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Modulatory mechanisms underlying high-frequency transcranial random noise stimulation (hf-tRNS): A combined stochastic resonance and equivalent noise approach

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ABSTRACT

Background: High-frequency transcranial random noise stimulation (hf-tRNS) is a neuromodulatory technique consisting of the application of alternating current at random intensities and frequencies. hf-tRNS induces random neural activity in the system that may boost the sensitivity of neurons to weak inputs. Stochastic resonance is a nonlinear phenomenon whereby the addition of an optimal amount of noise results in performance enhancement, whereas further noise increments impair signal detection or discrimination.

Objective: The aim of the study was to assess whether modulatory effects of hf-tRNS rely on the stochastic resonance phenomenon, and what is the specific neural mechanism producing stochastic resonance.

Method: Observers performed a two-interval forced choice motion direction discrimination task in which they had to report whether two moving patches presented in two temporal intervals had the same or different motion directions. hf-tRNS was administered at five intensity levels (0.5, 0.75, 1.0, 1.5, and 2.25 mA).

Results: The results showed a significant improvement in performance when hf-tRNS was applied at 1.5 mA, representing the optimal level of external noise. However, stimulation intensity at 2.25 mA significantly impaired direction discrimination performance. An equivalent noise (EN) analysis, used to assess how hf-tRNS modulates the mechanisms underlying global motion processing, showed an increment in motion signal integration with the optimal current intensity, but reduced motion signal integration at 2.25 mA.

Conclusion: These results indicate that hf-tRNS-induced noise modulates neural signal-to-noise ratio in a way that is compatible with the stochastic resonance phenomenon.

Introduction

Transcranial random noise stimulation (tRNS) is a non-invasive electrical brain stimulation technique characterized by alternating current delivered at random frequencies and intensities. This technique can be applied at its full frequency spectrum between 0.1 Hz and 640 Hz, at the low-frequency range between 0.1 Hz and 100 Hz (lf-tRNS), or at the high frequency range (hf-tRNS), between 101 and 640 Hz [1]. Early studies found that 10 min of hf-tRNS applied over the primary motor cortex (M1) induced an increment in cortical excitability with after-effects lasting up to 60 min [1–4]. In the last decade, several experimental procedures have been used to assess the effects of tRNS on different cognitive and sensory abilities in order to understand its mechanisms [5]. For example, it has been demonstrated that hf-tRNS improves behavioural performance on visual tasks [6], attenuates visual motion adaptation [7], facilitates facial identity perception [8] and enhances perceptual learning [9–14]. Moreover, five days of training with concomitant hf-tRNS over the bilateral dorsolateral prefrontal cortex (DLPFC) enhanced calculation time and arithmetic memory-recall-based learning [15].

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Though there is evidence that tRNS induces facilitation at the behavioural level, the lack of animal studies limits our understanding of the action of this technique [5]. One proposed mechanism is that tRNS is able to induce a repetitive opening of the Na^+ channels [1] shortening the hyperpolarization phase, as it has been found that high frequency (140 Hz) extracellular alternating current stimulation in rat hippocampal neurons caused an inward sodium current, resulting in a depolarization of the neural membrane [16]. This hypothesis is supported by pharmacological evidence showing that administration of sodium channel blocker carbamazepine (CBZ) reduced tRNS excitability effects [2].

An alternative intriguing explanation of tRNS effects is based on the stochastic resonance phenomenon. Stochastic resonance is a phenomenon whereby the addition of random interference (i.e., noise) can enhance the detection of weak stimuli or enhance the information content of a signal [17,18]. In particular, an increment in signal detection can be obtained when an optimal amount of external noise is added, whereas if too much noise is added, this can hinder signal detection or information content. There is psychophysical evidence that adding noise to a visual or an auditory stimulus can improve detectability and discriminability of a signal [19–23]. tRNS is a random intensity and frequency stimulation technique that might induce random activity and thus neural noise. The presence of an optimal amount of neural noise could enhance the sensitivity of neurons to a weak stimulus [24]. Recently, van der Groen and colleagues [6] found evidence in support of the stochastic resonance theory to explain the effects of hf-tRNS on the visual cortex. In particular, they tested the effect of different hf-tRNS intensities on a contrast detection task, with hf-tRNS applied over the primary visual cortex (V1). The results showed that contrast detection of a near threshold stimulus was improved while injecting random current over V1. However, this was evident only when the intensity of the random current was delivered at an optimal intensity level (approximately 1.0 mA). Further increasing the noise stimulation intensity worsened detection performance, bringing it to the same level as when no stimulation was applied. Importantly, the effect of the random noise stimulation was evident only when the stimulus presentation was near threshold (i.e., 60% correct detection).

In the present study, we used a similar approach to that of van der Groen and Wenderoth [6]. In particular, we tested whether hf-tRNS delivered at different intensities modulates motion direction discrimination in a way that is compatible with the stochastic resonance phenomenon. We also aimed to investigate whether delivering random current at an intensity above the optimal level could have a detrimental effect on motion direction discrimination. Therefore, the presence of facilitatory and suppressory effects of hf-tRNS at different current intensities may reveal the underlying modulatory mechanism of random noise stimulation. Specifically, we devised a two-interval forced-choice motion direction discrimination task in which observers had to discriminate whether two *globally* moving random dot kinematograms (RDKs) presented in distinct temporal intervals, had the same or different motion directions. Based on van der Groen and Wenderoth [6], the coherence level of the moving RDKs was adjusted to attain 60% correct direction discrimination before hf-tRNS stimulation. hf-tRNS was then applied bilaterally over the human medial-temporal complex (hMT^+; a visual area closely involved in dynamic information processing [25]), with current intensities ranging from 0.5 mA to 2.25 mA. In fact, it has been previously shown that the effects of hf-tRNS on visual motion processing are bounded to the targeted cortical areas (i.e., when bilaterally stimulating hMT^+, but not other areas) [7]. To anticipate the results, current intensities of 1.0 mA or 1.5 mA produced a significant improvement in motion direction discrimination performance, whereas performance was significantly impaired with respect to the baseline when stimulating at 2.25 mA. This suggests that if the stimulation intensity is increased above the optimal level, the induced random activity becomes large enough to hamper the performance.

