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Cognitive Exergame Training and Transcranial Random Noise Stimulation Effects on Executive Control in Healthy Young Adults

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Objective: In the present study, we investigated the efficacy of transcranial random noise stimulation (tRNS) combined with an exergame training (physical exercise combined with a videogame) chosen as potential techniques to boost brain functioning and to promote plastic effects in healthy young adults. The aim was to improve the motor response speed and the response time when inhibition was required. ***Method:*** Forty-nine participants were randomly assigned to four conditions. The protocol consisted of eight sessions of exergame cognitive training (or no training) associated with the active or sham stimulation of the left dorsolateral prefrontal cortex (left-DLPFC). ***Results:*** The results indicated faster simple reaction times following the exergame training, and faster reaction times in Go trials (while the ratio of NoGo trials remained unaltered) following tRNS. No interactions were present between the two procedures. ***Conclusions:*** These findings reveal better performance in both tasks with independent effects of the two techniques. Using noninvasive brain stimulation and exergame training may be a viable strategy to increase motor response speed and improve executive control.

Key Points

Question: Is it feasible to boost processing speed and inhibitory control using an adaptive cognitive game training and tRNS, either independently or combined, in healthy young adults? ***Findings:*** Eight sessions of hf-tRNS on the left-DLPFC improves executive control, while exergame training makes responders faster in a Simple Reaction Time task; no interaction was found between hf-tRNS and training effects. ***Importance:*** The absence of side effects, even with prolonged use, of noninvasive electrical stimulation and the user-friendliness of exergames, make them viable techniques for clinical practice. One example of this may be as potential adjuncts to rehabilitation training. ***Next Steps:*** Future studies may explore the cognitive and motor benefits of using these techniques, not only in clinical populations, but also as preventative means in an aging population.

Keywords: executive control, inhibition, high-frequency transcranial random noise stimulation (hf-tRNS), dorsolateral prefrontal cortex (DLPFC), exergame training

During the last 20 years, the use of the so-called "brain games" captured the interest of many researchers because of their beneficial effects on cognition and behavior (Palaus et al., 2017; Green and Seitz, 2015), and because of the structural changes they may induce in the brain (Momi et al., 2018, 2019). Playing brain games includes complex cognitive demands, and recent studies have found that training based on brain games, can significantly improve abilities in cognition and perception (Achtman et al., 2008; Green & Bavelier, 2008; Maillot et al., 2012).

Recently, a particular type of activity called "exergame" has been developed. Exergames ("exer," exercise, and "game," gaming) require the user to interact with the game by using the whole body. Exergames differ from action video games, which usually focus on combat, hand-eye coordination, and reaction time. Action video games are sedentary gaming, for instance, first-person shooters video game, and thus do not involve much physical involvement. Wii, Playstation, and Xbox are consoles that offer several types of exergames. The advantages of exergame training are not

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restricted to the physical benefits associated with physical activity (Siegel et al., 2009) or to the cognitive benefits of more traditional videogames (Best, 2013; Green & Bavelier, 2003), rather, they are extended to the combination of applying both (Eggenberger et al., 2015). In fact, physical activity has been shown to contribute to improving cognitive functions (Kramer & Erickson, 2007) such as cognitive control of attention (Hillman et al., 2009) and executive control (Staiano et al., 2010). Exergames are also associated with high levels of appreciation and compliance (Maillot et al., 2012). Moreover, studies with adult participants reported that a moderate level of physical activity increased short-term plasticity in the visual cortex (Lunghi & Sale, 2015) and improved cognition in the elderly (Hughes et al., 2009); although other studies did not support these findings (Campana et al., 2020).

A recent review article highlighted the growing use of exergames for rehabilitation, for instance, in people with multiple sclerosis (MS; Taylor & Griffin, 2015). De Giglio et al. (2015), used "Dr. Kawashima's Brain Training" (DKBT; Nintendo, Kyoto, Japan) with patients with MS. Results indicated improved performance in information processing speed, executive functions, and some aspects of quality of life (De Giglio et al., 2015). Interestingly, results were found with the same video game in healthy young adults, with obtained improvements in executive functions, working memory, and processing speed (Nouchi et al., 2013). In an elderly population sample, a beneficial effect in cognitive functions (e.g., executive functions and processing speed) has also been observed (Nouchi et al., 2012).

Other recent studies investigated the effects of action video games on several tasks involving perception, cognition (Momi et al., 2018), and motor skills. Results indicated significantly enhanced effects in the tasks directly related to the functions trained (Green & Bavelier, 2008). Furthermore, a neuroimaging study showed consistent findings in structural modifications of the brain related to video game playing: after 30 hr of action game training, structural brain changes associated with perceptual processes and attention were found, with long-lasting cortical thickness modifications of up to 3 months (Momi et al., 2018). Similarly, Kühn et al. (2014), found a positive correlation between the cortical thickness of left-DLPFC and left-FEFs and video game training length (Kühn et al., 2014). In a recent study, Nouchi et al. (2020) measured brain activity during the training games using NIRS before the intervention, and observed that brain activations at the DLPFC during Brain Training were associated with improved processing speed and inhibition performance.

In the present study, the exergame "Dr. Kawashima's Body and Brain Exercises" was chosen. This game is aspecific and it taps several cognitive functions, such as executive functions, processing speed, working memory, as well as motor functions, all combined in complex cognitive tasks. The game uses an adaptive approach, that is, the person is progressively pushed to work at his/her best. This adaptive approach limits the frustration/boredom of the participant because s/he does not face levels that are too difficult or too easy. The game provides visual and auditory feedback, which also acts as powerful motivators. The emphasis was on how the exergame training may affect executive control, behavioral inhibition, and processing speed which, as stated in Salthouse (1996), is assumed to represent how quickly many different types of processing operations can be carried out (Salthouse, 1996).

Cognitive control includes planning, execution, monitoring, and inhibition, the so-called executive functions (EF), which are associated with the prefrontal cortex activation (PFC), specifically with the dorsolateral prefrontal cortex (DLPFC; see Hoshi, 2006; Mazzucchi, 2012; Miller & Cohen, 2001; Miller et al., 2002; Wessel, 2018). This region has many extrinsic and intrinsic connections with several regions such as the supplementary motor area (SMA) and the presupplementary motor area (pre-SMA; Picard & Strick, 2001), the frontal eye field (FEF), and the posterior parietal associative cortices; most of these connections are reciprocal and may explain its top-down regulation role on information processing (Koechlin et al., 2003; MacDonald et al., 2000). Nouchi et al. (2020) observed an association between left-DLPFC activation during cognitive training at baseline, with improvements in inhibition and processing speed. Many studies marked the DLPFC for its involvement in cognitive control processes such as motor planning, organization, regulation (Grier, 2005), and control inhibition (Wessel, 2018) and the connection with the pre-SMA is particularly relevant when a suitable response or the inhibition of an inappropriate one is requested (Simmonds et al., 2008).

