Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Effects of transcranial static magnetic field stimulation over the left dorsolateral prefrontal cortex on random number generation

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HIGHLIGHTS

- We assessed the effects of single-session transcranial static magnetic field stimulation (tSMS) over left dorsolateral prefrontal cortex (DLPFC) on randomness.
- Randomness index on a random number generation task increased few minutes after tSMS application.
- tSMS over left DLPFC of healthy subjects can interfere with normal brain function.

ARTICLE INFO

ABSTRACT

Objective: Focal application of transcranial static magnetic field stimulation (tSMS) is a neuromodulation technique, with predominantly inhibitory effects when applied to the motor, somatosensory or visual cortex. Whether this approach can also transiently interact with dorsolateral prefrontal cortex (DLPFC) function remains unclear. The suppression of habitual or competitive responses is one of the core executive functions linked to DLPFC function. This study aimed to assess the impact of tSMS on the prefrontal contributions to inhibitory control and response selection by means of a RNG task.
Methods: We applied 20 min of tSMS over the left DLPFC of healthy subjects, using a real/sham cross-over design, during performance of a RNG task. We used an index of randomness calculated with the measures of entropy and correlation to assess the impact of stimulation on DLPFC function.
Results: The randomness index of the sequences generated during the tSMS intervention was significantly higher compared to those produced in the sham condition.
Conclusions: Our results indicate that application of tSMS transiently modulates specific functional brain networks in DLPFC, which indicate a potential use of tSMS for treatment of neuropsychiatric disorders.
Significance: This study provides evidence for the capacity of tSMS for modulating DLPFC function.

1. Introduction

Transcranial static magnetic field stimulation (tSMS) is a novel non-invasive brain stimulation (NIBS) technique capable to modulate cortical excitability, cortical oscillations, and influence motor and cognitive functions. tSMS is based on the transcranial application of a static magnetic field (120–200 mT at 2–3 cm from the magnet surface) (Rivadulla et al., 2014) over the skull. Recently, a

number of studies applying tSMS over different cortical areas (e.g., visual, motor, supplementary motor and somatosensory cortices) have demonstrated neurophysiological and/or behavioral effects in healthy subjects and patients (Arias et al., 2017; Carrasco-López et al., 2017; Dileone et al., 2018; Gonzalez-Rosa et al., 2015; Kirimoto et al., 2020, 2018, 2014; Lacroix et al., 2019; Lozano-Soto et al., 2018; Nakagawa et al., 2019; Nakagawa and Nakazawa, 2018; Nojima et al., 2019, 2016; Oliviero et al., 2011; Sheffield et al., 2019; Shibata et al., 2021; Silbert et al., 2013; Soto-León et al., 2022). These studies support the main idea that tSMS has general inhibitory effects by a reduction in the neuronal excitability, and one of the proposed mechanisms for this to happen is a mechanical mechanism (Hernando et al., 2020).

On the other hand, the main functions of the dorsolateral prefrontal cortex (DLPFC) are inhibition, coordination modulation of behavior, search, retrieval and always updating of relevant information, planning, preparation and anticipation through temporal signals, cognitive and emotional regulation and control, flexibility to change attention and behavior as conditions change (Stuss and Knight, 2002; Tirapu Ustárroz et al., 2012). Previous work has shown that other non-invasive modulation techniques such as transcranial magnetic stimulation (TMS) (Jahanshahi et al., 1998) or transcranial direct current stimulation (tDCS) (Capone et al., 2014) can modulate DLPFC function by evaluating this modulation on random number generation (RNG).

One attraction of RNG tasks is their apparent simplicity that involves several executive mental processes. RNG requires establishing the appropriate strategy, based on the selection of suitable responses and the elimination of those that seem to break the concept of subject randomness, the monitoring of the responses, holding information 'on line' and the possible modification of the strategy generation (Jahanshahi et al., 1998). In particular, RNG is strongly related to specific executive functions, such as updating and monitoring of information, and inhibition of prepotent responses of counting or cycling through the set of numbers (Miyake et al., 2000). The function of the left DLPFC is the selection of responses through the suppression of habitual or competitive responses (Jahanshahi et al., 2000, 1998; Jahanshahi and Dirnberger, 1999). However, DLPFC is also involved in the generation of random responses and more specifically, the left DLPFC plays a critical role in this network by exerting an inhibitory influence over temporal–parietal cortex, in order to suppress natural counting (Jahanshahi et al., 2000).

