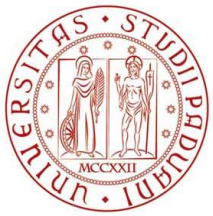

UNIVERSITÀ DEGLI STUDI DI PADOVA

Università degli studi di Padova

Dipartimento di Psicologia dello sviluppo e della socializzazione

Corso di dottorato di Ricerca in Scienze Psicologiche

CICLO XXIX

# TES AND ITS EFFECTS ON COGNITIVE FUNCTIONS: FEASIBILITY AND LIMITATIONS FOR A BROADER CLINICAL APPLICATION.

Coordinatore: Ch.mo Prof. Giovanni Galfano

Supervisore: Ch.mo Prof. Marco Zorzi

Dottoranda: Miriam Braga

ABSTRACT

Trascranial electrical stimulation (tES) is a neuromodulation technique which applies a mild current to modulate a wide variety of cognitive functions. It was shown that depending on the protocol applied, tES is effective in enhancing or interfering with cortical excitation, even if further research is needed in order to better understand its effects. In our studies, we focused on the online or offline effects of various tES protocols and on disparate tasks, in order to evaluate potential future application on clinical population.. To date, few studies investigated offline, transfer effects of tES, both after single or multiple sessions administration. Similarly, evidence assessing tES offline and long-term effects on cortical excitability is still lacking.

This doctoral thesis contributed to shed light on different aspects concerning tES. Firstly, we demonstrated that cathodal tDCS applied over right inferior frontal gyrus (rIFG) is effective in modulating selectively incongruent trials in a dots comparison task. Moreover, the effect was specific for offline measures, but not online, suggesting possible short-term after-effects of this protocol. Secondly, we showed that bilateral tRNS is more effective than anodal tDCS in inducing after-stimulation changes in attention both on behavioral performance and cortical excitation. Our studies confirmed that the two protocols are differentially effective, consistently with literature showing that different neural mechanisms underlie tDCS and tRNS neural after-effects. Finally, we demonstrated that despite the absence of online effects, coupling bilateral tRNS with cognitive training is effective to induce long-term changes, as assessed by behavioral measures and cortical plasticity investigations. Interestingly, the effects were still present a month after the end of the training. Taken together, our studies contributed to better understand the after-effects of tES and suggests that bilateral tRNS is best suited for clinical applications, even if further research is needed.

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PREFACE

Mounting evidence shows that Trascranial electrical stimulation (tES) can modulate a wide variety of cognitive functions. tES is applied both on healthy participants and clinical population to temporally change the behavioral outcomes inducing short-term amelioration.

Within tES, trascranial direct current stimulation (tDCS) with anodal polarity is the better known and applied in research, since it was shown that ten minutes of stimulation on motor cortex can induce online and after-effects lasting until one hour. Literature on anodal tDCS is progressively growing and a number of available studies showed its effects on various cognitive functions. Research focusing on other protocols, such as random noise stimulation (tRNS), is relatively novel and few studies are available compared to tDCS. However, it was shown that tRNS is particularly effective when combined to cognitive training.

In the first chapter, I focused on the literature available on tDCS and tRNS, in particular on the clinical applications on different populations. In the second chapter, I briefly presented EEG spontaneous oscillations as a useful method to study cortical changes in cognition. In the following chapter, I presented the experimental studies I conducted to address specific experimental questions.

In experiment 1, I studied the effects of cathodal tDCS on right inferior frontal gyrus (rIFG), a cortical site considered crucial in inhibitory abilities, while administrating a dots comparison task. The implications of this research are twofold. Firstly, it demostrated that inhibitory abilities are involved in Dots comparison task, since cathodal stimulation selectively modulated incongruent trials. Secondly, it showed the efficacy of cathodal tDCS in modulating inhibition, specifically for offline measures, but not online.

In the second experiment, I studied transfer effect of a single session administration of anodal tDCS and tRNS on attentional functions, in order to verify after-stimulation changes in performance and cortical excitation. The procedure of the study stands out in classic tES research, since we were interested in the effects obtained on tasks other - but related - than the one administered during the stimulation. Our study

revealed that the two protocols are differentially effective, consistently with literature showing that the neural mechanisms underlying tRNS after-effects are not shared with tDCS.

In the third experiment, we applied bilateral tRNS coupled with behavioral training based on a computer game (Labyrinth). Even if no online effect was detected, we demonstrated long-term effects both on behavioral measures and on EEG recording. Moreover, the effect was still present after a month, with a significant activation in left anterior sites compared to only-training group.

Finally, general conclusions are presented in the fourth chapter. tES research is a promising field for future clinical interventions on abnormal population. The possibility to obtain long-term changes in neural functioning is intriguing and tES research go in this direction. However, further efforts are needed to understand in detail its effects on cognition.

# CHAPTER 1
# TRASCRANIAL ELECTRICAL STIMULATION TECHNIQUES (tES)

## 1.1 A general introduction to tES

Transcranial Electrical Stimulation (tES) has been widely used in the last two decades to modulated the brain activity. tES is typically used to change (enhance or suppress) brain activity, or to study causal relationship between cortical site and behavior. There are 3 types of tES: trascranial Direct Current Stimulation (tDCS), trascranial Random Noise Stimulation (tRNS) and trascranial Alternating Current Stimulation (tACS). The most widely used tES is tDCS, both in anodal (excitatory) and cathodal (inhibitory) polarity. Anodal tDCS and bilateral tDCS (anode on interest site and cathode contralaterally) are often used in clinical populations (Miniussi et al., 2008). Cathodal tDCS alone is often used to answer experimental questions, mainly regarding causal relationships between cortical site and behavior. tACS and tRNS are more recent tools, and only lately studied from a physiological and behavioral point of view. These two techniques take advantage of the oscillatory waves elicited by a stimulation device to add noise to cortical neural processing, thereby enhancing or interfering with brain activity. While tACS applies a current of a specific frequency which can summate with the existent brain waves or interfere with them, tRNS is particular type of tACS and applies a random electric current to add random noise to the system. tRNS has been used to assure long-lasting, reliable effects of trainings, while tACS usage is limited because it is necessary a good knowledge of the bands naturally present in cortical site and of the precise phase when stimulation is applied (Abd Hamid, Gall, Speck, Antal & Sabel, 2015).

## 1.2 Transcranial direct current stimulation (tDCS)

Non-invasive brain stimulation methods are an important tool to modulate the neural activity of a specific cortical area. The use of these techniques allows to induce plastic modification of neural activity, through the modulation of cortical excitability, which could be crucial in research and therapy (Polania, Nitsche & Paulus, 2011).

Transcranial magnetic stimulation (TMS) is able to induce directly action potentials and modify cortical excitability though brief and strong electric currents administered with a metallic coil on the scalp. Electric current flowing inside the coil generates a magnetic field which go through the scalp, inducing a mild electric current on the cortical area underneath the coil.

Depending on the protocols, it is possible to obtain an activation or an inhibition underneath the coil (Miniussi, Harris & Ruzzoli, 2013).

Trascranial direct current stimulation (tDCS) is a procedure used to polarize cortical areas through the application of a mild electric current. The procedure induces transient changes in cortical activation based on polarity, intensity and duration of the stimulation. The applications of tDCS are very similar to TMS, both the techniques are able to modulate cognitive functions, they are not dangerous or invasive and they can be used for therapy and experimental investigation.

Some studies proposed that tDCS is able to enhance or inhibit a certain behavior, allowing to investigate the causal relationship between cerebral activity and induced behavioral effect (Miniussi, Harris & Ruzzoli, 2013). From an experimental point of view, this investigation might contribute to the study of cognitive functions, allowing to determine specific causal relationships between cortical site and behavior. Other techniques, such as fMRI, are only able to establish a simple correlation between activation and behavioral outcome.

The idea to apply the electric current to modify the cortical functions was still tested 200 years ago. In the first studies, electrical stimulation was tested on animals, to investigate the effects of electrical current on threshold potentials at rest when administered on the scalp (Terzuolo & Bullock, 1956; Creutzfeldt, Fromm & Kapp, 1962; Eccles, Kostyuk & Schmidt, 1962; Bindman, Lippold, Redfearn & 1964; Purpura & McMurtry, 1965; Artola & Singer, 1990; Malenka & Nicoll, 1999). This first studies in which a mild electrical current was applied through intracortical electrodes, showed that a modulation of cortical activity was possible, thus enhancing the excitability with anodal stimulation, or inducing a decrease with cathodal stimulation.

Further research on animals confirmed that 50% of electric current applied on the scalp is able to go through the skull entering the brain (Rush & Driscoll,1968) and these results were replicated on humans (Dymond, Coger & Serafetinides, 1975). Only recently this technique was applied more extensively due to its feasibility in clinical neuroriabilitation (Fregni et al., 2005; Hummel et al., 2005; Fregni et al., 2006 a,b,c; Boggio, Nunes, Rigonatti, Nitsche, Pascual-Leone & Fregni, 2007; Fregni, Liguori, Fecteau, Nitsche, Pascual-Leone & Boggio, 2008) and in psychological research (Jacobson, Koslowsky & Lavidor, 2012; Miniussi et al., 2013).

tDCS is able to modulate the activation or deactivation of cortical sites based on the combination of current intensity, dimension of the stimulated area, duration of the stimulation and montage of the electrodes (Agnew & McCreery, 1987).

The fourth parameter affecting the effects of the stimulation is the flowing direction, which generally depends on the position of electrodes and their polarity. Studies on motor cortex clarified

that only specific montages are able to affect the cortical excitability and modify different neural population (Priori, Berardelli, Rona, Accornero & Manfredi, 1998; Nitsche & Paulus, 2000).

Studies showed that neurons with different orientations were differently affected by the current flow (Creutzfeldt et al., 1962; Purpura & McMurtry, 1965) which suggests a strong relation between direction of the current and orientation of the neurons to induce changes in cortical excitability.

For example, it was proven that deeper neurons are often deactivated by the anodal stimulation and activated by the cathodal and that lower currents affect non-pyramidal neurons compared to pyramidals neurons (Purpura & McMurtry, 1965).

The first works applying direct current stimulation to humans were published by Priori and colleagues (1998). These studies showed that 0.3 mA intensity anodal stimulation was effective in decreasing cortical excitability if preceded by cathodal stimulation; viceversa, cathodal and anodal simulation alone did not show any effect (Priori et al., 1998).

Other studies found a potentiation for anodal and a decrease for cathodal in cortical excitability using a different montage (active electrode on motor cortex and control over supraorbital contralateral area) and with a longer stimulation, as revealed by motor evoked potentials (MEP), that is the modifications in muscular electric activity as revealed by the electromiography (Nitsche & Paulus, 2000). Consequently, different effects induced by different stimulation montages are likely, because the direction of the current flow is different (Jacobson et al., 2012).

The evidence that anodal is linked to cortical excitation while cathodal to cortical deactivation has been reported in several studies involving motor cortex (Fregni, et al., 2006; Stagg, O'Shea, Kincses, Woolrich, Matthews, & Johansen-Berg, 2009), but not in others (Rosenkranz, Nitsche, Tergau & Paulus, 2000; Tanaka, Hanakawa, Honda & Watanabe, 2009) nor in part of the literature concerning other cognitive functions (Kincses, Antal, Nitsche, Bartfai & Paulus, 2004; Marshall, Molle, Siebner & Born, 2005; Sparing, Dafotakis, Meister, Thirugnanasambandam & Fink, 2008).

A number of studies tried to understand whether this technique was safe and whether side effects were possible. tDCS was applied in more than 100 studies, both on patients and healthy participants and only few reported headache, nausea, a mild tickling under the electrodes, fatigue (Poreisz, Boros, Antal & Paulus, 2007). More detailed studies showed that 1mA intensity stimulations did not induced damages, either after anodal and cathodal stimulation (Nitsche, et al., 2004; Nitsche & Paulus, 2001; Nitsche, Liebetanz, Lang, Antal, Tergau & Paulus, 2003). No decrease in neuropsychological measures was found after a 2mA frontal stimulation for 20 minutes (Iyer, Mattu, Grafman, Lomarev, Sato & Wassermann, 2005) nor electrodes heating (Stagg et al., 2009). Even if higher intensities are necessary to induce cortical or tissues damages (Yuen et al., 1981;

Liebetanz, Koch, Mayenfels, König, Paulus & Nitsche, 2009), protocols establish very strict safety rules to minimize the possible risks for the participants.

Even if further research is necessary to better understand tDCS functioning, this technique has proven to be effective in neuropsychlogical rehabilitation. It induced benefits on stroke (Fregni et al., 2005; Hummel et al., 2005), Parkinson disease (Fregni et al., 2006d), chronic depression (Boggio et al., 2008; Fregni et al., 2006b), addiction (Fecteau, Fregni, Boggio, Camprodon & Pascual-Leone, 2010), and in fibromyalgia pain therapy (Fregni et al., 2006c) or after spinal cord damages (Fregni et al., 2006a).

### 1.2.1 tDCS and rehabilitation

Compared with rTMS, tDCS has some advantages. The main advantages are that this is a simple, non-expensive procedure, painless and it has a reliable sham condition, therefore providing more robust doubleblind clinical trials than TMS. In addition, tDCS is a good tool to be used simultaneously with cognitive training as it induces much less scalp sensation than rTMS and therefore is not prone to induce a-specific effects on attention. However, the main limitation is that it is less focal than TMS. It is generally delivered to the scalp even through large electrodes (20-35 $cm^2$). Therefore, it is not focal enough to target localized areas and to map cognitive functions accurately. However, it is possible to obtain more focal effects by reducing electrode size (Bastani & Jaberzadeh, 2013). Like rTMS, tDCS has been used to modulate cognitive performance in healthy subjects. Nevertheless, like rTMS, it is too simplistic to consider that anodal tDCS is beneficial and cathodal tDCS disruptive with regard to behavior in general. Other important factors such as the type of task, the site of application, the excitability status of the underlying cortical tissue, and the timing of stimulation are critical for the results.

*Alzheimer disease and Parkinson disease*

Boggio et al. (2009) investigated the effects of tDCS in patients with Alzheimer disease (AD) on recognition memory, working memory and selective attention. Results showed that after anodal tDCS on temporal and prefrontal stimulation, accuracy on a Visual Recognition Memory task was enhanced. The authors concluded that tDCS over the temporal and prefrontal areas can specifically affect recognition memory performance in patients with AD.

On Parkinson disease (PD) patients, Boggio et al. (2006) found that after a single session of 2 mA a-tDCS over the L-DLPFC patients improved in the accuracy of the 3-back memory task. Their

results were recently reinforced by a, tDCS combined fMRI single session study of Pereira and colleagues (2013), in which authors found an improvement on the phonemic fluency task after a single session a-tDCS over the L-DLPFC. Furthermore, fMRI analysis of connectivity demonstrated that a-tDCS applied over the L- DLPFC produced a greater activation of the specific functional networks engaged by the task compared to a-tDCS over temporo parietal cortex (TPC). However, the effects were short-lasting and did not generalize to everyday functioning. A subsequent study then investigated the efficacy of a multiple sessions protocol on multiple cognitive domains including executive function, attention, perceptual-motor abilities, learning and memory. Here, 10 consecutive sessions (over 2 weeks) of a- tDCS over L-DLPFC or a-tDCS over R-DLPFC or sham, were administered by a randomized between subject design on 18 patients (6 in each group). Cognitive functions were evaluated before, at the end of stimulation sessions and at 1 month follow-up. It was found that a-tDCS over both the left and right DLPFC compared to sham improved performance only on TrialMaking Test B at the 1-month follow-up but not on the other outcome measures. Overall, these studies demonstrate that a-tDCS over the prefrontal cortex might be able to improve executive functions. Ferrucci et al. (2008) investigated the effect of a single session protocol of a-tDCS or c-tDCS or sham over bilateral temporo-parietal areas (two electrodes on the scalp and one reference on deltoid). It was found that a-tDCS increased accuracy in word recognition memory, and conversely c-tDCS decreased accuracy. Boggio, Khoury, Martins, Martins, De Macedo & Fregni (2009) found that a-tDCS over left temporal cortex (L-TC) or a-tDCS over the L-DLPFC improved Visual Recognition Memory performance compared to sham. In a single case study, Penolazzi and colleagues examined the effectiveness of tDCS combined with Individualized Computerized Task (iCT) performance (Penolazzi, Bergamaschi, Pastore, Villani, Sartori & Mondini, 2014). An AD patient underwent 10 sessions a-tDCS over the L-DLPFC followed by iCT, including verbal working memory task, phonemic fluency task and continuous performance task. The authors found iCT combined with anodal stimulation to be better than iCT combined with the sham.

To sum up, there is some evidence from randomized controlled clinical studies showing a beneficial effect of a-tDCS on some specific components of memory. However, there is a great deal of methodological heterogeneity across these studies. Moreover, studies should focus on generalization of the results in everyday life.

*Unilateral spatial neglect*

Overall, the rationale for the studies using tCDS in patients with unilateral neglect is based on

Kinsbourne's interhemispheric conflict model (Kinsbourne, 1970). According to this model parietal lobes may exercise interhemispheric inhibition through the connections of the corpus callosum balancing allocation of visuospatial attention toward both hemifields. Brain lesions, as a result of stroke, impair this balance. For this reason, a-tDCS is applied to the lesioned hemisphere to increase cortical excitability and the c-tDCS to inhibit the over-activated unlesioned hemisphere. Ko, Han, Park, Seo & Kim (2008) enrolled 15 right-handed subacute stroke patients with left visuospatial neglect. Patients participated in a single session protocol of a-tDCS over the right parietal cortex (R-PC; damaged hemisphere). The authors found an improvement of performance in line bisection and cancelation tests, indicating a recovery of neglect symptoms. Sparing, Thimm, Hesse, Kust, Karne & Fink (2009) tested 10 right-handed patients with left visuospatial neglect due to right-sided vascular lesions. Here, a single session of a-tDCS over the right posterior parietal cortex (R-PPC; damaged hemisphere) or c-tDCS over the left posterior parietal cortex (L-PPC) was conducted. The authors found that both c-tDCS over the undamaged PPC and a-tDCS over the damaged PPC reduced symptoms of visuospatial neglect. A recent study assessed the impact of multiple sessions of tDCS on Neglect patients. A combined approach was followed by Brem, Unterburger, Speight & Jankle (2014), who combined tDCS and cognitive training. a-tDCS was applied over the R-PPC and c-tDCS over the L-PPC. It was found that with bilaterally tDCS improvement was significantly higher than during standard neglect therapy alone or sham. The authors highlighted for the first time the additive effects of tDCS and standard neglect therapy on functional improvement. Importantly, the beneficial effects of tDCS was maintained over a follow-up period of 1 week and 3 months. A subsequent study by Smit et al. (2015) evaluated the immediate and long-term effects of multiple sessions of tDCS on five severe chronic hemispatial neglect patients. Despite the same montage applied, the Authors found no improvement in the Behavioral Attention Test (BIT).

*Aphasia*

In patients who suffer from non-fluent aphasia the studies so far evaluated the immediate effect of tDCS on naming abilities. Monti et al. (2008) tested the effect of a-tDCS or c-tDCS over the left Broca's area on picture naming task accuracy. An improvement in accuracy after c-tDCS compared to a-tDCS and sham was found. Fiori et al. (2011) tested three aphasic patients with anomic difficulties using a picture-naming task, administering five consecutive sessions of a-tDCS over the Wernicke's area (CP5), vs. sham applied during intensive anomia training. The authors found a significant improvement in the picture-naming task accuracy. Other evidence shows no effect of consecutive sessions anodal tDCS on left Broca area (Volpato, Piccione, Garzon, Meneghello, &

Birbaumer, 2011; Polanowska, Lesniak, Seniow, Czepiel & Czlonkowska, 2013). Vestito, Rosellini, Mantero & Bandirini (2014) found that naming abilities, as assessed by a computerized naming task, improved in the a-tDCS group compared to the sham group when stimulating left perilesional sites.

### 1.2.2. Effects of tDCS on EEG oscillations power

Keeser et al. (2011) measured resting state electroencephalographic activity with 25 electrodes after each tDCS treatment session. Anodal tDCS was administered over F3 (electrodes 7X5cm, with the cathode above the right supraorbital region, 20 minutes, 2mA). An n-back task was conducted prior to tDCS experiment in a separate day to serve as a baseline task. After the EEG registration, the n-back task was repeated to assess the behavioral effects of stimulation. Approximately 5-10 minutes after the stimulation session, a resting-state EEG registration was performed. For the entire time of the registration (10 minutes), participants were required to keep their eyes open.

Results showed a reduced left frontal delta (1–6.5 Hz) activity in the anodal tDCS condition compared to sham tDCS and a decrease in current densities (sLORETA) in real tDCS compared to sham tDCS for the delta band localized in the left subgenual PFC/medial frontal gyrus, Brodmann area, in the subcallosal gyrus, in the anterior cingulate, in the medial frontal gyrus and in the left rectal gyrus. Authors found an enhancement in beta activity over Fz and F4, despite the unilaterality of the stimulation. No other significant results were found for any other frequency band. The reduction seemed more significant in the first five minutes, suggesting that effects could be more detectable immediately after stimulation. However, the results should be interpreted with caution, since the localization is based on a small number of electrodes.

These results underline that anodal tDCS is able to induce changes in areas connected to the stimulated sites, as shown when stimulating primary motor cortex (i.e., see Baudewig, Nitsche, Paulus & Frahm, 2001). Specifically, unilateral anodal stimulation induces a decrease in delta activity and an enhancement in beta waves localized in frontal areas.

Jacobson, Ezra, Berger, & Lavidor (2012) evaluated the effects of anodal and sham stimulation on right inferior frontal gyrus (rIFG). They found a significant decrese in theta band specifically in rIFG area. Moreover, behavioral inhibition performance was modulated by the stimulation.

Ulam, Shelton, Richards, Davis, Hunter, Fregni, & Higgins (2015) tested the effects of anodal tDCS on EEG oscillations and neuropsychological tests on patients with traumatic brain injury (TBI) undergoing subacute neurorehabilitation. They administered anodal over the left dorsolateral prefrontal cortex (F3), with the cathode placed at right supraorbital site, (Fp2). They found that tDCS was effective in decreasing Delta and increasing Alpha bands. Moreover, the change was correlated with amelioration in neuropsychological tests administered before and after the stimulation.

### 1.2.3 Experimental applications of tDCS

Firstly, electric stimulation techniques (tES) focused on visual and motor effects (Nitsche & Paulus, 2000), while recently some studies showed that they can ameliorate a number of cognitive abilities, such as working memory (Gladwin, den Uyl & Wiers, 2012; Teo, Hoy, Daskalakis & Fitzgerald, 2011; Sandrini, Fertonani, Cohen & Miniussi, 2012; Mulquiney, Hoy, Daskalakis & Fitzgerald, 2011; Ohn et al., 2008), attention (Weiss & Lavidor, 2012), language (Holland et al., 2011; Cattaneo, Pisoni & Papagno, 2011; Sparing et al., 2008; De Vries, Barth, Maiworm, Knecht, Zwitserlood & Flöel, 2010), decision making (Dockery, Hueckel-Weng, Birbaumer & Plewnia, 2009). However, the results on cognitive functions are more controversial than those relative to motor functions (Jacobson et al., 2012).

The AeCi model (anodal-excitation cathodal-inhibition) was tested in a number of studies and it seems more robust in motor functions domain (Nitsche & Paulus, 2000; Csifcsak et al., 2009; Furubayashi et al., 2008; Jefferson, Mistry, Singh, Rothwell & Hamdy, 2009; Jeffery, Norton, Roy & Gorassini, 2007; Lang, Nitsche, Paulus, Rothwell & Lemon, 2004; Stagg et al., 2009) than in cognitive functions. A meta-analysis conducted by Jacobson and colleagues (2012) compared the tDCS effects in different studies. For example, Tanaka and colleagues (2009), investigated whether tDCS was able to enhance motor functions. Participants were required to perform tasks measuring the maximum strength of left foot (PF; pinch force task) or in which it was required to use the foot rapidly (RT; reaction time), during or after anodal, cathodal and sham stimulation. The results clarified that anodal stimulation enhanced in a transient way the PF, while cathodal and sham did not modify the performance. Rosenkranz, Nitsche, Tergau & Paulus(2000), tested the effects of anodal and cathodal stimulation on motor cortex during a motor training. Results revealed a significant reduction of the performance 10 minutes after the training both with anodal and cathodal tDCS. The authors proposed that tDCS interfered with the performance during the training, probably preserving pre-existing cortical movement representations, interfering with the maintenance of cortical excitability changes established due to the demands of the training task.

Experimental research employed tDCS to investigate hypothesis. While functional magnetic resonance (fMRI) allows to investigate the co-occurence between activation of a certain area and behavior, tES allows to investigate causal relationships between events. With fMRI it is only possible to test the correlation between activation and behavioral data, thus imp impossible to decide anything about causal relationships between events. For example, fMRI doees not allow understanding which cortical area is activated before and which after, thanks to a very good

termporal resolution, but we cannot deduce anything about which site causes the behavioral outcome. Stimulation techniques such as TMS and tDCS allows an experimental modulation of behaviors.

First studies investigating tDCS effects focused on motor cortex and verified excitatory effects of anodal and inibitory effects of cathodal stimulations (Nitsche & Paulus, 2000; Nitsche et al., 2008). In cognitive research, the relation between facilitation and inhibition is more complex (Jacobson et al., 2011).

Dockery and colleagues (2009), proposed that anodal stimulation could induce a facilitation only if the task is well known or when the participant is well trained, while it could induce different effects if the task is new. For example, in the object naming procedure, the neural signal might be defined and distinguishable by the noise (other signals which might interfere), therefore the anodal stimulation could boost it enhancing the performance. In the same task, the cathodal stimulation might decrease the activation, but, since the signal is strong enough, the probability of an interference with the performance is low, so no significant change might be expected. In a novel task, the noise could be stronger, and in this case anodal stimulation could enhance the boise as well as the task-related signal. On the contrary, cathodal stimulation might decrease the noisy signals interference. If this was the case, cathodal could enhance the performance, enhancing the task-related signal and boosting the performance (Antal et al., 2004; Dockery et al., 2009). If those speculations were true, it would be possible to affirm that tDCS changes the performance based on the system status, which in turn is linked to the task administered during the stimulation (Bienenstock, Cooper & Munro, 1982).

In cognitive functions domain, a part of literature used tDCS to study inhibitory control in Stop Signal tasks[1] (Hsu et al., 2011; Ditye et al., 2012) or in Go/no go tasks[2] (Boggio et al., 2007), while others attempted to investigate its effect on working memory tasks (Zaehle, Sandmann, Thorne, Jäncke & Herrmann, 2011; Fregni et al., 2005).

The work by Hsu and colleagues (2011) applied a stimulation session (1.5mA for 10 minutes) on the pre-supplementary motor area (pre-SMA) or on motor cortex (M1) and every participant was applied anodal, cathodal and sham stimulation on different days separated by 24 hours one from each other. The active electrode was positioned over the interested area (pre-SMA or M1) and the

[1] Stop Signal Tasks (SST; Lappin & Eriksen, 1966; Logan & Cowan, 1984) ask to paricipants to perform a main task, but at the same time they have to pay attention to a signal that advise them to inhibit the prepotent answer. The task measure the ability to inhibit the spontaneous answer when a stop signal is presented (usually a sound).

[2] Go/no go tasks ask participants to answer to a stimulus presented in thecenter of the screen (e.g X) and not answer to a different stimulus (e.g a Y). The performance in jnhibitory control is measured using a percentage of the answers correctly inhibited.

reference was positioned over the cheek. The task administered was a Stop Signal Task (SST): participants were required to respond to a stimulus in a vast majority of cases (75%), while in some infrequent cases they had to inhibit the answer (when a central fixation point compared, in 25% of the cases). Results showed that anodal stimulation enhanced the performance in no go trials compared to cathodal and sham, but only when stimulating pre-SMA. The conclusion is that pre-SMA, but not M1, has a crucial role in inhibitory control and that tDCS is able to modulate the cortical activation, changing the performance. Ditye and colleagues (2012) showed that anodal stimulation over rIFG for four consecutive days induced a significant enhancement in a SST task, but the beneficial effects of tDCS were short-lasting, since no longer present after 24 hours. These results indicate that anodal stimulation can enhance inhibitory control if applied on areas crucial for this cognitive function (Dillon & Pizzagalli, 2007; Rubia et al., 2001; Aron et al., 2003). tDCS stimulation was used to understand the mechanisms involved in working memory as well. For example, Zaehle and collegues (2011) replicated the results obtained by Fregni and colleagues (2005) showing that anodal stimulation over left dorsolateral cortex (lDLC) could enhance the performance in working memory tasks (for example, the participant has to say if the letter in the center of the screen was previously presented or not), while cathodal interfered with the performance. Moreover, the electroencefalographic recording showed that anodal stimulation enhanced Alpha and Theta bands, while cathodal decreased them. This supported the conclusion that this EEG alteration could be linked to the change in working memory performance (Zaehle et al., 2011).

### 1.3 A special focus on trascranial random noise stimulation (tRNS)

tRNS is a special type of tACS. tRNS applies a low intensity alternating, randomized current where frequency is randomized as well. Like tACS, various forms of noise can be applied, depending on the frequency ranges (Antal et al., 2016). In most of the studies using tRNS, a frequency spectrum between 0.1Hz and 640Hz (full spectrum) or 101–640Hz (high-frequency stimulation) were used (Terney, Chaieb, Moliadze, Antal & Paulus, 2008; Fertonani, Pirulli & MIniussi, 2011). The probability function of tRNS follows a Gaussian or bell- shaped curve with zero mean and a variance, for which ± 99 % of all generated current levels are within 1mA. In the frequency domain all coefficients of the random sequence have a similar amplitude (“white noise”). tRNS over M1 had a anodal tDCS - like effect on the development of MEPs over time, enhancing the cortical excitability of this cortical area (Terney et al., 2008; Moliadze, Fritzsche & Antal, 2014).

Interestingly, a greater facilitation was achieved when anodal tDCS was applied before task execution and tRNS during the task (Pirulli, Fertonani & Miniussi, 2013), suggesting that the ideal timing of application of different electrical stimulation methods varies and depends on the stimulation type.

tRNS over the lateral occipital cortex facilitated facial identity perception (Romanska, Rezlescu, Susilo, Duchaine & Banissy, 2015). In contrast, tRNS to the right dorsolateral prefrontal cortex (DLPFC) impaired categorical learning in a prototype distortion task (Ambrus et al., 2011). These results demonstrate that depending on the involved cortical area and the type of protocols, tRNS can induce long-term positive but also negative changes of cognitive and brain functions.

With regard to the effect of tRNS on working memory performance, a study showed no effect of stimulation over the DLPFC on performance (Mulquiney et al., 2011).

The physiological mechanisms of tRNS are not clarified completely yet. Animal studies on tRNS that could elucidate the effects of this technique are completely missing (Antal, & Hermann, 2016). Although higher frequencies (e.g., 140Hz) have been shown to modulate brain activity, the neuronal membrane acts as a low-pass filter; therefore, high frequencies that are applied by tRNS are supposed to polarize neurons by a very small amount (Deans, Powell & Jefferys, 2007). However, as suggested by other studies, the stimulation of many synaptically connected active neurons can provide an amplification mechanism (Reato, Rahman, Bikson & Parra, 2010; Frohlich & McCormick, 2010). One potential online effect of tRNS might be associated with repetitive opening of Na+ channels, as was observed in a study investigating the application of AC stimulation to rat hippocampal slices (Schoen & Fromherz, 2008). Consistently, in a recent pilot study the Na+ channel blocker carbamazepine showed a tendency towards inhibiting MEPs 5–60 minutes after stimulation (Chaieb, Antal & Paulus, 2015). Interestingly, the partial NMDA receptor agonist D-cycloserine, the NMDA receptor antagonist dex- tromethorphan that could block the effect of tDCS, had no significant effect on the excitability increases seen with tRNS. Besides this, the effects of tRNS might be based on other mechanisms, such as stochastic resonance (Stacey & Durand, 2000). Stochastic resonance refers to the phenomenon that a signal that is too weak to exceed a threshold is amplified by adding noise, for example, when a neural oscillation in the brain is subthreshold. These, probably synaptically operated sub- threshold activities, driven by oscillatory inputs that neurons receive from other brain regions, are not strong enough to induce themselves action potential generation. If random noise is added, the sum of the two signals exceeds the threshold at

certain times. The frequency of the suprathreshold signal is determined by the existing subthreshold neural oscillation. It was suggested that tRNS might increase synchronization of neural firing through amplification of subthreshold oscillatory activity, which in turn reduces the amount of endogenous noise. The improvement of the signal-to-noise ratio in the central nervous system and the sensitization of sensory processing can lead to enhanced perception or cognitive performance (Miniussi et al., 2013; Miniussi & Ruzzoli, 2013; Moss, Ward & Sannita, 2004). However, it is not clear how this process can induce long-term changes in the human brain (Snowball et al., 2013; Cappelletti et al., 2013). A study reported that bifrontal application of tRNS for 5 days enhanced the speed of both calculation- and memory-recall-based arithmetic learning (Snowball et al., 2013). Six months later the behavioral and physiological modifications in the stimulated group relative to sham controls were still present. Similarly, in another study repeated bilateral parietal stimulation increased numerosity discrimination ability with an after-effect for several weeks (Cappelletti et al., 2013).

### 1.3.1 Safety

Further studies about the safety of tRNS have shown that this technique is comparable to the other TES regarding its discomfort. Terney et al. (2008) measured before and after tRNS the concentration of serum neuron-specific enolase (NSE) which is known to be a sensitive marker of neuronal damage (Steinhoff et al., 1999). In addition, the authors recorded EEG signal at rest one time before and three times after stimulation, to assess whether real stimulation had changed the electrophysiological bands of the participants. As result, they found no statistical difference between NSE concentration before and after treatment, nor on EEG recording.

### 1.3.2 Effects of low and high frequency tRNS on cognitive functions

To date, few studies have examined the effects of tRNS on different cognitive tasks. The reason why this technique has been neglected until now is probably due to the major popularity of another TES, the tDCS, whose functioning is better known.

*Motor/cognitive effects*

The first study which proposed tRNS as a promising experimental tool as been published by Terney et al. (2008), who investigated the effects of lf – tRNS and hf – tRNS in three different experiments (stimulation alone, cognitive task or motor task during the stimulation) as assessed by TMS-evoked MEPs and behavioral tasks analysis. Regarding to MEPs, results revealed a significant difference between sham and hf – tRNS, but no difference between sham and lf – tRNS Regarding to behavioral tasks, there was a significant difference in RTs between tRNS and sham condition in the fifth and sixth block of the trials, indicating that the participants became faster during the course of the experiment. However, when the task was repeated 1-2 hours after the stimulation, the benefit seemed to be vanished.

Furthermore, they observed also a MEPs' intensity decrease after mental effort and motor activation. This evidence appears in agreement with previous studies using tDCS (Antal et al., 2007).

For example, Terney and colleagues (2008) have shown that 10 minutes of tRNS applied over M1 with 1mA intensity can induce facilitatory after-effects lasting up to 1–1.5 hours and is capable of improving the performance in an implicit motor learning task. It was also reported that the high-frequency subdivision between 100 and 640Hz of the whole spectrum is functionally responsible for alteration of excitability in M1, superiorly to low frequency (0.1–100Hz) stimulation. In another study, tRNS on M1 enhanced motor skill learning compared to sham stimulation (Prichard et al., 2014). tRNS effects seemed to be more gradual, while tDCS resulted in large skill gains immediately following the onset of stimulation (Antal et al., 2016). Moreover, the after-effect of tRNS is intensity dependent. Moliadze, Atalay, Antal & Paulus (2012) studied the minimum tACS and tRNS intensity to detect an after effects when stimulating motor cortex. The site of the stimulation was M1, the duration was 10 minutes and the intensity might be 0.2 mA, 0.4 mA, 0.6 mA, 0.8 mA. At 0.4 mA of intensity we have an inversion from the excitatory to the inhibitory effect for the tRNS, but at the other intensities we don't see any difference. This suggests that inhibitory neurons inM1 might have lower thresholds, at least for this kind of stimulation.

*Perceptual learning*

A second study which tried to clarify the effects of tRNS on cortical activation has been published by Fertonani et al. (2011), whose aim was to investigate and compare the effects of tDCS and tRNS on a visual perceptual learning task. The current intensity of both tDCS and tRNS was set at 1.5mA for 22 minutes, with the active electrode on visual cortex (V1) and the reference on the right arm. Moreover, the authors added a control hf – tRNS condition in which the active electrode was placed over the vertex. In the experimental conditions, real stimulation was applied for the first five blocks, while in the last three blocks sham stimulation was administer. In the sham condition, all eight blocks were associated to simulate stimulation. Meanwhile the stimulation, the participants were required to perform an orientation discrimination task (ODT), as this paradigm has been widely used to study perceptual learning. Results indicate that there was a significant effect of the type of stimulation on the first to the sixth block, but a post-hoc comparison revealed a significant difference between hf – tRNS and all the other conditions, except for the first block, in which hf – tRNS was not different from anodal tDCS. In the seventh block, the stimulation effect was no longer present. Taken together, these results confirm the effectiveness of tRNS on perceptual learning, but underline that it is not fully interchangeable with anodal tDCS, at least in the visual domain. The authors conclude that the mechanisms of action of tRNS could be based on the repetition of subthreshold stimulations, which in turn could prevent the system homeostasis. This explanation is supported by the putative effects of tRNS, whose particular waves might induce temporal summation of small depolarizing currents, therefore potentiating the activity of the neural populations involved in cognitive tasks and facilitating brain plasticity by strengthening synaptic transmission between neurons (Cash and Yuste, 1998; Fertonani et al., 2011). In this framework, it is important to point out that different cortical areas are composed by different types of neurons, therefore it is not possible to generalize authors' results to cognitive functions other than visual ones.

*Facial perception*

A work by Romanska and colleagues (2015) found out that a session of tRNS over the lateral occipital cortex facilitated facial identity perception when administered before the task. The Authors found a specific enhancement for this ability. The montage was bilateral (P7 and P8). These results indicate that modulating facial perception with tRNS on lateral occipital cortex is possible.

*Categorical learning*

In contrast, tRNS to the right dorsolateral prefrontal cortex (DLPFC) impaired categorical learning in a prototype distortion task (Ambrus et al., 2011). In this experiment, participants were assigned to a group, sham, a-tDCS on rDLPFC, a-tDCS on lDLPFC, c-tDCS on rDLPFC or tRNS on rDLPFC. The montage was Cz-DLPFC like, with an electrode (the anode) on DLPFC, and the other (the reference for tDCS, the other anode for tRNS) on Cz which served as reference. Both the protocols were applied before and during the task. The Authors found significant decrease in accuracy in right a-tDCS, left a-tDCS and right tRNS. Results obtained are opposite to the hypothesis, as Fregni et al. (2005) found ain increase on accuracy in a sequential-letter memory task after anodal stimulation on lDLPFC in a sequential-letter memory task. Moreover, Mölle, Siebner, and Born (2005) found slowing in reaction time during bifrontal anodal and cathodal stimulation indicating that stimulation detained neuronal processing related to response selection and preparation in the n-back task. Zaehle and colleagues (2011) also investigated the effects of tDCS on the n-back working memory task, and found increased performance after anodal stimulation of the DLPFC. Following Antal et al. (2004), authors proposed that increasing the overall cortical excitability using anodal tDCS (and tRNS), we could result in an enhancement in the activational state of suboptimal neuronal patterns, thus facilitating of incorrect responses (Antal et al., 2004; Ambrus et al., 2011). Similar effects of tRNS and a-tDCS might be due to the montage used, which probably interfered with the performance.

*Working memory*

Mulquiney et al. ( 2011) investigated the effects of tRNS on a working memory task. In this study, Authors compared the enhancement when hf – tRNS, anodal tDCS and sham stimulation were administered whilst the participants were performing a Sternberg working memory task. The stimulation was administered over the left DLPFC (one electrode over F3 and the other on the contralateral supraorbital area) with an intensity of 1mA and the duration of 10 minutes both for tRNS and tDCS, using sham stimulation as a control condition. The possible effect of the stimulation was assessed with the CogState battery immediately before and after the stimulation.

The results revealed no effects of tRNS on CogState tasks after the stimulation. Anodal tDCS, on the other hand, improved only the performance on the more difficult 2-n back, but limited to reaction times measures. This results seem to indicate that tRNS is not able to induce changes in working memory performance, when applied over left dorsolateral prefrontal cortex.

*Cognitive training*

tRNS has also been studied in association with cognitive training. Cappelletti et al. (2013) assigned subjects to four groups: parietal tRNS with cognitive training, parietal tRNS without training, training without tRNS and tRNS over motor areas with training. The training consisted in a numerosity discrimination task, which was repeated for 5 sessions. Where required, tRNS was applied with two electrodes with an intensity of 1mA and a frequency randomly selected from 0 to 250 Hz. The electrodes were applied over P3 and P4 in two experimental groups and over bilateral motor areas in one of the control groups. Sham stimulation was delivered in the forth group. The results indicate a significant better performance in tRNS + training, motor tRNS + training and training alone, but training coupled with parietal stimulation resulted in a significantly larger improvement compared with training alone and to training coupled with motor stimulation.

Moreover, follow-up measures were added to assess if the change had been maintained after training. Results support the hypothesis that combining tRNS with an appropriate cognitive training may induce long-lasting effects. However, these results could not be generalized to other cognitive tasks, as authors did not find a difference in arithmetic, attention, executive function and visual pattern recognition performances between groups. In addition, these data support the hypothesis that we can find a greater improvement only in the case of association between stimulated areas and the task, as assessed by the results concerning the (motor stimulation) control group. Stimulating exactly the cortical areas involved in the task is therefore important to modulate the cognitive processes we are interested in.

*Arithmetic tasks*

Recently, Snowball et al. (2013) combined tRNS and NIRS to investigate the effects of the stimulation on arithmetic tasks. The electrodes (5X5cm) were positioned over the left and right lateral DLPFC (F3 and F4), as assessed by 10-20 system, for 20 minutes. Results indicate a

significant difference between tRNS and sham groups for arithmetic task, even if there was no difference for the drill. Moreover, results point out that tRNS was able to modulate both the peak amplitude and the peak latency of hemodynamic response. After a five days training, the concentrations of HbO2 and HbT in the left lateral PFC were smaller in the tRNS group than in sham group. It is important to underline that a decrease in the concentrations of HbO2 reflects a more efficient activation of this cortical region. Furthermore, improvement has been maintained even 6 months after the training, indicating that tRNS was able to induce long-lasting changes in left LDLPFC activity (see fig. 7B). These results are consistent with the literature (Zamarian, Ischebeck & Delazer, 2009; Arsalidou & Taylor, 2011) which suggests that left DLPFC is implicated in arithmetic processing and seem to indicate that tRNS coupled with proper training is able to modify cortical activity.

*Auditory cortex*

Doren, Langguth & Schecklmann (2014) investigated the effects of tRNS on auditory cortex. In this experiment, authors recordered resting state EEG before and after tRNS stimulation. The first EEG session was divided in 5 minutes of resting-state EEG and 7 minutes of EEG with auditory stimulation. Later, participants underwent 20 minutes of tRNS stimulation or sham stimulation. At the end, there was the last EEG registration, both resting-state (5 minutes) and with auditory stimulation (7 minutes). Results revealed effects for the 40 Hz tone but not for the 20 Hz one. In addition, Authors found a significant main effect of time for every EEG band, indicating that the treatment was effective. In addition, the modulation found within theta band seems to indicate a specific interference of tRNS and auditory theta, but these conclusions should be drawn with caution.

Claes, Stamberger, Van der Heyning, Ridder & Vanneste (2014) applied tRNS or tACS over auditory cortex (T3 and T4) with the purpose to test whether one of these techniques have an effect in reducing tinnitus and if stimulation repetition resulted in an improvement compared to the single session. Tinnitus causes loud and annoying noise even if no sound is coming from the environment. It seems to be caused by an enhancement in the neural activity, mainly represented by gamma waves in the auditory cortex. Results evidence no effect for tACS neither in the single session nor in the multiple sessions. On the other hand, there was a significant effect for both single session and multiple sessions of tRNS and there was a significant difference between the two groups, indicating

that multiple sessions seem to be more effective. Authors explain these results claiming that the possible functioning mechanisms of tRNS might interfere with the pathological synchronization of neural activity, reducing tinnitus discomfort and loudness.

### 1.3.3 Putative mechanisms of action

tRNS, unlike tDCS, is a polarity independent technique and therefore should prevent the system homeostasis. While with unidirectional currect we can presume that the channels of the neural membrane will adapt to different levels of activation, with tRNS we have a continuous change in electric field. tRNS might induce the temporal summation of small depolarizing currents, enhancing performance in a continuous modality (Fertonani et al., 2011).

Chaieb et al. (2009) studied the effects of hf – tRNS over the left sensorimotor area through BOLD response measurement. They applied for four minutes "white-noise" tRNS and sham stimulation on C3 with the reference over the contralateral supraorbital area, with a current intensity of 1mA. After the stimulation, participants entered the fMRI scanner, where they were required to perform a finger-tapping task with the right hand. The results show that short-duration tRNS stimulation was able to induce a transient reduction of BOLD response, indicating perhaps a sort of cortical inhibition. It has been reported, however, that longer periods of stimulation (10 minutes upward) seem to induce excitability (Terney et al., 2008). Authors suggest that the results could be explained by the homeostatic response to the consecutive tRNS—motor activation paradigm. It was reported in previous studies that the prior state of cortical activity modified by tDCS influences subsequent practice of a visuomotor coordination task (e.g. Antal et al. 2008), therefore the association between the cortical and motor activation could cause a stabilization of the system. In fact, regulatory mechanisms could come into play to stabilize the neuronal activity that encompasses both inhibitory and excitatory mechanisms within a dynamic range (Sejnowski, 1977). Later, Chaieb, Paulus & Antal (2011) tested the effects of different hf – tRNS duration. The active electrode was positioned over the left motor cortex (as determined by TMS), while the reference was positioned over the supraorbital contralateral area. The intensity was 1mA and the duration varied depending on the particular condition (4, 5, 6 minutes). The effects of real and sham stimulation were assessed through the MEPs of the first dorsal interosseus muscle (FDI), induced by TMS. The results show that when the stimulation lasted 4 minutes a tendency toward inhibition seemed to be involved,

even if not significant. After 5 and 6 minutes of stimulation, there was a significant increase in the excitability as assessed by MEPs.

