeks improved information processing speed (Bove et al., 2021). With a total of 750 min training on AKL-T03, the mean improvement of SDMT from baseline to post-training assessment was +6.10. In the present study, a 5.05-point increase of SDMT was observed after 20 min of a single session of AKL-T03 gameplay paired with 1 mA theta-tACS administration. Although the methods used to induce neuroplastic changes (cognitive training only vs. tACS paired with the cognitive task) are different in the two studies, the observed tACS effects may operate on similar mechanisms as those affected by cognitive training. Another possibility is that the neural networks are activated by cognitive task engagement, and then further modulated by tACS, resulting in synergistic neuro-enhancing effects, with the relevant network becoming more efficient, demonstrating improved SDMT scores within a relatively shorter timeframe.

It was noteworthy that the 1 mA stimulation was associated with a larger effect size and percentage of participants reaching the clinically meaningful improvement in SDMT (61.1% vs. 38.6%) than the 2 mA stimulation. Such a non-linear dose–response relationship has been reported previously (Moliadze et al., 2012). For example, when testing tACS stimulation intensities from 0.2 to 1.0 mA in 0.2 mA increments, the 0.4 mA and 1 mA stimulations had opposite effects on neurophysiological measures, and 0.6 and 0.8 mA intensity stimulations had no effect (Moliadze et al., 2012). While the amount of current flow in the...
brain would be widely expected to increase with increasing applied stimulation intensity (Bikson et al., 2015), individual anatomical differences could affect the amount of a set current flow reaches the target brain region, resulting in variability in individual neurophysiological and behavioral responses (Bestmann and Ward, 2017). In the current study for instance, some participants in the 1 mA group may have had a higher current flow into the target brain region than some participants in the 2 mA group, resulting in a greater change in SDMT score. Other than factors related to individual anatomical differences, the direction and magnitude of tACS effects are strongly influenced by the functional mediating factors including prevailing brain states (e.g. baseline differences in theta power) (Piene et al., 2020; Neuling et al., 2013; Ruhnau et al., 2016) and deviations of the individual intrinsic theta frequency from the applied tACS frequency (Kasten et al., 2019; Zanto et al., 2021). With the between-subject design and relatively small sample size, these anatomical and functional mediating factors could have led to a stronger effect in the 1 mA group compared to the 2 mA group, independent of stimulation intensity. Therefore, although both tACS doses were associated with improved SDMT, the relationship between stimulation intensity and the induced neurophysiological and behavioral effects may be complicated by additional factors. Nonetheless, understanding the dose-response to tACS would help optimize stimulation protocols and reduce inter-individual variability. To achieve this, further research will be required to fully control for functional and structural confounders such as baseline cognitive performance, prevailing brain states, and white matter track injury and grey matter atrophy relevant to cognition.

Studies have shown individual differences in response to tES. For instance, it was found that theta-tACS improved working memory in low-performers while the same protocol deteriorated behavior in high-performers (Tseng et al., 2018). Another study showed that effects of tES on cognitive function may be graded across different populations with different baseline performance (Hsu et al., 2015). Given that the current study recruited PwMS with a broader range of cognitive functioning, we tested whether there is an association between baseline SDMT performance and changes in SDMT score. Pearson’s correlation showed marginally significant association between baseline performance and the improvement in SDMT score when the two stimulation groups are pooled together ($p = 0.06; r = −0.31$), suggesting that people with MS who had a lower baseline SDMT score may benefit more from tACS. However, these results should be taken with caution since the sample size is relatively small. Future studies focusing on PwMS with clear cognitive impairment are needed to test whether this population would benefit most from tACS.

There are some limitations to the present study. First, since the application of tACS in MS is still in a nascent stage, we recruited not only PwMS with clear cognitive impairment but also those with no clearly defined cognitive impairment. Given that the efficacy of tES is related to pre-intervention performance (Hsu et al., 2015; Learmonth et al., 2015), the fact that the majority of recruited patients had a SDMT z-score $>−1.5$ (42 out of 60) makes it possible that the effects of tACS may have been underestimated. Second, MS is a condition with marked heterogeneity (Lucchini et al., 2000) – and MS duration, type, DMT, and cognitive fatigue could all influence treatment response. Related to this, the dynamics and heterogeneity of brain lesions may have affected the magnitude of the electric fields that reach the targeted brain area. Third, it should be noted that tACS was only applied during cognitive engagement, and the effect was only measured immediately after stimulation. Therefore, effects of isolated tACS (i.e. without cognitive engagement) and the sustainability of the effect are unknown. Studies exploring the sustainability of tACS effects and optimal stimulation protocols (e.g. with or without cognitive engagement) are warranted. Lastly, although SDMT is considered a standard measure for PwMS, with a “meaningful” change of 4 points characterized mostly with respect to worsening in function, it does not necessarily reflect performance in real-world cognitive tasks, especially in the earlier stages of diseases where changes in cognitive functioning can be mild and undetectable (Sumowski et al., 2018). While SDMT is subject to practice effect, two different versions of the test were used before and after tACS and further, no practice effect was observed in the sham control group.

Taken together, the findings provide evidence that tACS is a safe and well-tolerated non-pharmacological approach to improve cognitive function in PwMS, and that it shows evidence of preliminary efficacy. Frontal theta-tACS enhanced information processing speed in adults with MS, and higher stimulation intensity did not necessarily result in stronger effects. Mechanisms underlying tACS-induced SDMT improvement, such as changes in frontal theta activity, frontal network efficiency, and how the heterogeneity of brain lesions affects stimulation effect, should be investigated. Further, the safety and tolerability of the intervention support its investigation in domains other than cognition, such as pain and fatigue. Finally, the acceptability and portability benefits suggest that it will be possible to adapt tACS to remote, in-home settings, which would substantially improve access to rehabilitative treatments to mitigate cognitive dysfunction in PwMS.

**Data availability**

De-identified data will be shared with any qualified investigator upon request.

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**CRedit authorship contribution statement**

Wan-Yu Hsu: Conceptualization, Methodology, Data curation, Visualization, Writing – review & editing, Writing – original draft. Theodore Zanto: Conceptualization, Data curation, Writing – review & editing, Writing – original draft. Jee Eun Park: Data curation, Writing – review & editing, Writing – original draft. Adam Gazzaley: Conceptualization, Writing – review & editing, Writing – original draft. Riley M. Bove: Conceptualization, Writing – review & editing, Writing – original draft.

**Declaration of Competing Interest**

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**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.105090.

**References**


