



# Transcranial alternating current stimulation over the prefrontal cortex enhances episodic memory recognition

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## Abstract

It remains unknown whether transcranial alternating current stimulation (tACS) affects episodic memory and the effect of gamma oscillations delivered to the left prefrontal cortex (PFC) on long-term memory retention has not been fully investigated. We examined whether tACS over the left PFC enhances recognition of episodic memory. The study enrolled 36 healthy young adult volunteers. The participants were randomly assigned to either a tACS group [ $n = 18$ ; 14 females; mean age  $\pm$  standard deviation (SD):  $21.2 \pm 0.4$  years] or a sham-control group [ $n = 18$ ; 14 females; mean age  $\pm$  SD:  $21.2 \pm 0.4$  years]. Participants received either tACS or sham stimulation both during the learning task that was conducted on day 1 and during a recognition task on day 2. The recognition task was also conducted on days 1 and 7, and response accuracy was measured at all three time points (days 1, 2, and 7). Patients in the tACS group were better able to retain long-term memory than those in the sham-control group. These findings suggest that tACS over the left PFC enhances recognition of episodic memory in healthy young adults.

**Keywords** Memory · Oscillations · Prefrontal cortex (PFC) · Transcranial alternating current stimulation (tACS)

## Introduction

Episodic memory is a memory of a past event experienced by an individual (Manenti et al. 2012; Tulving 2002). When a person encounters new information, the brain rapidly encodes them and forms weak memory traces. Through a longer process of consolidation, weak memory traces are enhanced as long-term memory. If the encoded memory is recalled, it becomes unstable and susceptible to interference again (Javadi and Cheng 2013; Judge and Quartermain 1982; McDermott et al. 2000). Accurate encoding and successful retrieval of the information are very important to correctly remember information (Nyberg et al. 1996). In the memory consolidation process, reconsolidation is required to restore memory stability (Nader 2003).

Non-invasive brain stimulation has the potential to modify the reconsolidation of memory and studies in this field of research have found promising improvements in episodic

memory when transcranial direct current stimulation (tDCS) or transcranial alternating current stimulation (tACS) is applied in the encoding and/or the recognition phase of the learning and memory process (Javadi et al. 2012; Javadi and Walsh 2012; Pisoni et al. 2015; Sandrini et al. 2014, 2016). Recent tDCS studies have shown that the left prefrontal cortex (PFC) contributes to long-lasting effects through memory reintegration in older adults at risk for dementia (Manenti et al. 2017, 2018).

Furthermore, recent studies have reported that nerve oscillations may be essential for the reinstatement of episodic memory (Watrous and Ekstrom 2014; Wimber et al. 2012). tACS enables the manipulation and entrainment of intrinsic oscillations through the application of sinusoidal currents, which regulate oscillatory brain activity in the cortical region (Antal and Herrmann 2016; Antal and Paulus 2013; Paulus 2011; Tavakoli and Yun 2017). tACS has been shown to modulate higher cognitive processes, including memory (Herrmann et al. 2013; Tavakoli and Yun 2017). Oscillatory activity in the gamma and theta bands has been confirmed to facilitate information encoding and retrieval during memory operations (Osipova et al. 2006). Gamma oscillations over the left prefrontal cortex (PFC) have been shown to improve working memory (Hoy et al. 2015), and

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gamma oscillations over the left PFC during both encoding and retrieval were shown to result in enhanced declarative memory (Javadi et al. 2017). However, it remains unclear whether gamma oscillations influence episodic memory by facilitating the encoding and/or recognition steps of the memory formation process. Further, the effects of gamma oscillations over the left PFC on long-term memory formation have not been fully investigated.

In this study, we conducted a randomized, single-blind, repeated-measures, sham-controlled trial in a sample of healthy young adults. The aim of the current study was to examine whether tACS over the left PFC enhances recognition of episodic memory compared to the results following sham-control stimulation.