Response inhibition or inhibitory control is an executive function, which involves controlling one's attention, behavior, thoughts, and/or emotions to override a strong internal predisposition or external lure (Diamond, 2013). There are a number of psychological tasks that are used to measure inhibitory control including, for example, the Stroop task, Simon task, and Flanker task, among others (Diamond, 2013). Another prominently used measure is the Go/No-go task. In these tasks, participants are usually required to perform a quick motor response (e.g., pressing a button on a keyboard as fast as possible) when certain stimuli (i.e., targets) are displayed on a screen (Go-trials). Participants must withhold this reaction for other stimuli (i.e., nontargets; also called distractors or lures—NoGo-trials). In light of the strong inhibitory control involvement elicited by Go-NoGo tasks, this paradigm was chosen for the present study's exergame training. Precisely, a Go/NoGo task was created, with 80% frequency of Go-trials (Go) which emphasizes a prepotent tendency to respond and consequently inhibit the action when a NoGo-trial (NoGo) appears (Wessel, 2018; Wright et al., 2014).

Brain plasticity is the basis of learning and it depends on the connections among different neural populations. Noninvasive brain stimulation (NIBS) may be one way to contribute to the cortical changes to boost the learning rate. Transcranial electrical stimulation can modulate neural activity and modify the connection strength among neurons (Fertonani et al., 2011; Mulquiney et al., 2011; Snowball et al., 2013; Terney et al., 2008). Multiple studies used transcranial stimulation targeting DLPFC using different montages to investigate the inhibitory control mainly using the Go/NoGo task. A recent review by Brevet-Aeby et al. (2016), offered an extensive overview of NIBS techniques to investigate the relationship between the prefrontal cortex and impulsivity that is strictly related to executive control (Brevet-Aeby et al., 2016).

Many studies have investigated the effects of a direct current stimulation protocol when delivered over the DLPFC in relation to cognitive control. Nelson et al. (2014) showed that 10 min of bilateral tDCS over DLPFC (anode on left-DLPFC) during the first 10 min of an air traffic control task, was sufficient to result in increased target identification. In the same study, false alarms (FAs) diminished in case of both left- or right-DLPFC sides, when the stimulation was delivered during the last 10 min (Nelson et al., 2014). Beeli et al. (2008) reported a differential effect between anodal and cathodal stimulation in the number of FAs with the cathode placed over the right-DLPFC and the anode on the ipsilateral mastoid. A significant increase of FAs in a Go/NoGo task was obtained with cathodal stimulation, while no changes were found for anodal or Sham conditions. The administration of anodal tDCS or Sham stimulation over the left-DLPFC resulted in decreased reaction times in the Sternberg test for the high-interference probe (Working memory task in which the incorrect word had a 50% chance of having been used as a secondary task stimulus in the current trial) for the anodal tDCS condition only (Gladwin et al., 2012). In contrast, Soltaninejad et al. (2019) investigated the potential improvement of inhibitory control in adolescents with ADHD symptoms and observed an increase of the inhibition accuracy only when the left-DLPFC was stimulated with cathodal tDCS. No changes were observed following Sham stimulation.

Few studies have investigated the potential benefits of transcranial random noise stimulation (tRNS) (see Table 1). The advantage of tRNS over tDCS is that, while the latter allows neurons to counteract the induced changes in membrane potentials, the former, being an oscillatory type of stimulation, does not permit homeostasis of the neural system. In fact, tRNS has been shown to be more efficacious than tDCS in perceptual learning tasks (Fertonani et al., 2011; Pirulli et al., 2013), and the mechanisms of action of tRNS seem to be different from those involved in tDCS. At a neuronal level, while the increase in cortical excitability due to tDCS seems to rely on a modulation of NMDA receptors, thus increasing the amount of intracellular calcium (Liebetanz et al., 2002; Nitsche et al., 2003), the increase of cortical excitability brought about by tRNS seems to rely on sodium channels (Chaieb et al., 2015). More precisely, tRNS produces faster reopening of sodium channels, affecting both peak latency and amplitude of the inward sodium ions, thus facilitating the membrane's depolarization (Fertonani et al., 2011; Remedios et al., 2019; Schoen & Fromherz, 2008).

Newly, Brevet-Aeby et al. (2019) investigated the effect of tRNS with 1 mA offset, comparing 20 min of three consecutive sessions, separated by 30 min, of active tRNS (3 A), with one active and two Sham (1A2S) and three Sham (3S) tRNS conditions. The target area was the bilateral-DLPFC with the anode (referred to 1 mA offset) over the left-DLPFC. The aim was to investigate inhibitory control in healthy subjects. They found a decrease of reaction times in the Go-trials, just in the 3 A condition as compared to Sham (Brevet-Aeby et al., 2019). This result indicates that tRNS was able to boost the response execution after three consecutive active sessions, with no effect of a single session (1A2S). In this study, high-frequency tRNS (hf-tRNS) was used, which in addition to being the most recent technique, has shown encouraging results. Terney et al. (2008) found a consistent increment in cortical excitability after 10 min of hf-tRNS (but no effect of low-frequency tRNS, lf-tRNS) lasting up to 1 hr. In line with this result, the whole high-frequency band has been confirmed to be the most effective in enhancing cortical excitability, when compared to the narrower high-frequency bands (Moret et al., 2019). The efficacy of the high-frequency band has also been displayed in combination with perceptual training. Fertonani and colleagues (Fertonani et al., 2011; Pirulli et al., 2013) found that when stimulating the occipital cortex with hf-tRNS, an increase in performance in a perceptual learning task was obtained. In the same way, stimulation of the visual cortex with hf-tRNS combined with perceptual training was effective in improving visual functions, specifically visual acuity and contrast sensitivity in people with mild myopia (Camilleri et al., 2014, 2016). Similarly, in a cohort of adults with amblyopia, Moret and colleagues (Campana et al., 2014; Moret et al., 2018) found that eight sessions of hf-tRNS applied over the primary visual cortex (V1), combined with a contrast sensitivity training, led to significant improvements not only in contrast sensitivity but also in visual acuity, a visual function not directly trained. Finally, a recent study, revealed that tRNS, but not a-tDCS, when coupled with visual training, reduced the training period from months to weeks and led to fast improvement in patients with cortical blindness (Herpich et al., 2019).