Here, we explored the effect of tSMS over the left DLPFC on RNG. This task is closely linked to inhibitory control, and we hypothesize that modifying the cortical excitability of the left DLPFC, using tSMS, will increase the ability to generate random number sequences, by reducing the habitual suppressive responses. Such a demonstration could pave the way for the modulation of DLPFC function in patients with executive dysfunction, such as Parkinson's disease (Anzak et al., 2013; Brown et al., 1998; Dirnberger et al., 2005) or Huntington's disease (Aron et al., 2003; Ho et al., 2004), or disorders characterized by random behavior (schizophrenia, borderline personality disorder, attention deficit/hyperactivity disorder), or addictive behavior such as gambling (Salatino et al., 2022; Soyata et al., 2019).

2. Materials and methods

2.1. Participants

Twenty-seven right-handed healthy adults (8 males and 19 females) participated in this study. Their mean age was 32.74 years (SD = 9.38; range = 20–53). The sample size was calculated with G*Power 3.1 software, with $d = 0.8$, $\alpha = 0.05$, power = 0.95 and a

loss estimate of 15%. Exclusion criteria included physical, psychological, and neurological illnesses, history of substance use or being pregnant or in lactation period. None of them had electronic devices, metallic implants or were under medical treatment for any condition. All participants were informed of the protocol and signed the written informed consent before their participation in this study. This experimental protocol was approved by the ethics committee of the University Hospital of Toledo (No. CEIC-810) and conducted according to the Declaration of Helsinki.

2.2. Experimental design

We performed a double-blind, sham-controlled, cross-over experiment. A within-subject repeated measures design was used. All participants took part in the two conditions of RNG: a no-stimulation control (sham stimulation) and real tSMS over the left DLPFC. Here we tested for effect of tsms, and so we used sham rather than opposite site where effects may have been more subtle due to known lateralization of randomness behavior (Vanderhasselt et al., 2009). The kind of stimulation was blinded to the participants and experimenters. To avoid carryover effects (Carrasco-López et al., 2017; Chen et al., 2021; Gonzalez-Rosa et al., 2015; Oliviero et al., 2011; Sheffield et al., 2019; Vila-Villar et al., 2022), each of these stimulations was performed in two sessions on different days (at least one week apart) using the same protocol. The performance of the second RNG is unaffected by repeated performance or practice (Jahanshahi et al., 2006). The order of sessions (real or sham tSMS) was randomized across participants. Fourteen subjects started the study with the sham stimulation and thirteen with the real tSMS. To evaluate if subjects can identify the kind of stimulation received, at the end of each experimental session, the subjects filled out a forced-choice question about what type of stimulation (real or sham) they believed they had received.

In addition, to check safety, a record of possible adverse effects or subjective discomfort was made after the session.

Participants sat in a comfortable chair in front of the microphone in a sound-attenuated room and were instructed to keep their heads straight without moving throughout the experiment. In each session, the RNG-tSMS was performed continuously for approximately 24 minutes. The protocol consisted of 10 consecutive runs of RNG with 30 second breaks between runs. During the first two runs, the RNG without stimulation was performed to determine the previous baseline. After finishing the second run, a researcher placed the real or sham tSMS. The execution of the next 8 runs of the task continued for approximately 20 minutes of stimulation. The sequence of events is schematically presented in Fig. 1a.

2.3. Transcranial static magnetic field stimulation (tSMS) over the left DLPFC

For real tSMS we used a cylindrical NdFeB neodymium magnet with a diameter of 60 mm, a height of 30 mm, a weight of 370 grams and a nominal force of 1.177 N equivalent to 120 kg (Model MAG60r; Neurek, Toledo, Spain). For sham stimulation we used a non-magnetic stainless-steel cylinder with the same size, weight, and appearance as the real magnet (model MAG60s; Neurek, Toledo, Spain). We used the international 10–20 system of electrode placement to determine locations of the DLPFC, with F3 corresponding to the left DLPFC (Herwig et al., 2003; Homan et al., 1987) (Fig. 1b). The magnet or sham device was placed on F3 with the aid of an ergonomic helmet (MAGdpv1.1 Neurek SL, Toledo, Spain) specifically designed to correctly maintain stimulation on the left DLPFC in skulls of different sizes (Fig. 1b). A non-

magnetic cylinder was placed on position F4 to counterbalance the weight of the real/sham tSMS placed at F3.

