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Effect of transcranial direct current stimulation on prospective memory in healthy individuals: A double-blind randomized sham-controlled trial

Sağlıklı bireylerde transkraniyal doğru akım uyarımının prospektif bellek üzerine etkisi: Çift-kör randomize kontrollü çalışma

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Abstract

Aim: Prospective memory (PM) has an immense role in the activities of daily living and deficits of PM are common in various neuropsychiatric disorders. Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that yields favorable outcomes yet only a few studies concerning PM with hindering results exist. The present double-blind cross-over randomized sham-controlled study aimed to assess the effect of a single-session of left-righr/sham tDCS over the prefrontal cortex on event-related PM in healthy individuals.

Materials and Methods: 24 participants were administered a single session of 2 mA 20-minute left/right anodal or sham tDCS segregated by 7 days. An event-based PM task was utilized before and after tDCS every week to evaluate PM.

Results: No effects of tDCS on PM were found.

Conclusion: The present results argue against the effect of a single-session of tDCS over the prefrontal cortices on event-related PM. TDCS studies adopting divergent parameters are required.

Keywords: Brain stimulation; Cognition, Memory; Prospective memory; Transcranial direct current stimulation.

Öz

Amaç: Prospektif bellek (PB), günlük yaşam aktivitelerinde çok büyük bir role sahiptir ve eksiklikleri çeşitli nöropsikiyatrik bozukluklarda yaygındır. Transkraniyal Doğru Akım Uyarımı (tDAU), olumlu sonuçlar sağlayan bir nöromodülasyon tekniğidir ve PB üzerine etkisiyle ilgili sınırlı sonuçları olan yalnızca birkaç çalışma mevcuttur. Mevcut çift-kör, çapraz, randomize sham kontrollü çalışma, sağlıklı bireylerde tek seanslık sol/sağ/sham prefrontal tDAU'nun olaya dayalı PB işlevine etkisini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: 24 katılımcıya 7 gün arayla tek bir 2 mA 20 dakikalık sol/sağ anodal veya sham tDAU seansı uygulandı. Olaya dayalı PB testi, PB'yi değerlendirmek için her hafta tDAU'dan önce ve sonra uygulandı.

Bulgular: tDAU'nun PB üzerine etkisi saptanmadı.

Sonuç: Mevcut sonuçlar, prefrontal korteksler üzerine uygulanan tek bir tDAU oturumunun olaya dayalı PB üzerindeki etkisini göstermemiştir. Farklı parametrelerle yürütülen tDAU çalışmalarına ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Beyin uyarımı, Bellek, Biliş, Prospektif bellek, Transkraniyal doğru akım uyarımı.

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Introduction

Prospective memory (PM) is considered to be entailed by both successful retrievals of intentions through a bottom-up automatic-associative memory system and a top-down strategic monitoring system.[1,2] Quite a few lines of evidence suggest that PM depends on multiple cognitive functions like episodic memory and executive functions to work properly and simultaneously.[3–6] Among them, working memory attracts particular attention, peculiarly at high cognitive demands,[7] as it has a considerable role in both event-based and time-based PM,[3] prominently during nonfocal cue encoding, monitoring, detection, and retrieval processes.[8] The involvement of multiple processes and simultaneous performance of distinct cognitive functions in PM performance require the engagement of a frontoparietal network (FPN), chiefly constituted by multitudinous brain areas, including Broadman areas 10,40, the anterior cingulate cortices, and the insula.[9] A meta-analysis-based Attention to Delayed Intention (AtoDI) model further formulated that the retrieval phase of PM is principally maintained by a ventral FPN while the strategic monitoring phase is principally maintained by a dorsal FPN.[10]

