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Short duration transcranial direct current stimulation (tDCS) modulates verbal memory

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Transcranial direct current stimulation (tDCS) is a noninvasive method of modulating cortical excitability. The aim of this study was to investigate the effects of short-duration tDCS (1.6 seconds per trial) on memory performance, and whether the effects were affected by stimulation administered early or late in a trial. Participants memorize words under anodal and cathodal tDCS to the left dorsolateral prefrontal cortex (DLPFC) in two separate sessions in no-stimulation, early stimulation, and late stimulation trials. Early stimulation occurred during word presentation, whereas late stimulation occurred after word presentation. Early anodal tDCS led to significantly better accuracy and speed in a subsequent recognition test compared to anodal late or no-stimulation conditions. Early cathodal tDCS, on the other hand, led to significantly worse accuracy and speed in a subsequent recognition test compared with cathodal late or no-stimulation conditions. The results of this study suggest that short-duration tDCS can modulate memory performance and highlight the importance of period of stimulation.

Keywords electrical brain stimulation; transcranial direct current stimulation; memory; dorsolateral prefrontal cortex

Transcranial direct current stimulation (tDCS) is a noninvasive technique of brain stimulation that can induce temporary changes in cerebral cortical excitability by applying a weak direct current (DC) on the scalp.[1-3] The effects of tDCS are site-specific, with different behavioral changes observed after the stimulation of different cortical areas. For example, stimulating the various areas of the motor cortex influences thumb and leg movements, whereas attentional shifts between global and local feature processing are modulated by stimulating the posterior parietal cortex.[4-6] Therefore, depending on where it is administered, tDCS may benefit motor learning,[7] visual-motor coordination,[7,8] or decision making.[9] tDCS also appears to have clinical applications for patients suffering from Alzheimer's disease, stroke and depression.[10-12] In addition to the site of stimulation, the polarity of stimulation is also important: anodal stimulation increases cortical excitability, whereas cathodal stimulation decreases it.[13-15] Furthermore, it has been shown that anodal and cathodal stimulations have different cognitive effects (see below).

Recent developments in tDCS research have focussed on its effects on working memory in healthy participants and

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patients.[16,17] In a study involving stroke patients who had cognitive deficits, administering 25 minutes of anodal tDCS to the left dorsolateral prefrontal cortex (DLPFC) was found to improve their accuracy in a two-back working memory task.[18] Adopting a similar paradigm, Fregni et al.[19] applied 10 minutes of anodal stimulation to the left DLPFC of healthy participants and reported that their performance on a subsequent three-back memory test significantly improved compared with sham stimulation. Both studies reported that response times were not affected by tDCS stimulation, a result that is supported by other studies.[20,21]

Ohn et al.[22] extended the literature by demonstrating that 20 and 30 minutes of anodal tDCS improved working memory accuracy significantly more than 10 minutes of stimulation, indicating that the benefits of anodal tDCS increase with stimulation duration. Boggio et al.[16] reported that although 2 mA of anodal tDCS administered to the prefrontal cortex significantly improved working memory accuracy in patients with Parkinson's disease, a 1 mA stimulation did not. It seems then that stimulation intensity is a critical parameter in eliciting the effects of tDCS.[23]

In comparison, little attention has been devoted to the effects of tDCS on declarative memory. In one study, Elmer and colleagues[24] presented participants with a word list to memorize and applied sham, anodal, and cathodal tDCS to the right or left DLPFC. In a subsequent verbal recall test conducted 25 minutes after stimulation ended, it was reported that neither stimulation polarity had an effect on long-term memory retrieval. In contrast, Javadi and Walsh[25] have shown that administering anodal tDCS to the left DLPFC when participants were learning words improved their memory accuracy on a word recall test performed 45 minutes after stimulation; although cathodal stimulation impaired subsequent memory performance. The divergence in findings may be attributed to the former study selecting the mastoid for the reference electrode's position, whereas the latter study chose the right supraorbital area as the reference. The placement of electrodes has been found to yield considerable influence over the flow of direct current, which may alter the effects of tDCS.[14,26] Furthermore, participants in the study by Elmer et al. were stimulated at a lower intensity and for a shorter duration, which may not have been sufficient to fully induce the effects of tDCS on long-term memory.[16,22]

The aim of this study was to extend on previous research by investigating the effects of administering short-duration tDCS on declarative memory. Previous studies suggest that anodal tDCS administered to the left DLPFC improves cognitive ability, whereas cathodal stimulation impairs it.[22,23,27-31] Therefore, the first prediction is that anodal tDCS will lead to higher memory accuracy on the memory recognition task, and that cathodal tDCS will impair subsequent memory accuracy.

