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Reward motivation and neurostimulation interact to improve working memory performance in healthy older adults: A simultaneous tDCS-fNIRS study

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Abstract

Several studies have evaluated the effect of anodal transcranial direct current stimulation (tDCS) over the prefrontal cortex (PFC) for the enhancement of working memory (WM) performance in healthy older adults. However, the mixed results obtained so far suggest the need for concurrent brain imaging, in order to more directly examine tDCS effects. The present study adopted a continuous multimodal approach utilizing functional near-infrared spectroscopy (fNIRS) to examine the interactive effects of tDCS combined with manipulations of reward motivation. Twenty-one older adults (mean age = 69.7 years; SD = 5.05) performed an experimental visuo-spatial WM task before, during and after the delivery of 1.5 mA anodal tDCS/sham over the left prefrontal cortex (PFC). During stimulation, participants received performance-contingent reward for every fast and correct response during the WM task. In both sessions, hemodynamic activity of the bilateral frontal, motor and parietal areas was recorded across the entire duration of the WM task. Cognitive functions and reward sensitivity were also assessed with standard measures. Results demonstrated a significant impact of tDCS on both WM performance and hemodynamic activity. Specifically, faster responses in the WM task were observed both during and after anodal

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Appendix A. Supplementary data

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tDCS, while no differences were found under sham control conditions. However, these effects emerged only when taking into account individual visuo-spatial WM capacity. Additionally, during and after the anodal tDCS, increased hemodynamic activity relative to sham was observed in the bilateral PFC, while no effects of tDCS were detected in the motor and parietal areas. These results provide the first evidence of tDCS-dependent functional changes in PFC activity in healthy older adults during the execution of a WM task. Moreover, they highlight the utility of combining reward motivation with prefrontal anodal tDCS, as a potential strategy to improve WM efficiency in low performing healthy older adults.

Keywords

Working memory; tDCS; fNIRS; Cognitive aging; Prefrontal cortex

1. Introduction

Healthy aging in humans is invariably associated with a progressive decline in cognitive functioning. This decline affects not only low-level (i.e., sensory/perceptual) stages of processing, but also higher-level stages that enable more complex cognitive activities, such as learning, long-term memory, attentional control, reasoning, and decision-making (Baddeley, 2000; Conway et al., 2002; Miyake and Shah, 1999). The efficiency of working memory (WM), that is, the ability to maintain task-relevant information in a temporary active state for use in on-going task processing (Baddeley, 2010, 1992; Logie and Morris, 2015), is commonly held to be at the core of these activities (e.g., Unsworth et al., 2014), and sensitive to physiological age-related decline (Bopp and Verhaeghen, 2005; Park et al., 2002). Furthermore, WM efficiency is predictive of the transition from mild cognitive impairment (MCI), namely, a clinical condition in which the cognitive decline exceeds that of normal aging, but does not impair daily living (Petersen et al., 2001), to a diagnosable state of dementia (Belleville et al., 2014; Summers and Saunders, 2012; Vermeij et al., 2016).

With the hope of slowing this age-related decline in WM function, a growing number of studies have explored the effects of intensive computerized training, testing older adults with and without a clinical diagnosis (for recent reviews on computerized cognive training in middle life, late life and in patients with MCI, see Gates et al., 2019 a–b–c). However, although initial results reported widespread cognitive benefits, more recent studies indicate that WM training itself is far more likely to bring about modest and short-lived effects on WM, with little benefit on mood and other aspects of mental life (Talsma et al., 2017; see Melby--Lervåg et al., 2016; Vermeij et al., 2016). For this reason, a more recent approach has been to investigate whether WM training effects could be boosted by concomitantly stimulating the activity of the WM brain network using transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that conveys low-intensity electric current to the scalp through pairs of electrodes (anode/cathode).

Such approaches have been inspired by initial evidence suggesting that even a single application of anodal tDCS, mostly over the prefrontal cortex (PFC), can improve WM

performance in both healthy individuals and clinical populations (Fregni et al., 2005; for recent reviews see Bennabi et al., 2015; Brunoni and Vanderhasselt, 2014; Hill et al., 2016; Mancuso et al., 2016).

More recent work has explored the neural mechanisms underlying tDCS effects. Studies on motor cortex excitability have demonstrated that anodal tDCS brings about depolarization of the neuronal resting membrane potential, while cathodal tDCS can bring about hyperpolarization, causing respectively excitatory-inhibitory effects (Kropotov, 2016; see also Nitsche and Paulus, 2001, 2011).

These nonsynaptic mechanisms bring about relatively short-term effects, which usually last for a period of time that is approximately proportional to the stimulation time itself. Importantly, longer and repeated sessions of tDCS can result in longer-term after-effects, which occur through N-methyl-D-aspartate (NMDA) dependent mechanisms. These effects are similar to long-term synaptic potentiation (LTP) and depression (LTD) (Kropotov, 2016; see also Das et al., 2016; Pelletier and Cicchetti, 2015; Santarnecchi et al., 2015; Hummel and Cohen, 2006), and represent the most important feauture of this technique from a clinical perspective (Cruz Gonzalez et al., 2018; Kropotov, 2016).

Although anodal-excitation and cathodal-inhibition effects were found to be quite common in motor investigations, the pattern emerging from stimulation of non-motor areas is less clear (for a review, see Jacobson et al., 2012). Specifically, when focusing on the studies combining WM training with anodal tDCS, mostly over the dorsolateral prefrontal cortex, the results appear to be quite mixed. While a subset reported increments of training-induced benefits using tDCS (Au et al., 2016; Jones et al., 2017; Passow et al., 2017; Ruf et al., 2017; Stephens and Berryhill, 2016), other studies found small to null results, questioning the role of tDCS in the increase of WM training effects, particularly with regard to older populations (Hill et al., 2016; Horvath et al., 2015; Jantz et al., 2016; Mancuso et al., 2016; Nilsson et al., 2017).