2.4. Random number generation task

On each run of the task, participants were asked to say the numbers 1 to 9 in random order, to the best of their ability, for 100 trials per run. They were instructed to synchronize their responses with a pacing beep signal presented at a rate of once every 1200 ms. The concept of randomness was explained to the participants by the "hat" analogy used in previous studies (Jahanshahi et al., 1998). To do this, they were told to suppose that we had written the numbers 1 to 9 on pieces of paper and put them in a hat. To generate a random sequence, they would have to imagine that they took a paper at random from the hat, said the number that appeared, and returned it to the hat, and so on until completing the 100 trials per run (Fig. 1c).

The equipment used to design and carry out the experiment was a custom-made device composed of Raspberry Pi 400 connected to a microphone and a breadboard that contained a buzzer.

The complete task was recorded through the device for subsequent analysis of the measures of randomness. All subjects were naive to the RNG task and were not explicitly informed of the measures of randomness analyzed in the study.

2.5. Measures of randomness

A variety of measures have been used previously to quantify the randomness of responses. Factor analysis has grouped the different measures into three independent factors that ought to be considered when relating the production of random responses to the concept of randomness: repetition, cycling, and seriation (Ginsburg and Karpiuk, 1994; Peters et al., 2007). To further corroborate our findings, we obtained measures of each of these factors using procedures from previous studies (Ginsburg and Karpiuk, 1994; Jahanshahi et al., 1998). (See supplementary material).

**Randomness index: entropy and correlation function**

Finally, to facilitate the interpretation of the effect of the tSMS on the DLPFC, we calculated two additional measures relating to the generation of random sequence, the entropy (Shannon, 1948) and the correlation function (Cf) (Barbasz et al., 2008). To this end, we calculated a randomness index (RI) as the ratio between entropy (H) and Cf.

The entropy, the average symbol information, of a finite sequence x of N symbols repeatedly chosen from a set of n elements is given by $H(x) = -\Sigma_i p_i log_2(p_i)$, where p_i is the probability of an item i ($i = 1...n$) in the finite sequence. It takes a maximal value when probabilities of all items are equal, converging to $H_{max} = log_2(n)$. High entropy values could therefore indicate highly random sequences. As in previous RNG studies using entropy (Demir and Ergün, 2018; Gauvrit et al., 2016; Vandierendonck, 2000), this metric does not capture the structure of a sequence, but depends on the relative frequency of the item in a sequence. Entropy alone, therefore, is not sufficient for assessing randomness. Cf has been put forward to overcome this inconvenience (Barbasz et al., 2008). The Cf index measures the distance between two elements of a finite sequence, x, of N symbols that are repeatedly chosen from a set of n elements. Cf is given by $Cf(x) = \Sigma_i E(i)/N$, where E (i) is a number of pairs of an identical event separated by i ($i = 1...N-1$) position at the sequence with the N number of ele-

a) Time course of experiment
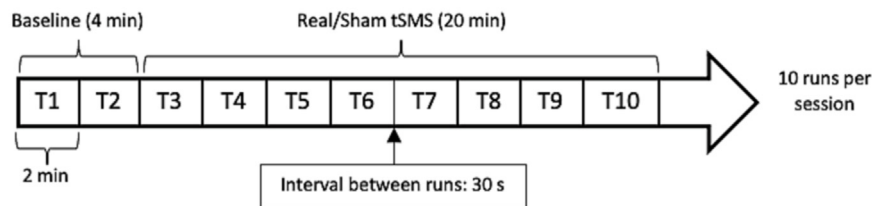
b) Stimulation location
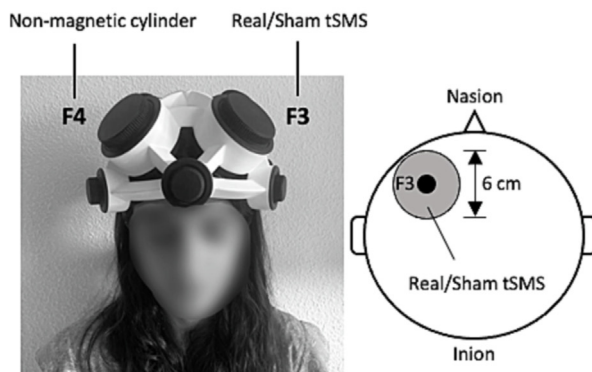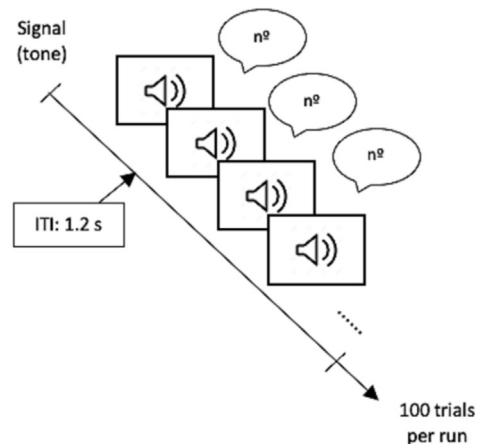
c) Random generation number task