We were also interested to see if different periods of stimulation have different effects on memory performance. Javadi et al. (unpublished data) used electroencephalography (EEG) to record the cortical activity of participants when they were encoding words for long-term memory. They noted that for 4-second trials in which participants had to imagine a word to memorize it, the brain underwent two different phases. The phase change occurred around 2 seconds after the word onset, leading the authors to propose that different brain mechanisms are involved in the two halves of the memorization. Based on their study, the second prediction is that tDCS will have a different effect depending on whether it is administered in the first half of a trial or the second half.

Method

Participants

A total of 13 university students took part in the experiment (6 females, mean age 22.42 years, range 18-28, seven began with anodal stimulation). All participants had normal or corrected-to-normal vision, and were right-handed, fluent English speakers who were naïve to the purpose of the study. In addition, none of the participants were taking any centrally acting medication. All participants gave a written, informed consent in accordance with the Declaration of Helsinki and the guidelines approved by the Ethical Committee of UCL. Participants were monetarily reimbursed for their participation in the study.

Design

The experiment adopted a 2 × 3 repeated-measures design. The first independent variable that was varied within subjects was stimulation polarity, which had two levels: anodal and cathodal stimulation. Participants attended 2 experimental days that were separated by at least 72 hours to minimize carryover effects.[16] Within one session, participants received either anodal or cathodal stimulation only. To eliminate potential order effects, seven of the participants were assigned to receive anodal stimulation first, whereas the others began with cathodal stimulation.

The second independent variable that was also varied within subjects was the time of stimulation onset during a trial in the training phase. Three conditions were used: early onset in the first half of a trial; late onset in the second half of a trial; or no stimulation for that trial, as shown in Figure 1B.

Stimuli

A bank of 1354 words was extracted from the MRC psycholinguistic database.[32] The words were controlled for number of letters (minimum = 3, maximax = 8, $\mu = 4.89$, standard deviation [SD] = 1.24), number of syllables (minimum = 1, maximum = 2, $\mu = 1.49$, SD = 0.50),

