Experimental Brain Research (2019) 237:919–925
https://doi.org/10.1007/s00221-019-05477-3

RESEARCH ARTICLE

Non-linear effects of cathodal transcranial direct current stimulation (tDCS) of the primary motor cortex on implicit motor learning

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Received: 20 September 2018 / Accepted: 14 January 2019 / Published online: 19 January 2019
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Abstract

Transcranial direct current stimulation (tDCS) of 1 mA for 13 min was reported to create a linear inter-dependency between the intensity and duration of the current and the effects of the stimulation. tDCS on the primary motor cortex (M1) has been shown to have an effect on both motor-evoked potential (MEP) and motor learning. However, recent findings have shown that the known linear effect is invalid in a 2 mA stimulation for 20 min, where cathodal stimulation led to excitability, rather than inhibition, as measured by MEP changes. Here we aim to replicate the non-linear effect of cathodal stimulation over the M1, using a cognitive task. Twenty-two healthy subjects participated in three sessions, where they were administered with a 2 mA anodal and cathodal stimulation for 20 min over the left M1, and a sham stimulation, while performing the serial reaction time task (SRTT). The overall analysis failed to show any effects of either polarity of tDCS on SRTT performance and hence did not replicate previous findings. However, given our goal to replicate the previously reported reversed polarity effects on MEP, we conducted an exploratory analysis to see whether there were any more subtle signs of a change in sign of the cathodal effect compared with anodal. Anodal stimulation led to faster performance than cathodal stimulation before 13 min of stimulation have passed, however, after 13 min, the pattern had switched, and performance under cathodal stimulation was faster. We conclude that cathodal tDCS has a non-linear effect, and the known polarity-dependent effects of tDCS shift after 13 min of stimulation, leading to an increased, rather than decreased, excitability.

Keywords Primary motor cortex · Serial reaction time task · Non-linear effect

Introduction

Transcranial direct current stimulation (tDCS) is a commonly used, non-invasive brain stimulation technique. tDCS is based on a direct, low-intensity electric current, applied on the person's scalp, and is considered safe and painless (Poreisz et al. 2007). The reported effects of direct currents on brain tissue in rats included increased accumulation of calcium ions, leading to increased cortical excitability (Priori et al. 1998). These findings prompted subsequent experiments by Nitsche and Paulus (2000) who demonstrated modulating effects of anodal (increases cortical excitability) and cathodal (decreases cortical excitability) tDCS on the motor cortex in which the effects outlasted the duration of stimulation. Many studies with healthy humans have demonstrated that tDCS induces lasting alterations in cortical excitability, for example, neuroimaging methods such as fMRI (Lindenberg et al. 2013) have provided proof of tDCS-induced local and connectivity-mediated brain hemodynamic changes (Nitsche and Paulus 2000). The lasting after-effect of tDCS is attributed to modulation of GABAergic and glutamatergic synapses (Stagg and Nitsche 2011). It is known that the duration and strength of the after-effect are dependent on the duration and intensity of the applied stimulation, and that this dependency is linear when using a 35 cm^2 electrode with current strength of up to 1 mA, and stimulation duration of up to 13–15 min (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003a).

A meta-analysis conducted by Jacobson et al. (2012) investigated the effect of both anodal and cathodal tDCS stimulation over the primary motor cortex (M1). They

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showed that the majority of tDCS studies performed on the M1 area were focused on a passive motor-evoked potentials (MEP) measure, that is related solely to the stimulated area (Fox et al. 2006). Most of those studies managed to replicate the findings of Nitsche and Paulus (2000), showing an increase in MEP due to anodal stimulation, and a decrease in MEP due to cathodal stimulation. These changes were temporary and varied in duration pending on stimulation duration and intensity (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003a).