Only a few studies combined cognitive training with tRNS on the DLPFC (Santarnecchi et al., 2015). Prichard et al. (2014) investigated different stimulation protocols, specifically tDCS and tRNS, on M1 unilaterally and bilaterally. They demonstrated a different time interaction with a motor training on a tracing task over 3 consecutive days while showing the beneficial effects of the stimulation in enhancing motor skill learning when compared to Sham stimulation (Prichard et al., 2014). In another study, 5 days of cognitive training were coupled with tRNS applied on the bilateral-DLPFC, showing a behavioral improvement in calculation speed and memory-recall-based arithmetic learning, with a long-term enhancement associated with hemodynamic responses specifically within the left-DLPFC (Snowball et al., 2013). Brem et al. (2018) investigated the possibility of a transfer effect, comparing four stimulation protocols tRNS, tDCS, multifocal tDCS, and multifocal tACS combined with nine sessions of 30 min of gamified tasks on executive functions including working memory, inhibition, and cognitive flexibility training. All the stimulation protocols, apart from the multifocal tACS, showed far transfer effects to fluid intelligence (Gf) (Brem et al., 2018). In another study, Cappelletti et al. (2013) coupled tRNS, targeting distinct brain areas, with intense cognitive training, obtaining a long-term improvement in a trained numerosity discrimination task. Importantly, the best outcome was achieved by the group trained with the stimulation targeting the parietal lobes, regions critical for quantifying processing. Additionally, they showed an improvement in time- and space-discrimination and cognitive skills untrained, indicating that a generalized transfer occurred (Cappelletti et al., 2013).

A summary table that includes the ones relevant for this study design was created (Table 1).

In light of the results of the aforementioned studies, the present study used a tRNS protocol since it appears to prevent homeostasis at the neural level and it shows promising results when combined with cognitive training (Brem et al., 2018; Cappelletti et al., 2013; Prichard et al., 2014; Snowball et al., 2013); the entire high-frequency band was selected because it induced a more significant increase in cortical excitability (Moret et al., 2019). Moreover, "Dr. Kawashima's: Body and Brain Exercises" was chosen for its feature of being a cognitive game: it trains in an adaptive

Table 1
Summary of Characteristics and Findings of the Cited Studies Using tES

Study	Type of stimulation and target regions	Stimulation parameters (intensity, duration, electrodes size)	Sample number experimental/ training tasks or assessment	Outcome measures
tDCS studies				
Beeli et al. (2008)	C-, a-tDCS right DLPFC (FC3) Ref. ipsilateral mastoid Sham	1 mA 5 min online 35 cm^2	35 (17 F) Watching a virtual roller coaster ride	Increase of the FAs in a Go/NoGo task was obtained with the cathodal stimulation while no changes were found for the anodal- or Sham stimulations.
Gladwin et al. (2012)	A-tDCS left-DLPFC C-tDCS right orbit Sham	1 mA 10 min offline 35 cm^2	14 (8 F) Sternberg task (9 blocks of 24 trials); high- and low-interference	Decreased reaction times only in high-interference condition, compared to Sham stimulation.
Nelson et al. (2014)	TDCS DLPFC bilaterally	1 mA 10 min online 35 cm^2	10 (early stimulation) 9 (late stimulation) Air traffic control task	More targets identified when the anode was placed on the left-DLPFC (the stimulation was delivered at the beginning of the task). FAs diminished in case of both left- or right-DLPFC sides, (the stimulation delivered the last 10 min).
Soltaninejad et al. (2019)	A-, c-tDCS left-DLPFC–right-SO (F3 and FP2) Sham	1.5 mA 15 min offline 35 cm^2	20 students with ADHD symptoms Go/NoGo task Stroop task	Increase of the inhibition accuracy was found in comparison with Sham.
tRNS studies				
Terney et al. (2008)	TRNS premotor cortex (2.5 cm anterior from the motor cortex)–CO Sham	1 mA 0.1–100 Hz 101–640 Hz 10 min offline 16 cm^2 (target) Current density:0.0625 mA/cm^2 84 cm^2 (reference)	80 (48 F) Motor learning task MEPs amplitude	Only high-frequency tRNS induced consistent excitability increases lasting 1 hr after stimulation.
tRNS studies				
Brevet-Aeby et al. (2019)	TRNS F4–F3 Sham	2 mA 100–500 Hz 1 mA offset 20 min 35 cm^2	33 (16 F) Three consecutive sessions of active tRNS (3 A), 1 active and 2 Sham (1A2S) and 3 Sham (3S); separated by 30 min Inhibitory control assessment	Decrease of reaction times in the Go-trials, just in 3 A condition as compared to Sham; no effect of a single session (1A2S).
Moret et al. (2019)	TRNS M1–CO Sham	1.5 mA 100–400 Hz 400–700 Hz 100–700 Hz 25 min offline 16 cm^2, 60 cm^2 (ref) Current density: 0.09 mA/cm^2	14 F MEPs amplitude	Only 100–700 Hz frequency band tRNS enhances excitability lasting 20 min after stimulation.
tRNS and tDCS +training studies				
Cappelletti et al. (2013)	TRNS P3–P4 TRNS C3–C4	20 min online 1 mA 0–250 Hz 35 cm^2	40 (22 F) 5 consecutive days of parietal or motor tRNS + numerosity discrimination training or stimulation/training only	33% improvement in the discrimination task when training + tRNS over P3–P4, brain areas critical for numerosity discrimination. A much smaller effect when stimulation was not associated with cognitive training, when cognitive training was not associated with brain stimulation, or when training was coupled with stimulation to a control region (motor areas). The optimal training design was training + parietal tRNS, showing a long-lasting effect up to 16 weeks after training. In contrast, training with no stimulation showed no such maintenance of learning.