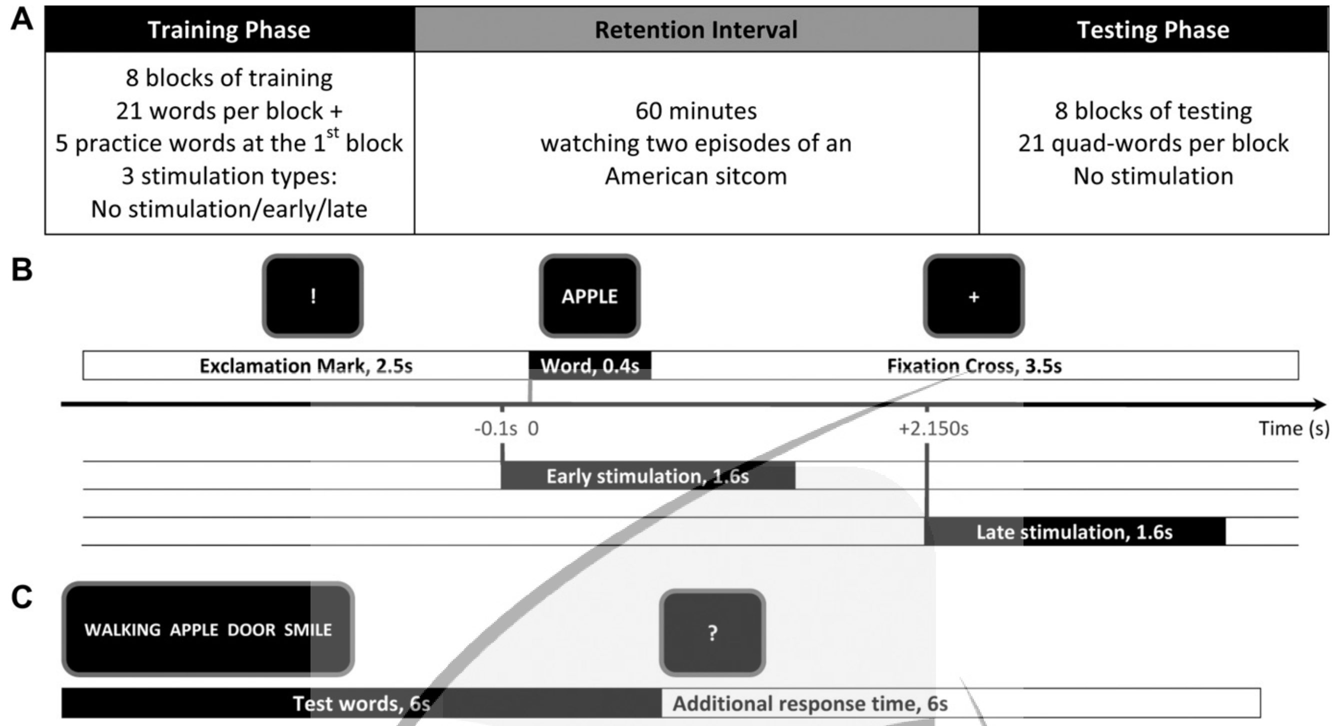

Figure 1 **A,** Procedure of one session composed of training, retention and testing phases. **B,** Procedure of trials in the training phase. The top row shows what participants see on the screen, while the black bars below the timeline represent the onset of either early or late stimulation. **C,** Procedure of the testing phase; the quad word, comprising one word from the trained words and three additional distracter words. Participants were free to respond anytime during this 12 seconds interval.

printed familiarity (μ = 558.48, SD = 31.41), concreteness (μ = 542.51, SD = 67.73), and imagability (μ = 555.60, SD = 55.21).

In the training phase, participants were presented with eight blocks of 21 randomly selected words. The first block had five additional words in front to allow participants to practise the memorization task. These additional words were discarded and not tested in the testing phase. A quad-word presentation was used in the testing phase: each previously displayed word was presented together with 3 new words randomly chosen from the bank (Figure 1C). A different set of words was used for the first and second sessions.

Apparatus

The experiment was run on a desktop computer with a 17-inch monitor, 75 Hz refresh rate, and a resolution of 1024 × 768. Stimuli were presented in capital letters using Arial font, subtending approximately 3-6 degrees of horizontal visual angle, and were displayed in white against a black background. Stimulus presentation and the recording of response time were achieved using MATLAB (v7.5; MathWorks Company, Natick, MA) and the Psychtoolbox v3.[33,34] Data analyses were performed using SPSS (v17.0; LEAD Technologies, Inc, Charlotte, NC).

tDCS

Direct electrical current was administered using a NeuroConn DC Brain Stimulator Plus unit (Rogue Resolutions, Wales, UK) and delivered via a pair of saline-soaked surface sponge electrodes, 35 × 35 mm (12.25 cm^2, current density 122.44 $\mu A/cm^2$) over target site and 55 × 55 mm (30.25 cm^2, current density 33.05 $\mu A/cm^2$) over nontarget site, attached to the skin of participants.

Based on previous neuroimaging studies on declarative memory[35-37] and other studies on working memory,[16,18,19,22] left DLPFC was selected as the main site of stimulation. The left DLPFC (F3 in accordance with the 10-20 international system for EEG electrode placement[38]) was chosen as the main site of stimulation, whereas the contralateral supraorbital area was selected as the reference electrode position.[3,26] For anodal stimulation, the anode was placed over F3 and the cathode was placed over the right supraorbital area. For cathodal stimulation of the DLPFC, the positions of the electrodes were swapped.

Participants either received 1.6 seconds DC stimulation or no stimulation in each trial. Stimulation was administered on a trial by trial basis either as early stimulation, i.e., in the first half of a trial (onset at 0.1 second before word presentation) or as late stimulation, i.e., in the second half of a trial (onset at 2.15 seconds after word presentation). In total, participants received 179.2 seconds of early and late stimulation (89.6 seconds of each type). They felt the sensation of stimulation only for the first few trials of each session. A poststudy debrief indicated that participants did not perceive the difference between stimulation conditions. Procedure of a trial along with the three stimulation conditions is shown in Figure 1B.