Evidence from functional magnetic resonance imaging (fMRI) studies shows that M1 plays a significant role in motor learning (Karni et al. 1998). tDCS studies have also explored the role of M1 in motor learning, by modulating the excitability of the M1, and examining the effect on active performance. Anodal stimulation over the M1 was shown to improve implicit motor learning on a serial reaction time task (SRTT; Nissen and Bullemer 1987; Nitsche et al. 2003b; López-Alonso et al. 2015a; see also a review by; Buch et al. 2017), as well as on an explicit motor learning task (Stagg et al. 2011). A review conducted by Reis and Fritsch (2011) explored the effect of both anodal and cathodal tDCS stimulation on motor learning tasks. While the improvement effect of anodal tDCS was shown repeatedly, some studies managed to show the opposite effect, a decrease in performance due to cathodal stimulation (Stagg et al. 2011), and some did not (Nitsche et al. 2003b; Reis et al. 2009). The standard montage for this kind of studies was a M1-contralateral orbit montage (Reis and Fritsch 2011). With this montage, many motor learning studies employed 1 mA intensity for 10–20 min, where 10 min application was not sufficient to improve learning (Kuo et al. 2008), however, 15 min (Nitsche et al. 2003b) or 20 min (Vines et al. 2008) improved the SRTT measures. For a stronger intensity, Kang and Paik (2011) failed to improve SRTT with 2 mA for 20 min. However, employing 2 mA for a shorter duration (13 min) improved performance in a different motor learning task (Forester et al. 2013).

In 2013, Batsikadze, Moliadze, Paulus, Kuo and Nitsche discovered a crucial new finding regarding the linear nature of the inter-dependency between the current's intensity and duration, and the after-effects of the stimulation. The increasing use of tDCS in high intensities and long durations in both research and clinical fields, as well as the non-linear effect of other non-invasive brain stimulation techniques [e.g., theta burst stimulation (TBS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS)], led researchers to ask whether a high-intensity, long-duration tDCS stimulation will reveal a non-linear excitability effect as well. Batsikadze et al. (2013) employed the M1-contralateral orbit montage with a 2 mA intensity for 20 min, and checked the effect of both anodal and cathodal stimulation on MEP. Surprisingly, they discovered that contrary to the common assumption, the 2 mA cathodal stimulation led to an increase in MEP.

The meaning of those findings is that the well-established linear connection between current characteristics (intensity, duration) and the stimulation's after-effects is invalid once a certain intensity and duration is reached, and that the efficacy of the after-effects cannot be enhanced simply by intensifying and prolonging the stimulation itself. Combining previous findings (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003b) with the findings of Batsikadze et al. (2013), we can assume that up to 13 min of stimulation, anodal tDCS will lead to increased excitability and cathodal stimulation will lead to decreased excitability. However, after 13 min of stimulation, cathodal stimulation will no longer lead to a decrease, but rather to an increase in the excitability of the M1 area. If this is true, it can easily explain the contradicting findings in the motor learning results under tDCS we reviewed above. For example, it could be that Kang and Paik (2011) failed to show the predicted facilitative effects in the SRTT, because their 20 min long 2 mA stimulation led to reversed polarity effects that washout the effect as found for 2 mA 13 min stimulation (Forester et al. 2013).

The purpose of the current study was therefore to test whether the important findings of Batsikadze et al. (2013) can be replicated in a cognitive task. Rather than showing the effect of high-intensity, prolonged cathodal stimulation on MEP, we aimed to examine whether this stimulation pattern will have the same impact on the performance in an implicit motor learning task. To accomplish this goal, a repeated measures experimental design was created, where all subjects went through anodal, cathodal and sham stimulations, in a high, 2 mA intensity and a prolonged, 20 min stimulation, while performing the SRTT. Behavior patterns in all stimulation conditions were compared, to see whether the cathodal stimulation will lead to increased excitability after about 13 min, and hence to improved performance of the task. The selected task is made of eight blocks, which allow to test stimulation effects on performance in blocks before and after the predicted turning point of 13 min. We predicted that we will see a linear stimulation effect on the SRTT performance in early blocks (before 13 min of stimulation have elapsed) but non-linear effects for later blocks.

Methods

Subjects

Twenty-two healthy subjects (6 males, 16 females), aged 23 ± 4.3, were recruited. The number of subjects is similar to the samples reported in previous tDCS-SRTT studies (between 8 and 22 subjects, see Table 1 at Buch et al. 2017). All subjects were right-handed, according to the

Edinburgh handedness inventory (Oldfield 1971). None of the subjects took any psychiatric medications, had a history of any neurological diseases, had any metal head implants or were pregnant during the time of the experiment. Participants were students in the University of Bar-Ilan, they all gave informed consent and were compensated for their participation with course credits or a financial compensation. This study was approved by the Bar-Ilan ethics committee and was conducted in accordance with the Declaration of Helsinki guidelines.