PM abilities gradually decline with age, [11–14] resulting in constraints in activities of daily living (ADL), [15,16] such as taking a proper dose of medication at intended periods[17,18] or buying the necessary things at a shop. In this context, it is not surprising that PM has been denoted to be a key predictor of functional independence in older adults,[19] not to mention the recently observed mediator role between aging and ADL.[20] To boot, deficits of PM might be a discriminating factor between Mild Cognitive Impairment (MCI) and healthy aging.[21] Notably, PM failures have been indicated to have a greater impact on the caregivers of individuals with dementia than retrospective memory failures.[22] Though not commonly evaluated, PM deficits have also been observed in a myriad of neurological disorders[23] like traumatic brain injury,[24] Parkinson's Disease,[25] MCI, and dementia[26] as well as psychiatric disorders such as schizophrenia,[27] autism spectrum disorder[28] and depression.[29] Further, the relationship between ADL and PM has also apparently been observed in a few neuropsychiatric syndromes, such as HIV-associated neurocognitive disorder,[30] multiple sclerosis,[31] and schizophrenia.[32]

PM is a complex higher-order cognitive function in charge of remembering and executing delayed intentions scheduled to be performed in a retrieval context.[33,34] PM has principally been divided into two subdomains: event-based PM concerning actions performed when a certain cue emerges and time-based PM concerning actions when a predetermined time frame passes.[35] A variety of PM measures, from questionnaires to experimental procedures have been used in the past decades[35] with disparate outcomes and relatively low convergent validity.[36] To explain the complex hierarchy underlying PM and preclude heterogeneity at best, well-developed descriptive and mathematical models[2] have been described. On the grounds of these models, neuropsychological tests and experimental procedures with plausible duration and acceptable longitudinal reliability have been put into use.[35]

Given the abovementioned substantial role of PM in ADL, selectively targeting the deficits of PM is a relatively neglected but crucially significant issue.[20] Gaining knowledge in PM modulation may not merely yield fundamental insights to firmly delineate neurophysiological mechanisms underlying PM but also provide a rationale for novel neuroscience-based therapeutic avenues in neuropsychiatric disorders. To this end, a variety of compensatory or restorative treatment approaches such as non-invasive brain stimulation (NIBS) techniques, cognitive training,[37,38] electronic aids, and cognition-aware technologies[39] are currently being investigated.[40] Additionally, a few studies endeavoured to determine the neural correlates of PM improvements.[41]

Transcranial direct current stimulation (tDCS) is a NIBS technique that has been based upon the conduction of weak electric currents to stimulate cortical regions and exert neurobehavioral effects.[42] In addition to its safety,[43] easy applicability, and cost-

effectivity;[44] tDCS has been contemplated to enhance cognitive functions by increasing the engagement of brain areas associated with cognitive tasks, furnishing the distinctive potential to streamline the compensatory mechanisms of the brain to overcome cognitive decline.[45] Despite ever-growing favourable empirical evidence,[46] the efficacy of tDCS over distinct cognitive functions is still far from firm conclusions.[47–49] Nevertheless, a considerable amount of promising results regarding cognitive enhancement after tDCS exist,[50,51] paving the way for the notion that tDCS may modulate PM on account of the close relationship among distinct cognitive functions and event-based PM. Respecting the wide distribution of electrical current in tDCS applications, tDCS is also asserted to modulate PM by way of increased activation in both ventral and dorsal FPNs associated with PM. Concerning PM, two studies tested the effect of a single-session of left anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) in healthy individuals.[52,53] Despite differences in the PM assessment, both studies reported inconclusive results, casting doubt on the utility of a single session of anodal tDCS over the left DLPFC in healthy adults.[52,53] Nonetheless, Rose et al. suggested that anodal tDCS over the right DLPFC or other brain regions might have differential effects on PM albeit this assumption has not been tested insofar. Evidence from distinct methodological approaches on the relationship of the right prefrontal cortical areas with PM performance is extant.[10,54–56] An experienced study group developed the AtoDI model of PM based on a well-designed neuroimaging meta-analysis that also supports the contribution of the right DLPFC in PM performance.[10] Accordingly, a Positron Emission Tomography study yielded support for the participation of both right and left prefrontal cortices in PM performance.[55]

Overall, data regarding the effect of left anodal tDCS over the DLPFC on PM is still scarce and the effect of right anodal tDCS over the DLPFC on PM is unclear. The present study aimed to figure out the effect of both left and right anodal tDCS over the DLPFC on PM in healthy individuals. We hypothesized that a single session of anodal left/right/sham tDCS over the DLPFC conducted in consequent weeks might modulate event-related PM in healthy young individuals.