An Equivalent Noise (EN) analysis was also performed in order to assess the components of global motion modulated by hf-tRNS at different intensities. Global motion processing is assumed to involve the integration of local motion signals in visual areas such as hMT^+. The modulation of motion discrimination performance by hf-tRNS may depend on changes in estimates of the local direction of moving dots, or on how these local motion estimates are integrated [26–28]. The EN analysis relies on the parameterization of the global signal perception as an integration over a finite number of *sampling* dots, with the addition of a fixed amount of *internal noise* to take into account the unavoidable rate of uncertainty carried by the estimate, even when a fully coherent stimulus is displayed. Clearly, a higher *sampling* number leads to a more efficient global motion direction discrimination. During the integration of globally moving dots, changes in *internal noise* would affect the precision with which each dot's direction is estimated, whereas changes in signal *sampling* levels would influence the number of such local estimates that can be integrated [26,27,29]. In order to determine how hf-tRNS modulates *internal noise* or global *sampling* when injecting random noise current at different intensities, we implemented and performed an EN analysis to estimate how *internal noise* and *sampling* are modulated by the optimal and sub-optimal current intensity levels. Consistent with our previous findings [27], the EN results showed that hf-tRNS at 1.5 mA does not modulate *internal noise* but increases *sampling* levels, that is the number of estimates that can be averaged over simultaneously. Such a result can be explained by the above-mentioned fact that *sampling* is associated with the effectiveness of the signal perception, while *internal noise* is related to the uncertainties that are implicit in the estimation process. On the other hand, hf-tRNS at 2.25 mA reduces sampling, affecting the integration mechanism necessary to extrapolate the direction of a global motion display. Importantly, optimal and sub-optimal current intensities did not modulate the amount of *internal noise*, suggesting that local estimates of motion direction do not vary with current intensity. We interpreted the results in terms of effects of stochastic resonance on directional tuning bandwidth and motion integration.

Experiment 1

The aim of Experiment 1A was to assess the modulatory effect of four different hf-tRNS intensities (0.5, 0.75, 1 and 1.5 mA) on a motion direction discrimination task. The rationale was based on the Stochastic Resonance phenomenon. Participants performed a motion direction discrimination task with a coherence near threshold (i.e., motion coherence producing 60% correct discrimination). We hypothesized that this weak motion signal can be boosted by adding external noise with hf-tRNS which contains a wide spectrum of high frequencies. In particular, we expected that increasing the stimulation intensity up to an optimal level would improve motion direction discrimination performance [6,24,30,31]. Experiment 1B was carried out as a control condition, using sham stimulation.

Methods

Participants

Three of the authors (AP, FG and CM) and twenty-one naïve participants (11 males, age range 18–40 yrs) took part in Experiment 1. Twelve participants took part in Experiment 1A and twelve

in Experiment 1B. Participants were all right-handed, and with normal or corrected to normal vision acuity. Each participant filled in a questionnaire in order to exclude participants with implanted metal objects, heart problems, history of seizure or any neurological disease. Methods were implemented following the World Medical Association Declaration of Helsinki [32]. The present study was approved by the Ethics Committee of the University of Lincoln. Written informed consent was obtained from each participant prior the enrolment in the study and they were paid for their time.

Apparatus

Stimuli were displayed on a 20-inch HP p1230 monitor with a refresh rate of 85 Hz. Stimuli were generated with Matlab PsychToolbox [33,34]. The screen resolution was 1280×1024 pixels. Each pixel subtended 1.6 arcmin. The minimum and maximum luminances of the screen were 0.08 and 74.6 cd/m^2 respectively, and the mean luminance was 37.5 cd/m^2. A gamma-corrected lookup table (LUT) was used so that luminance was a linear function of the digital representation of the image.

Stimuli

Stimuli were global motion random dot kinematograms (RDKs) made up by 400 white dots (diameter: 0.12 deg) presented at the centre of the screen within a circular aperture with a diameter of 12 deg. Dot density was 3.54 dots/deg^2. The duration of the RDK was 0.13 s. Dots drifted at a speed of 5.04 deg/s and had a limited lifetime of 47 ms (4 screen refreshes); after a dot vanished, it was replaced by a new dot at a different randomly selected position within the circular window. Dots appeared asynchronously on the display and had an equal probability of being selected as either signal or noise dots [35,36]. Short lifetime was implemented to minimize the presence of local "motion streaks" [37] that could provide strong static cues for motion direction discrimination. In addition, dots that moved outside the circular window were replaced by a new dot at a different randomly location within the circular window, thus maintaining the same density. Signal dots were either constrained to move globally leftward or rightward. Noise dots moved in random directions.

Stimulation technique

Stimulation was delivered by a battery driven stimulator (BrainSTIM, EMS; http://www.brainstim.it/index.php?lang=en) through a pair of saline–soaked sponge electrodes. The hf-tRNS in Experiment 1A consisted of an alternating current delivered at four different intensities of 0.5, 0.75, 1.0 and 1.5 mA with zero offset and applied with random frequencies ranging from 100 to 600 Hz. The total duration of the stimulation was approximately 20 min. In Experiment 1B sham stimulation was delivered at 1.5 mA and for 30 s before the task [38]. The stimulation in both Experiments 1A and 1B was delivered bilaterally; one electrode was placed over the left-hMT$^+$, while a second electrode was placed over the right-hMT$^+$. The two electrodes had an area of 16 cm^2 and the current density was maintained below the maximum safety limits [39,40]. The target areas were localized in all observers by using predetermined coordinates: 3 cm dorsal to inion and 5 cm leftward and rightward from there for the localization of the hMT$^+$. Such a localization technique has been found to be appropriate in previous brain stimulation studies [41–47] and is consistent with fMRI localizers [48].

Procedure

The procedure consisted of three phases

Phase 1: coherence threshold estimation. In Experiment 1A participants took part in four experimental sessions carried out in four different and non-consecutive days, while in Experiment 1B participants performed one session (Sham stimulation). However, the same procedure was used in both experiments. At the beginning of each session, observers performed a two-interval forced choice (2IFC) motion direction discrimination task (Fig. 1) to estimate the individual coherence threshold. The RDKs were presented at the centre of the screen. Participants had to report whether the RDKs presented in the two temporal intervals had the same or different motion directions. Each trial consisted of a fixation point presented for 1 s, followed by two 0.13 s RDKs, with an interval of 0.5 s between the two presentations. An adaptive staircase [MLP], [49,50] was used to track the coherence level producing an accuracy of 60% in motion direction discrimination. The staircase involved 32 trials.