Transcranial direct current stimulation (tDCS)

Direct current (2 mA) was applied through two saline-soaked sponge electrodes (surface area 35 cm^2). The current was induced by a battery-driven direct current stimulator (Magstim eldith DC-Stimulator Plus, neuroConn GmbH, Germany). The motor cortex electrode was placed over the C3 of the international 10–20 electroencephalogram (EEG) electrode system, corresponding to the left M1 region (Nitsche et al. 2003b). The reference electrode was placed on the contralateral orbitofrontal cortex, as this is the montage employed in the Batsikadze et al. (2013) study, that we aimed to replicate using a motor-cognitive task rather than passive MEP.

In a within-subjects design, subjects underwent all three stimulation conditions: (1) anodal stimulation, where the anodal electrode was placed over the C3 and the cathodal electrode was placed over the right orbit, (2) cathodal stimulation, where the cathodal electrode was placed over the C3 and the anodal electrode was placed over the right orbit, and (3) a sham stimulation, identical to the active conditions, where electrodes where placed on the C3 and right orbit. In the two stimulation conditions, the current was applied for 20 min, with the current being ramped up for 30 s in the beginning, and ramped down for 30 s at the end of the stimulation. In the sham condition, the current was ramped up for 30 s, applied for 30 s, and then ramped down for 30 s.

The order of the stimulation conditions was counterbalanced across subjects, with precisely 7 days between meetings, to avoid any lasting effects of the stimulation and a possible learning effect of the implicit motor learning task. Subjects came to their meetings on the same day and hour. They were blind to the stimulation condition and based on the debriefing session, did not know which session included active stimulation and which did not.

Serial reaction time task (SRTT)

Subjects were seated in front of a computer monitor (27 × 34 cm) at eye level. In front of the monitor, a keyboard was placed with four marked keys: "*n*", "*m*", "," and "." (from now on, they will be referenced as "1", "2", "3" and "4", respectively). Subjects were instructed to place their right hand over the keyboard, with one finger matching each marked key (index finger over key "1", middle finger over key "2", ring finger over key "3" and the little finger over key "4").

The SRTT was programed using E-Prime (version 2.0), and was based on the SRTT design elaborated in López-Alonso et al. (2015a). The monitor presented four black squares, aliened horizontally and evenly spaced. Each square represented one of the keys, in respect to the horizontal location. An asterisk appeared in one of the four squares, and subjects were instructed to strike the matching key as quickly and accurately as possible. As a key was pushed, the asterisk disappeared, and a new one appeared 500 ms later (Fig. 1).

Before starting the SRTT, subjects completed a practice block comprised out of 60 random-ordered trials. The experimenter was in the room with the subject during the practice block, to ensure all subject understood the instructions properly.

The SRTT was comprised out of eight experimental blocks, each consisting of 120 trials, and separated by a 30 s long breaks. Experimental blocks 1 and 6 were random blocks, where the asterisk appeared in a pseudo-random order. No runs of units (e.g., 1234 or 4321) or repeating patterns (e.g., 1212) appeared in the random blocks. Experimental blocks 2–5 and 7–8 were sequence blocks, where the asterisk appeared in a 12-digit sequence (121423413243), repeating itself 10 times in each block (a total of 120 trials per block). Subjects were not informed about the presence of the repeating sequence.

Procedure

Prior to the arrival to the lab, subjects were asked to complete a demographic questionnaire and the Edinburgh handedness inventory (Oldfield 1971), to verify that they are suitable subjects for this study.

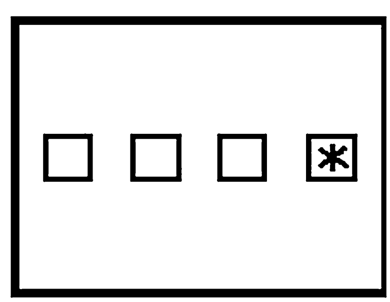

Fig. 1 Screen shot of the SRTT as viewed by subjects. Four black horizontally aliened squares with the asterisk appearing in a different square at every experimental trial

In each of the three meetings, subjects arrived at the lab and were seated in a chair in front of the computer monitor. First, subjects' heads were measured, and the C3 spot was identified and marked using an 10–20 EEG cap. Afterwards, the saline-soaked electrodes were placed. Approximately 2 min after the stimulation started, subjects began performing the SRTT.