Materials and Methods

Type of the study

A sham-controlled double-blind within-subjects design was employed in the present study. Recruitment and procedures commenced in the Department of Physiology, Faculty of Medicine. The flow diagram of the present study is shown in Figure 1. Participants were allocated into three sequence groups with a 1:1:1 ratio using a predetermined randomization list. Each sequence consisted of three administration days separated by wash-out periods with a duration of a week. Participants and the assessor were blinded to the stimulation type. On each administration day, baseline and post-tDCS assessments of PM were performed.

Population and sample of the study

24 healthy right-handed individuals aged 18 years or older who were willing to participate in the present study and participants who had at least 5 years of education were recruited. Written informed consent was obtained from each individual after adequate information about the study aims and procedures had been provided. Participants were excluded if they had active major depressive disorder, current or previous diagnoses of alcohol or drug use disorders, bipolar disorder or psychotic disorders, significant neurological or medical conditions, significant loss of hearing or visual acuity, and common tDCS contraindications (brain tumor or implant, skin lesions at the stimulation site, etc.).

Data collection tools

Prospective memory evaluation

An event-based PM task based on the Multiprocess Theory of PM[2,57] was administered. The task consisted of 2 consecutive blocks which correspond to retrospective and prospective components of PM. Block 1 (Ongoing Task) is a color-matching task and participants were depicted a square and a word thereafter in each trial.

Participants had to determine whether the color of the word had been the same or different in each trial and were demanded to press the button 'E' (match) or 'I' (non-match). After Block 1, participants were shown a word list containing 6 words. After a 15-minute break, Block 2 was initiated which introduced a novel prospective condition. In Block 2, participants were demanded to determine whether the color of the word matched the color of the square (Ongoing task- Retrospective Target) and also whether the word had been one of the words in the word list (Prospective Target) in each trial. Participants were demanded to press a different button ('Z') in Prospective Target trials. During baseline and post-assessments of 3 separate weeks, 6 different forms of the task containing 6 different word lists were administered.