## Materials and methods

### Participants

In total, 36 healthy young adults were recruited for this study, including 8 males and 28 females. The mean age (standard deviation, SD) of the patient group was 21.3 (0.5) years, with an age range of 21–22 years and a mean education level of 15.9 (0.2) years. All participants were strongly right handed, as indicated by a score of 0.9–1.0 on the Oldfield inventory (Oldfield 1971). The enrolled participants were randomly assigned into two groups of 18 participants each [tACS group: 14 females, mean age = 21.2 (0.4) years; sham-control group: 14 females, mean age = 21.3 (0.5) years]. All participants provided written informed consent prior to the experiment. The study was conducted in accordance with the Declaration of Helsinki and the experimental protocol was approved by the ethics committee of Niigata University of Health and Welfare (approval no. 18081-180925).

### Inclusion and exclusion criteria

All participants were native Japanese speakers, non-smokers, had normal or corrected-to-normal vision, and had no history of neurologic trauma or psychiatric disorder. Further exclusion criteria included past head injury, metal implants in the head area, seizures, and prior use of psychotropic drugs. Additionally, participants with relevant depressive symptoms, as determined by a Self-rating Depression Scale score of > 45 were excluded from the study (Zung 1965). To ensure comparable general memory and verbal intelligence scores, participants completed the Japanese version of the Wechsler Memory Scale-Revised (Koike and Sugishita 2011) before taking part in this study (Table 1).

### Study procedure

A randomized, single-blind, repeated-measures, sham-controlled design was used, with each participant taking part in only one group (tACS or sham-control group). There were three sessions on three different days: day 1, day 2, and day 7. Participants conducted learning tasks to evaluate episodic memory on day 1 (old words). They received stimulation (tACS or sham) on both days 1 and 2, and a recall test took place on days 1, 2, and 7. Recall performance was tested in a two-alternative forced choice (2AFC) recognition task (new/old words) (Fig. 1a).

### Transcranial alternative current stimulation (tACS)

A tACS stimulator (Eldith; NeuroConn GmbH, Ilmenau, Germany) was administered via two 5 cm × 7 cm saline-soaked surface sponge electrodes. To reduce contact impedance, a conductive gel was applied under the two electrodes before the montage (Manenti et al. 2013; Sandrini et al.

**Table 1** Baseline characteristics for participants

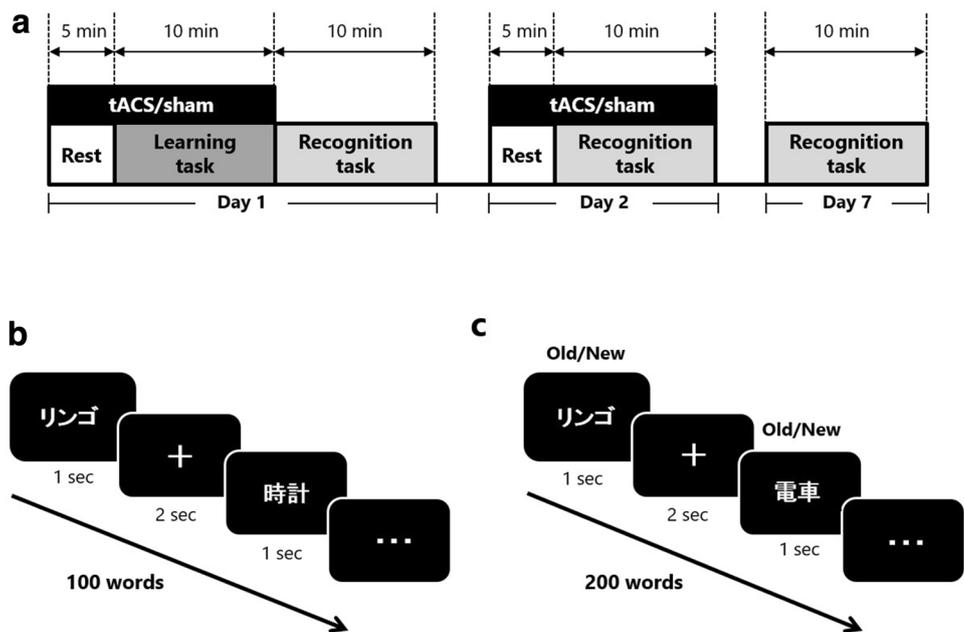
	tACS group	Sham group	<i>t</i> value	<i>p</i> value
Gender (male/female) <sup>†</sup>	4/14	4/14	–	–
Age (years) <sup>††</sup>	21.2 (0.4)	21.3 (0.5)	– 0.73	0.47
Education (years) <sup>††</sup>	15.9 (0.3)	16.0 (0.0)	– 1.46	0.15
Self-Rating Depression Scale score <sup>††</sup>	36.5 (4.8)	37.6 (6.0)	– 0.55	0.59
Wechsler Memory Scale-revised <sup>††</sup>				
Verbal Memory Index	84.8 (13.6)	80.9 (14.4)	0.82	0.42
Visual Memory Index	111.5 (6.3)	106.4 (10.9)	1.69	0.09
General Memory Index	90.1 (13.0)	85.4 (14.4)	1.03	0.31
Attention/Concentration Index	98.7 (15.6)	97.7 (14.1)	0.20	0.84
Delayed Memory Index	92.7 (12.3)	93.1 (9.3)	– 0.12	0.90

