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Modulating the excitability of the visual cortex using a stimulation priming paradigm

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ABSTRACT

Background: Transcranial random noise stimulation (tRNS) can cause long term increase of corticospinal excitability when used to prime the motor cortex, before measuring the motor response in the hand muscles with TMS (Terney et al., 2008). In cognitive studies, tRNS has been used to improve visual attention and mathematical skills, an enhancement effect that might suggest sustained cortical plasticity changes (Cappelletti et al., 2013; Snowball et al., 2013). However, while the behavioral evidence of increased performance is becoming substantiated by empirical data, it still remains unclear whether tRNS over visual areas causes an increase in cortical excitability similar to what has been found in the motor cortex, and if that increase could be a potential physiological explanation for behavioral improvements found in visual tasks.
Objective/hypothesis: In the present study, we aimed to investigate whether priming the visual cortex with tRNS leads to increased and sustained excitability as measured with visual phosphenes.
Methods: We measured phosphene thresholds (PTs) using an objective staircase method to quantify the magnitude of cortical excitability changes. Single-pulse TMS was used to elicit phosphenes before, immediately after, and every 10 min up to one hour after the end of 20 min tRNS, anodal tDCS (a-tDCS) or sham.
Results: Results showed that phosphene thresholds were significantly reduced up to 60 min post stimulation relative to baseline after tRNS, a behavioral marker of increased excitability of the visual cortex, while a-tDCS had no effect. This result is very similar in magnitude and duration to what has been found in the motor cortex.
Conclusions: Our findings demonstrate promising potential of tRNS as a tool to increase and sustain cortical excitability to promote improvement of cognitive functions.

1. Introduction

Electrical stimulation techniques (tES) have been used in the last decades to study cortical excitability. In particular, transcranial direct current stimulation (tDCS) can modulate cortical excitability of the motor cortex (M1) in humans and facilitate learning (Baudewig et al., 2001a, 2001b; Lang et al., 2004; Nitsche et al., 2000, 2007, 2003; Paulo et al., 2013). This effect has been studied measuring motor evoked potentials (MEP), recorded as a direct physiological peripheral response of a muscle to transcranial magnetic stimulation (TMS) over the motor cortex. In order to study the mechanisms underlying tDCS and its effect upon cortical excitability, Nitsche and colleagues compared MEPs before and after priming the motor cortex with 5 min of anodal tDCS. The results showed that MEPs' amplitude increased 40% when anodal stimulation was applied over M1, and this increase lasted for 10 min after the end of the stimulation (Nitsche et al., 2000). Interestingly, 10 min of facilitatory pre-conditioning anodal tDCS can lower MEPs up to 20 min relative to baseline (Siebner et al., 2004). Following these works, Antal and colleagues used a similar procedure but on the visual cortex, and measured visual phosphene thresholds (PTs). Specifically, subjects were primed with 10 min of a-tDCS and PTs were measured before, immediately after, 10 and 20 min after the end of the stimulation, using short trains of 5 Hz repetitive TMS. Results showed a significant reduction of PTs immediately after anodal stimulation (at 10 min post a-tDCS), and although the effect was short lived, it demonstrated that the visual cortex can be modulated in a polarity-dependent manner, similar to the motor cortex (Antal et al., 2003a).

Other subsequent studies have shown that tDCS can modulate the

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amplitude of visual evoked potentials (Antal et al., 2004a), alter the perception of phosphenes (Antal et al., 2003a, 2003b), affect motion detection (Antal et al., 2004b) and reduce the duration of the motion after-effect (Antal et al., 2004c). More recently tDCS has also been used to study higher cognitive functions such as attention (Gladwin et al., 2012), working memory (Berryhill et al., 2010; Fregni et al., 2005), long term memory (Rroji et al., 2015), learning (Reis et al., 2009), and also as a rehabilitation tool for patients with brain lesions (Fiori et al., 2011; Jo et al., 2009; Kang et al., 2009).

However, recent systematic reviews have raised doubts about the effectiveness of tDCS, arguing that single-session tDCS generates little to no reliable effects beyond MEP amplitudes changes (Horvath et al., 2015). The authors suggest that it is crucial to further investigate the effects of direct current stimulation, and especially to address the question of how it affects other areas of the cortex, besides M1. In the majority of published tDCS studies, the effects found on M1 are used as a model system to design stimulation protocols for other areas. However, the effects can vary strongly, indicating that different areas have different anatomical characteristics, from skull morphology to axons orientation, hence leading to different current flow distribution in the brain and to potentially different behavioral outcomes (Datta et al., 2011; Radman et al., 2009). Interesting modeling of the current distribution in the brain after electrical stimulation have shown that the effect can be diffuse, likely spreading to other circuits besides those directly under the stimulating electrodes (Miranda et al., 2013; Salvador et al., 2010). It is therefore very important to establish what is the actual effect of direct current stimulation, if one ought to use it to promote and increase cortical plasticity with the goal to improve behavioral functions (Antal and Paulus, 2008). Moreover, while there is clear evidence that facilitatory dual-stimulation protocols can substantially extend the benefit of brain stimulation in the motor cortex (Siebner et al., 2004), the evidence that the same mechanism might also work in other parts of the brain, to our knowledge, has not been shown in human studies, despite its potential application to cognitive augmentation (for a review see Karabanov et al., 2015; Hurley and Machado, 2017).

