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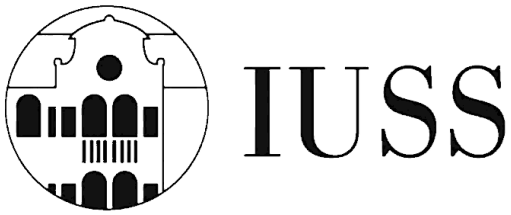

Comparing the Effectiveness of Anodal High-Definition-tDCS versus Bipolar tDCS Montages in Modulating Inhibitory Control: An Experimental Study

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ABSTRACT

Transcranial Direct Current Stimulation (tDCS) have acquired a great relevance in the neuropsychology field over the last decades. Nowadays, various configurations improved its efficacy, such as the High Definition -tDCS (HD-tDCS) montage, which allows a more focus and precise modulation over cortical regions, leading potential advantages in rehabilitative programs and experimental settings. However, direct evidence comparing the efficacy of HD-tDCS to the conventional bipolar tDCS in modulating cognitive function remains limited. For this reason, the present study aims to compare the effectiveness of bipolar tDCS and HD-tDCS in modulating inhibitory control. Experimental procedure involved three sessions, with anodal stimulation (2 mA; 20 min) for both the active conditions (bipolar, HD-), and one sham condition. tDCS was applied to the right Inferior Frontal Gyrus (rIFG), a region implicated in inhibitory control, with robust evidence about its involvement in the Stop Signal Task (SST). In parallel, the Double Response Task (DRT) was used as a control condition to disentangle tDCS effects on non-inhibitory action updating from "pure" inhibitory control. Preliminary results reported no differences between the experimental conditions, contrary to prior literature. This discrepancy may be attributed to the intrinsic variability of tDCS, from parameter settings differences between protocols to the interindividual variability in response to stimulation.

Keywords: bipolar tDCS; HD-tDCS; inhibitory control; rIFG; SST; DRT.

1. INTRODUCTION

1.1 Background

1.1.1 NIBS

Non-Invasive Brain Stimulation (NIBS) techniques encompass a range types of tools and instruments to stimulate and modulate the cortical neuronal activity, using non-invasive methodologies (Antal et al., 2022; Kesikburun, 2022; Liew et al., 2014). For this reason, NIBS techniques acquired a notable importance over the last decades, both for their application in experimental settings (Kuo & Nitsche, 2012) and in the field of clinical neuropsychology (Antal et al., 2022; Hara et al., 2021; Kesikburun, 2022; Liew et al., 2014). In the last 25 years, the number of publications regarding NIBS has grown exponentially, as shown in Figure1, as well as their specific application to motor stroke rehabilitation (Liew et al., 2014). This growing interest could be related to the versatility,

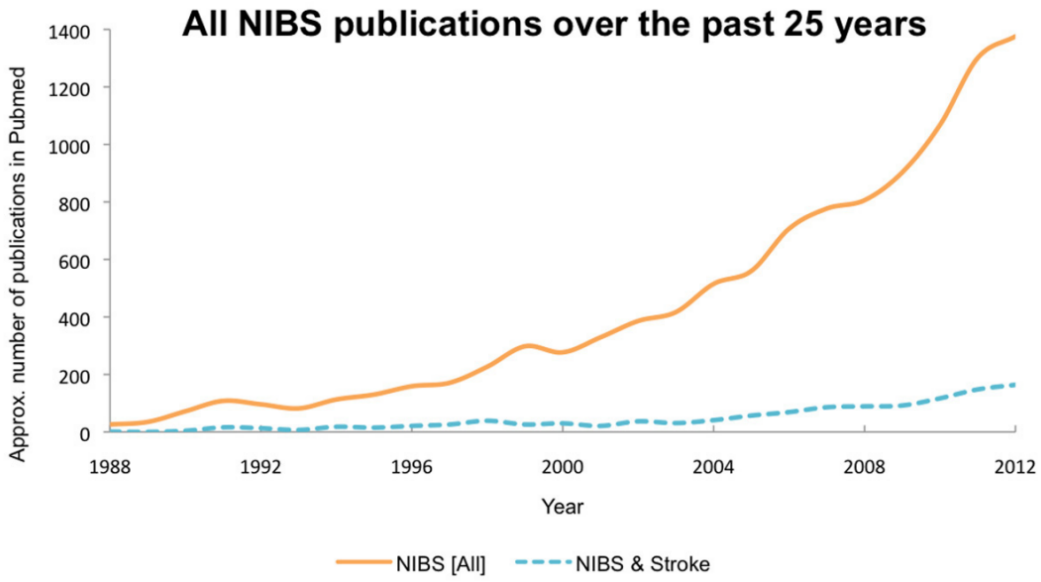

Figure 1 The orange line represents the number of publications on NIBS techniques from 1988 to 2012. The light blue line refers to the increase of studies about NIBS application on stroke treatment (Liew et al., 2014).

efficacy and safety properties of NIBS techniques, and for their excellent ratio between benefit and risk (Lefaucheur et al., 2017).

As illustrated in Figure 2, there are several types of NIBS techniques, each utilizing distinct methodologies to modulate neuronal activity. A primary distinction within NIBS techniques can be made between Transcranial Magnetic Stimulation (TMS) and Transcranial Electrical Stimulation (tES) techniques. TMS utilizes the application of magnetic fields to affect neuronal activity, whereas tES relies on the application of electrical fields for the same purpose (Kesikburun, 2022). TMS techniques includes Single-Pulse TMS, Paired-Pulse TMS, Repetitive TMS (rTMS), and Patterned rTMS. Conversely, tES techniques encompass tDCS, Transcranial Alternating Current Stimulation (tACS), and Transcranial Random Noise Stimulation (tRNS) (Liew et al., 2014; Kesikburun, 2022).

Furthermore, a distinction can be made basing on the type of stimulation, distinguishing *neurostimulation* from *neuromodulation* techniques. The former directly elicit neuronal activity by inducing neuronal firing, such as Single- and Paired-Pulse TMS. Therefore, these techniques are considered to establish causal role between the stimulated area's activity and the motor, sensorial or cognitive function outcome,

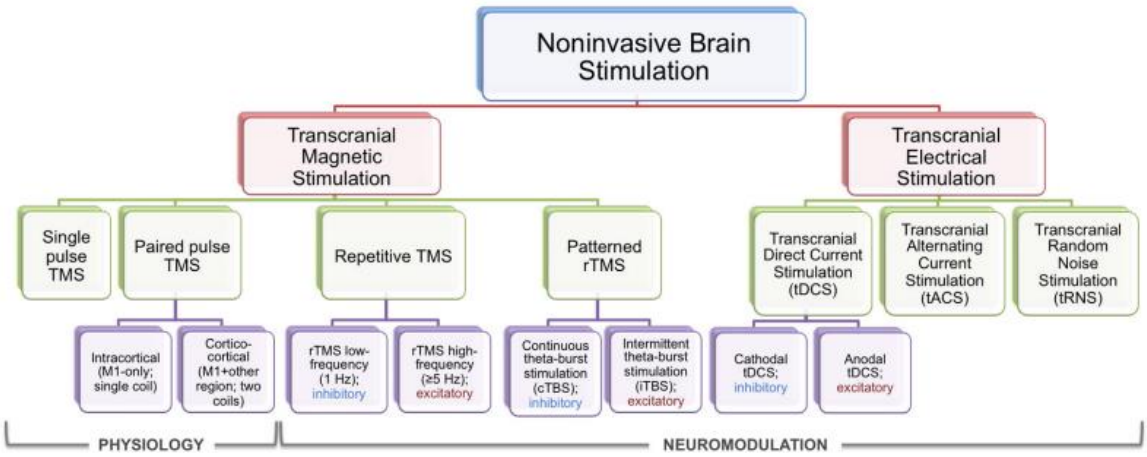

Figure 2 Different types of NIBS description and subdivision based on the function and type of tool implied (Liew et al., 2014).

resulting in TMS being applied in clinical assessment (Kesikburun, 2022; Liew et al., 2014). In contrast, neuromodulation techniques alter and modify the level of neuronal excitability, rather than directly inducing action potentials, such as rTMS, patterned rTMS and tES techniques. For instance, tDCS induces changes in spontaneous cortical activity by modifying the transmembrane neural potential without directly eliciting action potentials. Hence, these techniques can only establish a correlation between the altered activity and the stimulated brain areas. However, evidence highlights their significant roles in cognitive enhancement and therapeutic interventions (Antal et al., 2022).

Even for this reason, NIBSs are applied across various fields of neuropsychology, since they enable to investigate several component of neuronal functioning and the integrity of cortical brain regions with a reliable outcome, non-invasive application and moderate costs (Antal et al., 2022; Kesikburun, 2022; Lefaucheur et al., 2017). For instance, a prominent role of NIBS is present in neuropsychological assessment of motor cortex integrity, through Transcranial Magnetic Stimulation (TMS) application (Kesikburun, 2022), and even in after stroke and post traumatic events rehabilitation (Kesikburun, 2022; Lefaucheur et al., 2017). Additionally, the available evidence support the recommendation of NIBS techniques in treating neuropsychological disorders, as in the case of patients with chronic pain and fibromyalgia, with a reported reduction of the disorders symptomatology and an increase in life quality (Lefaucheur et al., 2017) following tDCS over the primary Motor Cortex (M1). Notably, tDCS over the Dorso Lateral PreFrontal Cortex (DLPFC) has been reported with a recommendation of level B (probable efficacy) in psychiatric disorders, as in non-drug resistant Major Depressive Disorder (MDD) and addiction treatment (Lefaucheur et al., 2017). In the same vein, repetitive-TMS (rTMS) obtained a recommendation of level B for bipolar depression treatment, as integration in the therapeutic strategy (Hsu et al., 2024). In addition, NIBS techniques are acquiring a prominent role in experimental neuropsychology, since they

allow to assess the possible enhancement and alterations of cognitive functions, both in clinical and healthy population (Antal et al., 2022). For example, tDCS seems to lead to an improvement of working memory, learning, and long-term memory in healthy subjects (Kuo & Nitsche, 2012).

1.2 tDCS Functioning

1.2.1 tDCS Instrumental breakthrough: Components and Structures

tDCS is a neuronal modulation technique that delivers a two-polarity low-intensity Direct Current (DC) via two electrodes directly positioned over the scalp. Anode has the positive polarity, while cathode has the negative polarity (Antal et al., 2022; Kesikburun, 2022; Liew et al., 2014). The tDCS's low amplitude current is delivered by a 9-volt (Russo et al., 2017) battery-powered DC generator (Liew et al., 2014), which is connected to the electrodes by two wires, red and black, which usually are respectively related to the anode and the cathode. The electric flow is always from anode to cathode (Kesikburun, 2022), and the direction of current plays an important role to facilitate or inhibit the neuronal activity, which also depends on the orientation of neuronal cells (Paulus, 2003). Conventionally, the neuromodulation effect is reported to be excitatory with anodal stimulation, and inhibitory with cathodal stimulation, so defining the anodal-excitation/cathodal-inhibition effect (AeCi) (Bindman et al., 1964; Nitsche & Paulus, 2000; Paulus, 2003; Priori et al., 1998). Although the AeCi dualism is consolidated for the motor stimulation, it is not present in non-motor domains, e.g., cognitive functions (as reported in chapter 1.3.1; Jacobson et al., 2012). Since the neuromodulation effect is polarity-dependent, and the current flow has always the same spread direction from negative polarity to positive polarity, the '*active'* electrodes is considered to be the one on the target region, where the stimulation must be applied, while the '*reference'*

electrodes is on a different position (Lerner et al., 2021; Liew et al., 2014). Based on where 'reference' electrodes are positioned, they can be 'cephalic', when the electrode is on the scalp, generally placed over the contralateral supraorbital region (Kesikburun, 2022), or 'extra-cephalic', when the electrode is positioned not on the scalp, but on another region of the body, e.g. on the subject's shoulder, arm or leg (Liew et al., 2014). Therefore, in presence of anodal stimulation the anode will be the 'active' electrode, positioned on the target area, defining an excitatory neuromodulation that facilitates the neuronal firing by decreasing the membrane potential of stimulated neuronal population. At the same time, in case of cathodal stimulation the cathode will be the 'active' electrode, decreasing action potential excitability of targeted brain regions (Kesikburun, 2022; Lefaucheur et al., 2017; Paulus, 2003). For this reason, the 'reference' electrode can affect the underlying neural tissue, hence its position should be carefully chosen and it is essential for avoiding unwanted additional effects of the stimulation (Bjekić et al., 2021).

The main variables for the tDCS after-effects are the intensity and the duration of the stimulation (Lefaucheur et al., 2017). In experimental and clinical neuropsychological application, the current intensity is usually between 0.5 mA to 2 mA (Kesikburun, 2022; Lerner et al., 2021; Liew et al., 2014), with a variable duration, since prolongation of stimulation period proportionally increases the after-effect duration (Nitsche & Paulus, 2000; Paulus, 2003). Typically, neurostimulation lasts between 10 and 30 mins (Jacobson et al., 2011; Kesikburun, 2022), where also a short duration, at least 3 minutes, can induce after-effects (Bindman et al., 1964; Nitsche & Paulus, 2000; Priori et al., 1998). The variations in time exposure to DC directly influence the after-effects period on the motor cortex, as seen by Nitsche & Paulus (2000), and at the same time M1 excitability changes became steadily significant after the end of tDCS application, rather than during stimulation (Santarnecchi et al., 2014). In contrast, the increase of intensity is not directly

related to tDCS efficacy, since DC intensity increase may shift the direction of stimulation effect, for example the doubling of the intensity from 1mA to 2mA can switch the cathodal inhibition procedure into M1 excitatory effect (Batsikadze et al., 2013). This effect could be related also to the cognitive domain, since cathodal-inhibitive effects are not usually present and one of the main reason could be the high mA level used (Schroeder et al., 2020). In addition, the intensity increasement induces a deeper stimulation and spread of electric fields into the brain, which could modulate different neuronal networks not related to the target areas, resulting in biological and clinical unexpected effects (Lefaucheur et al., 2017), as seen in the bilateral tDCS montage reported below.

1.2.2 tDCS Montages

Conventionally, electrodes in tDCS paradigms are placed according to the 10-20 EEG system, a simply and low-cost method (De Witte et al., 2018; Rich & Gillick, 2019). This procedure utilizes a 10-20 EEG cap that is centered on the subject head, through the measure of the middle point between the nasion and the inion, respectively the starting and ending point of the skull, and between the preauricular points; then the electrodes will be positioned on the cap reference points (De Witte et al., 2018). However, this method may not consider the inter-individual variability of subjects' neuronal structures, which in turn could lead to unexpected cortical excitability effects not focused on the target area (De Witte et al., 2018). Therefore, these limitations can be reduced by the combined use of Magnetic Resonance Imaging (MRI) and Neuro-navigation, in order to address the precise subject's target region location and brain structure; however, this procedure is not commonly used in literature, due to its expensive cost and experimental procedure complexity (De Witte et al., 2018; Lee et al., 2023). To limit these issues and to obtain a better stimulation outcome, over the last decades, MRI images are used to define *computational modeling of electrical fields*, a simulation of current spread on the

participants brain, which predict the spread of electrical field based on the skull impedance and cerebral structures. This simulation allows to assess if the target area could be stimulated in a correct fashion and the possible undesired effects, through different software (e.g., ROAST, SimNIBS) based on a common procedure, in which the MRI image is segmented in multiple layers, and the conductivity of each compartment is calculated, defining a *Finite Element Model* (FEM). Subsequently, virtual electrodes are applied to FEMs, showing the pattern of current spread (Huang et al., 2019).