Statistical analysis: independent *t* test

<sup>†</sup>Number

<sup>††</sup>Mean (Standard deviation)

**Fig. 1** **a** Participants conducted a learning task on day 1, and memory recognition tasks were administered on days 1, 2, and 7. Participants received stimulation (tACS or sham) over the left PFC on days 1 and 2. **b** Participants learned 100 well-known, easy words (“old words”) on day 1. Each word was displayed for 1 s, and a cross-symbol was displayed for 2 s between words. **c** The recognition task presented a total of 200 words, a combination of the 100 old words and 100 new words. Each word was displayed for 1 s, and a cross-symbol was displayed for 2 s between words. The recognition task was applied as a two-alternative forced choice task (new or old words)



2014, 2016). The active electrode was placed over the F3, which corresponds to the left PFC based on the international 10–20 extended systems for electrode placement. The reference electrode was placed on the left wrist to minimize any unintended effects on the cortex (Javadi et al. 2017). tACS was delivered at a current oscillating between  $-750$  and  $+750 \mu\text{A}$  at a frequency of 60 Hz. A stimulator was set to fade in and fade out, with fading in occurring the maximum amount of time within the 100 cycles, at the beginning and end of the stimulation period. For the sham treatment, the stimulation was set to fade in and fade out, and performed for only 10 s. Previous studies have suggested that changes in cortical excitability occur 5 min after stimulation (Nitsche and Paulus 2000). Furthermore, executing tACS at a frequency of 60 Hz during both encoding and retrieval has been shown to lead to enhanced memory (Javadi et al. 2017). Therefore, on day 1, we delivered current stimulation for 5 min and then delivered current stimulation again for 10 min during the learning task. On day 2, we delivered current stimulation for 5 min and then delivered it again for 10 min during the recognition task (Fig. 1a). All of the methods for tACS application in the current study complied with safety guidelines (Antal et al. 2017).

**Stimuli**

We extracted 400 words from Japanese noun words obtained at an elementary school in Japan. The Japanese noun words used in this study consisted of kanji words (73.8%) and katakana words (26.2%). The kanji words were controlled for number of letters and ranged in length from one to three letters, with a mean (SD) word length of 1.86 (0.04) letters.

Similarly, the katakana words were controlled for number of letters and ranged from one to four letters, with a mean (SD) word length of 3.39 (0.08) letters. The selected words were very familiar, and the participants knew all of the words. The experiment was administered on a PC computer with a 24" monitor. The participants learned 100 of these familiar words (called “old words”) as a learning task. Each word was presented for 1 s with a cross-symbol presented for 2 s between words (Fig. 1b). We presented a total of 200 words in the recognition task, a combination of the 100 old words and 100 new words. Different new words were used in each session. Each word was presented for 1 s with an intermittent cross-symbol presented for 2 s (Fig. 1c). Participants were instructed to press the “L” key on the keyboard when an old word was shown and the “A” key on the keyboard when a new word was shown. Participants were asked to react as accurately and as quickly as possible. All task sessions were performed in the same room and at the same time of day during each of the 3 days. Stimuli were presented on the computer monitor in white Meiryō font against a black background. Stimulus presentation and the recording of responses were performed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