Terney et al. (2008), in their early work, proposed that tRNS would induce a more rapid re-polarization of sodium channels after their depolarization, thereby making stimulated neurons ready for repeated excitation (Krause & Cohen Kadosh, 2013). Fertonani et al. (2011), moreover, proposed that the effects obtained with tRNS might be explained by the so called stochastic resonance (see also Miniussi et al., 2013), according to which noise added to the system is able to increase neural firing of the neural population involved in a specific task.

Snowball et al. (2013) found that the association between tRNS and training for five days enhanced the speed of both calculation- and memory-recall-based arithmetic learning and the change induced was long-lasting. Authors explain the decrease of HbO2 and HbT in left DLPFC considering the particular effects which tRNS may have on neural activity. Six months later the behavioral and physiological modifications in the stimulated group relative to sham controls were still present. Again, stochastic resonance can be bring into play, because the amplification of subthreshold oscillatory activity might results in a increase of neural firing synchronization within stimulated regions (Chaieb et al., 2009).

Despite these first evidences, little is known about tRNS functioning, because of the relative novelty of this technique compared to other tES. However, the mechanisms of action of tRNS might be not so different from other tES, for example the better known tDCS. Adding direct current on the scalp is able to induce a change also in neurophysiological measures, outlasting the stimulation period by up to 90 minutes (Nitsche and Paulus, 2001; Nitsche Lebetanz, Lang, Antal, Tergau & Paulus, 2003). In particular, a decrease in GABA concentration after both anodal and cathodal stimulation was observed, while not directly associated glutamate and glutamine (Glx) concentration (Stagg et al., 2009). Glx, in fact, decreased in cathodal but did not chance in anodal stimulation. Despite the fact that tDCS, tRNS and tACS functioning is based on the application of electric current, drawing any similitude by the comparison between one to each other might be quite risky.

Recent evidence, indeed, showed that tDCS and tRNS might rely on different mechanisms of functioning. While the neuroplasticity effects of tES are thought to be mediated by NMDA-receptor potentiation, the effects of tRNS might be associated with repetitive opening of Na+ channels, as it was observed in a study investigating the application of alternating current stimulation to rat hippo-campal slices (Schoen & Fromherz, 2008). Indeed, the sodium-channel blocker carbamazepine and

the GABA-A agonist lorazepam showed a tendency toward decreasing the efficacy of the stimulation (Chaieb, et al., 2015). Finally, it is proposed that tRNS might induce long-term hemodynamic changes in the human brain that might be related to neuroplastic reorganization, as found by Snowball et al. (2013). Further studies are necessary to shed light over the tES mechanisms and both short and long-term effects.

### 1.4. Limitations in tES research

tES techniques are not immune from methodological shortcomings that limit their potential.
Variability in tES outcomes is a critical point when designing clinical interventions on patients.
The great variety of tasks administered, populations, protocol parameters, cognitive functions investigated and experimental designs are an obstacle in trying to understand the real effects of tES. New, common shared guide lines on this topic might be helpful to properly address the question. (Polania, Nitsche & Ruff, 2018). This outcomes variability. although not necessarily negative, might indicate that different physiological characteristics, as well as different tasks administered or stimulated areas, might affect the results obtained.
Some authors pointed out that tES might be linked to a specific task enhancement, but also to other cognitive functions impairment (Iuculano & Cohen Kadosh, 2013). Usually, this eventuality is not tested, because attention is often focused on the specific task administered during the stimulation, but such a procedure is prone to a poor knowledge of the true effects of tES (Polania et al., 2018). When research is aimed at understanding how tES could be applied to impaired functions, all possible unexpected outcomes should be tested. A recent review inestigated the adverse effects of repeated sessions of tDCS on clinical populations, finding no evidence of adverse effects (Nikolin, Huggins, Martin, Alonzo & Loo, 2018). This evidence is in line with previous studies finding no negative impact of repeaed sessions tDCS (Runoni, Amadera, Berbel, Volz, Rizzerio & Fregni, 2011; Bikson et al., 2016).
Another critical point is linked to the one-session issue in electric stimulation. The vast majority of the studies available applied tDCS for a single session obtaining short-lasting, mild results, but whether these results were only limited to the task administered or involved other tasks/cognitive functions is still a open question. Some authors provocatively claimed that one session of tES has no reliable effect on cognitive functions and MEP amplitude modulation (Horvath, Forte & Carter, 2015). The authors did not find evidence that single-session tDCS has a reliable effect on cognitions in healthy adult populations, but no data about other samples (juvenile, elderly, patients) was

collected. Similarly, no effect was detected on EEG measures, ERPs, MEP and fMRI (in this latter case, a qualitative analysis was carried out). These negative evidence, as well as the different and various outcomes of tDCS, cast doubts on the real efficacy of tDCS on cognitive and motor functions.

Considering the mounting number of studies assessing the effects of tDCS in a great variety of cognitive domains, it is quite surprising that no index reached the significant level in those reviews. As each paper analyzed reported a significant finding on their respective outcome measure, one would expect to see an increased chance of finding a consistent/reliable effect, while it seems not to be the case.

Regarding tRNS, no study to date investigated whether the difference in the functional mechanisms might result in a difference in offline, transfer outcomes on cognitive functions even in one session or whether a specific training is required.

Moreover, it is well known that even subjective differences are crucial in determining different outcomes. Lopez-Alonso Fernández-del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran (2015) investigated the intra-subjects and inter-subjects variability to assess the potential confound effects of anodal tDCS. In general, it is well known that around 50% of the sample responded as expected (excitatory effect), while other 50% showed an unexpected response (no effect or inhibitory effect; Lopez-Alonso, Cheeran, Río-Rodríguez, & Fernández-del-Olmo, 2014; Wiethoff, Hamada, & Rothwell, 2014). In their results, inter-individual variation contributed much more than intra-individual variation to the total variance. Specifically, 60% or more of the subjects responded in each of the two stimulation sessions during 30 min after stimulation. Around half of the sample maintained this facilitatory response also in the second session. It is important to note that 78% of the responders to the first tDCS session displayed the same response (increase in cortical excitability) in the second session.

Other works confirmed that baseline status of the system is crucial in order to obtain reliable effects of the stimulation, and that often a general analysis is not able to detect any effect (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Learmonth, Thut, Benwell, & Harvey, 2015; London & Slagter, 2015).

Clearly, tES should be tested individually on each participant because a different outcome might be expected based on a number of different, somehow uncontrollable, features. A good starting point might be the study of each tES protocol on healthy normal functioning subjects in order to better understand the underlying mechanisms and define more appropriately the proper tool and parameters for clinical studies.

While tDCS has been widely studied and general consensus on its mechanisms of function has been reached, tRNS and tACS are potentially valid techniques even if very few studies are available. Focusing on tRNS, the evidence is not strong enough to design an intervention on clinical population since the addition of noise, the supposed mechanism of function of tRNS, might be detrimental in an impaired population. Moreover, no studies to date investigate the possible side effect of the stimulation, as Iuculano and Cohen Kadosh (2013) did with tDCS, so it is impossible to anticipate if the technique might be associated with detrimental effects or not.

# CHAPTER 2

# SPONTANEOUS EEG OSCILLATIONS IN COGNITION

Electroencephalography is a non-invasive technique that allows to detect the electrical scalp activity generated by brain structures. The electroencephalogram (EEG) is defined as electrical activity of an alternating type recorded from the scalp surface after being picked up by metal electrodes and conductive media (Pfurtscheller & Lopes da Silva, 1993).

From a physiological point of view, the EEG power reflects the number of neurons that discharge synchronously. A number of studies confirmed that EEG power, as well as Event Related Potentials (ERPs) are measures that reflect the capacity or performance of cognitive functions. However, it must be emphasized that power measurements are strongly affected by a variety of unspecific factors (such as the thickness of the skull or the volume of cerebrospinal fluid), by methodological and technical factors (such as inter-electrode distance or type of montage), but also by more specific factors, such as age, arousal and the type of cognitive demands during actual task performance.

Electroencephalographic recording is a completely non-invasive procedure that can be applied repeatedly to patients, normal adults, and children with virtually no risk or limitation. When brain cells (neurons) are activated, local current flows are produced. EEG measures the current flow generated by the synaptic excitation of the dendrites of many pyramidal neurons in the cerebral cortex. Differences of electrical potentials are caused by summed postsynaptic graded potentials from pyramidal cells that create electrical dipoles between soma (body of neuron) and apical dendrites (neural branches). Brain electrical current consists mostly of Na+, K+, Ca++, and Cl- ions that are pumped through channels in neuron membranes in the direction governed by membrane potential (Atwood, & MacKay, 1989). Only large populations of active neurons can generate electrical activity recordable on the head surface. Between electrode and neuronal layers current penetrates through skin, skull and several other layers. Weak electrical signals detected by scalp electrodes are massively amplified, and then displayed on paper or stored to successive analysis (Tyner, Knott, & MacKay, 1989). The highest influence to EEG comes from electric activity of cerebral cortex due to its surface position.

Event-related potentials (ERPs) are significant voltage fluctuations resulting from evoked neural activity. Evoked potentials are triggered by an external or internal stimulus (Teplan, 2002). ERPs are suitable methodology for studying the aspects of cognitive processes of both normal and abnormal nature (neurological or psychiatric disorders; Picton et. al., 2000). Mental operations, such as those involved in perception, selective attention, language processing, and memory, proceed over time ranges in the order of tens of milliseconds. Whereas PET and MRI can localize regions of activation during a given mental task, ERPs can help in defining the time course of these activations (Teplan, 2002).

The amplitudes of ERP components are often much smaller than the spontaneous EEG components, so they are not visible in the raw EEG recording. They are extracted from various sets of single recordings by digital averaging of epochs (recording periods) of EEG time-locked to repeated occurrences of sensory, cognitive, or motor events (Gevins, & Rémond, 1987). The spontaneous background EEG fluctuations, which are randomly distributed with respect to the stimulus onset, are averaged out, leaving the event-related brain potentials. Therefore, these electrical signals reflect only that activity which is consistently associated with the stimulus processing in a specific time-locked way. The ERP thus reflects, with high temporal resolution, the patterns of neuronal activity evoked by a stimulus.

## 2. 1 Brain waves classification

To obtain brain patterns of individuals' baseline cortical activity, subjects are typically instructed to close their eyes and relax. Some studies use an open-eyes recording to avoid a massive presence of alpha band waves which could mask the other frequency bands. The most common cortical wave shape is sinusoidal. Usually, EEG rhythms are measured from peak to peak, and normally range from 0.5 to 100 μV in amplitude. By means of Fast Fourier transform, power spectrum from the raw EEG signal is derived. In power spectrum the contribution of sine waves with different frequencies are visible. Although the spectrum is continuous, ranging from 0.1 Hz up to one half of sampling frequency, the individual's brain state may make certain frequencies more dominant. Brain waves have been categorized into five groups (Figure 1):

- gamma (<30 Hz)

- beta (12-30 Hz),

- alpha (8-12 Hz),

- theta (4-7 Hz),

- delta (0.1-4 Hz).

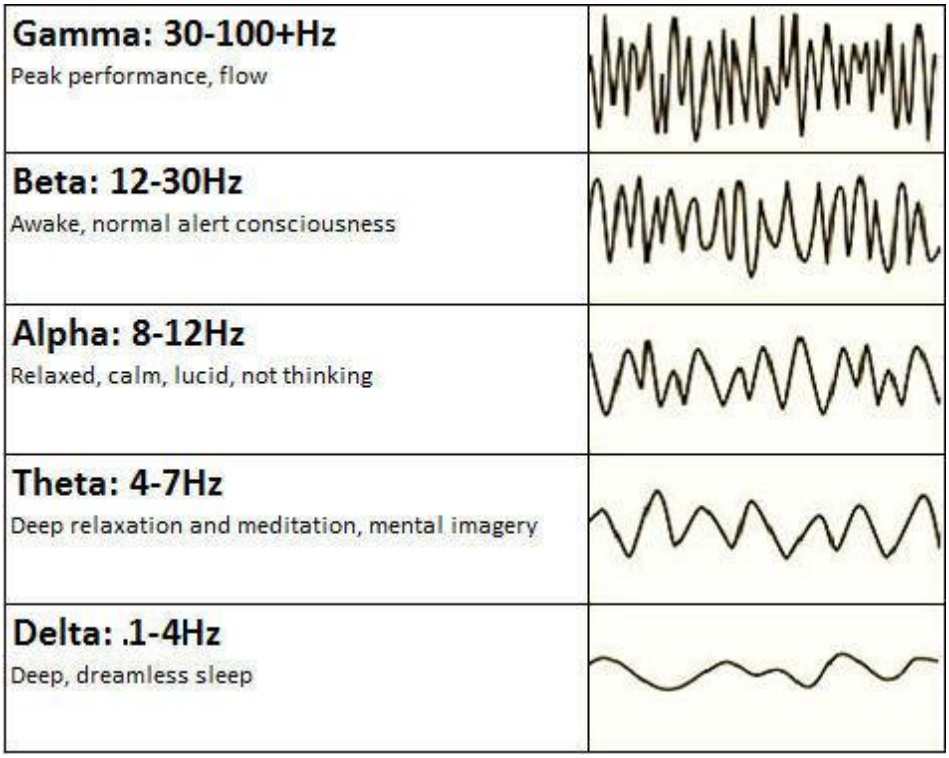



Figure 1. Brain waves. Taken by http://www.brainwavecollege.com/what-are-brainwaves.html

The best-known and most extensively studied frequency of the human brain is the alpha rhythm. Alpha can usually be observed mainly in the posterior and occipital regions with typical amplitude about 50 μV (peak-peak). Alpha activity is induced by closing the eyes and by relaxation, and abolished by eye opening or alerting by any mechanism (e.g., thinking or calculating). Most of the people are remarkably sensitive to the phenomenon of "eye closing", i.e., when they close their eyes their wave pattern significantly changes from beta into alpha waves. The precise origin of the alpha rhythm is still not known. Alpha waves are usually attributed to summated dendrite potentials. Evoked potentials (e.g., generated in brain stem) often consist of fibre potentials (axonal) and synaptic components (Teplan, 2002). EEG is sensitive to a continuum of states ranging from stress state, alertness to resting state, hypnosis, and sleep. During normal state of wakefulness with open eyes, beta waves are the dominant EEG frequency. In relaxation or drowsiness, alpha activity rises,

and when sleep appears the power of low frequency bands increase. Sleep is generally divided into two broad types: non rapid eye movement sleep (NREM) and REM sleep. NREM and REM occur in alternating cycles. NREM is further divided into stage I, II, III, and IV. The last two stages correspond to deeper sleep, where slow delta waves show higher proportions.

Theta is the dominant rhythm in the hippocampus of lower mammals. Its frequency ranges from about 3 to 7 Hz (Klimesch, 1999). Crucially, with increasing task demands theta synchronizes, whereas alpha desynchronizes (Pfurtscheller, 1992; Givens, 1996; Gevins, Smith, McEvoy & Yu, 1997). In other words, if EEG power in a resting condition is compared with a test condition, alpha power decreases (desynchronizes) and theta power increases (synchronizes). Other evidence showed that theta frequency covaries with alpha frequency, and theta and alpha band powers are related to each other, although in a reciprocal or 'opposite' way (Doppelmayr, Klimesch, Pachinger & Ripper, 1998).

Generally, research seems to indicate that an increase in lower alpha power may reflect the increased efforts (and probably difficulties) of subjects to maintain a state of alert wakefulness (Torsvall, 1987). This interpretation is also supported by Crawford et al. (1995) who have found that, in contrast to subjects with high-sustained attention, low-sustained attention subjects which have difficulties to inhibit distracting environmental stimuli show a significantly larger proportion of lower alpha power. It is showed moreover a double dissociation with cognitive performance: large alpha power correlated with a pronounced decrease in event-related band power, and small theta power correlated with a pronounced increase in band power indicate good cognitive performance. In particular, desynchronization of alpha was found for semantic memory performance and alerting (Klimesch, Pfurtscheller, & Schmike, 1992; Klimesch, Schimke & Pfurtscheller, 1993; Klimesch, Pfurtscheller & Schimke, 1993), whereas theta synchronization correlates with working memory or episodic memory performance (Klimesch, Doppelmayr, Pachinger & Russegger, 1997).

Delta and Theta activity are often related to inhibition. For example, in a go/no-go task, an increase in medial-frontal theta activity is consistent between different studies (Yamanaka and Yamamoto, 2010; Barry, 2009; Kamarajan et al., 2004; Kamarajan et al., 2006; Kirmizi-Alsan, Bayraktaroglu, Gurvit, Keskin, Emre & Demiralp, 2006) as well as other control-related processes such as response error and feedback processing (Bernat, Nelson, Steele, Gehring & Pactrick, 2011; Gehring and Willoughby, 2004; Trujillo & Allen, 2007; Yordanova, Falkenstein, Hohnsbein & Kolev, 2004;

Cavanagh, Zambrano-Vazquez & Allen, 2011; Cavanagh, Cohen & Allen, 2009; Cavanagh, Frank, Klein & Allen, 2010 Cohen, Elger & Ranganath, 2007).

Research has detailed Delta band activity associated with a myriad of cognitive functions, including reward processing (Bernat, Nelson, Steele, Gehring & Patrick, 2011), target detection (Schürmann, Basar-Eroglu, Kolev, & Basar, 1995; Gilmore, Malone, & Iacono, 2010), commission of motor errors (Cavanagh et al., 2011; Yordanova et al., 2004), and reward magnitude (Bernat, Nelson, Steele, Gehring & Patrick, 2012). Among all EEG spectral components, delta and alpha rhythms are reliable indexes of cortical inhibition both during sleep and in awake adult individuals who are not engaged in specific cognitive tasks (Cantero, Atienza & Salas, 2002; Czisch, et al., 2002; De Jongh, Baayen, De Munck, Heethaar, Vandertop & Stam, 2003; Laufs 2008; Spironelli, Busenello, & Angrilli, 2016) or it is conversely associated to abnormal functions in aphasic patients (Spironelli & Angrilli, 2009) schizophrenia (Spironelli, Angrilli, Calogero, & Stegagno, 2009), dislexia (Penolazzi, Spironelli, & Angrilli, 2008) and Alzheimer disease (Hier et al., 1991). In contrast to the delta effects exhibited in a gambling-feedback task, where theta and delta were sensitive to different stimuli (theta-loss and delta gain; Bernat et al., 2011), the delta activation was sensitive to the same experimental effect as theta (i.e., greater for no-go stimuli). This delta activity may dually reflect motor/cognitive inhibition (Harper, Malone & Barnat, 2014) and stimulus context updating, similar in function to the P3a (Polich, 2007). Moreover, other studies linked frontal theta to working memory (Raghavachari et al., 2001), memory load (Jensen, & Tesche, 2002) and memory consolidation during sleep (Popa, Duvarci, Popescu, Léna, & Paré, 2010).

Alpha and Beta bands are correlated to attentional functions in an opposite way. An enhancement of beta activity was found not only in visual cortex, but also in higher visual areas, lateral posterior and pulvinar complex (Wróbel, 2000). Other recent evidence (Sachett et al., 2015) found a synchrony between somatosensory cortex and rIFC in both the alpha and beta frequency bands. This synchrony manifested as an increase in the alpha-band early after cue, and as a subsequent increase in beta-band synchrony closer to stimulus processing. Differences in phase synchrony were not found in several proximal control regions. These results are the first to reveal distinct interactions between primary sensory cortex and rIFC in humans, and suggest that synchrony between rIFC and primary sensory representations plays a role in the inhibition of irrelevant sensory stimuli and motor responses (Sachett et al., 2015)

# CHAPTER 3

# THE PRESENT RESEARCH

## 3.1 The present work

The present doctoral thesis aimed at addressing some issues about brain stimulation and its feasibility in neurorehabilitation and clinical applications.

First of all, we aimed at evaluating the effects of unilateral cathodal tDCS (c-tDCS) on cognitive functions, In particular, we tested c-tDCS over non-numerical abilites, since no study to date investigate its effects, by stimulating rIFG, an area considered crucial in response inhibition (Hauser, Rotzer, Grabner, Mérillat, & Jäncke, 2013), in order to prove the role of this area in non numerical tasks (i.e. dots comparison tasks) and to better understand the efficacy of c-tDCS in cognitive functions domain. Moreover, we added a post-stimulation task associated to inhibitory functions, but not non-numerical cognition - the Verbal Stroop task- to understand whether the possible effects of the stimulation were still present within 30 minutes, as part of studies claimed (Nitsche & Paulus, 2000; Lopez-Alonso et al., 2015) This study might contribute to better understand the effects of one session cathodal stimulation on non-numerical tasks and to attribute a possible role to inhibitory functions in a dots comparison task, as other studies already suggested.

A second investigation included the combination of tES and resting state EEG oscillatory power recording to investigate the effects of single session application on cognitive functions (experiment 2) and training on executive functions (experiment 3). It is well known that EEG is a powerful tool to assess possible changes in plasticity (but see chapter 2). In the first case, we extended the knowledge about tES functioning by comparing single session anodal tDCS, unilateral montage and bilateral montage tRNS on the online task (a simplified version of the Mental rotation task). Crucially, we administered offline tasks others than that performed during the stimulation, following the indications by Iuculano & Cohen Kadosh (2013) to investigate both offline, and possible side effects of our protocols. The tasks administered were a landmark task (following Benwell et al., 2015) and a cued detection task (Van del Heijden & Eerland, 1973). Moreover, we acquired resting state EEG before and after the stimulation to assess possible long-term effects on cortical plasticity. This study might be useful to better understand the difference in techniques both in behavioral domain, duration of after-effects, and plasticity induced changes. Based on the

literature on tES, we would expect no significant offline difference in anodal group and sham group, nor modulation in transfer tasks, since anodal effects are reported to be short lasting, often related to online tasks, and no alteration in plasticity should be detectable after only one session without a coupled training. Regarding tRNS, we expect a better efficacy for bilateral tRNS, based on the available literature (Moliadze, Antal & Paulus, 2010; Chaieb, Kovacs, Cziraki, Greenlee, Paulus, & Antal, 2009; Chaieb et al., 2015), while unilateral tRNS might be similar to anodal tDCS in effects based on the similar montage, even if different activations might be observable (orbitofrontal cortex excitation for the former while deactivation for the latter).

In experiment 3, we assessed the effects of tRNS coupled with a behavioral cognitive training (Labyrinth) which exercises executive functions and attention. We measured the change induced by the training immediately at the end (post-training) and a month after the end of the training (follow-up). Moreover, we studied the possible transfer effects on tasks others (switch task, single task, dual task, Attentional Network task) and we recorded resting state EEG oscillatory power before, immediately after and a month later to assess possible long-term effects on cortical excitability. This study might be important to add new evidence about the effects of tRNS on attentive functions and possible long-term, reliable plasticity modulation in order to design possible interventions on clinical population (in particular, neglect patients). Here we expect an online modulation of training task, even if a difference in response to the stimulation between participants is possible (responders vs non responders). Moreover, we expect to detect a change in transfer tasks-, indicating a possible extension of the stimulation effect also to tasks others than the ones administered, following Cappelletti et a. (2013) and Snowball et al. (2013). Finally, we expect long-term effects on cortical plasticity in tRNS group, but not in sham group, thus indicating that coupling tRNS with training has long-lasting, reliable effects on human brain also on healthy participants.

## 3.2. Cathodal tDCS on right inferior frontal cortex affects inhibition, but only if you are familiar with the task: Evidence from a dots comparison paradigm.

*Introduction*

Numerical abilities have been studied both in term of symbolic and non-symbolic skills. Symbolic numerical abilities are related to the processing of Arabic numbers and number-words (for example 5, five etc), while the non-symbolic ones are related to numerosities (for example, the number of

dots in an array). Non -symbolic abilities are thought to rely on the Approximate Number System (ANS), which has been demonstrated to be related to mathematical achievement in children (e.g., De Smedt, Vershaffel, & Ghesquièrre, 2009; Halberda, Mazzocco, & Feigenson, 2008; Inglis, Attridge, Batchelor, & Gilmore, 2011; Libertus, Feigenson, & Halberda, 2011; Mazzocco, Feigenson, & Halberda, 2011a; Mundy & Gilmore, 2009; for a review, see De Smedt, Noel, Gilmore & Ansari, 2013). In other words, the ability to successfully select the more numerous set of dots when two sets are simultaneously presented seems to be related to the subsequent development of mathematical abilities in children. Many studies support the hypothesis of a deficient ANS in individuals with dyscalculia and showed reduced ANS acuity (Mazzocco et al., 2011a; Piazza, et al., Zorzi, 2010), slower and less accurate performance (Mussolin, Mejias, & Noël, 2010) or less precise estimates of dot collections (Mazzocco, et al. 2011a; Mejias, Grégoire, & Noël, 2012) in developmental dyscalculia compared to typically achieving children (but see De Smedt & Gilmore, 2011; Iuculano, Tang, Hall, & Butterworth, 2008; Landerl & Kölle, 2009; Rousselle & Noël, 2007, for contrasting evidence).

The nature of the mechanisms underlying numerosity comparison is an important research topic (Gebuis & Reynvoet, 2011, 2012 a, b). Task protocols and scripts have been made available to the research community in order to facilitate a comparison of results across labs. One key issue is how to control for non-numerical visual cues that are often correlated with numerosity (Gebuis and Gevers 2011; Gebuis and Reynvoet 2012a, b). More importantly, the tasks need to designed considering these confounds in order to measure correctly the ANS functioning.

Numerosity comparison accuracy is modulated by the ratio between the two sets, that is, the greater the difference between the two sets (and so the ratio between the two), the better is the performance achieved. Conversely, when the ratio is closer to 1, a correct comparison of the numerosities is more challenging and it requires better individual "acuity" of the ANS. It has been found that adults show more precise ANS, with the ability to discriminate between sets up to 0.9 ratio (Pica et al., 2004). Moreover, several studies suggest that ANS acuity is related to mathematical abilities in children (Mazzocco et al. 2011; Libertus et al., 2011), adolescents (Halberda, Mazzocco & Feigenson, 2008) and adults (Libertus, Odic & Halberda, 2012; Halberda, Wilmer, Naiman & Germine, 2012). Other studies reported conflicting results (see De Smedt et al. 2013, for a review) and other highlight that this relationship is evident in children but not in adults (Inglis et al., 2011). A recent meta-analysis confirmed that ANS ability is associated with math achievement (Schneider et al., 2017).

The task commonly used to assess ANS acuity is the numerosity comparison task where two sets of dots are simultaneously compared in order to select the more numerous (Clayton & Gilmore, 2014). The presentation of the dots is usually rapid to discourage participants from counting the number of dots. Inglis and Gilmore (2014) proposed that accuracy might be a reliable measure to assess ANS acuity, , even if also reaction times, "w" (Weber fraction) score and numerical ratio effect have also been used (Inglis & Gilmore, 2014).

*Dots comparison task*

Gebuis & Reynvoet (2011,2012 a, b) highlighted the importance of visual cues in dots comparison tasks. In particular, they pointed out that accuracy in these tasks is often influenced by the ability to differentially weight visual cues when making a numerosity choice (Gebuis and Reynvoet, 2012 a, b). They claimed moreover that the ANS ability is difficult to determine because of the confounding effect of these visual characteristics (Gebuis & Reynvoet, 2012 a, b). These visual cues are the total (or cumulative) surface area (the sum of the dots surface area in each set), item size (the average diameter of dots in each set), the convex hull (area occupied by the dots configuration), and density (occupied area extended divided by total surface area). The authors created a program able to generate non-symbolic number stimuli for which the visual cues can explain a very small portion of the variance, thus making it suitable to study ANS. In contrast, the influence of visual cues can be investigated by creating congruent and incongruent trials (Gerbuis & Reynvoet, 2011). In congruent trials, the more numerous is the set, the greater total surface area and convex hull are, conversely for incongruent trials the more numerous set has also the smaller total surface area and convex hull. Thus in the latter trials it is important to ignore competing information in order to correctly compare the numerosity of two sets. Typically, performance is more efficient in congruent trials and it is worse in incongruent ones. For this reason, it has been proposed that inhibitory ability might be involved in dots comparison tasks (Szũcs, Devine, Soltesz, Nobes & Gabriel, 2013).

Studies suggested that there is an interaction between area and convex hull in determining the performance in a dots comparison task (Clayton, Gilmore & Inglis, 2015). When both total surface area and convex hull are congruent with the sets numerosity, the best performance is achieved, while when both are incongruent the worst performance is expected. Conversely, when convex hull is incongruent, the congruency in total surface area gives an intermediate performance, while when convex hull is congruent no difference is expected (Clayton, Gilmore & Inglis, 2015).

The results regarding incongruent and congruent conditions in dots comparison task seem to indicate that inhibitory control is involved in such tasks (Clayton & Gilmore, 2014; Cappelletti, Didino, Stoianov & Zorzi, 2014; Clayton, Gilmore & Iglis, 2015). In addition, studies by Cappelletti et al. (2014) pointed out that older adults performance is impaired in dots comparison only for incongruent trials, but not for congruent ones. This seems to indicate that inhibition might be involved in resolving the conflict between physical properties in dots comparison tasks. A similar phenomenon has been recently observed in dyscalculic children (Budgen & Ansari, 2017)

*Inhibitory control*

Several studies have highlighted the importance of inhibitory control in dots comparison task performance (Fuhs & McNeil, 2013; Cappelletti et al. 2014; Gilmore, Attridge, Clayton, Cragg, Johnson, Marlow & Inglis, 2013; Nys & Content, 2012). Inhibitory control is defined as the ability to suppress the non-relevant information thus blocking prepotent response in favour of a more efficient performance (Dempster, 1992). Participants will consequently focus on the task-relevant information while the irrelevant ones will be suppressed or ignored (see for review: Dagenbach & Carr, 1994; Dempster & Brainerd, 1995; Harnishfeger, 1995; MacLeod, Dodd, Sheard, Wilson & Bibi, 2003). Regarding inhibition, studies often distinguish between cognitive or motor inhibition. Motor inhibition can be defined as the ability of stopping a course of action that is not optimal anymore (Verbruggen & Logan, 2008), while cognitive inhibition is linked to suppressing upcoming informations (Harnishfeger, 1995; Aron, 2007) or unwanted or irrelevant memories from coming to mind (Anderson & Hanslmayr, 2014; Storm & Levy, 2012; Penolazzi, Stramaccia, Braga, Mondini & Galfano, 2014; Stramaccia, Penolazzi, Monego, Castelli & Galfano, 2017).

A classic example of cognitive inhibition is shown by the Stroop task (Stroop, 1935), which involves stimuli comprising colour words, e.g. red/blue/black, written in the suggested or different colour inks. Trials can be classified as either congruent or incongruent. Congruent trials are those in which the colour word is consistent with the ink colour, for example the word red written in red ink. Incongruent trials are those in which word meaning differs from the ink used, for example the word red written in green ink. The participants are required to select the ink colour written on the page blocking the interference coming from the meaning of the word. Research showed that participants are less accurate and slower in incongruent trials compared to congruent ones (MacLeod, 1991).

Regarding the relationship between Stroop task and dots comparison, only one study to our knowledge found out a positive relationship between the tasks in healthy elderhood (Cappelletti et

al., 2014). It might be therefore interesting to further investigate the relationship in the young healthy population.

*Neural basis of inhibitory control*

It is widely believed that the prefrontal cortex, specifically dorsolateral prefrontal cortex and right inferior frontal gyrus, is involved in inhibitory tasks (Stramaccia, Penolazzi, Sartori, Braga, Mondini & Galfano, 2015; Anderson & Hanslmayr, 2014; for a review, see Aron et al., 2014). The activation of these sites seems to be linked to the ability to suppress irrelevant information in order to efficiently perform the task. Whether both the sites are involved in inhibition or if there is a dissociation between the sites based on the specific type of inhibition is still matter of discussion (Aron, Robbins & Poldrack, 2014). Some authors proposed that rIFC is linked to attentional monitoring or detection more than inhibition. For example, Stuss and Alexander (2007) commented that the activation of right lateral PFC during tasks such as a classical stroop task might be explained by a triad of frontal processes: energization, task setting, and attentive monitoring, rather than by suppressing an already initiated response as suggested by other authors. Sharp, Bonnelle, De Boissezon, Beckmann, James Patel, & Mehta (2010) compared trials with stop signal trails with trials with 'keep responding' signals, showing that both types of trials equivalently activated the rIFC and hence concluded that its function is attentional detection and not specifically inhibition. However, criticism for this conclusion arose because of the characteristics of "keep responding" task, which probably engages inhibition as well. Aron et al. (2014) conjecture that any stimulus that is salient/infrequent/unexpected will recruit inhibition, and therefore will activate rIFC. Consistently with this hypothesis, there is evidence that also drugs craving is associated with reduced rIFC activation (Whelan, Conrod, Poline, Lourdusamy, Banaschewski, Barker et al., 2012).

Regarding dots comparison task, a lack in those inhibitory abilities might be linked to inefficient inhibitory control and therefore to less accurate performance in incongruent trials, but not in congruent ones. Although a number of studies proposed a positive association between inhibitory skills and dots comparison performance (Fuhs & McNeil, 2013; Gilmore, et al., 2012; Clayton & Gilmore, 2015), only one study to date found evidence of this hypothesis on healthy aging ( Cappelletti et al., 2014). Specifically, the authors found that in healthy older adults the performance in incongruent trials was poor as compared to congruent ones. Moreover, the performance was

preserved in other numerical and mathematical tasks, but not in inhibitory tasks, suggesting that a decline in inhibitory abilities might be linked to a poor performance in incongruent trials.

In the present study, we investigated the causal relationship between activation of right inferior frontal gyrus and performance at the incongruent trials in a dots comparison task. Moreover, we added a verbal Stroop task at the end in order to assess the possible long term effects on inhibitory mechanisms, and to assess if the same type of inhibition might be involved in both the tasks. We employed cathodal tDCS which is thought to interfere with the cortical activity, even if different outcomes might be expected (Levasseur-Moreau, Brunelin, & Fecteau, 2013; Jacobson, Koslowsky & Lavidor, 2012). Firstly, we chose to apply cathodal stimulation to simulate detrimental inhibitory abilities in healthy participants, with the aim to replicate Cappelletti et al. (2014) results in older adult participants. The rationale of this choice can be summarized as follows:

a) It has been proven that, at least in the cognitive domain, anodal stimulation effects depend on the initial level of expertise of participants, that is the lower the baseline level, the greater the enhancement (Berryhill & Jones, 2012; Dockery et al., 2009; Hsu et al., 2014; Learmonth et al.,2015; Tseng et al., 2012; Benwell et al., 2015). In light of this evidence, it is unlikely that anodal stimulation could improve healthy participants performance (here Psychology students).

b) a convincing way to prove a role of rIFG in dots comparison tasks is to interfere with rIFG activation in healthy participants, thus simulating a sort of "ageing effect" for the inhibitory functions. A detrimental effect similar to Cappelletti et al. (2014) would therefore demonstrate the role of this cortical site and suggest possible future rehabilitative methods targeting this specific site.

c) in the memory domain, inhibitory abilities have already been modulated by cathodal tDCS on DLPFC (Penolazzi et al., 2014) but not by anodal tDCS nor on DLPFC (Penolazzi et al., 2014) nor on rIFG (Stramaccia et al., 2017) suggesting in the latter cases possible anatomical or instrumental constraints which could preclude the modulation.

d) it is well known that cathodal tDCS is able to induce both a decrease and an enhancement in cognitive domain (Filmer, Mattingley, & Dux, 2013; Moos, Vossel, Weidner, Sparing, & Fink, 2012; for a review, see Santarnecchi, Brem, Levenbaum, Thompson, Cohen Kadosh & Pascual-Leone, 2015). Either outtcomewould provide interesting suggestions about the mechanisms with which the rIFG is involved in the task and possible application on patients.

*Experiment 1:Ihnibition and dots comparison task*

First of all, we conducted a behavioural study to verify if the task we designed was able to induce the congruency effect observed in previous studies. More specifically, we expected:
a. a main effect of total area and convex hull on accuracy, that is less accurate performance when total area and convex hull are incongruent with the numerosity of the dots set (the more numerous is also the set with smaller total area and convex hull) and more accurate in the opposite situation;
b. an effect of congruency in the Stroop task, both verbal and numerical;
c. a correlation between the performance in the two tasks, if the inhibitory mechanisms involved are the same.

*Participants*

22 young healthy participants (BSc Psychology students; age 19-22 years, 11 males) took part in the experiment. They all had normal or corrected vision and were right handed according to the Oldfield test (at least 75%; Oldfield, 1971). They all were naive about the purpose of the experiment. The experiment received approval from the local ethical committee and all participants before starting the first session signed the informed consent according to the Declaration of Helsinki.

*Procedure*

Participants were seated on a comfortable chair in a dimly lighted room and were asked to complete some computerized tasks (distance from the computer screen: 60 cm). In the dots comparison task they were asked to decide which set of dots was more numerous. During a separate session on a different day, they came to the laboratory and completed the other tasks, a numerical and verbal Stroop task. The order of the two Stroop tasks was randomized to avoid sequence effects. We chose to administer the tasks on two separate days to avoid fatigue in our participants. The procedure is represented in Figure 1.

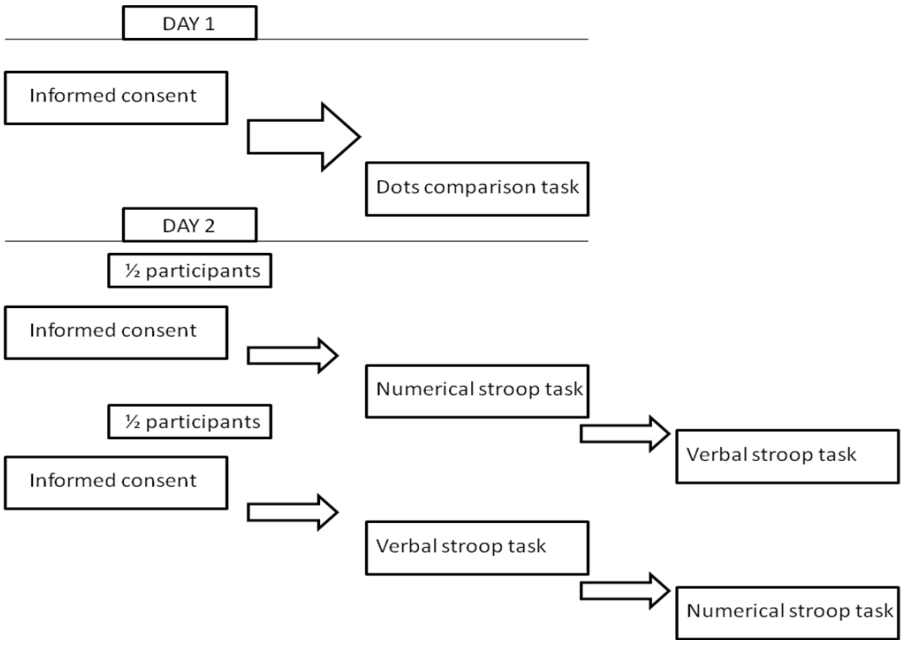



Figure 1. Procedure of Experiment 1.

*Materials*

*Dots comparison task*

The total number of trials was 384. At the beginning of each trial participants saw a fixation cross (about 1 cm wide) in the center of the screen and after 600 milliseconds it was replaced by two sets of dots, one on the left and one on the right side of the screen (600 ms). The numerosities employed and the resulting ratio conditions are listed in Table 1, but they were randomly presented during the experiment. Participants were instructed to indicate the more numerous set by pressing the right key or the left key respectively with the right and the left hand. The presentation of the sets was rapid (600 ms) to prevent participants from counting. They had 2 seconds to provide an answer, after this period a new trial was presented. After the response, the fixation cross re-appeared and a new trial begun (see Figure 2). Based on the characteristics of the task, there were 4 types of trials:

- congruent convex hull and congruent area (CC-CA)
- congruent convex hull and incongruent area (CC-IA)
- incongruent convex hull and congruent area (IC-CA)
- incongruent convex hull and incongruent area (IC-IA)

Each type of trial (CC-CA,CC-IA,IC-CA,IC-IA) was presented 8 times, for a total of 16 congruent trials and 16 incongruent trials.

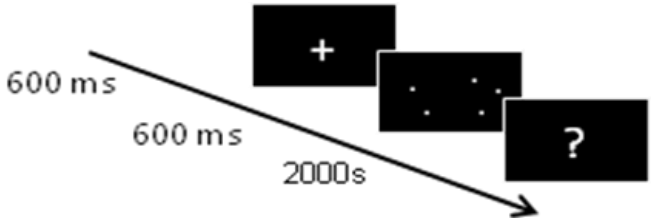



Figure 2. Sequence of events for each trial in the dots comparison task.

| Numerosity 1 | Numerosity 2 | Ratio | Number of trials |
|---|---|---|---|
| 20 | 32 | 0.62 | 32 |
| 22 | 32 | 0.69 | 32 |
| 24 | 32 | 0.75 | 32 |
| 26 | 32 | 0.81 | 32 |
| 28 | 32 | 0.88 | 32 |
| 30 | 32 | 0.94 | 32 |
| 34 | 32 | 0.94 | 32 |
| 36 | 32 | 0.89 | 32 |
| 38 | 32 | 0.84 | 32 |
| 40 | 32 | 0.80 | 32 |
| 42 | 32 | 0.76 | 32 |
| 44 | 32 | 0.73 | 32 |

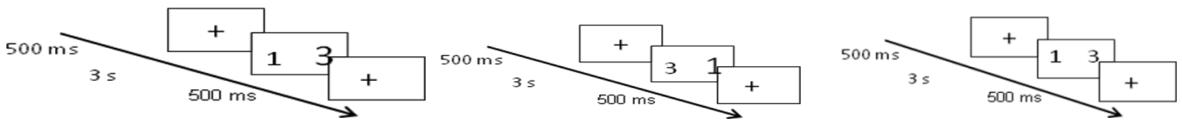
Table 1. Combinations of numerosities in the comparison taks, with corresponding ratio and number of trials (including both congruent and incongruent trials. ) The side of presentation of the reference dots set (32) was random but counterbalanced.

*Numerical stroop task*

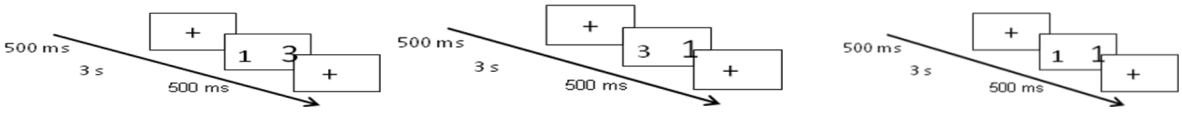
A numerical Stroop task was administered to assess inhibitory abilitites in our participants. The number Stroop task is based on an established paradigm that assesses the automatic processing of numbers as well as inhibitory processes using experimental stimuli that contain congruent and incongruent information (Henik & Tzelgov, 1982). In two separate blocks, participants viewed a

total of 416 (208 per block) pairs of Arabic numbers within the sets 1-3 and 7-9 . The pairs were 1-2, 1-3, 2-3, 7-8, 7-9, 8-9, 2-1, 3-1, 3-2, 8-7, 9-7, 9-8 and they were randomly presented. Note that for all pairs the digits were only 1 or 2 units apart to ensure that the magnitude comparison task was challenging. Crucially, the Arabic numbers could vary not only in magnitude (e.g. 3 vs 2; "magnitude task") but also in physical size (e.g. 3 vs 2; "size task"). Participants initially performed a practice block with 10 trials.

Trials were composed by three types of stimuli (64 trials for congruent and incongruent, 80 for neutral): a congruent stimulus corresponded to a pair of digits in which a given digit was larger in both the relevant and the irrelevant dimensions; a neutral stimulus was a pair of digits that differed only on the relevant dimension (magnitude or physical size); an incongruent stimulus consisted of a pair of digits in which one of the digits was at the same time larger in one dimension (e.g. magnitude) and smaller in the other (e.g. physical size). Apart for these constraints, numbers presented in each pairs were randomly selected. In the size task, the number stimulus could be paired to itself, therefore consisting of a neutral stimulus for the (e.g. 2 vs 2), or to another number stimulus which could be 1 or 2 units apart. In the magnitude task, the two number stimuli could be of the same physical size, therefore consisting of the neutral condition, or they could vary along two levels of physical size, as stimuli could appear in a vertical visual angle of 0.7° or 0.9° centered along the horizontal line of the computer screen to the left or the right of the fixation cross (see Figure 3). Participants were required to indicate the larger number in either magnitude or physical size by pressing either the left or the right key with the corresponding index if the larger number was presented either to the left or to the right. Following a 500 ms fixation cross, the number stimuli were presented for 3 seconds, during this time participant gave an answer. After the answer was given, the next fixation cross appeared and the following trial started immediately. For each task (magnitude or physical size), accuracy and RTs were recorded.




CONGRUENT INCONGRUENT NEUTRAL




CONGRUENT INCONGRUENT NEUTRAL

Figure 3. Magnitude task (upper row) and Size task (bottom row) in the numerical Stroop paradigm.

*Verbal stroop task*

The word Stroop task requires participants to answer as quickly as possible either a word ignoring the colour of the ink it is printed in (for instance 'RED' whether printed in colour red, green or in black for a neutral condition, "Word task"), or to name the colour in which words are printed ignoring their meaning (for instance to name the colour red whether displayed on the word 'RED', 'BLUE' or on 'XXX' for a neutral condition, "Colour task"). There were 90 trials for each task (Word or Colour), 30 were congruent, 30 incongruent and 30 neutral. Our version of the task was the same of the original research by Stroop (1935). At the beginning of each trial, a fixation cross was presented, replaced after 1 second by the target stimulus, a colour word which lasted 3 second. Participants were asked to decide as quickly as possible whether the stimulus was the word "RED" or "GREEN" (respectively the italian words "ROSSO" and "VERDE") irrespective of the colour (in the Word task, the neutral trial was the color word printed in black font), or whether it was displayed in red or green font irrespectively of the meaning of the word (in the Colour task, the neutral trial was the string XXX written in the green or red colour); they were instructed to press the left and right keys for red (word or colour) and green (word or colour) in two separated and between subjects counterbalanced blocks. For each task, accuracy and RTs were calculated for the three conditions: neutral (corresponding to the target word printed in black ink for the Word task or the target colour printed on XXX for the Colour task), congruent (target word printed in the corresponding colour or the target colour on the corresponding word), and incongruent (target word printed on a different colour like 'RED' printed in green, or the target colour printed on a different word, like colour red on the word GREEN). These three conditions allow measuring the participants' ability to inhibit task irrelevant information (Stroop, 1935). The procedure of the tasks and an example of each trial is presented in figure 4a and 4b.