Phase 2: assessing the level of accuracy at coherence threshold. In order to precisely estimate the individual coherence threshold producing an accuracy of 60% in motion direction discrimination, observers performed the same direction discrimination task as in *Phase 1* at the coherence level estimated with the MLP. The coherence was kept constant across a block of 40 trials, and if the resulting accuracy was higher or lower than $60\% \pm 2\%$, the observer was asked to perform additional blocks while the coherence level of the RDK was adjusted between blocks by increasing or decreasing the number of coherently moving dots, on average, in steps of 10 dots (SD = 5 dots), until they reached the desired level of accuracy ($60\% \pm 2\%$). The coherence level resulting in a performance of $60\% \pm 2\%$ correct discrimination was then considered as the participant's baseline (i.e., No-tRNS condition) and was used as coherence level for the stimulation conditions.

Phase 3: the main experiment. In phase 3 of Experiment 1A, participants performed five blocks of the 2IFC direction discrimination task while being stimulated with hf-tRNS. The coherence level was fixed at the value established in *Phase 2* of the experiment, and was kept constant across the five blocks. Each block consisted of 40 trials for a total of 200 trials. Accuracy was calculated by collating responses in each block. In each of the four experimental sessions, one stimulation intensity was applied; that is, either 0.5, 0.75, 1.0 or 1.5 mA. The different sessions (stimulation intensities) were delivered in different days. The order of stimulation intensity was randomized across participants. Observers were unaware of the type of stimulation applied in each session. The stimulation started 30 s before the first block and lasted until the end of the fifth block. The final accuracy in the No-tRNS baseline condition was the average of all the No-tRNS conditions (as found in *Phase 2*) across the four stimulation sessions. In Experiment 1B we used the same procedure of Experiment 1A, with except that participants performed only one stimulation session in which Sham stimulation at 1.5 mA was delivered for 30 s before the beginning of the task. Participants always performed five blocks of the 2IFC direction discrimination task. Additionally, each participant performed phase 1–3 of the experiment at the beginning of each stimulation session; that is, on each testing day.

Results

Fig. 2 shows the results of Experiments 1A and 1B. Results showed accuracy levels above baseline values only in the 1.0 and 1.5 mA stimulation conditions. Non-parametric tests were used establish the statistical significance of the results, because in 1A, a Shapiro-Wilk test for normality showed that residuals for the No-tRNS condition were not normally distributed ($p = 0.01$).

Firstly, a Friedman test was performed to test for possible differences between the performance values in the No-tRNS condition measured before each hf-tRNS session (i.e., hf-tRNS at 0.5, 0.75, 1.0 and 1.5 mA). The Friedman test reported no significant effect of No-

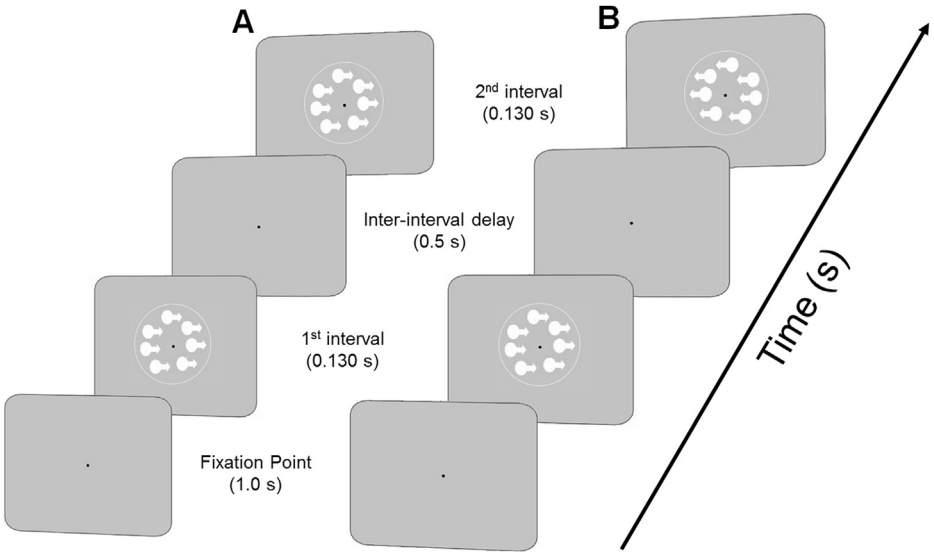

Fig. 1. Schematic representation of the procedure used in Experiment 1. (A) Example of a 'same' trial, when the RDKs in the two temporal intervals have the same motion direction. (B) Example of a 'different' trial, when the RDKs have opposite motion directions. The white circular frame is reported only for demonstrative purposes and was nor presented during the experiment.

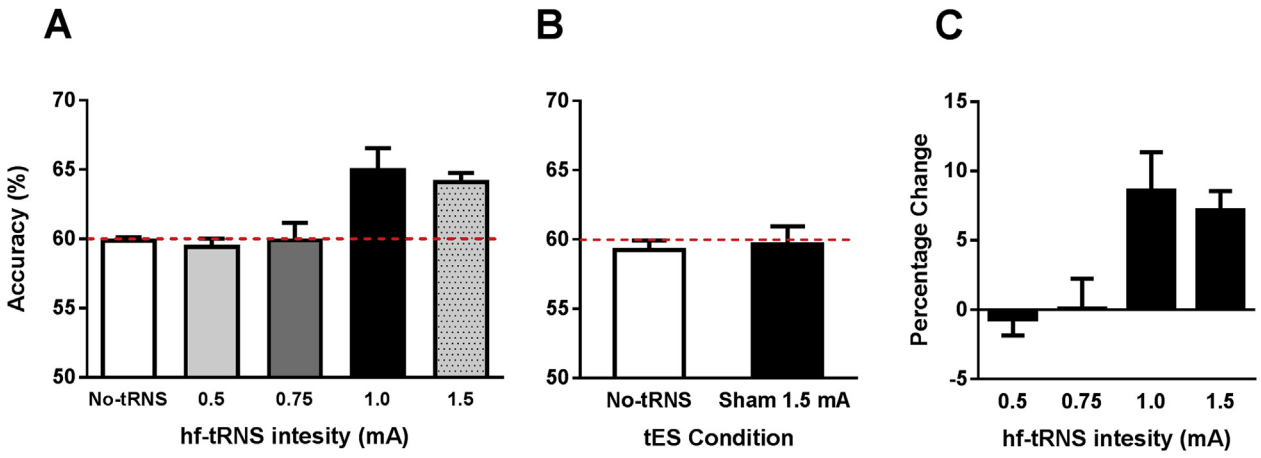

Fig. 2. Results of Experiment 1. (A) Mean accuracy (%) for each stimulation condition of Experiment 1A: No-tRNS, 0.5, 0.75, 1.0 and 1.5 mA. (B) Mean accuracy (%) for No-tRNS and Sham at 1.5 mA of Experiment 1B. The red dashed line represents the 60% accuracy. (C) Percentage change between hf-tRNS conditions and No-tRNS in Experiment 1A. Error bars ±SEM. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tRNS measures performed before each hf-tRNS session ($\chi^2 = 0.94$, $df = 3$, $p = 0.82$).