**Statistical analysis**

We recorded response accuracy and reaction time for data analysis. We defined the hits ratio of old words and the d-prime values as the outcome measures for response accuracy. Participants were asked for old or new words as a 2AFC task. Discriminability refers to the ability to distinguish target words from distractor words. D-prime,

which is adapted from signal detection theory (Snodgrass and Corwin 1988), is a discrimination possibility index that takes into consideration the ability to accurately identify targets and minimize false alarms (Haatveit et al. 2010). We calculated  $d$ -prime to confirm the accuracy of the performance ( $d$ -prime =  $z$  (hits) –  $z$  (false alarms)). Data taken on days 1, 2, and 7 were compared with a two-way repeated-measures analysis of variance (ANOVA) (intervention [tACS, sham]  $\times$  time [day 1, day 2, day 7]). Significant differences were further analyzed with a Bonferroni post hoc test. All analyses were performed with IBM SPSS Statistics software version 20 (IBM; Armonk, NY, United States), and the threshold for significance was set at 5%.

## Results

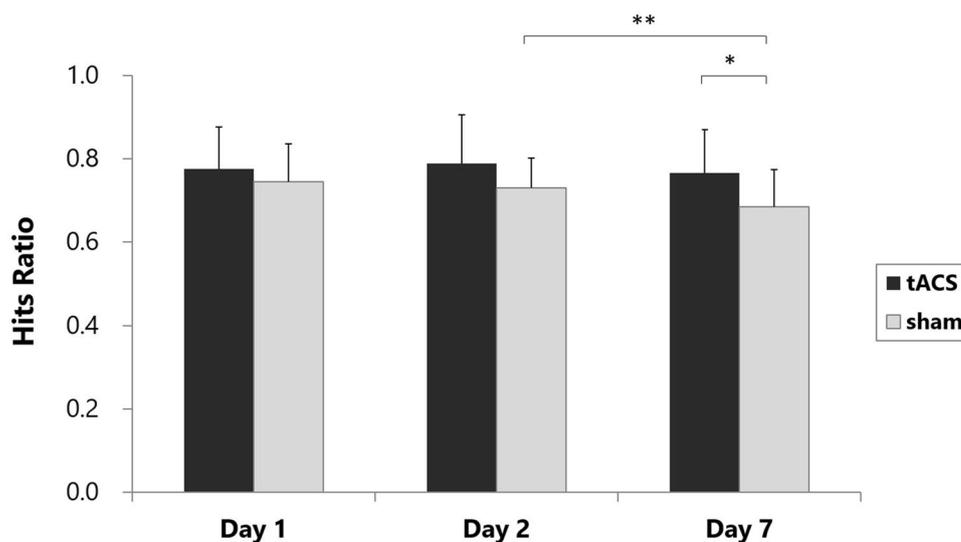
### Characteristics of participants

Baseline characteristics for the study participants are presented in Table 1. According to the independent  $t$  test, there were no differences in baseline characteristics between the tACS group and the sham-control group for any demographic or neuropsychological variables.

### Adverse events of tACS

All participants tolerated the tACS stimulation well. No other adverse effects, such as phosphene sensations, headache, dizziness, nausea, or vomiting, were noted during active tACS stimulation.

**Fig. 2** The plot shows the hit ratio for the tACS and sham groups on days 1, 2, and 7. A two-way repeated-measures ANOVA of the hits ratios revealed significant main effects of intervention, time, and the interaction of intervention and time. A post hoc analysis revealed significant differences between the tACS group and the sham-control group on day 7. The tACS group showed better memory recognition on day 7 compared to the sham group. \* $p < 0.05$ , \*\* $p < 0.01$



### Hits ratio

Figure 2 shows the mean hits ratio values for each day. A two-way repeated-measures ANOVA of hits ratios revealed significant main effects of intervention [ $F(1, 34) = 4.31$ ,  $p = 0.046$ ,  $\eta^2 = 0.112$ ,  $1 - \beta = 0.523$ ], time [ $F(2, 68) = 4.37$ ,  $p = 0.016$ ,  $\eta^2 = 0.114$ ,  $1 - \beta = 0.738$ ], and the intervention  $\times$  time interaction term [ $F(2, 68) = 1.71$ ,  $p = 0.019$ ,  $\eta^2 = 0.048$ ,  $1 - \beta = 0.347$ ]. A post hoc analysis revealed significant differences between the tACS group and the sham-control group at day 7 ( $p = 0.014$ ). There were also significant differences between day 2 and day 7 for the sham-control group ( $p < 0.001$ ).