The selection of electrodes placement should be defined by the type of montage chosen, since there are different types of setups, which may imply more than two electrodes and one DC battery-driven device during the stimulation. Hence, an important role in paradigm definition is the choice of the montage, since a single variation in the electrodes configuration, size, shape or placement could modify the DC diffusion pattern into the brain (Lefaucheur et al., 2017; Liew et al., 2014).

The conventional tDCS montage is the most reported in literature and it utilizes two sponge-enclosed rubber electrodes with an area of 20–35 cm^2 (Datta et al., 2009; Liew et al., 2014), using a single tDCS battery-driven device with two electrodes, one cathode and one anode. This montage could be *Bipolar* or *Monopolar*. Monopolar configurations use the 'active' electrode positioned on the target area, while the 'reference' electrode" is positioned on an extra-cephalic position. The Bipolar montage have both the anode and cathode positioned on the subject's scalp (Liew et al., 2014). The Bipolar montage, despite the consistent and reliable evidence in the literature, may define a spread stimulation on the cerebral cortex, since both electrodes affect the underlying neuronal regions; therefore, the Monopolar montage attempt to avoid this problem (DaSilva et al., 2011). At the same time, the Bipolar configuration may be *Unilateral* or *Bilateral*. Unilateral tDCS montage utilizes the 'active' electrode on the target region and the 'reference' electrode over the contralateral supra orbital region. Whereas in Bilateral

tDCS the ‘reference’ is positioned to the related contralateral brain area respect the ‘active’ electrode, e.g., anode on left M1 and cathode on right M1 (Halakoo et al., 2020), as reported in Figure 3 (Gorsler et al., 2022). These set-ups report different effects on cerebral stimulation, due to the different properties of the current flow (Halakoo et al., 2020).

Another method to solve the aforementioned issues could be the *High-Resolution* or *High-Definition* (*HD*) set-up, which improve the control of current flow on the target regions compared to Monopolar and Bipolar montages (Datta et al., 2009; Lerner et al., 2021; Liew et al., 2014), thanks to its smaller and usually circular shape electrodes which allows to have a better focality on the investigated region (Datta et al., 2009). At the same time, there are different types of *HD-tDCS* montages, as usually they have multiple anodal and cathodal electrodes on multiple target sites, using more than one DC generator (Lerner et al., 2021; Liew et al., 2014). Nevertheless, the ‘4 x 1’ set-up is the most common and used in literature so far (Edwards et al., 2013; Kuo et al., 2013; Parlikar et al., 2021), where the active electrode is positioned on the target region and the others four

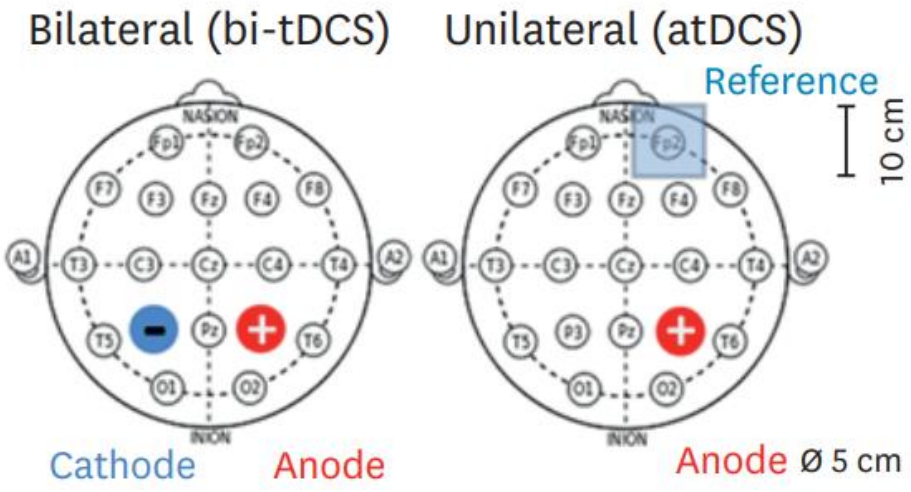

Figure 3 Bilateral tDCS and Unilateral tDCS montage. In Bilateral tDCS the 'reference' electrode is on the respective contralateral position of 'active' electrode. Unilateral tDCS set-up uses the 'reference' electrode on the contralateral supra orbital region (Gorsler et al., 2022).

reference electrodes are positioned around it forming a square shape, as shown in Figure 4. This montage allows to have a better control of current flow on the target areas, avoiding the effects accounted by the opposite polarity electrodes (Datta et al., 2009; Kuo et al., 2013), although it does not eliminate completely the confounding spatial distribution of the current (Lerner et al., 2021).

Moreover, an additional and less indagated configurations is the Concerns Electrode tDCS (CE-DCS) montage, a variant of the HD-tDCS set-up which utilizes only two electrodes, one small and one large circle electrode, as shown in Figure 5. The active electrode is positioned over the target area and with a predetermined distance a circle shape electrode is around it, working as reference (Bortoletto et al., 2016). The computational modeling of electrical fields about CE-tDCS montage is similar to the HD-tDCS configurations simulating electrical spreading priorities, showing also a significant neurophysiological effect: MEP (Motor Evoked Potential) amplitudes (Bortoletto et al., 2016).

Finally, tDCS effects show a high interindividual variability, depending on the

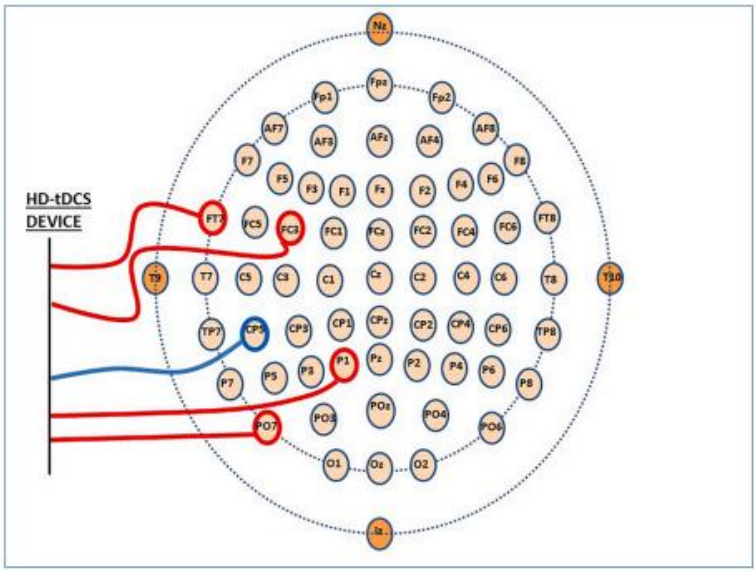

Figure 4 Illustration of HD-tDCS montage configuration with central cathodal current at the temporo-parietal junction (TPJ) and four anodal electrodes around the active electrode forming the typical square shape (Parlikar et al., 2021).

stimulated tissues activity (Hunold et al., 2023; Liew et al., 2014). Indeed, based on the electrodes position on the scalp and the anatomical conformation of the head, electric fields can influence different brain regions in a different fashion, even though they are positioned in the same subjects' target area (Datta et al., 2009; Kesikburun, 2022). This derives by the fact that the current flow, in all transcranial electrical stimulations, is influenced by a convergence of factors, including: the electrodes separation-distance defined by the scalp shunting, the brain surface morphology, as well as the differences in tissue conductivities, such as skull thickness, presence of sutures or scars, and eye cavities; differences in conductivity beneath the scalp, such as cerebrospinal fluid high conductivity channels (Datta et al., 2009). For these reasons, current flow simulation models combined with structural MRI images of each participant can limit the confounding factors, allowing a more precise stimulation of the required areas, even assessing the possible undesired stimulated brain regions.

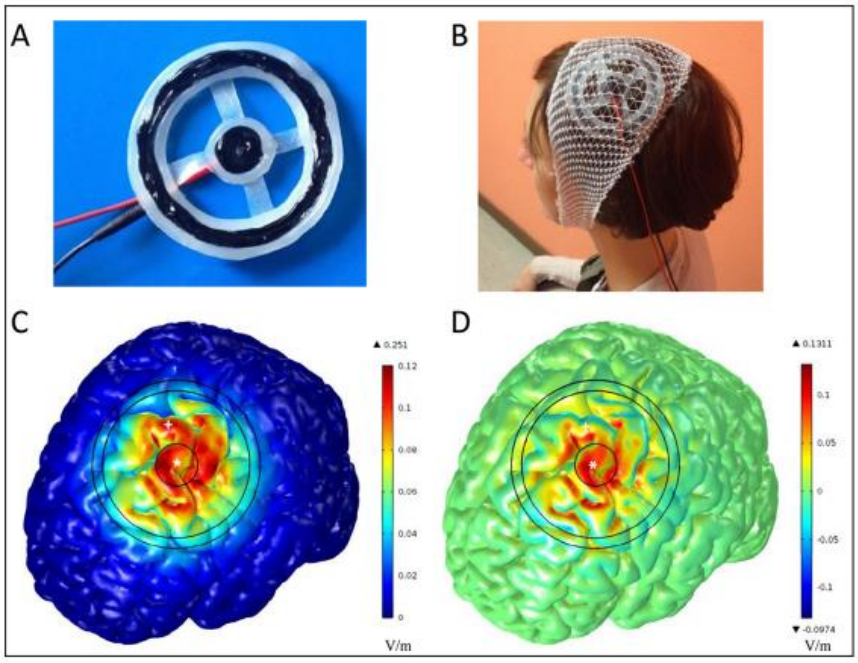

Figure 5 (A) Overview of the concentric electrodes (CE-tDCS) configuration and the distribution of the electric field magnitude (C) and of its normal component (D) on the cortical surface. The normal component flows into the cortex under the anode (red) (Bortoletto et al., 2016).

1.2.3 tDCS Neurofunctional Modulation: Basis and Functioning

The primary effect of tDCS on neurons activity is not to induce an action potential and the relative neuronal firing, as elicited by TMS, but it defines a subthreshold modification of cortical neurons resting membrane potentials. This modulation results by the membrane depolarization or hyperpolarization, which respectively enhance or decrease the neuronal firing, depending on the direction of the current flow relative to the axonal orientation (Bindman et al., 1964; Lefaucheur et al., 2017; Liew et al., 2014; Nitsche & Paulus, 2000; Priori, 2003). The alterations of resting membrane potentials represent the crucial mechanisms of the DC-induced after-effects, in which axon terminals are two or three times more susceptible than somas to the electric fields (Liebetanz et al., 2002). However, the tDCS modulatory effect on the brain is complex, since the influence depends by the distance and orientation of the axonal and dendritic axis with respect to the electric field (Lefaucheur et al., 2017). Evidence from comparative neuroscience shows how axonal orientation may determine the inhibitory or excitatory effect of stimulation, whereas dendritic orientation could affect only the magnitude of the DC resulting effect (Kabakov et al., 2012). Nevertheless, nowadays findings on tDCS applications in experimental setting primarily derive by current flow simulation models, which show how the type of stimulation, inhibitory or excitatory, spreads through and affects different neuronal populations (Huang et al., 2019). Indeed, these models have a main role in tDCS configuration and procedure since several components of brain anatomy and the type of stimulation affect the electric filed spread. For example, the application of cathodal stimulation on the surface of a gyrus seems to activate mainly the horizontal axonal and dendritic fibers that are parallel to the electrode surface, while on the contrary neuromodulation from anodal stimulation elicits more the perpendicular fibers compared to the electrode position (Holsheimer et al., 2007). In addition, the current direction is dramatically influenced by the pattern of sulci and gyri in the

stimulated area, where idiosyncratic differences in cortex anatomy across subjects may thus produce distinct patterns of current flow and hence neuromodulation (de Berker et al., 2013). Moreover, another relevant process in tDCS after-effects is the non-synaptic mechanism, where the membrane potentials changes persist along all the axon and not only at the synaptic cleft level, supporting the maintenance of the modulation effect during time (Ardolino et al., 2005). However, the resulting physiological effect of the stimulation depends on whether the affected network is dominantly inhibitory or excitatory (Lefaucheur et al., 2017), enhancing or decreasing its typical functioning. Additionally, the DC-effect is affected even by another significant aspect, the 'meta-plasticity' concept, which defines how the synaptic baseline elicits a relevant influence on tDCS outcomes, as reported by the "Bienenstock–Cooper–Munro (BCM) model" (Bienenstock et al., 1982). This theory consider that the neuronal activity influences the DC modulation effects, since synaptic depression occurs more in presence of a higher postsynaptic activity, whereas synaptic potentiation is more likely occurring when postsynaptic activity is low. Evidence supports this model, showing plasticity differences induced by tDCS between the application of the DC in a passive situation, when subjects are relaxed, or in an active condition, during the performance of a motor task (Antal et al., 2007). Finally, tDCS effects can influence also other non-neuronal tissues in the brain, since all tissues and cells are sensitive to electric fields, including endothelial cells, lymphocytes, or glial cells (Ruohonen & Karhu, 2012). These non-neuronal effect could be related to therapeutic action of tDCS in patients with cerebral diseases, for instance motor stroke rehabilitation, and other important pathological inflammation processes in the axonal microenvironment, e.g., sclerosis and Alzheimer's Disorder (AD) (Lefaucheur et al., 2017).

