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Published in:
Neuroscience Letters

DOI:
10.1016/j.neulet.2022.136691

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Sevilla-Sanchez, M., Hortobágyi, T., Carballeira, E., Fogelson, N., & Fernandez-del-Olmo, M. (2022). A lack of timing-dependent effects of transcranial direct current stimulation (tDCS) on the performance of a choice reaction time task. *Neuroscience Letters*, *782*, [136691]. https://doi.org/10.1016/j.neulet.2022.136691

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Neuroscience Letters 782 (2022) 136691

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

A lack of timing-dependent effects of transcranial direct current stimulation (tDCS) on the performance of a choice reaction time task

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ARTICLE INFO

Keywords:
Non-invasive brain stimulation (NIBS)
Long-term motor learning
Motor learning
Motor retention
Reaction time task

ABSTRACT

Anodal transcranial direct current stimulation (tDCS) can enhance the retention of a previously practiced motor skill. However, the effects of tDCS on the performance of the choice reaction time task are not fully understood. We examined the effects of anodal tDCS over the left primary motor cortex (M1) on the retention of a 4-choice visual-motor reaction time task (4-ChRT). Right-handed healthy participants (n = 100) were randomly assigned to five groups: three groups received anodal tDCS: before ($tDCS_{before}$), during ($tDCS_{during}$), or after ($tDCS_{after}$) motor practice. In addition, there were two control groups: with (CON_{mp}) and without (CON) motor practice. We evaluated the speed and precision of the 4-ChRT task before (PRE), during, and 24 h (POST) after the interventions. All groups, including the non-stimulation (CON_{mp}) and non-practice groups (CON), improved ($p < 0.05$) motor retention (Δ4-ChRT: 35.8 ± 36.0 ms). These findings suggest that the tDCS effects over M1 may differ for serial versus choice RT tasks, perhaps due to the different brain areas involved in each motor task.

1. Introduction

A critical element of motor learning is the ability to retain and recall a previously practiced motor skill. Performance may be enhanced immediately after the practice period (online skill gains). However, memory consolidation may also result in motor skill improvements that outlast the practice period (offline skill gains). The offline skill gains or motor retention occur within a specific time window after training and up to 24–48 h [1,2]. Newly learned motor skills are associated with functional and structural changes in the nervous system [3]. Specifically, the primary motor cortex (M1) is involved in movement control during the early learning phase [4-7].

Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), have gained popularity for their potential to enhance motor and cognitive functions both in healthy and patient populations. tDCS is a non-invasive, safe, and painless technique that can modulate cortical excitability and affect the function of several cortical areas [8,9]. Anodal tDCS of M1 has been examined using serial reaction time (RT) paradigms in which participants learn a motor sequence either implicitly or explicitly [10-18] and tDCS seems to enhance motor performance and retention. A serial RT task typically includes an embedded repeated cycle of responses, and a reduction of RT in these cycles without explicit knowledge is thought to reflect implicit learning [19]. Conversely, a 4-choice reaction time task (4-ChRT) presents the stimuli in a random and unpredictable fashion and is thought to mostly reflect response selection processes [20,21]. The 4-ChRT uses random stimuli and involves predominantly motor processes compared to other serial-learning tasks, which require more cognitive processes.

Abbreviations: tDCS, transcranial direct current stimulation; M1, primary motor cortex; 4-ChRT, 4-choice visual-motor reaction time; RT, reaction time; $tDCS_{before}$, tDCS applied immediately before motor practice; $tDCS_{during}$, tDCS applied during motor practice; $tDCS_{after}$, tDCS applied immediately after motor practice; CON_{MP}, control group with motor practice; CON, control group without motor practice; PRE, pre-test or baseline; POST, post-test after 24 h.

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https://doi.org/10.1016/j.neulet.2022.136691
Received 15 February 2022; Received in revised form 15 May 2022; Accepted 17 May 2022

Only a few studies evaluated the acute effect of tDCS in a choice RT task. In these studies, the task was used as a control condition to explore the effects of tDCS on a serial RT task [11,22,23]. The findings of these studies remain inconclusive since different tDCS protocols were used, as well as a small sample of participants. Furthermore, the effects of tDCS on a simple choice RT task can often be masked by fatigue [23] or due to a lack of attention resulting in a ceiling effect [22]. Thus, we examined the effects of tDCS on motor retention by evaluating the performance of the choice RT task 24 h after practice.