Another Friedman test including the stimulation intensity (i.e., No-tRNS, 0.5, 0.75, 1.0 and 1.5 mA) reported a significant effect of the stimulation intensity ($\chi^2 = 22.52$, $df = 4$, $p < 0.001$). In order to test for differences between the different stimulation conditions, we conducted a series of Wilcoxon Signed Rank tests corrected using False Rate Discovery (FDR) at 0.05 [51] and calculated the Cohen's *r* effect size of the statistic [52,53].[2] The results are reported in Table 1. Overall, the test showed that accuracies in both 1.0 mA and 1.5 mA hf-tRNS conditions significantly differ from the No-tRNS, the 0.5 and the 0.75 mA conditions.

Additionally, a one-sample Wilcoxon Signed Rank test was used to compare the results of the experimental conditions to the median accuracy of 60%. The Wilcoxon Signed Rank test reported a significant difference between the median accuracy of 60% and the median of hf-tRNS at 1.0 mA ($p = 0.011$, $r = 0.74$) and the hf-tRNS at 1.5 mA ($p = 0.003$, $r = 0.86$). Comparisons between 60% and the median of No-tRNS condition ($p = 0.527$, $r = 0.18$), 0.5 mA ($p = 0.421$, $r = 0.23$) and 0.75 mA ($p = 0.929$, $r = 0.026$) were not significant.

For Experiment 1B (Fig. 2B), a Shapiro-Wilk test for normality showed that the residuals for the No-tRNS and Sham 1.5 mA conditions were normally distributed ($p > 0.05$). However, as for Experiment 1A, we used non-parametric statistics. It should be noted that Experiment 1B was conducted after Experiment 1A, and in Experiment 1B we used a stimulation intensity of 1.5 mA. This is because, though in Experiment 1A the accuracy for 1.0 mA and 1.5 mA were very similar (64.95% vs. 64.11%, respectively), we decided to choose the current intensity producing less dispersion

[2] We reported the Cohen's *r* for both the Mann-Whitney test and the Wilcoxon Singed rank test. Cohen's r was calculated as $r = \frac{z}{\sqrt{N}}$ were *z* is the z-score obtained from the statistics and *N* is the number of total observations [52,53]. For Cohen's *r* a large effect is 0.5, a medium effect is 0.3, and a small effect is 0.1.

Table 1
Z scores and p-value of the Wilcoxon Signed Rank Tests (corrected using FDR at 0.05) for Experiment 1A.

	Stimulation Intensity (mA)											
	0.5			0.75			1.0			1.5		
	Z score	*p-value*	*r*	*Z score*	*p-value*	*r*	*Z score*	*p-value*	*r*	*Z score*	*p-value*	*r*
No-tRNS	−0.628	0.78	0.13	−0.78,	0.94	0.16	−2.668,	**0.02**	0.54	−2.903,	**0.013**	0.59
0.5				−0.267,	0.88	0.05	- 2.937,	**0.013**	0.60	- 2.903,	**0.013**	0.59
0.75							- 2.578	**0.020**	0.53	−2.277,	**0.04**	0.46
1.0										−0.311,	0.88	0.06

around the mean (SD 5.53% and 2.27% for 1.0 and 1.5 mA, respectively). Besides, in Experiment 1, the Sham condition was tested in a separate group of participants. The rationale behind this choice was that the dependent variable of Experiment 1 was the stimulation intensity. Therefore, in order to establish a proper control condition on the current intensity and avoid possible confounds due to the sensation of stimulation, the intensity of the Sham stimulation should have matched that of the hf-tRNS intensity producing the highest performance improvement. Since it was not possible to know the "optimal" level of stimulation intensity in advance, and thus randomize the Sham condition in the same group of participants, we decided to administer the Sham stimulation at the "optimal" current intensity level in a separate group of participants. A Wilcoxon Signed Rank tests reported that there was no significant difference between the No-tRNS and the Sham at 1.5 mA ($p = 0.78$, $r = 0.06$). Moreover, a one-sample Wilcoxon Signed Rank test did not report any significant difference between the No-tRNS ($p = 0.29$, $r = 0.31$) or the Sham at 1.5 mA conditions ($p = 0.70$, $r = 0.11$) with respect to the median accuracy of 60%.

A Mann-Whitney *U* test was performed to compare the accuracy between the Sham condition at 1.5 mA and the other hf-tRNS conditions: 0.5, 0.75, 1.0, and 1.5 mA. The Mann-Whitney *U* test did not reveal a significant difference between Sham condition with respect to 0.5 mA (U = 71, *corrected-p* = 0.95, $r = 0.01$), 0.75 mA (U = 71, *corrected-p* = 0.95, $r = 0.01$), and 1.0 mA (U = 35.5, *corrected-p* = 0.07, $r = 0.43$). On the other hand, we found a significant difference between hf-tRNS at 1.5 mA and the Sham at 1.5 mA (U = 28, *corrected-p* = 0.04, $r = 0.52$). Moreover, no significant difference was found between the No-tRNS condition in Experiment 1A and 1B (U = 51, *corrected-p* = 0.22, $r = 0.25$).

Fig. 2C shows the percentage change of performance in Experiment 1A between the hf-tRNS conditions and the No-tRNS condition. The percentage change was calculated as follows:

$$\text{Percentage Change} = \frac{tRNS - NoStim}{NoStim} 100 \quad (1)$$

A Friedman test reported a significant effect of the stimulation intensity ($\chi^2 = 19$, $df = 3$, $p < 0.001$). Table 2 illustrates Wilcoxon Signed Rank tests results (corrected using FDR at 0.05) conducted between the different stimulation intensities. Overall results showed a significant improvement for 1.0 and 1.5 mA with respect 0.5 and 0.75 mA stimulation conditions.