Table 1 (*continued*)

Study	Type of stimulation and target regions	Stimulation parameters (intensity, duration, electrodes size)	Sample number experimental/ training tasks or assessment	Outcome measures
tRNS and tDCS + training studies				
Snowball et al. (2013)	TRNS F3–F4 Sham	20 min online 100–600 Hz 25 cm^2	25 (12 F) 5 consecutive days of tRNS + arithmetic training: calculation and drill	Five consecutive days of tRNS-cognitive training enhanced the speed of both calculation- and memory-recall-based arithmetic learning. Defined hemodynamic responses were consistent with more efficient neurovascular coupling within the left DLPFC. Six months after training revealed long-lasting behavioral and physiological modifications in the stimulated group relative to Sham.
Prichard et al. (2014)	TDCS M1–SO TDCS M1–M1 TRNS M1–SO TRNS T6–SO Sham	20 min online 1 mA 100–640 Hz 16 cm^2 Current density:0.0625 mA/cm^2	91 (25 F) Tracing task over the first 3 days	TDCS (M1-SO) and tRNS (M1-SO) enhanced motor skill learning compared to sham stimulation. In all groups, this appeared to be driven by online effects without an additional offline effect. tDCS (M1-SO) resulted in large skill gains immediately following the onset of stimulation, while tRNS (M1-SO) exerted more gradual effects. Control stimulation tRNS (T6-SO) did not enhance skill learning relative to Sham.
Brem et al. (2018)	MftDCS a-F3, c-Fz, a-F4, c-T7, c-T8, a-P3, a-P4, c-Oz MftACS F3, Fz, F4, PO7, PO8, P3, P4 TDCS a-F3, c-AF8 tRNS F3-F4	MftDCS 2.7 mA 20 min MftACS 2.7 mA 40 Hz, 20 min TRNS 1 mA 100–500 Hz 20 min TDCS 2.5 mA 20 min Online (all) Pi-electrodes (3.14 cm^2)	80 (36 F) Nine sessions of stimulation combined with cognitive gamified training	Greater improvements in fluid intelligence (Gf) for tRNS, tDCS, and multifocal tDCS (mftDCS) protocols compared to no-contact control group; mftACS did not demonstrate similar benefits.

Note. Main results of the studies investigating the effects of tDCS and tRNS on cognitive functions underlying inhibition process with and without a combined cognitive training and/or the change in cortical excitability due to the stimulation. TDCS = transcranial direct current stimulation; A-tDCS = anoldal-tDCS; C-tDCS = cathodal-tDCS; DLPFC = dorsolateral prefrontal cortex; FAs = false alarms; ADHD = attention deficit hyperactivity disorder; tRNS = transcranial random noise stimulation; MEPs = motor evoked potentials; MftDCS = multifocal tDCS; MftACS = multifocal transcranial alternating current stimulation; CO = contralateral orbit SO = supraorbital; FC3, F3, Fz, F4, FP2, M1, T6, T7, T8, P3, P4, Oz, PO7, PO8, P3, P4, AF8 = cerebral location of international 10–20 system electrode placement.

procedure, it increases compliance, and it requires the use of the whole body, therefore it stimulates the motor system.

The aim consisted of evaluating the effectiveness of the exergame, “Dr. Kawashima’s: Body and Brain Exercises,” and the potential effects of the stimulation protocol chosen. Any benefits of tRNS when associated with this exergame in improving executive control response, precisely the motor and cognitive processing speed and the inhibitory response were also explored. Finally, the present study seeks to determine whether any individual effects are elicited due to the potential synergistic effects resulting from the interaction between the stimulation and the training.

An improvement in reaction times was expected, in both Simple Reaction Time task and Go/NoGo task, as well as a reduction in FAs, especially in the stimulation conditions. Moreover, since tRNS seems to boost the effect in conjunction with training, a better performance in the group which received both training and real stimulation was expected.

Method

Participants

Forty-nine young healthy adults took part in this study and gave written informed consent according to the Declaration of Helsinki. All participants were assessed for stimulation contraindications (Rossi et al., 2009) by means of a specific questionnaire. Because the experimental design involved the use of the entire body to perform the training, motor difficulties were considered an exclusion criterion. Participants were randomly assigned to one of the four conditions (see Table 2): Sham stimulation + training (S_T), active stimulation + training (A_T), active stimulation with no training (A_NT), or control (C).

Table 2
Characteristics of the Participants for Each Condition

		Age		Education	
Group	*N*	*M*	*SD*	*M*	*SD*
S_T	12 (4 M)	23.8	4.5	16.6	2.3
A_T	12 (4 M)	25.6	7.3	17.3	1.9
A_NT	12 (4 M)	23.8	4.0	17.8	2.7
C	13 (4 M)	21.1	2.2	15.1	2.0

Note. *M* = mean; *SD* = standard deviation; S_T = Sham stimulation + training; A_T = active stimulation + training; A_NT = active stimulation with no-training; C = control; M = male.

Apparatus

To perform the assessment tasks, stimuli were generated and responses were collected, using Psychotoolbox 3.0 and Matlab R2014a (8.3), and were displayed on a Hp p1230 screen with 1280 × 1024 resolution. Manual responses were given by pressing the spacebar on a standard computer keyboard. Viewing distance was 57 cm. The laboratory was equipped with an Xbox 360 and a Kinect device that has a depth sensor camera capable of detecting the movement of the person. Cognitive exercises of the exergame "Dr. Kawashima's Body and Brain Exercises" were carried out using a 40" liquid-crystal display (Samsung UE40K5510AKXZT) with a 1920 × 1980 resolution. Viewing distance was approximately 2 m. For tRNS, a battery-driven stimulator (BrainSTIM, EMS) and two electrodes, 4x4 cm size, and a nonelastic bandage to hold them were used. The stimulator was placed inside a pouch tied at the waist and placed on the back of the participant.

Assessment

The participants were required to perform two tasks: a Simple Reaction Time (sRT) task and a Go/No-Go task. sRT task consisted in pressing as quickly as possible the keyboard spacebar whenever a blue rectangle (2.5 × 5°, R0 G0 B255) appeared in the centre of a grey screen (R128 G128 B128). To assist the participant in keeping the attention to the right position, a white fixation cross appeared for 200 ms immediately before the target. The interstimulus interval (ISI) was set as 0.8 s, plus a random interval ranging 0.0 s–0.8 s, to avoid automatic responses. The stimulus timeout was set at 2 s. During sRT task, 40 consecutive trials were presented.

The Go-NoGo task had the same parameters but consisted of two stimuli: a blue rectangle, the Go stimulus, which required the subject to respond as quickly as possible, and a red rectangle (R255 G0 B0), the NoGo stimulus; in this case, the participant was asked to inhibit the motor action. The total trials were 50 stimuli, 40 Go trials (80%) and 10 NoGo trials (20%), to evoke a prepotent motor response, and consequently an inhibitory control requirement (Wessel, 2018).