The facilitatory effects of tDCS on learning may vary whether it is applied before, during, or after the practice. tDCS before motor practice enhances performance by priming M1 [10,23-26] but most studies delivered tDCS during motor practice [12,13,16,27-30]. Anodal tDCS over M1 seemed to facilitate the motor retention in a serial RT task [12,13]. tDCS after motor practice can also improve skill retention [31]. However, there were no effects of tDCS on motor retention of an RT task when tDCS was applied before [32], during [14,29], or after [33] motor practice. Therefore, further studies are needed to clarify the tDCS effects on motor retention in these tasks.

Taken together, the aim of the present study was to determine the timing effects of tDCS, over M1, on motor retention, by evaluating the performance of choice RT task 24 h after the practice session.

2. Material and methods

The present study used a randomised blind design.

2.1. Participants

Right-handed participants with no current or a history of neurological disease, psychological disorder, drug or alcohol abuse, or use of neuropsychiatric medication were recruited ($n = 100$, 68 males, age 20–34 years). This sample size was determined using a power analysis (G*Power 3.1) based on medium effect size (0.25) and critical alpha and b-errors of 0.05. Participants signed an informed consent document approved by the university's ethics committee (Appendix B). The study was conducted according to the declaration of Helsinki. Participants were asked to refrain from caffeine or alcohol the day before the experimental session.

2.2. Procedures

Participants were randomly assigned to five groups, 20 per group. Three groups received anodal tDCS: before ($\text{tDCS}_{\text{before}}$), during ($\text{tDCS}_{\text{during}}$), or after ($\text{tDCS}_{\text{after}}$) motor practice. Two control groups were: with (CON_{mp}) and without (CON) motor practice. The pre-test (PRE) and the post-test 24 h after intervention (POST) consisted of a single block of 40 trials with the right-dominant hand. Motor practice consisted of 12 blocks of 40 trials (a total of 480 trials), with 15 s of rest between blocks also with the right hand (Fig. 1). We selected this period motor practice based on studies of serial reaction times suggesting that performance started to decrease after 480 total trials possibly due to fatigue [11].

2.3. tDCS

The 1-mA current was induced through saline-soaked sponge electrodes (size: 7x5cm; surface area: 35 cm^2; current density: 0.03 mA/cm^2) for 20 min connected to aDC stimulator (tDCS Stimulator Clinical Version, TCT research Limited, Hong-Kong), with a 10-s on and off ramping. The stimulating anode electrode was positioned over electrode site C3 (international 10–20 EEG system), i.e., left M1, contralateral to the right-hand performing the tests and the motor practice. The reference cathode electrode was placed over the right supraorbital cortex [34,35]. We applied anodal stimulation over M1 because of its role in motor retention [5,6] and based on evidence suggesting that anodal tDCS of M1 improves the retention of serial RT task [17,36].

2.4. Visuomotor reaction time task

We used a version of the RT task named 4-ChRT [19]. Participants sat in a chair in front of a computer screen positioned at eye level. The tests and the motor practice were performed with the right-dominant hand only. Participants placed the right index, middle, ring, and little fingers on the "C", "V", "B", and "N" keyboard keys. Four 3 × 3 cm horizontally aligned white squares with black trim were presented in the middle of a computer monitor on a white background; the squares were 1.5 cm apart. At the beginning of the 4-ChRT, the blank squares were presented for 1000 ms before the first stimulus was displayed. As soon as a visual stimulus (asterisk) appeared in one of the four squares (for up to 500 ms), participants were instructed to make a response with the spatially