Fig. 1. Procedure and experimental task. Each session was divided into 10 runs, each lasting 2 minutes, with 30-second rest intervals between runs. The first two were carried out without stimulation and the next 8 after placing the (real/sham) transcranial static magnetic field stimulation (tSMS) helmet (a). Stimulation with tSMS, real or sham, was applied on the F3 position of the International System 10–20 of scalp electrode placement, corresponding to the left dorsolateral prefrontal cortex (DLPFC). A non-magnetic cylinder was placed on position F4 to counterbalance the weight of the (real/sham) tSMS placed at F3 (b). Random number generation (RNG): after the appearance of the auditory signal stimulus, every 1.2 seconds, the participants had to say out loud a number between 1 and 9 to generate a random sequence (of 100 numbers per run) (c). ITI: Intertrial Interval.

ments. It takes a maximal value when all items are the same and this could indicate that it is the least random sequence. We calculate the *RI* (ratio between *H* and *Cf*) to evaluate the performance of the RNG to quantify the effects of the tSMS on DLPFC-dependent performance in RNG.

2.6. Statistical analysis

The randomness measures described previously were calculated for each subject and session. More concretely, we calculated the measurements for each of the 10 blocks (of 2 minutes) of the task.

Randomness index: entropy and correlation function

The *H* and *Cf* for each of the 10 blocks of task was calculated and normalized by the second baseline block (T2). The normalized entropy index and normalized correlation function were used to calculate the *RI*.

To analyze the effects of real or sham tSMS on the left DLPFC, *RI* was analyzed in a two-way repeated measures ANOVA, with STI-MULATION (real or sham) and TIME (9 time points, T2...T10) as factors. In case of significant effects, post hoc paired *t*-tests were performed using a Bonferroni correction or follow-up ANOVAs. The Greenhouse-Geisser correction was applied when the sphericity assumption was violated. Moreover, the average of the 8 intervention times (T3...T10) was calculated in the two groups and compared with a *t*-test to study the overall effect of tSMS on the *RI*.

As a check that the RNG measures are not affected by practice or by repeated performance, *RI* of sham sessions were analyzed in a mixed ANOVA with SESSION (SESSION1/SESSION2) as between subject factor and TIME (9 time points) as repeated measures factor. In case of significant effects, the post hoc paired *t*-tests were performed using a Bonferroni correction or follow-up ANOVAs.

The Greenhouse-Geisser correction was applied when the sphericity assumption was violated.

Finally, the sensation of the participants (real or simulated) was evaluated using the χ^2 test. In addition, we tested for a difference in reaction times between the two groups (averaged over the 8 intervention times, T3...T10) using a paired *t*-test. For the statistical analyses, the JASP version 0.16.1 software was used, and they were performed blind to the stimulation condition of the participants. Results were considered significant at $p < 0.05$.

3. Results

The experimental procedure was well tolerated and none of the subjects needed to interrupt or terminate the session due to side effects. Subjects were blind to stimulation type received (real, sham) and forced choice questioning at the end of session did not show significantly correct identification of the real tSMS vs sham sessions ($\chi 2 = 0.681$, $p = 0.409$). More specifically, 48% of subjects got the type of stimulation correct when using real stimulation and 63% when using simulated stimulation.

3.1. Effects of tSMS on the randomness index

The evolution of the entropy and correlation function over time was different for the real tSMS and sham tSMS groups. The entropy in the real group was overall higher than in the sham group (Fig. 2a). The correlation function index, *Cf*, also shows a clear difference between the two groups, with lower values in the sham group, which would indicate a greater randomness for the real group (Fig. 2b).