Word and Colour tasks were administered separately and in a counterbalanced way. We expected participants to be less rapid and accurate in incongruent trials in both the tasks (as found in Cappelletti et al., 2014).

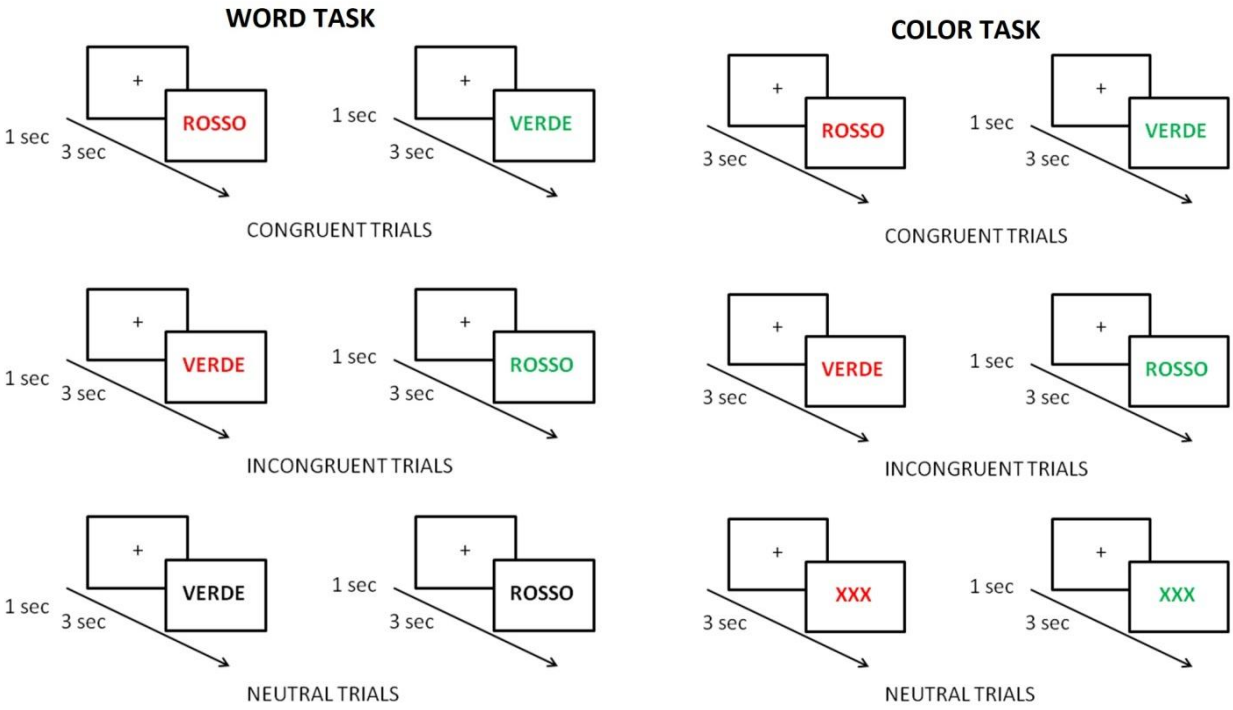



Figure 4. a) on the left, "Word task" trials and procedure; b) on the right, "Color task" procedure.

*Results*

*Dots comparison task*

Accuracy after data cleaning (3SD) were submitted to an ANOVA with convex hull and area as within-subjects factors. The results showed a main effect of convex hull ($F(1,21)=91.83$, $p<.001$, $\eta_p^2=.81$) and area ($F(1,21)=10.98$, $p=.003$, $\eta_p^2=.34$). The interaction between the two factors just missed the conventional significance level ($F(1,21)=4.31$, $p=.05$, $\eta_p^2=.17$). Results are shown in figure 5. Post-hoc analysis showed a significant difference between congruent and incongruent area ($t(21)=-3.31$, $p=.003$) and between congruent and incongruent convex hull ($t(21)=9.58$, $p<.001$). Moreover, the difference between congruent and incongruent convex hull was significant both when area was congruent ($t(21)=9.70$, $p<.001$) or incongruent ($t(21)=-9.53$, $p<.001$). Similarly, the difference between congruent and incongruent area was significant both when convex hull was congruent ($t(21)=-3.29$, $p=.005$) or incongruent ($t(21)=-3.14$, $p=.005$). Performance was better when participants performed congruent convex hull trials. In contrast, performance was worse for congruent area compared to incongruent area trials. This latter result is similar to the one reported

by Clayton, Gilmore and Iglis (2015) when comparing numerosity comparison data obtained with the Panamath protocol (Halberda) and the Gebuis and Reynvoet (2011) protocol, thereby suggesting that the paradoxical effect of area congruency might be attributed to imperfect control of the continuous visual variables in our stimuli (as in the Panamath protocol).

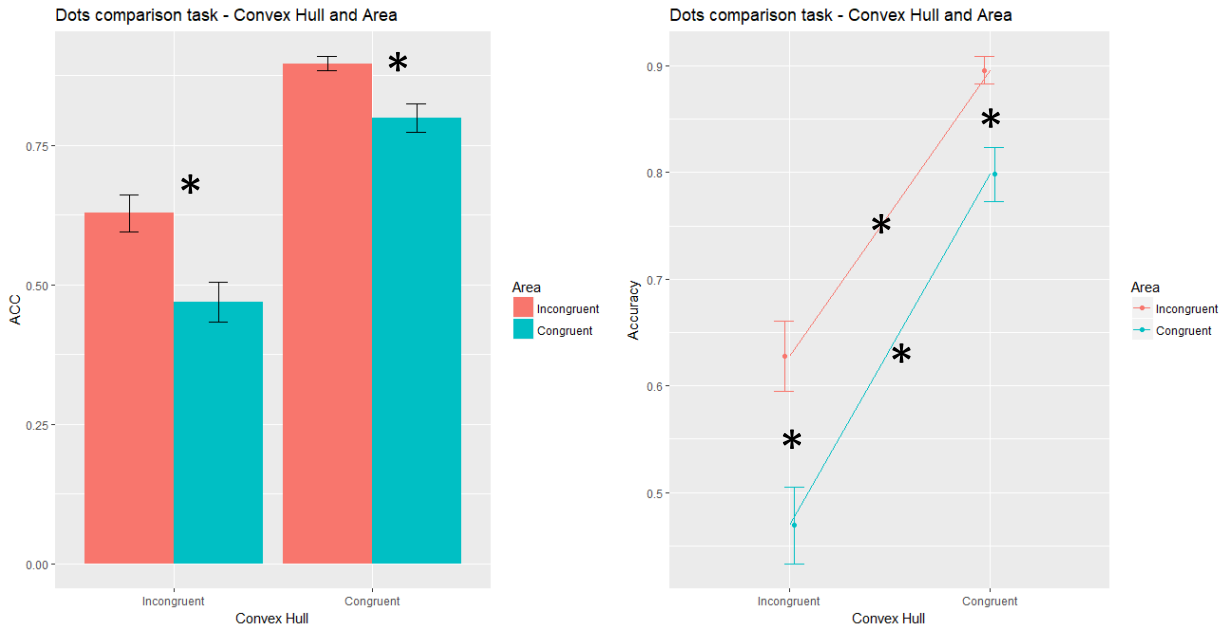



Figure 5. Performance (percentage of correct responses) in the numerosity comparison task as a function of congruency in convex hull and area.

*Numerical and verbal stroop*

We analyzed separately dots comparison, numerical Stroop and verbal Stroop tasks.

Regarding the magnitude task in the numerical Stroop, on correct RTs we found a main effect of the within-subjects factors condition ($F(2,40)=116.14$, $p<.001$, $\eta_p^2=.85$) and numerical distance ($F(1,40)=108.17$, $p<.001$, $\eta_p^2=.84$) but no interaction ($F(2,40)=2.20$, $p=.1$, $\eta_p^2=.10$). Post-hoc analysis clarified that performance was enhanced for congruent trials compared to incongruent ($t(20)=13.71$, $p<.001$) and neutral trials ($t(20)=8.36$, $p<.001$) and worse for incongruent trials compared to neutral trials ($t(20)=-7.15$, $p<.001$), while for neutral trials it was intermediate, and significantly different both from congruent and incongruent trials (see Figure 6). Regarding numerical distance, the performance was better when stimuli were 2 units aparts compared to 1 unit apart ($t(20)=-10.18$, $p<.001$, see figure 5). On accuracy, we found a main effect of condition

(F(2,40)=22.06, p<.001, $\eta_p^2$=.52), distance (F(1,40)=51.10, p<.001, $\eta_p^2$=.72) and the interaction distance x condition (F(2,40)=20.27, p<.001, $\eta_p^2$=.50). T-tests clarified that the performance was affected by the numerical distance when trials were neutral (t(20)=2.96, p=.02) and incongruent (t(20)=6.70, p<.001) but not when they were congruent (t(20)=1.91, p=.1; see figure 6).

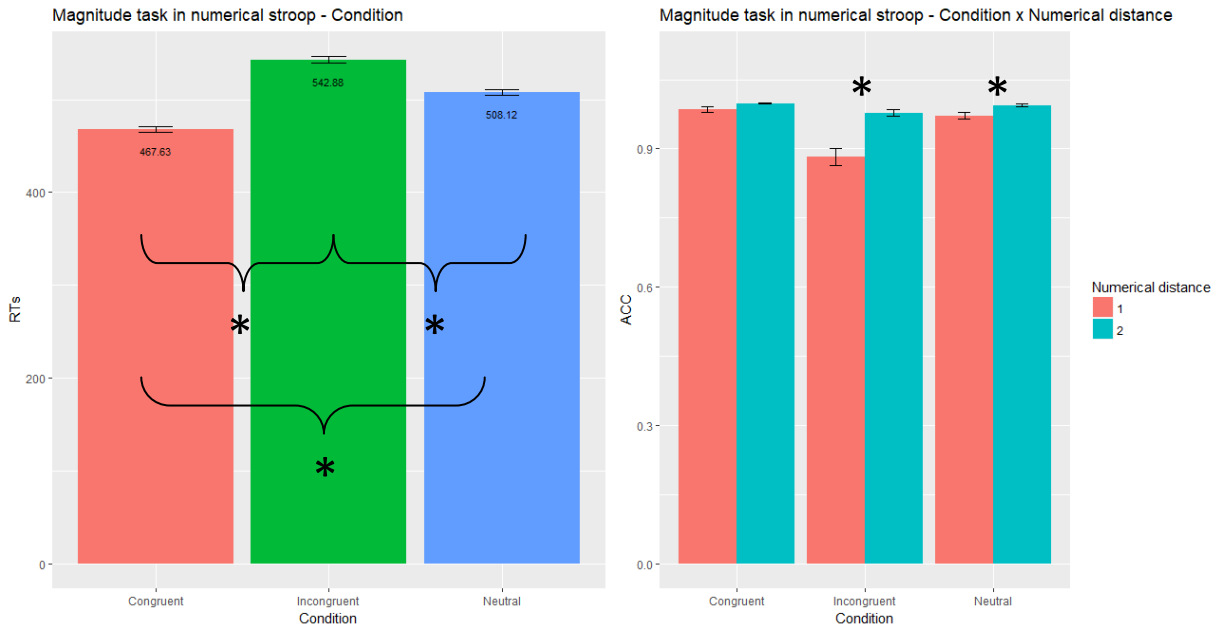



Figure 6. On the left main effect of condition on RTs. On the right, main effect condition x numerical distance on accuracy.

In the size task numerical stroop, we found a main effect of condition (F(2,40)=189.84, p<.001, $\eta_p^2$=.91) for RTs (see figure 7). Post-hoc analysis showed a significant difference between congruent and incongruent trials (t(20)=5.91, p<.001), incongruent and neutral (t(20)=-12.65, p<.001) and congruent and neutral (t(20)=-9.46, p<.001). On accuracy, all trials analysis showed a main effect of the condition (F(2,40)=35.98, p<.001, $\eta_p^2$=.64). The main effect is presented in figure 7. Post hoc clarified a difference between congruent and incongruent trials (t(20)=8.36, p<.001) and between neutral and incongruent (t(20)=-10.65,p<.001), but not between congruent and neutral trials (t(20)=.20, p=.8).

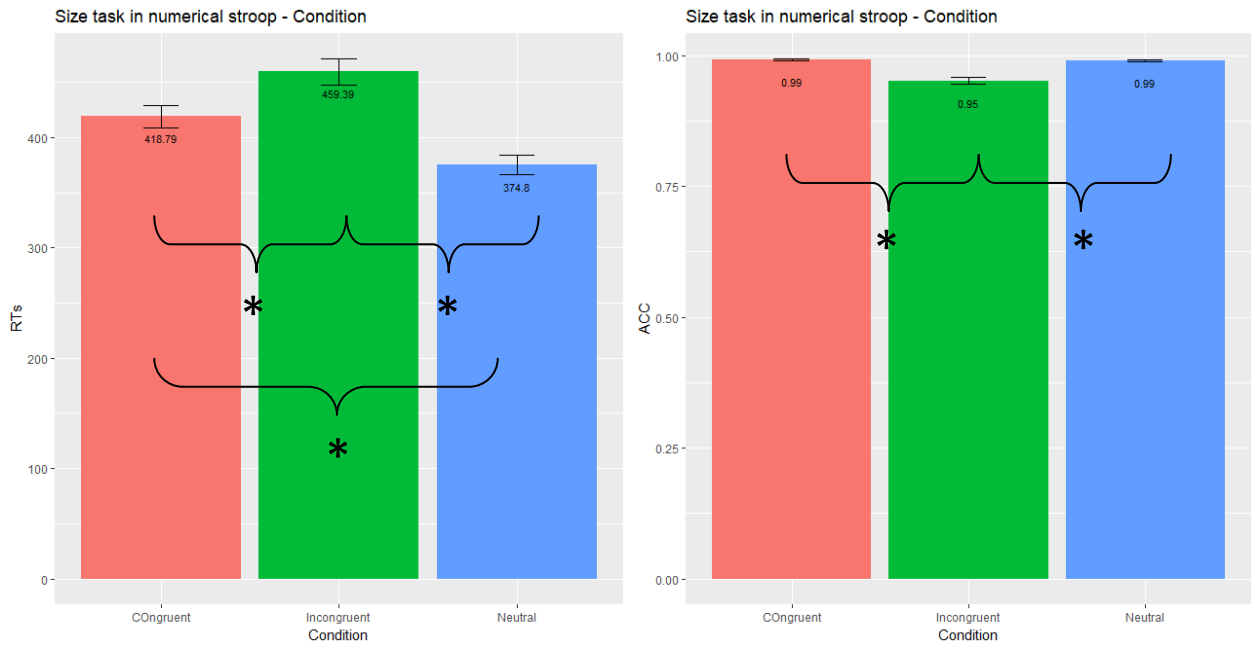



Figure 7. On the left, main effect of condition on RTs in all trials (congruent, incongruent, neutral) analysis. On the right, main effect of condition on accuracy.

In the verbal stroop, we performed ANOVAs on RTs and accuracy for the Word and Color tasks separately. In the Word task, we found a main effect of the within-subjects factor condition ($F(2,40)=6.55$, $p=.003$, $\eta_p^2=.25$). Similarly, in the Color task the effect of condition was significant ($F(2,40)=5.19$, $p=.01$, $\eta_p^2=.21$). Figure 8 shows the results. In Word task, we found a significant difference between congruent and incongruent trials ($t(20)=3.29$, $p=.006$) and between congruent and neutral trials ($t(20)=3.50$, $p=.006$), but not between neutral and incongruent trials ($t(20)=-.63$, $p=.54$). In Color task, we found a significant difference between incongruent and congruent trials ($t(20)=2.30$, $p<.05$) and between incongruent and congruent trials ($t(20)=-2.51$, $p<.05$), but not between congruent and neutral trials ($t(20)=-.35$, $p=.73$). On accuracy, in Word verbal stroop alone we found a main effect of condition ($F(2,40)=4.76$, $p=.01$, $\eta_p^2=.19$), while no effect was detected for Color verbal stroop ($F(2,40)=.48$, $p=.6$, $\eta_p^2=.02$). Figure 9 shows the congruency effect on accuracy.

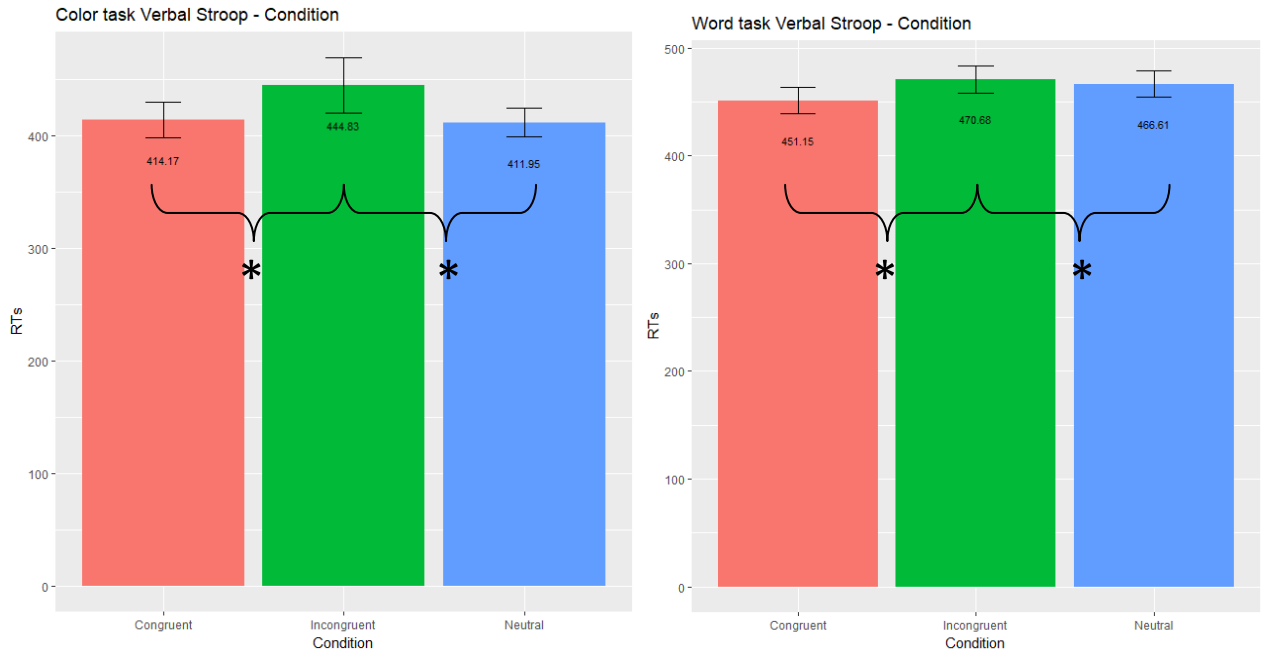



Figure 8. On the left, main effect of condition on RTs in the Color task; on the right, main effect of condition on Word task.

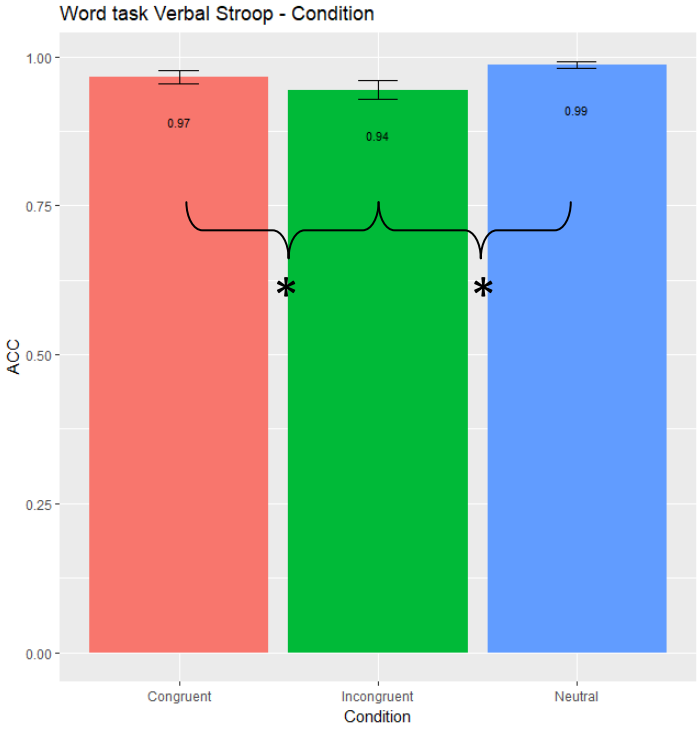



Figure 9. Main effect of condition on accuracy in Word task.

Post-hoc comparisons clarified that the difference between incongruent and neutral trials was significant (t(20)=2.90, p=.03), and between incongruent and congruent trials (t(20)=.2, p=.03) while between congruent and neutral trials the comparison was not significant (t(20)=2.02, p=.09).

*Correlations between tasks*

Correlation analysis between each Stroop task (Color and Word verbal, Magnitude and size numerical) and dots comparison task trials did not show the expected pattern of results. While performance across the Stroop tasks was correlated, no significant correlation was found between dots comparison trials in incongruent conditions, while a significant correlation was found between congruent convex hull and congruent area trials ($r$(19)=.47, p=.03) and interestingly between Word stroop congruent trials and area congruent trials ($r$(19)=.44, p<.05).

*Discussion*

Our pilot results suggest that no common mechanism can be involved in incongruent trials in dots comparison and Stroop tasks, as suggested by the absence of correlations with both numerical Stroop and verbal Stroop. These results are inconsistent with the ones reported by Cappelletti et al. (2014), maybe because of the different samples tested (young adults in the present study vs. older adults). Therefore, it is still possible that an active manipulation of inhibitory abilities might affect both the tasks, thus indicating a possible relation between them.

*Experiment 2*

*Active modulation of inhibition*

In experiment 2, we applied c-tDCS to modulate the inhibitory functions. We reasoned that the possible modulation of inhibition, as assessed with the classic version of a verbal stroop task, could be extended to dots comparison incongruent trials, thus revealing the causal relationship between modulation of inhibition and dots comparison incongruent trials. The absence of correlation between the baseline behavioral tasks but an effect of the stimulation on incongruent trials of both

verbal stroop and dots comparison might be prone to a wide variety of explanations. We administered the verbal Stroop task but not the numerical Stroop task in order to reduce the duration of the experiment. The verbal Stroop was retained because it is the classic paradigm, it has been widely used to assess inhibitory abilities (e.g., Milham, Erickson, Banich, Kramer., Webb, Wszalek, & Cohen,, 2002; Zied, Phillipe, Karine, Valerie, Ghislaine, & Arnaud, 2004; Verbruggen, Liefooghe, & Vandierendonck, 2004) and the cognitive functions implied by the two tasks do not overlap besides the putative role of inhibition .

Regarding the stimulation, we chose a cathodal tDCS stimulation, with an extracefalic control electrode montage (cathode on the rIFG, anode on the contrlateral arm) and we used a small electrodes size (4x4) in order to prevent possible effect on cerebral areas others than our target (rIFG). We applied these constraints in order to enhance the possible effects of the stimulation, as suggested by Nitsche, Cohen, Wassermann, Priori, Lang, Antal et al. (2008).

*Participants*

20 participants (10 males, mean age=23) took part in the experiment. They all were naive about the aim of our study.

*Procedure*

Participants signed the informed consent before taking part in the experiment. They were informed that they had to return to the laboratory after two days to complete the second part of the research. 24 hours are the interval necessary to avoid carry-over effects in electrical stimulation techniques (Nitsche at al., 2008). One half the participants were assigned to the sham-stim group and received the sham stimulation on the first session (electrode montage but no active stimulation) and the real stimulation on the second, while the other one half of the participants (stim-sham group) was assigned the opposite order.

After the montage was completed, participants performed the two tasks, dots comparison and Stroop, in the same order in the first and in the second session, to avoid an order effect.

Since we wanted to verify the effect through time, three blocks were included: pre, online and offline. Participants always performed this task during the stimulation (online). Also the post stimulation dots is maintained fixed. The pre stimulation block was counterbalanced between

participants, i.e. half of the participants performed the stroop baseline first and the other half the dots baseline first. Figure 10 shows the procedure.

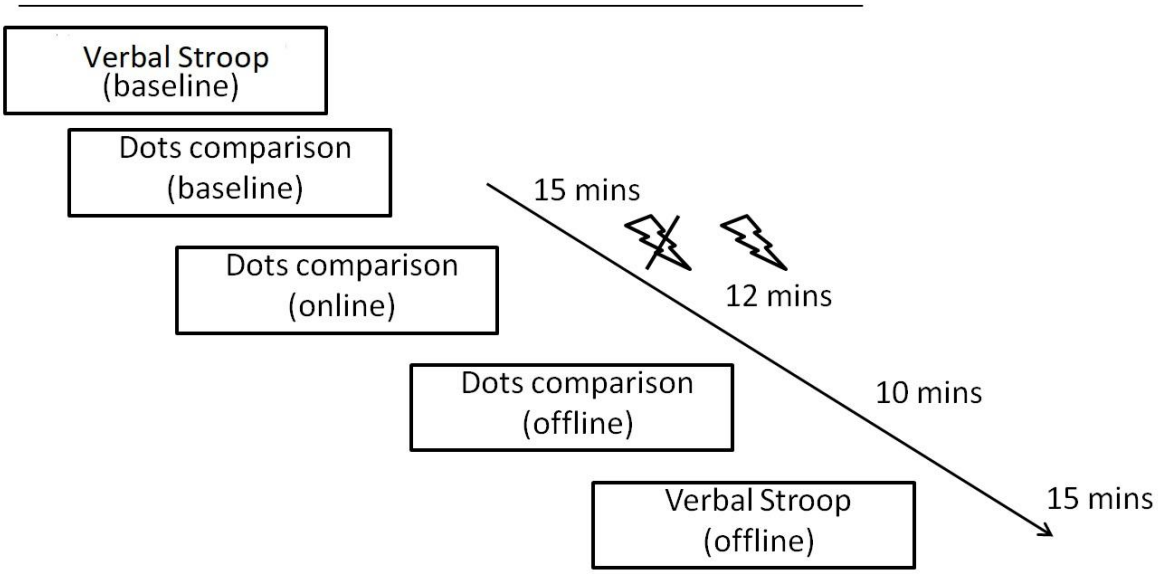



Figure 10. Procedure of the experiment 2. Real stimulation and sham stimulation was administered on different days. The order of the baseline measures (Verbal stroop and Dots comparison) was counterbalanced between participants.

*Stimulation*

Cathodal stimulation (c-tDCS) was applied over the rIFG (FC4 on 10-20 system, Jasper, 1958) as the crossing point between T4-Fz and F8-Cz (e.g. Jacobson, Javittm Lavidor, 2011; Stramaccia et al., 2015) while the anode was applied over a extracefalic position (the right arm). We chose this montage because previous research showed that extracefalic reference helps ruling out the involvement of cortical sites others than the one stimulated (Nitsche et al. 2008).

We chose cathodal tDCS because rIFG has been already modulated by this type of stimulation, but not anodal, in order to affect inhibitory control (Penolazzi et al., 2014). Figure 11 shows the montage.

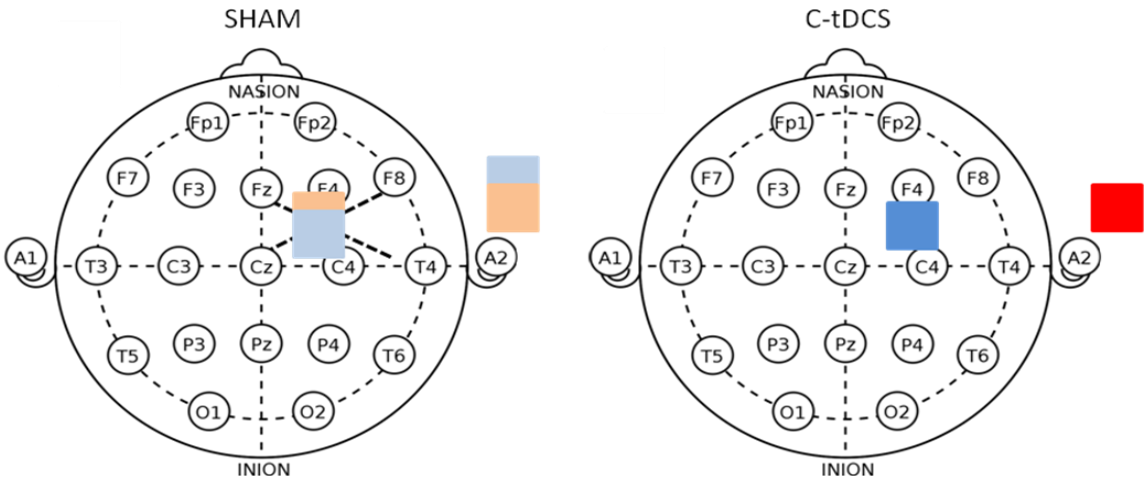



Figure 11. The montage in experiment 2. The different colors in sham group graphically indicate that the electrodes montage was counterbalanced between participants, in a half with the "anode" on the right, in a half on the left.

*Tasks*

In the active modulation of inhibition experiment, we administered dots comparison task during the stimulation phase with the twofold aim of activating the circuit involved in the task and evaluating the possible online and immediately-offline effect of the manipulation. Moreover, we administered a control task (the Verbal Stroop task) to assess whether stimulation selectively affected inhibitory mechanisms. We chose the Verbal Stroop because in the pilot experiment no correlation was found at baseline between numerical Stroop and dots comparison task, and to be more consistent with the literature about inhibition in cognition. Similarly, we chose to administer only one Stroop task because of the time constraints due to the stimulation wash-out effects. We preferred a Color Task Verbal Stroop to be more consistent with literature and because it appeared more convincing in obtaining congruency effects as showed in our pilot results on RTs.

*Dots comparison task*

The number of trials in dots blocks was maintained fixed (448 trials for pre and online, 336 trials for offline). A different number of offline trials for time constraints due to the stimulation after-affects duration. 112 were convex hull and area congruent trials, 112 were convex hull incongruent and area congruent, 112 were convex hull congruent and incongruent, 112 were totally incongruent. All other details were identical to experiment 1.

*Verbal stroop task*

We administered a block before the stimulation (pre) and one at the end of the dots comparison task (post). The targets are the same of experiment 1. The words were the italian words red (ROSSO) and green (VERDE), which could be written in a color that was either congruent or incongruent with the word meaning (e.g., RED written in red ink vs. RED written in green). Neutral trials were the ones in which the same words were written in black ink, so no interference between color and meaning could be possible. Participants were required to report the color in which the word was written ("Color task") inhibiting the automatic processing of the word meaning, as in experiment 1.

*Results*

*Dots comparison task*

Accuracy after data cleaning (3 SD) was submitted as dependent variable to an omnibus ANOVA with area (congruent or incongruent), convex hull (congruent or incongruent), protocol (sham vs c-tDCS), and time (pre vs online vs post) as within subjects factors. Group (sham-stim or stim-sham) was included as between subjects factor to control for the order of the sessions (first sham and then stimulation or vice versa), expecting no effect. Note that the two groups had the same number of participants (N=10) and assignement to the groups was random. However, one participants in the Stimulation-then-Sham group was removed from the analysis due to technical issues with the experiment software . We found a main effect of time ($F(2,34)=9.26$, $p<.001$, $\eta_p^2=.35$), protocol ($F(1,17)=6.44$, $p=.02$, $\eta_p^2=.28$) and convex hull ($F(1,17)=118.37$, $p<.001$, $\eta_p^2=.87$), an interaction area x time ($F(2,34)=8.16$, $p=.001$, $\eta_p^2=.32$) and group x area x protocol ($F(1,17)=8.65$, $p=.009$, $\eta_p^2=.34$). Inspecting the three-way interaction using post-hoc t-tests we found no differences between groups (all ps>.7), thereby ruling out significant baseline differences. Surprisingly, we found also a four-way interaction group x protocol x convex hull x time ($F(2,34)=8.74$, $p<.001$, $\eta_p^2=.34$). In order to better understand the four ways interaction, we splitted the data based on the only between subjects factor, the group. Considering the two subgroups, we found a three way interaction time x convex hull x protocol ($F(2,18)=7.88$, $p=.003$, $\eta_p^2=.47$) only in the sham-stim subgroup, but not in the stim-sham group ($F(2,16)=2.65$, $p=.1$, $\eta_p^2=.25$). Figure 12 represents the

three way interaction. The difference at offline time between sham and stimulation for incongruent trials was significant (t(9)=3.57, p=.01), while no difference was found for congruent trials.

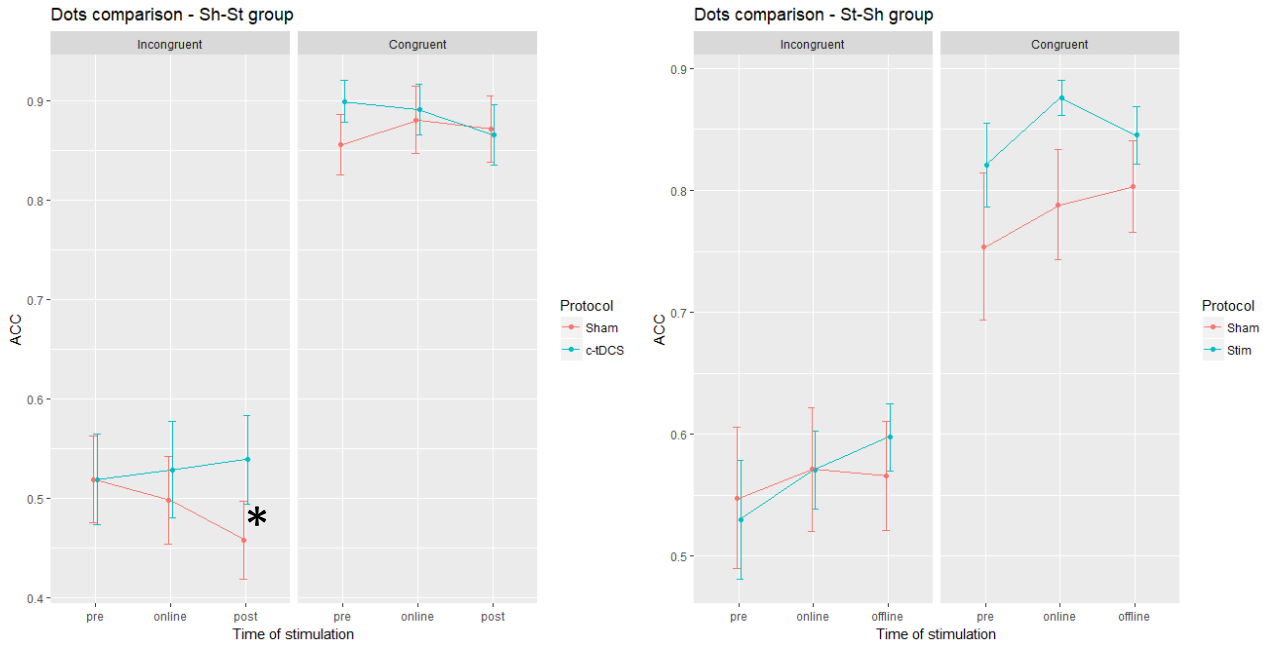



Figure 12. three ways interaction between condition, protocol and time for the two groups (sham-stim and stim-sham),.

*Verbal stroop task*

RTs for correct answers were submitted as dependent variable to an ANOVA with protocol, congruency and time (pre vs post) as within subjects factors. Group (sham-stim and stim-sham) was included asbetween subjects factor in light of the previous Dots Comparison results. The ANOVA showed a main effect of protocol ($F(1,18)=5.65$, $p=.02$, $\eta_p^2=.24$), congruency ($F(2,36)=19.52$, $p<.001$, $\eta_p^2=.52$) and time ($F(1,18)=42.46$, $p<.001$, $\eta_p^2=.70$), and an interaction group x protocol ($F(1,18)=53.82$, $p<.001$, $\eta_p^2=.75$), group x protocol x congruency ($F(2,36)=9.01$, $p<.001$, $\eta_p^2=.33$), group x time x protocol ($F(1,18)=38.55$, $p<.001$, $\eta_p^2=.68$) and group x congruency x time ($F(2,36)=3.98$, $p=.02$, $\eta_p^2=.18$). Interesting for our hypothesis, also the four ways interaction group x time x congruency x protocol was significant ($F(2,36)=8.15$, $p=.001$, $\eta_p^2=.31$). To better inspect the four ways interaction, we calculated a cost (incongruent - congruent trials) for each participant and we subsequently subtracted the mean RTs of the post session from the mean RTs of the pre session (pre minus post). We submitted the values to an ANOVA with group (sham-stim or stim-sham) as between subjects factor and protocol (sham or c-tDCS) as within subjects factor. From this analysis, we found no significant main effects but a significant interaction between group and

protocol (F(1,18)=6.79, p=.02, $\eta_p^2$=.27) Figure 13 shows the results. Post hoc t-test clarified that no difference is found between protocols for both groups; a significant difference between groups emerged for the sham condition but not for c-tDCS (t(9)=-3.14, p=.02).

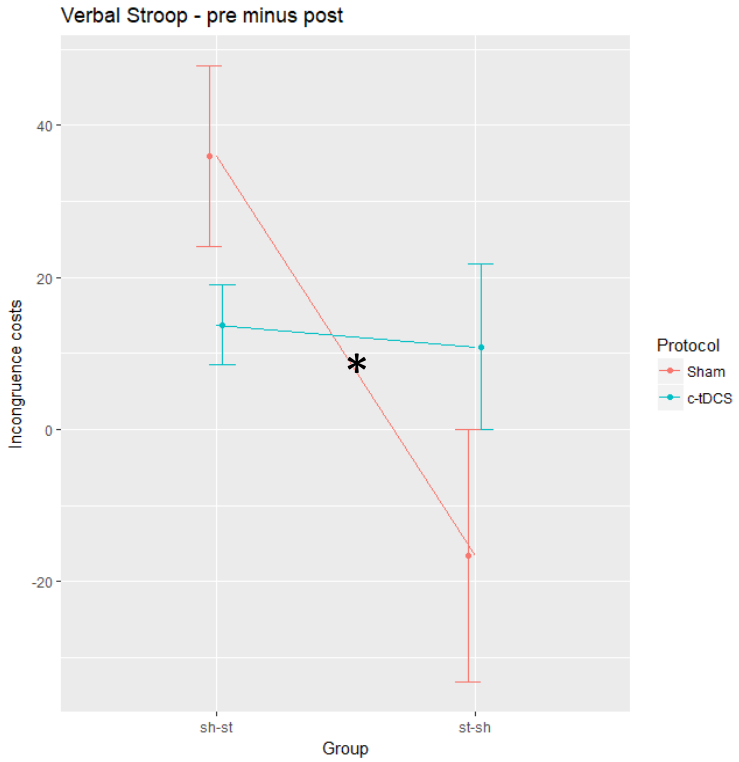



Figure 13. Protocol x Group interaction on Incongruence costs.

Subsequently, we conducted an ANOVA on accuracy scores. From the results, we found a main effect of condition (F(2,38)=17.37, p<.001, $\eta_p^2$=.92) and time (F(1,19)=3.77, p<.001, $\eta_p^2$=.83), but no main effect of the protocol was detected (F(1,19)=1.40, p=.2), nor any interaction.

*Correlations between the tasks*

We calculated a difference between pre - post, meaning that a negative value in the dots task indicates a more accurate performance after the stimulation, while a negative value for the Stroop tasks means a slower performance in pre compared to post.

The correlation between incongruent trials in Stroop and dots comparison tasks just missed significance (r=-.63, p =.05), but only in the sham-stim group and for the active stimulation protocol. The negative correlation means that an enhancement in dots comparison accuracy is correlated with more rapid Stroop RTs in the post stimulation session compared to the first one.

For stim-sham group, no correlation was significant.
Finally, no significant correlation was detected in pre alone, replicating the previous behavioral results.

*Discussion*

With our manipulation we successfully modulated dots comparison performance and, interestingly for our hypothesis, we selectively affected incongruent trials, but not congruent ones. The main result suggests that rIFG is causally involved in incongruent trials performance during a numerosity comparison task. This is in line with the conclusions drawn by Clayton, Gilmore & Inglis (2015) about the importance of inhibition and it is consistent with the results previously obtained by Cappelletti et al. (2014) on older adults. Interestingly, the modulation obtained was not a deterioration in performance as expected, but an enhancement in accuracy during the stimulation compared to sham condition. This is consistent with other studies finding a paradoxical effect of anodal and cathodal tDCS (Jacobson et al., 2012). One possible explanation of contradictory results is the effect of cathodal stimulation in reducing the neural noise, thus facilitating the signal related to the task and useful to successfully complete it (Miniussi, Harris & Ruzzoli, 2013). Another possible explanation is that cathodal tDCS might inhibit some cortical sites and enhance others, in a cortical balancing logic (Krause, Marquez-Ruiz & Cohen Kadosh, 2013).
Moreover, the effect was specific for the group who received sham stimulation first, but it was absent for the group with opposite assignment. The implications for this finding are twofold. First, an effect was obtained when participants performed the task after one baseline session, thus suggesting that a good knowledge of the task might be important to obtain results with c-tDCS. This is consistent with studies showing that expertise is a basic condition to obtain effects with electrical stimulation (Berryhill & Jones, 2012; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Hsu, Tseng, Liang, Cheng, & Juan 2014; Learmonth, Thut, Benwell & Harvey, 2015; Tseng, Hsu, Chang, Tzeng Hung, Muggleton et al., 2012; Benwell, Learmonth, Miniussi, Harvey & Thut, 2015) and with the model of the optimal level of noise proposed to explain the different outcomes induced by electrical stimulation (Miniussi et al., 2013). Second, brain stimulation was not able to induce reliable immediate effects, but it interacted with the level of familiarity/expertise with the task. This is again in line with other research showing that individual differences in behavioral performance are a critical variable to explain the modulation or even the absence of effects (Kim, Kim, Chang, Kim, Kim, & Im, 2014; Krause & Cohen Kadosh, 2014). Finally, no online effect was detected, but

immediately after the end of the stimulation, suggesting that the cortical modulation was delayed. On the verbal Stroop, we found a significant interaction between group and protocol on congruent, incongruent and neutral trials. The lack of post-stimulation effect is in line with literature about tDCS and seems to indicate that the possible effect on the dots might be lost few minutes after the end of the stimulation. Another possible explanation is that we did not modulate inhibition, thus not affecting the verbal Stroop task. It is possible that an aspecific enhancement in performance was obtained with c-tDCS, with a generic reduction of neural noise thus facilitating the performance at the more difficult trials, the incongruent ones. This speculation is in line with models proposed to explain tES paradoxical effects (Miniussi, Harris & Ruzzoli, 2013)

*General Discussion*

The present study found that cathodal tDCS seems able to modulate the performance in a dots comparison task, acting specifically on incongruent trials. Contrary to our hypothesis, an enhancement in accuracy was found. This result might be explained with the paradoxical effect which might induce a facilitation in the performance after cathodal stimulation (Jacobson , Koslowsky & Lavidor, 2012; Miniussi, Harris & Ruzzoli, 2013) due to a possible reduction of the neural noise with a consequent enhancement in the cortical activation.

However, we did not find any significant correlation between baseline dots comparison task and numerical Stroop task, nor verbal Stroop task. This result contrasts to those of Cappelletti et al. (2014) who found a correlation between incongruent trials in verbal and numerical Stroop and dots comparison. The difference might be related to the different samples employed in the two studies (healthy young subjects vs. older adults) or to differences in the tasks employed.

It seems that no apparent relationship can be found between our dots and Stroop tasks. Our results suggest an effect of the stimulation based on the task which is investigated. In dots comparison task, there was a significant enhancement in accuracy, but only in incongruent trials. In the Stroop task, no reliable offline effect was found. Moreover, only one subgroup showed a modulation, that is the sham-stim group, suggesting that higher familiarity with the task (here induced by the repetition) is necessary to obtain reliable effects. Moreover, the effect was specific for incongruent trials, suggesting a relationship between rIFG and incongruent trials of dots comparison task.

The simultaneous  lack of effects on verbal Stroop task might be index that the dots comparison effect was lost, or that the two tasks relied on different neural mechanisms. It is however possible that rIFG has a different role in the two tasksIn this logic, it might be that rIFG is involved only in

motor inhibition, while other sites, such as DLPFC, are more important for cognitive inhibition (for a review, see Aron et al., 2014).

The lack of any difference in the baseline tasks and in pre-stimulation measure, however, is prone to two possible and interesting explanation. First, it seems to suggest that no reliable relationship could be found between the two types of incongruent trials, thus contradicting other evidence (Cappelletti et al., 2014). Secondly, it seems to confirm that the change we find after the stimulation is really related to the manipulation itself and not to a intrinsic relation between the tasks.

The importance of this research is linked to the possible therapeutic use of tDCS. tDCS is a non - invasive tool and it does not induce annoying sensations on the skin (Nitsche et al., 2008). It can be used also on clinical population and in sham-controlled experimental studies. The positive effect in incongruent trials in dots comparison task after the stimulation with cathodal tDCS might suggest that this type of protocol is able to reduce the neural noise and to facilitate the performance when inhibitory abilities are required. This means that it is possible to project treatment using cathodal tDCS in order to enhance inhibition in impaired population. For example, older adults might benefit of this protocol to exercise inhibitory function which is thought to be declining in this population (Cappeletti et al., 2014).

It is important to point out that the present study is not immune from flaws. For example, the effect of the group (Sh-St or St-Sh) was unexpected, so we did not control for possible differences between groups in baseline. However, the absence of statistical difference between groups found in our analysis seems to rule out this possibility. Further research is needed to rule out this possibility and assure that ctDCS effect was genuine.