Since the initial findings on DC stimulation, tDCS neuronal functioning modulations and after-effects have been supposed to be related to cortical excitability modifications,

due to neuronal polarizations alterations (Elbert et al., 1981; Nitsche & Paulus, 2000; Priori, 2003; Rosenkranz et al., 2000), although the underlying mechanism and neurophysiological processes involved in these changes are still debated (Antal et al., 2022; Liew et al., 2014; Stagg & Nitsche, 2011). Reliable evidence about the tDCS neurophysiological and neurochemical mechanisms alterations derive by pharmacological trials, both on humans and animals (Nitsche, Fricke, et al., 2003). These experiments in the administration of a specific drug allows to understand the entailed mechanism in the tDCS long lasting effects. Indeed, a prominent study conducted by Liebetanz et al. (2002) was the first to delve into the mechanisms related to membrane potential changes in human subjects, since a blocking voltage-dependent calcium channels (Na^+-channels) drug, Carbamazepine, defined an elimination of anodal after-effects on motor cortical excitability for the stabilization of voltage-dependent membrane potential. These results demonstrated how excitatory effects of anodal tDCS derives by a membrane potential depolarization (Liebetanz et al., 2002), supporting the first neuromodulation theorizations. Further studies replicated the Carbamazepine effects and showed the same anodal effects suppression from the intake a N-methyl-D-aspartate (NMDA)-receptor antagonist, Dextromethorphan, and a calcium-channel (Ca^+-channel) blocker, Flunarizine (Nitsche, Fricke, et al., 2003). Moreover, the study conducted by Liebetanz et al. (2002) found even a Dextromethorphan suppression effect both in anodal and cathodal DC stimulations. This evidence underpins the main role of membrane polarization changes in tDSC after-effects, related to the magnitude of polarization, the Na^+-channels and Ca^+-channel conductance modifications (Liew et al., 2014), as well as a crucial involvement of NMDA-receptors activity in neuronal modulation. Indeed, other studies report an increase in the effects of anodal stimulation after the administration of a partial NMDA agonist D-cylcoserine (Nitsche, Jaussi, et al., 2004), corroborating the NMDA role in DC-induced effects. These data support the idea that the duration of

anodal-mediated excitability enhancement may be under the control of glutamatergic mechanisms. Furthermore, a magnetic resonance spectroscopy (MRS) study reports how excitatory stimulation produces a local reduction of GABA concentration, while inhibitory tDCS results in a diminished glutamatergic neuronal activity with a highly correlated GABA reduction (Stagg et al., 2009), due to the close biochemical relationship between the two neurotransmitters. Therefore, tDCS neuronal modulation could derive by the modification of calcium-dependent glutamatergic neurons activity, due to an alteration of NMDA-receptors functioning and for an alteration of GABA level in this neurophysiological changes (Antal et al., 2022; Lefaucheur et al., 2017). These evidence are in line with the main role of NMDA-receptors and glutamate neurotransmitter in neuroplasticity mechanisms, since glutamate is the primary excitatory neurotransmitter in the brain, which mediates the Long-Term Potential (LTP) and Long-Term Depression (LTD) (Lüscher & Malenka, 2012). Thereby, nowadays LTP and LTD are supposed to have a prominent role in tDCS long-lasting effects (Antal et al., 2022), deriving mainly by the aforementioned pharmacological evidence. The potentially prominent role of neuroplasticity in tDCS-induced effects is reported even in comparative neuroscience, as shown in rodents, with anodal tDCS application on M1 showing LTPs generations in the target neuronal population (Fritsch et al., 2010). Another experiment on mice brains shows how applying the DC stimulation Hz over the hippocampus, there is an induction of LTP or attenuation of LTD (Kronberg et al., 2017). Finally, another relevant role is attributed to brain-derived neurotropic factor (BDNF), which has a main role in LTP, since the BDNF secretion mediates and influence the NMDA receptors activity (Fritsch et al., 2010). Overall, these findings suggest that the magnitude of membrane polarization, the conductance of sodium and calcium channels, the magnitude of NMDA receptor activity, as well as BDNF secretion contribute to determine and maintaining the tDCS modulations. These factors have a prominent role in LTP formation. For these reasons,

nowadays the LTP is considered the main mechanism involved in tDCS after-effects, both for their generation and lasting.

1.3 Experimental Neuropsychology Applications

At the begging of 21th century, tDCS has emerged and acquired significant importance as a reliable tool for directly investigating and modulating human brain activity (Lefaucheur et al., 2017). This development was primarily driven by systematic investigations, during the half of 20th century, of DC stimulation effects both on humans and animals, delving into the neurophysiological mechanisms involved in tDCS neuronal modulation, as well as the behavioral and neuronal functioning alterations (Paulus, 2003). Indeed, this growing interest is reflected in various studies from that period, including comparative neuropsychological research using EEG paradigms to assess changes in neuronal firing and DC monopolar montages on the scalp to detect alterations in alertness (Priori, 2003).

Initially, the DC-induced effects on human have been assessed primarily through stimulations on primary cortices, i.e., motor, auditory, visual, and sensorimotor cortices. The first consistent evidence about the DC application effects was established on human M1 by Elbert et al. (1981) and Priori et al. (1998), marking the beginning of a systematic exploration of tDCS physiological effects and brain activity modulation (Lefaucheur et al., 2017). The former study showed a faster motor response to an acoustic stimulus, after a positive DC application, anodal condition, compared to negative stimulation, cathodal condition (Elbert et al., 1981). Whereas the latter experiment assessed MEPs alterations following DC current application over M1 through a TMS detection, in which anodal stimulation defined a reduction of MEPs mean size, increasing the underlying cortex excitability (Priori et al., 1998). Further evidence supports and underpins these results,

such as several replications of the anodal tDCS effects on MEPs' amplitude increasing, through a TMS detection, and even of cathodal alterations on diminishing the MEPs amplitude and increasing the mean size, due to a reduction of the neuronal excitability (Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000; Santarnecchi et al., 2014). Concerning the motor learning alterations, many evidence were related to the implicit motor learning during the Serial Reaction Time Task (SRTT), involved in processes underlying a broad range of behaviors, including the cognitive and biological principles of learning and memory (Robertson, 2007), showing a facilitation in SRTT during anodal tDCS (Kang & Paik, 2011; Nitsche, Schauenburg, et al., 2003; Rosenkranz et al., 2000). The aforementioned behavioral responses enhancement may derived by an increment of synaptic plasticity on the stimulated target areas, i.e., the M1 (Fritsch et al., 2010).

The same mechanism is supposed to be implied on sensory modalities alterations induced by tDCS. For example, to assess tDCS efficacy on modulating visual perception a cathodal stimulation (7min, 1mA, 35cm^2) was applied over the visual cortex, which altered the participant contrast detection perception (Antal et al., 2001). After the same stimulation protocol, even the phosphene threshold, a measure of visual cortex excitability, was diminished by the anodal stimulation, while the opposite effect derived by the cathodal condition (Antal et al., 2003). In addition, a further study found a tDCS effect on visual attentional processes, when an anodal stimulation (30min, 2mA, 35cm^2) was applied on the right parietal cortex, improving visual exploration and orienting during a multisensory exploration task (Bolognini et al., 2010).

Finally, the somatosensory evoked potential (SEP) amplitude increased after the application of the anodal condition (10min, 1 mA, 35cm^2) on the left medial nerve, showing also an alteration in excitability of cortical somatosensory processing (Matsunaga et al., 2004). In contrast, cathodal tDCS (7min, 1mA, 35cm^2) on the right somatosensory area, C4 position of 10-20 international system, reduced the ability to

discriminate different frequencies vibrating on contralateral finger, compared to baseline and anodal conditions, which did not elicit any significant difference (Rogalewski et al., 2004).

1.3.1 tDCS Applications on Cognitive Functions

The initial evidence of tDCS outcome on motor and sensory cortices entailed a reliable effect on neuronal functioning modulation, which was based on the task and on the stimulation's polarity. For this reason, in the last decades experimental applications were focused and extended on the possible modulation of high-order cognitive processes, i.e., associative cortices, mainly on prefrontal cortex.

Regarding the high-order function investigation and application, a significant branch of studies has examined the role of tDCS in modulating emotion processing, with a primary focus on stimulation of the left dorsolateral prefrontal cortex (DLPFC). The pioneering study by Fregni et al. (2006) was the first to administer consecutive session, for 5 days, of anodal tDCS (20min/5days, 1mA, 35cm^2) on DLPFC, reporting and eliciting an increase of positive mood and emotions in patients with depression. Subsequent research has corroborated these findings, such as by anodal tDCS application on left DLPFC in depression treatment (Lefaucheur et al., 2017). Whereas further experimental investigations entailed changes also in behavioral performance due to anodal tDCS applications, both in healthy subjects and patient populations. Indeed, anodal tDCS over the left DLPFC (15min, 2mA, 2 x 23cm^2) in MDD patients has been related to faster Reaction Times (RT) in presence of negative words during an Emotional Stroop Task, since patients reported a decrease of 'negative bias', a pervasive prioritizing processing of negative information present in this clinical population (Brunoni et al., 2014). Moreover, anodal DC application (30min, 2mA, 60mm diameter) on left prefrontal cortex elicited faster RTs in detection of emotional expression, during a Visual Search

Task, only in depressed patients, while no differences in accuracy between patients and subjects group were reported (Pilloni et al., 2024). Finally, healthy subjects obtained faster RTs in negative emotion expression processing and higher accuracy in emotion expression recognition by anodal tDCS (20min, 1mA, 35cm^2) on left DLPFC compared to cathodal and sham conditions (Nitsche et al., 2012). Additionally, anodal tDCS (30min, 1.5mA, 2 x 35cm^2) on DLPFC elicited a higher accuracy in Emotion Recognition Task both in healthy subjects and mainly for happiness and disgust in the clinical group compared to the baseline, increasing even the clinical group Working Memory (WM) performance in Digit Span Backward (Brennan et al., 2017). Therefore, the modulation of left DLPFC has a main role in emotion processing and regulation, but at the same time it is not univocal for this cognitive function.

This point is especially important, since the aforementioned evidence is linked to another significant area of research investigating the interplay between transcranial stimulation and memory functions. Firstly, a main distinction should be done between Working Memory (WM) and Long and Short Term Memory (LTM and STM) (Baddeley, 2003). Initial studies have primarily focused on WM, revealing an enhanced accuracy during the Three-Back Letter Working Memory Task performance following anodal tDCS on left DLPFC (10min, 1mA, 2 x 35cm^2 and 2 x 25cm^2; Fregni et al., 2005; Ohn et al., 2008). In contrast, evidence did not observe differences in accuracy performance, but a reduction of RTs after anodal stimulation (15min, 1mA, 35cm^2) on the same target area (Zaehle et al., 2011). Similarly, a study reported the same RT alterations after an anodal tDCS (20min, 2mA, 35cm^2) on left DLPFC, decreasing RTs, while no changes were reported for accuracy (Teo et al., 2011). These findings could be related to the theta and alpha waves modulation from anodal and cathodal tDCS, increasing and decreasing, respectively, even though any evidence is reported for cathodal effects on behavioral performance (Zaehle et al., 2011). At the same time, there are less evidence about the

tDCS effects on LTM and STM, although current flow neurophysiological effects are supposed to be directly related to these processes. Findings showed a disruption in STM after cathodal tDCS stimulation (5min,1.5mA, 1 x 28cm^2 and 1 x 100cm^2) over the left DLPFC in associative verbal learning, while LTM and anodal differences were not present (Elmer et al., 2009). Likewise, anodal tDCS (13min, 2mA, 2 x 35cm^2) only over right Anterior Temporal Lobe (ATL) increased the accuracy in a visual memory task, while there were not reported differences from left lobe and cathodal condition (Chi et al., 2010). Finally, tDCS effect are found also in false memories production, which are reduced by 73% through an unilateral and bilateral anodal tDCS stimulation (5min, 2mA, bilateral: 2 x 35cm^2, bilateral: 1 x 35cm^2 and 1 x 100cm^2) applied on the left ATL compared to sham conditon, during the encoding and retrieval stages (Boggio et al., 2009). Taken together, the reported findings, along with the evidence in the literature suggest an absence of substantial results regarding the effects of tDCS on the modulation of LTM and STM. Whereas they underpin the reliable effects of excitatory tDCS over left DLPFC in enhancing WM. Probably, because this brain region is mainly associated to executive functions, along with the involvement of medial, orbital/ventro medial PFC (Nejati et al., 2018).

Indeed, another cognitive function that has been investigated in relation to tDCS modulation of the DLPFC is decision-making, both in clinical populations and healthy individuals. For instance, patients with addiction disorder and healthy control subjects have reported enhancement in decision making and cognitive flexibility following anodal tDCS (20 min for 3 days, 2 mA, 2 x 35cm^2) applied to the left DLPFC, showing a better performance, higher adaptive choice and more flexible ability, respectively for Iowa Gambling Task and Wisconsin Card Sorting Test (Soyata et al., 2019). While other studies delved into the tDCS effects to modulate risk-taking behaviors. Notably, Fecteau et al. (2007) conducted the first study to indagate how anodal tDCS applied over right DLPFC

could influence risk-taking decisions during a Risk Taking Task. In this study, online tDCS (2mA, 2x 35cm^2) was administered 5 minutes before the task and lasting throughout its duration. Although evidence show that tDCS effects are higher after the finish of stimulation (Santarnecchi et al., 2014). The study results indicate an increased risk aversion following anodal stimulation compared to sham and cathodal conditions, underlying a modified decision making ability due to the neuronal modulation (Fecteau et al., 2007). The same methodology reported reduction of risking-taking behaviors, showing a larger effect for subjects with higher impulsivity traits (Cheng & Lee, 2016). Similar results were replicated on veterans participants, where an anodal tDCS application (25min, 2mA, 25cm^2) over the right DLPFC, twice a day for 5 days, defined a reduced risk-taking behaviors in veterans participants on active stimulation sample and this effect lasted for two months (Gilmore et al., 2018). On the other hand, both these two last experiments did not report a significant effect on Balloon Analogue Risk Task (BART), a reliable behavioral measure of impulsivity (Canning et al., 2022). Overall, these findings underline that anodal tDCS over right DLPFC effectively increased risk aversion and reduce risk-taking behaviors, although evidence do not support the role of this region in to modulate impulsivity performance. As underpinned also by previous evidence, this region is related in the top-down regulation during decision making (Fleck et al., 2006), and tDCS protocols may have a reliable effect on risk-taking behaviors and evaluations.

tDCS effects have been delved into another prominent high-order function related to the precedent investigation, the inhibitory control ability. Evidence about inhibitive control enhancement after tDCS application (25min, 1mA, 25cm^2) comes from primarily through the assessment with the Stop Signal Task (SST), a behavioral task established to measure response inhibition, following the application of unilateral anodal and cathodal tDCS over the right Inferior Frontal Gyrus (rIFG). Anodal condition elicited a facilitation

in Stop Signal Response Times (SSRTs), a direct measure of the duration that occurs to stop the response, while cathodal stimulation decreased SSRTs and both were found with significant differences from sham and bilateral stimulation (Jacobson et al., 2011). Stramaccia et al. (2015) replicated the results and demonstrated how the cognitive function alterations last in time even 15 minutes after the stimulation end, underlying a potential main role of rIFG in the SST task. Indeed, the experiment shows that anodal stimulation (15min, 1.5mA, 16cm^2) on rIFG defines a significant difference in SSRTs compared to control conditon and anodal stimulation over right DLPFC (Stramaccia et al., 2015). These results are corroborated by a meta-analysis that reports a moderate effect size for right IFG, while a null effects is reported for right DLPFC in the inhibitory control task after anodal stimulation (Schroeder et al., 2020). Moreover, the study reports a small and significant effect size on response inhibition (g = .21), and a larger effect size of tDCS in SST (g = .32) compared to the Go-No/Go Task (GNG) (g = .10) (Schroeder et al., 2020).