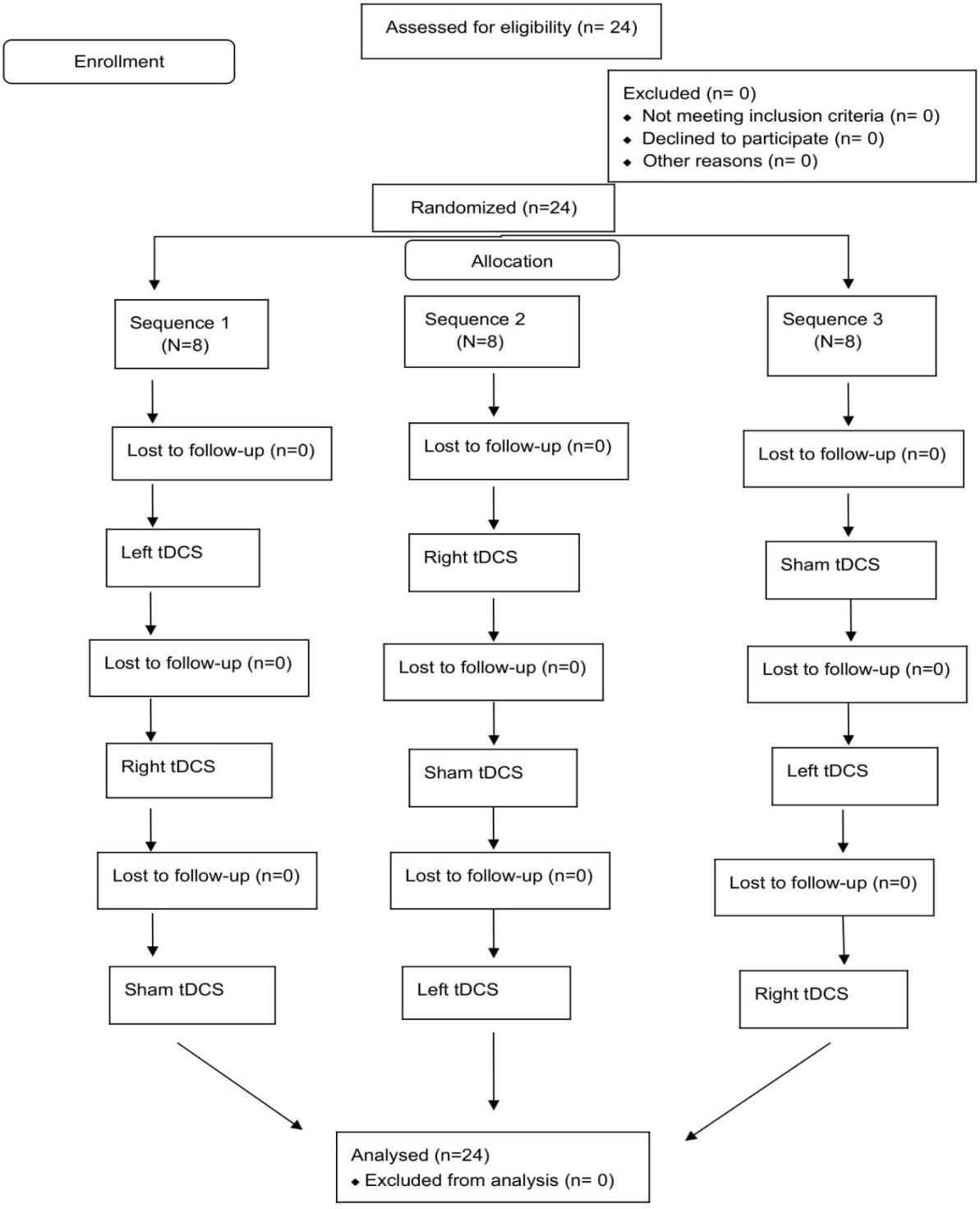

Figure 1. The flow diagram of the study

The outcome variables of the task were as follows:

- Correct Ongoing Task Accuracy 1 (COTA1): An index changing between 0 and 1, which corresponds to correct ongoing task accuracy in Block 1
- Reaction Time Ongoing Task 1 (RTOT1): Reaction Time in Ongoing Task of Block 1.
- Correct Ongoing Task Accuracy 2 (COTA2): An index changing between 0 and 1, which corresponds to correct ongoing task accuracy in Block 2
- Reaction Time Ongoing Task 2 (RTOT2): Reaction Time in Ongoing Task of Block 2.
- The Proportion of Prospective Memory Hits (PPMH): An index changing between 0 and 1 which corresponds to the proportion of correct PM hits.
- The Proportion of Prospective Memory False Alarms (PPMFA): An index changing between 0 and 1 which corresponds to the proportion of correct PM false alarms.
- Prospective Memory Hits (PMH): The number of total hits in Prospective Target Trials
- Prospective Memory False Alarms (PMFA): The number of total PM false alarms in Block 2.

The primary endpoint of the present study was the d prime scores from the Signal Detection Theory which has been calculated from the formula below:

D prime (d') = z (Hit Rate) – z (False Alarm Rate).