To account for the inconsistency of these results, different hypotheses have been proposed. One emphasizes the dependency of tDCS effects on task demands (Dedoncker et al., 2016; Gill et al., 2015; Stephens et al., 2017) in combination with inherent inter-individual variability, reflected in terms of “baseline” cognitive capacity, education, and cognitive reserve (Arciniega et al., 2018; Berryhill and Jones, 2012; Li et al., 2015; Wiegand et al., 2016). The second hypothesis suggests that the variability of tDCS effects is due to inter-individual genetic differences, which are primary determinants of individual rates of neuroplasticity and/or neurotransmitter system efficiency (Dahlin et al., 2008; Stephens et al., 2017; Wiegand et al., 2016). A third relatively more recent account highlights the role of neuronal morphology, age, and cortical atrophy in explaining the variability of tDCS effects (Antonenko et al., 2018; Filmer et al., 2019; Mahdavi and Towhidkhah, 2018; Woods et al., 2019a).

Despite the fact that these hypotheses are not mutually exclusive, a lively debate has been generated. In our opinion, this debate is symptomatic of a primary limitation inherent in the prior work, due to the currently poor understanding of the functional consequences of using

tDCS during WM tasks, particularly when it is applied to frontoparietal brain regions that are both selectively engaged during high-level cognitive processing and highly sensitive to the physiological age-related decline (Bäckman et al., 2011, 2010; Braver et al., 1997; Braver and Barch, 2002; Melby-Lervåg et al., 2016).

To overcome this limitation, in the last few years several studies employed different functional neuroimaging techniques, before, during or after the delivery of different kinds of transcranial electrical stimulation, in order to directly investigate the neural underpinnings of this stimulation (Bergmann et al., 2016; Falcone and Callan, 2019; Soekadar et al., 2016; Woods et al., 2019b; Wörsching et al., 2016). However, most of the studies investigating the effects of tDCS over the PFC have focused on resting-state activity (Callan et al., 2016; Hone-Blanchet et al., 2016; Keeser et al., 2011; Merzagora et al., 2010; Peña-Gómez et al., 2012), while only a small minority examined the effects of prefrontal tDCS on specific cognitive functions, such as arithmetic abilities (Clemens et al., 2013; Hauser et al., 2016), decision-making (Chib et al., 2013; Weber et al., 2014), and word fluency (Ehlis et al., 2016). Moreover, to the best of our knowledge, only two previous studies have investigated the neural correlates of prefrontal tDCS using tasks tapping WM efficiency (Jones et al., 2015; Wörsching et al., 2018). Further, both these studies focused on young participants, and only the first one (Jones et al., 2015) specifically monitored tDCS-dependent functional changes in PFC activity related to the execution of a WM task. Because of the relevance of the results of Jones and colleague's study (2015) for the purposes of the present research, we next review the study design and findings in greater detail.

In Jones et al.'s study (2015), the researchers conducted two separate experiments, which evaluated whether supplying a passive or an active rehearsal strategy (Experiment 1), or providing high or low motivational incentives (Experiment 2) would boost the effects of prefrontal anodal tDCS in the WM performance of two groups of young healthy participants: 10 with high WM capacity and 10 with low WM capacity. In each experiment, anodal (and sham) tDCS was delivered for 10 min over the left PFC (between F3 and F7 sites of the International 10–20 EEG system; Jasper, 1958) at an intensity of 1.5 mA. Furthermore, tDCS-induced alterations in the cortical activity of the left PFC were investigated employing functional Near Infrared Spectroscopy (fNIRS). This technique measures non-invasively task-related changes in oxy- (HbO) and deoxy-hemoglobin (HbR) concentration as a proxy of brain activity. In both experiments, fNIRS channels were placed so as to monitor the same site where the tDCS was delivered (left PFC), and the hemodynamic activity was monitored before and immediately after the stimulation.

A number of key findings were reported in the Jones et al.'s study (2015). First, fNIRS results in Experiment 1 demonstrated that anodal tDCS over the left PFC led to a significant increase of HbO levels compared to sham for both high and low WM capacity participants, with the greatest increase when an active rehearsal strategy was provided (Jones et al., 2015).

However, the behavioral results of Experiment 1 indicated that only the high WM capacity participants benefited from the combination between anodal tDCS and active rehearsal

strategy, while low WM capacity participants did not show any WM performance improvement.

The results of Jones et al. (2015) Experiment 2 are of greatest interest and relevant for the current investigation. In Experiment 2, the combination of high motivational incentives and anodal tDCS led to a significant performance improvement in both high and low WM capacity participants (Jones et al., 2015). These findings dovetail nicely with a recent theoretical development in cognitive neuroscience, namely, the Value-Based Cognitive Control (VBCC) framework (Botvinick and Braver, 2015; Yee and Braver, 2018). The VBCC framework suggests that the presence of reward incentives increases the motivational value of cognitive control, which directly translates into increased activation drive within the frontoparietal control networks that are known to be critical for WM function (Etzel et al., 2016; Westbrook and Braver, 2016). Surprisingly, however, the fNIRS results of Jones et al. (2015) second experiment did not reveal a significant effect of tDCS and reward motivation on hemodynamic activity in the left PFC. The only modulation of hemodynamic activity they found was a globally higher HbO level in low compared to high WM capacity participants, across all motivational conditions (both high and low reward) and after both sham and anodal tDCS (Jones et al., 2015).