Additionally, the meta-analysis conducted by Narmashiri & Akbari (2023) supports the previous evidence, since the investigation of tDCS effects in 67 studies, including the aforementioned, addresses a significant effect in performance increase over WM, inhibition control, cognitive flexibility and theory of mind (ToM), both in RTs and accuracy, by anodal stimulation, but either by cathodal stimulation (Narmashiri & Akbari, 2023). However, current evidence underlines how most of the literature involving tDCS application over cognitive functions, and non-motor cortical areas, did not find a significant effect for cathodal tDCS (Jacobson et al., 2012; Schroeder et al., 2020). Likewise, only one result concerns cathodal tDCS effects on inhibition during the SST, in which an extracephalic stimulation (19min, 0.5mA, cathode 9cm^2, anode 36cm^2) over the right IFG decreases control inhibition performance, resulting in an SSRT increase (Friehs & Frings, 2019). A possible explanation derives by the higher current flow used

in other experiments that could switch the stimulation from inhibitory to excitatory, besides the reference electrode placement, in extra-cephalic position, might play an important role in stimulations effects (Schroeder et al., 2020). Therefore, these variables may underpin further evidence on tDCS inhibitory effect, indeed nowadays, as suggested by Jacobson et al. (2012), the AeCi effect concept may be apply only on motor functions, since an absence of this dichotomy is reported for tDCS on cognitive functions.

Taken together, these findings underline the consistent and reliable effect of tDCS in modulating associative areas, as well as primary cortices and the relative cognitive functions, primarily in an excitatory fashion as previously discussed. At the same time, all the reported studies employed a bipolar tDCS configuration, which is associated with concerns about the widespread current distribution (as mentioned in chapter 1.4; Datta et al., 2009; Diana et al., 2021). Hence, employing a tDCS configuration that allows a more focality and precise stimulation, such as HD-tDCS, could potentially enhance the stimulation effectiveness and the underlying cognitive function (Kuo et al., 2013; Lerner et al., 2021). For example, studies reported a significant effect of HD-tDCS in inhibitory control enhancement over rIFG (Guo et al., 2022; Hogeveen et al., 2016).

1.4 Conventional Bipolar and High Definition- tDCS Montage Comparison

Bipolar tDCS montage is considered the conventional setup in experimental and clinical tDCS application, since it is one of the first configuration that has been developed (Nitsche & Paulus, 2000) and the most employed in the literature (Liew et al., 2014). Although numerous evidence supports the efficacy of conventional bipolar tDCS, both in rehabilitative programs and experimental setting, a significant limitation of this montage is the widespread current distribution across non-target cortical regions following its application (Datta et al., 2009). Indeed, current-modeling studies have further

demonstrated the low spatial specificity of this approach, indicating that the electric fields can extend widely and peak over unintended areas (Datta et al., 2009; Diana et al., 2021). Hence, HD-tDCS montage has been developed to address this issue and it is reported to be an enhanced version of conventional tDCS configuration, since HD-tDCS is considered to be more focal, better sustained, and longer lasting in terms of its effects (Kuo et al., 2013; Lerner et al., 2021). In particular, the HD-tDCS electrodes' characteristics contribute to reduce the uncontrolled diffusion of tDCS-induced electric fields, thereby improving the spatial precision with which the electrical current can target specific cortical regions (Datta et al., 2009; Diana et al., 2021). Indeed, the available evidence from computational models indeed suggests that, at equal total current injected, combining the modeling of electric fields with the HD montage ensures both higher focality (+80%) and intensity (+98%) than conventional approaches (Dmochowski et al., 2011). Additionally, recent evidence reports the same difference, via computational models of current flow, in which HD-tDCS shows a focal and limited stimulation in the target area without affecting and spreading into other brain regions, as shown instead by conventional tDCS (see Fig. 9; Diana et al., 2021).

Concerning HD-tDCS configurations, the first and most extensively reported setup in the literature is the 4 x 1 montage, illustrated in Figure 4, which was initially described and projected by Datta et al. (2008, 2009). Over the past decade, alternative configuration types have been developed. The 3 x 1 setup is a modified version of the 4 x 1 setup, which uses three reference electrodes instead of four, as detailed by Santos et al. (2018). Another variant is the dual-site, or double, 4 x 1 configuration, which employs two 4 x 1 montages simultaneously to stimulate two different target areas (Hill et al., 2018). Furthermore, the 2 x 2 montage uses two active and two reference circle electrodes, as described by Donnell et al. (2015). Finally, the montage setup can be entirely based on the current flow simulations models. Indeed, a recent review reported that electrodes configurations (e.g.,

position, number and size) based on computational models leads to reliable outcome (Parlikar et al., 2021).

The HD-tDCS efficacy is demonstrated and documented by applications in both healthy and patients' population. Neurophysiological changes has been established in research on human motor system activity, by applying anodal stimulation over the primary motor cortex and demonstrating subsequent increases in corticospinal excitability (Edwards et al., 2013; Kuo et al., 2013), showing also a significant effect in EEG signal detection (Masina et al., 2021). Further, HD-tDCS evidence reports the efficacy in neurological disorders, such as pain, fibromyalgia (Pellegrini et al., 2021), and aphasia (Fiori et al., 2019). Additionally, this configuration defined findings about the modulation of cognitive functions, as inhibitory control and executive functions (Hogeveen et al., 2016). Specifically, Hogeveen et al. (2016)'s study has shown an

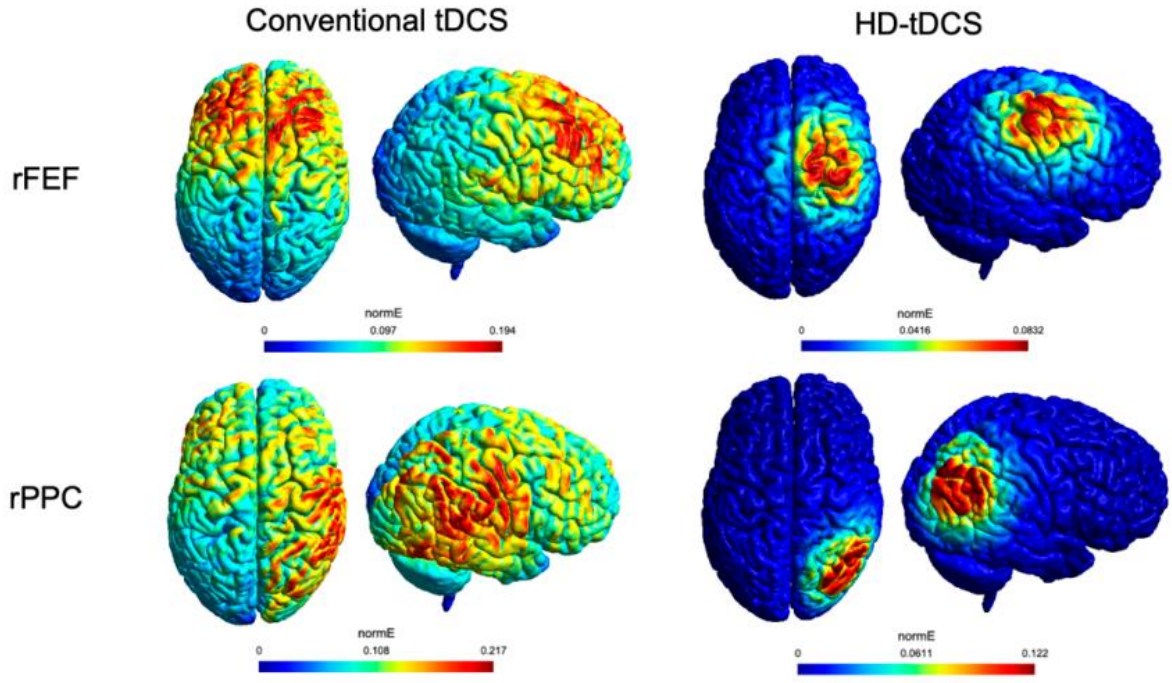

Figure 6 Stimulation of the electric field (normE-V/m) performed with SimNIBS. Side and top views of the right posterior parietal cortex (rPPC) and the right frontal eye field (rFEF) are provided for conventional tDCS (left panel) and HD-tDCS (right panel) (Diana et al., 2022).

increase in the SST performance after an anodal stimulation on rIFG, but no significant difference in performance has found between HD and conventional. Indeed, although the reliability of HD-tDCS montage is consolidate in literature, the differences between the two configurations effectiveness and effects are still debated.

1.5 Inhibitory Control: Stop-Signal Task and right Inferior Frontal Gyrus

Inhibitory control refers to a central cognitive capacity critical for the interruption and correction of planned or already initiated motor actions in favor of higher-order goals (Newman et al., 1985; Verbruggen et al., 2019). It is a core of executive cognitive function, and we experience this ability in everyday life (Diamond, 2013). Neuropsychological research identifies inhibitory control as being primarily associated with a network of right-lateralized prefrontal regions, including the right inferior frontal gyrus (rIFG), supplementary premotor regions, and the motor cortex (Aron et al., 2014; Banich & Depue, 2015). Dysfunctions in these cognitive control processes, as well as in the associated neural circuits, have been implicated as key mechanisms underlying in a range of mental disorders such as ADHD, binge eating disorder, obesity, and addiction (Schroeder et al., 2020). Notably, the application of tDCS over these brain regions has been shown to improve inhibitory control and alleviate symptoms across a variety of mental disorders (Schroeder et al., 2020), as demonstrated in studies on ADHD and addiction (Lefaucheur et al., 2017), as well as impulsive behaviors (Jacobson et al., 2011). Moreover, it has been found to enhance inhibitory control in healthy individuals, as evidenced by improved performance on behavioral tasks specifically designed to assess inhibitory control function, e.g., SST (Friehs & Frings, 2019), Stroop test (Frings et al., 2018), Go/No-Go (Campanella et al., 2018), and Flanker task (Dubreuil-Vall et al., 2019).

The SST, in particular, investigates action cancellation following stop signals, with a certain delay, after stimulus presentation for an unrelated go-decision (Logan et al., 1984; Verbruggen et al., 2019). Thanks to its specific characteristics, this task offers several advantages to study the inhibitory control abilities in healthy subjects. Indeed, the SST is more sensitive to neurocognitive disorders, facilitating its translational application across various clinical conditions (Mar et al., 2022; Schroeder et al., 2020). Additionally, it is not subjected to a ceiling and floor effect, through an adaptive adjustment of task difficulty to the ongoing performance, and there is evidence against a learning effect (Best & Verbruggen, 2019).

Regarding the neuronal correlates of inhibitory control, a particular focus should be placed on the rIFG, since this region is known to function as a 'brake' to suppress initiated actions; indeed, it plays a crucial role in control inhibition (Aron et al., 2014; Zhang et al., 2017). Neuroimaging studies consistently show the rIFG involvement in effective stopping during trials in both healthy and clinical populations (Whelan et al., 2012), since patients with structural and functional impairment in rIFG exhibit significant deficits in inhibitory control performance (Bari & Robbins, 2013). Further, neuroimaging evidence report a main role of the rIFG activity in SST performance (Aron et al., 2004, 2014). Moreover, the relationship between increased rIFG responsiveness and SST behavioral performance is supported even by anodal tDCS studies over this regions, with evidence pointing to an enhanced SST accuracy response by reducing the latency for successful stops, compared to other right-lateralized prefrontal regions (Friehs et al., 2021; Schroeder et al., 2020; Stramaccia et al., 2015).

Taken together, the abovementioned results suggest that anodal tDCS over rIFG activity could improve response inhibition. While this effect is established for conventional tDCS montages, evidence reports inconclusive findings concerning the potential advantages of HD- montages (Guo et al., 2022; Hogeveen et al., 2016),

highlighting the need to investigate whether anodal HD-tDCS can modulate inhibitory performance effectively (Hogeveen et al., 2016).

1.6 tDCS Advantages and Limitations

The application of tDCS offers several significant advantages, which can be summarized in three main aspects: safety, cost-effectiveness, and versatility. These benefits have presumably contributed to the exponential increase in its popularity and use in both rehabilitative programs and experimental settings (Antal et al., 2022; Russo et al., 2017). First and foremost, tDCS reports a very highly safety profile (Bjekić et al., 2021; Lefaucheur et al., 2017; Woods et al., 2016), since it is a non-invasive technique, and the adverse effects associated with it are mild and highly subjective (Russo et al., 2017), such as mild headache or local sensory discomfort, e.g., itching, burning sensation or tingling sensations under the electrodes (Bjekić et al., 2021; Poreisz et al., 2007). Furthermore, these discomfort sensations are primarily attributed to the application of electrical current on the scalp. but they can be mitigated and avoided by applying gel, cream or wet-wrapped sponge over the electrodes (Lefaucheur et al., 2017). Another example could be the presence of erythema under the electrodes, which is caused by tDCS-induced vasodilation (Woods et al., 2016). Therefore, the reported issues are categorized as "tolerability" aspects, which refers to the presence of uncomfortable and unintended effects, rather than "safety" aspects, which are related to inducing damaging or harmful effects (Woods et al., 2016). Indeed, literature reported the absence of any negative short- or long-term, structural or functional damage (Bjekić et al., 2021). Second, a significant advantage of tDCS is its low-cost, since the devices, equipment, and application price are significantly more affordable, up to ten to one hundred times less expensive, than other treatment options (Bjekić et al., 2021) and other stimulation techniques, such as TMS

(Lefaucheur et al., 2017). Third, the tDCS's versatility is a key factor in its widespread application, since the techniques allows an easy management, administration, and customization about the type of protocol to use. Notably, it can be administered in home-based settings by patients, which can lead to higher patient compliance and reduced cost for medical staff and facilities (Bjekić et al., 2021; Lefaucheur et al., 2017), although recommendations for tDCS self-administration have recently been proposed to ensure the safe use of remotely-supervised at-home tDCS (Charvet et al., 2015). This type of autonomous treatment must be carefully managed, since uncontrolled domiciliary utilization of tDCS devices exposes the patient to potential adverse events caused by misuse or overuse, e.g., skin burns (Wang et al., 2015), unnecessary or dangerous repetition of the sessions (Lefaucheur et al., 2017). Four, tDCS can be easily combined with pharmacotherapy, as shown by Brunoni et al. (2013), with a combined use of tDCS and Sertraline (an antidepressant of the selective serotonin reuptake inhibitor class), requiring decreasing dosage injects in clinical trials. Finally, tDCS reports a very reliable placebo procedure, thanks to the fade-in and fade-out method, compared to other NIBS techniques, which allows to have the sham, control condition very difficult to detect by the participant, and optimal for experimental settings (Ambrus et al., 2012).