D prime has long been considered a useful outcome metric which allowed to account for both hits and false alarms to overcome the effect of bias. D prime has also been considered the standard outcome measure of working memory[58] and has recently been applied to a prospective memory task.[59]

Transcranial direct current stimulation

A 20-minute 2 mA tDCS session was administered through Neuroconn DC-Stimulator Plus (Neurocare Group, Ilmenau, Germany) and 5x7 cm rubber electrodes encased in saline-soaked sponges with 30-s ramp-up and ramp-down each week using the below-mentioned counterbalanced electrode setups:

Sequence 1: Week 1: Left anodal DLPFC (F3)/contralateral supraorbital; **Week 2:** Right anodal DLPFC (F4)/contralateral supraorbital; **Week 3:** Sham tDCS

Sequence 2: Week 1: Right anodal DLPFC (F4)/contralateral supraorbital; **Week 2:** Sham tDCS; **Week 3:** Left anodal DLPFC (F3)/contralateral supraorbital

Sequence 3: Week 1: Sham tDCS; **Week 2:** Left anodal DLPFC (F3)/contralateral supraorbital; **Week 3:** Right anodal DLPFC (F4)/contralateral supraorbital

Both right and left tDCS setups over the DLPFC were chosen respecting the previously designated relationship of PM with the right DLPFC[54–56] and the left DLPFC.[34,60] F3 and F4 electrode locations were determined in compliance with the 10-20 EEG System. The sham protocol consisted of 30-s ramp-up and ramp-down stimulation to mimic sensations of active tDCS without constant current delivery between two phases. Adverse events were collected using a questionnaire form derived from the relevant literature. Impedances were kept below 5 kiloohms.

Data analysis

Statistical analyses were utilized using SPSS 25.0 (IBM SPSS Statistics, Armonk, NY, USA). Normality tests revealed that d prime values were normally distributed while other outcome variables were non-normally distributed (Shapiro-Wilk test p-values<0.05). Analysis of variance was administered to assess baseline differences in d prime values between three sequence groups while Kruskal-Wallis tests were utilized to assess other differences among baseline values of the three sequence groups in the demographic variables and the PM outcome variables. A linear mixed model analysis of covariance (ANCOVA) was utilized to assess the Stimulation Type*Time Point interactions (Stimulation Type and Time Point as independent variables; memory outcomes as dependent variables; age, gender and the number of educated years as

covariates). Bonferroni correction was performed for comparison of 8 longitudinal PM outcome variables (0.05/8).

Ethics committee approval

Ethical approval was obtained from the institutional Ethical Committee (decision number 112 dated: 29.01.2019). All procedures were utilized in accordance with the Declaration of Helsinki.

Results

The mean age of the whole sample was 20.045 (±1.783) and the mean years of education of the whole sample was 13.833 (±1.255) while the proportion of the males was 45.8% in the whole sample. Baseline demographic and cognitive differences among the three sequence groups were shown in Table 1, while changes in the PM performance measures after anodal left/right/sham tDCS administrations were shown in Table 2. No significant baseline and longitudinal differences were found. Changes in the d prime values of the prospective memory performance after tDCS administrations are shown in Figure 2.

Table 1. Baseline differences in demographics and prospective memory performance among three sequence groups

Demographics	Sequence 1 (*n*= 8)	Sequence 2 (*n*=8)	Sequence 3 (*n*=8)	*P-values*
Age (years)	19.5 (1.7)	20.0 (4.5)	20.0 (3.5)	0.274
Education (years)	13.000 (1.500)	14.500 (4.000)	14.000 (1.750)	0.112
Cognitive measures				
COTA1	0.901 (0.098)	0.910 (0.187)	0.901 (0.089)	0.836
RTOT1 (ms)	1223.042 (511.042)	998.796 (211.594)	0.892 (0.324)	0.074
COTA2	0.909 (0.097)	0.883 (0.167)	0.801 (0.173)	0.654
RTOT2 (ms)	1442.371 (749.446)	1312.950 (560.498)	1258.950 (479.841)	0.475
PPMH	0.833 (0.541)	0.500 (0.458)	0.583 (0.791)	0.350
PPMFA	0.017 (0.035)	0.008 (0.040)	0.026 (0.044)	0.385
PMH	5.000 (3.250)	3.000 (2.750)	3.500 (4.750)	0.383
PMFA	1.500 (2.000)	0.500 (2.250)	1.500 (2.500)	0.194
D prime	3.040 (0.402)	2.403 (0.438)	2.531 (0.503)	0.542