The absence of an effect of tDCS in the fNIRS results of Jones et al. (2015) may have been due to specific limitations of their experimental design that we aim to resolve in the present investigation. First of all, in their Experiment 2, hemodynamic activity was monitored only in the left PFC. Because approach motivation has been shown to specifically increase the activity of the left PFC (Ohmann et al., 2018; for a review see Kelley et al., 2017), HbO levels in this area may have reached an upper plateau in both anodal and sham conditions, specifically due to the presence of heightened reward motivation in both conditions. A more extended distribution of the fNIRS optodes could provide further important information, especially in light of the fact that tDCS effects might not be circumscribed to the site of stimulation (Mondini et al., 2018; Turi et al., 2012; Vermeij et al., 2017). Second, Jones et al. (2015) estimated PFC activity through fNIRS in an asynchronous way with respect to tDCS. Specifically, left PFC activity was not monitored during the stimulation period itself, but only before (*pre*) and immediately after (*post*) the delivery of tDCS. Therefore, given that both the physiology and the duration of tDCS effects on the neural tissue are still to be fully understood (for recent evidence, see Molero-Chamizo et al., 2018), it is possible that tDCS effects would have been detected if fNIRS were to be employed *concurrently* with tDCS stimulation.

Finally, Jones et al. (2015) exclusively studied healthy younger adults, and this may have reduced their sensitivity to detect combined reward motivation plus tDCS effects on frontoparietal WM function.

Indeed, to the best of our knowledge, no study has yet employed functional neuroimaging to study the effect of prefrontal anodal tDCS in relation to WM task performance in healthy older adults; consequently, the neural correlates of the potential beneficial effects of tDCS on age-related WM decline remain unclear.

The current study aimed to fill this gap, extending Jones et al. (2015) study design to examine the combined effects of reward motivation and anodal tDCS over the left PFC, in improving the WM efficiency of healthy older adults. With the hope of more sensitively detecting the effects of anodal tDCS on hemodynamic cortical activity, we employed fNIRS to concurrently monitor both the left and right PFC, as well as the bilateral posterior parietal cortex (PPC), because of its sensitivity to (spatial) WM load and reward motivation (Etzel et al., 2016; Wisniewski et al., 2015). Moreover, the hemodynamic activity of the bilateral motor cortex was also monitored, because of the motor planning required in our task. Critically, a multi-modal approach was adopted, in which hemodynamic activity from each of the three regions of interest (ROIs) was monitored not only before and after the stimulation, but also during the delivery of the stimulation itself. Finally, an "online" tDCS protocol was employed, stimulating the left PFC during the execution of the rewarded WM task. Indeed, recent evidence suggests the superiority of "online" tDCS over "offline" tDCS for the enhancement of cognitive performance (Andrews et al., 2011; Katsoulaki et al., 2017; Martin et al., 2014; Oldrati et al., 2018). With this approach, we predicted that we would observe significant improvement in older adult's WM performance in the reward motivation combined with anodal tDCS condition, relative to sham stimulation, accompanied by increased frontoparietal cortical activity, as measured with fNIRS.

2. Method

2.1. Participants

Right-handed individuals between the ages of 60 and 80 years were recruited through a participant panel of research volunteers of the University of Padova, via local community centres, and through public advertisements. Exclusion criteria included a prior or current history of neurological and psychiatric illness, and the presence of any condition incompatible with tDCS, according to the most updated safety guidelines (Bikson et al., 2016).

An accuracy level lower than 40% for each task block was considered as a further exclusion criterion, in order to have enough trials for the fNIRS analysis. All participants completed the Edinburgh Handedness Inventory (Oldfield, 1971) assessing hand dominance to exclude left-handed individuals.

Twenty-eight subjects took part in the study (mean age = 70.4 years; SD = 5.2; mean education = 14.4 years, SD = 3.6; 9 males). Three participants did not come back for the second session for personal reasons, one had to be excluded due to technical problems with tDCS (high impedance), and one because was not able to complete the task. Another participant could not complete the first session because of uncomfortable skin sensation, attributed to tDCS. One participant had to be excluded during the analysis phase, due to accuracy below 40% on all WM task blocks. Therefore, the final sample included 21 participants (mean age = 69.7 years; SD = 5.05; mean education = 14.1 years, SD = 3.25; 9 males).

All participants provided written informed consent, and were paid for their participation. The amount they received (up to 25 euro) was partially based on their performance on the

task blocks involving reward. The study protocol was in accordance with the Helsinki Declaration on human rights and was approved by the Ethics Committee of the School of Psychology, University of Padova.

2.2. Experimental procedure

2.2.1. Design and procedure—Each participant was required to attend three sessions (see Fig. 1). The first two sessions were organized as follows. Participants performed three blocks of the same event-related visuo-spatial WM task (see Fig. 2) during which both the presence of reward and tDCS were manipulated. The first ("baseline") and third ("post tDCS") blocks were identical, and were performed without reward or tDCS. The second block included randomly intermixed low and high performance contingent rewards, as well as the delivery of tDCS over the left PFC.

Across all blocks of the first two sessions cortical hemodynamic activity was monitored by means of fNIRS. The only difference between the two sessions was the type of tDCS protocol applied in the second block (anodal vs. sham, with the order counterbalanced across participants). The two sessions were spaced apart for all participants, with a minimum interval of 2 days, in order to minimize any potential carryover effects of anodal tDCS.