Results

Response time (RT) for each trial was measured from the moment of the asterisk appearance on screen (go signal) until the first button push. RTs that were less than 120 ms or longer than 900 ms were discarded either as anticipatory or excessively lengthy, respectively. Discarded trials were 6.9% of the total RTs. Only correct RT trials were included in the analysis (total of 48.1% of the data, chance level for SRTT is 25%). No significant effect of gender was found [$F_{(1,20)} = 0.007$, $p = 0.932$, $\eta_p^2 = 0.0001$].

A repeated measures analysis of variance (ANOVA) was conducted, with factors of stimulation condition (anodal/cathodal/sham) and experimental block (blocks 1–8) as independent variables, and correct RT as the dependent variable. The data was normally distributed and sphericity was assumed. The repeated measures ANOVA revealed a significant main effect of block [$F_{(7,15)} = 18.48$, $p = 0.0001$, $\eta_p^2 = 0.718$]. This finding reflects the implicit learning process expected in the SRTT (Fig. 2). The ANOVA did not reveal a significant main effect of stimulation condition [$F_{(2,20)} = 0.16$, $p = 0.853$, $\eta_p^2 = 0.016$], nor a significant block × stimulation condition interaction [$F_{(14,8)} = 1.09$, $p = 0.470$, $\eta_p^2 = 0.561$].

Each SRTT block lasted about 2 min 15 s including the short breaks between blocks. Because the SRTT started after 2 min of stimulation, the third block took place after 6 min 30 s to 8 min 45 s, that is certainly before 13 min of stimulation had passed. Block 8 was performed after 17 min 45 s of stimulation up to 20 min. For block 8, we could safely assume that it was fully conducted after the predicted reversal point took place (that is 13 min after stimulation). Since these two blocks, the third and the eight, reflect a similar learning effects being located two blocks after the random block, we planned to compare them to reveal learning effects under linear (block 3) and non-linear (block 8) stimulation conditions.

A repeated measures ANOVA was conducted with factors of stimulation condition (anodal/cathodal) and experimental block (blocks 3 and 8) as independent variables, and correct RT as the dependent variable. The purpose of this analysis was to compare the effect of the stimulation before and after the predicted shift in the effect of the cathodal stimulation, which presumably occurs after 13 min of stimulation. The repeated measures ANOVA revealed a significant main effect of block [$F_{(1,21)} = 15.24$, $p = 0.001$, $\eta_p^2 = 0.421$] with faster performance at the eight block, as expected in learning paradigms. Crucially, the ANOVA also revealed a significant block × stimulation condition interaction [$F_{(1,21)} = 4.34$, $p = 0.05$, $\eta_p^2 = 0.171$]. This interaction indicates that in the early stages of the task, before the switch in the effect has occurred, the performance under the anodal stimulation was faster than the performance under the cathodal stimulation (as verified with posthoc Bonferroni comparisons, $p < 0.05$), replicating typical previous results of stimulation effects in the SRTT (Nitsche et al. 2003b; Stagg et al. 2011; López-Alonso et al. 2015a). However, in the last stages of the task, after approximately 19–20 min of a 2 mA stimulation, the performance under the cathodal stimulation was faster than the performance under the anodal stimulation (Fig. 3). The post hoc comparisons were conducted using Bonferroni corrections ($p < 0.05$).