*Conclusions*

The present study contributes to the understanding of inhibitory control involvement in dots comparison tasks. We actively modulated incongruent trials of dots comparison task, enhancing the performance. The behavioral positive effect on dots was however coupled with a lack of reliable effects on Stroop task performance, thus suggesting a possible very short effect of cathodal stimulation, or that the two tasks considered did not share the same neural mechanisms. Baseline performance did not suggest any relationship between incongruent trials in dots and Stroop task, thus confirming that different mechanisms might be involved (for example, cognitive vs motor inhibition). New evidence should be collected in order to better understand our results.

## 3.3. Single session tES transfer effects and its role in cortical plasticity: A comparison between tDCS AND tRNS.

*Introduction*

In clinical practice, transcranial electrical stimulation (tES) has been applied since it is a well-tolerated, portable device (Nitsche, Cohen, Wassermann, Priori, Lang, Antal, et al., 2008; Brunoni, Nitsche, Bolognini, Bikson, Wagner, Merabet et al., 2012). Mounting evidence is showing that tES is able to induce a cortical modulation not only limited to the task administered during the stimulation, but also long-lasting, and in some cases also extending to other tasks, whether with tRNS (Snowball, Tachtsidis, Popescu, Thompson, Delazer, Zamarian, et al., 2013; Cappelletti, Gessaroli, Hithersay, Mitolo, Didino, Kanai et al., 2013) or with tDCS (Richmond, Wolk, Chein, & Olson, 2014;Mrtin, Liu, Alonzo, Green, Player, Sachdev & Loo, 2013; Au, Katz Buschkuehl, Bunarjo, Senger, Zabel et al., 2016). Despite this evidence, the limited knowledge about the principles of tES functioning is likely to contribute to the emerge of contradictory results, thus making it difficult to project a proper treatment for clinical population. While the association of tES and cognitive training enhances the effect of the latter across many cognitive domains, the effects on non-trained tasks are somewhat mixed, with some evidence for improvements in different cognitive functions such as working memory, cognitive control, number sense and arithmetic abilities, even if not conclusive (Elmasry, Loo & Martin, 2015; Katz, Au, Buschkuehl, Abagis, Zabel, Jaeggi & Jonides, 2017).

tES has been applied in a range of dysfunctions in order to obtain more beneficial effects of cognitive training. It was applied in spatial neglect and stroke treatment (Park et al., 2013), in eating disorders, in schizophrenia (Nienow et al., 2016), PTSD (Saunders et al., 2015) in major depression (Vanderhasselt et al., 2015).

In the clinical practice, a specific enhancement in online-task alone is far from useful to induce the desired change. However, no research so far suggests that transfer of skills across different tasks is possible in both healthy subjects and clinical population. In general, a large part of the research

involving tES has been focused on the modulation of a task administered during the stimulation, or on the analysis of offline effects of the stimulation alone. Stimulation is typically more effective when administered during a specific task, assessing the efficiency of a cortical site which was also the target of the ongoing stimulation (Miniussi et al., 2013). This specific procedure allowed researchers to study the causal relationships between the stimulated area and the task administered in an experimental logic. Moreover, the change induced has been reported to be short-lasting and transient: in other words, it was impossible to affect in any way the everyday life of experimental subjects (Nitsche & Paulus, 2000), whereas the change induced might last even several hours after the stimulation (Paulus, 2011).

However, this experimental practice is not relevant for clinical applications, which require a long-lasting, reliable effect. For this reason, a combination of behavioral training and stimulation was implemented to boost the possible effects of the stimulation. In this logic, studies analyzed not only the online effect of the stimulation, but its long-lasting outcomes and, critically, its transfer effects on different tasks or cognitive functions (Cappelletti et al., 2013).

Durability of the effects are a crucial factor for clinical practice. Even if washout may be common within a short time after a training intervention (Melby- Lervåg & Hulme, 2013), some research suggests that effects last even several months after the intervention (Au et al., 2016). Some studies suggest that improvements after tDCS interventions may remain weeks or even months after the stimulation. Persistent, long-term changes have also been detected as a function of learning or training in a number of domains, such as motor skill training (Reis et al., 2009), math training (Looi et al., 2016), episodic memory retrieval (Manenti, Sandrini, Brambilla, & Cotelli, 2016) and working memory training (Jeon and Han, 2012; Park, Seo, Kim, & Ko, 2014; Jones, Stephens, Alam, Bikson, and Berryhill, 2015).

To our knowledge, no studies to date investigated the transfer effects of electrical stimulation achieved in only one session. The best-known tES techniques, anodal and cathodal tDCS, have online effects or short-lasting carry-over effects which makes them suitable for experimental questions. Most studies investigated only within one measurement session, leaving long-term retention effects unexplored, thus making it impossible to evaluate other possible effects induced by the stimulation (for a review, see Enriquez-Geppert et al., 2013). On the contrary, tRNS, a randomized, mild current applied over the scalp, has been often applied in training alone, but only

few times in only one session (Terney et al., 2008; Fertonani, Pirulli & Miniussi, 2011). Moreover, only one study assessed the effects of different tRNS montages (Moliadze et al., 2010).

In rehabilitation and in clinical practice it is important to find new ways to enhance cognitive training. It is not sufficient to ameliorate transitionally and short lasting a single task performance, but we should be able to activate in a long term way cortical sites we are interested in.

In the present study we investigated the transfer effects of a-tDCS and tRNS on attentional domain. We chose to modulate attention because of the common use of tDCS on visuospatial domain in clinical practice (Sunwoo et al., 2013; Ko et al., 2008; Brem et al., 2014; for a review, see Slazar et al., 2017). Based on the literature of tDCS, which found very short after-effects, and its mechanisms of functioning, our hypothesis was that tRNS protocol, but not tDCS, would be able to induce an enhancement. Indeed, even if very few studies investigated the effects of tRNS in one session, it seems that tRNS induced plasticity is more resistant to washout than tDCS effects (Chaieb et al., 2015). We hence expected long-lasting, transfer results only for one protocol, the one usually coupled with long term enhancement (Cappelletti et al., 2013; Snowball et al., 2013; for a review, see Krause & Cohen Kadosh, 2013). Moreover, we chose to compare two montages for tRNS, unilateral tRNS (U-tRNS) and bilateral tRNS (B-tRNS), a solution that, to the best of our knowledge, was employed only by another study before (Moliadze et al., 2010). In this research, the Authors found that the distance between active electrode and reference is critical to obtain any effect. For example, for extracefalic montage, positioning the reference over the contralateral orbitofrontal cortex is more effective than on the arm (Birkson et al., 2010; Nitsche et al., 2007). Moreover, bilateral montage is thought to act on cortical balance between hemispheres in tDCS (Sparing et al., 2009; Lazzaro et al., 2014), by activating one hemisphere and inhibiting the other, and a similar pattern might be expected also in tRNS. Though the two techniques probably act on different mechanisms (Chaieb et al., 2015), we expected a better effect of B-tRNS compared to U-tRNS.

*Models of spatial attention and neural substrates*

Visuo-spatial skills are the ability to understand, reason and remember the spatial relations among objects or space. Strongly related, visuo-spatial attention allows humans to selectively process

visual information through prioritization of an area within the visual field. A region of space within the visual field is selected for attention and the information within this region then receives further processing. Research shows that when spatial attention is evoked, an healthy observer is typically faster and more accurate at detecting a target that appears in an expected location compared to an unexpected location (Posner, 1980) and in one hemifield compared to the other - the left- (pseudoneglect; Bowers & Heilman, 1980). Prominent part of the literature suggests an involvement of the fronto-temporo-parietal circuit, mainly lateralized in the right hemisphere (Corbetta & Schulman, 2002). fMRI investigations showed that tasks involving visuo-spatial attention activated mainly a circuit composed of the Frontal Eye Field (FEF), the temporo-parietal junction (TPJ), the superior frontal cortex (SFC) and the posterior parietal cortex (PPC; Corbetta & Schulman, 2002). Supporting this model, clinical evidence showed that a lesion of the network is able to induce an attentional bias towards the ipsilesional side of the space, resulting in the (left) hemispatial neglect for right hemisphere lesions (Vallar & Papagno, 2011). Conversely, an intact and efficient right hemisphere circuit results in a slight bias to the contralateral (left) side, a phenomenon called "pseudoneglect" which is commonly observable in healthy participants (Bowers & Heilman, 1980). Other contributions seem to indicate inter-hemispheric balance as a key role in hemispatial neglect (Sparing et al., 2007, 2009; Benwell et al., 2015; Giglia et al., 2011).

The right dominance theory proposed that the right hemisphere is dominant in spatial selective attention (Mesulam, 2001). This theory mainly took advantage of the prominent evidence regarding spatial neglect, which is more frequent for right hemisphere lesions (Heilman et al., 1985; Bowen et al., 1999; Ringman et al., 2004; Becker and Karnath, 2007), suggesting a specific role of the right hemisphere. This theory assumes that the asymmetry consists in the left hemisphere control on the rightward shifts, while the right hemisphere controls both right and left hemifields (Mesulam, 2001). However, there is evidence for bilateral activation during spatial attention tasks (Kastner et al., 1999; Corbetta et al., 2000; Hopfinger et al., 2000; Woldorff et al., 2004; Sereno et al., 2001; Silver et al., 2005; Hagler and Sereno, 2006; Jack et al., 2007; Swisher et al., 2007), casting doubts on a rigid right hemisphere control of spatial attention. Moreover, neuroimaging studies revealed that the circuits for attention are largely bilateral and show a preference for contralateral targets (Schulman et al., 2010). Other contributions using neuroimaging techniques suggested that attending a location activates the intraparietal sulcus, whereas target detection produces activation of the right tempoparietal junction. Neuroimaging studies therefore challenge the theory that only the right hemisphere is engaged in spatial attention, or only a small portion of the right hemisphere

(Schulman et al., 2010). According to the hemispheric rivalry model (Kinsbourne, 1987), unilateral neglect is the consequence of an interhemispheric imbalance. In the case of a lesion to one hemisphere, the intact hemisphere becomes released and hyperactive (as the interhemispheric inhibition from the damaged hemisphere is no longer effective) and biases attention towards the ipsilesional side of space. The finding that hemineglect occurs more often after right than left hemispheric lesion is explained by the assumption that the contralateral bias of the left hemisphere is stronger than the contralateral bias of the right hemisphere (Kinsbourne, 1987).

It is also important to emphasize that different spatial-attentional tasks engage partially distinct neural circuits. Cicek et al. (2009) found right IPS, anterior cingulate girus (ACG) and right LPS activations during the Landmark task, while Cavezian et al. (2011) reported that the landmark task activated a predominantly right hemisphere network including superior and inferior parietal cortices. These studies therefore agree that the landmark task activated predominantly the right hemisphere. However, Corbetta et al. (2012) found out that a detection task activates primarily the intraparietal sulcus (IP) when a location was attended before visual-target presentation, and the right temporo-parietal junction when the target was detected, particularly at an unattended location. The right TPJ (and precuneus) was specifically engaged during target detection. Anterior IPs and ventral IPs showed both cue and target responses, while right TPJ and precuneus showed little if any response to the cue (Corbetta et al. 2012). Moreover, extinctions in bilateral targets observed in right hemisphere lesioned neglect patients suggest that a greater activation in the non-lesioned hemisphere could induce an impairment in processing contralateral left stimuli, thus over estimating the opposite right part of space (Vuilleumier & Rafal, 2000).

*EEG resting-state correlates of visual attention*

Oscillatory brain activity reflects the synchronization of neurons into functional networks as an essential component of signal trasmission (e.g., Buzsáki, 2006) and it seems to play a role both in normal (e.g., Fries, 2005; Wang, 2010; Thut et al., 2012; Lopes da Silva, 2013) and in abnormal function of the brain (e.g., Schnitzler and Gross, 2005; Uhlhaas and Singer, 2015). Alpha band oscillations (8–13 Hz) in occipital cortex are thought to be crucial for the study of visuospatial attention. The neural mechanism of allocation of visuospatial attention has been attributed to

anticipatory modulation of occipito-parietal alpha-band (8–12 Hz) oscillations during cue-target delays (Foxe et al. 1998; Worden et al. 2000). Moreover, alpha oscillations have been related to thalamo-cortical activity (Hughes and Crunelli 2005; Lopes da Silva 1991). Some studies found that occipito-parietal alpha oscillations are attenuated when visual information is attended compared with auditory information (Foxe et al. 1998; Fu et al. 2001). When visuospatial attention is covertly allocated, a modulation of alpha activity is also observed (Rihs et al. 2007; Worden et al. 2000). Conversely, increased anticipatory alpha synchronization is typically observed ipsilateral to the locus of attention, probably reflecting suppression of processing of unattended locations (Kelly et al. 2006; Rihs et al. 2007; Rihs et al. 2009; Worden et al. 2000), while decreased synchronization has been observed contralateral to attention, perhaps reflecting enhancement of processing for attended locations (Kelly et al. 2009; Rihs et al. 2009; Sauseng et al. 2005; Thut et al. 2006; Yamagishi et al. 2008).

Also beta oscillations are found to be indicative of visuospatial attention. Attentional blink describes the failure to detect the second of two targets in rapid serial streams of sensory input when both targets are separated by less than ∼500 ms. This failure to detect the second target has been associated with reduced phase synchronization in the beta-frequency band (Gross et al., 2004), whereas a separate study reported enhanced gamma-band synchronization preceding correct detection of second targets (Nakatani et al., 2005). These results suggest that beta- and/or gamma-frequency synchronization during target processing could subserve effective integration within a broad and distributed attention network (see also Kopell et al., 2000). The suggestion that beta-frequency phase synchronization subserves long-range functional coupling is supported by further lines of evidence. The failure of attentional target selection in the attentional blink paradigm (Marois et al., 2004) and attentional lapses in general (Weissman et al., 2006) are typically attributed to restrictions of functional interactions in a frontoparietal attention network rather than to processing limitations at sensory processing stages. Consequently, the observed relationship between long-range beta-band synchronization and target selection could reflect changes in effective neuronal communication within this network. This suggested role of beta-frequency synchronization has also been derived from earlier studies during task intervals that require selective spatial attention (Brovelli et al., 2005) and perceptual integration (Liang et al., 2002).

It should be noted that synchronization at beta frequencies is not the sole candidate for mediating long-range interactions between cortical areas, and it might also have more specific functional roles within local neuronal groups. For example, some studies link beta synchronization in primary visual

cortex, but not in extrastriate visual area V4, to the maintenance of a visual percept (Milke et al., 2006, but see also Gail et al., 2004). Furthermore, in a working-memory context, beta synchronization in area V4 has been linked to successful maintenance of a remembered shape (Tallon-Baudry et al., 2004).

Van Ede et al. (2011) found that orienting to an upcoming tactile event involves a spatially specific contralateral suppression of alpha- and beta-band oscillations in the sensorimotor cortex. Moreover, the contralateral suppression of beta-band oscillations is associated with faster responses to subsequently presented tactile stimuli. Control measures showed that these results cannot be explained by motor planning or execution.

Also neurofeedback training of sensorimotor rhythm (SMR: 12–15 Hz) and beta1 band (15–18 Hz) components led to significant and protocol-specific effects in healthy subjects. The data can be interpreted as indicating a general attention-enhancing effect of SMR training, and an arousal-enhancing effect of beta1 training, thus suggesting a role of beta in attention (Egner & Gruzelier, 2004).

*Visuospatial attention measures and their neural substrates*

We engaged participants in a mental rotation task during the stimulation, and two visuospatial task after the stimulation (landmark and cued detection). Some studies found that the stimulation of right parietal cortex, but not left, modulated the online performance at the mental rotation task (Harris & Miniussi, 2003). Although the right lateralization of this task is not confirmed also by fMRI investigations, which found mainly a bilateral activation, it is likely that a parietal involvement would be crucial to complete the task (Cohen et al., 1996; Richter et al., 1997, 2000; Vingerhoets et al., 2002; Zacks, 2008; Tomasino and Gremese, 2016). In visuospatial abilities, it seems like the degree of lateralization can be modulated by stimulus and strategy: more bilaterally activation are observed for bodily and motor strategies (for example, "imagine rotating the object"), while more right activation is clear for non-bodily and non-motor strategies (for example, "imagine the object rotating in space"; Tomasino and Gramese, 2016). This is consistent with dissociations observed in patients with unilateral brain lesions, where right-sided lesions are associated with mental rotation

impairments for objects (but not hands) and non- motor (but not motor-based) rotation strategies, whereas the opposite holds for left-sided lesions (Tomasino et al., 2003; Tomasino and Rumiati, 2004). It is also consistent with similar findings on line bisection, where activation becomes more bilateral (due to increasing left-sided activations) if stimuli are presented in near vs. far space (i.e., within reach) and if the bisection task is active (i.e., involving a motor component) rather than purely perceptual, as in the landmark task (Weiss et al., 2003).

However, other evidence suggest the relevance of right-lateralization in visuospatial tasks. Behavioral studies show that tapping memory task for spatial location are performed better for stimuli presented to the left hand (Witelson, 1976) or in the left visual field (Kimura, 1969; Durnford and Kimura, 1971; Tucker et al., 1999; Postma et al., 2006). Lesion studies indicate that injury to the right hemisphere, especially the parietal lobe, results in dramatic impairments in the spatial domain that are evident in drawing, construction, and orientation tasks as well as in left-right disorientation and apraxia for dressing (Brain, 1941; McFie et al., 1950; Hecaen et al., 1956; Vallar, 1998). The rightward bias can be induced experimentally by temporarily disrupting right parietal cortex through repetitive transcranial magnetic stimulation (rTMS), while left-sided rTMS has no spatially biasing effect (Fierro et al., 2000). Finally, fMRI studies requiring line bisection judgments (Fink et al., 2001; Çiçek et al., 2009) reveal activations predominantly in right parietal and premotor cortex.

Benwell et al. (2014) found that most participants displayed a systematic leftward bias (pseudoneglect) during long line landmark task performance while no systematic bias was observed with short lines, in line with the previously reported line-length effect (Benwell et al., 2013; Heber et al, 2010; McCourt and Jewell, 1999; Rueckert et al., 2002; Thomas et al., 2012). EEG findings establish that an increased engagement of areas of the right lateralized, ventral attention network contributes to the genesis of the spatial bias, and that this engagement is stimulus-driven, independently on the task administered. The authors found a high amplitude ERP response to long compared to short lines corresponded in timing to the N1-component and was right lateralized to areas of the temporo-parietal junction. Furthermore, the difference in peak N1-amplitude between long and short line processing correlated with the difference in line bisection bias between long and short lines, thus suggesting that N1 amplitude is indicative of the bias showed by participants.

Moreover, stimulating right posterior parietal cortex with tDCS, Roy et al. (2014) found a modulation of reorienting index in healthy subjects, thus suggesting a relationship between this cortical site and reorientation of attention.

Few EEG studies have looked at the neural correlates of line bisection in healthy participants (Foxe et al., 2003) and at the neural correlates of the above rightward shifts (see Newman et al., 2013; O'Connell et al., 2011; Perez et al., 2009). Results obtained by O'Connell et al. (2011) and Benwell et al. (2014) suggest a common neural substrate for the rightward shifts observed with decreased line length and increased perceptual load respectively: the right-lateralized TPJ activity at the latency of the N1-component. Moreover, Benwell et al. (2014) showed that rightward shift is associated with a decrease in right lateralized TPJ activity and that this degree of attenuation correlates with the degree of the rightward shift in behavioral bias.

*Brain stimulation and spatial attention*

Some studies investigated the effects of trascranial stimulation on attentional abilities. Sparing et al. (2009) found that depending on the position of anode it was possible to modulate the bias in attention towards the contralateral hemispace. Anode applied over right posterior parietal cortex induced a shift toward the left hemispace, while applied on the left posterior parietal cortex it induced a shift toward the right. These results are in line with the hemispheric rivalry proposed by Kinsbourne (1977), which postulates that an efficient activation in the right hemisphere results in a contralateral bias, while a lesion to a part of the circuit causes an ipsilesional bias because of the inter-hemispheric balance. Supporting this hypothesis, Sunwoo et al. (2013) found that both single tDCS over rPCC and dual tDCS over PPC (anode on the right, cathode on the left) induced a positive effect on neglect patients, but stronger for the latter protocol. This difference might be due to the simultaneous deactivation of the left hemisphere and activation on the right, assuming an inter-hemispheric mechanism. Causal evidence supporting this theory shows that inhibiting the left hemisphere activation results in a decrease in the rightward bias in neglect patients (Sparing et al.,

2009), as well as activating the lesioned hemisphere (Sparing et al., 2009) or stimulating both the hemispheres with opposite polarities at the same time (Brem et al., 2014).

More recently, Benwell et al (2015) modulated a version of the landmark task by using biparietal anodal tDCS on P5 and P6 (as Giglia et al., 2011). They found a rightward bias when applying the anode on the left and the cathode on the right, but not a leftward bias with the opposite montage. However, the effect was weak considering all the 38 participants, but stronger when analyzing a small subset of low performance subjects. This is in line with the previous studies underlining that tDCS effectiveness depends on the baseline expertise/performance level of each participant (Berryhill & Jones, 2012; Dockery et al., 2009; Hsu et al., 2014; Learmonth et al., 2015; Tseng et al., 2012; Benwell et al., 2015).

*The present study*

The present study aimed at evaluating the transfer effects in the attentional domain induced by trascranial direct current stimulation (tDCS) and random noise stimulation (tRNS) applied over the posterior parietal cortex (P4). To make a direct comparison possible, in the present study we manipulated also the montage in the tRNS stimulation (unilateral and bilateral), because, to the best of our knowledge, only one study to date investigated the effects of tRNS depending on the positioning of the electrodes on the scalp (Moliadze et al., 2010). tRNS is a powerful tool in order to boost the activity of a neural population and to date it has been employed mainly to potentiate cognitive learning and training (Cappelletti et al., 2013; Snowball et al., 2013). Regarding tDCS, some authors proposed that electric stimulation is able to activate only the sites involved in a task, the so-called “Stochastic resonance” (Miniussi, et al., 2013; Fertonani, et al. 2011). Whether also tRNS activates only the sites involved in a task, as it seems true for tDCS, or also cortical sites far from the focus of the stimulation is still an open question.

In the present study we assessed the after-stimulation transfer effects to tasks other than the one administered during the stimulation to evaluate and compare the long-term effects of different tES techniques, namely anodal tDCS (a-tDCS), unilateral tRNS (U-tRNS) and bilateral tRNS (B-tRNS) on attentional functions. We aimed firstly to assess the effects of the protocols on an online task, a version of the mental rotation task, which would be for the first time modulated by tES, and on two

offline tasks administered after the end of the stimulation, the landmark task and a cued-detection task. The advantage of the present study is twofold, for it could be possible:

a. to evaluate and to compare the long-term, transfer effects of new minimally invasive protocols and

b. to investigate the possible long-term plasticity changes induced by our manipulation.

We tested four different experimental groups on 48 hours-separated days to reduce over learning effects in our participants. We chose a mental rotation as an online task because it is thought to activate mainly the posterior parietal cortex. Some studies reported right activation (Harris & Miniussi, 2003; Funnell, Corballis, & Gazzaniga, 1999; Corballis, Funnell, & Gazzaniga, 2002), while others bilateral activation (Cohen et al., 1996; Richter et al., 1997, 2000; Vingerhoets et al., 2002; Zacks, 2008; Tomasino and Gremese, 2016). The tasks aimed to test the possible behavioral generalization of the effects were a landmark task (Milner et al., 1993) and a cued detection task, including bilateral targets (a modified version from Posner, 1980). The landmark task has been chosen because its performance to left targets is detrimental in right-unilateral neglect patients and it is facilitated in healthy subjects, while performance to right targets is detrimental in left-sided lesions, thus mirroring the efficiency of right and left hemisphere (Fink et al., 2001; Çiçek et al., 2009; Tomasino et al., 2003; Tomasino and Rumiati, 2004) and has been massively used to study the attention bias both in healthy participants and in clinical population (Schenkenberg et al., 1980; Jewell and McCourt, 2000). The attentional task we administered was a simple detection task with both unilateral (right or left) and bilateral targets (both sides), to which we also added a central cue (which could be valid, invalid or partially valid in the 30% of the times). We additionally included catch trials to make the task more difficult. The reason why we added this task was that tDCS on rPPC has been sbown to enhance reorienting in healthy population (Roy et al., 2014).

In addition, we registered five minutes resting-state EEG immediately after the end of the stimulation to assess possible long-term plasticity-induced changes and possibly correlate them with the behavioral outcomes.

Possible outcomes are the followings:

a) only online effects of tDCS and tRNS, meaning that it is impossible to induce a long-term plasticity with only one session of stimulation for both the techniques;

b) offline and online effects for both the techniques, meaning that both the protocols are able to induce long-term effects; analysis of the type of trials modulated (longer left, longer right; invalid, valid, bilateral) should suggest the hemisphere activated by each protocol; EEG data could confirm the hypothesis;

c) an offline effect only for one of the two techniques, tDCS or tRNS, and in this latter case whether the effect depends on the montage (unilateral or bilateral) or not. If yes, it might be due to a specific cortical activation (U-tRNS), if not it might reflect inter-hemispheric mechanisms (B-tRNS); again, EEG data could be crucial to understand the cortical changes induced by the stimulation.

It is worth noting that in this study the possible offline effects are transfer effects because during the stimulation a different task was administered (the Mental rotation task).

*Method*

*Participants*

Sixty healthy participants (mean age: males 23.32 (± 2.18), N=28; females 21.67 (± 1.79), N=32), took part in the experiment. They all had normal or corrected vision, were right handed according to the Oldfield test (at least 75%) and didn't fit any of the exclusion criterions for brain stimulation. The experiment received approval from the local ethical committee and all participants before starting the first session signed the informed consent according to the Declaration of Helsinki. All participants were paid for the time spent in our laboratory.

*Apparatus and stimuli*

All the tasks were performed in a quiet, slightly lighted room, at a distance of approximately 50 cm from a 17-inch computer monitor. EEG montage was completed in the same room, as well as tES montage and stimulation.

*Online task*

*Mental rotation task*

Participants performed a mental rotation task (Shepard & Metzler, 1980) during the stimulation for a total of 15 minutes. Targets were two tridimensional colored tridimensional shapes presented contemporary on the left and on the right of the screen, at the same distance from a fixation cross (about 1cm wide, 1.15° of visual angle). The order of the targets were randomized and since we had a fixed total duration of the task but a variable time of response (maximum 10 seconds), we chose to present a random selection of targets until the end of the 15 minutes, to preserve the total duration of the stimulation period between participants. The reason why we chose to administer this paradigm was that we aimed to induce a long-term activation of the circuit involved. Two tridimensional colored targets appeared on a computer screen at the same distance of the fixation cross (the center of the figure was 4 cm distant from the center of the screen (4.58° of visual angle), and for sake of simplicity we maintained this distance for all the figures presented, independently on their orientation). An example of the trials is presented in Figure 1. The duration of the permanence of the stimuli on the screen depended on the participant's performance (maximum 10 seconds). It is well known that for brain stimulation many factors are to be considered in order to induce a reliable effect. One of those is the novelty of the task and a medium difficulty (Miniussi, Harris & Ruzzoli, 2013) because otherwise it could be possible to induce a ceiling effect for a well-known (or repeated) task, or a floor effect for a very difficult task. We aimed to avoid those risks by (a) using a novel task, thus avoiding a baseline measure, and (b) letting the participants take the time they needed to think and respond accurately.

Participants were required to evaluate whether the shapes were the same rotated or different (mirrored on the horizontal axis or structurally different) by pressing one of two possible keys, Z and M on the computer keywords, respectively. All the targets were the same of the original work by Shepard and Metzler (1980).

Participants were instructed to respond when they were sure, pressing the right key when they thought the stimuli presented were the same rotated, and the left key when the stimuli were different

or reflected. In instructions, we recommended to imagine objects rotating in space, as it was shown that this strategy enhanced right hemisphere activations (Weiss, 2003).

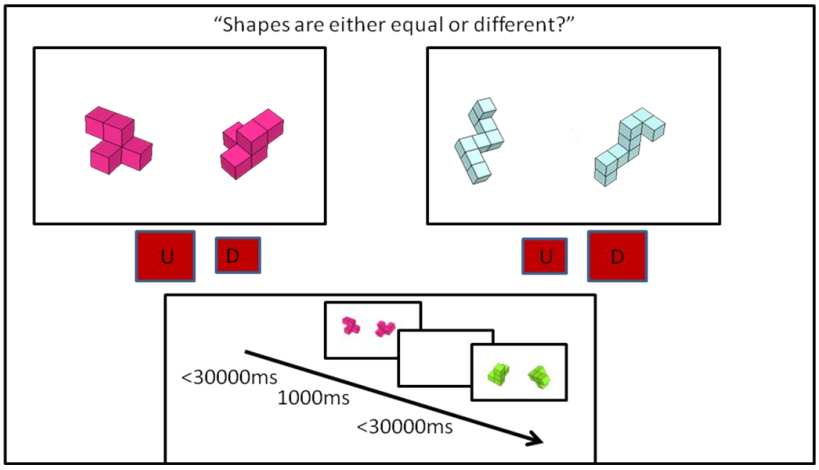



Figure 1. Example of mental rotation trial.

*Offline tasks*

*Landmark task*

After-stimulation tasks were the Milner landmark task (Milner et al., 1993) and a cued attentional task. We chose the landmark task because it is thought to activate mainly the right hemisphere (Fink et al., 2000a, 2001, 2002; Cicek et al., 2009). We preferred the landmark on a classic line bisection task to avoid a great amount of variability in each participant response and to be more consistent with other works using tES (Giglia et al., 2011; Benwell et al, 2013, 2015).

The landmark task was similar to the one proposed by Benwell et al. (2013, 2015) in which pre-bisected black and white lines of 100% Michelson contrast were presented on a grey background and participants were asked to judge which end of the line (left or right) appeared to be longer.

The stimuli were five horizontal segments (18 cm long), four of which were previously bisected by a vertical line, while one was not bisected (control target). Participants were required to indicate

which side of the segment was longer, whether the left one (pressing the left key, Z) or the right one (pressing the right key, M). Crucially, participants were given the possibility to say that the two sides of the segment were equal, by pressing at the same time the right and the left key (ZM). We added those trials to have a more precise measure of right and left overestimation. Stimuli are presented in the Figure 2. Two targets were bisected either on the left or on the right of the true half, and two levels of difficulty were added (easy and difficult) to which participants were required to report which side was longer side, either the right or the left. A fifth control target to which the participant didn't have to respond was added to rule out the eventuality of responding by chance. Participants was given the possibility to say that right side was as long as right side, in order to have a measure of their degree of hesitation and have a more accurate index of right and left bias.

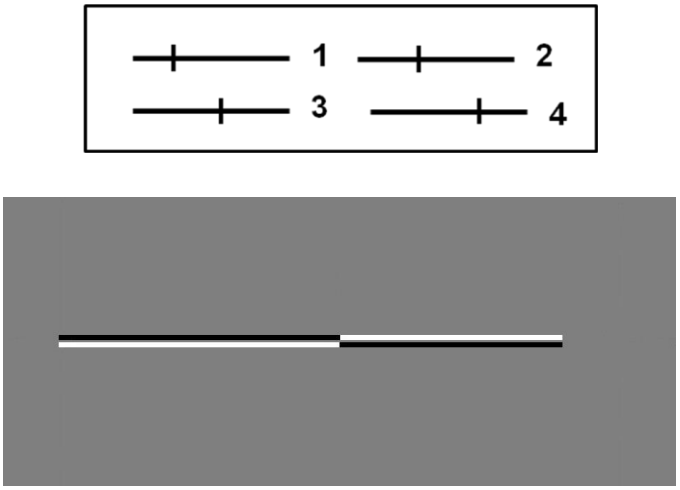



Figure 2. Landmark task stimuli.

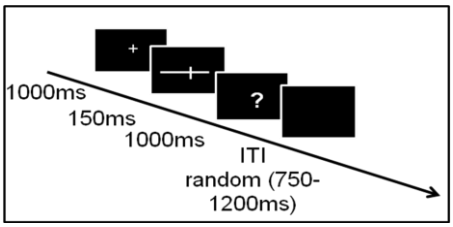



Figure 3 Procedure of Landmark task.

Lines measured 18 cm in length by .5 cm in height and, at a viewing distance of 50 cm, subtended 20.41° (width) by .57° (height) of visual angle. Lines were transected at .55 cm (difficult condition) or .99 cm (easy condition) from the veridical center. This represented respectively .63° or 1.13° of visual angle relative to veridical centre. Figure 3 depicts a schematic representation of the trial procedure. Each trial began with presentation of a fixation cross (.57° (height) x .57° (width) of visual angle) for 1 second followed by presentation of a transected line for 150 msec. The transection mark was always centered on the fixation cross (i.e., the eccentricity of the line endpoints varied across trials while the transector always appeared at the same position), therefore preventing use of the fixation cross as a reference for bisection judgments. The fixation cross then appeared during the response period, when participants indicated which end of the line the transection mark had appeared most far to, by pressing either the left or right response key. Participants responded using left hand index for left longer lines (Z) and right hand index for right longer lines (M) and were instructed to keep their gaze on the fixation cross throughout each trial. The subsequent trial began as soon as the response was given. Trials lasted approximately 2 sec. Trial type (location of transector in line and difficulty) was selected randomly. 30 trials were added to allow participants to familiarize with the task. The number of trials was 100 for longer right and longer left trials, one half (50) easy and one half (50) difficult, for a total of 200 trials. Moreover, 50 catch trials were added, for a total of 250 trials.

*Cued spatial detection task*

We also administered a cued spatial detention task. This paradigm can be used to test a possible modulation in re-orienting of attention after the stimulation, as described in Roy et al. (2014) after a-tDCS. The task was a simple detection task with a central cue (a white arrow on a black background, 33% of validity). Participants were instructed to simply report the target (a white dot), which could appear on the right, on the left or on both sides on a computer screen. Note that arrow cues can induce a reflexive-like shift in attention (Tipples, 2008; Guzzon et al., 2010; Galfano et al., 2011).

Participants were instructed to respond as soon as possible to the position of the targets, by pressing the right key with the right hand when the target appeared on the right, the left key with the left end when the target appeared bilaterally, no key when no target appeared.

Each trial started with a central fixation cross (1 second), followed by a central arrow pointing either toward the left or to the right (200 ms). After this period, a bilateral mask appeared (1 second) followed by the rapid presentation (80 ms) of a target (a white circle) appearing either on the left, on the right or on both sides. After this presentation, the masks reappeared until the participant pressed a key. In some trials (catch trials) the target was absent. The masks were added in order to avoid the visual permanence of the targets on the screen. The total number of trials was 540 for each participant, 160 were valid, one half with the target appearing on the right (80) and one half on the left (80); 160 were invalid, one half with a target on the right (80) and one half on the left (80). Bilateral targets and corresponding "partially predictive" cues were 160. Catch trials were 60. We had therefore a total of 160 valid cues (33%) and 380 invalid cues (66%). It is worth noting that the 380 invalid trials were not necessarily predictive of the opposite direction because we inserted also bilateral target in which both sided had to be chosen. Procedure of the task is shown in Figure 4.

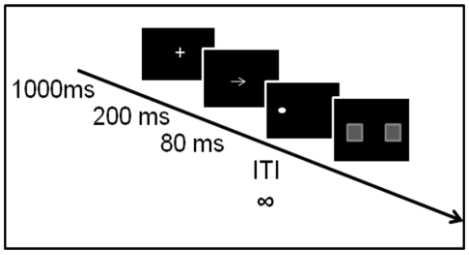



Figure 4. Experimental procedure of cued detection task.

*Procedure*

The procedure of the experiment is presented in figure 5.

Participants came to the laboratory on two consecutive days. After reading and signing the consent to participate at the research, they were seated on a comfortable chair in front of the computer (mean distance: 50 cm). In the session 1, firstly the EEG montage was completed. We applied a 32 channels cap (ElectroCap) with 7 external channels (two on mastoids, two below eyes, two on the

cantii and the last one on the Nasion). After the montage (around 10 minutes), we recorded the 5 minutes resting-state EEG signal. After the EEG recording, participants were required to complete the two "transfer" tasks: the landmark task and the cued-detection task. The order of the two tasks was counterbalanced between participants to avoid sequential effects, but it remained the same between sessions (participant who performed first the landmark task, in the second session did the same) to avoid that effect of the previous trial covered up the effect of the stimulation. At the end of the first session, we recorder the eye movements calibration for each participant to extract the coefficient for eye movement correction during the EEG data pre-processing. In the second session, participants returned to the laboratory and were immediately stimulated while they performed the mental rotation task. After this time, the EEG montage was conducted (around 10 minutes per participant) and the 5 minutes resting state EEG was recorded. Finally, the tasks in the same order as in the day before were performed. The mean duration between the end of the stimulation and the end of the task was 45 minutes (10 minutes montage, 5 minutes recording, up to 15 minutes landmark, up to 15 minutes cued-detection task).

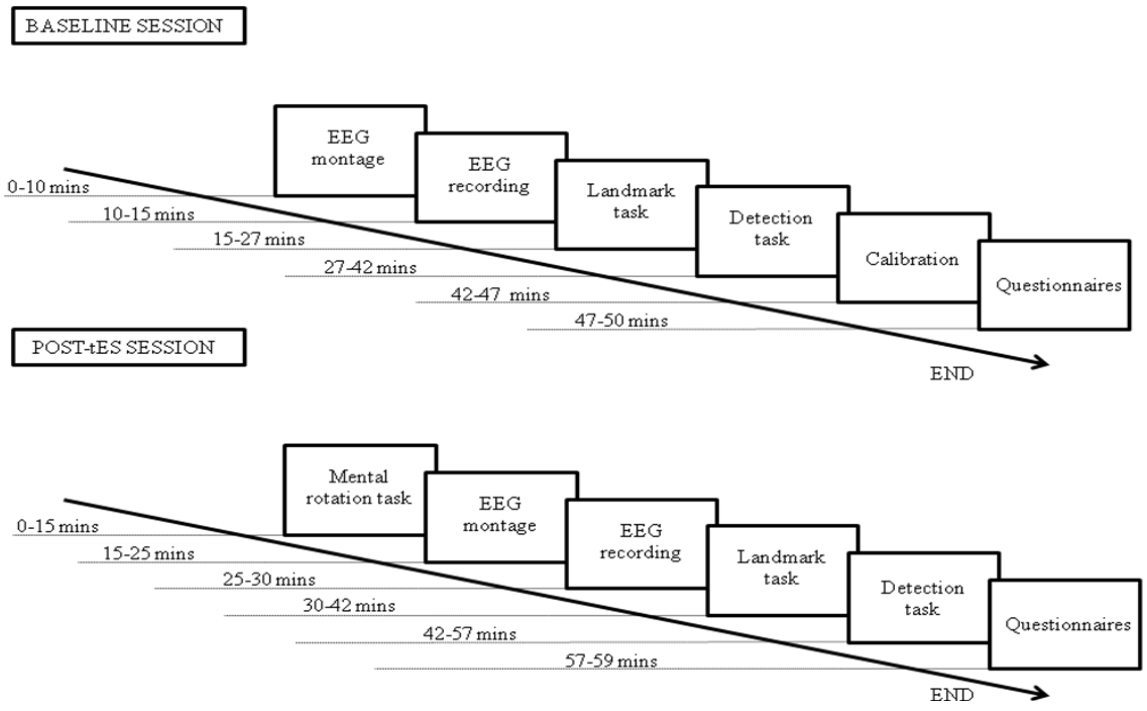



Figure 5. Procedure of the experiment.

*Stimulation*

Depending on the group to which each participant was randomly assigned, they could receive on the second session a-tDCS (1 mA, 15 minutes, fade in/out: 30s), U-tRNS (maximum 1 mA, 15 minutes), B-tRNS (high frequency, 0.1-1 mA, 15 minutes) or sham stimulation (only the first and last 30s, 1mA). The montage of the electrodes is shown in Figure 6. The dimension of the sponges were 4 x 4. For a-tDCS and U-tRNS, participants received the stimulation over the right posterior parietal cortex (P4 according to the 10-20 system), while the second electrode was positioned over the contralateral supraorbital region. For B-tRNS, the montage was bilateral, with an anode over P4 and the other positioned contralaterally, i.e., over P3. Participants assigned to the sham (control) group received a half a bilateral montage, a half a unilateral montage, to rule out specific effects only due to the positioning of the electrodes.

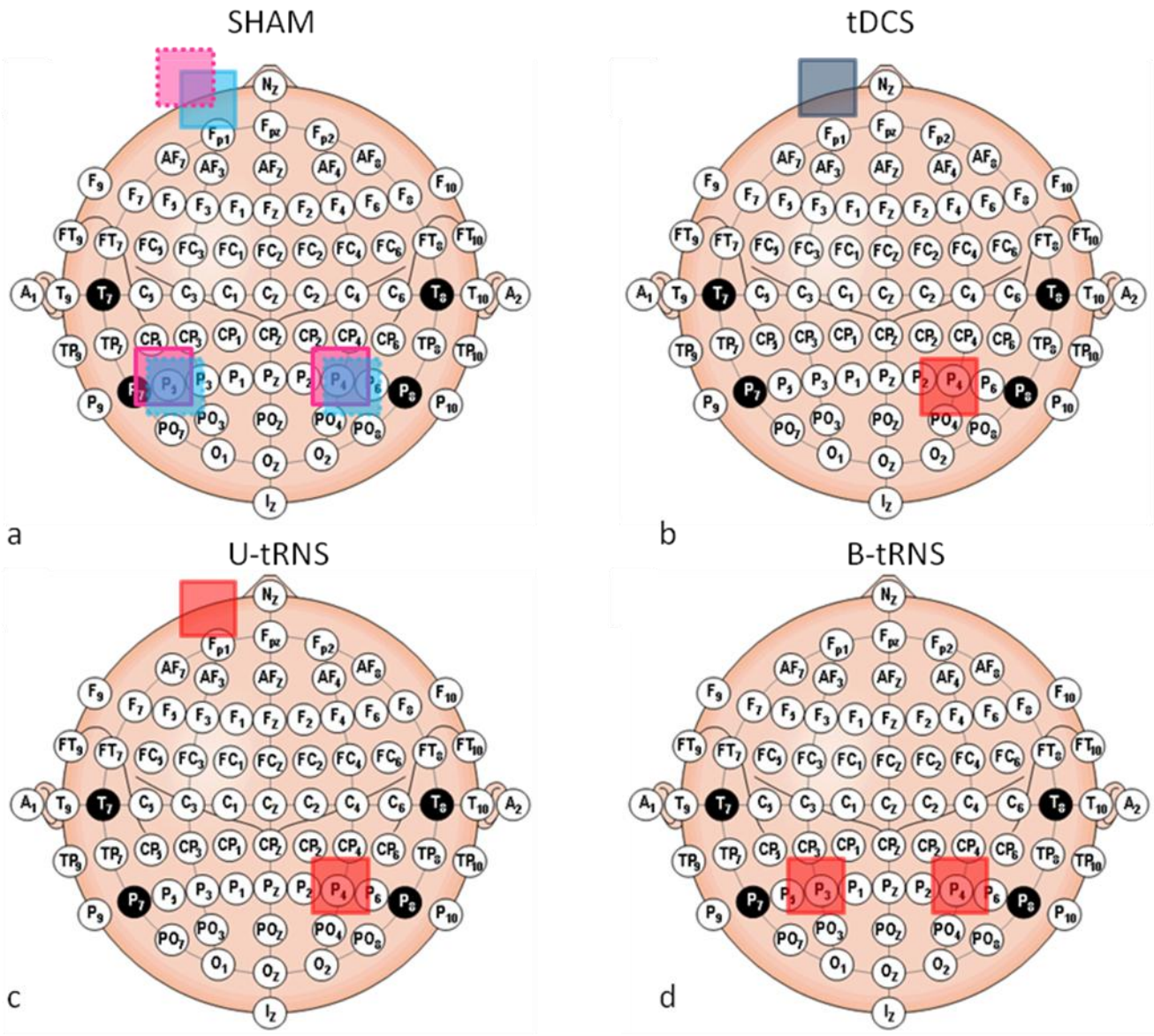



Figure 6. Position of electrodes in each experimental group. In a) sham montage is presented. In this group, we counterbalanced the position of electrodes, unilateral and bilateral. In both cases, we counterbalanced also the position of anode and cathode, although irrelevant. In b) tDCS montage is presented, with anode on P4 (red square) and the cathode over supraorbital region (blue square). In c), the two anodes were positioned over P4 and supraorbital area, while in d) they were positioned over P4 and P4, bilaterally.

*EEG data acquisition*

In the first session and in the second, participants underwent two resting state EEG recordings in order to verify whether an effect on cortical plasticity was inducted by our manipulation. Since the tasks were mainly visuospatial tasks, we expected a modulation of beta band, usually related to attentive functions (Wróbel, 2000; Sachett et al., 2015).

We chose to record resting state EEG because this kind of recording is often linked to long-term changes in plasticity as expected with tRNS. In addition, a significant modulation of EEG resting state activity is associated to the experimental manipulation itself, not to the task executed, providing thus evidence of possible generalizations of stimulation effects.

Electrophysiological activity was recorded with 31 tin electrodes by means of an elastic cap (ElectroCap) and positioned according to the International 10-20 system (Oostenveld and Praamstra, 2001); seven more electrodes were applied below the eyes (Io1, Io2) on the two external canthi (F9, F10), nasion (Nz) and mastoids (M1, M2). Overall, 38 EEG locations were recorded. All cortical sites were online referred to Cz, and re-referenced offline to the mean activity of the whole scalp with the average reference procedure. Data were stored in NeuroScan 4.3 (NeuroScan Labs, Sterling, VA, USA). The impedance was kept below 5 kΩ. EEG was recorded in AC mode and stored for later analysis. After data collection, EEG signals were corrected for blinking and eye movement artifacts with BESA software (Brain Electrical Source Analysis, Graefelfing, Germany).

*Data Analysis*

Data were analyzed using mixed effects models in the R environment (R Core Team, 2016) using the packages "lme4" (D Bates, D Sarkar, MD Bates, L Matrix, 2007) and "sjPlot" (D Lüdecke, C Schwemmer, 2017) in order to account for the subjective difference between participants, for the different number of observations per cell and for repeated measures designs. In particular, we applied generalized mixed models in order to proper analyze data with a logistic distribution when appropriate (Jaeger, 2008). Firstly, we compared models to select the one explaining the greater amount of variance. Secondly, we inspected the effect detectable in the selected model.