The study was single-blinded, since participants were not aware of the hypotheses tested and did not know which tDCS condition they were administered during each session.

In the final (third) session, a cognitive assessment battery was administered to each participant, in order to obtain standard measures of cognitive functions, reward sensitivity, and cognitive reserve.

2.2.2. WM task—In all task blocks, participants performed a novel event-related visuo-spatial WM paradigm that was programmed with E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). The task was displayed on a LCD computer monitor at a viewing distance of approximately 57 cm. Task trials involved visual presentation of a set of four different items arranged in a square formation around a central fixation point, with participants instructed to encode and retain this 4-item set over a short retention period, while binding together item identity and location (see Fig. 2). Each trial began with the presentation of a fixation cross at the center of the screen for 500 m s, which was followed by the presentation of four consonants of the Italian alphabet, displayed in capital letters, appearing in white font on a black background for 1500 m s, and located at the edges of a notional square of 2° × 2° of visual angle placed at the center of the screen. Each consonant could only appear once in a given display, allowing a unique binding of the consonant with its location on that trial, which participants were instructed to actively maintain over a 3000 m s delay interval. Following this delay, a single probe letter in lowercase appeared at the center of the screen for 1000 m s, during which participants were required to make an old/new judgment regarding the probe status. If the probe was judged old, participants were to indicate this by pressing one of four buttons on the response box, using the index and middle fingers of both left and right hands to indicate the corresponding spatial location of the previously presented item (response buttons were arranged in compatible spatial positions to the visual display format; see Fig. 2). If the item was judged to be new, this was

to be indicated using a fifth response key, using the right thumb, to press a button located centrally at the bottom of the response box. The probe item matched one of the letters from the memory set on 80% of the trials, whereas on the other 20% of trials the probe letter was randomly selected among the available set of non-displayed letters. The position of the probe letter in the memory array was equally balanced among the four possible positions across trials.

Across the three blocks an almost identical trial structure was utilized, with the following exceptions. In the “reward + tDCS” block (100 trials), trials were initiated with the presentation of a reward cue at the center of the screen for 1000 m s, indicating the reward value of the trial, which was then followed by the fixation cross.

Fifty trials were associated with a possible win of 2 Euro cents (low reward), and 50 trials with a possible win of 20 Euro cents (high reward). The reward cue presentation was random and both cues were of equal luminance.

In order to obtain the available reward for that trial, the response had to be accurate and indicated within 1000 m s from probe presentation.

Performance feedback was given in the form of either a green check mark (rewarded) or red cross (no reward) superimposed on the same reward cue displayed at the beginning of the trial, and presented at the center of the screen for 1000 m s after each response. In the baseline and the post-tDCS blocks (50 trials each), performance feedback was also given but with just the green check mark or red cross, and only when the response was made within 1000 m s of probe onset. If the response was slower than 1000 m s, no feedback was shown, but the response time was registered, if within the time limit of 1500 m s. Across all blocks and trials, and inter-trial interval of 6000–8000 m s (randomly jittered) occurred after delivery of performance feedback, to allow the hemodynamic response to return to baseline. During this time interval, a blank screen was presented.

At the beginning of the two task sessions, participants familiarized (or refreshed) themselves with the task in a practice block, completing 10 training trials. They had to perform correctly at least 6 out of the 10 trials to proceed to the subsequent experimental blocks. Otherwise, the practice block was repeated until such a criterion was reached (an average of 25.2 ± 19.5 and 14.5 ± 5.6 practice trials were required in session 1 and 2, respectively). Participants were asked to minimize head movements and not to talk (e.g., rehearsing the letters aloud) for the entire duration of the session, to reduce motion artefacts in the fNIRS signal. However, they were allowed to repeat the letters mentally if they wanted, as well as to use any other strategy that they considered as the best for their task performance. Before starting the “reward + tDCS” block of the first session, participants were told that the amount of money collected in each of the two sessions would be part of their payment for participation. At the end of the second session, during the debriefing period, participants were asked to rate their reward motivation on a 7-point scale. Furthermore, they were also asked to rate the perceived task difficulty on the DP15 rating scale (Delignières, 1993).

2.2.3. tDCS parameters—During the execution of the "reward + tDCS" block, a direct current stimulation of 1.5 mA intensity was delivered by a battery driven constant-current stimulator (BrainSTIM, EMS-CE certified), through two electrodes. In both anodal and sham conditions, the anode was placed over the left PFC directly between F3 and F7 (referring to the International 10–20 system; see Fig. 3), while the return electrode (cathode) was placed on the contralateral shoulder. The dimension of both electrodes was 5 × 7 cm but, in order to record simultaneously the hemodynamic changes on the stimulated area, two holes were created in the anode electrode to lodge an fNIRS detector and a source. The dimension of each hole was 9 mm in diameter and, therefore, it did not substantially impact the amount of current density delivered. For the anodal tDCS, stimulation lasted 26 min, with a fade-in and fade-out of 30 s. Sham stimulation included 30 s of ramping up and down stimulation, to give the participant a physical sense of stimulation associated with current change (Gandiga et al., 2006).

Before starting the task, the experimenter checked that the impedance was lower or equal to 5 kU. A film of conductive gel was placed below each electrode to facilitate the decrease of the impedance. The use of gel instead of the sponge wrappers was motivated by the requirement of placing the anodal electrode under the cap employed for the fNIRS recording. The experience of side effects was assessed through an interview at the end of each session. However, to minimize the risk associated with tDCS, safety guidelines were scrupulously followed, and participants were monitored throughout the stimulation sessions, and asked to report any discomfort immediately. Almost no one reported any discomfort.