ms: milliseconds; DLPFC: dorsolateral Prefrontal Cortex; COTA1: Correct Ongoing Task Accuracy in Block 1; RTOT1: Reaction Time Ongoing Task in Block 1; COTA2: Correct Ongoing Task Accuracy in Block 2; RTOT2: Reaction Time Ongoing Task in Block 2; PPMH: Proportion of Prospective Memory Hits; PPMFA: Proportion of Prospective Memory False Alarms; PMH: The number of Prospective Memory Hits; PMFA: The number of Prospective Memory False Alarms. Male/female ratios are shown for gender. Means (standard deviations are shown for D prime values. Medians (Interquartile Ranges) are shown for other variables. The value for the d prime shows the result of the analysis of the variance test. Other *P*-values show the results of the Kruskal-Wallis tests.

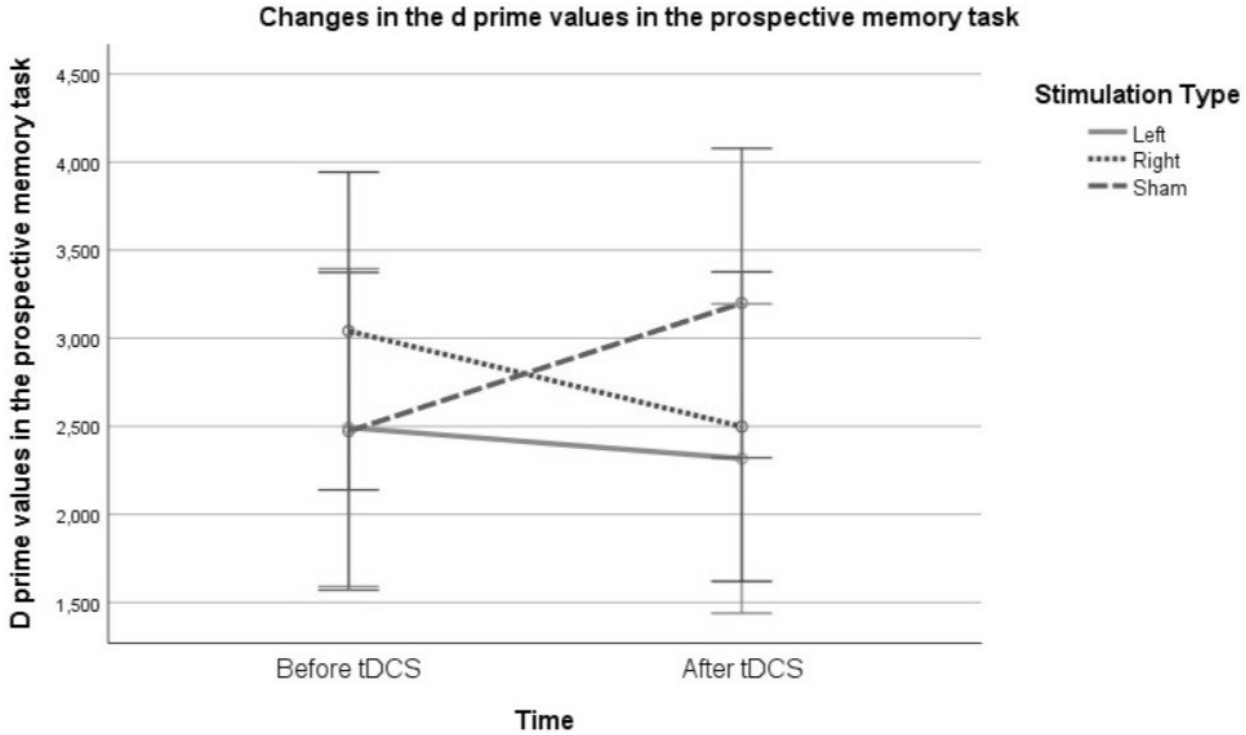

Figure 2. Changes in the d prime values of the prospective memory performance after tDCS administrations. tDCS: transcranial Direct Current Stimulation

None of the fixed or random effects of the longitudinally assessed PM outcomes were significant. There was no significant stimulation type*timepoint interactions for COTA1 (F=0.704; *p*=0.497), RTOT1 (F=0.728; *p*=0.485), COTA2 (F=0.045; *p*=0.956), RTOT2 (F=1.179; *p*=0.312), PPMH (F=0.133; *p*=0.875), PPMFA (F=0.532; *p*=0.589), PMH (F=0.133; *p*=0.875), PMFA (F=0.117; *p*=0.890) and d prime values (F=3.084; *p*=0.050).