Regarding the possible participants' side effects, as previously mentioned, tDCS is considered highly safe, since the only issues being reported are related to the sensation and discomfort provoked by the electrical stimulation on the stimulated region site (Bjekić et al., 2021; Woods et al., 2016). While, concerning the efficacy and application of the technique, tDCS protocols present certain limitations in both experimental (e.g., investigation of cognitive functions) and clinical (e.g., treatment effectiveness) neuropsychological applications. These limitations arise due to the intrinsic variability of tDCS, which is influenced by several factors. Firstly, the non-linear effects from the variations in the tDCS setup, e.g., of active and reference electrodes size, shape,

positioning, number, or current intensity (Antal et al., 2015; Schroeder et al., 2020). Second, the interindividual variability, where different stimulation effects derive by the individual's head anatomy, since even with identical set-up and parameters, different electric fields may result (Datta et al., 2012; Hunold et al., 2023). As mentioned above, to reduce these confounding factors, it is recommended to adopt computational modeling of electrical fields, and a combined use of neuro-navigation protocols based on participants' or patients' structural MRI. This approach allows for more precise targeting of the brain areas requiring stimulation. However, the inclusion of MRI protocols significantly increases costs and complexity of the experimental procedure.

1.7 tDCS Exclusion Criteria

During the preparation and setting-up of tDCS applications, particular attention should be placed on exclusion criteria, which may vary based on the experimental setting or clinical protocol utilized; however, there are commonalities across studies and NIBS techniques (Thair et al., 2017). These criteria are established to ensure subject's safety during tDCS and to optimize the stimulation effectiveness. The exclusion criteria include the absence of the following conditions: a history of epilepsy; concussion; stroke; migraines; use of psychoactive substance or drug; metallic implants in the head; a medical diagnosis of physiological or neurological disorders; and adverse effects to previous tDCS or other brain stimulation techniques (McLaren et al., 2018; Thair et al., 2017). Indeed, although there have been no reported seizures in humans during tDCS experiments, brain stimulation may alter seizure threshold, so participants with particularly sensitive seizure thresholds should be excluded (Nitsche et al., 2008). Additionally, the brain injuries, as concussion and stroke, may cause brain changes, meaning tDCS responsiveness and current flow may differ in this population (Datta et al., 2010). Furthermore, subjects with

a history of migraines may experience headaches or an increased risk of migraine attacks due to tDCS (Poreisz et al., 2007). Moreover, the intake of psychoactive, psychotropic substance or drugs is an important exclusion criteria, since psychopharmacological treatment or psychotropic substance intake concurrently with the tDCS application can alter tDCS effects, as channel sodium channel blockers, calcium channel blockers, and NMDA receptor antagonist (McLaren et al., 2018), and participant cognitive functions, i.e. psychopharmacological treatment, psychotropic drugs or psychoactive substance as caffeine (Herrmann et al., 2017). Therefore, these aspects define a confounding factor to assess cognitive performance. For this reason, it is recommended to prohibit coffee consumption before experimental sessions involving tDCS, and even for all NIBS techniques.

1.8 Hypothesis and Aims of the Study

The current project aimed to assess the difference in effectiveness of HD-tDCS and bipolar tDCS in modulating inhibitory performance during the SST, in order to determine which configuration had a higher efficacy to modulate the rIFG. This objective was intended to fill the gap about the lack of empirical evidence regarding effects and effectiveness differences between the two montages, conventional and HD-, particularly in their potential capacity to enhance cognitive functions. The study evaluated these effects by assessing the performance modification during the SST following anodal stimulation of the rIFG, since the well-established relationship in literature between this neural correlate and the behavioral task.

The stimulation protocols and configurations were based upon an optimized computational model of electric field distribution (Huang et al., 2016, 2019). The study investigated the effects of tDCS configurations during two different behavioral tasks, the

SST, the experimental condition, and the Double Response Task (DRT), the control condition.

Regarding the SST, the expected results hypothesized a higher effectiveness and focality in stimulating participants' rIFG compared to conventional tDCS, according to modeling predictions. This way, eliciting a relative inhibitory control performance enhancement, i.e., SSRTs decrease. This hypothesis was called "HP2", and it represented the main aim of the study. Subsequently, the HD-tDCS condition was hypothesized to elicit a higher effect compared to the sham tDCS condition (HP1a). Likewise, bipolar tDCS was hypothesized to define a stronger modulation on rIFG, and a relative reduction of SSRTs, compared to the sham condition (HP1b). Therefore, the alternative hypothesis (H1) assumed the presence of a significant differences between the three tDCS conditions, with both active tDCS montages leading to a faster SSRTs compared to sham condition, and HD-tDCS determining a more effective performance, i.e., decreased SSRTs, compared to the conventional bipolar montage; the hypothesized results were supported by meta-analytic evidence (Schroeder et al., 2020). Conversely, the null hypothesis (H0) posited the absence of significant difference in SSRTs between the three conditions, indicating a null effect.

Whereas, DRT was considered as a control condition, therefore no significant differences were expected between the three tDCS conditions, since the rIFG and inhibitory capacity are supposed to be not directly involved in the cognitive processes required by the task (i.e., non-inhibitory action updating). For these reason, the RT related to the DRT, including the GoRTs (response time to the primary stimulus), and the RT latency of the additional response (DRT, the response time from the onset of the double-response signal; Verbruggen et al., 2010), should not be modulated by the stimulation and should obtain the same performance in all three conditions. In line with the SST hypothesis, H1 proposed a presence of significant differences between the three

stimulation conditions during DRT performance. In contrast, H0 would suggest the absence of significant effects in DRT performance across the different stimulation conditions.

2 MATERIALS And METHODS

2.1 Participants

42 right-handed participants (30 females, mean age = 25.05 years, SD = 2.97, min = 20, max = 37) completed the experiment. The total number of dropouts was of two participants, while three participants were excluded from the analysis since their accuracy ratio was over the threshold (i.e., lower or higher) in the SST performance, as explained in chapter 2.6.2. Subjects were both Italian and English speakers, and they voluntary participated to the study, without a monetary compensation. Before the experiment, they were tested for absence of color-blindness and exclusion criteria for tDCS eligibilities (Keel et al., 2001).

2.2 Questionnaires

Different questionnaires were used to assess the inclusion criteria of recruited participants: right-handedness, the absence of exclusion criteria for brain stimulation eligibility, and the absence of poor sleep quality.

The Edinburgh Handedness Inventory (Oldfield, 1971) evaluates the subjects' right-handedness, concerning ten questions to investigate manual dominance during daily objects use (e.g., spoon, toothbrush, scissors, etc.).

tDCS eligibility was assessed using an exclusion criteria for brain stimulation studies questionnaire (Keel et al., 2001), which consider: susceptibility to, or history of, seizures

or migraine, history of neurological or psychiatric disorders; history of substance abuse or dependence, history of brain surgery, tumor or intracranial metal implantation; current use of psychoactive medications, current pregnancy, presence of pacemaker or other implanted devices.

The participants' sleep quality was investigated using the Pittsburgh Sleep quality Index (PSQI) (Buysse et al., 1989), and its Italian validated translation (Palagini et al., 2016); this questionnaire assesses the impact of perceived sleepiness on diurnal functioning in the last month-period, defining the presence of a poor sleep quality (PSQI > 5).

Eligible participants filled the Morningness-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976) or the Italian validated translation (Terman & Terman, 2005) for Italian speakers, a questionnaire that evaluates the subjects' chronotype based on the individual differences in alertness and activeness during the day, by assessing preferences for sleep and wake times. This questionnaire was used to match the experimental sessions with the subjects' chronotype, in order to reduce and control the potential confounding factors accounting the impact of chronotype on performance.

After each session, subjects completed the Sensation Questionnaire (Fertonani et al., 2015), which evaluates possible cutaneous or adverse-effects during and after tDCS. While, after the last session participants judge, for each of them, whether they were real or placebo and their level of confidence in this judgment, to check the efficacy of the blinding procedure.

2.3 tDCS techniques involved: Conventional and HD-tDCS

The convectional tDCS montage involved two squared-shape (5x5cm^2) electrodes, each wrap in a sponge, and a single battery-driven device delivering a DC of 2 mA

(density = 0.08 mA/cm^2) (Jacobson et al. 2011). This set-up previously reported effective results in modulating SST performance and it consists in active electrodes on the rIFG (crossing point between T4-Fz and F8-Cz; 10-10 EEG system) and reference electrodes over the contralateral supraorbital area (Jacobson et al., 2011).

The HD-tDCS montage consisted in six circle-shape small (3 anodes x 3 cathodes; 9.5 mm radius) electrodes, each delivering 0.667 mA. The electrodes were connected to a series of three triggered battery-driven devices (total current = 2mA; density = 0.23 mA/cm^2), ensuring a safe stimulation in line with the parameters established by tDCS application guidelines (Antal et al., 2017; Gandiga et al., 2006; Nitsche, Liebetanz, et al., 2003; Nitsche, Niehaus, et al., 2004). These electrodes set-up are defined thanks to the modeling routines implemented in the ROAST toolbox (Huang et al., 2016, 2019), which allows to define the maximum stimulation intensity of the rIFG, concerning the conductivity values assigned to the different tissues within a high-resolution T1-weighted MRI image (Huang et al., 2016), thus taking advantage of the flexibility of volumetric segmentation of MRI data allowed by ROAST. Based on the current flow simulation model and the predicted location of rIFG at xyz = 46 22 -2 (Neurosynth; Yarkoni et al., 2011), the optimal electrodes position for healthy participants was found in anodes on F4 - F6 - FC6 sites, and cathodes on F10 - FT10 - P10 sites (10-10 EEG system). In addition, three “trigger adapters” were linked to the tDCS stimulators, and they allowed to synchronize the start and stop phases of the tDCS device, defining a simultaneously activation of the three stimulators device.

As shown in Figure 7, the HD-tDCS montage delivers maximal stimulation intensity to the rIFG target, for this reason it was considered as the optimal setup, while the conventional montage resulted in the highest stimulation of a more dorsal middle frontal region. For both conventional and HD-tDCS, the active stimulation was delivered for 20 minutes with a linear fade-in/fade-out ramp of 15 seconds, in an offline protocol, before

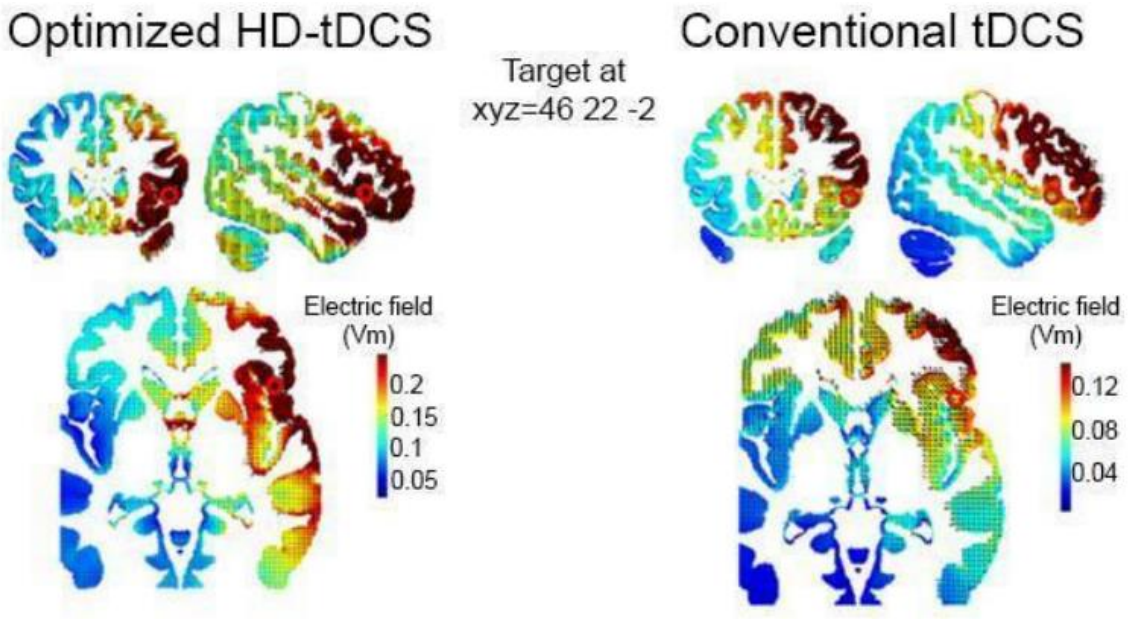

Figure 7 The figure shows the different tDCS intensity at the rIFG target (coordinates reported) elicited by optimized HD tDCS vs. conventional tDCS.

the behavioral task performance. The stimulation's after-effects were predicted to last 20 minutes after the end of the current deliver. The sham sessions maintained the same parameters, but the intensity was ramped down to 0 mA after 30 seconds stimulation and delivered again for 30 seconds at the end of the 20 minutes period. This procedure proved effective in blinding participants to stimulation conditions (Gandiga et al., 2006; Mattavelli et al., 2019; Palm et al., 2013; Pisoni et al., 2015), while eliciting no after-effect (Nitsche & Paulus, 2000; Woods et al., 2016). A sham, placebo, stimulation was performed as a control conditon, in order to collect a subjects' baseline performance.

The aforementioned settings were programmed on tDCS stimulators using the program *Brainstim*, which allowed to select the values about mA, duration and the ramped down time of the stimulation.

The electrodes positions were defined using a cap reporting the 10-10 system EEG.

2.4 Behavioral Task and Stimuli

In order to measure the cognitive performance alterations, the Stop Signal Task (SST) was adopted, since it provides a reliable measure of response inhibition, as previously mentioned (Mirabella, 2014; Verbruggen & Logan, 2008). In addition, the SST is chosen for its properties, compared to available paradigms for measures cognitive performance, since: a) it is sensitive to neurocognitive disorders, making it relevant for translational implications given the transdiagnostic nature of altered response inhibition in a variety of clinical conditions (Bartholdy et al., 2017; Mar et al., 2022; Schroeder et al., 2020); b) lack of ceiling and floor effects, via an adaptive adjustment of task difficulty to the ongoing performance, representing a crucial prerequisite for assessing tDCS-related modulations; c) evidence against learning effects (Best & Verbruggen, 2019); d) well-established pattern of associated brain activity, highlighting the prominent engagement of the rIFG (Aron et al., 2004, 2014); e) meta-analytic evidence of a significant modulation of SST inhibitory performance when applying anodal tDCS to the rIFG, coupled with a non-significant effect on another widely employed tasks of inhibitory control such as the Go/No-Go (Schroeder et al., 2020).