For reaction times and equal number of observation per cell designs, we applied analysis of variance (ANOVA) using the package "ezANOVA" (MA Lawrence, MMA Lawrence, 2016), Rmisc (Hope, 2013) and Reshape2 (H Wickham - 2013) in R envirovment.

For EEG data, ANOVA was carried out for the delta EEG band with Group as between subjects factor (sham, tDCS, U-tRNS, B-tRNS) and session (pre and post) and cluster as within subjects factor. For visualization, we used ggplot2 (Wickham, 2009) package in R.

*Results*

*Mental Rotation*

We analyzed accuracy data because participants had no time pressure and accuracy was emphasized in the instructions. In the model we entered group and stimuli and their interaction as fixed effects, while participants and stimuli were included as random intercept terms, to account for both participant- and stimulus-related variability (Baayen, Davidson & Bates, 2008), while avoiding convergence issues due to the small number of observations per single item. Moreover, we added a model with the stimulus as fixed effect (stimulus model), a model with orthogonal fixed effects (stimulus + group) and a model with the interaction term (stimulus x group). We used the Akaike's information criterion (AIC; Akaike, 1973) to select the model that was more likely the best one to describe our data, following Burnham, Anderson, & Huyvaert (2011).

Interaction effects for the selected model were further investigated in terms of simple effects via multiple contrasts with the ''testInteraction" function in the ''phia" R package (De Rosario-Martinez, 2015), adjusting the false discovery rate with FDR adjustment (Benjamini & Hochberg, 1995). The ''effects" R package (e.g., Fox & Hong, 2009) was used to investigate effects within specific models.

First, we compared the models to find the best one in explaining variance. From this comparison, the model with the interaction group by type of stimulus and a random intercept for subject and type of stimulus was chosen because the value of AIC was the best between models (see table 1). According to Burnham, Anderson, & Huyvaert (2011), we selected the model including the interaction term (stimulus x group model) for it was 21 times better that the model including the

fixed effect of stimulus (stimulus model) and 29.6 times better that the model including the additive effect of stimulus and group without the interaction term (stimulus + group model). The stimulus x group model best fit the data compared to competing models (AIC (stimulus)=7122.1, AIC (stimulus + group) = 7126.8, AIC (stimulus x group)=7110.2).

By means of "phia" package, we further inspected the simple effects via multiple contrasts with an FDR adjustment. The comparison between the two targets, equal and different, and all the groups revealed significant difference between sham-tDCS ($\chi^2$=10.80, p=.003), tDCS - U-tRNS ($\chi^2$=4.67, p=.046), tDCS-B-tRNS ($\chi^2$=21.39, p<.001), U-tRNS-B-tRNS ($\chi^2$=5.62, p=.035) and it missed significance when comparing sham-B-tRNS ($\chi^2$=3.05, p=.09). Interestingly, the B-tRNS group was the only one which showed no difference between the targets ($\chi^2$=2.04, p=.2). See Figure 7 to inspect the adjusted means in the model.

| Model | Df | AIC | BIC | LogLik | Deviance | p |
|---|---|---|---|---|---|---|
| m.0 | 3 | 7127.4 | 7147.6 | -3560.7 | 7121.4 | - |
| $m_{Stimuli}$ | 4 | 7122.1 | 7149.2 | -3557.1 | 7114.1 | .007 |
| $m_{Group}$ | 6 | 7132.0 | 7172.6 | -3560.0 | 7120.0 | 1 |
| $m_{Group+Stimuli}$ | 7 | 7126.8 | 7174.0 | -3556.4 | 7112.8 | .007 |
| $m_{GroupxStimuli}$ | 10 | 7110.2 | 7177.7 | -3545.1 | 7090.2 | <.001 |

Table 1. Comparison between models to explain Mental Rotation accuracy data.

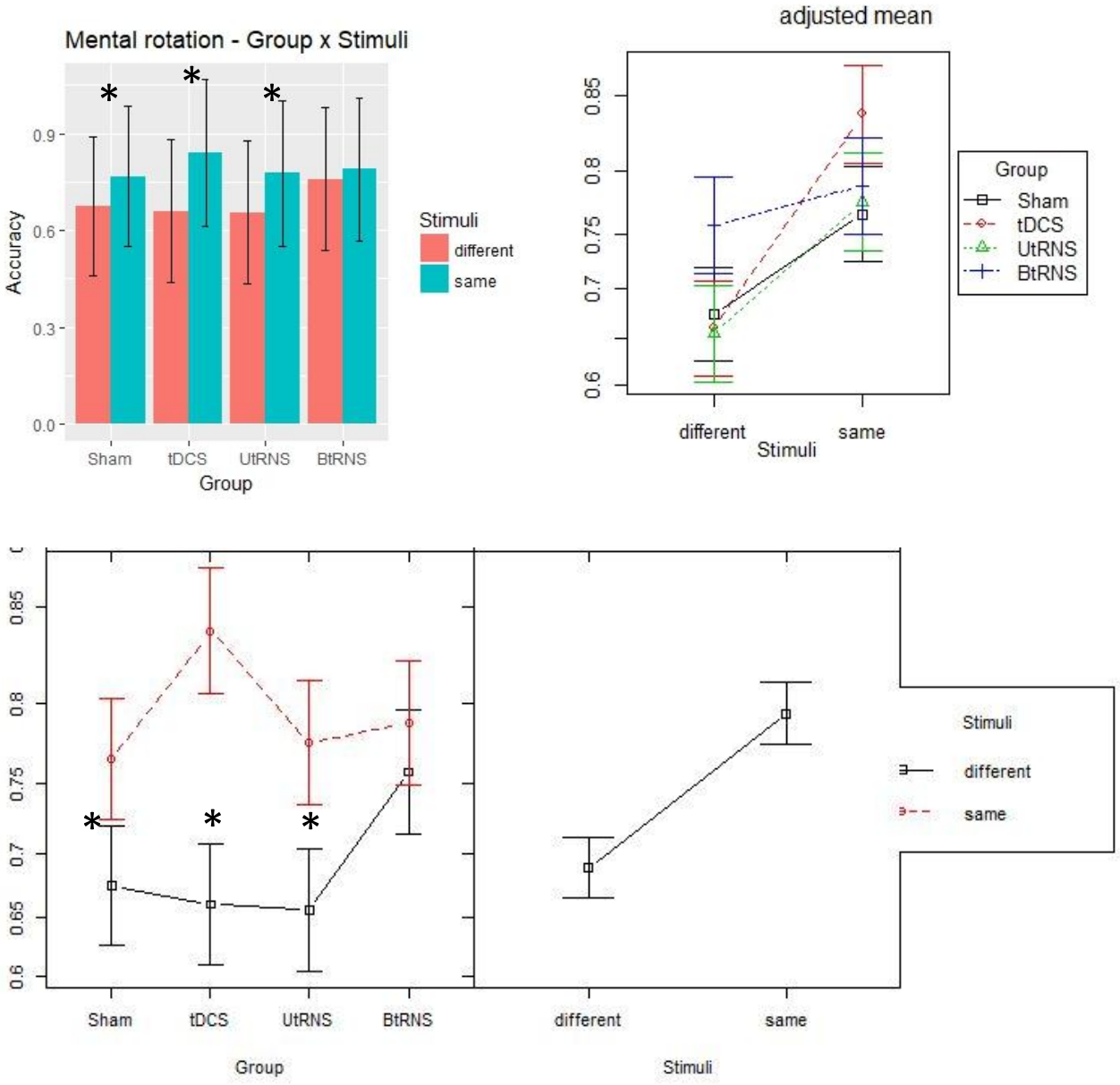



Figure 7 Adjusted means of the fitted model and effect plot of the interaction.

*Landmark Task*

Control trials where a non-bisected line appeared were excluded from the analysis. Data obtained from the practice phase were dismissed as well. We analyzed both accuracy and RTs to evaluate the presence of positive effects on one outcome which could in turn result in a worsening in the other (e.g. speed-accuracy trade-off). We analyzed both correct and incorrect responses to detect a possible leftward or rightward bias, following Benwell et al. (2014). This is because we were more

interested in a possible perceptual bias than in the participants' precision in answering correctly. Firstly, we assessed if the task was able to detect the effect of pseudoneglect at baseline, that is a faster, more accurate performance at the longer left lines than at the longer right ones. In order to do so, we analyzed RTs and accuracy after removing the trials in which participants responded slower or faster of 3 standard deviations from the mean value. In baseline data, we found main effects of difficulty ($F(1,56)=96.95$, $p<.001$, $\eta_p^2=.63$) and type of target ($F(1,56)=85.79$, $p<.001$, $\eta_p^2=.61$), a two-way interaction between these two factors ($F(1,56)=18.08$, $p<.001$, $\eta_p^2=.24$) and no effect of group on RTs. The lack of group effects rules out the possibility of difference in pseudoneglect scores between groups in baseline. The results are presented in figure 8. The effect of pseudoneglect is evident in both difficulties, with slower RTs when the target is longer right than longer left ($t(59)=9.14$, $p<.001$); in particular, slower RTs for longer right than longer left in easy ($t(59)=10.02$, $p<.001$) and difficult targets ($t(59)=5.05$, $p<.001$). Similarly, the difference between difficulties was always significant, both when the targets were longer left ($t(59)=-5.26$, $p<.001$) and longer right ($t(59)=-7.61$, $p<.001$).

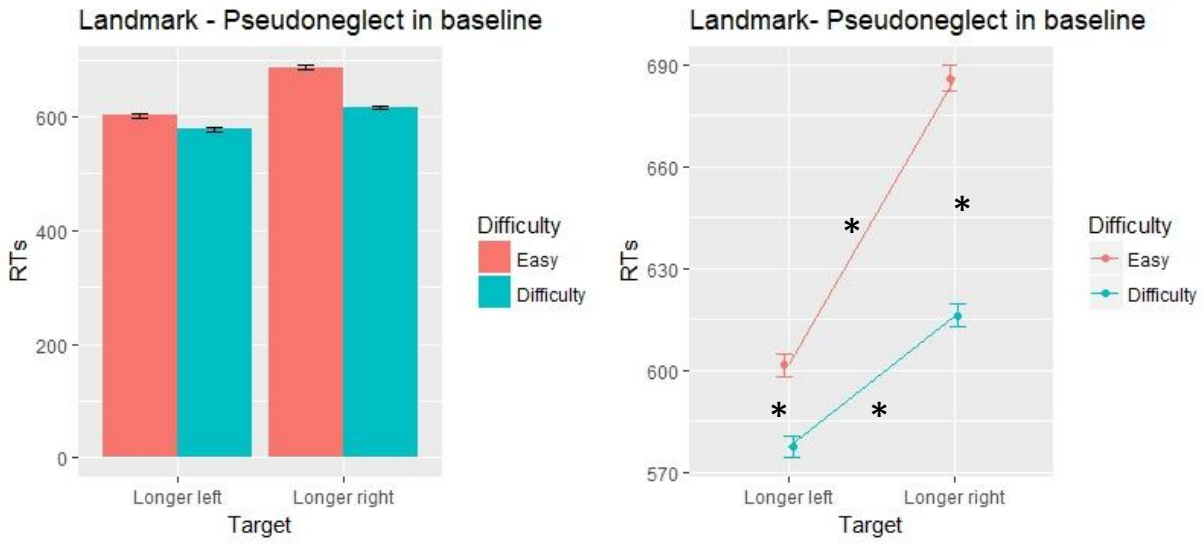



Figure 8. Significant difference between longer right and left in baseline session,

Similarly, on accuracy we found a main effect of difficulty ($F(1,56)=353.93$,$p<.001$, $\eta_p^2=.86$), and type of target ($F(1,56)=168.52$,$p<.001$, $\eta_p^2=.75$) and a significant interaction between the two factors ($F(1,56)=295.88$,$p<.001$, $\eta_p^2=.84$). Results are depicted in figure 9. Planned comparisons showed that the difference between longer left and longer right was significant for both easy ($t(59)=-15.47$, $p<.001$) and difficult targets ($t(59)=-4.43$, $p<.001$).

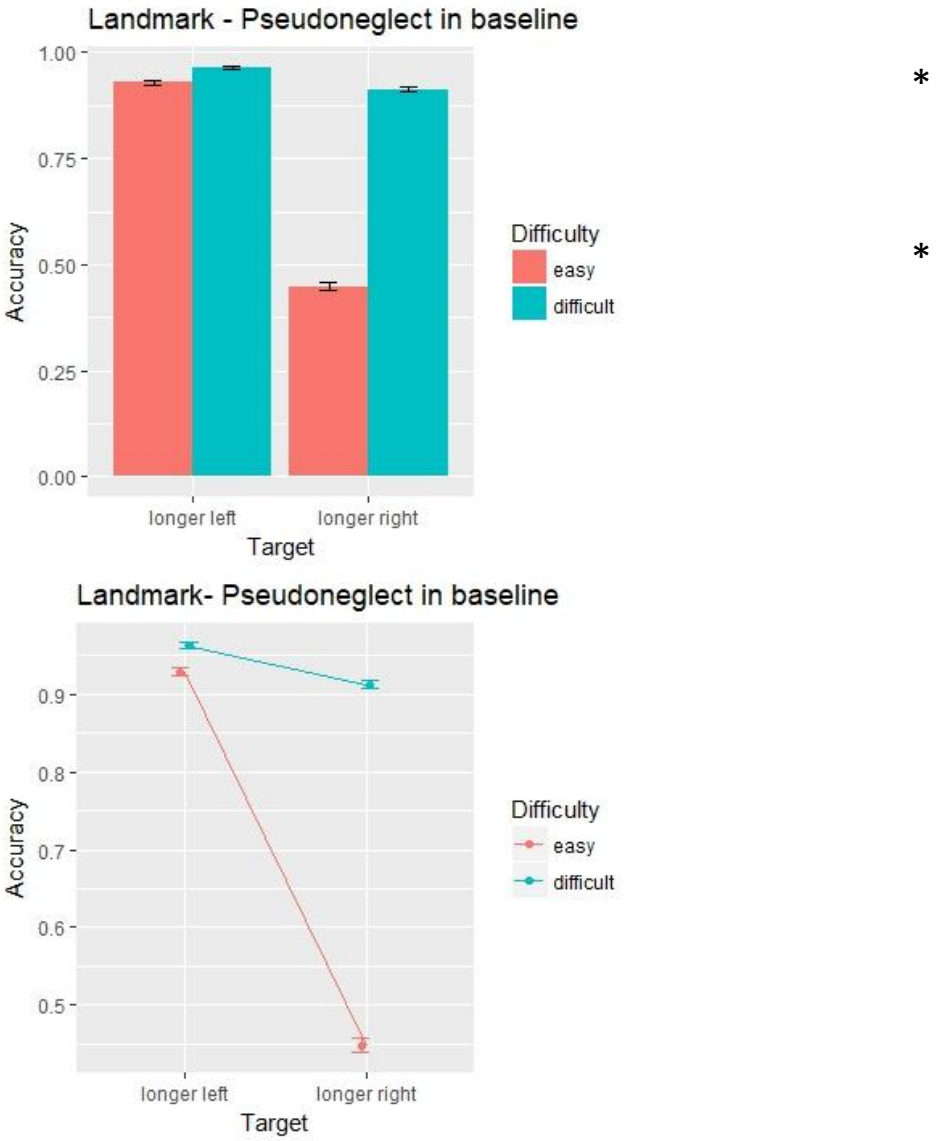



Figure 9. Pseudoneglect effect on accuracy data.

*Experimental manipulation effects*

Regarding the effect of the stimulation group on the RTs, considering all responses, we found a main effect of the target ($F(1,56)=111.37$, $p<.001$, $\eta_p^2=.67$), the difficulty ($F(1,56)=206.21$, $p<.001$, $\eta_p^2=.79$), the session ($F(1,56)=11.92$, $p=.001$, $\eta_p^2=.18$), the interaction group x session ($F(3,56)=3.51$, $p=.02$, $\eta_p^2=.16$), target x difficulty ($F(1,56)=51.22$, $p<.001$, $\eta_p^2=.48$) and target x difficulty x session ($F(1,56)=7.26$, $p=.009$, $\eta_p^2=.12$). Interestingly for our purpose, the four-way

interaction between group (sham, a-tDCS, U-tRNS, B-tRNS), session (first vs. second), difficulty (easy vs. difficult) and length (longer left vs. longer right) was significant ($F(3,56)=2.78$, $p<.05$, $\eta_p^2=.13$). In order to better understand the four way interaction, we subtracted the first session from the second one, thus obtaining an index of change between sessions. We chose to subtract sessions rather than running an ANCOVA with first session as covariate because we found an interaction between baseline and group. We hence ran independent sample, FDR corrected t-tests on the differences previously computed for all possible combination of targets, in order to evaluate possible significant effects. From the analysis, we found a significant difference between the change in B-tRNS and U-tRNS groups when the target was easy longer right compared to sham ($t(224)=3.18$, $p=.03$ and $t(224)=3.14$, $p=.03$, respectively), and a significant difference in B-tRNS compared to sham when the target was difficult longer left ($t(224)=3.13$, $p=.03$). For difficult longer right targets, the difference between B-tRNS and sham missed significance ($t(224)=2.59$, $p=.07$). Figure 10 depicts the differences.

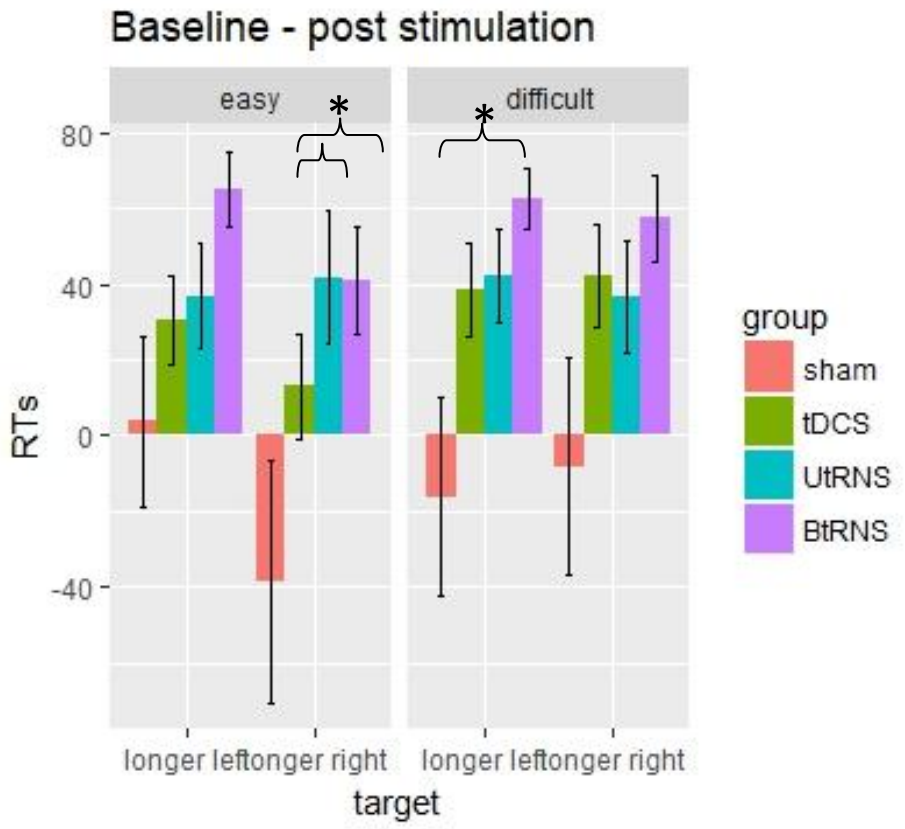



Figure 10 Three ways interaction between group, target and difficulty on pre - post difference scores.

The ANOVA on accuracy scores did not show significant effects of the group, nor did the bilateral accuracy scores, thus ruling out the presence of speed-accuracy trade off (namely, more rapid but incorrect answers).

*Cued detection Task*

Catch trials were removed from the analysis, and data obtained from the practice phase were dismissed. Responses faster or slower of 3 SD from the mean value were also removed. Both RTs and accuracy data were analyzed.

First of all, we inspected if the task was able to induce the validity effect in the first session, before any manipulation was made. We expected RTs to targets appearing in the cued location to be faster than targets appearing in the opposite position. We hence submitted the correct trials RTs in the first session (baseline session) to an ANOVA with target (right, left, bilateral), cue (rightward, leftward) as within subjects factors and group (sham, a-tDCS, U-tRNS and B-tRNS) as between subjects factor. Results showed a main effect of target ($F(2,112)=49.24$, $p<.001$, $\eta_p^2=.47$) and an interaction between cue and target ($F(2,112)=14.94$, $p<.001$, $\eta_p^2=.21$). On accuracy data, only the effect of target type was significant ($F(2,112)=8.41$, $p<.001$, $\eta_p^2=.13$). Both on RTs and accuracy, no effect of group at the baseline session was detected (respectively, $F(3,56)=.29$, $p=.8$ and $F(3,56)=8.84$, $p=.5$), meaning that no difference is detectable between subjects before administering the stimulation protocol. Figure 11 shows the results on baseline RTs.

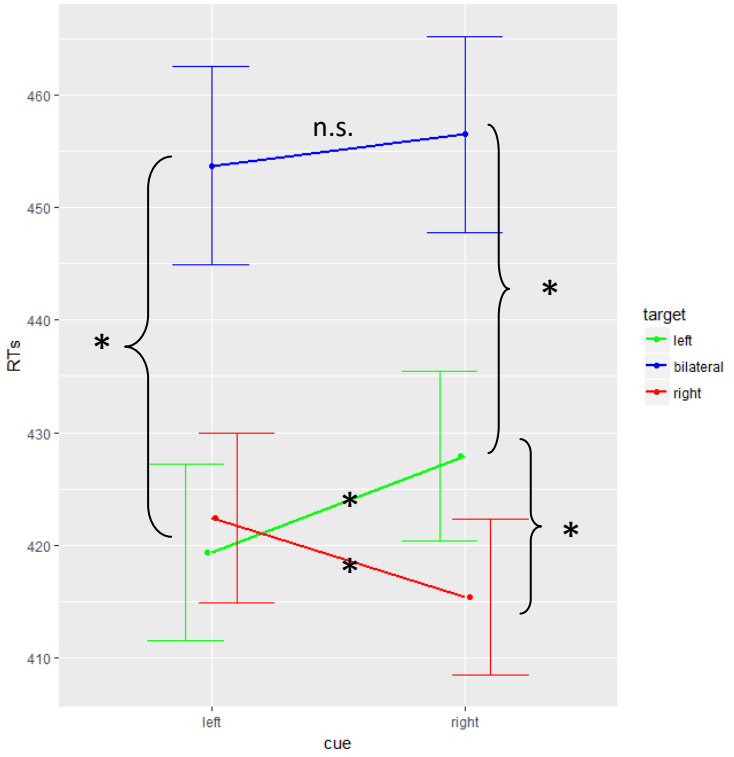



Figure 11. Interaction target x cue.

Since in baseline data we found a great variability in RTs, and a small effect of cue validity, we decided not to analyze this task to evaluate the effects of stimulation. The results are probably due to the design of the task (only 33% of valid trials and a relatively low number of trials per cell).

## EEG RESULTS

After data collection, the EEG signal was corrected for blinks and eye movement artifacts according to Ille and colleagues (2002) by BESA software (Brain Electrical Source Analysis, 5.1 version). Each EEG epoch was divided into 2048-ms time intervals, and thus included 150 samples with 0.488 Hz FFT resolution. Given the constraint of the Fast Fourier Transform (FFT) to use $2^n$ samples, the width of each interval was necessarily forced to 1024 samples, corresponding to a 2048-ms interval. Artifact rejection was performed on each epoch, with both amplitude and derivative (with respect to time) thresholds[3] (250 µV and 100µV/ms, respectively). The remaining

[3]Using BESA software, artifact rejection includes an Amplitude threshold criterion, that rejects the trial within which the difference between the maximum and the minimum amplitude is exceeded, and a Derivative threshold criterion, that

epochs were then visually inspected for any residual artifact. On average, 19% of the trials were rejected evenly distributed among groups. For each participant, the FFT was averaged across those epochs that, after windowing with a tapered cosine, were free of residual artifacts. The High-Beta band[4] (20-35 Hz, effective β range: 20.50-35.14 Hz) was analyzed. Based on the mean distribution of high-beta band, electrodes were clustered into four regions of interest with two spatial factors consisting of two levels each: anterior-posterior asymmetry and laterality. Each quadrant therefore included the averaged amplitude of 5 electrodes: Anterior Left (AL: Fp1-F3-FC3-F7-FT7), Anterior Right (AR: Fp2-F4-FC4-F8-FT8), Posterior Left (PL: CP3-P3-P7-TP7- O1), and Posterior Right (PR: CP4-P4-P8-TP8- O2). This clustering allowed us to include, in our statistical analyses, most of the scalp activity, through the use, in agreement with previous work on resting state (Spironelli and Angrilli, 2017), of 20 out of 30 electrodes placed on the left and right side of the cap. Individual ANOVAs were carried out for each EEG band including the factor Group (four levels: Sham vs. a-tDCS vs. U-tRNS vs. B-tRNS) and three within-subject factors: Session (two levels: Pre- vs. Post-stimulation), Region (two levels: Anterior vs. Posterior) and Laterality (two levels: Left vs. Right hemisphere). Post-hoc comparisons were performed using the Tukey HSD test ($P< 0.05$).

We detected an effect of the high-beta EEG band specific for B-tRNS group. The ANOVA revealed a main effect of the cluster ($F(3,168)=3.31$, $p=.02$, $\eta_p^2=.06$) and a significant interaction between group and session ($F(3,56)=2.97$, $p=.04$, $\eta_p^2=.14$), while the interaction between group, session and cluster was not significant. Specifically, there was a significant beta enhancement in post-stimulation for B-tRNS group compared to sham (see Figure 12). No significance in pre-stimulaton measures was found.

rejects each trial within which the largest amplitude difference between two adjacent time samples is exceeded.
[4]We indicated the typical frequency range and the "effective range", that is the real width of the EEG band.

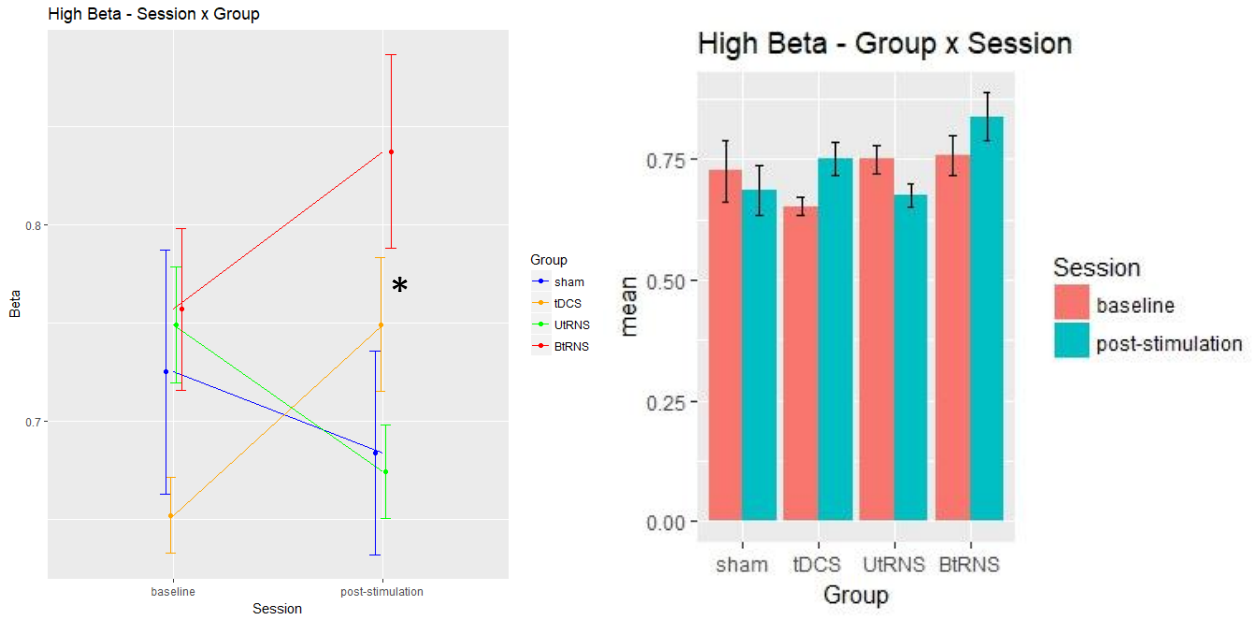



Figure 12. High Beta group x session effect.

CONNECTIVITY ANALYSIS

Following Bullmore and Sporns (2009) we calculated a value of modularity for each subject and each session, which is a useful to understand complex network organization. Starting from EEG resting-state data, we generated a matrix of values for each node of the system (in our experiment, each electrode) and compared them to evaluate possible relationships between the nodes.

A network is composed by several modules composed by nodes highly interconnected to each other and sparsely connected with other nodes. The greater the modularity index is, the greater the density of intramodular connections between neighboring regions. Modularity might allow the brain to adapt to different environments (Kashtan & Alon, 2005) and a disruption in modularity index has been linked to neuropsychiatric disorders (Aaron et al., 2010) and aging (Meunier et al., 2009).

In order to verify possible effects on modularity, we calculated a value from High beta band, After calculating values, we submitted them to an ANOVA with group as between factor and session as within subjects factor. We found a significant interaction between group and session ($F(3,56)=2.94$, $p<.05$, $\eta_p^2=.14$) and no main effects. Planned one-tailed, independent sample comparisons between the change of each experimental group through sessions and sham clarified that the effect was

specific for B-tRNS (t(56)=2.57, p=.03) and not significant for other groups. B-tRNS group showed a significant difference also when compared to tDCS (t(56)=2.24, p=.03) and UtRNS (t(56)=2.42, p=.03). Moreover, a significant difference between sessions was found only in BtRNS group (t(14)=-3.83, p<.05). See Figure 13 to inspect the results. This output is consistent with EEG beta result and seem to suggest a long-term, reliable effect on cortical plasticity only induced by B-tRNS, but not tDCS nor U-tRNS.

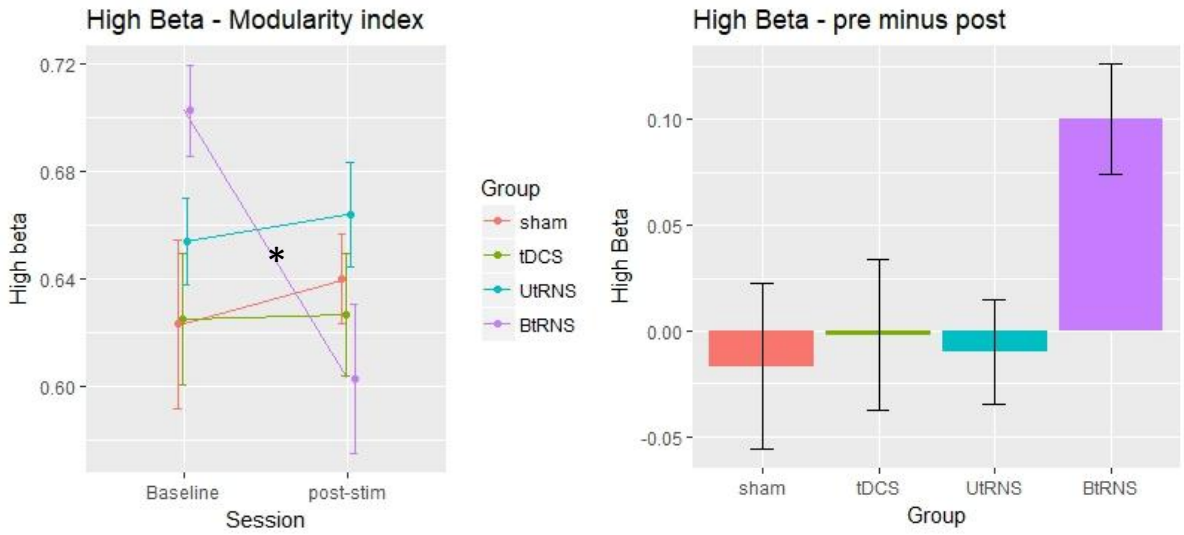



Figure 13. group x session interaction and change through sessions plotted.

A decrease in modularity index has been linked to a better performance in 2-back task (Stanley et al., 2014), probably because a recruitment of cognitive resources requires a more integrated, distributed processing between network modules. Our results are in line with previous research on high cognitive functions and are consistent with EEG results.

Correlations

We performed FDR corrected, Pearson correlations between behavioral and EEG data. In order to obtain a index for each participant, we subtracted post measure from baseline for accuracy in mental

rotation, RTs in landmark single trials (longer left difficult, longer right difficult, longer left easy, longer right easy) and in EEG High Beta values.

No correlation resulted significant between High beta modularity index and mental rotation performance, nor between High beta EEG values and mental rotation.

Interestingly, only in BtRNS group High beta change through sessions correlated with RTs change in difficult longer left target ($r(13)=-.58$, $p<.05$) and in longer right difficult target ($r(13)=-.55$, $p<.05$), while the correlation missed significance in easy right targets ($r(13)=-.47$, $p=.09$) and it was not significant for easy longer left targets ($r(13)=-.34$, $p=.2$). No other correlation resulted significant. A negative correlation means that a smaller value in EEG (greater beta in second session compared to the first one) is associated to a greater value in RTs (faster RTs in second session compared to the first one), thus indicating an enhancement in the performance. Figure 14a and b shows the correlations.

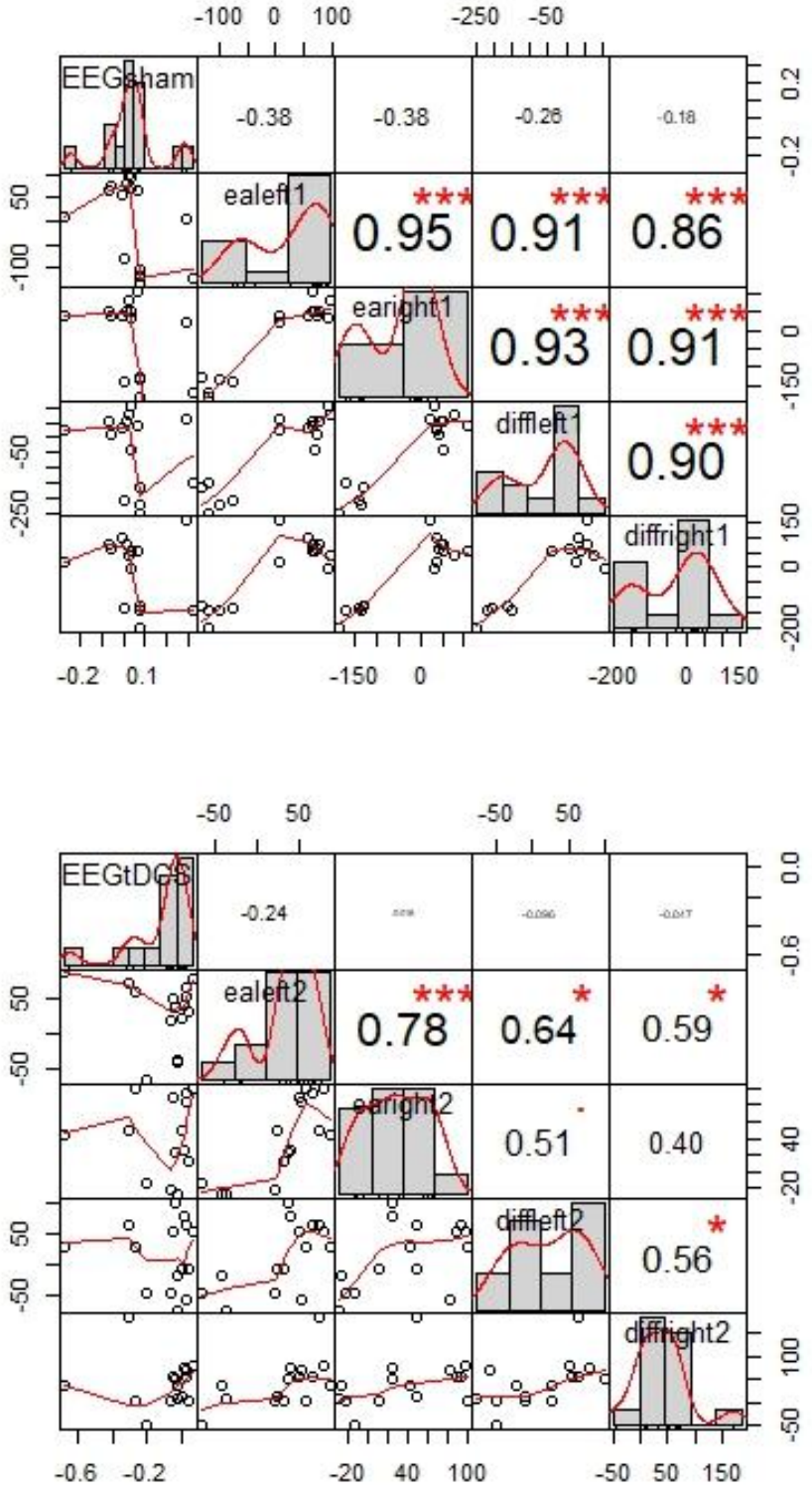



Figure 14a. Correlations between EEG beta values ("EEGsham", above, and "EEGtDCS", below) and landmark trials RTs (easy longer left, "EAleft", easy longer right, "EAright", difficult longer left, "diffleft", difficult longer right, "diffright")

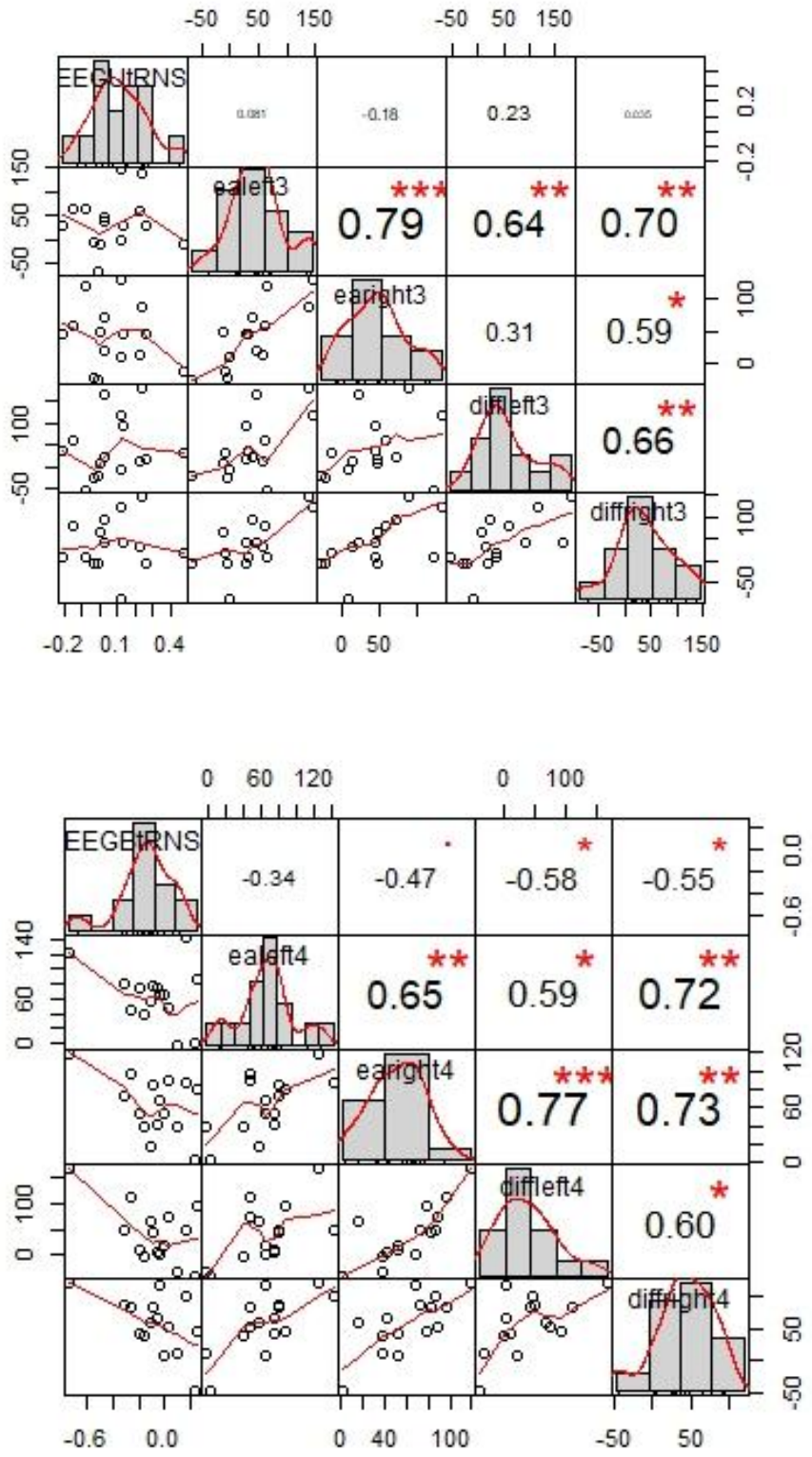



Figure 14b. Correlations between EEG beta values ("EEGUtRNS", above, and "EEGBtRNS", below) and landmark trials RTs (easy longer left, "EAleft", easy longer right, "EAright", difficult longer left, "diffleft", difficult longer right, "diffright").

# DISCUSSION

## *Behavioral results*

There is growing evidence that tES is able to induce shifts in attention based on the sites on which it is administered. Stimulating the rPPC had the effect to enhance leftward shifts in attention (*pseudoneglect*), while interfering with this site resulted in a rightward bias (neglect-like effects , Giglia et al., 2011). Other studies tested the effects of tDCS on simple detection tasks (Sparing et al., 2009) or on a modified version of the ANT task (Fan et al., 2002) with a cue (Roy et al., 2014). These studies found that a-tDCS on the right posterior parietal cortex (with a bilateral montage) is able to facilitate the detection of left-side stimuli, while c-tDCS induced an enhancement for right targets. The authors explained the results assuming that the enhancement in processing one side of space is attributable to inter-hemispheric balance (Sparing et al., 2008, 2009) resulting in a reciprocal inhibition between hemispheres. This interpretation is consistent with the results obtained by Giglia et al. (2011) who demonstrated a neglect-like effect stimulating with c-tDCS the right posterior parietal cortex both unilaterally and bilaterally, with a more evident effect in the latter montage. Here we compared the transfer effects of a-tDCS, U-tRNS and B-tRNS on the attentional domain. We applied a task which is supposed to activate mainly the posterior parietal cortex (Harris & Miniussi, 2003) while administering a-tDCS, U-tRNS and B-tRNS. The presence of three different groups served the purpose of comparing both the type of stimulation (a-tDCS vs. U-tRNS) and type of tRNS montage (U-tRNS vs. B-tRNS). We found a number of different modulations: online and long-term after-effects for B-tRNS and tDCS, and only offline effects for U-tRNS. Online enhancement of the mental rotation task was stimulus-specific, with better performance in B-tRNS group at "different" stimuli, and a better performance at "same" stimuli for tDCS. No reliable online effect was found for U-tRNS. The dissociation between enhancements depending on the type of targets is intriguing. At a first glance, the results suggest separated neural effects for the techniques. Studies investigating the effects of mental rotation task found that the complexity of the stimuli required more attentive demand than simple transformations stimuli (Bethell-Fox, & Shepard, 1988). Moreover, "same" stimuli were rotated images, while "different" stimuli were shapes with a further transformation, a mirrored- and then rotated image. Since a greater effort was required in "difficult" stimuli, better performance for these trials might suggest a strong

enhancement in the underlying neural mechanisms, as suggested by B-tRNS performance. On the other hand, a better performance at "same" targets might be index of a milder effect on cognitive processing. It is worth noting that the B-tRNS is administered bilaterally, thus potentially activating both hemispheres or acting on inter-hemispherical balance (Terney et al., 2008), while a-tDCS was applied over the rPPC with the cathode over the supraorbital contralateral site (as done in great part of the studies published so far). However, another explanation for our results is possible. During the task, we instructed participants to imagine the tridimensional figures rotating in space to force mainly the activation of right hemisphere as suggested by Weiss (2003). However, all the participants answered with the right hand to "different" stimuli, while to the left hand to "same" stimuli. It is therefore possible that stronger right hemisphere activation enhanced responses to "same" stimuli (as in the case of tDCS). This is possible considering that tES effects are not limited to the area stimulated (Notturno, Marzetti, Pizzella, Uncini, & Zappasodi, 2014) and could suggest the first possible conclusion, that B-tRNS acted on cortical balance, while a-tDCS activates mainly the site stimulated.

The critical hypothesis of the work was that a-tDCS and tRNS could result in different post-stimulation, transfer outcomes, in light of the literature investigating the possible neural effects of the techniques. Immediately after the mental rotation task, participants underwent 5 minutes resting-state EEG recording and started the two transfer tasks, which were counterbalanced between participants and remain in the same order between sessions. We counterbalanced tasks to avoid sequential effects. Moreover, this procedure allows ruling out that selective effects on one task and not on the other might be simply due to the different amount of time passed from the beginning of the stimulation. From these tasks we found effects for the B-tRNS group in the landmark task, resulting in a better accuracy in the "longer left" and "longer right" targets, while in U-tRNS group the effect was specific for "longer right" targets. The implication of the results are twofold.

Both tRNS montages produced a modulation, but only B-tRNS showed mild online effects, thus suggesting that the effects in U-tRNS group might be either delayed, or a learning effect. Another possible explanation is that the orbitofrontal electrode in UtRNS montage might have interacted with activation, inducing unexpected results.

The different types of stimuli modulated could indicate the possible cortical mechanisms underlying the two techniques. For B-tRNS, bilateral stimuli were affected, thus suggesting a bilateral modulation, while U-tRNS effects are not clearly interpretable, due to the lack of online effects.

No effect was detected for tDCS, suggesting that probably only an online effect is possible with our design. This result is consistent with previous literature on tDCS (for a review, see Enriquez-Geppert et al., 2013).