Discussion

The present pilot double-blind cross-over study attempted to assess the effect of single-session Left/right anodal/sham tDCS over the DLPFC on both the prospective and retrospective components of event-based PM. Null hypotheses were confirmed in the present study. Contrary to expectations at first sight, the present results were not without rhyme and reason and should be ripped from an inclusive perspective as an array of factors like stimulation parameters, individual differences, assessment tools, and relevant cognitive functions might culminate in the observed null effects.

The alteration of event-based PM with a single-session of anodal tDCS over the left DLPFC is not supported, in line with the previous single-session tDCS studies.[52,53] Ellis et al. dispensed no effect of a single-session of tDCS over the left DLPFC on event-based PM in healthy young adults.[53] Further, Rose et al. reported no alterations in both event-based and time-based PM performance after a single-session of anodal tDCS over the left DLPFC in both healthy young and older adults.[52] Conforming with these preliminary results, we also achieved null results of a single-session of anodal tDCS over the left DLPFC in healthy adults. Besides, the present results reflecting the inefficacy of a single-session of right anodal tDCS over the DLPFC were the first in the tDCS literature. In contrast to a previous rTMS study over the right DLPFC,[54] the null hypothesis was supported in the present study. This might be explained by the difference in modulation potency between rTMS and tDCS. Albeit the prior study selected a PM task with low working memory demands, a possible difference between the modulation of working memory between rTMS and tDCS might also contribute to the discrepant results[54] as rTMS has been indicated to be more beneficial in all working memory measures than tDCS.[48] Besides, the time-based PM might be more dependent on the function of the right DLPFC,[34,61] and the effect of right anodal tDCS over the DLPFC on time-based PM merits further inquiry.

The present result might also be due to a variety of factors including tDCS and task parameters as well as the selection of a sample without cognitive deficits. Therefore, the present results may not simply exclude the participation of the prefrontal cortical areas in PM. Mounting literature indicated that a single-session of tDCS might not be adequate to enhance working memory in healthy volunteers[62–64] and have a slightly distinguished effect in individuals with brain diseases.[65] Respecting the role of working memory in PM performance, our null results might also be due to insufficient efficacy on working memory. Bearing this in mind, further studies may also incorporate working memory assessment simultaneously. Consequently, the present results, along with the previous tDCS studies, do not reinforce the use of a single-session of tDCS in PM modulation.

Since tDCS has a broad parameter space composed of copious components, further research should also take into consideration that distinct stimulation parameters from the electrode sizes to the current strength may result in differential outcomes.[42] Of particular importance is the number of sessions. Multi-session tDCS was considered to be more beneficial and appropriate for therapeutic effectiveness[45] as it was depicted to exert plasticity-related effects rather than acute physiological changes.[66] In accordance with these assumptions, accumulating evidence for better outcomes with multi-session tDCS over the DLPFC has been obtained.[66] In this respect, the efficacy of multi-session tDCS over the DLPFC on event-based PM remains to be established. Alternatively, another useful tool for PM modulation may be High-Definition tDCS (HD-tDCS) which enables fine-grained selective stimulation of smaller brain regions. By virtue of the neuroimaging

literature, the effect of HD-tDCS over the lateral rostral prefrontal cortices, insula, anterior cingulate cortices, and parietal cortices[9,34,67,68] on event-based PM should be ascertained. Priority should be given to the left frontopolar cortex as it was depicted to be a highly associated region with PM performance in functional neuroimaging studies,[34] and intermittent theta burst stimulation over the left frontopolar cortex has been found to enhance event-based PM in an ecologically valid virtual-reality based PM task.[69]