The effects of conventional and HD-tDCS on response inhibition alteration were tested with a visual version of the SST, in which participants provided a frequent “go” response (75% of total trials), but they had inhibit the initiated response when a “stop” signal was occasionally presented following the “go” stimulus (25% of the trials). The delay between go and stop signals (i.e. stop-signal-delay, SSD) was dynamically adjusted depending on each response, which allowed modulating task difficulty with the SSD increase of 50ms in case of correct response or a SSD shorten of 50ms in presence of a wrong response; This guaranteed a $p(stop|signal) \approx 0.5$. Participants performed 200 trials (150 go and 50 stops), splitted in 3 blocks, with the SSD adjustment being continuously maintained

regardless of block breaks. As suggested by current best practices to ensure the elicitation of a prepotent motor response (Verbruggen et al., 2019), the task design entailed low inhibition probability, fast trial pace and individual SSD tracking. SST's stimuli consisted in a fixation cross at the beginning of every trial with a varying duration (500-1500ms), followed by a green left- or right-ward arrow (i.e., the "go" signal), centered in a black circle. In the "no-go" trial the go stimulus was followed by a stop-signal, represented by the arrow turning from green to red. Participants were instructed that responding as fast and accurately as possible and stopping successfully, was equally important, since the "go" response is provided to the arrow direction by pressing the corresponding buttons

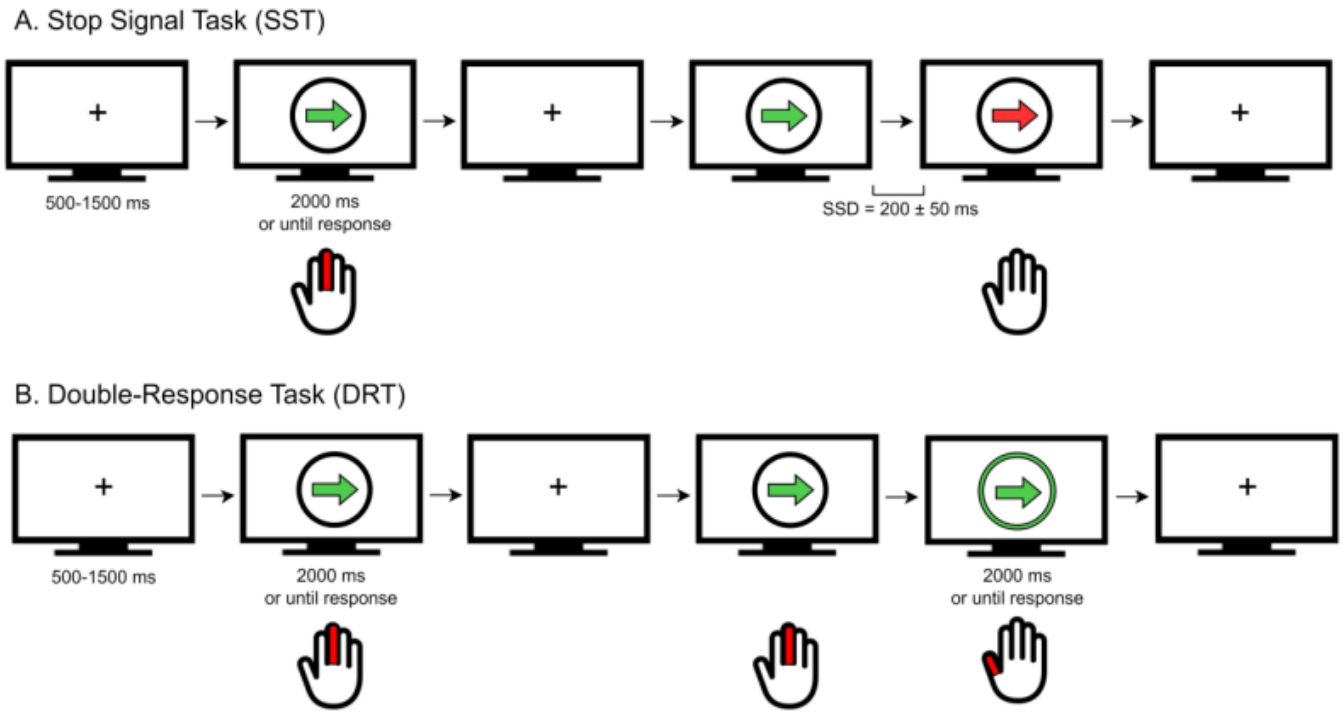

Figure 8 A) Stop Signal Task (SST). Participants were asked to respond, as fast and accurately as possible, to the arrow direction with their right index or middle fingers (i.e., go-trials), and to inhibit their response when the arrow turns red following the "go" stimulus (i.e., stop- trials, corresponding to 25% of the total number of trials).

B) Double-Response Task (DRT). Participants were asked to respond, as fast and accurately as possible, to the arrow direction as the go-trials in the SST, and to provide an additional response when the circle around the arrow turns green following the go-response (i.e., double-response trials, corresponding to 25% of the total number of trials). In both tasks, successive trials were separated by a fixation cross with a varying duration of 500-1500 ms.

on the keyboard ("j" = left, "k" = right) with their right index or middle fingers, respectively. While "no-go" response consists of blocking the response in presence of red arrow appearance, and whether the button was pressed before the red arrow appearance the trial was considered failed. The figure 8A report the overmentioned stimuli.

The Double-Response Task (DRT) represented a control task aimed to disentangle non-inhibitory action updating from response inhibition, both associated with the rIFG (Maizey et al., 2020; Verbruggen et al., 2010). Participants were instructed to provide a second infrequent additional response with the right thumb by pressing the spacebar, following a "go" response, when the circle around the arrow turned green (i.e., double-response signal), regardless of the arrow direction, as shown in figure 8B). As for the SST, there were 150 go and 50 double-response trials, i.e., 200 trials overall divided in 3 blocks.

Following Maizey et al. (2020), the SST and DRT blocks were alternated, for an approximated duration of both the entire tasks of about 12 - 13 minutes. The order of the initial block (SST or DRT) was counterbalanced across participants. "Go" stimuli in both tasks, as well as double-response stimuli in DRT, remained on the screen either until response or up to 2000ms.

The Stop Signal Reaction Times (SSRTs), and the RT latency of the additional response, relative to the onset of the double-response signal, were considered as outcome measures of the SST and DRT, respectively.

2.5 Procedure

The protocol for this study was reviewed and approved by the Ethics Committee of Istituti Clinici Scientifici Maugeri SpA SB, Pavia (Italy; code: 2668CE). All methods were implemented in accordance with the Declaration of Helsinki and best practices for the safe application of tDCS (Antal et al., 2017).

The study consisted in three tDCS sessions (HD/conventional/sham), each of them divided by at least 72 hours, lasting 1.30 hour each one, in a within-subjects design. The sham session was applied either with conventional or HD montage by randomly splitting the participants into two sub-groups. Session order was counterbalanced across participants, and both the participant and the experimenter applying tDCS were kept blind on the stimulation condition (real or sham), as a third researcher was responsible for tDCS programming. Thanks to the absence of written part during the tasks, the study was performed both by Italian and English speakers, without any language exclusion criteria.

Participant were recruited through a predefined email that contained all the information about the study components, such as information about the experiment modalities and the exclusion criteria for subjects' eligibility. Subsequently this preliminary part, subjects received via e-mail the following material, that they had to complete in advance: PSQI questionnaire (Buysse et al., 1989), Edinburgh Handedness Inventory (Oldfield, 1971) Morningness-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976), in order to assess the required exclusion criteria. All questionnaires were implemented using the Limesurvey platform.

The PSQI questionnaire investigate the subjects sleep quality level, and in absence of a poor sleep quality (PSQI > 5) participant could take part to the study, otherwise they could do the questionnaire again after one month, as defined in the questionnaire guidelines (Buysse et al., 1989). Edinburgh Handedness Inventory assesses the participant's handedness, in order to check the correct participants' righthandedness. Moreover, MEQ was administered to define the time schedule of the three sessions based on the subjects' chronotype.

Only during the first session, participants filled the consensus form, the experimental notice form and the exclusion criteria questionnaire. Once the participants signed all the documents and did not report any issues concerning the experiment procedure, the task

instructions were shown to them. Subsequently, in the first part of the experiment, the EEG cap configuration with international 10-10 system was positioned on the participants' head and the central point, Cz, was centered though measuring the half point between nasion and inion, and the preauricular points. Then, the electrodes were positioned on the cap, according to the condition (conventional or HD-) (as reported in the chapter 2.3) and saline solution was applied on electrodes' sponge, in order to decrease the conductance, which diminishes the electrical current spread though the resistance level defined by the subject's airs and skin. After the correct positioning of the electrodes, the center of the cap was centered once again, in order to avoid possible modification in the cap setup. Afterwards, the tDCS device was turned on and the stimulation start, with a duration of 20 minutes for all the three conditions. Throughout all the stimulation duration participants were asked to relax and to watch a neutral short video-clip (Mattavelli et al., 2022), in order to define a passive situation during the current application, as suggested by the BCM model (Bienenstock et al., 1982). When the stimulation was over, the cap and electrodes were removed, and a brief instruction resume of the task was presented to the participants, with also a short trail test before the task run, in order to be sure that participants understood the instructions. As a precaution and possible exclusion criteria, experimenters timed the period between the stimulation ending and the task finish, in order to assess that the period is within 20 minutes, the expected time of after-effects lasting.

After the experimental part, participants filled the sensation questionnaires related to the possible tDCS side effects, and only after they finished their third session participants were asked to judge, for each of them, whether they were real or placebo and their level of confidence in this judgment, to check the efficacy of the blinding procedure.

2.6 Data Analysis

2.6.1 Data Sampling

Data sampling for this study was calculated based on a Bayesian sequential design with maximal N (Schönbrodt & Wagenmakers, 2018). In this design, data collection continues until (1) a predetermined level of evidence (Bayes Factor (BF)) is obtained, or (2) a maximal number of participants is reached. The threshold for evidence was set at BF > 10 in this study, so that Bayes factors were updated in a sequential fashion after each completed participant until the threshold of BF > 10 on all monitored tests (relative to HP1a,b) or the maximal N was reached, whichever comes first. Maximal N was determined a priori using a Bayes Factor Design Analysis with Fixed N (https://tellmi.psy.lmu.de/felix/BFDA_app) to obtain a profile of Distribution of Informed Bayes Factors; the statistical analysis graphical representation is reported in Figure 9. Based on the obtained distribution for H1 (Fig 9), at least 48 observations were needed to obtain a Bayes factor larger than 10 with a probability of p = 0.8, considering an effect size of δ = 0.65. The given effect size was determined based on previous

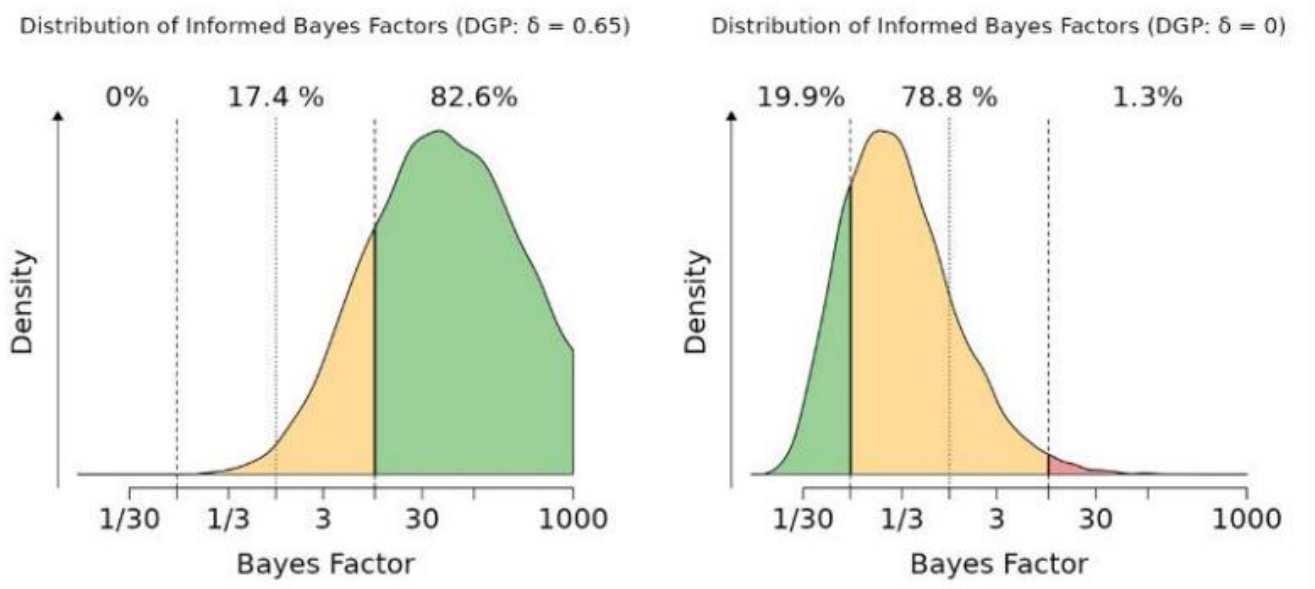

Figure 9 The figure shows the Distribution of Informed Bayes Factors for H1 (left) and H0 (right).

evidence from a meta-analysis (Schroeder et al., 2020) showing the effects of tDCS on the inferior frontal cortex and response inhibition performance. The given sample size significantly extended compared to similar studies and it thus appeared adequate to appropriately test the planned protocol. In addition, since Bayes Factors might be unstable at small sample sizes, we also selected a minimum sample size of 20 participants to be reached before activating the stopping rule.

The choice of this design is an efficient alternative to open-ended sequential designs, given the number of planned sessions (three per participant) that might limit resources availability (e.g., reducing the pool of potentially available participants while increasing the risk of dropouts compared to single-session experiments).

Following this sampling plan, we recruited healthy young adults (aged 18-40 years). Only participants completing all sessions are included in the analyses. Participants failing to comply with the instructions or withdrawing their consent, during or after completion of all sessions, were discarded.

2.6.2 Dependent Variables Analysis

Stimulation after-effects were tested based on the SST performance, which was assessed concerning the following terms: a) go-trial reaction time (GoRT); b) failed stop-trial reaction time (FsRT); c) mean rate of stopping, i.e., p(stop|signal); d) stop-signal reaction time (SSRT). The first three values served the purpose of data quality-check, based on the predictions of the race model (Verbruggen & Logan, 2008) that a) GoRT should be longer than FsRT; b) due to the SSD staircase method, individual p(stop) should approximate 0.5. On these grounds, we excluded participants with GoRT faster than FsRT, or p(stop|signal) falling outside the '0.25 - 0.75' range (Verbruggen et al., 2019). SSRT was then calculated a) after excluding trials with RTs higher than 2,000 ms (missing responses); b) based on the block-wise integration method, i.e. (SSRT = nth RT – mean

SSD). This method entails estimating SSRTs for each block separately and then computes the average of these three estimates, and is considered the most reliable in estimating the latency of response inhibition (Verbruggen et al., 2013). While, DRT performance was assessed in terms of a) GoRT; b) RT latency of the additional response (DRT2), i.e., RT of the additional response from the onset of the double-response signal (Verbruggen et al., 2010). All the values of interest were extracted by using an ad-hoc R script (R 4.3.1).