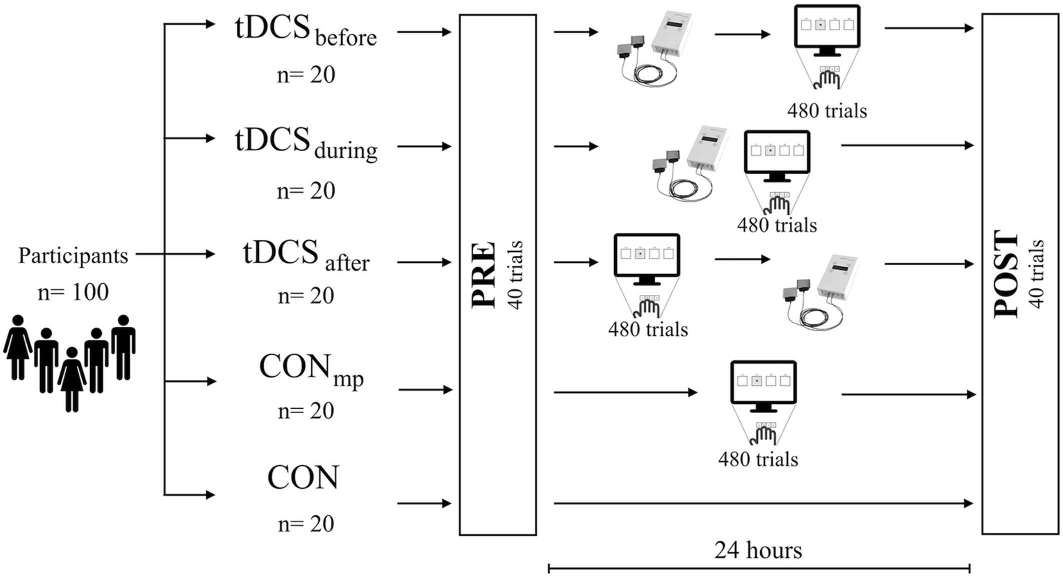

Fig. 1. Study design. Experimental protocol. tDCS, transcranial direct current stimulation; CON_{MP}, control group with motor practice; CON, control group without motor practice; PRE: the pre-test or baseline; POST: the post-test 24 h after intervention.

corresponding key. Once a response was given, the stimulus disappeared, and then the next visual stimulus appeared. The sequence was always presented in a pseudorandom fashion order in which the stimulus appeared with the same frequency in each of the four positions. The number of errors and the RT between the appearance of the visual stimulus and the pressing of the key were recorded. The task was designed using Superlab Pro v.4.0 software (Cedrus Corporation, San Pedro, CA).

2.5. Data processing

The speed was evaluated by measuring the mean RT between the stimulus onset and the correct key press. A response was considered correct when the participants pressed the correct key paired with a particular stimulus. Each participant's mean RT was calculated separately for each block of trials of a given experimental condition. Individual trials exceeding ± 2SDs were excluded from the analysis (about 3% of trials) [37]. One of the assessors administered tDCS and a second technician analysed the data.

2.6. Statistical analysis

We report the data as mean ± SD. Normality was checked with the Shapiro-Wilk test (Jamovi software [38], GAMLj module [39], lme4 R package [40]). GAMLj estimates variance components with restricted (residual) maximum likelihood (REML), which produces unbiased estimates of variance and covariance parameters. To compare the online performance for RT and errors, two independent mixed models were used with the following configuration: Group as the inter-subject factor ($tDCS_{before}$, $tDCS_{during}$, $tDCS_{after}$, and CON_{mp}), Block as the intra-subject factor (from block 1 to block 12), and the interaction (Group × Block). To compare the offline performance for RT and errors in two independent mixed models, we used for both model Group ($tDCS_{before}$, $tDCS_{during}$, $tDCS_{after}$, CON_{mp}, and CON), Time (PRE and POST), and Group × Time interactions as independent variables (fixed effect). Sex and age were not introduced as a fixed factor and covariate, respectively, because these variables did not improve the model (i.e., parsimonious method), as evaluated by the Akaike information criterion (AIC). The participant intercept was set as the random effect. Within-subject and between-subject changes were evaluated by ANOVA F omnibus test employing the Satterthwaite approximation of degrees of freedom and estimating the coefficients with their 95% confidence intervals for the fixed effects in the mixed model. Furthermore, the variance of the random coefficients was obtained. Simple effects analysis was applied with ANOVA (type III sums of squares) and employing the Kenward-Roger method for degrees of freedom calculation. The level of significance was established at $p < 0.05$.