Discussion

The results of Experiment 1 showed that hf-tRNS intensity at 1.5 mA improved performance in the motion direction discrimination task. This result is compatible with the stochastic resonance phenomenon in which the injection of an optimal level of external noise in motion sensitive areas strengthens the near-threshold motion signal, increasing the observers' discrimination performance [6,12,22,30]. However, the stochastic resonance framework also predicts that when an excessive amount of noise is injected into the system the behavioural performance can be disrupted [18,20]. Our initial hypothesis was that, since we administered a *bilateral* stimulation, a current intensity of 1.5 mA would have injected an excessive amount of noise to induce a performance decrement. This hypothesis was based on the stimulation parameters of previous studies which found a peak of performance when bilateral stimulation was delivered around 0.75 mA and 1.0 mA [6], and studies that delivered *unilateral* stimulation and reported enhanced performance with hf-tRNS at 1.5 mA [11,27]. In fact, we initially expected that the intensity range used (from 0.5 mA to 1.5 mA) would have been wide enough to detect an improvement either at 0.75 mA or at 1.0 mA and a worsening of performance at 1.5 mA. However, our results showed that the optimal noise level introduced by hf-tRNS was at 1.5 mA. Therefore, we designed a second experiment in which we assessed the effects of hf-tRNS at 2.25 mA, i.e., at an intensity exceeding by 0.75 mA the optimal stimulation level. If the effects of hf-tRNS were due to the stochastic resonance phenomenon, such high stimulation intensity should worsen participants' performance.

Experiment 2

Methods

Stimuli and procedure

Stimuli and procedure were the same as in Experiment 1, except for the stimulation parameters. Two of the authors (AP and FG) and a new sample of twenty-two participants (9 males, age range 18–40 yrs) took part in this experiment. A between-subjects designed was implemented. One group of twelve participants performed the experiment with hf-tRNS at 2.25 mA, whereas another group of twelve participants performed the experiment

Table 2
Z scores and p-value for Wilcoxon Signed Rank test (corrected using FDR at 0.05) for Experiment 1A.

	Stimulation Intensity (mA)								
	0.75			1.0			1.5		
	Z score	*p-value*	*r*	*Z score*	*p-value*	*r*	*Z score*	*p-value*	*r*
0.5	−0.267,	0.79	0.05	- 2.934,	**0.01**	0.60	- 2.903,	**0.01**	0.53
0.75				- 2.578	**0.02**		−2.275,	**0.03**	0.46
1.0							−0.356,	0.79	0.15

with Sham stimulation at 2.25 mA [39,40]. Participants were randomly assigned to the two groups.

Results

Fig. 3 shows the results of Experiment 2. For the hf-tRNS 2.25 mA group, a Shapiro-Wilk test for normality showed that for the No-tRNS condition were not normally distributed ($p = 0.05$). For the hf-tRNS 2.25 mA group, a Wilcoxon Signed Rank tests reported that there was a significant difference between the No-tRNS condition and the hf-tRNS at 2.25 mA ($p = 0.009$, $r = 0.54$). Moreover, a one-sample Wilcoxon Signed Rank did not report any significant difference between the median accuracy of 60% and the No-tRNS condition ($p = 0.56$, $r = 0.16$), but it showed a significant difference between the 60% accuracy and the hf-tRNS at 2.25 mA ($p = 0.008$, $r = 0.77$).

For the Sham group, a Shapiro-Wilk test for normality showed that all conditions were normally distributed ($p > 0.05$). A Wilcoxon Signed Rank test reported that there was no significant difference between the No-tRNS condition and the Sham condition at 2.25 mA ($p = 0.61$, $r = 0.10$). For the Sham group one-sample Wilcoxon Signed Rank tests also showed that there was no significant difference between the median accuracy at 60% and the No-tRNS ($p = 0.305$, $r = 0.30$) and between the median accuracy at 60% and the Sham at 2.25 mA ($p = 0.97$, $r = 0.03$). Most importantly, a Mann-Whitney U test showed that there was a significant difference between hf-tRNS at 2.25 mA and the Sham at 2.25 mA ($U = 37$, $p = 0.043$, $r = 0.41$).

The 2.25 mA hf-tRNS condition was also compared to hf-tRNS intensities of Experiment 1. A Mann-Whitney U test showed that performance with hf-tRNS at 2.25 mA was significantly different from hf-tRNS at 0.5 mA ($U = 29$, *corrected-p* $= 0.008$, $r = 0.54$), from hf-tRNS at 0.75 mA ($U = 25.5$, *corrected-p* $= 0.008$, $r = 0.55$), from hf-tRNS at 1.0 mA ($U = 11$, *corrected-p* $= 0.002$, $r = 0.76$) and from hf-tRNS at 1.5 mA ($U = 5.5$, $p = 0.002$, $r = 0.81$).

Discussion

The results of Experiment 2 showed that increasing the current intensity above the optimal level had a detrimental effect on direction discrimination performance, by reducing the accuracy significantly below 60%. As in Experiments 1A and 1B, under the stimulation conditions, the task was performed with the same coherence level producing approximately 60% correct discrimination before stimulation. These results strongly suggest that a stochastic resonance phenomenon drives the modulatory effects of hf-tRNS when combined with visual tasks.

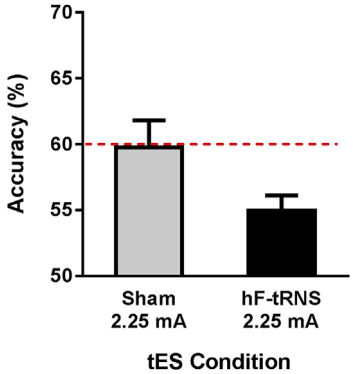

Fig. 3. Results of Experiment 2. Mean accuracy (%) for Sham at 2.25 mA and hf-tRNS at 2.25 mA. The red dashed line represents the 60% accuracy. Error bars ±SEM. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Experiment 3

In a subsequent experiment, we assessed how hf-tRNS stimulation intensities at 1.5 mA and 2.25 mA can modulate neural mechanisms involved in global motion processing. In order to do this, we implemented a variant of the equivalent noise analysis (EN) [27]. EN relies on the idea that visual integration is limited by two factors: *internal noise* and *sampling*. For the integration of drifting dots *internal noise* would affect the precision with which each dot's direction can be estimated, whereas *sampling* refers to the number of dots over which the average direction is computed [26,27,29]. Therefore, the aim of the following EN analysis is to assess how the optimal and sub-optimal hf-tRNS intensities modulate *internal noise* and *sampling*.

Method

Stimuli and procedure

Stimuli and procedure were adapted from Experiments 1 and 2. However, differently from the previous experiments we did not estimate the individual 60% threshold (as in *Phase 1* and *Phase 2* of Experiments 1 and 2), but observers had to perform only five blocks (*Phase 3*) of the 2IFC motion direction discrimination task at the maximum coherence level. A new sample of twenty participants (10 males, age range 18–40 yrs) took part in this experiment and were randomly assigned to one of the four groups (of five participants each) divided by stimulation condition (i.e., hf-tRNS at 1.5 mA, hf-tRNS at 2.25 mA, Sham stimulation at 1.5 mA and Sham stimulation at 2.25 mA). The analysis was limited to a smaller number of participants compared to Experiments 1 and 2, because of the reduced variability among participants, which resulted in smaller standard errors on the associated EN parameter. Such a result is made explicit in the following paragraph and in Table 3, reporting the estimates of the EN parameters.