Previous studies have reported that a 2 mA DC stimulation can be safely applied over the DLPFC for up to 20 minutes.[16,23,39] As such, the electrical current strength selected for this study was 1.5 mA. Because of the smaller electrode size used at the target size (35×35 mm), the current intensity at the target site (122.44 $\mu A/cm^2$) was higher as compared with previous studies. Computer simulations showed that this current intensity at the target site has similar effects to larger electrode sizes in terms of current diffusion in the brain and other tissues such as skin.[40] The total electrical charge delivered to the participants, however, was significantly lower in this study compared with other studies (1.5 mA $\times$ 179.2 seconds = 268.8 mA.s in this study versus 2 mA $\times$ 1200 seconds = 2400 mA.s in Iyer et al.[23]).

Procedure

The procedure of the session is shown in Figure 1A. Each session was blocked into three phases: training phase, retention interval, and testing phase.

For the training phase, the respective electrodes were placed on the left DLPFC and right supraorbital area. Participants were informed that they were required to perform a word memorization task. They were told that individual words would be briefly presented, followed by a fixation cross that would appear for 3.5 seconds to represent the “imagination period.” Participants were asked to sustain their attention and use the entire “imagination period” to silently imagine the word to remember it for a subsequent memory test. They were also instructed to imagine each word separately from the others. Figure 1B summarizes the procedure in a typical training phase trial.

The surface sponge electrodes were removed after the training phase was completed. Before the testing phase commenced, participants watched two episodes of the American sitcom “Friends,” which lasted for 60 minutes. Based on the intervals used in previous studies, the comparatively short duration of stimulation used in this study suggests that this 60-minute duration was sufficient for the brain to recover its prestimulation state during the test.[41,42]

In the testing phase, participants were told that four words would be presented in a line on the computer screen in each trial, of which only one was a previously presented word (old word) they had seen in the training phase. Their task was to identify the old word by pressing a key on the keyboard that corresponded to the word’s position along the line. Participants were told that the words would stay on screen for 6 seconds, after which the words would disappear and they then had 6 more seconds to make their response, Figure 1C. They were instructed to respond as accurately and fast as possible. Participants were encouraged to respond even if they could not select the target word with a high level of confidence. The order of the old words in the testing phase was randomized and different from the order in which they appeared in the training phase. At the end of each block, the percentage accuracy for that block was shown on screen for 3 seconds as feedback for participants.

The entire procedure was repeated for the second experimental session with a different stimulation polarity from the first session.

Statistical analysis

The effect of tDCS was assessed with a two-way repeated measure analysis of variance (ANOVA) with stimulation polarity (anodal/cathodal) and stimulation time (early/late/no stimulation) as within-subject factors. Performance percentage and reaction time were measured as dependent variables. A significance level of $P < 0.05$ was used. Bonferroni-corrected post hoc paired-samples two-tailed t tests were used to study the difference between conditions: comparison between early, late, and no-stimulation for anodal and cathode stimulations and comparison between anodal and cathodal no-stimulation. The dependent variables were checked for normal distribution.

Results

All participants completed both experimental sessions. Trials in the testing phase were split according to whether the target word was presented with early stimulation, late stimulation or no stimulation during the training phase.

The performance percentages of participants in the word recognition task were subjected to a 2×3 repeated measures ANOVA. The main effect of stimulation polarity was significant, $F(1, 12) = 8.74$, $P = 0.016$ and the main effect of stimulation time was nonsignificant, $F(2, 24) = 0.14$, $P = 0.870$. The interaction effect between stimulation polarity and time was highly significant, $F(2, 24) = 9.98$, $P < 0.001$.