In recent years, tDCS studies have produced controversial results. For instance, studies of visual perceptual learning (VPL) have demonstrated improvement of functions after multiple training sessions using visual tasks, following cathodal tDCS, a procedure classically considered an inhibitory technique (Batsikadze et al., 2013; Berryhill et al., 2010; Dockery et al., 2009; Elmer et al., 2009; Fricke et al., 2011; Moliadze et al., 2012; Pirulli et al., 2014; Williams et al., 2010). More recently, Peters and colleagues showed that, contrary to their prediction, anodal tDCS blocked consolidation of learning in a contrast detection task (Peters et al., 2013).

One promising direct current stimulation procedure is tRNS, the most recently developed neuromodulatory technique. It is thought to interfere with noise processing and ongoing neuronal oscillations in the brain, and therefore modulate neuronal excitability. Terney and colleagues (Terney et al., 2008) showed that 10 min of weak random electrical stimulation within the high-frequency band (101–640 Hz) targeting the motor cortex (M1) was sufficient to significantly alter cortical excitability up to 60 min after the end of the stimulation. Specifically, they showed that 10 min tRNS over the primary motor cortex, induced an excitability increase up to 20–50%, as subsequently measured in MEPs' amplitudes, as revealed by single and paired-pulse TMS. A following study extended these results by demonstrating that even shorter duration stimulation protocols (5 min tRNS) can induce significant after-effects on the corticospinal excitability (Chaieb et al., 2011).

Since motor learning is always associated with enhancement of M1 corticospinal excitability (Muellbacher et al., 2002; Pascual-Leone et al., 1999; Sczesny-Kaiser et al., 2016), and evidence from recent studies suggest a link between tES-induced corticospinal excitability and skill learning (Boggio et al., 2006; Galea and Celnik, 2009; Reis et al., 2009), it is crucial to investigate further the relationship between these two parameters.

Behavioral studies showed that perceptual learning coupled with online tRNS can boost learning of complex visual motion and, crucially, these improvements are sustained in time (Herpich et al., 2015) However, it is still unclear how different types of tES influence the activity of different cortical areas, and whether stimulation with tRNS over other brain areas, besides M1, causes similar changes in cortical excitability.

Here, to investigate the modulatory effect of tES, we compared the effect of tRNS and a-tDCS on cortical excitability of the primary visual cortex of healthy adults.

To quantify the effect of tRNS and a-tDCS, we measured phosphene thresholds at different time intervals, after we primed the visual cortex with either techniques, in separate experiments. tRNS significantly reduced PTs at every time interval we tested and up to 60 min post stimulation, likely indicating increased cortical excitability. On the contrary, a-tDCS had no effect on PTs at any interval we tested.

2. Material and methods

2.1. Preliminary phosphene threshold

Participants were sitting in a semi-darkened room, positioned on a chin-rest forehead combination bar to stabilize their head while blindfolded, and they were instructed to keep their eyes closed throughout the entire testing session (de Graaf et al., 2017). They were allowed to adapt to darkness for at least 2 min and a baseline estimation of the PTs was registered. Subjects were instructed to keep fixation on an imaginary central fixation cross, directly in front of them and report the presence or absence of a phosphene. Initially the TMS coil was positioned with the handle pointing leftward parallel to the ground with the center placed 2–4 cm above the inion corresponding to Oz based on the 10–20 electroencephalogram standard measures, and then moved to locations roughly corresponding to O1 and O2 (for the left and right hemisphere, respectively). We started by applying single pulse TMS over Oz initially at 50% of maximum stimulator output. If the subject did not perceived any phosphene at this stimulation intensity, it was increased in steps of 5% until the subject perceived a phosphene and maximum up to 80% of the stimulator output. If the subject still did not perceive any phosphene the coil was moved 0.5 cm to the left or right and the procedure was repeated until a TMS pulse evoked a bright and reliable phosphene. The location of the coil where stable phosphenes were reported was marked on a swimming cap worn by the subject. After an interval of 5 min, the participant was stimulated again on the marked spot, and if this stimulation induced a reliable phosphene, the point was marked on the cap for the subsequent testing. A phosphene was considered stable and reliable only when the subject perceived it always at the same location in the visual field and with the same appearance in at least 3 out of 5 stimulations.

Once the hotspot was identified, the REPT (Rapid Estimation of Phosphene Threshold, (Abrahamyan et al., 2011)) procedure was used to determine individual PTs, more systematically. Participants were instructed to respond to the presence or absence of the phosphene by pressing the left or right "shift" key on the computer keyboard after the automatically triggered single-pulse TMS stimulation (with at least 3 s interval between each stimulation). REPT is a procedure that employs a Bayesian adaptive staircase protocol for estimating psychophysical thresholds. This procedure has shown to be more accurate, reliable and faster relative to other procedures (Modified Binary Search Algorithm, MOBS (Tyrrell and Owens, 1988)) (see (Abrahamyan et al., 2011)). For each participant at least 2 REPT were collected during the preliminary session to assess for PTs stability.

2.2. Phosphene detection task

Using the coordinates from the preliminary session, participants