The results detected after tDCS and U-tRNS deserve specific attention as well. Regarding tDCS, we expected a lack of effect based on the available literature on tES. So far, it seems unlikely that the neural effect of this protocol might induce a long-lasting plasticity change in absence of proper training (Enriquez-Geppert et al., 2013). Our results go in this direction finding an online facilitatory effect which probably gradually expired after the end of the stimulation. We hence conclude that tDCS has an online positive effect on mental rotation when applied on rPPC, but also that the effect is short-lasting. Conversely, for U-tRNS, we detected no online effect thus suggesting a lack of modulation in this group, with a mild facilitation on right longer left lines after the stimulation, but only when the target was easy. The difference in the modulation between the two tRNS groups could be due to the montage applied, since in one group a bilateral stimulation of the homologue areas was administered, while in the other a posterior and frontal stimulation was administered. Our results suggest that bilateral stimulation might be more suited to obtain results, probably because it acts on hemispheric balance, while unilateral montage in tRNS might induce unexpected results. It is worth noting that despite using a unilateral montage with one electrode o the supraorbital area, tRNS studies found the expected modulation (Fertonani et al., 2011; Terney et al., 2008). In conclusion, further research should be conducted to clearly understand the effect of montage in tRNS stimulation.

It is important to point out that the present study has some limitations. First of all, the between-subjects design does not allow to fully control for differences between subjects in baseline, although it is useful when comparing different protocols with an experimental design which could be prone to learning effects in healthy subjects. However, this is unlikely, because the participants were randomly assigned to either of the four groups and all were young participants with the same characteristics (age, all righthanded). To prove that no difference in perceptual measures in baseline was present, we found no difference in pseudoneglect scores in the first session between groups. However additional emphasis should be put on this aspect, since tES effects are sensitive to individual differences. A more comprehensive evaluation of baseline abilities related to the possible change in performance due to the stimulation might have been interesting to better assess the different effects of each protocol, although this investigation was not the core hypothesis of the present work. This research was aimed at better understand the post-stimulation outcomes of

different tES protocols in order to possibly plan future interventions on clinical populations. Further research is needed to rule out possible inter-individuals effects not due to the stimulation itself.

*Cortical plasticity evidence*

We also recorded resting-state EEG signal in each session to evaluate possible post-stimulation, after-effects on cortical plasticity subsequent to tES. Previous studies investigated both after (Miller, Berger, & Sauseng, 2015) and online effects of tES on cortical excitability (Sood, Perrey, Hayashibe, & Dutta, 2015; Hill, Rogasch, Fitzgerald, & Hoy, 2017), even coupled with training (Snowball et al., 2013), but to the best of our knowledge no study focused on EEG outcomes related to transfer after-effects of tES. This is the first study demonstrating that a single session tES is able to induce long-lasting effects on behavioral domain which affects cortical plasticity changes at rest after the stimulation. From our results, only B-tRNS was capable of changing cortical excitability selectively in the high-beta band range, while sham, U-tRNS and tDCS did not show reliable changes through sessions. This is consistent with a recent study founding that tDCS has short-lasting effects on cortical excitability (Miller, Berger, & Sauseng, 2015). The modulation of beta suggests that a specific cortical process has been modulated with our manipulation. Notoriously, beta activity is related to attention (Gola, Magnuski, Szumska, & Wróbel, 2013; Hernández, Marqués, & Alvarado, 2016; Gao, Wang, Ding, Wang, Liet al., 2017). Consistently with this result, we observed a modulation of the modularity index, which indicates how much different cortical sites (nodes) cooperate and are integrate. In particular, the "modularity" is an aggregation index and a high value suggests that the nodes are strictly connected inside a module, but also that a weaker connection with other nodes is possible (Bullmore & Sporns, 2009). We found a reduction in modularity index in tRNS group in the second session compared to the first one, which coupled with EEG evidence suggests that a significant enhancement in beta and a more wide-connected network in beta might be linked to a more efficient outcome in this group compared to the others. The enhancement in beta was cluster-aspecific, i.e., distributed to the whole scalp activity, involving all the system, consistently with modularity index decrease. Interestingly, we found a negative correlation between change in High beta values through sessions and the change in performance in the difficult longer left and longer right targets, selectively for B-tRNS group but not for the other groups. The correlation indicates that an enhancement in high beta oscillations is

related to a better performance in the landmark task. This evidence corroborates previous results and shows a relation between EEG measures and behavioral outcome, but only in B-tRNS group.

## CONCLUSIONS

Overall, the results indicate that while both a-tDCS and B-tRNS had an online effect on the mental rotation task, although on opposite targets, the mechanisms of functioning of the two techniques might be different. Specifically, considering the offline tasks, only in the B-tRNS a reliable change in the performance was detected. In the landmark task, we found a better performance both to longer left and longer right targets, while in U-tRNS group only longer right targets were enhanced,.Our results suggest that B-tRNS could be more suited for training and to induce both online and transfer effects, while a-tDCS seems to be more effective on tasks administered during the stimulation. This conclusion is corroborated by the correlation between behavioral outcome and High beta change, with an enhancement in beta associated to a better performance in landmark task, specifically for B-tRNS group. This evidence is in line with the literature, in which tRNS is considered the best tool in order to obtain long term effects, while for a-tDCS the possible homeostasis of the system could induce no reliable long-term effect. In addition, the effect depends on the montage, for we found no reliable effect for the U-tRNS. This suggests that the modulation we found might depend on inter-hemispheric balance mechanisms and not only on a single cortical site specifically.

## 3.4. Effects of the combination of executive training with bilateral tRNS: Insights from the Labyrinth game.

### INTRODUCTION

Cognitive training has been employed in a number of studies to induce a long-term enhancement both in clinical and healthy population. Despite the positive evidence collected through the years, the effects of cognitive training are not always conclusive. For example, cognitive training outcomes depends on many factors, like baseline performance. The consensus in not conclusive: some authors proposed a better impact on lower baseline scores (Zinke, Zeintl, Rose, Putzmann, Pyddie & Kliegel, 2014; Zinke, Zeintl, Eschen, Herzog & Kliegel, 2012), while others proposed that individuals with high baseline level are better prepared to take advantage of the intervention (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). Some experimental designs may induce ceiling effects, influencing the relationship between starting abilities and the improvement achieved. Motivation is another important factor which could influence the training outcomes (Jaeggi et al., 2014; Jaeggi, Buschkuehl, Jonides, & Shah, 2011; Katz, Jaeggi, Buschkuehl, Stegman, & Shah, 2014; Prins, Dovis, Ponsioen, ten Brink, & van der Oord, 2010; Au et al., 2015), as well as age, for old adults seem to improve less on untrained tasks as well as on training task itself (Zinke et al., 2014; Brehmer, Westerberg, & Bäckman, 2012; Schmiedek, Lovden, & Lindenberger, 2010; Wass, Scerif, & Johnson, 2012), even if other work suggests that age is not related to task improvements (Karbach & Verhaeghen, 2014). These age-related disparities are consistent with well-established differences in age-related WM performance (Park, Lautenschlager, Hedden, Davidson, Smith, & Smith, 2002) and theoretical perspective on cognitive plasticity and aging (Lövdén et al., 2010). However, it remains unknown whether age-related differences in cognitive training performance are due to differences in baseline performance or other factors related to aging. Even psychological traits such as conscientiousness and neuroticism (Studer-Luethi, Bauer, & Perrig, 2015; Studer-Luethi, Jaeggi, Buschkuehl, & Perrig, 2012) may also impact the outcome of training. Finally, other factors, such as gender, have been found to influence the

outcome of training in some studies (Söderqvist, Bergman Nutley, Ottersen, Grill, & Klingberg, 2012) but not others (Klingberg et al., 2005). It remains possible that a number of other factors that have been largely unexplored (e.g., socioeconomic status, although see Segretin et al., 2014) may play a role, at least in some interventions.

*Application of tES during cognitive training*

Trascranial electrical stimulation techniques (tES) are a non-invasive tool, which seems to enhance cortical excitability underneath the electrodes. While a number of studies investigated single session effects on a number of cognitive functions, the coupling of tES and cognitive training is a more recent goal. Some studies found training effects and, in some cases, also extending to other tasks when applying tRNS (Snowball et al., 2013; Cappelletti et al., 2013) or tDCS (Richmond et al., 2014; Martin et al. 2013; Au et al., 2016). Despite this evidence, the understanding of tES principles is still limited (as shown by several contradictory results in the literature), which makes it difficult to project a proper treatment for clinical population.

While the association of tES and cognitive training enhances performance across many cognitive functions, the effects on non-trained tasks are somewhat mixed, with some evidence for improvements in different cognitive functions such as working memory, cognitive control, number sense and arithmetic abilities, even if not conclusive (Elmasry, Loo & Martin, 2015; Katz et al., 2017). For example, Wiethoff and colleagues (2014) and López-Alonso, and colleagues (2014) have shown that less than half of the participants demonstrate improved performance, even in tDCS experiments that successfully demonstrate an effect on cognition overall. This suggests that only a part of participants in each study may be responding to the stimulation. Moreover, age, sex and cortical excitability may affect the effectiveness of tES (Krause and Cohen Kadosh, 2014) such as genetic factors (Brunoni et al., 2013; Plewnia et al., 2013) and anatomical differences (Kim et al., 2014). In addition to these physiological characteristics, it is also possible that psychological characteristics, such as baseline cognitive ability, may influence the outcome of stimulation, with a selective benefit in individuals with low, but not high baseline abilities (Gozenman & Berryhill, 2016; Tseng et al., 2012; Uehara, Coxon, & Byblow, 2015; McCambridge, Bradnam, Stinear, & Byblow, 2011; Reinhart, Xiao, McClenahan, & Woodman, 2016; Sikstrom et al., 2016; London & Slagter, 2015) or in older population compared with high performing individuals (Dedoncker,

Brunoni, Baeken, & Vanderhasselt, 2016; Hill, Fitzgerald, & Hoy, 2016; Hsu, Ku, Zanto, & Gazzaley, 2015; Summers, Kang, & Cauraugh, 2015).

Transcranial Electric Stimulation (TES) is a promising tool to enhance or inhibit cortical activation under the electrodes (for a review, see Cohen Kadosh, 2013 and Paulus, 2011).

Transcranial Random Noise Stimulation (tRNS) has shown a valuable potential in increasing neuronal excitability, in particular when applied over motor cortices. The applicability of tRNS is due to the fact that it is able to induce an excitatory effect similar to anodal-tDCS, while avoiding the characteristic discomfort caused by direct current stimulation. This peculiarity makes tRNS suitable to experimental research, as it is considered easier to blind (Ambrus et al., 2010).

tRNS has proven to be effective in a wide variety of cognitive functions, such as perceptual learning (Fertonani et al., 2011), motor functions (Terney et al., 2008; Moliadze et al., 2012), auditory cortex (Van Doren et al., 2014) , facial perception (Romanska, Rezlescu, Susilo, Duchaine and Banissy (2015), categorical learning (Ambrus et al., 2015), n-back task (Mölle, Siebner, & Born, 2005); Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011).

*The present study*

Labyrinth is an adaptive game, able to train attentional and executive abilities in healthy participants (Montani et al., 2013). The first validation data suggest an enhancement more clear in those participants whose initial level was worse (Montani et al., 2013), in line with part of the literature on brain/cognitive training (Gozenman & Berryhill, 2016; Heinen et al., 2016; Tseng et al., 2012; Uehara, Coxon, & Byblow, 2015; McCambridge, Bradnam, Stinear, & Byblow, 2011; Zhou et al., 2015; Reinhart, Xiao, McClenahan, & Woodman, 2016; London & Slagter, 2015). Moreover, the training was able to enhance not only the performance at the game itself, but also to transfer the benefits to other untrained abilities, as assessed by the orienting and alerting index in the Attention Network Task (ANT, Fan et al. 2002) administered immediately at the end of the training.

Further unpublished studies from our lab suggest that this training is able to activate the frontal right sites of the brain, consistently with the hypothesis that Labyrinth works on executive and attentional abilities. The two weeks training with Labyrinth induced a long-lasting gamma band enhancement on right frontal cortex lasting a month after the training itself.

Brain neuromodulation has been used to enhance the natural cortical plasticity induced by cognitive training. For instance, Cappelletti et al. (2013) used tRNS on parietal cortex to enhance numerical abilities inducing a long-lasting effect still detectable after sixteen weeks. The benefits of the training were transferred to quantity judgments, such as time and space discrimination, but not to quantity un-related tasks such as executive and attentional tasks, suggesting that the improvement was task specific. Snowball et al. (2013) applied tRNS on the dorsolateral prefrontal cortex (DLPFC) in five days while participants were performing complex arithmetic tasks. The authors also recorded brain oscillations with fNIRS. Results showed that the combined training was able to enhance the behavioral performance both in calculation and also in memory-recall-based arithmetic learning. Moreover, the fNIRS results revealed to a more efficient left lateral prefrontal cortex activation (lLPFC). Authors explained this result because this area is considered heavily implicated in arithmetical processing (Zamarian, Ischebek & Delazer, 2009; Arsalidou & Taylor, 2011). The effects of training were still detectable after six months. Fertonani et al. (2011) showed that high frequency tRNS on visual cortex, but not tDCS, was able to enhance perceptual learning. The effect was present in the first six blocks, but not at the very end of the training (seventh block), where no difference between tDCS and tRNS was detectable.

The present study had the purpose to test both the behavioral and electrophysiological effects of neuromodulation coupled with training with Labyrinth. We chose tRNS because: i) literature indicates that it was effective in enhancing cognitive training (Cappelletti et al., 2013; Snowball et al., 2013), ii) unlikely anodal tDCS, it seems to overcome the homeostasis of the system (Fertonani et al., 2011), iii) it works on brain plasticity inducing long-term effects (Chieb et al., 2015; Antal et al., 2016), iv) it is painless and it does not induce directly a neural activation, so it is suited to be applied also on clinical population and on damaged brains (Terney et al., 2008). We also wished to test the effects of the combination on resting-state brain activity through EEG recording, to test whether the possible enhancement of the training was detectable also in the spontaneous EEG oscillations of the brain. This had a twofold benefit: i) understanding the effects of Labyrinth training on the plasticity of the brain (in the sham group) and ii) evaluating whether the training is suited to be applied also on brain impaired population, such as stroke patients, since the literature about the application of tRNS on clinical population is limited.

## MATERIALS AND METHODS

*Participants*

Participants were 28 students (15 males, 13 females, mean age=22.29, sd=3.20) of the University of Padua, all right-handed as assessed by the Oldfield questionnaire (Oldfield, 1970). They all were blind to the purpose of the study. All participants were tested with the Raven Progressive Matrices (Raven, 1941) in a previous, separate session to rule out a difference in intelligence scores, which could invalidate the results. Moreover, participants underwent a session of executive and working-memory pre-testing task to assess their initial level. Participants were randomly assigned to the sham group (N=14), to the tRNS group (N=14) independently of the scores obtained in these initial tasks. A third control group was added (N=15), whose participants performed only the EEG recording.

*Procedure*

The 28 participants were randomly assigned to one of the three experimental groups: training + sham group (only Labyrinth administered, coupled with sham stimulation) or training + tRNS group (Labyrinth + tRNS). Each participant underwent a pre-training session in which firstly their EEG resting-state signal was recorded (38 channels), and then the behavioral tasks were administered (one-back working-memory task; simple detection task; ANT; switch task). This session was aimed at testing the initial level of each participant before the training. The training consisted in seven sessions, distributed in two weeks for practical issues. One half of the participants of each training group performed the training four days in the first week and three days in the second, and one half did the opposite. In this way, we aimed to counterbalance the effects of the timing of the training and overcome the problem of non-consecutive sessions. Participants came to the laboratory at the same time on each of the training days and were administered both tRNS and training or only training, depending on the experimental group they were assigned in. Each session lasted up to 50 minutes and the Labyrinth session itself lasted 40 minutes. Participants underwent the electrodes montage at the very beginning of each session and stimulation started just before running Labyrinth. After assuring the participant was ready to continue, the behavioral training started and ended automatically after 20 minutes to give him/her some minutes to rest and to remove the electrodes. After a short pause, participant could start the second part of the training, which lasted 20 minutes. Finally, the participant was dismissed.

The day after the end of the training, all the participants came to the laboratory and underwent the resting state EEG recording and were administered the same behavioral tasks as in the first session. After a month, participants returned to the laboratory for the follow-up session, and were again administered the tasks and their resting-state EEG was recorded. All participants received monetary compensation for their participation in the experiment.

To control for the possible effect of the Labyrinth training on EEG signal, we also recruited a control group (N=15) who did not perform the training, nor the transfer tasks. Participants of this group were simply required to undergo two EEG resting-state recordings (baseline and after a week recordings, which served as comparison with pre-training and post-training of experimental groups, respectively). The comparison between control group and sham should control for the training alone effect, while the comparison between sham and tRNS group should control for the training + stimulation effect.

*EEG data acquisition*

All the participants underwent a 10 minutes pre-training EEG resting-state session (Neuroscan, 38 channels) recorded with eyes open to avoid an extreme alpha band activity, which could invalidate the results. They were seated on a comfortable chair at a distance of about 50 cm from a 19-inch computer monitor. They were instructed to maintain the fixation on a cross presented in the center of the screen trying to minimize every movement to avoid artifact production.

EEG recordings were acquired the day before the training (baseline recording), the day after the end of the training (after-training recording), and one month after the end of the training (follow-up recording). Since previous results showed a modulation in gamma band after Labyrinth training, we expected to find a change in this band waves. More specifically, we expected to replicate the previous results with training-only group, and to obtain a more pronounced activation in stimulation + training group.

Electrophysiological activity was recorded with 31 tin electrodes by means of an elastic cap (ElectroCap) and positioned according to the International 10-20 system (Oostenveld & Praamstra, 2001); seven more electrodes were applied below the eyes (Io1, Io2) on the two external canthi (F9, F10), nasion (Nz) and mastoids (M1, M2). Overall, 38 EEG locations were recorded. All cortical sites were online referred to Cz, and re-referenced offline to the mean activity of the whole scalp with the average reference procedure. Data were stored in NeuroScan 4.3 (NeuroScan Labs, Sterling, VA, USA). The impedance was kept below 5 kΩ. EEG was recorded in AC mode and

stored for later analysis. After data collection, EEG signals were corrected for blinking and eye movement artifacts with BESA software (Brain Electrical Source Analysis, Graefelfing, Germany).
At the end of each EEG recording, and after the participants had washed their hair, they underwent the behavioral task, in a random order. Each participant was administered the single task, the dual task, predictable switch task, unpredictable switch task and the ANT task (Fan et al., 2002). The order of the tasks was counterbalanced to avoid sequence effects between the tasks.

*Labyrinth*

The game was the same administered by Montani, De Filippo De Grazia & Zorzi (2013). The main character, a little man, is controlled by the participant by means of the arrows on the screen and he moves into a maze. The aim is, depending on the task, to collect a diamond, to reach home and escape from a snake. The walls that form the maze are variable: both their quantity and location change at every trial accordingly with the task difficulty. The only constraint in the random distribution of the walls is that the software avoids the appearance of closed areas because this would consists in impossible trials.
The maze difficulty changes accordingly with the type of task. Indeed, the game includes three different tasks, the ”Diamond Task”, the “Snake Task” and the combination of the two tasks (dual task).
Overall, every task has eight difficulty levels, across a continuum ranging from the less demanding (level 1) to the more demanding (level 8). In the diamond task ,the easiest maze is the one with as few walls as possible and the number of walls increases in conjunction with the improvement of performance. Conversely, in the snake task, the easiest maze is the one with as many walls as possible and accordingly, the number of walls decreases with the improvement of performance.
The aim of the game depends on the nature of the current task. In the diamond task, the man has to collect the diamonds that are randomly distributed across the play area. The diamond task resembles the open-ended version of the Travelling Salesman Problem (TSP), a task that strongly involves planning and is also representative of many real-world situations (Cutini, Di Ferdinando, Basso, Bisiacchi & Zorzi, 2008). Given a set of spatial locations represented by points on a map, the task consists in finding an itinerary that visits each point exactly once, ensuring that total travelled distance is as short as possible in order to successfully complete the task. While the classic TSP requires to return to the starting point, the open-ended version introduces a distinction between start- and end-point so that participants have to perform an open path instead of a loop.

TPS can be solved with multiple close-to-optimal solutions and usually healthy participants change strategy during the pathway to optimize performance. Therefore, the task achievement requires to control and to modify the plan accordingly with the evaluation of both the current position and the remaining path. Basso, Bisiacchi, Cotelli, & Farinello (2001) showed that TBI patients tend to use a fixed strategy until the end of the task without considering the alternative options, consistent with the hypothesis that TBI patients are unable to inhibit the current strategy in order to chose a better one (see also Cutini et al., 2008, for a computational model of normal and impaired performance in the TSP).

In the diamond task, the number of diamonds ranges from one, in the less demanding level, to eight in the more demanding level. The task requires a plan that allows to collect every diamond available within the time limit. Usually the best overall strategy is to follow the shortest path passing through the diamonds.

In the snake task, the man has to avoid to be caught by a snake and to reach a 'shelter' house that appears at a random location. The range of difficulty depends on the running speed of the snake. The achievement of this task requires a very different strategy compared to the diamond task. The best strategy is sometime just the opposite: indeed, if the man takes the shortest way to arrive at the shelter house, it is likely that the snake will catch him.

Avoiding to be caught often requires to choose a longer way, sometimes moving even in the direction opposite to the house location. Likewise, depending on the location of the house and the disposition of the maze walls, another good strategy may be to stop for a while, in a strategic location, waiting for the snake to take a wrong route. In this way, reaching the house becomes possible provided that the gamer chooses the right moment and moves quickly. Therefore, accomplishment of the tasks requires adopting complex strategies involving the ability to plan and sometimes also inhibiting the most 'automatic' action.

The diamond ,the snake task and the dual task alternate between each other with a frequency that is adjusted according to the performance score. The difficulty of this 'switch condition' has four levels ranging from a completely predictable switching, when one task follows the other, to a completely random switch.

The two medium levels involve a switch every two trials and a switch every three trials, respectively. In some trials, the gamer has to perform the two task simultaneously. In these trials the participant has to avoid the snake and to collect the diamonds at the same time. Contrary to the standard snake task, in this case the shelter house appears only after all diamonds are collected. Overall, the successful performance requires reaching two simultaneous aims: collecting every

diamond and avoid the snake within the time limit. The dual task condition is administered only if the percentage of success is higher than 60%. When the gamer achieves this performance level, the probability to receive a dual task trial is 30%. Accordingly, the participant can reach enough expertise in the two single tasks before managing the more difficult dual task condition. If the trial is performed correctly the player receives some points, whereas if the participant fails to reach the goal some points are subtracted from the score.

Following Wilson, Dehaene, Dubois & Fayol (2006) Labyrinth uses a multidimensional learning algorithm for continuous, online adaptation of task difficulty to the current performance of the gamer. Adaptation

was implemented using three dimensions of difficulty:

1) Time limit: the time limit to perform the task. The level of difficulty is ranging from 5 to 100 seconds. It is updated every trial.

2) Task difficulty: overall it has six levels but the difficulty depends on the task. In the diamond task it is related to the number of diamonds that have to be collected (from 1 to 8), while in the snake task it is related to the snake speed. In both the tasks the difficulty consists also in the number of walls of the maze. It is updated every trial.

3) Switch condition: the type of switch, predictable vs. unpredictable. It has four levels (every trial, every two, every three, random). This dimension is updated every 12 trials.

The combination of the three dimensions forms the 'training space'. This can be described as a cube with the three dimensions of difficulty as sides (Wilson et al., 2006). Every trial corresponds to a point within this cube (with the coordinates defined by the values of the three difficulty dimensions) and every point is associated with a certain probability of success. Higher probability is associated with easy trials and the opposite for the hard trials. Each user will be associated with a different probability of success matrix. The task of the algorithm is to estimate the 'space of performance' of the user accordingly with the current performance. After sampling points within the space, the algorithm uses the responses of the player to build an interpolated model of the entire performance space. Then, it selects a random point in the space, which it estimates to correspond to the level required to maintain performance at 75% of accuracy. Moreover, with the game advancing, the algorithm updates the 'space of performance' accordingly with the success or failure of the gamer.

*Single and dual tasks*

In the dual task, each trial started with a black screen (1000 ms), followed by a white fixation cross (about 1cm wide, 800 ms). The lateralized visuospatial target was a white disk (diameter: 8 mm) presented against a black background for a duration of 150 ms. The target could appear unilaterally, on the left or the right side of the display (lateral distance from fixation: 170 mm), or bilaterally (both on the left and on the right side). Simultaneously with the lateralized target(s), a visual shape (a line drawing chosen randomly among triangle, square and circle) appeared and lasted for 500 ms and was presented in the center of the screen. After the shape disappeared, a noisy screenshot was presented until the beginning of the following trial, in order to minimize retinal after-image. In the dual task participants were required firstly to report the position of the target and then to select the shape they saw in the previous trial, choosing the right one in a list. In the single task, participants only had to report the position of the target, pressing either the left or right key depending on where it appeared, or both keys at the same time if the stimuli appeared on both sides. During the instructions, the presence of a shape in the centre of the screen was not stressed, in a way that participants could completely ignore it.

*Switch task*

In this task participants had to switch between two instructions (answer to the letter or to the number), depending on the position of the target. They saw four squares on the screen inside which the target could appear (answer the letter when it appears above, the number when it appears below). Crucially, in a first block of the task participants could predict the square in which the following target would appear, because the presentation followed a clockwise order (*predictable switch task*), while in the second block participants were aware that the target could appear in a random position (*unpredictable switch task*). In the predictable task, they had to use two consecutive times the same instruction (repeat trial), while they had to switch the third time (switch trial). The two tasks were run separately and in the same order (the single and then the dual task).

*ANT task*

Following Montani et al. (2013) we administered a version of the Attention Network Test (ANT; Fan et al., 2002) to test possible long-term effects of the training on the attentive domain, because the training was supposed to activate attentional abilities.

The ANT was designed by Fan et al. (2002) to evaluate the efficiency of the three attention networks involved in alerting, orienting, and executive attention (Posner & Petersen, 1990).
The ANT is essentially a combination of the spatial cue task (Posner, 1980) and the flanker task (Eriksen, 1995). Therefore, it includes alerting and spatial cues as well as flankers.
The different measures are obtained with a series of subtractions among the different conditions. Alerting is calculated subtracting from double cued trials no cued trials (no cue - double cue), orienting subtracting positional cued trials from central cued trials (central - up or down), while conflict subtracting congruent trials from incongruent (incongruent - congruent). The reliability of the ANT makes it an ideal tool for assessing the efficiency of the attention networks in a variety of populations as wells as changes in efficiency as a result of training or rehabilitation (Fan et al., 2002).

*Stimulation*

The stimulation was delivered by a battery-driven electrical stimulator (Brainstim, Bologna) through two conductive rubber electrodes (5x5 cm), filled with saline solution and positioned over the participant's scalp, assessing the exact points using 10-20 system (Jasper, 1958) and following a standard procedure (Terney et al., 2008). The stimulation was administered over the bilateral frontal cortex, with the center of the electrode over the crossing point between F4-FC4-TP4-TP8, and contralaterally on the homologous region (see Figure 1). We chose this setting because the results of a previous unpublished study assessing the electrophysiological effects of Labyrinth suggested that Labyrinth was able to activate the right frontal sites, in particular in the area between F4-FC4-TP4-TP8. Notwithstanding the temporal localization in EEG recording is hazardous, in particular with few electrodes, the correlations between the behavioral outcomes and EEG spectral power strongly suggested that the right frontal sites are the best candidates which Labyrinth could work on. Moreover, the characteristics of the training itself suggested that the executive functions might be involved and, if this is the case, the right hemisphere is the best candidate for administering the stimulation. However, we chose a bilateral montage because, so far, this montage has proven to be the more efficient to obtain long-term outcomes in training (Cappelletti et al., 2013; Snowball et al., 2013). The stimulation was administered for 20 minutes (maximum intensity: 1mA) with a fade in/out time of 20 seconds and an oscillation frequency selected above 100 Hz (high frequency), which was proven to be more effective in inducing reliable effects (Terney et al., 2008; Capelletti et al., 2013) and safe for participants (Fertonani et al., 2011; Ambrus et al., 2010). tRNS stimulates

under both the electrodes, which means that there is no reference electrode but two anodes that equally stimulate on the bilateral frontal cortex.

During the stimulation participants were asked to play with the training game in silence and avoid excessive movements. After the end of the training, participants were asked to fill in a questionnaire reporting the sensations experienced during the stimulation sessions (adapted by Fertonani et al. 2011).

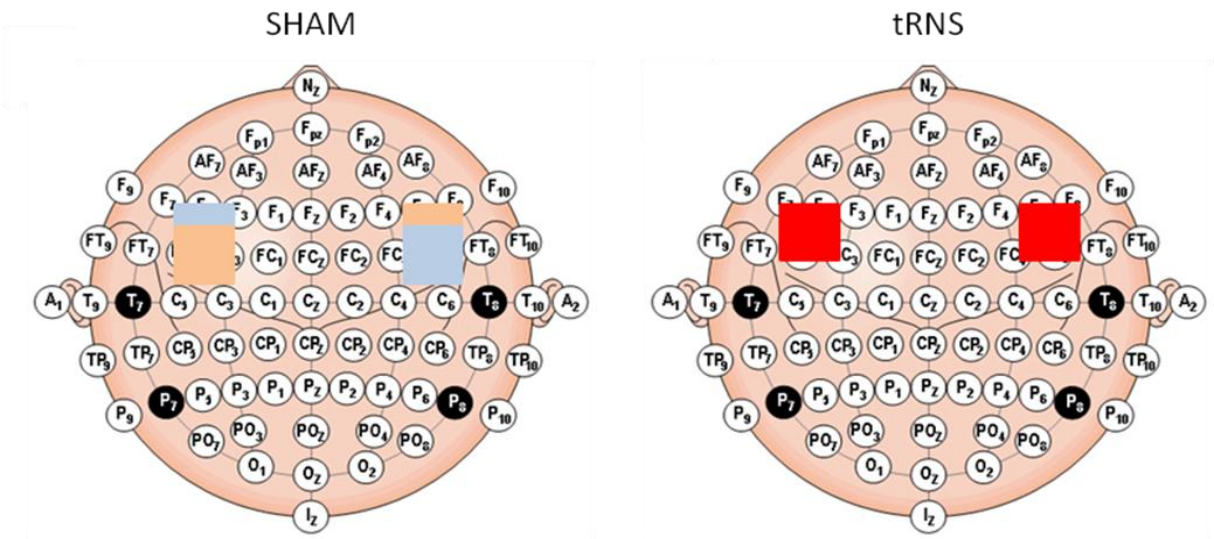



Figure 1. Montage in sham group (on the left) and tRNS group (on the right).

*Data analysis*

Data were analyzed using mixed models in R environment (R Core Team, 2016). Mixed models have proven to be more suitable to analyze accuracy (binomial distribution) data with repeated measures and to account for subjects' variability.

As a general procedure, we firstly compared models to select the one explaining the greater amount of variance. We used AIC (Akaike information criterion; Akaike, 1973) to select the best models, or BIC were AIC was not useful to choose appropriately. Secondly, we inspected the effect detectable in the selected model.

Data were analyzed using "ordinal "(Christensen, 2015) and "lme4" (Bates, Maechler, Bolker, & Walker, 2015) packages where appropriate. Moreover, to inspect the interaction effects, we employed the ‘‘testInteraction" function in "phia" package (De Rosario Martinez, 2015), adjusting the false discovery rate with Holm adjustment (Holm, 1979) and FDR correction (Benjamini & Hochberg, 1995). For data visualization, ggplot2 (Wickham, 2009) package was employed.

Ant task was analyzed using "ez" package in R, after calculating an index for alerting, orienting and conflict following Fan et al. (2002).

*Results*

*Questionnaires*

The questionnaires aimed to assess possible negative sensations due to the stimulation did not show a difference between groups in the sensations experienced. Moreover, all the sham group participants reported to have been truly stimulated, and did not realize they were not really stimulated.

*Behavioral tasks*

*Labyrinth*

Data were analyzed using *ordinal* (Christensen, 2015) and MASS package (Venables & Ripley, 2002) in R environment. Since we had not the same number of trials for the dual, the single, the switch and the repeat conditions in the task, we were not allowed to calculate a difference between these values in order to obtain a cost. Considering the nature of the data, we were only allowed to analyze the performance considering the "level" reached by each participant, which was automatically saved by the algorithm trial by trial. It is worth noting that Labyrinth is an adaptive game, therefore the level of difficulty depends on the ability of the participant and on the rapidity of learning through sessions. The algorithm was designed to control for the performance of the participant, which was maintained on 75% accuracy. Hence, neither accuracy nor time were good indicators to describe participants' performance. For this reason, the level reached by each participant in each session was transformed into an ordinal value (1-7 possible levels, from the easier to the more difficult). We finally submitted the values to our analysis.

First of all, we explored the effects of the type of task (snake task, diamond task or dual task) on the reached level using the *polr* function in *MASS* package. From this analysis, we found an effect of session ($\chi^2$=162.97, p<.001) and of the type of task ($\chi^2$=9.51, p=.009) but no effect of the group. See Figure 2.

Secondly, we analyzed possible effect of the group by comparing models including fixed terms (session or group or both) and the random effects intercepts (subjects and session). We chose this setting to avoid convergence issues which came out when adding a random slope to the models.First

of all, we chose the more appropriate model to describe our single tasks data comparing the null model to the model with only the session (session model), the model with the group alone (group model) the model with the orthogonal factors session and group (session + group model), the model with the interaction between session and group (session x group) for each type of task (snake task and diamond task), including the random intercepts for subject and session in each subgroup of trials.

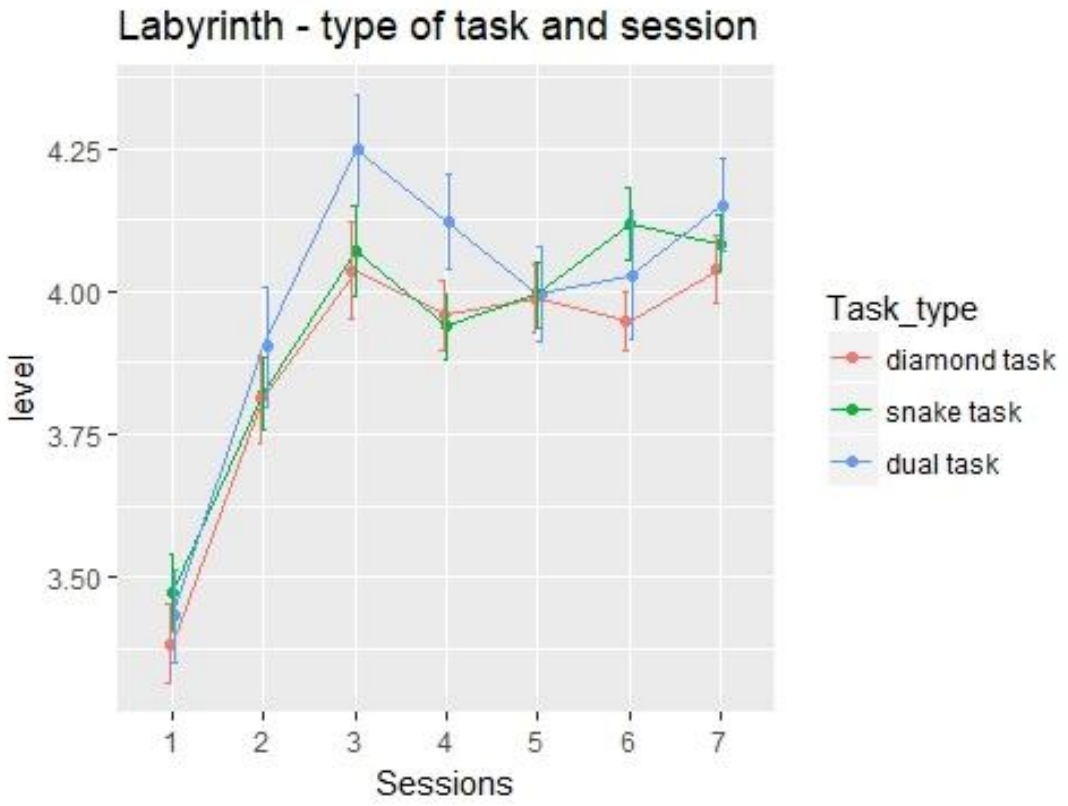



Figure 2. Type of task and session effects.

Since the level is an ordinal variable (seven possible levels), we applied the *clmm* function in R *ordinal* package (Christensen, 2015). Considering the diamond task, results suggest that the session model was the one more proper to describe our data ($AIC_{session\ model}$= 96398; $AIC_{group\ model}$= 96419; $AIC_{sessionxgroup\ model}$= 96405; $AIC_{session+group\ model}$= 96400). Figure 3 (left panel) presents the time course of the performance through the sessions. See Table 1a. Considering the snake task, the comparison showed that the session model was the more proper one to describe data ($AIC_{session\ model}$= 95693; $AIC_{group\ model}$= 95715; $AIC_{sessionxgroup\ model}$= 95694; $AIC_{session+group\ model}$= 95695). See Table 1b to inspect the results.

| Model | AIC | LogLik | DF | p |
|---|---|---|---|---|
| Null Model | 96417 | -48199 | - | - |
| Group Model | 96419 | -48199 | 1 | .93 |
| Session Model | 96398 | -48184 | 5 | <.001 |
| Session + Group Model | 96400 | -48184 | 1 | .93 |
| Session x Group Model | 96405 | -48180 | 6 | .32 |

Table 1a

| Model | AIC | LogLik | DF | p |
|---|---|---|---|---|
| Null Model | 95714 | -47848 | - | - |
| Group Model | 95715 | -47848 | 1 | .72 |
| Session Model | 95693 | -47832 | 5 | <.001 |
| Session + Group Model | 95695 | -47832 | 1 | .72 |
| Session x Group Model | 95694 | -47852 | 6 | .03 |

Table 1b

| Model | AIC | LogLik | DF | p |
|---|---|---|---|---|
| Null Model | 14427 | -7204.4 | - | - |
| Group Model | 14429 | -7204.3 | 1 | .66 |
| Session Model | 14417 | -7193.3 | 5 | <.001 |
| Session + Group Model | 14418 | -7193.2 | 1 | .64 |
| Session x Group Model | 14429 | -7192.7 | 6 | .99 |

Table 1c.

In order to analyze dual task, we considered as factors group and session. As above, we compared null model with session model, group model, group + session model and group x session model, adding random intercepts (subject and session) to avoid convergence issues. From the results, the session model was again the best to explain our data ($AIC_{session\ model}$= 14417; $AIC_{group\ model}$= 14429; $AIC_{sessionxgroup\ model}$= 14429; $AIC_{session+group\ model}$= 14418). See table 1c.

Since the data show that there is a ceiling effect during the sessions, we analyzed how participants reached the maximum level (around 4) in the first session. We hence split the trials of the first session into four bins and then analyzed how the performance changed in time (i.e., across bins). We employed ordinal mixed models to account for the different number of observations per cell and to add random intercepts (subject and time points). We computed the models above considering the new time points and group as factors (time points model, group model, group + time points model, group x time points model) and finally compared the models to find the best to describe our data. Again, the best model was the one with the time points as only factor ($AIC_{time\ points\ model}$= 26900; $AIC_{group\ model}$= 26915; $AIC_{time\ pointsxgroup\ model}$= 26905; $AIC_{time\ points+group\ model}$= 26902). Figure 3 (right panel) represents the change within the first session.

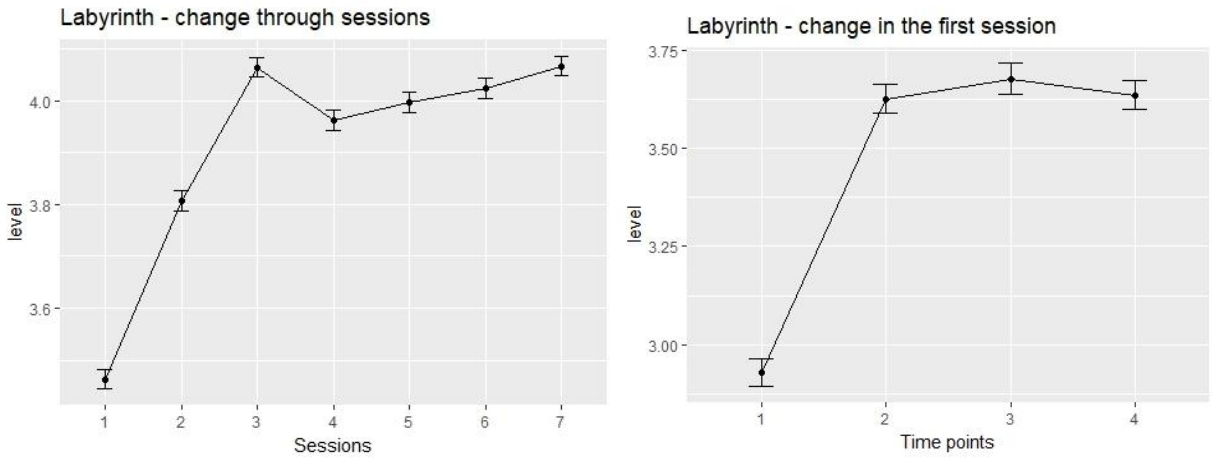



Figure 3. On the left, change in level through the sessions, on the right change in level in the first session.

Lastly, we investigated whether baseline performance was related to the training outcome. In order to do so, we correlated slopes of the regression lines for each participant (training effect through sessions) and intercepts of the regression lines (baseline ability). Consistently with previous studies, results showed a strong negative correlation ($r(26)=-.88$, $p<.001$) suggesting that the worse the performance was at the beginning of the training, the better the improvement through sessions. See Figure 4.

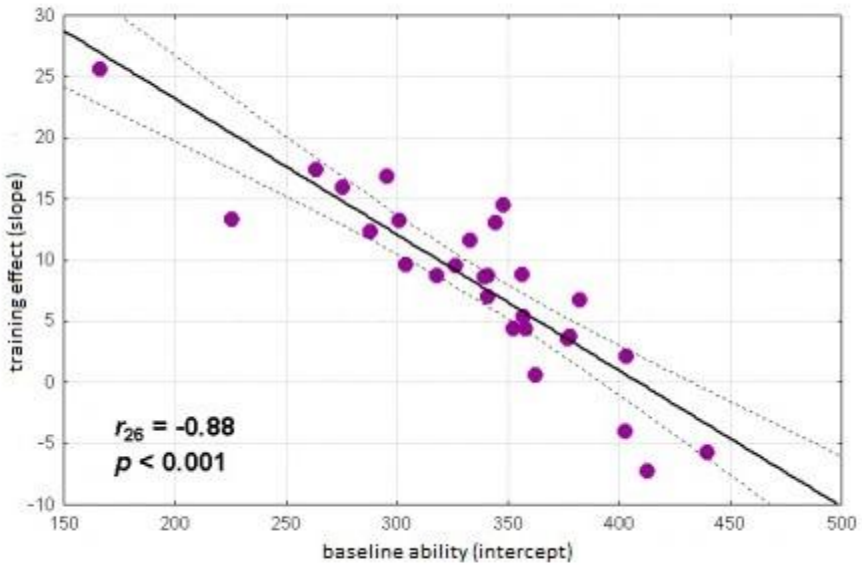



Figure 4. Negative correlation between the slopes and the intecepts for each participant.

*Transfer tasks*

*Single task*

We prepared the data by removing incorrect answers when analyzing accuracy and discarding trials slower or faster than 2.5 SD.

We chose the more appropriate model to describe our data by comparing all the possible models with group, session and side as fixed factors and subject and session as random factors. We applied glmer to analyze accuracy. From the comparison, the best model was side x session model ($AIC_{sessionxside}$=1992.9; $AIC_{sidexgroup}$=1993.8, $AIC_{session+side}$=1994.3; $AIC_{side}$=1994.8). Figure 5 shows the model.

Finally, we applied lmer to analyze RTs with a linear distribution. From the comparison, the side x session x group model proved to be the best to explain our data ($AIC_{sessionxgroupxside}$=49221; $AIC_{side+sessionxgroup}$=49232, $AIC_{sessionxgroup}$=49241). Figure 6a shows the selected model.

Post-hoc comparisons using *testInteraction* function, Holm corrected, shows that the difference between right and left target was significant only in tRNS group ($\chi^2$=15.35, p=.002) for session 1 vs. 2 and for 1-3 sessions ($\chi^2$=9.44, p=.04). The difference between groups was significant for sessions 1 vs. 2 ($\chi^2$=52.10, p<.001) and 1 vs. 3 ($\chi^2$=42.74, p<.001). Moreover, maintaining fixed the session, a significant difference between groups was found for the comparison bilateral - left in the third session ($\chi^2$=8.69, p=.03). Maintaining fixed the type of trial (right, left, bilateral), a significant difference between groups was found comparing sessions 1 vs. 2 ($\chi^2$=18.16, p<.001) while for sessions 1 vs. 3 comparison it just missed significance ($\chi^2$=6.12, p=.05). Considering right targets, the difference was significance between sessions 1vs. 2 ($\chi^2$=9.53, p=.01) and sessions 1 vs. 3 ($\chi^2$=8.50, p=.02). Considering the left targets, the difference was significant between sessions 1 vs. 2 ($\chi^2$=26.86, p<.001) and 1-3 ($\chi^2$=38.79, p<.001). Although a difference between groups at baseline was significant in bilateral ($\chi^2$=15.33, p<.001), right ($\chi^2$=9.52, p=.01) and left targets ($\chi^2$=16.88, p<.001), the difference just missed significance in bilateral targets when analyzing the third session ($\chi^2$=6.85,p=.05). Figure 6b shows the three way interaction.