2.6.3 Statistical Analysis

The Statistical analyses were performed for the independent variables (SSRTs, DRT2s, GoRTs) using Bayesian Paired Sample t-tests, on JASP (0.17.1.0). Bayes Factors (BF) with informed priors were calculated to quantify the observed evidence in terms of odds ratio between the null and the alternative hypothesis evaluated against a threshold of BF ≥10 (conventionally with BF ranges 1-3= anecdotal, 3-10 = moderate, 10-30 = strong, 30-100 = very strong evidence in favor of the alternative hypothesis; Stefan et al., 2019). In this context, the evidence in favor of the alternative hypothesis is indicated as "BF10" and the evidence in favor of the null hypothesis "BF01". As to HP1a and HP1b, two separate paired-sample Bayesian t-tests were performed to compare the effects of HD-anodal and conventional anodal with sham stimulation on SSRTs. As to HP2, a paired-sample Bayesian t-test was used to compare the effects of HD and conventional anodal stimulation on SSRTs. While HP1a and HP1b tested the efficacy of HD-anodal and conventional anodal stimulation in modulating SSRTs separately, HP2 directly compared them. As the two HPs were clearly not independent, the following outcomes were foreseen: Scenario 1) if sufficient evidence to support HP1a and HP1b, and also HP2 were observed, therefore it was possible to conclude that both types of stimulation modulate SSRTs, still with larger effects of HD-anodal compared with conventional stimulation; Scenario 2) if sufficient evidence to support HP1a and HP1b were observed, but not HP2,

so it was possible to conclude that both types of stimulation modulate SSRTs, with none being superior to the other; Scenario 3) if sufficient evidence to support HP1a and HP2 but not HP1b are observed, hence it was possible to conclude that only HD-anodal stimulation modulates SSRTs, while this is not the case for conventional anodal stimulation, against previous evidence (Jacobson et al., 2011; see Schroeder et al., 2020); Scenario 4) if sufficient evidence to support HP1b but not HP1a were observed, and HP2 was supported but in the opposite direction (i.e., SSRTs for conventional anodal are faster than SSRTs for HD-anodal), it was possible to conclude that only conventional anodal, and not HD-anodal, stimulation modulates SSRTs.

Concerning DRT, secondary analyses were performed on DRT scores, DRT2 and GoRT, allowing to assess whether any observed modulation was specific to response inhibition or more generally related to non-inhibitory action updating (Verbruggen et al., 2010).

Thus, Bayesian Paired Sample t-tests were performed twelve, mirroring the analyses on the SSRTs, to compare anodal HD-tDCS vs. sham, conventional tDCS vs. sham and anodal HD-tDCS vs. conventional tDCS. Observing no evidence for a modulation of DRT, when evidence for any of our HP1a, HP1b or HP2 should be obtained, would be considered to support the specific modulation exerted by tDCS on inhibitory control, as opposed to non-inhibitory action updating.

3. RESULTS

3.1 Descriptive Statistics

The present data are preliminary results, since the experiment did not reach yet the predetermined level of evidence, neither the maximal number of participants. Indeed, Bayesian paired-samples t-tests for SSTR were conducted across all conditions in 42

Table 1 *Descriptive Statistic*

	ssrt_sham	ssrt_HD	ssrt_bipolar
Valid	42	42	42
Mean	303.167	304.214	305.405
Std. Deviation	127.856	148.562	140.879
Minimum	144.000	107.000	158.000
Maximum	668.000	619.000	695.000

subjects. Whereas two participants were excluded from the analysis in the DRT condition due to missing data in one out of three conditions.

Table 1 presents the observed mean SSRT for each condition. The sham condition had a mean SSRT of 303.167 ms (*SD* = 127.856), in the HD- condition it was equal to 304.214 ms (*SD* = 148.562), and in the bipolar condition was 305.405 ms (*SD* = 140.879).

Table 2 reports the observed mean DRT for each condition. The sham condition showed a mean DRT of 459.476 ms (*SD* = 139.617), the HD condition had a mean of 461.902 ms (*SD* = 105.214), and of the bipolar condition was equal to 453.195 ms (*SD* = 91.13).

3.2 Questionnaire

The questionnaire related to the blinding procedure obtained a 7.32% of correct responses on the judgement of all three administered conditions (HD-, bipolar, sham) by

Table 2 *Descriptive Statistics*

	doubleRT_correct_sham	doubleRT_correct_HD	doubleRT_correct_bipolar
Valid	42	41	41
Missing	0	1	1
Mean	459.476	461.902	453.195
Std. Deviation	139.617	105.214	91.130
Minimum	320.000	307.000	354.000
Maximum	1.214.000	931.000	873.000

confronting them with t-tests. Therefore, the blinding procedure proved to be effective, according to the predictions.

3.3 tDCS Conditions Effects

3.3.1 SRRT

Although preliminary, the Bayesian Paired Samples t-test for SSRT across three stimulation conditions (HD-tDCS | Bipolar tDCS | Sham tDCS) revealed no difference between conditions (HP1a = 0.153 | HP1b = 0.137 | HP2 = 0.151; Table 3). The data were examined using an informed prior criteria set to t ($\mu = 0.35$, df = 3, r = 0.102), to compare whether the data fit under the alternative hypothesis (BF_{10}) or the null hypothesis (BF_{01}). Firstly, hypothesis HP1a, comparing the effects of HD-tDCS with Sham tDCS condition over the rIFG in modulating SST performance (i.e., SSRTs), showed BF_{10} of 0.153 and BF_{01} = 6.547 with a 95% CI [-0.104, 0.396] (Fig. 10), resulting in a moderate evidence in favor of the null hypothesis. Similar results were reported for HP1b, which confronted bipolar-tDCS with Sham tDCS, since Bayesian paired samples T-Tests revealed BF_{10} = 0.137 and BF_{01} = 7.308 95% CI [-0.120, 0.390] (Fig. 11), indicating a moderate effect in

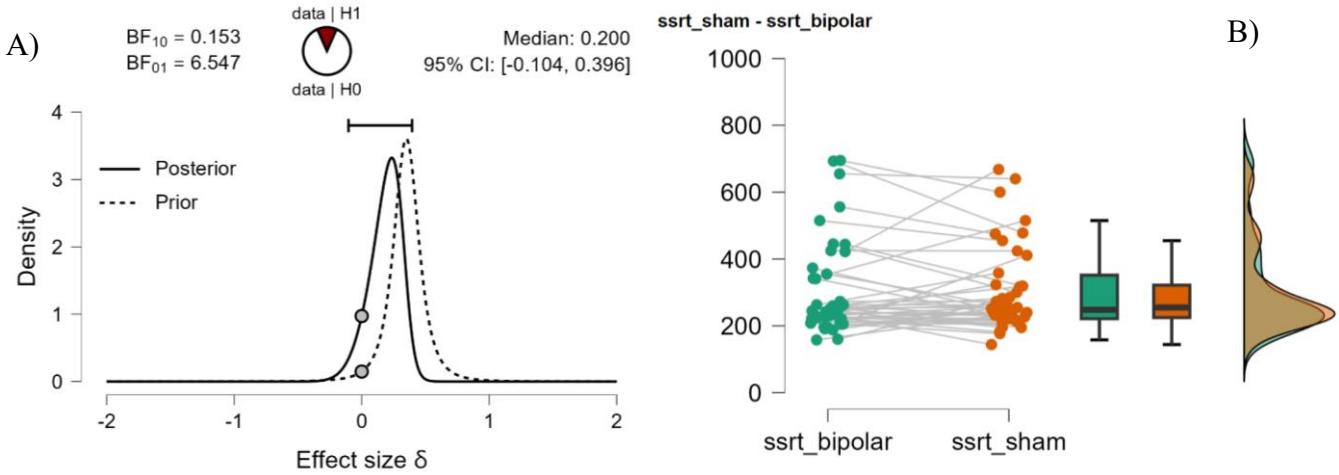

Figure 10 HP1a: graphical representationcomparing the SSRT performancebetween HD-tDCS and sham. A) Graphical representation of Bayes Factors monitoring to the current data collection phase. B) raincloud plots.

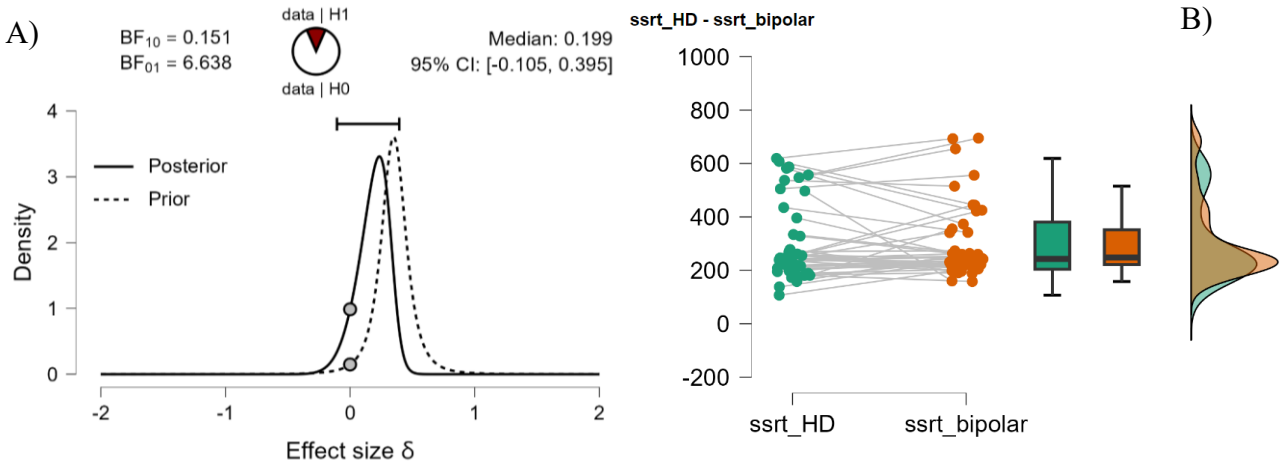

Figure 11 HP1b: A) Graphical representation of BF analysis B) graphical representation of SSRT performance between bipolar tDCS and sham tDCS. A) Graphical representation of Bayes Factors monitoring to the current data collection phase. B) raincloud plots.

favor of the null hypothesis. Finally, for hypothesis HP2, the direct comparison between the anodal HD-tDCS and anodal bipolar tDCS during the rIFG stimulation, yields a BF_{10} of 0.151 and a BF_{01} of 6.638 with a 95% CI: [-0.105, 0.395] (Fig. 12), further supporting a moderate effect of the null hypothesis. These results suggest moderate evidence against the alternative hypothesis in all three experimental conditions, showing an absence of difference for either active tDCS condition in modulating the SST performance, both compared to sham and between them, or that the effect was not strong enough to be

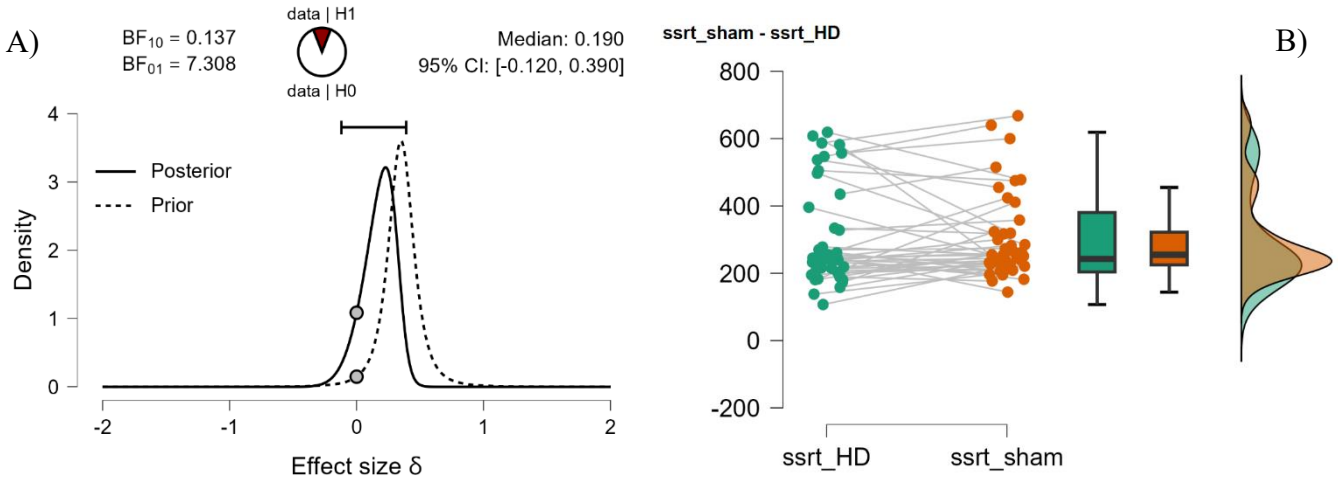

Figure 12 HP2: A) Graphical representation of BF analysis B) graphical representation of SSRT performance between bipolar tDCS and bipolar tDCS. A) Graphical representation of Bayes Factors monitoring to the current data collection phase. B) raincloud plots.

relevant. For these reasons, the preliminary results do not belong to any scenarios hypothesized.

3.3.2 DRT

Although preliminary, Bayesian Paired Samples t-tests for DRT2, across the three stimulation conditions (HD-tDCS | Bipolar tDCS | Sham tDCS), yielded no difference between the conditions (HP1a = 0.120 | HP1b = 0.068 | HP2 = 0.161; Table 3). The data were examined using an informed prior criteria set to t ($\mu = 0.35$, df = 3, r = 0.102), to compare whether the data fit under the alternative hypothesis or the null hypothesis. The first hypothesis HP1a, which compared the effects of HD-tDCS with Sham tDCS over rIFG in modulating dual-response latency (i.e., DRT), reported a BF_{10} of 0.12 and BF_{01} of 8.36 with a 95% CI [-0.145, 0.363] (Fig. 10), underling moderate evidence in favor of the null hypothesis. Likewise, the hypothesis HP1b, comparing bipolar tDCS with Sham tDCS, shows BF_{10} = 0.068 and a BF_{01} = 14.6 with a 95% CI [-0.337, 0.310] (Fig. 11), reporting strong evidence in favor of the null hypothesis. Finally, the comparison between the two active stimulations, hypothesis HP2, yields a BF_{10} of 0.161 and BF_{01} = 6.218 with a 95% CI [-0.102, 0.401] (Fig. 12), suggesting a moderate effect in favor of the null hypothesis. At the same time, Bayesian Paired Sample t-test for GoRT revealed no difference between the three conditions (HP1a = 0.92 | HP1b = 0.205 | HP2 = 0.423;

Table 3 *Bayesian Paired Samples T-Test*

Measure 1		Measure 2	BF_{10}	error %
ssrt_sham	-	ssrt_HD	0.153	0.062
ssrt_sham	-	ssrt_bipolar	0.137	0.053
ssrt_HD	-	ssrt_bipolar	0.151	0.061
goRT_correct_sham	-	goRT_correct_HD	0.092	0.018
goRT_correct_sham	-	goRT_correct_bipolar	0.205	4.246×10^{-4}
goRT_correct_HD	-	goRT_correct_bipolar	0.423	0.002
doubleRT_correct_sham	-	doubleRT_correct_HD	0.120	0.041
doubleRT_correct_sham	-	doubleRT_correct_bipolar	0.068	3.943×10^{-4}
doubleRT_correct_HD	-	doubleRT_correct_bipolar	0.161	0.067

Table3). The data were examined using an informed prior criteria set to t ($\mu = 0.35$, df = 3, r = 0.102), to compare whether the data fit under the alternative hypothesis or the null hypothesis. The effects of HD-tDCS with Sham tDCS over rIFG in modulating the response time to the primary stimulus (i.e., GoRT; HP1a) resulted in a BF_{10} of 0.092 and BF_{01} of 10.866 with a 95% CI [-0.194, 0.363]; the obtained Bayesian Factors underline strong evidence in favor of the null hypothesis. Similarly, the comparison between bipolar tDCS and Sham tDCS (HP1b) reported a BF_{10} of 0.092 and BF_{01} of 4.866 with a 95% CI [-0.066, 0.409], resulting in moderate evidence in favor of the null hypothesis. Finally, the direct comparison between the two active conditions, HD-tDCS and bipolar tDCS (HP2), obtains the following results: $BF_{10} = 0.423$ and $BF_{01} = 2.363$ with a 95% CI [-0.194, 0.363]. These data support anecdotal evidence in favor of the null hypothesis.