Transcranial Random Noise Stimulation

The stimulation protocol was set at high-frequency (100–640 Hz) random noise for 25 min with a current intensity of 1.5 mA and 0 mA offset. The current linearly increased in intensity up to 1.5 mA during the first 30 s of stimulation. The current density was 0.09 mA/cm^2, within the safety limits (i.e., below 0.1 mA/cm^2) (Poreisz et al., 2007). In the Sham condition, the current linearly increased for the first 30 s up to 1.5 mA and then decreased to 0 mA the next 30 s. The current was delivered using a pair of rubber electrodes covered by sponges soaked in saline solution. The electrodes were 16 cm^2 large, positioned above the left-DLPFC and the V1 both localized according to the 10–20 EEG system.

Exergame Training

The exergame "Dr. Kawashima's Body and Brain Exercises" is a sensory-cognitive-motor game training consisting of an interactive video game-based cognitive exercise. The Kinect sensors detect position and timing information and create the physical image on the screen. This exergame includes 20 unique games, ranging from math, logic, reflex, and memory, all physical-related exercises using the full-motion abilities. Each activity focuses on a specific cognitive function such as working memory, reaction times, processing speed, and executive functions, besides requiring motor planning and execution. Each game includes three difficulty levels, and in each level the difficulty increases depending on the outcome so that the difficulty of the game is adjusted to match the player's ability. The players could track their daily progress. One of the most crucial features of this exergame is the time available to perform a task: to complete a task the maximum time available is fixed, and the sooner an activity is performed, the higher is the result obtained, and consequently, the level reached. This was thought to induce the participant to become more efficient in less time. Ten activities have been chosen to train processing speed, reaction times, and inhibition, besides requiring motor planning and attention, specifically in this order: numerical balloons, colored balloons, traffic policeman, turbulent mice, turn and discover, memory step, golden ball, what time is it, radar and perfect couple. The order of the activities was maintained identical for all sessions of training.

Experimental Procedure

This study was approved by the local Ethics Committee (Protocol Number: 2397).

The experiment was explained to the participants. In the initial screening phase, exclusion criteria for stimulation through a specific questionnaire and the absence of physical difficulties and pain were verified. Participants were then randomized into four groups. One group received hf-tRNS on the left-DLPFc and V1, and was trained with 10 activities of the exergame "Dr. Kawashima's Body and Brain Exercises." A second group received Sham stimulation on the left-DLPFc and V1, and was trained with the same activities of the same exergame. A third group underwent hf-tRNS with no training, and the control group performed only the assessment (nor the real or Sham stimulation neither the training) at the baseline (T0) and after the same time interval (about 2/3 weeks) of the other groups (T1). The assessment consisted of two tasks performed in this order: Simple Reaction Time task and Go/No-Go task. Each task had a practice test of 10 trials to familiarize with the task.

The adaptive exergame training was carried out in eight sessions of ~45 min each, with hf-tRNS applied during the first 25 min. The protocol lasted 2/3 weeks, for a total of 10 sessions, consisting of eight-training sessions plus two sessions dedicated to the assessment, the pre-test (T0) and post-test (T1), scheduled from 1 to

3 days before and after the intervention (see Figure 1). For each participant, the same researcher conducted the assessment at T0 and T1, and a different researcher conducted the training procedure.

Data Analysis

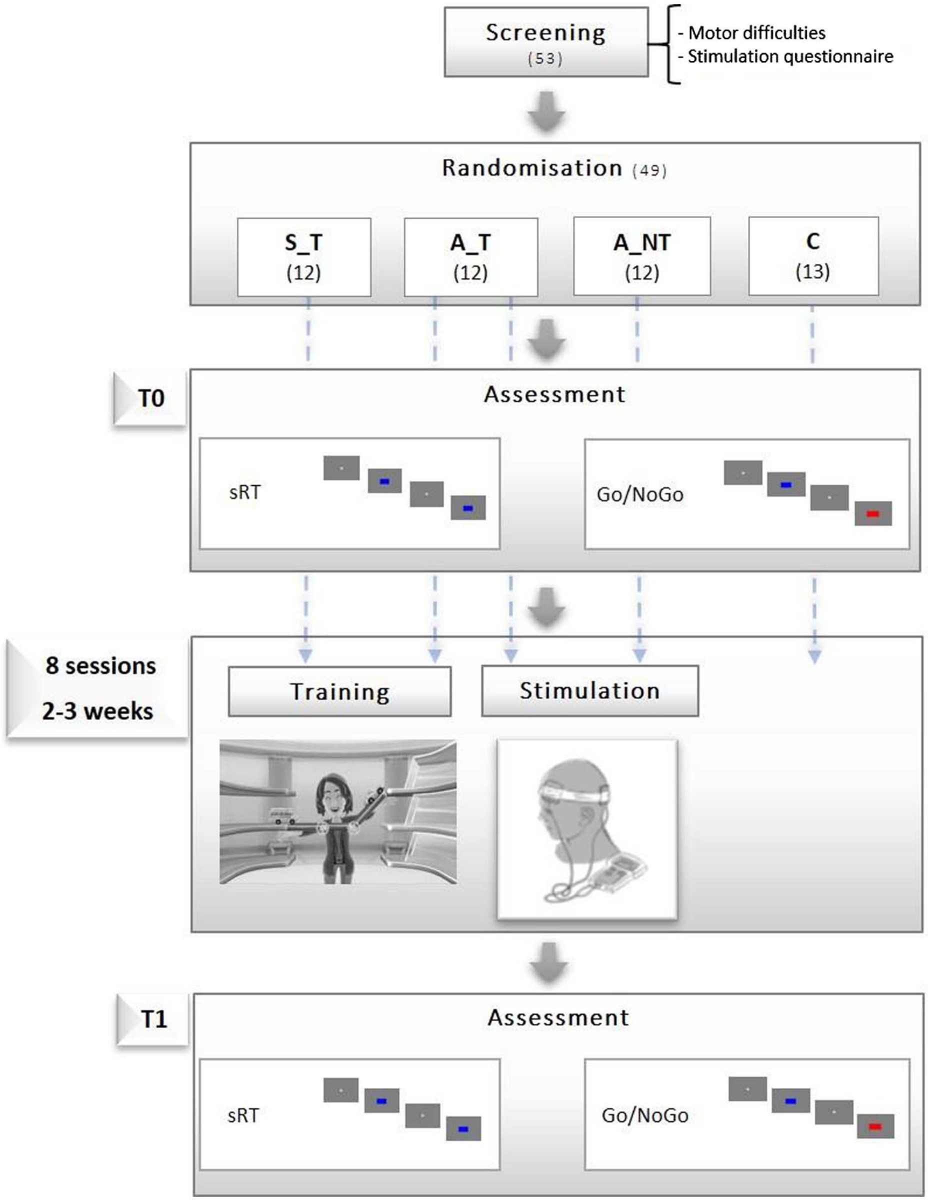
For the effect size, a priori power analysis was performed using the software program G * Power 3.0.10 (Faul et al., 2009). Given an effect size Cohen's f of 0.25 (this effect size corresponds to Cohen's $d = 0.5$, an intermediate effect size according to Cohen's (1988) criteria), an α of 0.05 (one-sided) and a power of 80%, a sample size of $n = 48$ was determined.