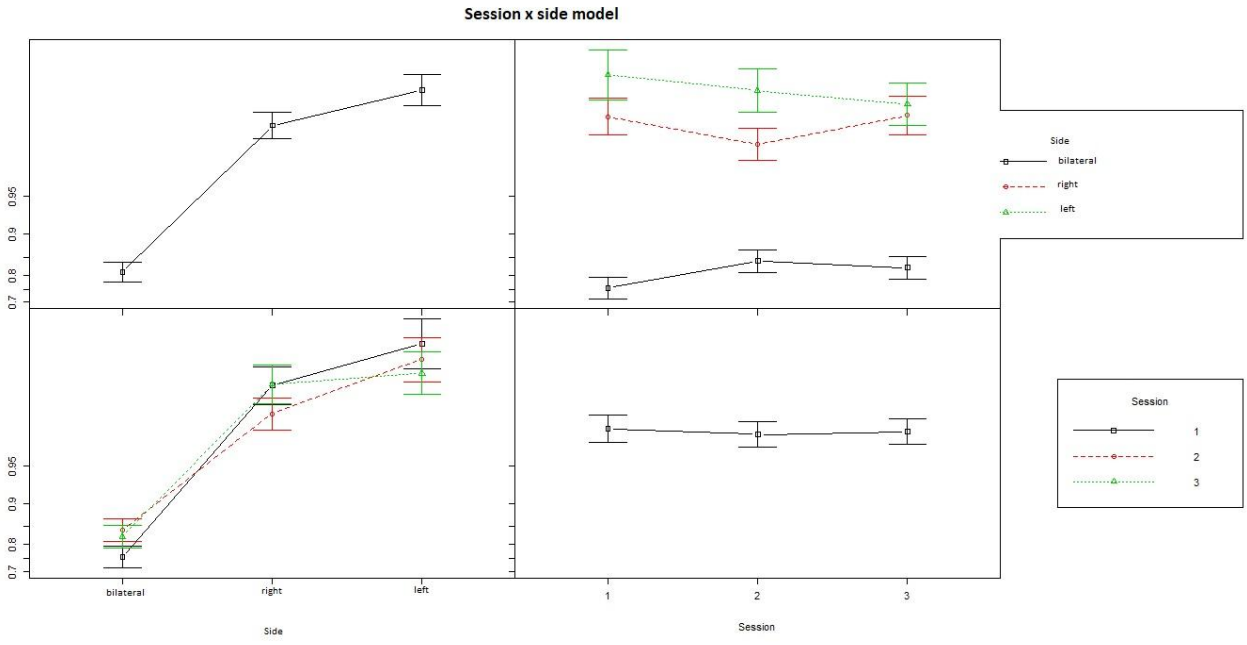



Figure 5. session x side model in single task accuracy.

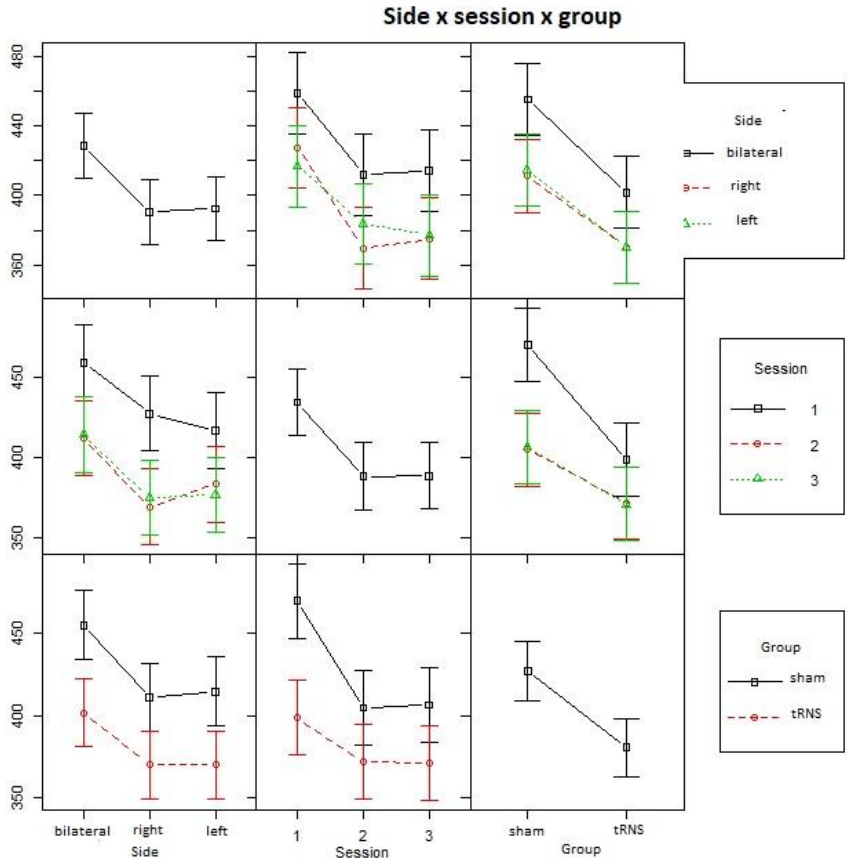



Figure 6a Best model to explain RTs data in single task.

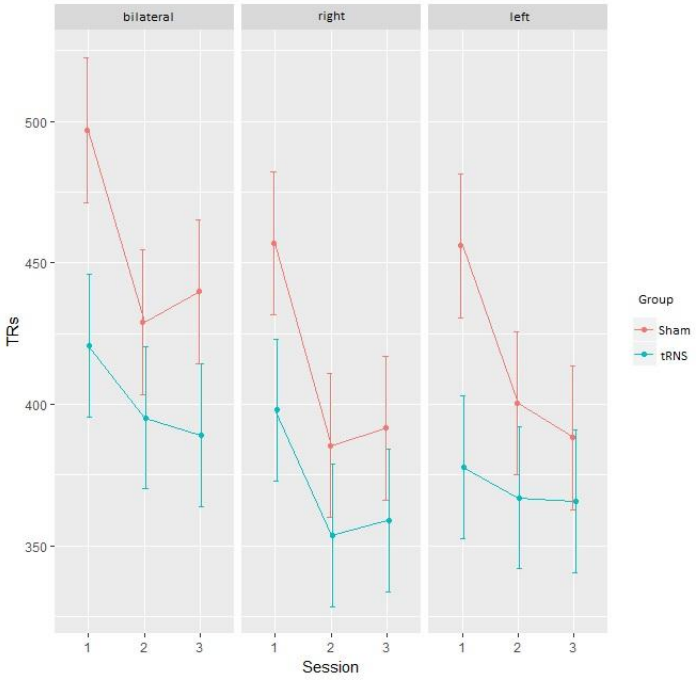


Figure 6b. Three-way interaction in single task RTs.

*Dual task*

In the dual task, we analyzed separately accuracy and RTs conditioned to the shape presentation (that is, accuracy and RTs when responding to the dot in those trials where the correct shape is finally chosen). We compared all possible models including group, session and event as fixed factors and subject, session and side as random factors, where possible due to convergence issues. We compared the models on RTs for the lateralized targets through linear mixed models, after removing incorrect shape-answers trials. The model which best fits the data was the session x side model ($AIC_{sidexsession}$=47782; $AIC_{sessionxsidexgroup}$=47790; $AIC_{side}$ =47782; $AIC_{session}$=47831). Regarding accuracy on visual targets, the binomial mixed models comparison showed that the best model was session + side model ($AIC_{session+side}$=2074.1; $AIC_{side+session+group}$=2075.9). Finally, we analyzed the accuracy at the shape separately. The best model to explain data was the session x group model ($AIC_{sessionxgroup}$=4402.6; $AIC_{side+groupxsession}$=4404.3). The adjusted means of the model are presented in figure 7. Post-hoc comparisons using testInteraction function in "phia" package (Holm adjusted) showed that a difference between groups was detected in sessions 2 vs. 3 ($\chi^2$ = 9.64, p=.004) and in sessions 1 vs. 3 sessions ($\chi^2$ =19.03, p<.001), but not in sessions 1 vs. 2 sessions ($\chi^2$ = 1.44, p=.23), confirming that a delayed effect of the group was detectable after the end of the training.

In addition, the best model to describe the accuracy at the shape discrimination conditioned to a correct performance at the target detection was the one with side + group x session as factors, even if a very small difference in AIC has been detected ($AIC_{side+groupxsession}$=2405.5; $AIC_{sessionxgroup}$=2405.9 and $BIC_{sidexsession}$=2409.1). Further investigation clarified that the difference between groups was significant when comparing sessions 1 vs. 3 ($\chi^2$ = 11.31, p=.002) but not sessions 1 vs. 2 ($\chi^2$ = 2.28, p=.13) nor sessions 2 vs. 3 ($\chi^2$ = 3.64, p=.12), suggesting a continuous, positive enhancement in the performance when participants were stimulated. See figure 8.

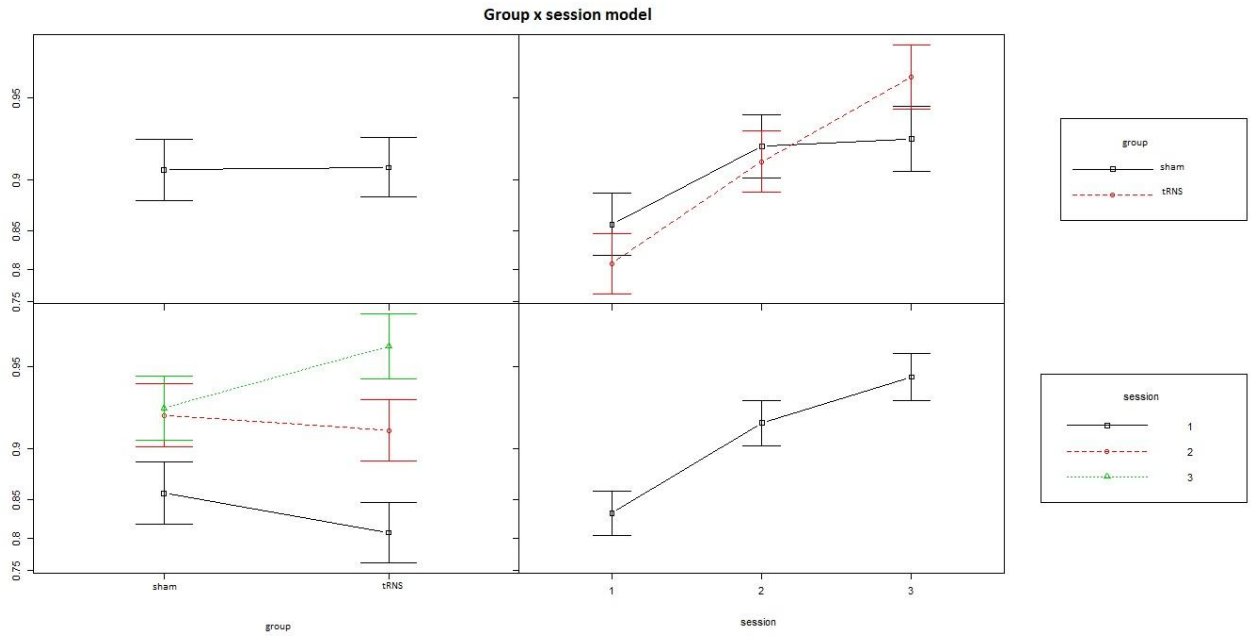



Figure 7. Effect of group x session for dual task shape after adjusting the means, independently on the performance at the main instruction (target detection).

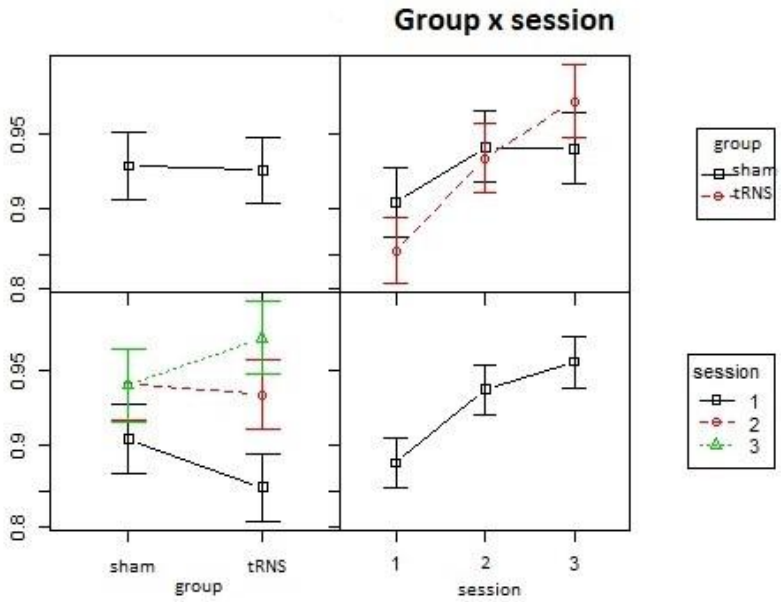



Figure 8. Interaction group x session in dual task shape performance when successfully reported target position.

*Switch task*

*Random switch task*

After correcting data removing trials slower or faster than 2.5 SD from the mean value, we compared all possible models with group, session and event (shift vs. repeat) as fixed factors and subject and session as random effects intercepts. The reason why we chose this setting was to avoid convergence issues which arose when adding random slopes. We applied linear mixed models to analyze RTs to correct answers. From the comparison, the best model to describe our data was the event x session x group model ($AIC_{eventxsessionxgroup}$=183628; $AIC_{event+group}$=183666; $AIC_{event+session}$=183656; $AIC_{eventxgroup}$=183651; $AIC_{sessionxevent}$=183649). An inspection of the model through testInteraction function clarified that the difference between groups was significant when comparing sessions 1 vs. 2 ($\chi^2$ = 6.73, p=.02) and sessions 2 vs. 3 ($\chi^2$ = 9.12, p=.008) and was not significant comparing sessions 1 vs. 3 ($\chi^2$ =.24, p=.6). Figure 9 shows the selected model plotted.

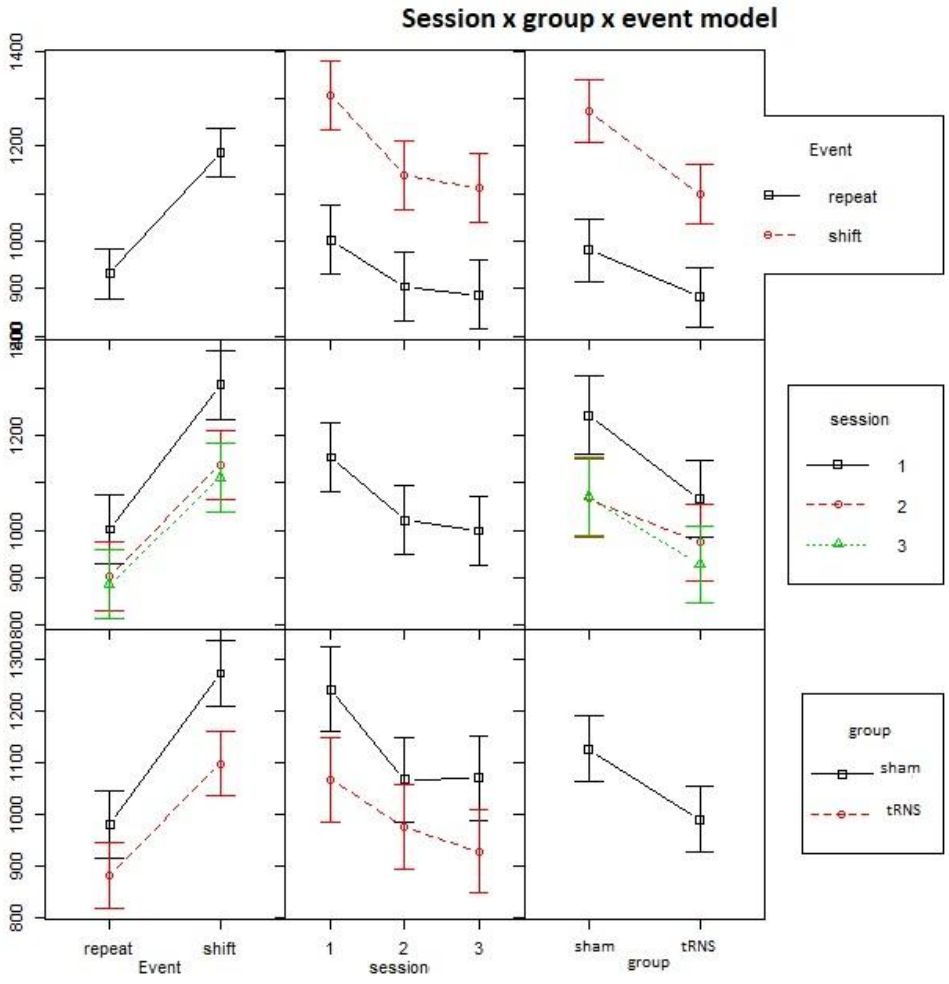


Figure 9. adjusted means for the session x group x event model in random switch task.

Further inspection clarified that the difference between the events, e.g., shift vs. repeat, was always significant (all ps <.001), with a significant slower performance for shift trials compared to repeat trials. Moreover, the interaction session x event was significant when comparing sessions 1 vs. 2 ($\chi^2$ = 6.24, p=.03) and sessions 1 vs. 3 ($\chi^2$ = 11.43, p=.002) Considering the interaction group x event, the interaction was significant ($\chi^2$ = 17.18, p<.001).

Regarding accuracy, we applied logistic mixed models to select the best model to describe our data. All possible combinations of fixed factors were included (group, session and event) and random slopes (session, subject and event). The comparison between models clarified that the best model was the event + session x group model ($AIC_{event+sessionxgroup}$=8543.5; $AIC_{groupxsession}$=8550.5; $AIC_{groupxevent}$=8550.5). Figure 9 represents the adjusted means of the selected model. Post-hoc comparison showed that the effect was specific for event (all ps<.001) and session x group. In this latter case, the difference was significant for sessions 1 vs. 3 ($\chi^2$ = 8.07, p=.01) and just missed significance for sessions 1 vs. 2 ($\chi^2$ = 4.15, p=.08). Moreover, the change in sham group is progressively significant through post-training sessions and follow-up sessions ($\chi^2$ = 10.89, p=.009) but no difference was found for tRNS group ($\chi^2$ = 1.96, p=.4) thus ruling out that the enhancement in RTs might be due to a worsening in accuracy. Figure 10 shows the model.

*Predictable switch task*

We compared all the possible models with group, session and event (shift or repeat) as fixed factors and subjects and session as random factors. We did not include event in random factors because these models encountered convergence issues due to the relative low number of trials per cell. The best model for RTs was the group x session x event model ($AIC_{event}$= 64160; $AIC_{event+group}$= 64160; $AIC_{evento+sessione}$= 64134; $AIC_{sessionxevent}$= 64076; $AIC_{sessionxeventxgroup}$= 64069). Figure 10 shows the model. See Figure 11.

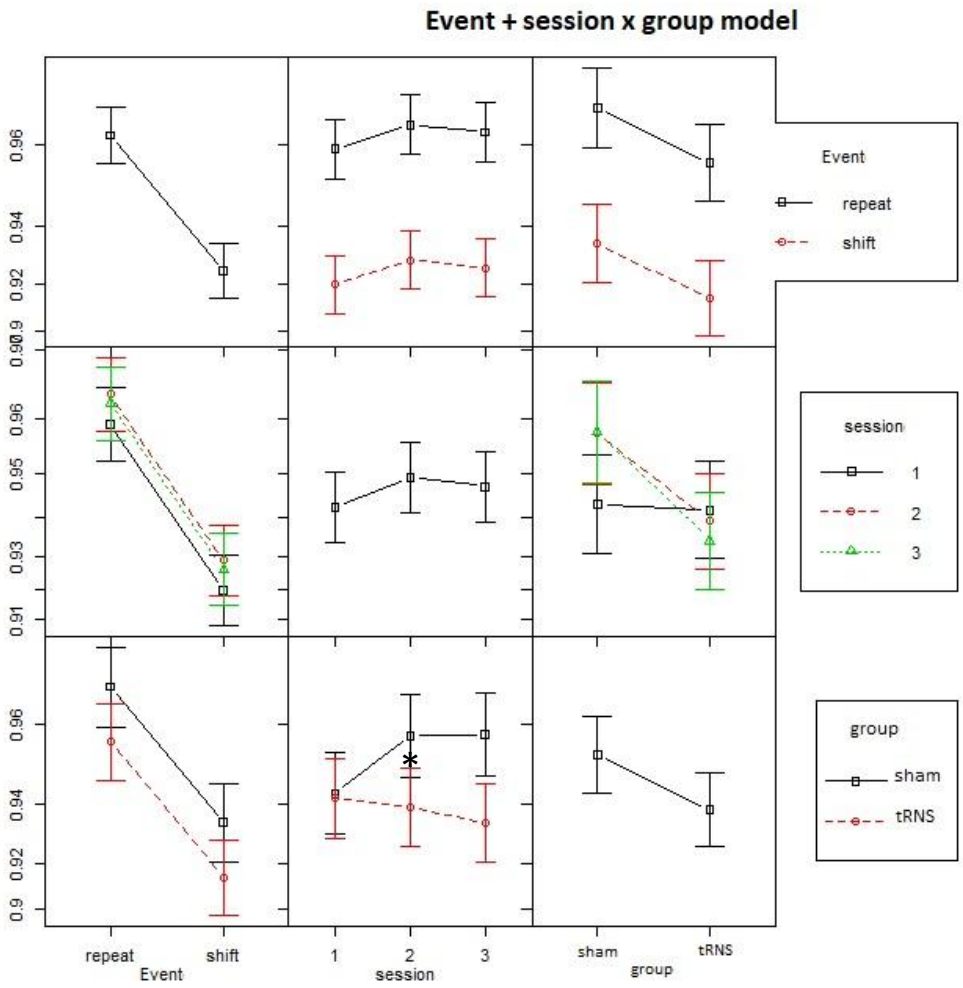



Figure 10. adjusted means for event + session x group model. While no reliable change is detectable for tRNS group, an enhancement in accuracy for sham group is present.

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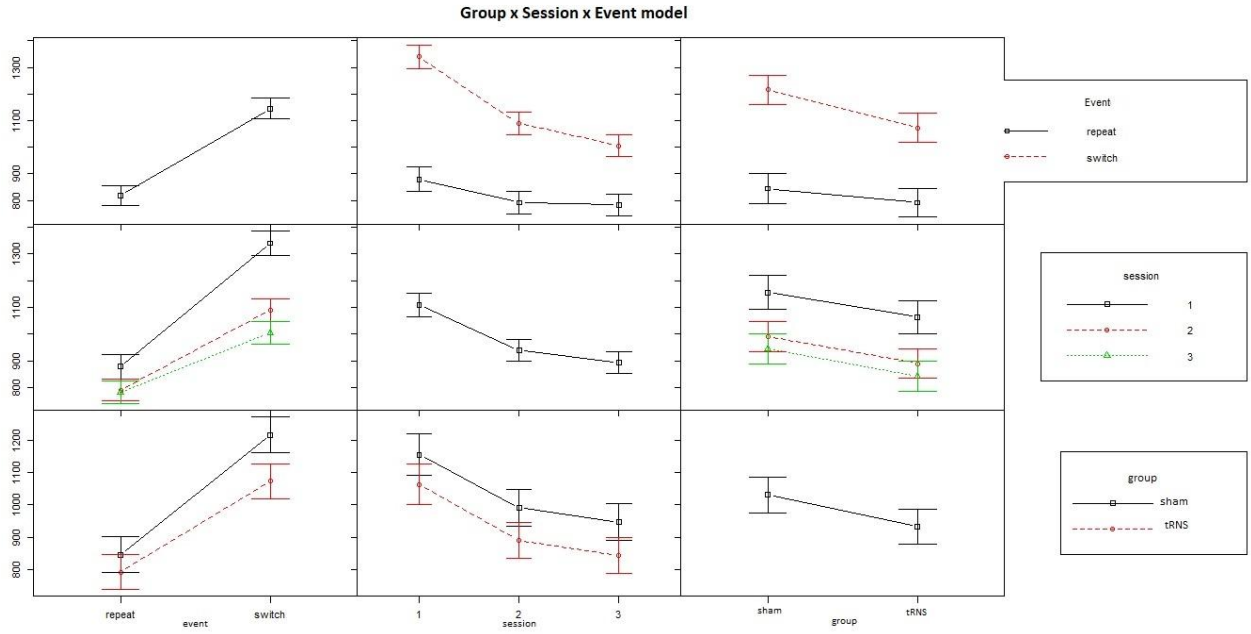


Figure 11. group x session x event adjusted means in predictable switch task.

Post hoc multiple comparisons using testInteraction function mainaining fixed the sessions and investigating the interaction group x event clarified that the effect was specific for session 1 ($\chi^2$ = 12.77, p=.001) and approached significance for session 2 ($\chi^2$ = 4.24, p=.08), while it disappeared in session 3 ($\chi^2$ =.38, p=.54), suggesting a baseline difference between the groups before starting the training.

Regarding accuracy, the model with Event as factor was the best to explain data ($AIC_{event}$=1811.2; $AIC_{event+group}$=1812.9; $AIC_{event+session}$=1814.1; $AIC_{eventxgroup}$=1814.8). As expected, performance was better for repeat than for shift trials ($\chi^2$ =37.43, p<.001).

*Ant task*

First of all, we calculated the three indexes of alerting, orienting, conflict in agreement with Montani et al. (2013). Here we calculated an index for each measure, so an ANOVA analysis is the one more suited to analyze this type of data. Alerting was calculated subtracting from double cued trials no cued trials (no cue - double cue), orienting subtracting positional cued trials from central cued trials (central - up or down), while conflict subtracting congruent trials from incongruent (incongruent - congruent). We submitted the values calculated to an ANOVA separately for each index. For alerting and orienting, there were no effects of session, group, or interaction group x

session. For conflict, the effect of session missed significance ($F(84,1)=3.20$, $p=.07$) and there was no effect of group or group by session interaction.

*Resting-state EEG data*

After data collection, the EEG signal was corrected for blinks and eye movement artifacts according to Ille, Berg & Scherg (2002) by BESA software (Brain Electrical Source Analysis, 5.1 version). Each EEG epoch was divided into 2048-ms time intervals, and thus included 150 samples with 0.488 Hz FFT resolution. Given the constraint of the Fast Fourier Transform (FFT) to use $2^n$ samples, the width of each interval was necessarily forced to 1024 samples, corresponding to a 2048-ms interval. Artifact rejection was performed on each epoch, with both amplitude and derivative (with respect to time) thresholds[5] (250 μV and 100 μV/ms, respectively). The remaining epochs were then visually inspected for any residual artifact. On average, 17.80% of the trials were rejected evenly distributed among groups and sessions. For each participant, the FFT was averaged across those epochs that, after windowing with a tapered cosine, were free of residual artifacts. In the next step, EEG amplitude was normalized within each electrode as the contribution of each band to the whole 0.488–100 Hz spectral range, and expressed as a percentage. Normalization allowed us to quantify the relative contribution of each EEG band with respect to total spectral power (% value) in various sessions (pre- and post-training, as well as follow up) and also to compare the same scalp locations in all samples (controls vs. sham, and sham vs. tRNS groups). We analyzed all the typical EEG bands, but only Delta[6] (0.5-4 Hz, effective δ range: 0.49-3.904 Hz), Alpha (8-12 Hz, effective α range: 8.29-11.71 Hz) and Gamma bands (35-50 Hz, effective γ range: 35.62-49.29 Hz) showed significant results. Based on the mean distribution of Delta, Alpha and Gamma bands, electrodes were clustered into four regions of interest with two spatial factors consisting of two levels each: anterior-posterior asymmetry and laterality. This clustering allowed us to include, in our statistical analyses, most of the scalp activity, through the use, in agreement with previous work on resting state (Spironelli and Angrilli, 2017), of 20 out of 30 electrodes placed on the left and right side of the cap. To highlight the effect of our experimental manipulation, we computed an index of normalized EEG activity for each band as the difference post-training minus pre-training: therefore, positive EEG % referred to higher values after the training, whereas negative values to higher values before the training. Individual ANOVAs were carried out for each EEG band

[5]Using BESA software, artifact rejection includes an Amplitude threshold criterion, that rejects the trial within which the difference between the maximum and the minimum amplitude is exceeded, and a Derivative threshold criterion, that rejects each trial within which the largest amplitude difference between two adjacent time samples is exceeded.

[6]For all EEG bands, we indicated the typical frequency range and the "effective range", that is the real width of every EEG band.

including the factor Group (two levels: Sham vs. tRNS) and two within-subject factors: Region (two levels: Anterior vs. Posterior) and Laterality (two levels: Left vs. Right hemisphere). Post-hoc comparisons were performed using the Tukey HSD test ($p< 0.05$), and the Greenhouse-Geisser correction was applied when necessary, that is when variables with more than two levels were involved.

Sham - Control group comparison

First of all, we analyzed sham and control group to assess possible difference due to the training itself. We divided the scalp into clusters and computed a difference between post-training and pre-training measures. We carried our separated ANOVA on difference post - pre to detect changes through session on delta, alpha, and gamma bands. To analyze Delta band, we divided the scalp into four clusters of four electrodes (Fp1, F3, F7, FT7 vs. Fp2, F4, F8, FT8 vs. CP3, P3, P7, O1 vs. CP4, P4, P8, O2). We found a main effect of the Laterality factor ($F(1,27)=8.28$, $p=.008$, $\eta_p^2=.25$), but no main effect nor interaction including the Group factor. For Alpha band, we divided the scalp into four clusters of four electrodes (F3, FC3, C3, FT7 vs. F4, FC4, C4, FT8 vs. CP3, P3, TP7, P7 vs. CP4, P4, TP8, P8). On these values, the ANOVA revealed a significant three-way Group by Region by Laterality interaction ($F(1,27)=6.44$, $p=.02$; $\eta_p^2=.19$). Post-hoc comparisons clarified that the difference between sham and control in left anterior and right posterior sites was significant (see figure 12).

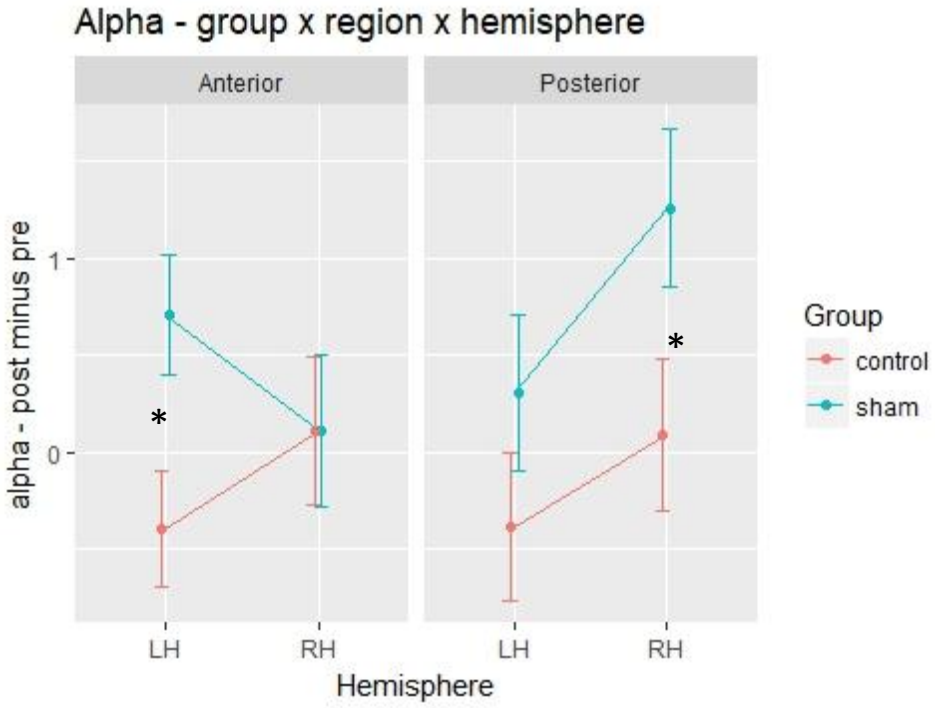

Figure 12. *Sham - tRNS group comparison*: Alpha band three ways interaction (group x hemisphere x region).

To analyze gamma band, we divided the scalp into four clusters of five electrodes (Fp1, F3, FC3, F7, FT7 vs. Fp2, F4, FC4, F8, FT8 vs. CP3, P3, TP7, P7, O1 vs. CP4, P4, TP8, P8, O2). On these values, we found the three ways interaction Group by Region by Laterality ($F(1,27)=5.56$, $p=.03$, $\eta_p^2=.17$), but no difference was detected in post-hoc comparisons (see figure 13).

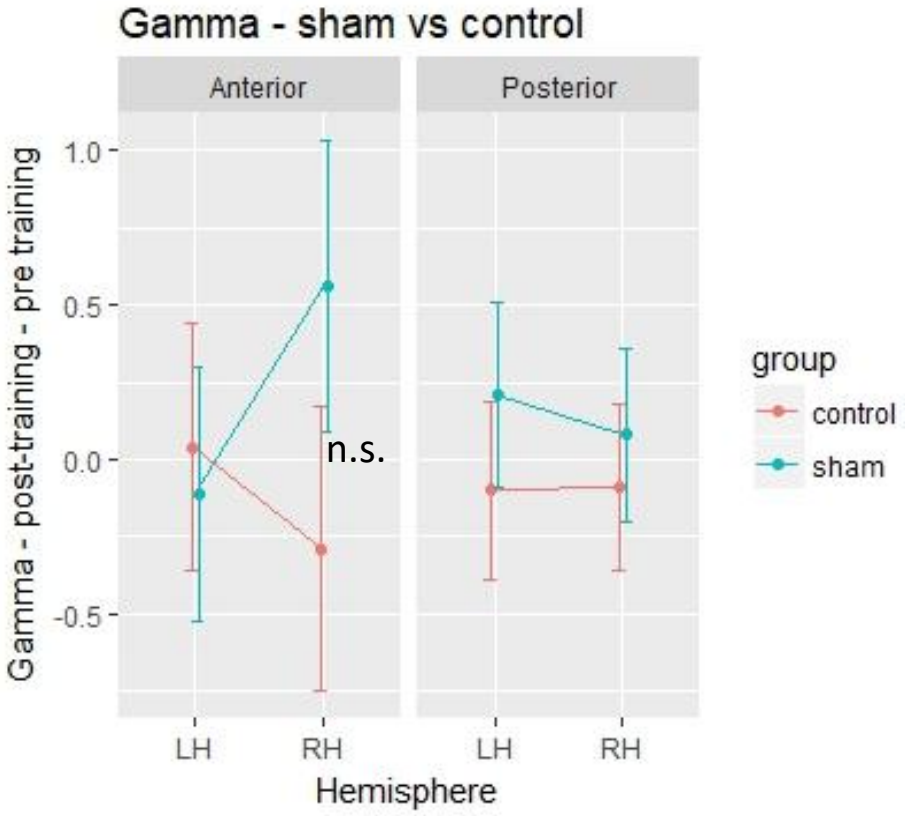


Figure 13. Gamma three ways interaction. No significant effects were found in post-hoc comparisons.

Sham - tRNS group comparison

Secondly, we compared sham group with tRNS group to detect the possible effect of the combination between training and stimulation compared to the effect of the training alone. We analyzed both the post training effect (post-training minus pre-training) and the long-term effect (follow-up minus pre-training).

*Delta band*

To analyze delta, we divided the scalp in four regions of four electrodes each (Fp1, F3, F7, FT7 vs. Fp1, F4, F8 FT8 vs. CP3, P3, P7, O1 vs. CP4, P4, P8, O2). Considering the training effect, we found a significant Group by Region x Laterality interaction ($F(1,26)=9.15$, $p=.006$, $\eta_p^2=.26$) with a significant increased Delta % in the sham group on the left anterior sites compared to tRNS group ($p<.001$). In addition, the sham group showed significant greater delta % on anterior left vs. right sites ($p<.05$), whereas tRNS group revealed a bilateral delta % distribution. See figure 14.

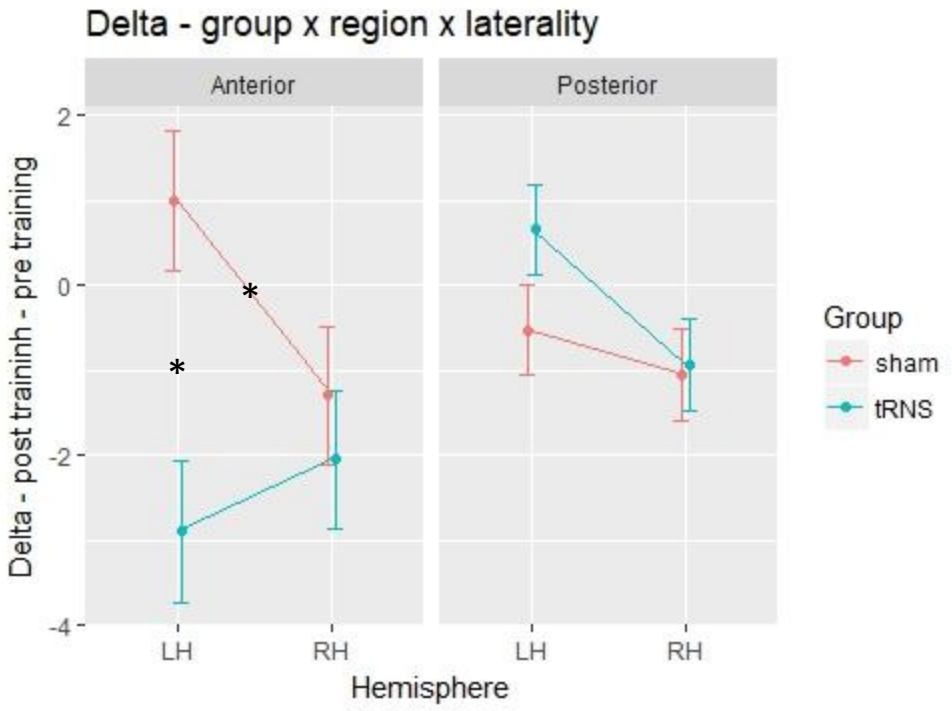


Figure 14. Above, post stimulation effect (post - pre) on delta.

Considering the long-term effect (follow-up minus pre-training), we found the three-way interaction Group by Region by Laterality ($F(1,26)=6.02$ $p=.02$). See figure 15.

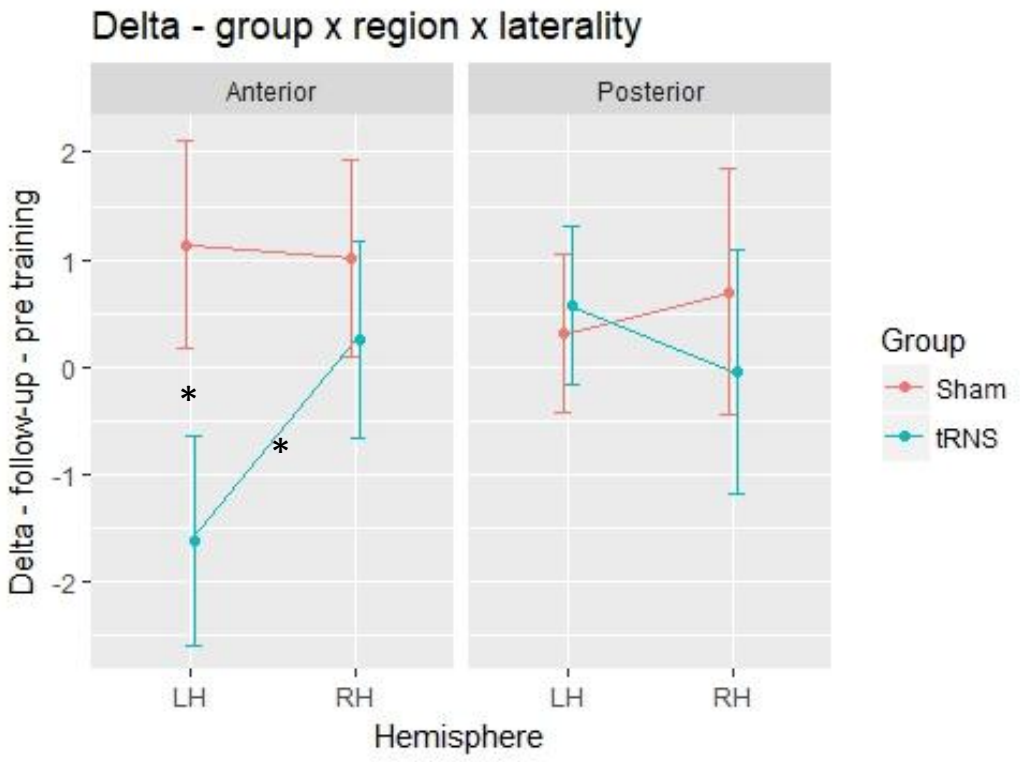


Figure 15. Long term effect (follow-up - pre) on delta EEG band.

The tRNS group showed significant lower delta % on anterior left vs. right sites ($p<.01$), whereas sham group had a bilateral distribution of delta rhythm on the whole scalp. Considering the between group differences, tRNS participants revealed, compared with sham group, significant lower delta % on anterior left regions ($p<.01$).

Considering the comparison long-term effect vs. post-training, we conducted a further ANOVA on the same values by adding the Time factor (follow-up vs. post-training) to the previous two within subjects factors Region and Laterality. We found the main effect of the Time factor ($F(1,26)=6.62$ $p=.01$), with overall higher delta % on the long term effect (.29%) compared with the training effect (-.89%). Interestingly, the three-way interaction Group by Region by Laterality ($F(1,26)=10.16$ $p=.004$) revealed that, regardless of Time session, (i.e., both during Training and Follow-up), the tRNS group showed significant lower delta % on anterior left vs. right sites ($p<.05$), whereas sham group had a bilateral distribution of delta rhythm on the whole scalp (Figure 16).

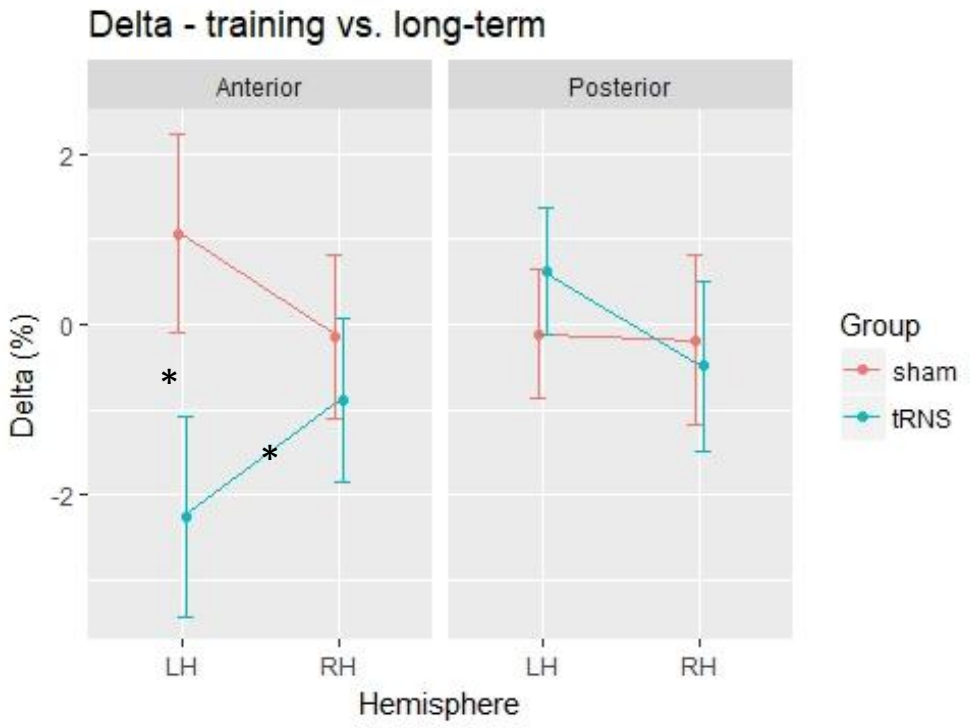


Figure 16. Group x region x laterality on delta.

Considering the between group differences, tRNS participants revealed, compared with sham group, significant lower delta % on anterior left regions ($p<.001$).

*Alpha band*

To analyze Alpha band, we divided the scalp into four clusters of four electrodes (F3, FC3, C3, FT7 vs. F4, FC4, C4, FT8 vs. CP3, P3, P7, TP7 vs. CP4, P4, P8, TP8). Regarding the training effect (post-training - pre-training) we found a Group by Region by Laterality interaction ($F(1,26)=11.02$, $p=.003$, $\eta_p^2=.25$). As can be seen in Figure 17, the sham group showed significant greater alpha % on posterior right vs. left sites ($p<.05$), whereas tRNS group had a bilateral distribution of alpha rhythm on the whole scalp. Considering the between group differences, tRNS participants revealed, compared with sham group, significant lower alpha % on anterior left ($p<.05$) and posterior right regions ($p<.01$).

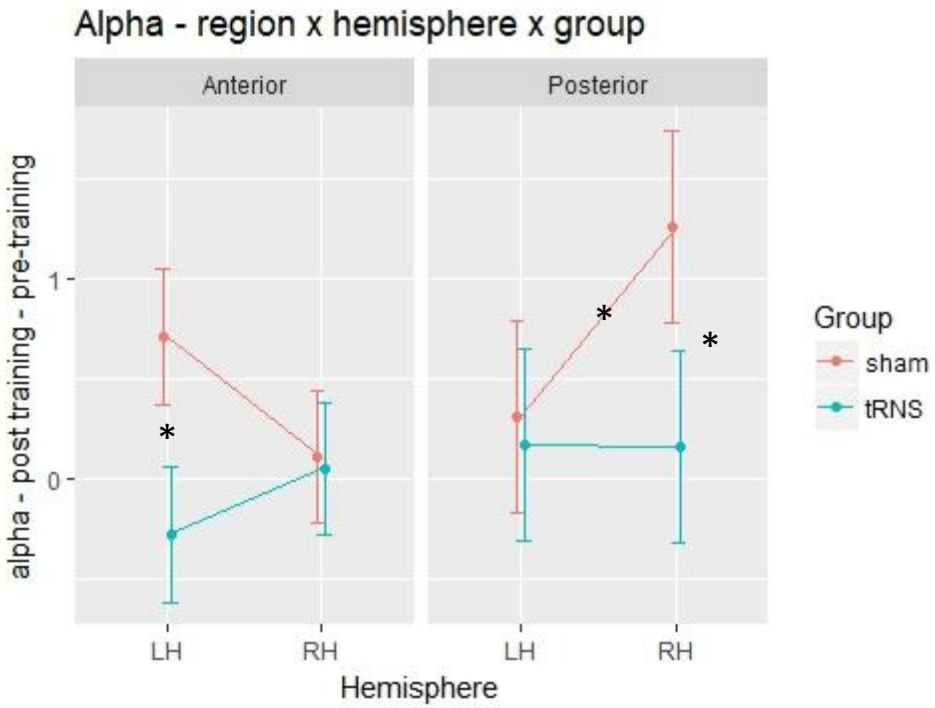


Figure 17. Group x hemisphere x region training effect.