A paired-samples t test comparing participants’ accuracies in the no-stimulation and early stimulation trials under anodal ($t(12) = 2.62$, $P = 0.022$) and cathodal ($t(12) = 2.82$, $P = 0.015$) stimulation conditions were significant, indicating that administering anodal stimulation early in a trial led to an improvement in memory accuracy over nonstimulation trials, whereas memory accuracy was impaired after cathodal tDCS in the first half of a trial. Comparing early stimulation and late stimulation in anodal and cathodal conditions using paired-samples t test analysis also showed a significant difference, $t(12) = 2.52$, $P = 0.027$ and $t(12) = 2.34$, $P = 0.037$ respectively, indicating

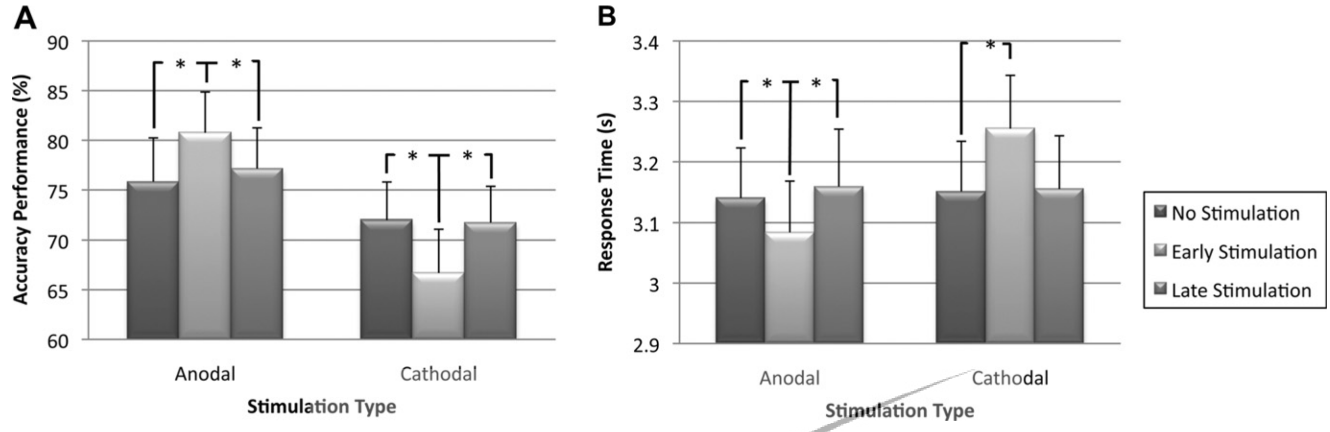

Figure 2 **A,** The proportion of correct responses. **B,** The mean reaction times; * represents significance on a Bonferroni-corrected paired-samples t test, $P < 0.05$; Error bars represent one standard error.

the importance of onset timing of the stimulation (Figure 2A). A comparison between the anodal and cathodal no-stimulation conditions was nonsignificant, $t(12) = 1.77$, $P = 0.102$. No other comparisons were significant ($t < 1$).

The reaction times of participants were also subjected to a 2 × 3 repeated measures ANOVA. The main effect of stimulation polarity was nonsignificant, $F(1, 12) = 3.60$, $P = 0.082$, indicating that participants were not significantly faster at responding in anodal-stimulation trials ($\mu = 3.09$ seconds, SD = 0.08 second) than in cathodal-stimulation trials ($\mu = 3.103$ seconds, SD = 0.08 second). The main effect of stimulation time was nonsignificant, $F(2, 24) = 0.31$, $P = 0.735$, indicating that the response speeds were similar when participants responded in no-stimulation ($\mu = 3.091$ seconds, SD = 0.07 second), early stimulation ($\mu = 3.089$ seconds, SD = 0.08 second), or late stimulation ($\mu = 3.102$ seconds, SD = 0.08 second) trials. The interaction effect between stimulation polarity and time was, however, significant, $F(2, 24) = 9.34$, $P < 0.001$.

A paired-samples t test comparing participants' reaction times in the no-stimulation and early stimulation trials under anodal stimulation was significant, $t(12) = 2.40$, $P = 0.033$, indicating that administering anodal stimulation early in a trial led to a mean faster response time over a non-stimulation trial. The opposite pattern of results was observed when comparing no-stimulation and early stimulation trials under cathodal stimulation, $t(12) = 2.20$, $P = 0.048$, depicting a reduction in response time after cathodal tDCS in the first half of a trial. Comparing early stimulation and late stimulation in the anodal condition using a paired-samples t test analysis also showed a significant difference, $t(12) = 2.51$, $P = 0.027$ but not in the cathodal condition $t(12) = 1.72$, $P = 0.111$ (Figure 2B). A comparison between the anodal and cathodal no-stimulation conditions was nonsignificant, $t(12) = 0.93$, $P = 0.367$. No other comparisons were significant ($t < 1$).