Another arguable point is the differences between the PM measures in their ecological validity as well as the difficulty and reliance on other cognitive functions. Rose et al. administered the Virtual Week task which provided a highly ecologically valid assessment of both event-based and time-based PM performance while Ellis et al. employed an event-based PM task with both focal and nonfocal cues.[52,53] We adopted an event-based PM task with nonfocal cues strictly based on the multinomial model of event-based PM.[2] Distinct features may alter longitudinal outcomes as the saliency of the prospective cues has been reported to affect the success of prospective remembering.[1] Furthermore, the working memory load in the selected PM task[7,54] as well as the working memory capacity of the individuals[70,71] may also interfere with the cue detection and task performance. Remarkable correlations have also been reported between PM accuracy and the performance of other cognitive functions like executive functions and episodic memory.[6] Taken together, future studies might carefully dissect the task features before determining the PM task in accordance with the study hypotheses.

Aside from the above, it is also non-negligible that the efficacy of single-session tDCS on PM may be discernible in different samples, such as older individuals with or without prospective memory deficits who are considered to have more room for improvement. Consistent with this notion, differential cognitive effects of tDCS between healthy individuals and neuropsychiatric samples have been observed.[47,72] Moreover, the impact of tDCS parameters like current density and strength has also been indicated to be higher in neuropsychiatric samples than in healthy individuals.[72] Diverse outcomes have also been reported between young and older adults, conceivably due to both differences in the room for improvement as well as the morphological and physiological changes in the brain.[73] On the other hand, the cognitive effects of tDCS have been pronounced to be related to baseline performance rather than age in healthy older adults.[74–76] A largely consistent wealth of evidence also emphasized the role of baseline performance in the cognitive effects of tDCS, thereby observing higher benefits in low performers.[77–80] However, the effect of tDCS on PM in individuals with PM deficits or neurocognitive disorders has not been examined thus far. To conclude, the present results might not allow us to dispense with the possibility that tDCS might be fruitful in individuals with PM deficits.

Study limitations

Some limitations of the present work should be mentioned. First, the integrity of the blinding was not evaluated. We also did not assess time-based PM and cognitive functions that were closely related to PM. Finally, the sample of the present study mainly consisted of young adults. On that account, the results should not be generalized to middle-aged or older adult samples.

Conclusion

A single session of both left/right anodal tDCS over the DLPFC is likely inadequate to enhance event-based PM in healthy individuals. Notwithstanding the lack of efficacy, the present study contributed to the incipient literature on PM modulation and provided instructive data regarding the current stimulation parameters. Hence, further research should refine the knowledge to pinpoint optimal stimulation targets. In that vein, more efforts scrutinizing the modulation of PM with the stimulation of other brain regions with similar or distinct parameters are required to unfold the mechanisms underlying PM better.

Ethics Committee Approval

Ethical approval was obtained from the institutional Ethical Committee (decision number 112 dated: 29.01.2019). All procedures were utilized in accordance with the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from each individual after adequate information about the study aims and procedures had been provided.

Author Contributions

Study conceptualization, design: S. Aksu, E.Özsayın, A. E. Aslan, Y. Kaya, S. Karamürsel. Supervision: S. Karamürsel. Data collection and analysis: S. Aksu, E.Özsayın, A. E. Aslan, Y. Kaya, S. Karamürsel. Literature review: S. Aksu, E.Özsayın, A. E. Aslan, Y. Kaya, S. Karamürsel. Manuscript writing: S. Aksu, E.Özsayın, A. E. Aslan, Y. Kaya, S. Karamürsel. Final review: S. Aksu, E.Özsayın, A. E. Aslan, Y. Kaya, S. Karamürsel

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Conflict of Interest

Authors declare no conflict of interest

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Statements

These results have not been presented anywhere previously.

Peer-review

Externally peer-reviewed

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