3. Results

Every participant completed the study without adverse effects due to tDCS.

3.1. The effect of tDCS on speed

Fig. 2 shows the speed performance during motor practice. There were no between-group differences in RT ($F_{3,76} = 2.20$, $p = 0.09$), Blocks ($F_{11,836} = 1.38$, $p = 0.18$) nor was there a Group*Block interaction ($F_{33,836} = 1.01$, $p = 0.46$) ($p > 0.05$ across the comparisons, β = -17 and $CI_{95\%=}$ −41 to 7; β = 14 and $CI_{95\%}$=-10 to 38; β = -4 and $CI_{95\%}$=-28 to 20, for $tDCS_{before}$ vs CON_{mp}, $tDCS_{during}$ vs CON_{mp} and $tDCS_{after}$ vs CON_{mp}, respectively). The use of mixed model was an appropriate because variability was high in the random component (participant intercept) ($\delta = 1.449$; ICC = 0.82).

There were no between-group differences in RT at PRE ($p > 0.05$). Fig. 3 shows the RT values by groups at PRE and POST. There were main effects for Time ($F_{1,\ 97} = 99.08$, $p < 0.001$) and a trend for Group ($F_{4,\ 97} = 2.13$, $p = 0.08$). However, there was no significant Time*Group interaction ($F_{4,\ 97} = 1.66$, $p = 0.17$). The mean RT was faster at POST (384 ± 35 ms) compared to the PRE condition (419 ± 48 ms), irrespective of the stimulation condition (ß= 35, $CI_{95\%}$= 28 to 42, $t_{97} = 9.95$, $p < 0.001$) ($\Delta_{4\text{-ChRT}}$: 35.8 ± 36.0 ms). $tDCS_{after}$ was the only group that showed a higher performance in the Test compared to CON (ß= 27, $CI_{95\%}$= 3 to 50, $t_{97} = 2.23$, $p = 0.02$). In addition, there was no significant Time × Group interaction in the mixed model.

3.2. The effect of tDCS on accuracy

During motor practice, there were no between-group differences in error ($F_{376} = 0.94$, $p = 0.43$). However, there were differences between Blocks ($F_{11,836} = 2.18$, $p = 0.01$) without a significant Group*Block interaction ($F_{33,836} = 1.16$, $p = 0.25$). Overall, the average error increased in the middle of the motor practice (block numbers 3,5,6,7,8,9,10) compared to block number 1 ($p < 0.05$).

There were no between-group differences in error at PRE ($p > 0.05$, Table 1). In the 4-ChRT, there were no main effects for Time ($F_{1,97} = 0.09$, $p = 0.77$) or for Group ($F_{4,97} = 1.94$, $p = 0.11$), nor Time*Group interaction ($F_{4,97} = 1.58$, $p = 0.19$).