Taken together, the results both for DRT2 and GoRT yielded no differences between the stimulation conditions, favoring moderate evidence of the null hypothesis. The findings underline that either active tDCS configuration did not modulate a difference in DRT2 and GoRT or the effect was not strong enough to be considered.

As obtained in SSRT, the present preliminary results showed a consistent effect across participants for both hypotheses, reinforcing as expected the conclusion that there is no substantial difference in DRT and GoRT across tDCS conditions.

4. DISCUSSION

The SST performance results did not reveal any differences across the three experimental conditions (HD-tDCS, bipolar tDCS, Sham tDCS), as indicated by the absence of substantial variations in measured RTs. Indeed, the comparison between HD-tDCS with bipolar tDCS condition effects (HP2), with the relative BF_{10} of 0.151 and a BF_{01} of 6.638, suggests that the observations under the null hypothesis are 6.638 times

more probable than in the alternative hypothesis scenario. While the BF_{10} of 0.153 and BF_{01} = 6.547, concerning the comparison of HD-tDCS and Sham tDCS (HP1a), reports that, under the null hypothesis, the observations are 6.547 times more probable to be obtained than under the alternative hypothesis. Finally, the comparison between bipolar tDCS and Sham tDCS (HP1b) gives a BF_{10} = 0.137 and BF_{01} = 7.308, meaning that the obtained observations are 7.308 times more probable under the null hypothesis rather than in the alternative hypothesis scenario.

The present findings support moderate evidence in favor of the null hypothesis, due to an absence of difference between the sessions. These results imply that the stimulation administered over the rIFG could have not produce the anticipated enhancement in inhibitory control, as evidenced by the absence of significative SSRTs modulation across the three conditions. Therefore, it seems that the anodal stimulations may not modulate the rIFG, defining an absence of evidence in both the conditions considered (HD-, bipolar). For these reasons, the present results are in contrast with previous literature that show a reliable effect of anodal tDCS in enhancing inhibitory control when applied to the rIFG, compared to sham condition. Notably, prior research has reported significant reductions in RTs, improving inhibition ability, following both anodal bipolar tDCS (Hogeveen et al., 2016; Jacobson et al., 2011; Stramaccia et al., 2015) and anodal HD-tDCS (Guo et al., 2022; Hogeveen et al., 2016). These studies collectively suggested that anodal stimulation over rIFG modulates neural activity eliciting the cognitive control enhancement, particularly in tasks requiring response inhibition, such as the SST (Schroeder et al., 2020).

The possible absence of rIFG modulation and the subsequent lack of evidence in favor of this modulatory effect in the current study raise important questions regarding the factors that may have contributed to the discrepancy between our findings and the established literature. Several possibilities could explain this divergence. Firstly, the

intrinsic limitations of tDCS procedure may have played a crucial role in it, which include the interindividual differences between participants and the tDCS parameters settings, i.e., electrode size, placement, current intensity etc. Indeed, interindividual variability is a pervasive limit in tDCS application, which could influence the degree to which tDCS may modulates the neuronal areas, leading to unexpected cortical excitability effect not focused on the target area (De Witte et al., 2018). It is determined by numerous factors, e.g. neuronal structure differences in sulci, gyri or cerebrospinal fluid high conductivity channels (Datta et al., 2009; de Berker et al., 2013). Nonetheless, the sample size should reduce the confounding factors derived by this aspect. Whereas, the stimulation parameters modifications are a consistent limitation in tDCS application, since even a slight change in it may produce a different DC diffusion pattern (Lefaucheur et al., 2017; Liew et al., 2014). Regarding the electrodes position there are two main aspects to be considered. The first pertains the employment of a different EEG cap, since this experiment adopted a 10-10 EEG system cap, while the reference studies (Hogeveen et al., 2016; Jacobson et al., 2011) used a 10-20 EEG system cap. However, this procedural modification should not define an issue since the 10-10 EGG system cap is corroborated to have a higher spatial resolution (Rojas et al., 2018): moreover, another study using this type of electrodes template found significant results (Guo et al., 2022). The other substantial modification, with respect to the previous literature, was the employment of an HD-tDCS configuration tailored on current flow model (Roast; Huang et al., 2016). This montage was not reported by any prior studies and presents a different configuration compared to the most adopted HD-tDCS in literature, such as 4 x 1, which is considered the “gold standard”. However, the reliability and effectiveness of the HD-tDCS configuration based on computational modeling of electrical fields showed reliable evidence about its robustness (Parlikar et al., 2021). In addition, the current flow model used to define the HD-tDCS’s electrodes configuration was tailored to produce a focal

stimulation on rIFG, preventing the possible current spread issues. Therefore, it is unlikely that this aspect probably had a role in the present results. Another important aspect, which could instead be more prominent in the present findings, is the current intensity level. Indeed, it the role current that intensity has on brain modulation effects (Batsikadze et al., 2013; Lefaucheur et al., 2017) is still debated in the tES field. The present study differs in this sense from prior research, since in the inhibitory control literature it was previously used an intensity of 1mA for the bipolar tDCS condition (Hogeveen et al., 2016; Jacobson et al., 2011; Stramaccia et al., 2015), and 1mA (Hogeveen et al., 2016) or 1.25mA (Guo et al., 2022) for the HD-tDCS conditions. Hence, this parameters modification could have an impact on the rIFG modulation, since evidence reports that intensity increasement can induce a deeper stimulation and spread of electric fields into the brain, which in turn could modulate different neuronal networks not related to the target areas, resulting in biological unexpected effects (Lefaucheur et al., 2017). It is however important to note that the parameters settings taken in consideration in the present study follow the literature guidelines (Kesikburun, 2022; Lerner et al., 2021). Moreover, a third potential issue could be related to the participants' baseline in the inhibitory control capacity, since individuals with lower baseline inhibitory control may benefit more from tDCS treatments, as they have greater range for improvement. In contrast, participants with higher baseline performance might not see benefits or may even experience performance impairments due to overstimulation (Vergallito et al., 2022). On the other hand, a large sample, as the one considered in this study, size should prevent this issue.

In summary, the main limit of the present study could be related to the pervasive and intrinsic limitations present in the tDCS application. As showed, one of the main difference from previous studies was related to the stimulation parameters, and specifically the current intensity level, set at 2mA. This could be one of the reasons that

determined a difference in the absence of proper rIFG modulation. Additionally, a confounding role may be played by the interindividual variabilities in brain anatomy and between the participants. Indeed, the HD-tDCS tailored configuration could report a different modulation compared to the one predicted by the current flow model, causing a modulation of the non-targeted regions. However, this highlights an important and critical aspect. Even though the HD-tDCS montage did not report the expected results, the absence of a bipolar significant effect, compared to the sham condition, was unexpected and of interest, since the settings (i.e., montage) were the same reported by the precedent studies (Hogeveen et al., 2016; Jacobson et al., 2011; Stramaccia et al., 2015). Therefore, this result underlines a critical issue about the reproducibility of tDCS effects, in line with the consistent evidence related to this topic (Hunold et al., 2023; Schroeder et al., 2020).

A relevant aspect considered and underlined by the present study was the reduction of the possible confounding factors by the context-dependent variables, thanks to the precautions adopted by the assessment of subjects' chronotype and sleep quality level. Indeed, this is important crucial factor that was not considered in the overmentioned studies. Moreover, the findings regarding the blinding procedure reported a reliability and effectiveness of the sham condition, since a low range (7.32%) of participants was able to judge in a correct fashion the experimental condition administered. This finding underpins the reliability of the reported sham condition settings in tDCS application (Gandiga et al., 2006; Mattavelli et al., 2019; Palm et al., 2013; Pisoni et al., 2015).

5. CONCLUSIONS

NIBS techniques have been established as reliable tools for investigating and modulating neuronal function in both rehabilitation programs and experimental research

settings. Over recent decades, a growing body of evidence has supported their efficacy in these areas. Among these techniques, tDCS developed a prominent role in these fields. Indeed, it has emerged as effective treatment for neurological and psychiatric disorders, such as chronic paint, fibromyalgia, addiction and MDD. Moreover, tDCS has gained a key role in experimental settings applications due to its safety, versatility, easy management, and low-cost, allowing to modulate in a reliable and consistent fashion both primary and associative cortices. The former refers to the first application of tDCS on healthy subjects, with the aim to modulate M1 and visual cortex, eliciting the relative MEPs alterations and phosphene threshold modifications. Concerning the latter, further studies applied the same procedure and theoretical components to the possibility to influence cognitive functions. This through tDCS applications on prefrontal cortices, mainly DLPFC, which shows corroborate effects in cognitive functions modulation, such as decision making, emotions processing, WM and inhibitory control. The reported experimental findings are particularly relevant for clinical applications, since these same protocols could be applied to patients with specific cognitive functions deficit, in order to restore or to enhance them. For example, it could decrease the negative bias in MMD patients, increasing in turn WM in MDD patients, and it seems to decrease craving in patient with addiction disorder.

Concerning the contemporary relevance of tDCS technique in experimental neuropsychology setting, the present study aimed to compare the efficacy of conventional bipolar and HD-tDCS montages in modulating activity in the rIFG. This comparison addressed a gap in the literature concerning the efficacy of HD- configuration relative to bipolar montage, since basing on computational modeling of electrical fields HD-tDCS was hypothesized to provide a greater effectiveness and focality on the target area modulation, potentially leading to an enhanced modulation of brain regions and less dispersion of current flow on non-targeted areas. The two active stimulation’s effects,

bipolar and HD-, were assessed and compared measuring the behavioral performance, specifically RT alterations, during the SST, a reliable measure of inhibitory control. Prior research has shown that anodal tDCS over the rIFG can reduce RTs during the SST, thereby enhancing inhibitory control. While, DRT was employed as control condition, measuring the RTs alterations, since this task considers non-inhibitory action updating, and it is related to rIFG functioning as well. Therefore, it was expected that HD-tDCS, through its more focal stimulation of the rIFG, would yield greater improvements in SST performance than bipolar tDCS, reflecting enhanced inhibitory control. In contrast, no differences were expected in DRT performance, as this task was used to disentangle inhibitory control from non-inhibitory action updating.

Preliminary results from Bayesian paired-samples t-test revealed no significant differences between the three stimulation conditions (HD-tDCS, bipolar tDCS, and sham tDCS) for both tasks. These findings suggest either an absence of stimulation effects or a too weak, non-systematic effect to be detected. The results were consistent across both behavioral tasks, with a moderate effect in favor of the null hypothesis in most comparisons.

The present findings are inconsistent with prior literature, which has reported a significant effect of bipolar tDCS compares to sham condition during SST performance following anodal stimulation on rIFG (Guo et al., 2022; Hogeveen et al., 2016; Jacobson et al., 2011; Stramaccia et al., 2015). Similar results have been observed for HD-tDCS, where anodal stimulation elicited a decrease SSRT, as well as after bipolar tDCS. The main explanation of these inconsistent results compared to the previous ones could at the same time derive and point out to the reproducibility issues related to tDCS, mainly involving a difference between studies in the parameters setting, and interindividual variabilities. In the present study the main parameter variation was represented by the current intensity, employing a higher value, 2mA, compared to precedent works on the

same topic. Furthermore, the HD-tDCS configuration was tailored to the computational modeling of electrical field (ROAST), providing a tailored an ad-hoc montage for this condition. This tailored configuration could have defined a different current spread pattern with respect to modeling predictions, even though the available literature evidence report a reliability on this type of configurations based on computational current flow modeling (Parlikar et al., 2021). However, the absence of bipolar tDCS conditon effects, compared to sham conditon, highlights a critical and relevant aspect of the present results. Indeed, the bipolar tDCS montage was the same used in literature studies with a significant effect on SST performance. Therefore, the bipolar tDCS preliminary results underlines the importance to consider the difficulties of reproducing tDCS effects and their variability in the experimental procedure, since they are a critical component of tDCS application, as also evidenced in previous works (Hunold et al., 2023; Schroeder et al., 2020).

One potential approach to mitigate these limitations could be the use of individualized tDCS configurations, achieved through the acquisition of individual MRI scans and subsequent computational modeling of current flow for each participant (De Witte et al., 2018; Lee et al., 2023). This procedure may prevent the issues derived by the electrodes placement template, i.e., 10-10 EEG system, although it is very expensive in term of cost and time. Moreover, the sham conditions settings showed an high level of reliability, underpinning the precedent findings about the effectiveness of the blinding condition of tDCS technique (Gandiga et al., 2006; Mattavelli et al., 2019; Palm et al., 2013; Pisoni et al., 2015).

Undoubtedly, tDCS is a reliable technique for brain modulation. For this reason, even though these preliminary results did not yield a significant effect for the active stimulation conditions, this study provides an important foundation for investigating and deepen the comparative efficacy of different tDCS montages. This line of research could generate

relevant new evidence regarding the capacity to modulate target regions and their corresponding cognitive functions with greater precision and effectiveness; indeed, a branch of studies that consider this systematic research on comparison is not defined yet and this coupling is not directly investigated yet. HD- configuration has the potential to be a prominent montage to optimize the tDCS's modulation effects and reduce the undesired stimulation in non-targeted areas, as reported by computational modeling of electrical fields (Diana et al., 2021; Dmochowski et al., 2011). Nevertheless, HD-tDCS role in cognitive functioning enhancement compared to bipolar montage is debated yet and until now is only theoretical, since studies reports similar effects of the bipolar setup. Therefore, this study represents an important starting point for examining differences in the efficacy of HD-tDCS and bipolar tDCS, and overall, the clinical potential and the experimental benefits of employing the HD-tDCS. Additionally, the present study introduces innovative exclusion criteria, such as the inclusion of sleep quality index and considerations of participants' chronotype, not present in the reference studies. These measures have an important relevance in experimental neuropsychology, since they allow to control and decrease the possible confounding factors that may influence cognitive performance during the behavioral tasks.

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