The effects of real and sham tSMS for the randomness index (*RI*) are shown in Fig. 2 (c and d). For the *RI*, the two-way repeated mea-
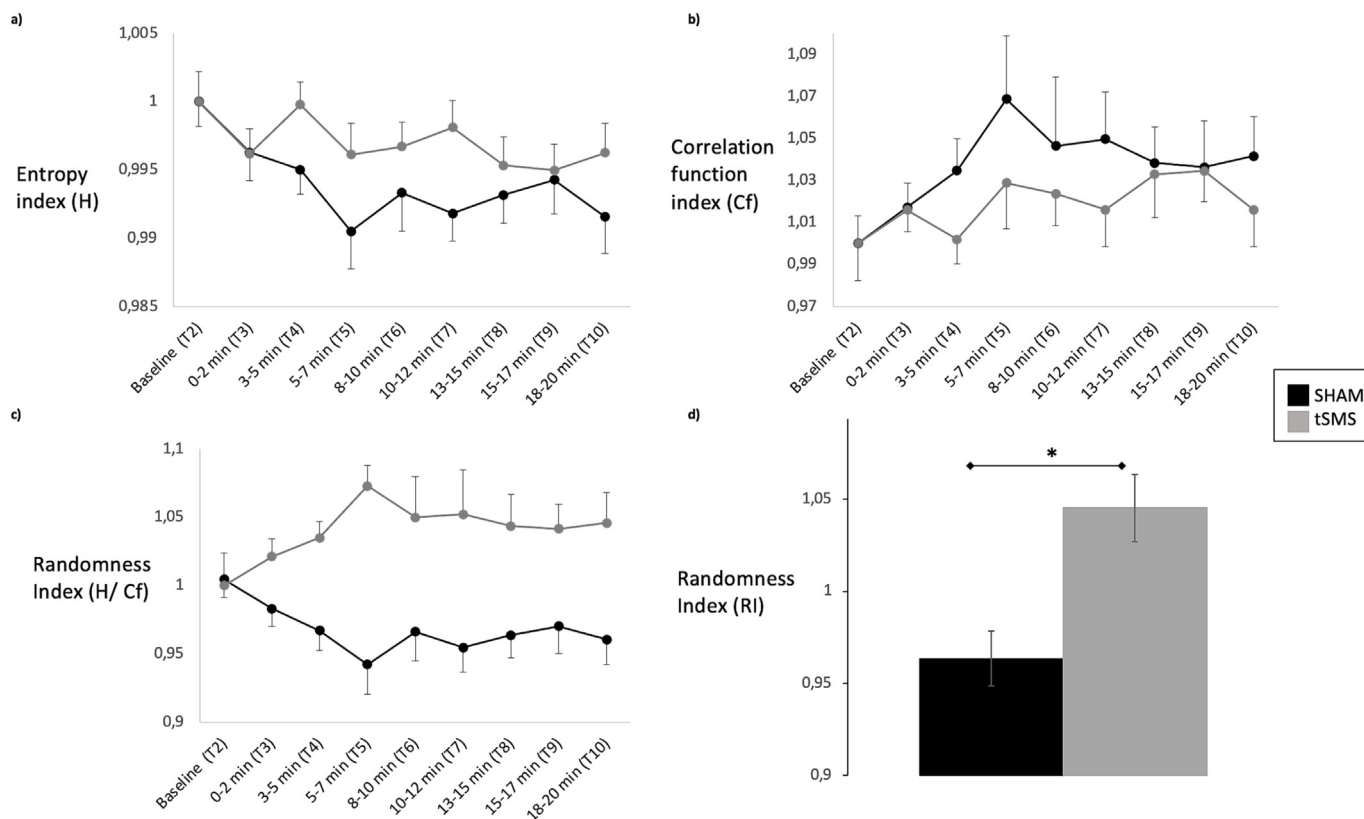

Fig. 2. Mean values over time of Entropy (a), Correlation function (b), Randomness Index (c), grand average over all intervention times (T3...T10) of Randomness Index (d). * $p < 0.05$ *t*-test. Error bars = SEM; RI: Randomness index; H: Entropy index; Cf: Correlation function index; tSMS: transcranial static magnetic field stimulation.

sured ANOVA showed significant effects for STIMULATION (F[1, 26] = 5.121, p = 0.032) and for the interaction STIMULATION*TIME (F[8, 206] = 2.482, p = 0.014). Post hoc analysis revealed significant differences between baseline and 5–7 minutes after stimulation started (T5) for real tSMS (t = -4.181, p_{bonf} = 0.006) (Fig. 2c). When averaging all intervention times, we can see a significant difference between the two groups (t test: t[26] = -2.469, p = 0.020), having a higher RI for the intervention with real tSMS (Fig. 2d).

RI was not affected by the repetition of the task. RI of the sham group, showed no significant differences between the first and second session of the study (SESSION*TIME: (F[8, 200] = 0.916, p = 0.504).

Regarding reaction time, the sham group had longer reaction times than the real group (0.258 ms and 0.254 ms respectively) without a significant statistical difference (t test: t[27] = 0.393, p = 0.697).