The median of reaction times (RTs) was calculated for each participant. For the Go/NoGo task, besides the median RTs for Go trials, the number of correct responses related to Go trials (HITs) and the number of incorrect responses of No-Go trials (FAs) was also calculated (Table 3).

Furthermore, for the Go/No-Go task, another variable was calculated which combines speed and accuracy, the so-called Inverse Efficiency Score (IES; Townsend & Ashby, 1978) (Equation 1):

Figure 1

Schematic Representation of the Experimental Procedure



Note. S_T = Sham stimulation + training; A_T = active stimulation + training; A_NT = active stimulation with no-training; C = control; T0 = pre-test; T1 = post-test. See the online article for the color version of this figure.

Table 3
Results of Simple Reaction Time Task and Go/NoGo Task

	sRT				Go/NoGo							
	T0		T1		T0				T1			
	RT ms				Go_RT ms				Go_RT ms			
Groups	*Mdn*	*SD*	*Mdn*	*SD*	*Mdn*	*SD*	HITs %	FAs %	*Mdn*	*SD*	HITs %	FAs %
S_T	238	18	229	14	290	26	99.6	8.3	287	21	99.8	6.7
A_T	253	42	237	25	322	31	98.3	5.8	297	18	99.0	3.3
A_NT	241	26	245	17	312	27	97.5	4.2	292	19	98.8	7.5
C	231	13	229	17	305	33	98.7	4.6	303	23	98.5	7.7

Note. T0 = pretest; T1 = posttest; RT ms = reaction time in milliseconds; Go_RT ms = reaction time of Go trials in milliseconds; *Mdn* = median; *SD* = standard deviation; S_T = Sham stimulation + training; A_T = active stimulation + training; A_NT: active stimulation with no-training; C = control; HITs = correct responses; FAs = false alarms.

$$\mathrm{IES} = \frac{\text{reaction time(RT)}}{\text{proportion of correct response}}\,\mathrm{ms} \qquad (1)$$

In this formula, the RT is the median Go-RT of a single participant and the proportion of correct responses is the accuracy of a single participant. Data analyses and the statistics have been computed using SPSS (21.0).

Results

There was no significant difference between groups in terms of age $F(3, 45) = 1.87$, $p = .15$, neither any significant difference between age variances, as assessed by the Levene test $F(3, 45) = 1.573$, $p = .209$.

Simple Reaction Time

To evaluate any difference between groups at T0 we ran a two-way ANOVA with sRT as dependent variable and Stimulation and Training as Between-Subject factors with Age as covariate, to control any difference attributable to the age. No significant effect was found for Stimulation $F(1, 44) = 3.52$, $p = .07$, $\eta_p^2 = 0.07$, Training $F(1, 44) = 2.28$, $p = .14$, $\eta_p^2 = 0.05$, nor for the interaction Stimulation × Training $F(1, 44) = 0.08$, $p = .78$, $\eta_p^2 = 0.002$.

To verify the presence of within-session practice effects, we merged all groups' RTs answers at T0 (before intervention), and we performed a paired-simple *t* test comparing First half versus Second half measurements. No significant difference was found $t(48) = 0.94$, $p = .349$.

To investigate the effect of the treatment, a repeated-measure ANOVA with Time (T0, T1) as Within-Subjects and Stimulation and Training as Between-Subject factors was carried out. The results revealed no significant effect of Time $F(1, 45) = 2.76$, $p = .10$, $\eta_p^2 = 0.06$; regarding the interactions, only Time × Training showed a significant effect $F(1, 45) = 4.50$, $p = .039$, $\eta_p^2 = 0.91$.

However, since homoscedasticity of RT data, as assessed by a significant Levene test $F(7, 90) = 5.59$, $p = .0001$, was not respected, we also run the same ANOVA on Log-transformed data. This second analysis confirmed the previous results: no significant effect of Time $F(1, 45) = 2.48$, $p = .12$, $\eta_p^2 = 0.05$ and a significant Time × Training interactions $F(1, 45) = 4.50$, $p = .039$, $\eta_p^2 = 0.91$.

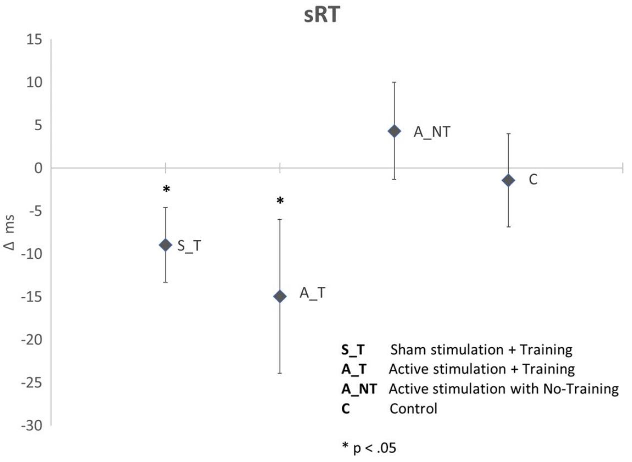
To explore the interaction Time × Training we run two paired-sample *t* tests. Post hoc comparisons reported a significant improvement for just the groups who received the training $t(23) = 2.43$, $p = .023$, $d = 0.70$. The same *t* test on Log-transformed data yielded the same results. Trained participants were, on average, 12 ms faster (see Figure 2). Neither the interaction Time × Stimulation nor the interaction Time × Training × Stimulation was significant, indicating that Stimulation was not able to modulate the performance in any group.

Go/No-Go Task

Similar analyses using the median-Go-RT (Go-RT) were conducted for Go/No-go data, adding the IES measure, which also takes into account any change in the accuracy of the response.

To assess any difference between groups in Go-RT at the baseline, a two ways ANOVA was conducted, with T0-Go-RT as dependent variable and Stimulation and Training as Between-Subject variables and Age as covariate, to control any difference attributable to the age. No significant effect was found for

Figure 2
Simple Reaction Time Results



Note. The mean of reaction time increase/decrease: Δ ms = RTs(T1)− RTs(T0) for each experimental condition in millisecond. Negative values correspond to an improvement.