2.2.4. fNIRS—The fNIRS data were acquired with a multi-channel, frequency-domain NIR spectrometer (ISS Imagent™, Champaign, Illinois) equipped with 64 laser diodes (32 emitting light at 690 nm and 32 at 830 nm) and 8 photo-multiplier tubes. Source and detector locations on the participants' head were chosen using the AtlasViewer software (Aasted et al., 2015) in order to sample the inferior and middle frontal gyri, supplementary motor area, and intra-parietal sulcus (IPS) in both hemispheres (Fig. 3). The array consisted of 38 standard channels with source-detector distance of 3 cm and 2 short-separation (SS) channels with source-detector distance of 0.8 cm (Brigadoi and Cooper, 2015), one located in the left frontal part of the array and the other in the symmetric right frontal part of the array.

Standard channels were divided into three ROIs, symmetrically placed in both hemispheres: 12 channels formed the frontal ROI (F channels in Figs. 3), 14 channels formed the motor ROI (M channels in Figs. 3) and 12 channels formed the parietal ROI (P channels in Fig. 3). A soft black tissue cap (EasyCap, Germany) was used to reliably anchor sources and detectors on the participants' head. A further elastic band was employed to improve the stability of the probe and the contact between optodes and skin. The sampling frequency was set to approximately 7.8 Hz.

2.2.5. Cognitive assessment—Each participant was invited to attend a final assessment session in which various standard neuropsychological tests were administered, together with questionnaires assessing cognitive reserve and reward sensitivity. Specifically,

the Mini Mental State Examination (MMSE; Folstein et al., 1975) was employed as an initial assessment of the general cognitive status.

Subsequently, a more comprehensive evaluation of executive functions was performed by means of the Frontal Assessment Battery (FAB; Appollonio et al., 2005), the Trail Making Test A and B, and the phonemic fluency test (both from the ENB 2; Mondini et al., 2011). Verbal and spatial short term memory were assessed respectively using the verbal short term memory test (immediate and delayed recall; from ENB 2; Mondini et al., 2011) and the Rey–Osterrieth Complex Figure Test (copy and recall; Osterrieth, 1944; Rey, 1941), while verbal working memory was assessed using the digit span test (forward and backward) and the Brown Peterson technique 10″ and 30″ (both from ENB-2; Mondini et al., 2011). In addition, the Corsi Block tapping task (forward and backward; Corsi, 1972) was employed to evaluate spatial working memory. Finally, the Cognitive Reserve Index questionnaire (CRIq; Nucci et al., 2012) was employed as a proxy measure of cognitive reserve, while the Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) scale (Carver and White, 1994) was administered to have a measure of reward sensitivity. A minimum score of 24 at the MMSE was considered as an inclusion criterion for each participant (mean score of the sample = 28.4; SD = 1.3).

2.3. Data pre-processing and analysis

2.3.1. Behavioral analysis—The information about age, education, all the neuropsychological tests scores, and the self-assessed measure of task difficulty collected at the end of the second session, were correlated with the mean correct response times (RTs)[2] and the accuracy rates at the “baseline” block of the first session. This correlation analysis was performed to test the concurrent validity of the task and to investigate the role of age, education and task difficulty perception on the “baseline” WM performance. At the same time, mean correct RTs and accuracy rates at the “reward + tDCS” task block, separately for sham and anodal tDCS sessions, were correlated with scores on each of the BIS/BAS sub-scales, and with the self-assessed measure of reward motivation collected at the end of the second session. This second analysis was performed with the aim of assessing the relation between task performance during the presence of motivational incentives and both standard and self-assessed measures of reward motivation. All the standard tests scores were normalized (Z scores), and Pearsons’ correlation coefficient was employed for all these analyses.

Mean correct RTs and mean accuracy rates, for each task condition and in each of the two tDCS sessions were then submitted to a repeated measures analysis of variance (rmANOVA) with *Stimulation* (anodal vs. sham) and *Task Condition* (“baseline”, “low reward”, “high reward”,[3] and “post tDCS”) as within-subject factors. Greenhouse-Geisser correction was employed when appropriate, while the Bonferroni correction was employed to correct for multiple comparisons when post hoc comparisons were performed. Partial eta squared (n^2_p) was used as measure of effect size.

[2]Correct responses faster than 200 m s were discarded from all the analyses.
[3]For the sake of clarity, we remind the reader that 50 high reward trials were randomly intermixed with the 50 low reward trials in the “reward + tDCS” block.

2.3.2. fNIRS analysis—Data pre-processing was performed using some of the Homer2 NIRS processing package functions (Huppert et al., 2009) based in MATLAB (Mathworks, MA USA). For each participant, channels with very low optical intensity or signal-to-noise ratio <2, likely due to bad skin-optode coupling, were discarded from further analysis (an average of 8.93 ± 9.87% of discarded channels). Signal-to-noise ratio was computed as the ratio between the average intensity signal and its standard deviation. Intensity data were converted to attenuation changes and motion artefacts were corrected by applying the wavelet motion correction technique.