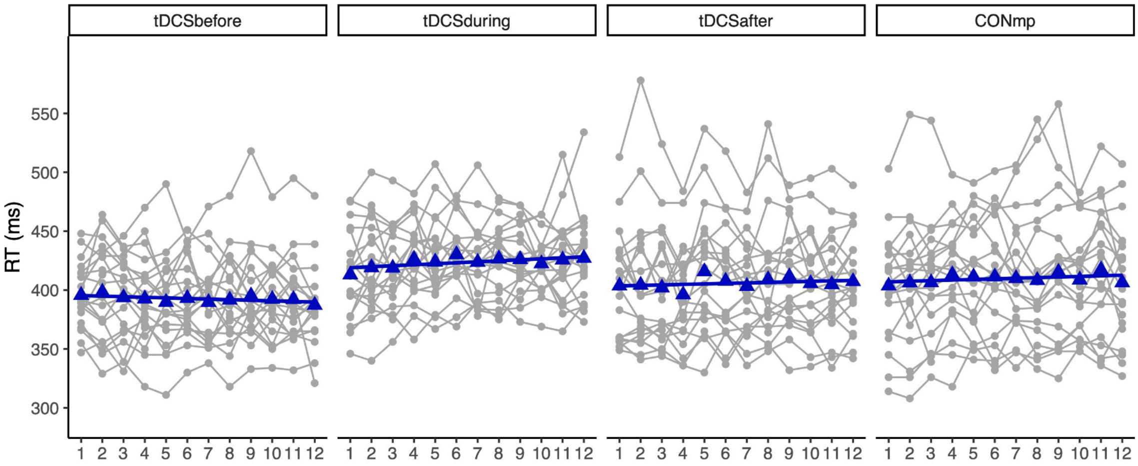

Fig. 2. Online effects of tDCS on motor practice in the 4-ChRT. Individual data cluster by groups at the motor practice are reported, and the thick blue line and the triangles is the group means. No difference was seen in the motor performance between the groups. Data are mean ± 95% confident interval. tDCS, transcranial direct current stimulation; COM_{MP}, control group with motor practice.

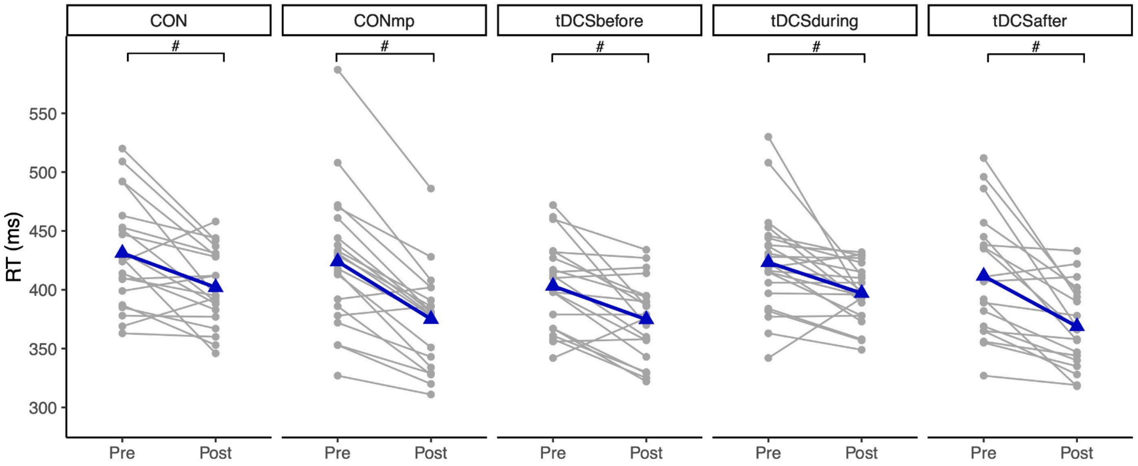

Fig. 3. The performance during motor retention in the 4-ChRT. Individual data by groups at PRE and POST are reported, and the thick blue line and the triangles is the group mean. tDCS, transcranial direct current stimulation; CON_{mp}, control group with motor practice; CON, control group without motor practice. #p < 0.001.

Table 1
Accuracy performance in the 4-ChRT. The number of errors mean in absolute values at PRE and POST conditions by groups (Mean ± SD).

	$tDCS_{before}$	$tDCS_{during}$	$tDCS_{after}$	CON_{mp}	CON
	n = 20	n = 20	n = 20	n = 20	n = 20
PRE	2 ± 2	2 ± 2	2 ± 1	2 ± 1	1 ± 1
POST	2 ± 2	2 ± 1	2 ± 1	2 ± 1	1 ± 2

Note: tDCS, transcranial direct current stimulation; CON_{mp}, control group with motor practice; CON, control group without motor practice. * $p < 0.05$, ** $p < 0.01$.

4. Discussion

We examined the effects of the timing of tDCS, relative to the motor practice, 4-ChRT performance. All the groups, including the non-stimulation (CON_{mp}) and non-practice (CON) groups, improved RT 24 h after practice. tDCS over M1 does not enhance motor retention in 4-ChRT.