The reported results did not change when we added session order as a between-subject variable to account for general practice effects: a main effect of block [$F_{(1,19)} = 15.32$,

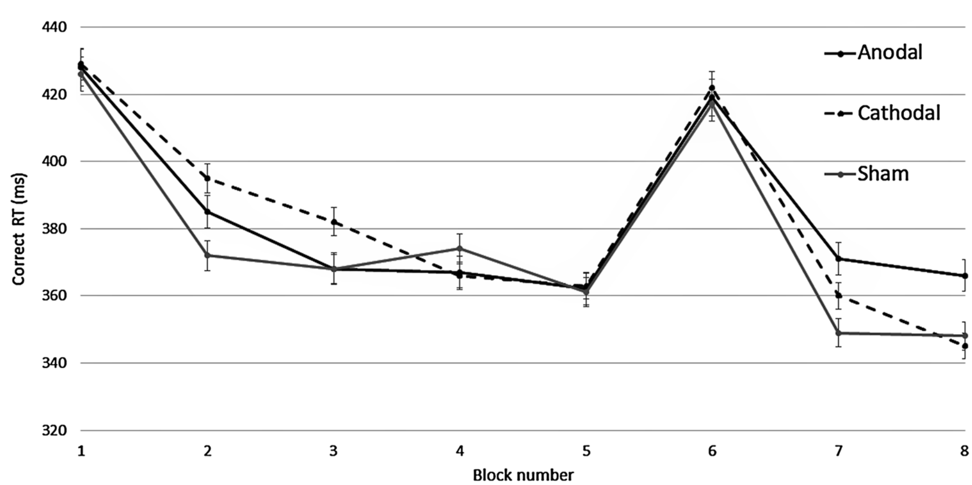

Fig. 2 RT in SRTT across stimulation conditions. Reaction time and SE in milliseconds across all stimulation conditions (anodal/cathodal/sham) and experimental blocks (1–8). Note the steep RT increase in block 6 (under all conditions) indicating an implicit motor learning has occurred

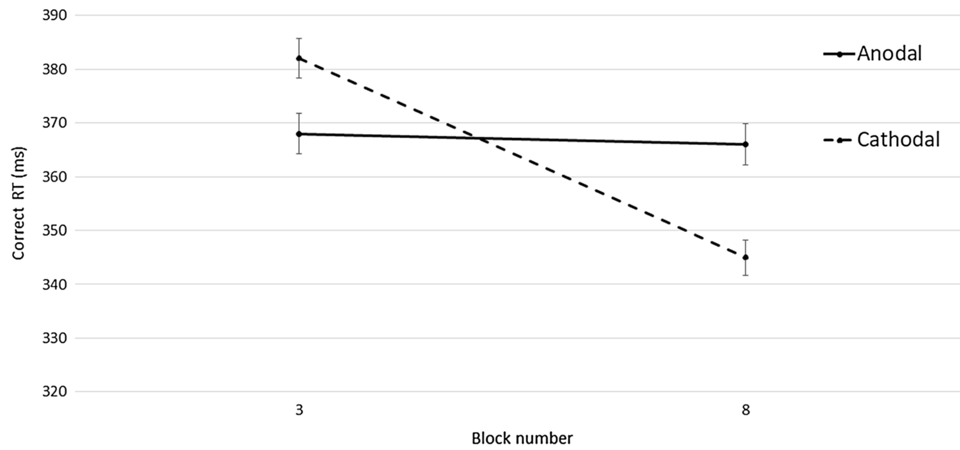

Fig. 3 RT patterns in tDCS conditions before and after the switch. Reaction time and SE in milliseconds in experimental blocks 3 and 8 in the anodal and cathodal stimulation conditions. This graph presents the switch in the stimulation effect. In block 3 prior to the switch, subjects under anodal stimulation were faster than under cathodal stimulation. In block 8 after the switch, subjects under cathodal stimulation were faster than under anodal stimulation

$p=0.001$, $\eta_p^2=0.446$] and a block × stimulation condition interaction [$F_{(1,19)}=5.86$, $p=0.026$, $\eta_p^2=0.236$] were significant when considering session order effects.

Discussion

Here we employed a 20 min 2 mA stimulation over the motor cortex aiming to compare online stimulation effects before and after 13 min of stimulation, which was reported to be a crucial point where tDCS effects might reversed, at least when measuring it with MEP (Batsikadze et al. 2013). First, we need to acknowledge that our study has failed to replicate the expected basic finding of SRTT studies, at least up to the point of 13 min long tDCS stimulation. Previous SRTT studies managed to show that anodal stimulation has improved performance in the SRTT, shortening RT significantly (Nitsche et al. 2003b; López-Alonso et al. 2015a). Although the RT figures we recorded present a faster performance under anodal stimulation, as expected, until about block 5, these RT differences failed to reach significance, despite having sample sizes and average RTs comparable to previous SRTT studies. It could be that our subjects had larger variance than what was found in other studies. We cannot conclude therefore that subjects' performance under anodal stimulation was improved in comparison to the sham condition, although there is an average advantage of about 25 ms for the anodal stimulation (up to Block 6), in line with the expected pattern.