This algorithm performs a series of wavelet transformations of the data, but before applying the inverse wavelet transformation, sets to zero all wavelet detail coefficients that were assessed to be outliers of the distribution (<first quartile - α times the interquartile range or > third quartile + α times the interquartile range; the α parameter was set to 0.8 in the current data). This preprocessing step of outlier removal is thought to be effective in removing motion artefacts present in the original data (Brigadoi et al., 2014; Molavi and Dumont, 2012). Residual motion artefacts were identified as portions of signal exceeding a threshold in change of amplitude (AMPthresh = 1) or/and a threshold in change of standard deviation (STDEVthresh = 20) within a predefined time-window (tMotion = 0.5 s). Trials still contaminated by motion artefacts (2 trials in two different participants) were discarded. A band-pass filter (cut off frequencies: 0.01 and 3 Hz) was applied on the motion corrected attenuation changes to mainly remove slow drifts. HbO and HbR concentration changes were then computed using the modified Beer–Lambert law (Delpy et al., 1988). An age-dependent differential pathlength factor (DPF) was computed for each participant (Scholkmann and Wolf, 2013).

The mean hemodynamic response for each task block, participant and channel was recovered using a General Linear Model (GLM) approach. A set of Gaussian functions with standard deviation of 2s, and with means separated by 2s, were used as temporal basis functions during the interval between −2 and 15s from stimulus onset (Gagnon et al., 2011).

For each standard channel, the SS channel signal with the greatest correlation was chosen and its signal was added in the design matrix of the GLM as additional regressor of no interest, to account for physiological noise contamination. The iterative weighted least square method proposed by Barker et al. (2013) was selected for solving the GLM matrix equation. All analyses were time-locked to the presentation of the memory array. The mean values of both HbO and HbR mean hemodynamic responses in the interval between 5 and 11 s after stimulus onset were computed for all participants, channels and task blocks for both tDCS sessions and chosen as metric for statistical analyses.

Channels were separated according to the ROI to which they belonged to (either frontal, motor or parietal) and separate statistical analyses were performed for each ROI. Then, for each ROI, mean hemodynamic response values, separately for HbO and HbR, were submitted to an rmANOVA with *Stimulation* (anodal vs. sham), *Task Condition* (“baseline”, “low reward”, “high reward” and “post tDCS”), *Hemisphere* (left vs. right) and *Channel* (6 levels for the frontal and parietal ROI and 7 levels for the motor one) as within-subject factors.

For the behavioral data analysis, the Greenhouse-Geisser correction was employed when appropriate, while the Bonferroni correction was employed to correct for multiple comparisons when post hoc comparisons were performed. Partial eta squared (n^2_p) was used as measure of effects size.

3. Results

3.1. Behavioral effects

Mean correct RTs and accuracy rates, as a function of task condition and for the two types of stimulation, are reported in Table 1.

First, we examined the concurrent validity of this WM paradigm, by examining performance in relation to other relevant neuropsychological and self-reported measures. Our main prediction was that we would observe significant correlations between performance on the WM task and the score obtained on the neuropsychological tests examining both spatial and verbal WM. A correlation between age and RTs was also expected, as well an association between WM task performance during the delivery of motivational incentives and the scores obtained on the reward sensitivity standard measures.

Results showed that response times in the WM task increased with age ($r = 0.64$, $p < .005$) and were inversely related with the self-rated measure of task difficulty ($r = -0.59$, $p < .005$), so that participants with faster RTs perceived the task as more difficult.

Significant correlations were also found between RTs on the WM task and performance on Trail Making Test A and B ($r = 0.44$, $p < .05$ and $r = 0.43$, $p < .05$, respectively) indicating that responses at the WM task were associated in sensible ways with measures indexing visual search and speed of processing.

Baseline task performance was also significantly correlated with scores on standard neuropsychological tests of short-term memory and WM. Specifically, higher scores on the verbal short-term memory test delay recall were correlated with faster RTs in the baseline block ($r = -0.52$, $p < .05$); similarly, higher accuracy in the baseline block was associated with higher WM span, either measured with the backward Corsi block tapping test ($r = 0.50$, $p < .05$) or the forward Digit span test, ($r = 0.63$, $p < .005$).

The analyses also showed the presence of a significant correlation between the mean accuracy in the “reward + tDCS” block of the sham session and the self-rated reward motivation level ($r = 0.46$, $p < .05$), such that higher accuracy rates were associated with higher perceived reward motivation. At the same time, RTs in the “reward + tDCS” block of the anodal session were correlated with BAS total scores of the BIS/BAS scale ($r = 0.47$, p $< .05$).

Taken together, these results are consistent with our predictions and strongly confirm the concurrent validity of our experimental task in assessing both verbal and spatial WM, and its sensitivity to reward motivation.

Next, we examined WM task performance (RTs and accuracy rates) in relationship to experimental factors using rmANOVAs. Our aim was to investigate the effects of anodal tDCS, combined with motivational incentives, on WM task performance. For the sake of clarity, we remind that in every rmANOVAs, we considered *Stimulation* (anodal vs. sham) and *Task Condition* ("baseline", "low reward", "high reward", and "post tDCS") as within-subject factors.

Our main prediction was to find a significant difference between performance during and after anodal tDCS, when compared with sham. Furthermore, we expected to find a significant difference in the performance on trials rewarded with high vs. low incentives.

Results showed that, both in terms of RTs and accuracy rates, performance was influenced by the *Task Condition* (RTs: $F_{(3,60)} = 12.53$, $p < .001$, $n^2_p = .38$; accuracy: $F_{(3,60)} = 7.82$, $p < .0001$, $n^2_p = .28$). In particular, participants were faster in the last block ("post tDCS"), when compared with "baseline", and also with respect to both "high reward" and "low reward" conditions (all *ps* < .005). This might indicate a practice effect. At the same time, in the "post tDCS" and in the "low reward" condition, participants were also more accurate when compared to "baseline" ($p < .0001$ and $p < .005$, respectively). Neither the type of reward (high vs. low) nor the type of stimulation affected RTs and accuracy rates (min $p = .44$). Therefore, the results of these two rmANOVA were not congruent with our prediction.