Our findings demonstrate that the groups, which performed the practice blocks, did not improve their performance compared to the control group without motor practice. Thus, tDCS, regardless of its application time, did not potentiate motor improvement. Likewise, although the task in this study was not sensitive to the effects of motor practice, tDCS could have enhanced the effects of training per se, showing a superior performance to the control groups. The lack of effect of tDCS has been reported for simple [32] and choice RT tasks [11,22,23]. However, it is possible that the tDCS effects were masked because participants lost their focus and concentration during practice [22,23].

All the groups improved performance 24 h after, regardless of whether or not they had completed the practice blocks. Thus, our findings show that the application of tDCS before, during, or after the practice blocks did not improve task retention. These data agree with previous data showing no effects of M1 tDCS on motor retention 24 h after practicing a choice RT task [11-13]. Our findings differ from other studies that reported a potentiating effect of tDCS on motor retention before [10], during [16], and after [31] motor practice in choice RT tasks. Pre-practice tDCS improved motor performance 48 h after practice as expressed through reduced variability [10]. In contrast, we did not observe tDCS-induced improvements in accuracy at a shorter follow-up interval at 24 h. In the study that applied tDCS during motor practice [16], the authors selected a visuomotor task with 8 targets, a much more complex task than our 4-ChRT task. Moreover, the effects of tDCS on retention diffeed from our results when tDCS was applied after motor practice in a bi-hemispheric configuration [31]. That is, tDCS-effects on motor retention of a choice RT task are inconclusive.

The highly variable responses to tDCS may in part underlie the inconsistencies between studies. For example, ~50% of healthy volunteers had no or minimal response to tDCS [41,42]. Indeed, individual responses to tDCS are highly variable [43-45]. A ceiling effect in the choice RT task could have also abolished tDCS effects. The control group, which did not perform the practice blocks, reached a retention level similar to that of the other groups that did perform the motor practice, suggesting that the test trials were already sufficient for participants to reach peak performance.

While participants performed 480 trials as in a previous RT study [46], our groups improved little across training. Participants were healthy young adults and perhaps performed already at a peak level. Still, stroke patients with motor impairments could benefit from tDCS while practicing (extensively) combined with drugs [47] and transcranial magnetic stimulation [46,48]. A lack of tDCS effects may be due to task simplicity. tDCS may be effective when the task is complex [46]. The stimulation area over M1 may also be sub-optimal as M1′s role in learning this particular task might be limited. Indeed, anodal tDCS over the supplementary motor area improved RT [49].

One limitation is that although we used a stimulation protocol recommended previously [34,35], stimulation parameters other than the ones used here could have produced different results. Also, the stimulation location did not impact the areas associated with the choice RT task. A lack of differences in performance between intervention groups vs. the no-practice control group is another limitation. We also failed to measure any neurophysiological outcomes. Future studies using transcranial magnetic stimulation are warranted to explore the mechanisms underlying improvements in choice RT performance after tDCS.

5. Conclusion

A single motor practice session accompanied by tDCS before, during, or after motor practice does not enhance the retention in a choice RT task. tDCS effects over M1 may differ for serial versus choice RT tasks, perhaps due to the different brain areas involved in each motor task.

6. Availability of data and material

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

7. Code availability

The code for running the experimental control software is available from the corresponding author on reasonable request.

8. Consent to participate

All participants provided written informed consent before study-specific procedures were conducted.

9. Consent for publication

Participants signed informed consent to publish their data.

10. Open access

11. Ethics approval

The research protocol was approved by the local Ethics University Committee and carried out according to the Declaration of Helsinki principles.

Funding

This work was supported by the "Ministerio de Ciencia, Innovación y Universidades" of Spain by an FPU fellowship [grant numbers FPU16/01264].

CRediT authorship contribution statement

Marta Sevilla-Sanchez: Conceptualization, Methodology, Investigation, Writing – original draft. **Tibor Hortobágyi:** Writing – review & editing. **Eduardo Carballeira:** Formal analysis, Visualization, Writing – review & editing. **Noa Fogelson:** Writing – review & editing. **Miguel Fernandez-del-Olmo:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We thank the students for their participation and enthusiasm.

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