Equivalent noise analysis

In our experiments, a matrix of K points is displayed as a visual stimulus. Among them, a given number $P < K$ exhibits a coherent motion towards either the left or right, while the others move in random directions. The observer's task is to discriminate the direction of the coherent component of the RDKs, and the probability of correct response is measured after several trials. The accuracy f in the perception of coherent motion grows concordantly with the value P, going from being trivially equal to 1/2 when (no coherent dots) to asymptotically tend to a certain maximum value $f_{\max} \leq 1$ as (all dots are coherent).

Such a relationship can be parameterized by means of an effective EN model adapted from Dakin et al. [26] and Ghin et al.

Table 3
Average accuracy $\bar{f}_{\max}$ and sampling size $\bar{n}_{samp}$ with relative standard deviations $\sigma_{f_{\max}}$ and $\sigma_{\eta_{samp}}$ for hf-tRNS and Sham stimulation at 1.5 mA and 2.25 mA, respectively.

Stimulation type	Stimulation Intensity (mA)			
	1.5		2.25	
	Sham	hf-tRNS	Sham	hf-tRNS
$\bar{f}_{\max}$	0.974	0.967	0.982	0.973
$\sigma_{f_{\max}}$	0.008	0.012	0.008	0.011
$\bar{n}_{samp}$	1.2	2.2	1.4	0.7
$\sigma_{\eta_{samp}}$	0.3	0.3	0.4	0.2

[27]. The model is based on the assumption that the signal is extracted from the stimulus through a simultaneous sampling over a finite number of dots n_{samp}, with the addition of a given amount of internal noise that limits the accuracy to a maximum value $f_{\max}$. When applied to the present case, this implies that a set of n dots (the subscript is dropped for simplicity) is randomly selected by the participant: if *at least* one among them is coherent, the coherent motion is perceived, otherwise a random guess is made. Therefore, the accuracy f to actually retrieve the motion is equal to

$$f = \frac{1}{2} + \left(f_{\max} - \frac{1}{2}\right) g \tag{2}$$

where g is the probability of selecting, among a set of K elements, a n-tuple (i.e., a string of n elements) of which at least one belongs to a given subset of elements.

The probabilities described above (Eq. (2)) can be computed through combinatorics: the total number of n-tuples that can be formed in a set of K elements is given by the binomial coefficient

$$\binom{K}{n} = \frac{K!}{n!(K-n)!} \tag{3}$$

and, as a consequence, its reciprocal is the probability of forming each particular -tuple.

If one considers the subset complementary to P, formed by the $K - P$ elements that *do not* belong to, the number of -tuples that can be formed in it is

$$\binom{K-P}{n} = \frac{(K-P)!}{n!(K-P-n)!} \tag{4}$$

and these are *all* the -tuples of K that do not contain any element of. Therefore, the probability of selecting any -tuple that does not contain elements is the ratio of the two binomial coefficients

$$h(P,n) = \frac{(K-P)!(K-n)!}{K!(K-P-n)!} \tag{5}$$

and the probability of selecting one that contains at least one element of P is simply

$$g(P,n) = 1 - h(P,n) \tag{6}$$

Finally, the dependence of on P, for several values of n, is depicted in Fig. 4.

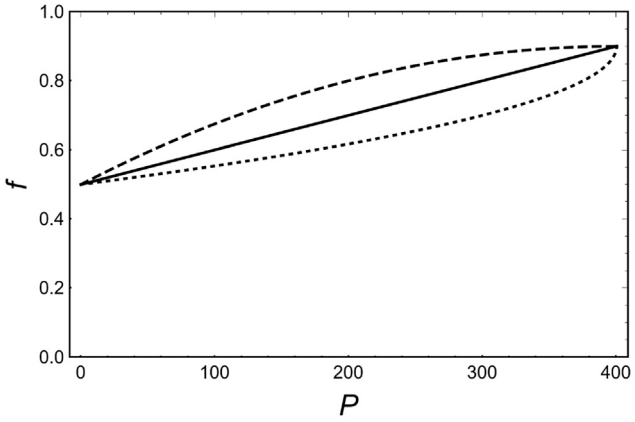

Fig. 4. Dependence of the accuracy on the number of coherent dots P, for n = 1/2(dotted line), 1 (solid line), and 2 simultaneous samplings (dashed line). The total number of points is set to 400, while is set to 1.

Once the maximum accuracy, and the accuracy $f*$ corresponding to a given value $P*$, are known, the only missing ingredient is the effective sampling size: it can be found by solving the equation

$$f(P*, n) = f* \tag{7}$$

with respect to. In order to do that, it is necessary to extend the factorials (which are only defined on non-negative integers) to the domain of real numbers. The Gamma function is defined in such a way that, when the argument x is a non-negative integer, leading to the final expression

$$f(P,n) = f_{\max} - \left(f_{\max} - \frac{1}{2}\right) \frac{\Gamma(K-P+1)\Gamma(K-n_{samp}+1)}{\Gamma(K+1)\Gamma(K-P-n_{samp}+1)} \tag{8}$$

that can be solved numerically, giving the effective number of samplings n_{samp} associated to each subject (the subscript '*samp*' is now reinstated).

As a consequence of the above discussion, each observer will be characterized by peculiar values of (the intrinsic maximum accuracy) and n_{samp} (the size of the sampling). These two quantities can be estimated by performing two separate accuracy measurements. In the experiments discussed above (i.e., Experiments 1 and 2), in which the total number of dots composing the stimulus was set to $K = 400$, the first and second experiments were performed by varying P and evaluating the coherence threshold that results in a 'low' accuracy. The third experiment was performed instead by simply evaluating the accuracy corresponding to a fully coherent stimulus (i.e.,. In particular, in order to evaluate $f_{\max}$), observers performed the same task as reported for Experiments 1 and 2, but the RDK coherence was set at maximum. Note that the paradigm is conceptually equivalent to that used by Refs. [27,29], making use of two highly informative data points with orthogonal confidence intervals.