4. Discussion

In this study, we examined the effects produced by tSMS over the left DLPFC on randomization measures of RNG task. We report that tSMS over the left DLPFC for 20 minutes increases the randomness of participants' responses over a 20 minute period after stimulation.

More specifically, we evaluated the effects of the tSMS over the left DLPFC, which has previously been implied in the generation of random responses using transcranial magnetic stimulation (Jahanshahi et al., 1998). For the purpose of comparison with previous work, we chose to measure the effects of tSMS on the performance of a RNG task. The RNG task is a simple task that involves several cognitive functions and can be evaluated from different measures of randomness. The measures of entropy and correlation function relate to randomness, chaos and complexity within sequences of information, and enable quantification of the randomness index through these mathematical quantities, rather than more heuristic measures of performance in RNG tasks. Our results suggest that tSMS has the capacity to transiently alter DLPFC function. Previous work investigating the potential of tSMS for modulating DLPFC function has yielded varied results. For example, Watanabe et al. (2021) observed that applying tSMS for 30 minutes over the left DLPFC did not affect performance in a Go/noGO task (Watanabe et al., 2021). On the other hand, tSMS over the left DLPFC decreased performance in a working memory n-back task without affecting the reaction times (Chen et al., 2021). With respect to the RNG task, random number generation in human subjects can be accompanied by lateral head turns and eye position (Loetscher et al., 2010, 2008). As for eye movement we have no control, the participant was allowed to move his eyes freely, with that measure we could have discussed the modulation of the neural mechanisms that Loetscher et al. (2010) mention in the conclusion of their paper.

Our main results are that the tSMS on the DLPFC has affected the RI in such a way that the sequences generated in the tSMS group obtained a higher RI related to a higher randomness of the sequence. The effect of tSMS on this index was observed within a few minutes after the start of stimulation.

Our results align with the effects on RNG of other NIBS techniques applied over the DLPFC. For example, Jahanshahi et al. (1998, 1999) studied the effect of the application of short rTMS trains on the left DLPFC and observed a change in the pattern of count by increasing the usual count in steps of one and decreasing the count by two (Jahanshahi et al., 1998). Other work using tDCS over left DLPFC observed that the counting (say numbers in order) increases after anodal stimulation – reflecting a reduced capability of generating random sequences - compared to cathodal stimula-

tion (Capone et al., 2014). Under the assumption that anodal tDCS increases cortical excitability within the targeted brain region, these results would be the opposite effects we observed in our study with tSMS – which has been shown to predominantly decrease cortical excitability (Dileone et al., 2018; Gonzalez-Rosa et al., 2015; Lozano-Soto et al., 2018; Oliviero et al., 2011). While direct comparison of the effects of different NIBS techniques is fraught with complication, these results indicate that tSMS may provide a viable alternative for modulating specific behaviors underpinned by DLPFC function. One advantage of tSMS is its capacity for perfect sham control (Carrasco-López et al., 2017; Gonzalez-Rosa et al., 2015; Oliviero et al., 2011), as showcased here by the inability of participants to identify real versus sham stimulation, in our double-blind experimental design. This may be of benefit in tasks where the sensory effects of TMS or transcranial direct and alternating current stimulation could complicate the interpretation of results (Bergmann and Hartwigsen, 2021; He et al., 2020).

A deficit in inhibitory control is the main problem in several neuropsychiatric disorders (Bénard et al., 2019; Perry and Carroll, 2008; Spillane et al., 2010; Watanabe et al., 2017, 2016). Inhibitory control can be learned, trained and improved, just like other cognitive skills (processing, sequencing, attention). In addition, inhibitory control could also be improved or reduced by non-invasive brain stimulation techniques (including tSMS). This study is a starting point in the translation of this new, non-invasive stimulation technique to clinical questions, but before reaching the end, studies will have to be carried out to correctly establish the treatment regimen (stimulation time and number of sessions).

5. Conclusion

In the present study we evaluated the effects of tSMS on the randomness measure of a RNG task by applying tSMS over the left DLPFC of healthy subjects. We confirmed that tSMS over the left DLPFC has behavioral consequences in healthy humans. The tSMS over the left DLPFC increased the capability of generating a random sequence by increasing the randomness index. Thus, we conclude that focal static magnetic fields can interfere with normal brain function, offering a novel technique that is both portable and safe to influence human brain activity and behavior.

Conflict of Interest

Funding

Acknowledgements

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.02.163.

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