However, in line with previous evidence showing an association between individual WM capacity and performance on rewarded WM task after anodal tDCS (Jones et al., 2015), we decided to test two additional rmANCOVA models, considering as covariate the Z score of the backward Corsi span and the forward Digit span tests, which were found to be significantly related to performance at the experimental WM task. Our prediction was of significant association between baseline WM capacity, measured with the two standard tests, and the effect of tDCS on the experimental WM task performance.

Results yielded a significant three-way interaction between the factors *Stimulation*, *Task Condition* and the covariate backward Corsi span ($F_{(3,57)} = 3.44$, $p < .05$, $n^2_p = .15$), indicating that the visuo-spatial WM span, measured with the backward Corsi test, explained a significant part of the RTs variability. Results of the post-hoc comparisons revealed that, when taking into account the covariate backward Corsi span, RTs in the anodal tDCS session were faster in both the "low reward" and "high reward" conditions, as well as in the "post-tDCS" one, when compared to "baseline", while no significant differences were found in the sham (see Fig. 4). As such, the results of this rmANOVA were consistent with our predictions.

To better explore the relation between WM baseline performance and tDCS effect, we then calculated the difference in RTs between baseline and low reward, as well as baseline and high reward and baseline and post-tDCS, for both anodal and sham sessions, and we correlated these values with the backward Corsi span Z scores. The results indicated that the higher correlation that emerged from this analysis was between the backward Corsi span

scores and the RTs difference from “baseline” to the “post tDCS” task block, in the anodal session ($r = -0.42$; $p = .056$).

This coefficient, despite not significant per se, was found to be significantly different (z = −2.17; p < .05) from the one representing the correlation between the backward Corsi span and the RTs difference from “baseline” to the “post tDCS” in the sham session ($r = 0.27$; $p = .22$).

Therefore, we correlated the backward Corsi span scores with the ΔRT calculated comparing anodal and sham conditions [ΔRT = (RTs Baseline Anodal − RTs Post tDCS Anodal) − (RTs Baseline Sham − RTs Post tDCS Sham)], obtaining a significant negative correlation (r = −0.461, p < .05; see Fig. 5).

Taken together, these results indicate that it is unlikely that the negative trend found between the backward Corsi span scores and the performance improvement in the anodal session could be explained by regression to the mean, and suggest greater anodal tDCS benefit in participants with low WM span.

3.2. fNIRS results

On the basis of the behavioral results, which showed both the presence of a potential practice effect but also a significant effect of anodal tDCS in improving RTs, we expected to find a significant modulation of the hemodynamic activity as a function of Task Condition, in all the three ROIs considered. Moreover, we expected to find an increased cortical activity associated with delivery of anodal tDCS, when compared with sham, especially within the prefrontal and parietal cortices.

3.2.1. Frontal ROI—Results of analyses focusing on hemodynamic activity in the bilateral frontal regions were consistent with the behavioral results, and with our prediction. Specifically, hemodynamic activity in this ROI showed a similar decrease in the blocks following “baseline”, regardless of the type of stimulation and hemisphere ($F_{(3,60)} = 18.67$, $p < .001$, $\eta^2_p = .48$).

Moreover, activity (HbO) was increased in the “reward + tDCS” conditions relative to “post-tDCS”, and was significant for the “high reward” condition ($p < .01$; see Fig. 6a). A hemispheric asymmetry was present, with channels located in the left frontal ROI exhibiting higher HbO activity compared to their symmetric counterpart ($F_{(1,20)} = 5.25$, $p < .05$, $\eta^2_p = .21$; see Fig. 6a). This result, despite not reflecting a pure effect of stimulation, is consistent with the fact that anodal tDCS was delivered over the left PFC, as well as with the verbal nature of the stimuli employed in the WM task.

Most critically, the pattern of HbO activation was impacted by the Stimulation condition, showing stronger activity during anodal tDCS relative to sham, but this further interacted with channel (*Channel:* $F_{(5,100)} = 3.78$, $p < .005$, $\eta^2_p = .159$; *Stimulation* × *Channel:* $F_{(5,100)} = 3.56$, $p < .01$, $\eta^2_p = .15$), such that this pattern of increased activity during anodal stimulation was preferentially expressed bilaterally in channel F5 ($p < .05$; see Fig. 7).

This result was consistent with the behavioral results, and therefore with our predictions, and was also confirmed by an additional rmANOVA conducted on channel F5 only, with *Stimulation*, *Task Condition* and *Hemisphere* as factors. Results confirmed not only a significant effect of *Task Condition* (greatest activity in "baseline", $F_{(3,60)} = 8.35$, $p < .001$, $\eta^2_p = .29$), but also a main effect of *Stimulation* ($F_{(3,60)} = 5.75$, $p < .05$, $\eta^2_p = .22$), with significantly higher HbO activity during anodal tDCS, which did not further interact with *Hemisphere* (p > .1).

To test whether the results were impacted by pre-existing differences between stimulation conditions even during "baseline" task blocks (i.e., non-random sampling across groups, since during "baseline" no stimulation was applied), we re-ran this analyses but including only the "baseline". As expected, in this result the effect of *Stimulation* was not significant ($F_{(1,20)} = 0.28$, $p = .60$, $\eta^2_p = .01$). Conversely, when rerunning the analysis after excluding "baseline", the effect of *Stimulation* remained significant ($F_{(1,20)} = 5.56$, $p < .05$, $\eta^2_p = .21$).