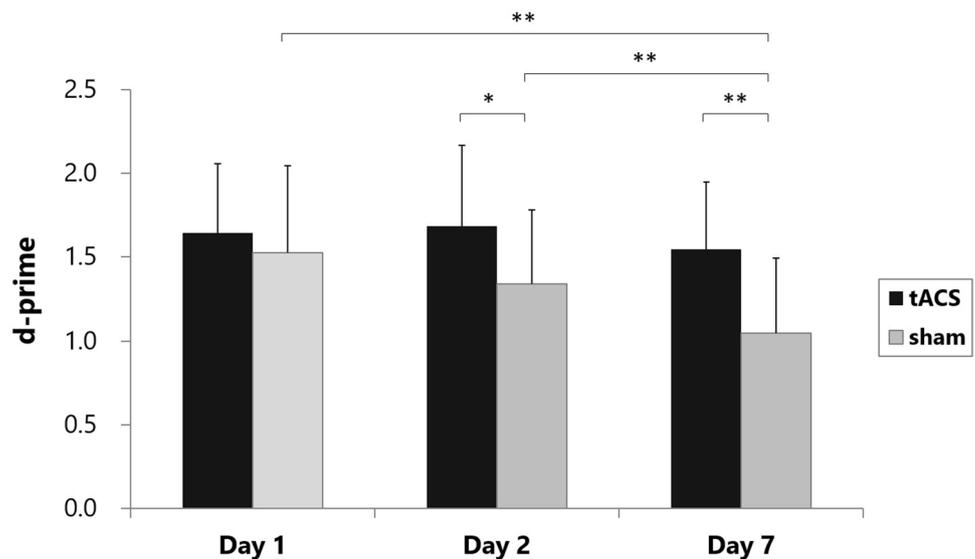
### D-prime

Figure 3 shows the mean  $d$ -prime values for each day. A two-way repeated-measures ANOVA of  $d$ -prime values revealed significant main effects of intervention [ $F(1, 34) = 5.39$ ,  $p = 0.026$ ,  $\eta^2 = 0.137$ ,  $1 - \beta = 0.616$ ], time [ $F(2, 68) = 12.21$ ,  $p < 0.001$ ,  $\eta^2 = 0.264$ ,  $1 - \beta = 0.994$ ], and the intervention  $\times$  time interaction term [ $F(2, 68) = 4.86$ ,  $p = 0.011$ ,  $\eta^2 = 0.125$ ,  $1 - \beta = 0.785$ ]. A post hoc analysis revealed significant differences between tACS and the sham-control group at day 2 ( $p = 0.035$ ) and day 7 ( $p = 0.002$ ). There were also significant differences between day 1 and day 7 ( $p < 0.001$ ) as well as between day 2 and day 7 ( $p < 0.001$ ) for the sham-control group.

### Reaction time

A two-way repeated-measures ANOVA of reaction time revealed no significant main effects of intervention [ $F(1, 34) = 0.487$ ,  $p = 0.49$ ,  $\eta^2 = 0.014$ ,  $1 - \beta = 0.104$ ], time [ $F(2, 68) = 1.024$ ,  $p = 0.365$ ,  $\eta^2 = 0.029$ ,  $1 - \beta = 0.222$ ], or

**Fig. 3** The plot shows the d-prime values from the tACS group and the sham group on days 1, 2, and 7. A two-way repeated-measures ANOVA of d-prime values revealed significant main effects of intervention, time, and the interaction of intervention and time. A post hoc analysis revealed significant differences between the tACS group and the sham-control group on days 2 and 7. The tACS group showed better memory recognition on days 2 and 7 compared to the sham group. \* $p < 0.05$ , \*\* $p < 0.01$



the intervention  $\times$  time interaction term [ $F(2, 68) = 0.123$ ,  $p = 0.884$ ,  $\eta^2 = 0.004$ ,  $1 - \beta = 0.068$ ].

## Discussion

This study revealed that tACS delivered over the left PFC enhances episodic memory response accuracy without improving reaction time. These findings suggest that tACS oscillations over the left PFC may enhance recognition of long-term memory in healthy young adults.