Discussion

Our findings show that participants receiving 1.5 mA of anodal tDCS performed significantly better on memory accuracy as compared with cathodal stimulation, which impaired memory. The advantage in memory performance under anodal stimulation cannot be attributed to slower response times in the word recognition task, as higher performance was accompanied by significantly faster reaction times. These results support the first hypothesis that anodal tDCS will lead to higher memory accuracy on the memory recognition task, and that cathodal tDCS will impair subsequent memory accuracy.

However, the exact functional role that anodal tDCS plays in improving memory accuracy remains unclear. Memory enhancement could have resulted from the stronger encoding of target words, or alternatively better retention of encoded words. Furthermore, other systems could have been engaged by left DLPFC stimulation, including learning capacity, planning skills, and verbal fluency.[9,30,41,43] These factors may have contributed to the memory advantage seen in anodal stimulation.

The results showed that stimulation during the first half of each trial (early stimulation) was significantly more effective than stimulating in the second half (late stimulation). Therefore, this study has highlighted the importance of determining the appropriate stimulation duration and onset time to achieve the most effective effects of tDCS with a small amount of induced electric charge (time × electrical current).

The results in this study seem to contradict previous literature by demonstrating that 1.6 second of stimulation has a modulatory effect on verbal memory. Nitsche and colleagues[14,44-46] reported that the application of tDCS over the motor cortex for less than 5 minutes had no significant *lasting* effects on motor-evoked potentials (MEPs) beyond the duration of the stimulation, whereas this experiment was not dependent on a persistent effect of stimulation. In fact, this study shows that the modulatory effects of tDCS on memory are not dependent on the persistent effects of stimulation per se; but rather, the short-term effects of stimulation during the encoding period.

In terms of cumulative effects in the current study, the no-stimulation trials under both stimulation polarities showed slightly different memory performance: the performance accuracy for anodal no-stimulation trials was nonsignificantly higher than cathodal no-stimulation trials, hinting at a general improvement and impairment for the anodal and cathodal stimulations, respectively.

Similarly, previously used sham stimulations frequently use a short time window of current stimulation at the start of a time window[3] and are also without effect. The same argument as to why this is not relevant in considering the effects seen in this study applies; this sham stimulation does not take place during task performance or behavioral measurement.

In this study we used a smaller electrode size for the DLPFC compared with some other studies[10,18,22,41,43] to make the stimulation more focused. Furthermore, we used a smaller electrode for the main electrode compared with the reference electrode (35 $\times$ 35 mm and 55 $\times$ 55 mm, respectively) to increase the ratio of the stimulation intensity at the main electrode against that at the reference electrode (approximately 2.5:1).

The results of this study point to the wider benefits that anodal tDCS may have. Although cathodal stimulation suppresses cortical excitability, anodal tDCS has been shown to enhance cortical activity and subsequently improve behavioral patterns.[13,15,47] Depending on where it is administered, anodal tDCS offers advantages in tasks involving probabilistic classification learning, motor learning, and visuomotor coordination.[7,8,30] As this and other studies have shown, anodal tDCS applied to the left DLPFC improves both short-term and long-term memory accuracy.[18,19,25] Indeed, tDCS has already been shown to improve the working memory of patients with Parkinson's or Alzheimer's disease.[11,16] It will, therefore, be meaningful to conduct a study similar to this on elderly subjects or patients with memory deficits and ascertain if anodal tDCS similarly yields long-term memory advantages for them.

However, the mechanism of action of tDCS on memory performance remains unclear. Memory enhancement derived from stimulating the left DLPFC could have resulted from the stronger encoding of target words, or alternatively, the better retention of encoded words or even the engagement of other systems. For example, a number of studies have highlighted the contribution of the left DLPFC in different tasks such as planning[41,43] and decision making[9,30] is studied.

In conclusion, when delivering DC stimulation at 1.5 mA, the main effect of stimulation polarity was significant, indicating that anodal tDCS led to higher memory accuracy compared with cathodal stimulation. Compared with no-stimulation trials, the effects of early anodal and cathodal stimulation were significant but the effects of late stimulation were nonsignificant.

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