As aforementioned, experimental constraints forced us to perform the two experiments (1 and 2) on different groups of participants. Therefore, instead of estimating the pair of parameters pertaining to each participant, we had to compute the average and standard deviation of accuracies and coherence thresholds from the experiments, and then estimate the parameters. Such procedure entailed the insurgence of an additional source of uncertainty, due to the distribution of low accuracies $f*$. More in detail, we first computed the averages $\overline{P*}$, and $\overline{f}_{\max}$, which were used to compute the average sampling size $\overline{n}_{samp}$ by inverting Eq. (8). Then we computed the standard deviations σ_{P*}, and, related to the sampling size uncertainty by the propagation formula

$$\sigma_{n_{samp}} = \frac{\sqrt{\sigma_{f*}^2 + \left(\frac{\partial f}{\partial P}\right)^2 \sigma_{P*}^2 + \left(\frac{\partial f}{\partial f_{\max}}\right)^2 \sigma_{f_{\max}}^2}}{\frac{\partial f}{\partial_{n_{samp}}}} \tag{9}$$

Results

The results are summarized in Table 3. The lower bounds of some uncertainty intervals for were forced to the positive semi-axis because the parameterization of Eq. (8) only holds for positive values of. In fact, it is clearly impossible to extract any signal from a sample of non-positive size. In particular, an observer with $n_{samp} =$ 0 represents a completely random responder.

From Table 3 it is evident that the standard errors associated to the $\overline{f}_{\max}$ parameter are smaller than the standard errors associated

to the other parameters, a result that allowed us to consider a small number of participants in Experiment 3. Moreover, from Table 3 it is also evident that only the sampling size of hf-tRNS at 1.5 mA and 2.25 mA differ from the Sham condition, but not $\bar{f}_{max}$. Fig. 5 shows the dependence of the accuracy on the coherence, for each current intensity and stimulation type. It also shows means and standard errors of the two input data points. The curves related to the 1.5 mA stimulation (Fig. 5A) and the curves related to the 2.25 mA stimulation (Fig. 5B) show a significant difference between the coherence-to-accuracy dependences of hf-tRNS (red curve) and Sham (blue curve), with hf-tRNS significantly increasing sampling size in the case of 1.5 mA stimulation, and significantly decreasing sampling size in the case of 2.25 mA stimulation. Statistical significance can be inferred by the lack of overlapping between the two curves.

General discussion

In the present study, we compared the effects of different hf-tRNS intensities on performance in a global motion direction discrimination task and assessed if its neuromodulatory mechanisms can be explained within the stochastic resonance framework. Overall, the results showed that when an optimal level of hf-tRNS is applied bilaterally over the area hMT$^+$ motion direction discrimination performance is enhanced, whereas if a lower or higher level of current stimulation is used, this has a detrimental effect on performance. It has been suggested that due to its electrical parameters and its non-focal action at the neural level, tRNS might induce random activity at the neural level (i.e., neural noise) [1,11,54]. If this is the case, then different intensities of hf-tRNS should also correspond to different levels of injected noise. Noise is a critical component in the stochastic resonance phenomenon. In a non-linear systems, like the brain, the addition of external noise can push a weak signal over the sensory threshold and evoke a positive response in the nervous system [19,21,30,55–57]. The results of Experiments 1A and 1B showed that if a stimulus was presented near threshold (i.e., at a motion coherence level producing 60% correct responses in direction discrimination), hf-tRNS applied at 0.5 mA and 0.75 mA had no effect and performance did not differ from either a No-tRNS condition or a Sham condition at 1.5 mA.

However, intensities at 1.0 and 1.5 mA induced a significant increment with respect to the baseline level of 60% of correct discrimination and the No-tRNS condition. Importantly, hf-tRNS at 1.5 mA significantly boosted global motion discrimination when compared to Sham stimulation at 1.5 mA.

The mean percentage increase in accuracy with respect to the No-tRNS condition was 8.57% (SD = 9.66%) for the 1.0 mA and 7.18% (SD = 4.73%) for the 1.5 mA. Although hf-tRNS at 1.0 mA resulted in a higher percentage change and a slightly higher accuracy performance, it also had higher variability with a standard deviation that was almost twice the standard deviation for hf-tRNS at 1.5 mA. Therefore, we considered the hf-tRNS at 1.5 mA to be the optimal stimulation level.

The results partially replicated those of our previous study [27] in which the application of hf-tRNS at 1.5 mA over the left-hMT$^+$ decreased global motion coherence thresholds with respect to the Sham condition and selectively for the visual hemi-filed contralateral to the stimulation site. Though the results from Experiment 1A are in line with the stochastic resonance framework, this theory also affirms that if an excessive amount of noise is added to the signal, it can degrade the information content [17,18,58]. In agreement with this prediction, the results of Experiment 2 showed that when hf-tRNS at 2.25 mA was applied, direction discrimination performance was impaired with respect to both the 60% of correct response in the No-tRNS condition and the Sham condition at 2.25 mA. Thus, in agreement with the stochastic resonance phenomenon, our results showed that when a visual stimulus is presented near threshold, excessive external noise affected global motion direction discrimination. Overall, these findings on motion discrimination are consistent with those of van der Groen and Wenderoth [6] on contrast detection. The authors showed that amongst a range of hf-tRNS intensities from 0.0 to 1.5 mA, hf-tRNS at 1.0 mA was the optimal stimulation level in order to improve contrast detection performance with near-threshold stimuli. The modulation obtained with the hf-tRNS was also comparable to the results showed in a second condition in which visual noise was added to the stimulus. Our study partially replicated but also significantly extended the findings of van der Groen and Wenderoth [6]. In particular, we found that the same mechanism of stochastic resonance applies not only to contrast detection tasks [6] but also to motion direction discrimination while stimulating more lateralized visual areas such as hMT$^+$. We argue that this finding points to the stochastic resonance phenomenon as a more general mechanism of action of hf-tRNS in the visual cortex, regardless the type of the task.