Nevertheless, since the purpose of the current study was to replicate the reversed polarity findings by Batsikadze et al. (2013), using an implicit motor learning task, the SRTT, rather than measuring MEP, we conducted several follow-up analyses. We assumed that according to the previously reported linear connection between current intensity and effect size, for up to 13 min of stimulation, we will observe an increased excitability under anodal stimulation, and a decreased excitability under cathodal stimulation. However, in view of the conclusions of Batsikadze et al. (2013), we assumed that after 13 min of stimulation, a shift in the polarity-dependent effects will occur, leading to an increase in the M1 excitability under cathodal stimulation. Indeed, as we showed here, subjects' performance in the third experimental block, that was performed after about 8 min of stimulation, reflected the expected linear inter-dependency, causing performance under anodal stimulation to be faster that performance under cathodal stimulation. However, subjects' performance in the eight experimental blocks, that was performed after 18 min of stimulation, reflected the expected shift in polarity that was found by Batsikadze et al. (2013).

Our results might explain a previous failed attempt to replicate MEP results using a behavioral measure, performance in a simple reaction time task. A M1-contralateral orbit montage with both anodal and cathodal polarities of 1 mA and 2 mA for 20 min showed mixed patterns: 10 min 1 mA application was not sufficient to improve learning (Kuo et al. 2008), however, 15 min (Nitsche et al. 2003b) or 20 min (Vines et al. 2008) improved the SRTT measures. For a stronger intensity, Kang and Paik (2011) failed to improve SRTT with 2 mA for 20 min. However, employing 2 mA for a shorter duration (13 min) improved performance in a different motor learning task (Forester et al. 2013). Based on the current results, perhaps the long stimulation duration of 2 mA caused non-linear stimulation effects, that generated a mixed pattern of slower and faster RT such that the average effect was null. It is important to keep in mind that if there are non-linear effects on behavior as there are on MEPs, then they are likely to be weak, since the motor learning RTs are not a direct index of stimulation effects as the MEP is. The MEP might be more sensitive to stimulation effects, because it is an after-effect measure rather than online, and in fact this is what Ambrus et al. (2016) claimed, with a significant stimulation effect on MEP in the SRTT but not on performance.

Recent tDCS studies highlight the high variability in the response pattern of subjects following tDCS. A study examining MEP after 10 min 2 mA anodal or cathodal stimulation showed extremely high variability in MEP. About third of the subjects (36%) showed facilitation after anodal stimulation and inhibition after cathodal stimulation, but the opposite pattern has also been observed in 21% of them. Another third (38% of subjects) showed facilitation after both anodal and cathodal stimulation, leading to nearly 75% of subjects experiencing facilitation after tDCS stimulation in both polarities (Wiethoff et al. 2014). It has been shown that there is a great amount of variability in response to tDCS, both inter-individual and intra-individual (López-Alonso et al. 2014, 2015b; Chew et al. 2015; Tremblay et al. 2016).

Since the early experiment in tDCS as a neuromodulation technique for humans (Nitsche and Paulus 2000), the use of it in research and clinical domains has increased tremendously, and alongside it, so have the intensities and durations of the stimulation (Batsikadze et al. 2013). Moreover, having tDCS machines being sold to the public for self-administered home use (Fitz and Reiner 2013), the importance of fully understanding the way it affects the human brain is extremely high. Our study is contributing to the methodological body of research, by showing that a 2 mA, 20 min cathodal stimulation does not have a linear effect, but rather it starts by decreasing excitability, as expected, and due to the long duration of the stimulation, the effect switches after about 13 min, and causes an increase of excitability instead (Batsikadze et al. 2013) and an improved motor learning as we showed here.

Acknowledgements This study was supported by the Israel Science Foundation, Grant no. 367/14.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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