Stimulation $F(1, 44) = 3.64$, $p = .06$, $\eta_p^2 = 0.08$, Training $F(1, 44) = 0.61$, $p = .44$, $\eta_p^2 = 0.14$, nor for the interaction Stimulation × Training $F(1,44) = 2.59$, $p = .11$, $\eta_p^2 = 0.06$.

To check the presence of within-session practice effects, we merged all groups Go trials RTs at T0 (before intervention), and we ran a paired-simple t test comparing First half versus Second half measurements was performed. No significant difference was found $t(48) = -0.69$, $p = .496$.

A repeated measure ANOVA with Time (T0 and T1) as Within-Subject and Stimulation and Training as Between-Subject variables was carried out. A significant result for the main effect Time $F(1, 45) = 10.80$, $p = .002$, $\eta^2 = 0.19$ and for the interaction Time × Stimulation $F(1, 45) = 7.003$, $p = .011$, $\eta^2 = 0.14$ was found.

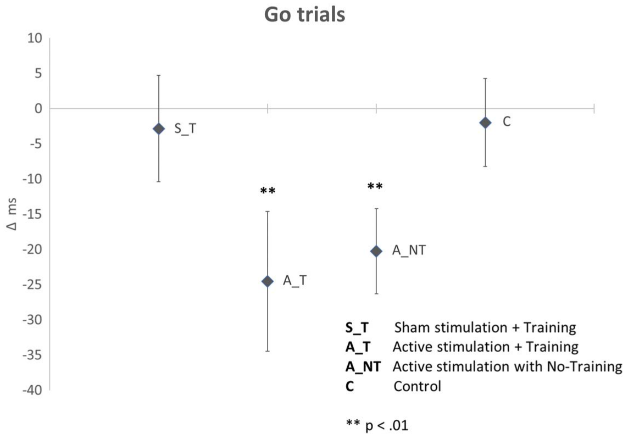
A significant result for the main effect Time $F(1, 45) = 9.86$, $p = .003$, $\eta^2 = 0.18$ and for the interaction Time × Stimulation $F(1, 45) = 7$, $p = .01$, $\eta^2 = 0.14$ was found.

Homoscedasticity of Go-RT data, as assessed by the Levene test between all groups and conditions, was respected $F(7, 90) = 0.78$, $p = .61$. However, in order to check if even subtle differences in variance between groups and conditions could explain the significant results of the ANOVA, we also run a second ANOVA on Log-transformed data. This second analysis confirmed the previous results: no significant effect of Time $F(1, 45) = 9.86$, $p = .003$, $\eta^2 = 0.18$ and for the interaction Time × Stimulation $F(1, 45) = 6.74$, $p = 0.013$, $\eta^2 = 0.13$.

To further explore the interaction between Time and Stimulation, T0 versus T1 measurements for stimulation conditions were compared using two paired-sample *t* tests. Only the groups which received stimulation showed a significant improvement $t(23) = 3.936$, $p = .001$, $d = 1.14$. The same *t* test on Log-transformed data yielded the same results. This result showed the effect of the stimulation in inducing a better performance with a mean improvement of 22 ms (see Figure 3).

Comparable results for IES-scores were found, which also considered the accuracy: a repeated measure ANOVAs with Time (T0, T1) as Within-Subject and Stimulation and Training as Between-Subject revealed a significant effect of Time $F(1, 45) = 9.79$, $p = .003$, $\eta^2 = 0.18$ and interaction Time × Stimulation $F(1, 45) = 6.73$, $p = .013$, $\eta^2 = 0.13$ too. The paired sample *t*-test post hoc comparisons revealed a significant improvement in the stimulation groups only $t(23) = 3.538$, $p = .002$, $d = 1.02$, confirming that participants who received the stimulation improved Go-RT, and that this was not due to an RT-accuracy trade-off.

Figure 3
Go/NoGo Results



Note. The mean of Go trials reaction time decrease: Δ ms = RTs(T1)−RTs(T0) for each experimental condition. Negative values correspond to an improvement.

Even though the IES-scores considered the accuracy and the speed together in a single variable, in this study, cognitive control was the main area of interest, a process mostly related to the number of FAs committed. Therefore, the difference (T1 − T0) for both HITs and FAs was calculated in order to investigate any change in accuracy (HITs) and inhibition control (FAs) after the treatment. A multivariate analysis of variance (MANOVA) with HITs and FAs as dependent variables and Stimulation and Training as Between-Subject was performed. The results showed no effect of Stimulation $F(1, 45) = 0.78$, $p = .38$, $\eta^2 = 0.017$ or Training $F(1, 45) = 0.11$, $p = .91$, $\eta^2 = 0.000$ in HITs; also, no effect of Stimulation $F(1, 45) = 0.006$, $p = .94$, $\eta^2 = 0.000$ nor of Training $F(1, 45) = 1.89$, $p = .18$, $\eta^2 = 0.040$ were found regarding FAs, indicating that all groups maintained the same pattern or response after the treatment.

In sum, the groups which received stimulation were faster in Go-RT, preserving the same accuracy and inhibition control in responding.

Discussion

The present study investigated the role of hf-tRNS on the left-DLPFC and that of an exergame training in enhancing cognitive performance in healthy young adults. The main aim was to investigate whether eight sessions of adaptive cognitive game training and tRNS, either independently or combined, could boost cognitive functions by involving processing speed and inhibitory control.

An orthogonal design was developed. Participants were randomly assigned to four groups: the first group performed eight sessions of exergame training with active noninvasive brain stimulation; the second group performed eight sessions of exergame training together with Sham stimulation; the third group performed no exergame training but received the active stimulation; the fourth group, received no training or stimulation. All groups were assessed twice at the beginning of the study and at the end of it. We selected two tasks, sRT and Go/NoGo tasks, to have a measure of processing speed, and of executive and inhibitory control.

We expected the exergame training to improve (i.e., faster reactions) performance in the Simple Reaction Time and the Go/NoGo tasks, due to the increasing demand for faster and more accurate responses. We opted for an exergame and not a videogame because exergames continuously stimulate the motor system and provide aerobic activity which may enhance cognitive functioning (Kramer & Erickson, 2007). Furthermore, we hypothesized an improvement in speed and accuracy in the Go/NoGo task due to the cognitive element of the exergame chosen: the players were trained with many activities involving executive control. For instance, "Colored balloon" is a similar paradigm to the Stroop task: the participant is asked to burst a balloon matching a color-word that is written with an incongruent colored ink. This incongruency generates interference as well as the necessity to inhibit an automatic response especially when the color of the balloon matches the ink-color of the word. Also in the game "Turbulent mice" the player has to hit a specific type of mouse (while avoiding hitting the other one), activity that reflects a classic Go/NoGo task.