On long-term effect (follow-up - pre training) no significant effects were found. However, the ANOVA carried out on the comparison long-term effect vs. post-training, with Group as between subjects factor and Time, Region and Laterality as within subjects factors revealed a significant four-way interaction ($F(1,26)=4.24$, $p<.05$). Figure 18 shows a bilateral distribution of alpha % on anterior sites on both Training and Long-Term effects, regardless of group, but significant lower alpha % on tRNS participants' anterior left regions, compared with sham group ($p<.01$ on both time sessions). Considering the posterior sites, sham participants showed significant greater alpha % on right vs. left regions ($p<.01$) on the training effect, and a bilateral alpha distribution on the long-term effect, whereas the tRNS group always exhibited a bilateral alpha distribution. In any case, tRNS group showed significant lower alpha % on posterior right sites compared with sham group ($p<.001$ and $p<.05$ on training and long-term effect, respectively).

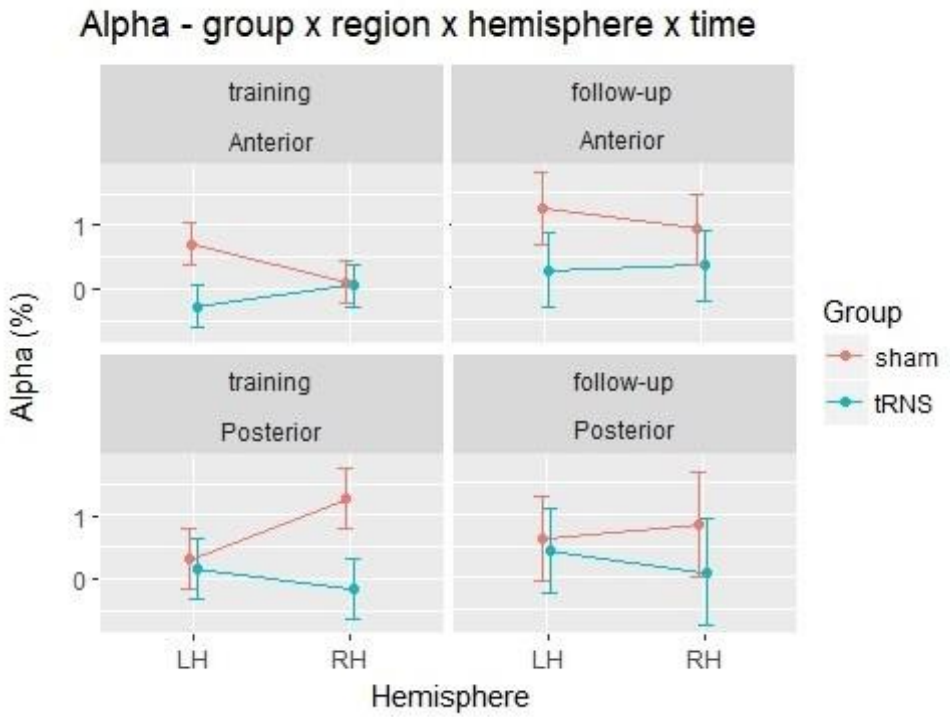


Figure 18. Four-way interaction group x hemisphere x region x time.

*Gamma band*

To analyze gamma band, we divided the scalp in four regions of five electrodes each (Fp1, F3, FC3, F7, FT7 vs. Fp1, F4, FC4, F8 FT8 vs. CP3, P3, TP7, P7, O1 vs. CP4, P4, TP8, P8, O2). We hence calculated the difference between post-training and baseline to analyze the training effects and between follow-up and baseline to analyze the long-term effects.

Regarding post-training effects, we found, crucially for our hypothesis, the three-way Group by Region by Laterality interaction ($F(1,26)=14.52$, $p<.001$, $\eta_p^2=.36$). Results are presented in figure 19.

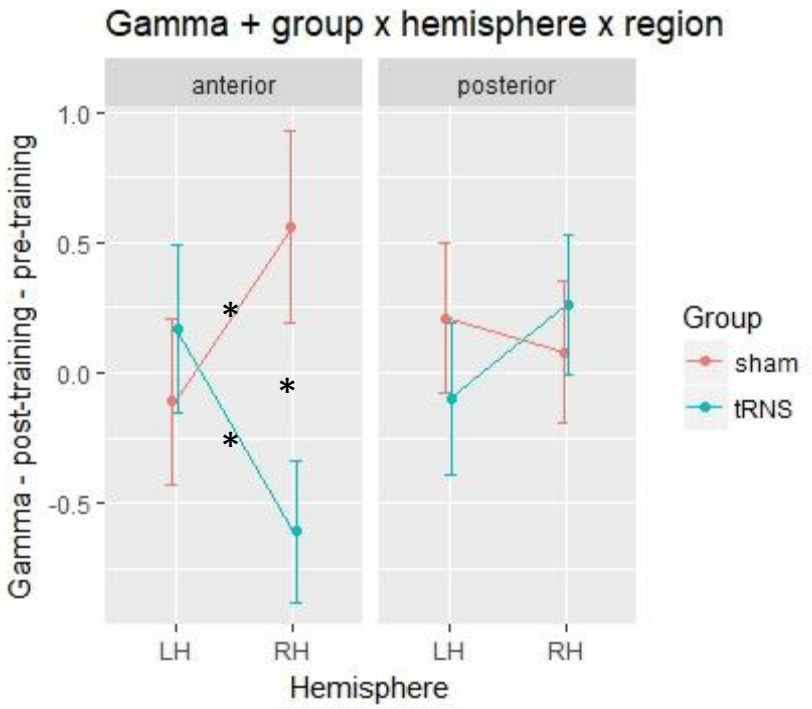


Figure 19. group x hemisphere x region

The sham group showed significant greater gamma % on anterior right vs. left sites ($p<.05$), whereas tRNS group exhibited the opposite pattern, anterior gamma % being greater on left rather than right sites ($p<.05$). Considering the between group differences, tRNS participants revealed, compared with sham group, significant greater gamma % on anterior left sites ($p<.001$). No differences were found on posterior clusters.

No effect was found considering long-term effect (follow-up - baseline). However, the ANOVA carried out on the comparison long-term effect vs. post-training, with Group as between subjects factor and Time, Region and Laterality as within subjects factors revealed a main effect of time ($F(1,26)=5.27$, $p=.03$), with overall higher gamma % on the training effect (.34%) compared with the long-term effect (-.13%). Interestingly, the four-way interaction Group by Time by Region by Laterality was significant ($F(1,26)=4.35$, $p<.05$; Figure 20).

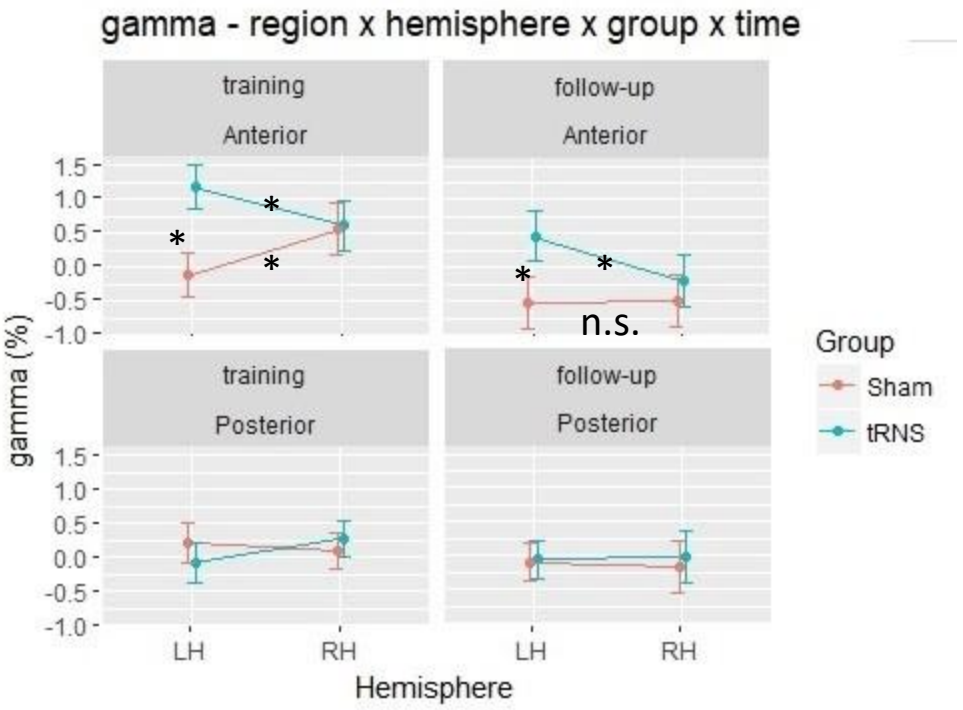


Figure 20. Four ways interaction, above anterior sites, below posterior sites.

Figure 20 revealed that the pattern found on anterior regions during the training effect (significant greater gamma % on right vs. left sites in sham participants, but on left vs. right sites in tRNS participants) was maintained one month after the training session only in the tRNS group, that exhibited significant greater left vs. right gamma % also in the long-term effect ($p<.01$). The sham group showed, at this time, a bilateral distributed gamma %. In addition, tRNS group showed significant greater gamma % on anterior left sites compared with sham group ($p<.001$ on both training and long-term effect).

No effect were found on posterior clusters of electrodes.

*Correlations between EEG and behavioral tasks*

A significant correlation between laterality index in delta (right minus left in anterior sites) and efficiency in predictable switch was found ($r(12)=-.63$, $p<.01$). Figure 21 shows the correlation.

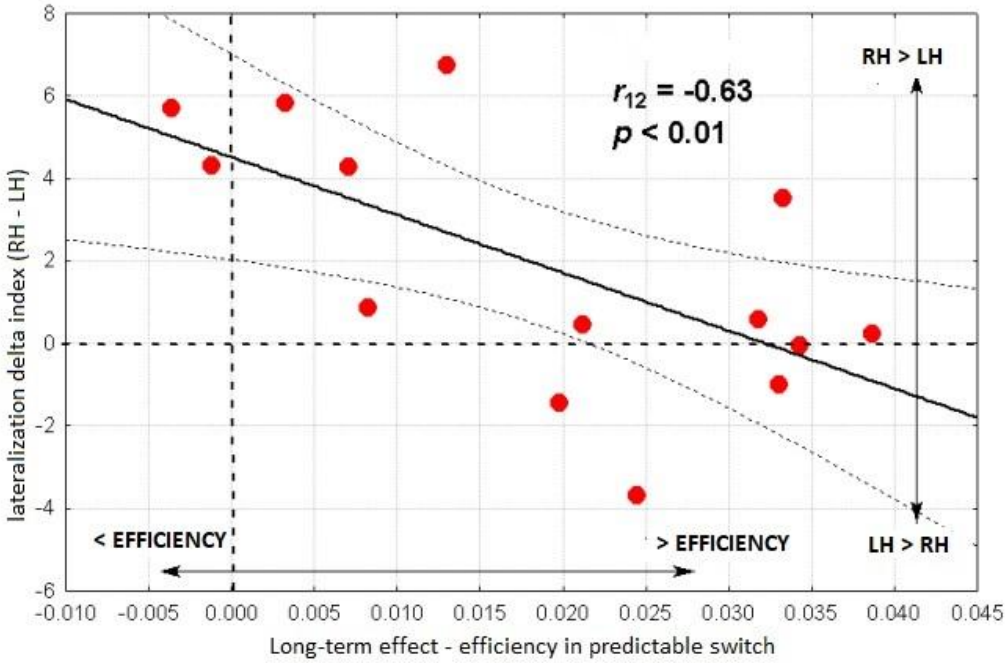


Figure 21. correlation between predictable switch efficiency and delta lateralization index.

Significant correlations were also found between laterality index (right minus left) for anterior sites in gamma after the end of the training and the dual costs for left stimuli ($r$(12)=-.59, p<.05) and the dual costs for right stimuli ($r$(12)=-.55, p<.05). See figure 22.

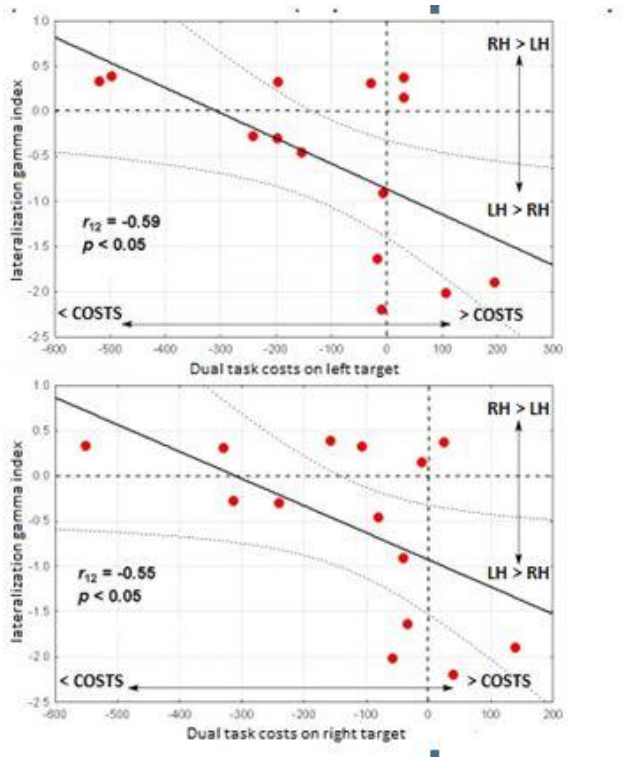

Figure 22. Correlations between lateralization gamma index and dual costs on left (above) and right targets (below).

A significant correlation was moreover found between gamma lateralization index (right minus left) in the follow-up and the dual costs on right targets ($r(12)=-.54$, $p<.05$), whereas on left targets it missed conventional significance ($r(12)=-.47$, $p=.08$). See figure 23.

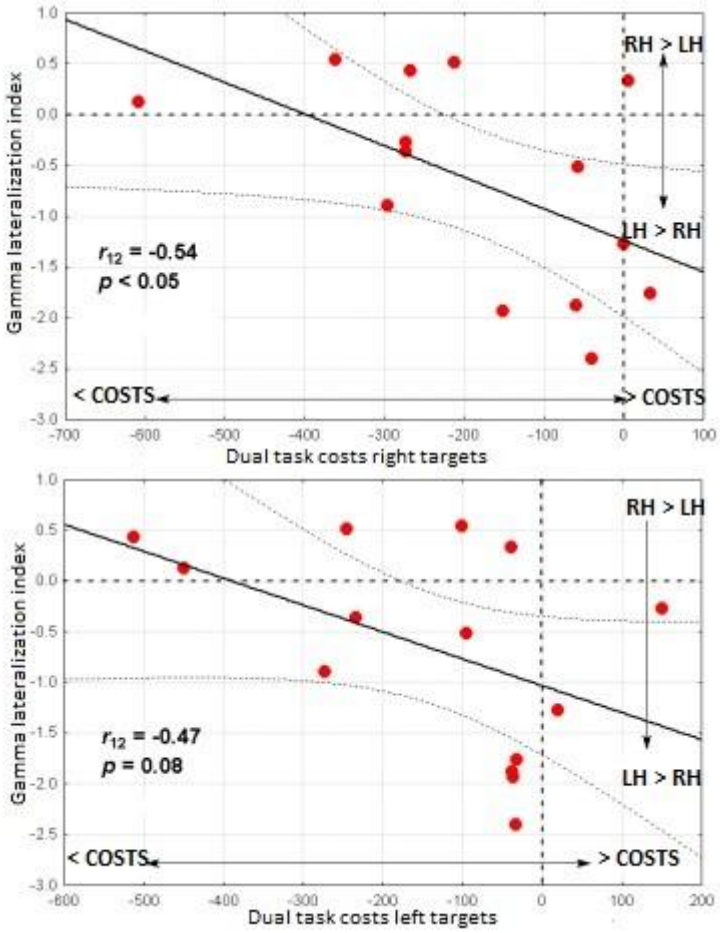


Figure 23. Correlation between gamma lateralization and dual costs in the follow-up, on right targets (above) and left targets (below).

## DISCUSSION

### *Effects on the behavioral training*

No effect of the stimulation protocol (tRNS vs. sham) on the behavioral training was detected. This lack of modulation might be due to the poor sensitivity of the training, which is not best suited for healthy participants but was developed for a clinical population, as confirmed by the strong correlations between baseline performance and amelioration through sessions. It is possible that no effect was detectable because of the ceiling effect reached after few minutes from the beginning of the training, which could make it impossible to detect changes at a behavioral level. We expected an offline modulation of the subsequent tasks, since mounting evidence shows that tRNS might be able to induce long-term changes in cortical plasticity, detectable also after some weeks (Cappelletti et al., 2013; Snowball et al., 2013). The combination of the stimulation with cognitive task or training might be also crucial to obtain long-lasting changes, generalizable changes (Harris, Miniussi & Ruzzoli, 2013). We tested whether our results were due to the presence of seven sessions distributed in two weeks, with a weekend between them, because some authors proposed that this design might introduce a confound on the effects of cognitive training (for a review, see Enriquez-Geppert et al., 2013). In this logic, we inspected the time course of the performance in the two groups, thus finding no different dynamic and confirming that performance of the two groups was almost identical. Our results confirm that a medium-difficulty task might be crucial to obtain reliable effects. Our results also suggest that the cognitive training administered was not sensitive enough to detect any change in our healthy, young participants and that an optimal training is required to have a sensitive index of how performance changes during the sessions.

Despite the absence of modulation in the present experiment, a strong, negative correlation has been found between intercepts and slopes for each participant. This means that the worse is the performance at the beginning of training, the stronger is the enhancement through the sessions. These results strongly support the purpose to extend our Labyrinth training to clinical populations showing impaired performance in executive functions or attention in order to evaluate possible short and long-term beneficial outcomes.

However, even in absence of online results due to lack of sensitivity in the task, one would expect that neural circuit would still be repeatedly activated, and the association with tRNS could boost this activation. This expectation is in line with our previous experiment showing that tRNS is able to induce long-lasting plasticity changes, and with part of the literature (Cappelletti et al., 2013; Snowball et al., 2013). Thus, we still expected offline, transfer effects on the other tasks administered and on EEG spontaneous oscillations.

*Effects of the training on the EEG*

EEG results are in line with the predictions we made. The comparison sham - control group clarified that, although no significant difference was present in gamma and delta EEG bands, a modulation of alpha rhythm was shown, possibly due to the training alone. This is possible primarily because an enhancement of alpha, i.e., an increased active inhibition was observed on the left anterior hemisphere, which might be due to the right anterior hemisphere activation. Literature have shown that alpha band often is modulated during attentional processes. For example, Kelly et al. (2006) and Worden et al. (2000) found that alpha activity increase over posterior sites contralaterally to the unattended location which could serve to suppress possible task-irrelevant information (those presented in an uninteresting portion of space). Other authors proposed that alpha might be linked to top-down, inhibitory control processes (Klimesch, Sauseng & Hanslmayr, 2007). Since our Labyrinth training was supposed to activate frontal right sites and executive functions, it is not surprising that a modulation of contralateral alpha band was found in sham group, and posteriorly in the right hemisphere. This modulation was not present in the tRNS group as well, thus confirming that the effect on alpha was probably due to the training alone.

On the other hand, a modulation of gamma and delta was found when inspecting the training and long-term effect, but was not found when comparing sham and control group as well, confirming an experimental, group-specific effect. Delta band revealed that the cortical inhibition was enhanced on the left anterior sites in sham group, while it was significantly lower in tRNS group. No difference was found on right hemisphere nor posteriorly. The results in sham group are consistent with alpha results, with a deactivation of left hemisphere, while in tRNS group it might indicate that a different pattern of activations is present, with a stronger activation of left anterior sites. Indeed, delta modulation is often associated to inhibitory processes, with an enhancement linked to deactivation of a certain neural circuit (Harmony et al., 1996; Harper, Malone & Bernat, 2014). Whereas a greater delta on left sites might indicate a more efficient right circuit in sham group, a significant difference with tRNS might indicate a more pronounced left activation in this latter group. Interestingly, this difference was still present after a month, indicating a possible long-term effect probably due to the stimulation itself. According with this interpretation, gamma modulation mirrored delta results, with a significant difference over the left and an opposite pattern in sham compared to tRNS. Immediately after the training, an enhancement in left anterior gamma was

found in tRNS group compared to sham, while no difference was detectable in the right hemisphere. The effect was still present after a month, with tRNS greater gamma on the left.
Gamma results are intriguing and might suggest a long-term, left hemisphere enhancement present only when participants were actively stimulated. Gamma modulation is often associated with high order top-down mechanism (Kaiser & Lutzenberger, 2005), but also spatial selective attention (Muller, Gruber & Keil, 2000) and motor tasks (Cheyne, Bells, Ferrari, Gaetz, & Bostan, 2008). Results in gamma are consistent with delta modulation, in an activation-deactivation logic.

While training alone seems to activate right frontal sites, but in a short-term way, as suggested by alpha modulation, coupling training with tRNS seems to boost contralateral left activity, as confirmed by delta and gamma opposite pattern. The long-term modulation tRNS group - specific, which lasted until a month after the end of the training support this interpretation. The dissociation found in the EEG modulation might be the sign that training alone and training + tRNS could have activated different cortical sites. While we expected a stronger or long-lasting activation of the same circuit involved in the Labyrinth training when associating tRNS, we found a very different pattern. Training alone probably modulated right hemisphere anterior sites, while training + tRNS activated contralateral hemisphere, the left, in a long-term way. The possible reasons for a left enhancement are twofold:

a. a possible contralateral activation due to inter-hemispheric mechanisms;

b. the effect of the right hand used to answer during all the duration of the training. We stimulated bilateral frontal sites, so a possible involvement of the left motor cortex is plausible.

Our results suggest that tRNS modulated in a long-term way gamma and delta band. This is consistent with literature showing that training coupled with tRNS induces long-term change in EEG signal (Snowball et al., 2013). However, it is important underline that the present research analyzed the EEG signal in a resting state condition, thus providing evidence of the impact on cortical activity of the combined mechanism of action of Labyrinth training and tRNS stimulation. The modulation of delta and gamma bands might be index that tRNS affect activation and inhibition neural circuits, inducing a simultaneous activation or deactivation of specific cortical sites. In particular, it is possible that the motor activation required by our training (continuous use of right hand) acted as an activator of left motor cortex, thus inducing a long-term modulation of these cortical areas. On the other hand, the behavioral training might have modulated short-term alpha on left cortex, probably necessary to suppress contralateral (left) activation to allow an efficient right

circuit involvement, consistently with previous results showing that Labyrinth training was able to activate right circuit.

*Transfer effects to other cognitive functions*

Only mild transfer effects were detectable on the tasks administered, probably because of the small power due to the number of participants (14 per group). In random task switching we found significantly faster RTs when comparing post-training and baseline and post-training- follow up sessions. Consistently, accuracy enhanced only in sham group through the sessions, while for tRNS group it remained constant, indicating that no speed accuracy trade off is present in this group which could explain a faster performance. In the single task, a better performance was shown in the follow-up session only in the tRNS group, even if a significant difference with sham was still present at baseline. Globally, tRNS group performance still improved in the follow-up session, while in sham group it did not. In dual task, we found a significant effect of the group on the secondary task accuracy (report the shape), both when unconditioned to main task success, but -more importantly-, when a success in the main task was recorded. These effects were specific for follow-up sessions, meaning that a continuous enhancement in the performance was shown in this group. In ANT task no effect was found, as well as predictable switch, probably because of the baseline difference between the groups.

It is possible that while no direct evidence coming from the training itself was found, circuit involved might be anyway activated, with a long-term effect on both behavioral tasks and EEG gamma band. The evidence coming from the EEG gamma and delta bands supports this hypothesis. (Cappelletti et al., 2013; Snowball et al., 2013).

DISCUSSION

Implications of our results are twofold. First of all, our study suggests that it is possible to induce a long-term effect on behavioral tasks and neural substrates even if no online effect is detected. Specifically, we speculate that our training was not sensitive enough to induce reliable performance changes in healthy participants, thus determining a ceiling effect and preventing any behavioral modulation. If this was the case, a cortical modulation might still be present in absence of clear results. This possibility is in line with studies showing that an optimal difficulty of the online task is required in order to obtain reliable effects (Miniussi, Harris & Ruzzoli, 2014). However, our

evidence seems to indicate that reliable, long-term neural modulation is still possible. Analysis of transfer tasks showed that a positive effect on dual, single, and unpredictable switch task was found in tRNS group, in particular when considering follow-up measures. In sham group, results indicate that our training alone was not able to induce long-term changes in behavioral outcome.

Secondly, although a reliable long-term modulation was found on EEG data, the direction of the effects was not as expected. Sham and tRNS groups showed opposite EEG patterns, with a significant alpha modulation consistent with a right hemisphere circuit activation in the former, and a significant delta and gamma modulation consistent with a left hemisphere circuit activation in the latter. Results suggest that although training alone activated right frontal circuit, involved in attention and executive functions mechanism, tRNS + training likely activated left frontal sites. This evidence is difficult to explain when considering stochastic interpretation of tES outcomes (Miniussi, Harris & Ruzzoli, 2014; De Berker, Bikson &Bestmann, 2013). Possible explanations of this unexpected pattern might be that bilateral tRNS activated bilaterally the frontal cortex, thus determining an inter-hemispheric dynamic.

An alternative possible interpretation is that an activation of motor cortex might be induced by the hand used to respond. This is likely because participants were instructed to perform the training with their right dominant hand, thus possibly inducing a contralateral motor sustained activation. If this was the case, our results might indicate that a proper motor training, coupled with tRNS, might be effective to induce a long-term plasticity effect over frontal cortex. Whether the behavioral effects found are due to a specific neural circuit activation or to an aspecific motor activation in tRNS group is still an open question. Several studies reported a better performance in working memory performance following left frontal stimulation (Ohn et al., 2008; Jo, Kim, Ko, Ohn, Joen & Lee, 2009; Andrews, Hoy, Enticott, Daskalakis & Fitzgerald, 2011) and attention (Boggio et al., 2007; Kang, Kim, & Paik, 2012). Here a possible left frontal enhancement as confirmed by EEG oscillations might have affected attentive and memory abilities by enhancing bilateral single task RTs, unpredictable switch RTs and the secondary task in dual task.

The results concerning the training-alone sham group suggest that Labyrinth was able to activate right-frontal circuit, but in a short-term way. In other words, although the expected right-frontal activation was achieved, the effect vanished in the longer term when training was not coupled with tRNS. It is important to point out that possible beneficial effects on clinical population have not been tested yet. Our results are encouraging and suggest that a proper training on clinical patients is

appropriate to evaluate possible positive effects on attentional and executive deficits. Moreover, further research coupling Labyrinth with tRNS with a different protocol, for exemple instructing participants to use the non-dominant hand, might induce the desired long-term activation of right-frontal circuit.

Overall, our results indicate that our training coupled with tRNS might not have been appropriate to activate the circuit we expected to. First of all, poor online sensitivity might have affected the lack of difference between groups during the training itself. However, an activation of right-frontal circuit might be expected because a right activation pattern seems to be present in the sham group. Probably, the hand used to respond (the right hand) coupled with a bilateral frontal cortex stimulation might have induced motor excitation instead of right hemisphere potentiation. If this was the case, our results might suggest that coupling tRNS with a proper motor training might be useful to induce a plasticity potentiation of one hemisphere thus acting on cortical balance. Whether a right potentiation might be induced by the proper use of our Labyrinth training in right-handers or not, is still an open question. However, results of sham group suggest that the cognitive training alone was still able to activate the right frontal cortex, but also that this activation was short-lasting if not coupled with tRNS stimulation. This is consistent with literature showing the effects of tRNS and training (Snowball et al., 2013; Cappelletti et al., 2013). The motor cortex activation due to the hand used to respond is also consistent with part of the tRNS literature (Terney et al., 2008).

Further research should be carried out to understand the precise effects of tRNS on cortical oscillations.

# CHAPTER 4

# GENERAL DISCUSSION

There is growing evidence that tES alone, administered during a given task, or coupled with learning task or training, can induce reliable modulatory effects. Many studies have focused on single session, single task effects thus neglecting possible side effects, or wider modulations, due to the stimulation. However, other studies applied tES during a learning task (for example, see Fertonani et al., 2011) or a -multi-session training assessing also possible transfer effects (for example, see Cappelletti et al., 2013).

However, analysis of the literature shows some gaps in tES research. For example, only one study to date investigated tDCS online and offline effects after a single session, even on tasks different from the ones administered during the stimulation. This was the case of Muquiney's (2011) work assessing the effects of anodal tDCS on working memory. Only two studies directly compared tDCS and tRNS effects: in their pioneering work, Terney et al. (2008) compared anodal tDCS and low and high frequency tRNS effects on motor functions, thus suggesting similar facilitatory effects for anodal tDCS and high frequency tRNS; Muquiney et al. (2011) found significant improvement in a n-back task following anodal tDCS coupled with Sternberg's working memory task. Technical analysis of tRNS effects are sparse in the literature as well. Moliadze et al. (2010) studied the effects of both tDCS and tRNS electrodes positioning finding that the distance between the two electrodes (active and passive or both active) correlated negatively with the duration and magnitude of induced after-effects. A recent work investigated the changes in cortical excitability before and after combined application of tRNS and a pharmacological agent, by means of single pulse TMS. The Authors found that tRNS aftereffects could be suppressed by benzodiazepine and seems to be not NMDA receptor dependent, suggesting that tDCS and tRNS effects might depend upon different mechanisms. Importantly, the involvement of mechanisms other than expected, or possible side effects due to the stimulation administration are critical in order to apply tES in rehabilitation (Iuculano & Cohen Kadosh, 2013).

This doctoral thesis aimed at shed light on some critical aspects of tES research. Specifically, three investigations were presented: the effects of cathodal tDCS on inhibitory functions (Experiment 1), the plasticity-induced effects of anodal tDCS or tRNS in a single session (Experiment 2) and the plasticity-induced effects of bilateral tRNS immediately after a seven-sessions training and after a

month (Experiment 3). The common aspect concerning the studies is the modulation of attentional or numerical functions by means of tDCS (anodal or cathodal), unilateral or bilateral tRNS.

Concerning Experiment 1, we expected an effect on inhibitory functions which could affect selectively only incongruent trials in both online task (dots comparison task) and offline task (Stroop task). Since the literature is inconsistent about the effects of cathodal tDCS in cognitive functions (Jacobson, Koslowsky & Lavidor, 2012), one could expect either detrimental or enhancement effects.

Experiment 2 was designed to investigate the possible transfer effects achieved in one session applying anodal tDCS or unilateral and bilateral tRNS on right posterior parietal cortex during a mental rotation task. This research investigated also the changes in resting state EEG immediately after the stimulation to correlate the possible changes in EEG signal with the behavioral outcomes.

Experiment 3 coupled a seven-sessions, executive functions training with bilateral tRNS over frontal regions, and investigated at the end of the training and after a month its effects both on cortical plasticity (as assessed with EEG recording) and on trasfer behavioral measures.

Globally, the results suggested several points of discussion regarding tDCS and tRNS potential in clinical application and possible unexpected effects.

First of all, our first research showed that 12 minutes of cathodal tDCS applied of rIFG is able to modulate selectively incongruent trials, but not congruent in a dots comparison task, thus suggesting a specific effect over inhibitory functions. Moreover, the effect was present only in the group who received the sham condition first. No reliable effect was detected in the Stroop task. This lack of effect might be due to wash-out of the immediate modulation of cathodal stimulation. Another possible explanation is that the tasks did not share common neural mechanisms, as suggested by baseline absence of correlation between the tasks.

Several conclusions can be drawn from this experiment. Firstly, it appears clear that a selective modulation of inhibition is possible using cathodal tDCS over rIFG. This conclusion is in line with previous research, showing that both cathodal tDCS on DLPFC (Penolazzi et al., 2014) and anodal tDCS on rIFG (Stramaccia et al., 2015; Jacobson et al., 2012; Jacobson et al., 2011) was able to induce effects on inhibitory functions.

Moreover, the effect was found only in one subgroup of participant. This is intriguing, because the only factor which differed between the subgroups was the order of administration of the conditions,

and no difference was found at baseline. A convincing explanation of the results might be the different experience with the tasks in the two groups. While in the stim-sham group the stimulation was immediately administered in the first session, with the only exception of the practice block, in the sham-stim group an entire session was administered before stimulating. Our data suggest that expertise with the task is required to induce effects using cathodal stimulation. This is consistent with literature showing that expertise is a basic condition to obtain effects with electrical stimulation (Berryhill & Jones, 2012; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Hsu, Tseng, Liang, Cheng, & Juan 2014; Learmonth, Thut, Benwell & Harvey, 2015; Tseng, Hsu, Chang, Tzeng Hung, Muggleton et al., 2012; Benwell, Learmonth, Miniussi, Harvey & Thut, 2015) and with the model of the optimal level of noise proposed to explain the different outcomes induced with stimulation (Miniussi et al., 2013). Finally, no online effect was detected, suggesting a delayed modulation induced by c-tDCS. Conversely, the lack of effects on the Stroop task might be due to possible different mechanisms involved in the task, as suggested by the lack of baseline correlation between Stroop and dots comparison task. However, this result is in contrast with previous studies (Cappelletti et al., 2013; Clayton, Gilmore & Iglis, 2015) An alternative possible explanation is that the stimulation effect might gradually disappear during time, thus determining no effect on the subsequent task. This is likely because no training was coupled with c-tDCS and it is well known that tDCS has short-lasting offline effects (Poreisz, Boros, Antal, & Paulus, 2007).

Experiment 2 was a direct comparison of anodal tDCS and tRNS effects on attention functions. Here we applied a somehow original design, since we administered the stimulation during a mental rotation task, while assessed its effects on tasks other, namely a landmark task and a cued detection task. Moreover, we recorded EEG signal both before and after the stimulation. The aim of the study was to assess possible offline effects induced by a single session design. Moreover, we aimed at comparing unilateral and bilateral montage in tRNS, since only one study to our knowledge implemented this manipulation (Moliadze et al., 2010) and found that the strength of the effect depended on the distance between the electrodes. From this study, we expected a stronger effect for bilateral tRNS than unilateral tRNS. The resting-state EEG could moreover show possible long-term changes in cortical excitability, which we expected in particular for tRNS based on the literature available (Chaieb et al., 2015). To our knowledge, this is the first study assessing the offline, transfer and plasticity effects of a single session of anodal tDCS, unilateral and bilateral tRNS on attention.

The results showed that bilateral tRNS was more prone at obtaining both online and offline, reliable modulation of cortical excitability. We found an online, even if mild, enhancement at different targets during the mental rotation task and an enhancement in landmark performance to both longer right and longer left targets. Consistently with the behavioral results, a modulation of high beta frequency and beta modularity index was found only in bilateraltRNS group, suggesting a specific modulation of this protocol. Anodal tDCS showed only a reliable, online effect on mental rotation task, but no offline effect, nor EEG modulation, consistently with previous research. A mild effect for unilateral tRNS group was found on longer right targets in the landmark task, probably due to the frontal activations due to the orbitofrontal electrode, which might have activated left and inhibiting right hemisphere thus facilitating right shifts. The lack of online modulation in unilateral tRNS group might be due to a delayed effect of this type of protocol. The difference in transfer effects between tDCS and tRNS is consistent with Chaieb et al. (2015) who found that the two techniques probably act on different neural mechanisms, showing consequently different offline effect.

Globally, the results confirmed that bilateral tRNS was a better tool in order to obtain offline, reliable results, even during only one session. Correlation analysis clarified that the change in beta band between sessions was associated to the change in performance, but only in the bilateral tRNS group. Specifically, greater post-stimulation Beta is associated to a better performance in landmark task. This evidence makes tRNS suitable for clinical rehabilitation. However, possible side effects of the stimulation might be induced, and more research needs to be done in order to better understand the possible unexpected outcomes (Iuculano & Cohen Kadosh, 2013).

Experiment 3 investigated the potential of bilateral tRNS when applied during an executive functions training. The hypothesis was that a long-term potentiation in the training outcomes was possible only if applying tRNS during the sessions, but not sham stimulation. We recorded EEG signal before, immediately after and a month after the end of the training.
The results obtained are somewhat unexpected. First, we found no effect of tRNS during the training. In other words, no online effect was detected. A deeper inspection of the results clarified that the task was not sensitive enough to show any change in the performance. After few minutes, participants reached the ceiling level and no enhancement was showed through the following sessions. We still expected offline results on the transfer tasks, since even if a lack of sensitivity was evident in the online task, a great effort might be possible in the participants even if no behavioral change was achievable. Consistently, we found behavioral effects on the transfer tasks.

In unpredictable task switching we found a significant improvement in reaction times for tRNS compared to sham group. Reliability of the results is confirmed by the simultaneous lack of effect on accuracy, which confirms that faster responses were not due to less accurate performance. Secondary task accuracy in dual task was significantly enhanced selectively for tRNS group Moreover, a significant effect of the group was still present in the secondary task when participants correctly reported the side of appearance of the target in the main task.. In single task, better performance was always present for bilateral, right and left targets compared to sham, but a significant difference in baseline between groups was also present. Interestingly, performance was faster in third session for tRNS group selectively in bilateral targets. which are the trials requiring greater attentional resources (Walker, Kentridge & Findlay, 1994; Fink et al. 2000).

A gamma and delta EEG modulation was found when inspecting the training and long-term effect, but was not found when comparing sham and control group as well, confirming an experimental, group-specific effect. Delta band revealed that the cortical inhibition was enhanced on the left anterior sites in sham group, while it was significantly lower in tRNS group. No difference was found on right hemisphere nor posteriorly. Moreover, in sham group an enhancement in left hemisphere alpha was found, indicating a deactivation of left hemisphere, while in tRNS group a stronger activation of left anterior sites is suggested. Indeed, delta and alpha modulations are often associated to inhibitory processes, with an enhancement linked to deactivation of a certain neural circuit (Harmony et al., 1996; Harper, Malone & Bernat, 2014). Interestingly, the only effects still present after a month were restricted to the tRNS group. Gamma modulation mirrored delta results, with a significant difference over the left and an opposite pattern in sham compared to tRNS. Immediately after the training, an enhancement in left anterior gamma was found in tRNS group compared to sham, while no difference was detectable in the right hemisphere. The effect was still present after a month, with tRNS greater Gamma on the left.
Gamma results are intriguing and might suggest that long-term changes were possible only when participants were actively stimulated, in line with previous studies (Cappelletti et al., 2013; Snowball et al., 2013). Gamma modulation is often associated with high order top-down mechanism (Kaiser & Lutzenberger, 2005), but also spatial selective attention (Muller, Gruber & Keil, 2000) and motor tasks (Cheyne, Bells, Ferrari, Gaetz, & Bostan, 2008). Results in Gamma are consistent with delta modulation, in an activation-deactivation logic.

While training alone seems to activate right frontal sites, but in a short-term way, as suggested by Alpha modulation, coupling training with tRNS seems to boost contralateral left activity, as

confirmed by delta and gamma opposite pattern. The dissociation found in the EEG modulation might be the sign that training alone and training coupled with tRNS could have activated different cortical sites. Despite the initial speculations, we did not find a stronger or long-lasting activation of the same circuit involved in the Labyrinth training when associating tRNS, but an opposite modulation. It is possible that motor response using the right hand enhanced the excitability of left frontal sites, crucially involved in our bilateral stimulation. This is in line with previous research on motor cortex (Terney et al., 2008) and suggests that a proper motor training coupled with tRNS might induce effects lasting even until a month.

On the other hand, the behavioral training might have modulated short-term alpha on left cortex, probably necessary to suppress contralateral (left) activation to allow an efficient right circuit involvement, consistently with previous results showing that Labyrinth training was able to activate right circuit. If this was the case, a proper training coupled with tRNS might induce a long-term activation in expected cortical sites, being also suited for clinical population. Further study will clarify whether a different stimulation protocol (i.e. with an extracefalic reference) is prone to induce a modulation of the right frontal circuit.

The implications of this last experiment are many. Firstly, our research suggests that a lack of online effects is not necessary linked to a failure in modulating cortical functions with tRNS. Moreover, tRNS effects might be still present a month after the end of the training. This encourages to extensively study the effects of tRNS during a training and find the optimal task in order to induce the desired cortical modulations.

Our research suggests that bilateral tRNS is a powerful tool, even if less studied, in order to induce long-term effects on cognitive functions. Coupled with a proper cognitive training, it might be effective to induce plasticity changes in normal and abnormal brain. However, further research has to be carried on in order to better understand all possible effects of tRNS. Similarly, cathodal stimulation might induce brief offline positive effects on inhibitory functions. Conversely, anodal tDCS seems to be more prone to one session experimental designs, since no offline effects was detectable in our research.

Globally, our studies suggest that tES is a powerful tool to modulate cognitive functions both in a single session or coupled with training. However, evaluation of the proper protocol iscrucial because different outcomes are possible depending on specific experimental features. For example, our research pointed out that anodal tDCS has online, but not after-effects, when a training is

lacking (study 2) compared to bilateral tRNS. On the other hand, cathodal stimulation applied when administering a dots comparison task is effective in obtaining facilitative after-effects, but not online effects (study 1). Consistently, bilateral tRNS applied for the total duration of Labyrinth training induced offline, long-term effects but did not modulate the training itself (study 3). To sum up, the take-home message is that tRNS, compared to anodal and cathodal tDCS, seems more effective in inducing long-term changes. Moreover, the facilitatory effect seems to be due to inter-hemispheric mechanisms, since no modulation was found in the unilateral tRNS group as well. In light of this speculation, we believe that bilateral tRNS might be the proper protocol to enhance cognitive training, even if our results are limited to healthy participants. Specifically, bilateral tRNS might be useful to strengthen cognitive training, possibly inducing long-term, generalizable changes. However, our results are not conclusive and further research is needed to shed light on this point.

Future directions

Although we believe that our results might be useful for future studies assessing the effects of tES on cognitive functions, we are aware that our studies present some limitations that warrant further investigation. As we discussed throughout the thesis, individual differences are crucial in order to obtain reliable effects with tES. As consequence, it is possible that our results might be due to the specific population investigated, that is, university students. New studies based on participants from different cultural contexts are therefore necessary to generalize the present results. Similarly, participants of our experiments were all young, healthy subjects, thus making it impossible to extend our results to older adults or to clinical populations. Moreover, different protocols and parameters should be tested to investigate the proper stimulation method in order to maximize the effect of tEs. This point seems to be particularly important since despite the great potential of Labyrinth training, alore or coupled with tES, to date no study investigated its impact on clinical populations. For this reason, we do believe that a next important step in our research might be the extention of Labyrinth to a clinical population, in particular neglect patients, in order to investigate the baseline effect of training (i.e. without stimulation), and finally evaluate possible effect of the combination with tRNS.

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# APPENDIX

CRITERI DI ESCLUSIONE ESPERIMENTI CON tES (tDCS, tRNS, tACS)

Gentile partecipante, per poter prendere parte all'esperimento è necessario che ci assicuriamo che Lei sia idoneo a partecipare. Le chiediamo di compilare il presente questionario.

1. Le capita di avere di frequente severi mal di testa (almeno due volte a settimana)? SI NO
2. Ha avuto eczemi e/o dermatiti sul cuoio capelluto negli ultimi sei mesi? SI NO
3. Ha allergie a particolari materiali? SI NO
4. Se sì, quali? _____
5. Ha una storia di epilessia o aver avuto in passato episodi epilettici? SI NO
6. Ha parenti di primo grado (padre, madre, fratelli, nonni, zii) con una storia di epilessia? SI NO
7. Ha sofferto di disturbi neurologici? SI NO
8. Ha mai ricevuto una diagnosi di trauma cranico? SI NO
9. Presenta inserti metallici o clip chirurgiche nel capo oppure nel collo? SI NO
10. Ha mai subito interventi al capo oppure al collo? SI NO
11. Ha problemi cardiaci o dispositivi cardiaci (ad es. pacemaker)? SI NO
12. Ha protesi acustiche? SI NO
13. Ha mai fatto uso di psicofarmaci (ansiolitici, antidepressivi, neurolettici, stimolanti)? SI NO
14. Ha mai sofferto di attacchi di panico, di claustrofobia o di disturbi d'ansia? SI NO
15. Per le donne: sospetta un possibile stato di gravidanza? SI NO

NOME E COGNOME (in stampatello): _____

DATA DI NASCITA:_____

INDIRIZZO E-MAIL:_____

FIRMA:_____

**Codice Partecipante:_____ Data: _____**

**Esperimento/Sperimentatore: _____**

Che sensazione ha percepito durante la stimolazione elettrica? Risponda alle seguenti domande indicando il grado di intensità con il quale ha percepito ognuna delle sensazioni indicate, utilizzando una scala come la seguente:

- ***Nessuno*** **= non ha avvertito alcuna sensazione del tipo descritto**
- ***Lieve*** **= la sensazione descritta è stata appena avvertita**
- ***Moderato*** **= la sensazione descritta è stata avvertita**
- ***Abbastanza*** **= la sensazione descritta è stata avvertita in grado considerevole di intensità**
- ***Molto*** **= la sensazione descritta è stata avvertita come forte**

Durante le sessioni di stimolazione ha percepito:

Prurito: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Dolore: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Bruciore: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Calore: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Pizzicore: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Sapore ferroso: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Affaticamento: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Altro_____: □ Nessuno □ Lieve □ Moderato □ Abbastanza □ Molto

Quando sono insorte le sensazioni? (può indicare più di una risposta)

□ All'inizio □ Verso la metà del blocco □ Alla fine

Per quanto tempo sono durate?

□ Sono subito svanite □ Sono svanite verso la metà del blocco □ Verso la fine

Quanto le sensazioni provate hanno influenzato la qualità della Sua prestazione?

□ Per nulla □ Poco □ Abbastanza □ Molto □ Moltissimo

Se lo ritiene opportuno, descriva brevemente le sensazioni da Lei provate riguardo a:

- Prurito:
- Dolore:
- Bruciore:
- Calore:
- Pizzicore:
- Sapore ferroso:
- Affaticamento:
- Altro:

Pensa di essere stato/a sottoposto/a a reale stimolazione oppure a una sua simulazione?

- ☐ STIMOLAZIONE REALE
- ☐ SIMULAZIONE DI STIMOLAZIONE