Moreover, in a subsequent study van der Groen and Wenderoth [31] investigated whether decision making is sensitive to the

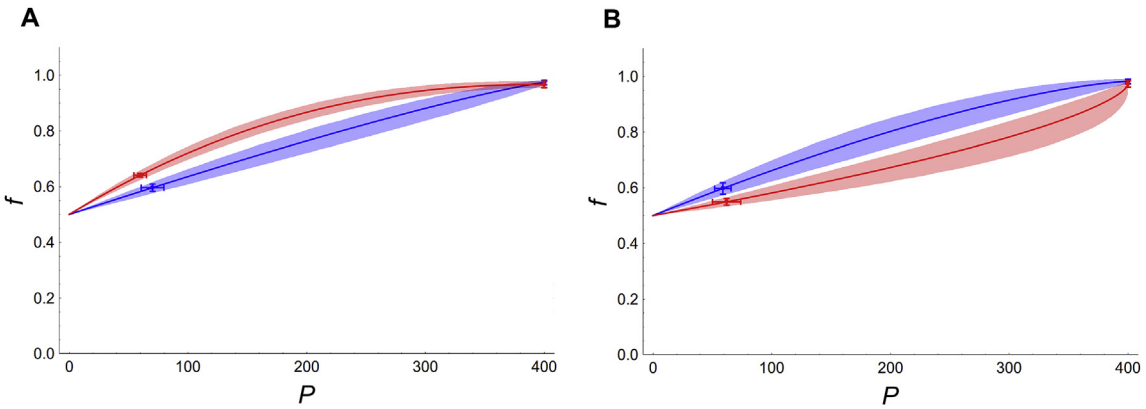

Fig. 5. Confidence regions of the accuracy as a function of the number of coherent points. (A) Individual plots refer to the 1.5 mA Sham (blue curve) and the 1.5 mA hf-tRNS (red curve). (B) 2.25 mA Sham (blue curve) and 2.25 mA hf-tRNS (red curve). Error bars ±SEM. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

stochastic resonance phenomenon. Fitting data using the drift diffusion model [59–61] the authors showed that adding noise via bilateral hf-tRNS while participants were judging direction of coherent motion, stimulation could increase perceptual decision. Specifically, the authors found that hf-tRNS could enhance the drift rate, related to the speed and efficiency of information processing. Discrepancies in the optimal hf-tRNS intensities between our study and van der Groen and colleagues [6,31] might be explained in terms of differences in the stimulation paradigm, type of task and the visual area stimulated. It has been demonstrated that differences in electrodes montage lead to variability in the direction in which the current reaches the layers in the cortex and consequently how neurons are affected [4]. Moreover, differences in the stimulation paradigm, such as the stimulation period, can lead to different outcomes. For example, while in our study stimulation was delivered at one single intensity for the entire stimulation session (approximately 20 min), van der Groen and colleagues applied different stimulation paradigms in which either the same stimulation intensity was applied for 20 trials followed by 20 trials of no stimulation [31], or stimulation intensities were randomized within the stimulation session, and delivered at repeated short stimulation intervals of 2 s [6].

Global motion processing is thought to involve the integration of local motion cues in higher visual areas, particularly hMT^{+} [26]. In order to further assess how hf-tRNS-induced stochastic resonance could modulate the mechanisms underlying global motion processing, we implemented an Equivalent Noise (EN) analysis similar to that used in previous studies [26,27,29,62]. According to EN, visual motion integration relies on two factors: *internal noise* and *sampling* [26,63]. While *internal noise* would influence the precision with which each dot's direction can be estimated, *sampling* determines the number of dots involved in the computation of coherent direction. Therefore, as already stated in the introduction section, variations in the effectiveness of the signal perception with respect to variations of the signal coherence would be encoded by variations of the *sampling*, while leaving *internal noise* unaffected. In fact, the EN analysis revealed that hf-tRNS at 1.5 mA induced an increment in *sampling*; that is, higher direction discrimination accuracy can be achieved by integrating less coherently moving dots (see Fig. 5A). This result is also consistent with our previous results [27]. It is possible to assume that values of *sampling* might be associated to the intensity in which neurons signal motion direction [63]. In this scenario, we argue that if random noise stimulation increases the activity of neurons near the firing threshold and synchronize their activity through a non-linear amplification of subthreshold oscillatory activity [11,24,27,64], it also would result in an incremented *sampling*. The significant difference in *sampling* between hf-tRNS at 1.5 mA and Sham stimulation at 1.5 mA supports this hypothesis. The same EN analysis also revealed that when hf-tRNS at 2.25 mA was delivered, *sampling* significantly decreased with respect to the Sham stimulation at 2.25 mA; that is, even the presentation of a large amount of dots globally moving in the same direction produced low direction discrimination accuracy (see Fig. 5B). Therefore, one can speculate that if excessive external noise is applied to the system, it could increase the activity of neurons coding for different directions with respect to the coherent signal, thus hindering *sampling*. Overall, these results further support the hypothesis that a stochastic resonance phenomenon underlies the effects of hf-tRNS. Additionally, it should be noted that, similarly to our previous study [27], we did not find changes in the amount of *internal noise* due to the stimulation. *Internal noise* could be linked to neural the bandwidth of motion direction selectivity [63]. It is possible that while hf-tRNS is able to modulate neural excitability and firing rate, it does not alter the direction selectivity bandwidth of single neurons. Stochastic resonance results from the combination of a threshold, a subthreshold stimulus and noise [17]. Thus if a suprathreshold signal is used, the injection of additional noise should have no or little impact on the signal. This is in agreement with the previous findings of van der Groen and Wenderoth [6] and the results of our Experiment 3; that is, when a suprathreshold stimulus is used then hf-tRNS at 1.5 mA or 2.25 mA did not produce any significant performance improvement or decrement. It should be noted that in our case the suprathreshold stimulus was a moving pattern with 100% coherence.

Recent findings on hf-tRNS have highlighted the notion that generalization of results should be done with caution and that more attention is needed to selection of stimulation parameters for replicability [65,66]. These suggestions are legitimate also considering that in the last decade the use of non-invasive transcranial brain stimulation in clinical settings has grown exponentially. At the current stage, there is still little evidence about hf-tRNS mechanisms of action, and how stimulation effects can be influenced by parameters such as stimulation intensity, stimulation duration, electrode position and individual differences. For instance, we focused on stimulation intensity, and hf-tRNS at 1.5 mA was found to be the “optimal” current intensity boosting performance in a motion direction discrimination task performed near threshold. However, improvements were not limited to this condition, but also when delivering hf-tRNS at 1.0 mA. Our results are also in agreement with those of van der Groen and Wenderoth [6] in showing some degree of variability amongst participants on the optimal stimulation intensity.

In conclusion, our results support the notion that certain hf-tRNS effects on psychophysical performance are mediated by a stochastic resonance mechanism. Specifically, we showed that when an optimal level of external noise is injected into the system, the signal-to-noise ratio is increased with a consequent improvement in direction discrimination. On the other hand, when a suboptimal level of external noise is used, performance is largely affected. Using an Equivalent Noise analysis, we demonstrated that *sampling*, the number of directional signals integrated in the global motion display, is modulated by hf-tRNS in a way that is compatible with stochastic resonance. Single cell recording studies are necessary, in order to test whether these conclusions are borne out at the neural level.

Conflicts of interest

The authors declare that they have no competing financial interests.

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