Additionally, it was assumed that online-tRNS application would have led to an increase in the effect of the training (Cappelletti et al., 2013; Pirulli et al., 2013). Since left-DLPFC, the target area, is involved in the top-down regulation of cognitive control (MacDonald et al., 2000), it was hypothesized that tRNS application would have increased this regulation resulting in a faster performance in sRT task (due to the strong connections with the pre-SMA and SMA and the crucial involvement of DLPFC in information processing) (Koechlin et al., 2003), and faster and more accurate responses for Go/NoGo task (due to the specificity of DLPFC which has been correlated with the inhibitory response; Grier, 2005; Simmonds et al., 2008; Wessel, 2018). Due to a likely synergetic effect, a better performance was expected in the group which carried out the exergame training when combined with the active stimulation, as a result of an increase in the cortical excitability of the DLPFC already involved and prompted by the exergame activity.

Observing sRT results, faster RTs were performed only in the groups which carried out the training, regardless of whether a group received the stimulation or not. This improvement is likely due to the exergame practice, which requires the participant to be progressively fast as the game moves on to the next level.

Concerning the Go/NoGo task, only the groups which received the stimulation showed improved performance as a reduction of the RTs of Go-trials. Thus, these results could indicate that the stimulation might induce a reduction of the RTs in the Go-trials but not in sRT task. This might reflect the specificity of the stimulation for the former task. Go/NoGo is a higher level demanding task compared to sRT task. It consists of a set of semi-independent processes, including stimulus encoding, stimulus-response association, rate of information processing, speed-accuracy trade-offs, and motor response (Karalunas et al., 2012); also, it involves inhibitory control, related to the activation of the frontal area (Simmonds et al., 2008). The stimulation could have played a fundamental role by enhancing the excitability of left-DLPFC and consequently, improving the processes involved in this task, perhaps by strengthening the processing speed, which is crucially involved in any motor and cognitive activity (Nouchi et al., 2020; Takeuchi & Kawashima, 2012).

DLPFC is part of a network that includes premotor and somatosensory areas and it is also thought to be responsible for transforming the input sensory signals into distinctive output motor orders (Heekeren et al., 2004; Miller & Cohen, 2001). This process may have been reinforced by the hf-tRNS. The stimulation may have contributed by increasing neural activation, thus enhancing the excitability (Shafi et al., 2012). A similar result was shown by Brevet-Aeby et al. (2019), who showed that three consecutive active-tRNS sessions decreased RTs at the Go trials as compared to Sham.

What the present study reveals is that participants who received eight sessions of stimulation showed a decrease of about 22 ms in a task where inhibition is required. Although performance at T0 was unrelated to the magnitude of the improvement, it is suggested to tale this effect with caution because of the small sample size. What has been achieved is a higher speed in a simple decision-making task involving stimulus-response association and inhibitory control.

Limitations of the Study

The number of trials of both tasks was kept low, 40 and 50 trials, respectively, to avoid any practice effects, this was adequately reflected by the nonsignificant difference in performance between pre- and post-test in the control group. Nevertheless, the limited number of trials might be partially responsible for the unobserved effect on FAs, a measure of a potential improvement in the inhibitory control.

The lack of the exergame effect in improving Go-RT could be as a result of the multiple cognitive domains trained, the insufficient practice, and/or to the fact that it was not powerful enough to provoke the adequate cortical change, detectable through a behavioral response or to transfer the learning to other skills (Lee et al., 2012). A possible explanation as to why the stimulation did not affect the sRT compared to Go-RT, could be ascribed to the reduced complexity of the task which did not benefit from the potential enhancement of cortical excitability. In the same way, the stimulation parameters over the left-DLPFC might be not crucial for affecting sRT. Perhaps by stimulating the premotor or motor areas, directly involved in sRT task, an improvement in this task may have been obtained.

In contrast to other studies that found an improvement from the combination of tRNS and motor or cognitive training (Brem et al., 2018; Cappelletti et al., 2013; Prichard et al., 2014; Snowball et al., 2013) and to what was initially hypothesized in the present study, this study did not show improved performance when the two techniques were coupled.

The assessment should be expanded to investigate any potential cognitive improvement due to the training coupled with hf-tRNS, especially considering the significant improvements achieved by the effect of the exergame and the stimulation independently. Furthermore, a more heterogeneous sample using objective measurements such as accelerometer and heart rate recording to quantify the energy consumption would allow for better generalizability of the results. Also, follow-up sessions should be implemented to consider the duration of the treatment effects.

Regarding safety, this study revealed good tolerance to eight sessions of tRNS of 25 min each: no participant reported any side effects, and none were able to feel any cutaneous perception of the stimulation. This information was recorded with a questionnaire at the beginning and end of each session. Thus, it can be concluded that participants could not discriminate real from Sham stimulation. This is a fundamental outcome considering the lack of safety records for several sessions in combination with an exergame.

In sum, a double dissociation was observed: the tRNS over the left-DLPFC improved the performance in the Go/No Go task by making the participants faster while preserving their accuracy, but did not affect the performance in the sRT; the exergame training decreased the response times sRT task but did not affect the performance in the Go-RT task. This is the first exploratory study investigating the effects of eight sessions of exergame training and hf-tRNS, alone and combined. Thanks to participants' comments about their experience, exergame training might be an enjoyable and sustainable way to encourage physical activity and cognitive exercises, despite a larger sample is needed and long-term effects of the intervention and potential transfer to other cognitive tasks need to be further investigated.

Promising results that support the use, even prolonged use, of noninvasive electrical stimulation and the absence of any side effects, makes it the most feasible research option for comparing it to a Sham condition. In future studies, it would be interesting to investigate this motivating protocol with an older sample of participants, since it is well known that RTs slow down with age. Woods et al. (2015) estimated 0.55 ms/year as the latency increase with age (Woods et al., 2015). These encouraging results suggest the potential cognitive and motor benefits of using these tools. Furthermore, thanks to the low cost and the home-based nature of these techniques, they are both feasible and sustainable, not only for active aging, but also for several practical applications such as athletic training and cognitive rehabilitation training.

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