Although several studies have shown that tDCS induces changes to episodic memory, a recent meta-analysis reported that the effects of tDCS on episodic memory accuracy are small and non-significant (Galli et al. 2018). tDCS is a non-invasive technique that allows the modulation of cortical excitability in humans (Nitsche and Paulus 2000; Priori 2003). It is thought that neuronal cell membranes below the anode are depolarized while those below the cathode are hyperpolarized, leading to increases and decreases in cortical excitability, respectively (Antal et al. 2017; Lefaucheur et al. 2017; Nitsche and Paulus 2000). In contrast, tACS is a non-invasive technique that is believed to entrain or synchronize neuronal networks (Antal and Paulus 2013). tACS has been shown to modify brain rhythms, especially when the externally superimposed oscillation is close to the natural frequency of the cortical area being stimulated (Schutter and Hortensius 2011). Oscillatory activity in the gamma bands has been confirmed during memory encoding and retrieval operations (Osipova et al. 2006). Therefore, it is possible that tACS with gamma oscillations temporarily entrains gamma rhythms during encoding and retrieval, and thus modifies memory-related neuronal networks. tACS may

be an effective auxiliary method to strengthen reconsolidation of memory.

In this study, the tACS group showed increased response accuracy, as measured by hits ratio and d-prime, compared to the sham-control group. Previous studies have shown that episodic memory is enhanced when anodal tDCS is applied over the left PFC during learning (Sandrini et al. 2016) and after memory consolidation (Sandrini et al. 2014). Encoded memory becomes unstable when it is recalled and reconsolidation is required to restore its stability. This reconsolidation process may take longer than 5 h to complete (Javadi and Cheng 2013). The present study applied gamma oscillations both at the time of encoding and during a recognition session 24 h later.

Gamma rhythms can act to combine perceptual and contextual information from diverse brain regions into episodic representations (Nyhus and Curran 2010). A previous study showed that delivering gamma oscillation tACS over the left PFC at the same frequency band (either 60 or 90 Hz) during both encoding and retrieval resulted in enhanced declarative memory. However, memory improvement did not occur for different stimulation frequencies during encoding and retrieval (Javadi et al. 2017). Similarly, memory performance was improved when stimulation was applied during both encoding and post-learning slow wave sleep at the same 60 Hz frequency by tACS (Crowley and Javad 2019). Thus, these studies suggest that memory performance is enhanced by gamma oscillations during both encoding and post-learning sessions. As evidenced by these findings, memory recognition may be enhanced by the reinstatement of contextual conditions between encoding and retrieval. Gamma oscillation applied during a combination of both encoding and recognition sessions can potentially affect memory reconsolidation. Accordingly, it is possible that gamma oscillations delivered during

both encoding and recognition sessions modulate activity in the left PFC to enhance memory recognition in healthy young adults.

However, our study has several limitations regarding these methods. Further studies are needed to elucidate the neurophysiological effects of tACS. On the basis of previous studies, we used a stimulation intensity between  $-750$  and  $+750$   $\mu\text{A}$  (Hoy et al. 2015) and a stimulation frequency band of 60 Hz (Javadi et al. 2017); but it remains unknown whether these stimulation conditions are optimal for tACS delivery. In this study, we did not adapt tACS of other frequency bands. It is necessary to particularly confirm the influence of the frequency of brain vibrations within a specific frequency band, in particular, theta waves (3–8 Hz) (Vosskuhl et al. 2018). Furthermore, our protocol did not have any control site condition or a no-reactivation group to show that the behavioral effect was specific to reconsolidation. These condition comparisons should be considered. In addition, this study conducted a test session on day 7. Since the long-term effects of tACS have not been previously investigated, we chose an interval between the two testing sessions that were expected to have no effect on tACS, as has been previously reported (Javadi et al. 2017). Unfortunately, we were not able to verify the sustained effects from day 7 onwards. Thus, our findings should be interpreted with caution. Future studies are needed to confirm optimum tACS stimulation conditions and the long-term effects of memory retention. Finally, future studies are needed to verify the effects of tACS on older adults.

## Conclusion

tACS delivered over the left PFC enhanced episodic memory retention compared to results from sham-control stimulation. These results suggest that tACS over the left PFC may enhance recognition of episodic memory in healthy young adults.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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