The analyses on the HbR mean hemodynamic response values, for all the 12 frontal channels, revealed greater HbR activity in the left compared to the right hemisphere ($F_{(1,20)} = 17.6$, $p < .001$, $\eta^2_p = .468$; see Fig. 6a) and a different pattern of activation across channels ($F_{(5,100)} = 3.05$, $p < .05$, $\eta^2_p = .132$), which further interacted with hemisphere ($F_{(5,100)} = 2.49$, $p < .05$, $\eta^2_p = .11$). In particular, post-hoc comparisons demonstrated that the greater HbR activity in the left compared to the right hemisphere was localized in channel F1 ($p < .005$) and channel F5 ($p < .05$). No other main effects or interactions were found to be significant.

3.2.2. Parietal ROI—Matching the pattern observed behaviorally and in frontal ROIs, the parietal channels also showed a pattern of declining HbO activity across task conditions (i.e., "baseline" > others), regardless the type of stimulation and hemisphere (*Task Condition:* $F_{(3,60)} = 17.52$, $p < .001$, $\eta^2_p = .467$; see Fig. 6c). However, unlike the frontal ROIs, there was no main effect of *Hemisphere* ($F_{(1,20)} = 3.18$, $p = .09$, $\eta^2_p = 0.13$) or *Channel* ($F_{(5,100)} = 2.23$, $p = .057$; $\eta^2_p = .10$).

However, *Hemisphere* did interact with *Task Condition* ($F_{(3,60)} = 3.75$, $p < .05$, $\eta^2_p = .158$), with higher HbO activity in the right compared to the left hemisphere during "baseline" and during the "high reward" condition (*all ps* < .05), independently from the stimulation type (see Fig. 6c).

Unlike the frontal ROIs, there were no further effects of *Stimulation*.

The analyses on the mean HbR hemodynamic response values did not reveal any significant effects.

3.2.3. Motor ROI—Like the other ROI channels, the motor ROIs also exhibited a main effect of *Task Condition*: higher HbO activity during "baseline" compared to the "post tDCS", regardless the type of stimulation and hemisphere ($F_{(3,60)} = 3.85$, $p < .05$; $\eta^2_p = .014$; see Fig. 6b).

A main effect of *Channel* was also observed, but it was not modulated by stimulation type, hemisphere or task condition ($F_{(6,120)} = 2.83$, $p < .05$, $\eta^2_p = .124$).

The analyses on the HbR mean hemodynamic response values revealed that HbR activity was differently modulated across channels depending on the stimulation type ($F_{(6,120)} = 2.55$, $p < .05$, $\eta^2_p = .113$); however, post-hoc comparisons revealed no significant difference between anodal and sham stimulation in any of the channels.

4. Discussion

The present study represents the first investigation of the effects of combined anodal tDCS and reward motivation on older adult WM performance and on their hemodynamic cortical activity measured with fNIRS. We hypothesized that anodal tDCS over left PFC, combined with the increased reward motivation, would significantly improve WM performance and modulate cortical activity of healthy older adults, especially within the prefrontal and the parietal cortices. This hypothesis was based on the results of Jones et al. (2015), who for the first time reported a 'double-boost' benefit of anodal tDCS and high motivation on WM performance in both high and low WM capacity young participants. In the work of Jones et al. (2015), however, no effect of this combination on brain activity was found, potentially because tDCS was administrated "offline" and not simultaneously with fNIRS recording, and probably because only the activity of the left PFC was monitored. Therefore, in the current study we monitored not only bilateral PFC, but also parietal and motor regions, in order to better determine the specificity of these effects.

Moreover, we employed an "online" stimulation paradigm and we utilized an important methodological innovation, in that fNIRS activity was recorded concurrently with tDCS stimulation as well as during baseline and post-tDCS blocks.

We discuss the results first in terms of the validity of our experimental paradigm, and second in terms of the effects of tDCS stimulation + reward motivation on cortical activity and WM performance in healthy older adults. Finally, together with a review of the limitations of the present study and with our conclusions, we provide some ideas for future investigation within this research field.

4.1. Validity of the WM task employed

A number of convergent results provided validation of our new task as a sensitive probe of visuospatial WM in older adults. First, behavioral performance was found to be associated, in expected ways, with neuropsychological test scores and self-report measures.

Specifically, participants' performance during the "baseline" block, namely, before any stimulation and reward motivation manipulation occurred, exhibited significant correlations with scores on standard neuropsychological tests indexing both verbal and spatial processing (Trail-Making, visual search), as well as verbal and spatial short-term and WM (forward digit span, Corsi block tapping). Conversely, during the task block in which reward motivation was manipulated (with trial-by-trial incentives), significant associations were

found with both standard measures of reward sensitivity (BAS) and also in self-reported measures of motivation.

In terms of fNIRS activity, we observed a somewhat left-lateralized pattern of activity in PFC, but a mostly right-lateralized pattern of activity within parietal cortex. This hemispheric asymmetry could be due to both the verbal nature of the stimuli employed, which would explain the higher left PFC activity, and the visuo-spatial demands of the task, that would have triggered the right PPC involvement (Corballis and Häberling, 2017). Alternatively (or in addition), the left prefrontal lateralization could also reflect the reward manipulation employed during the task (Ohmann et al., 2018; for a review see Kelley et al., 2017). Indeed, while the right parietal lateralization was detected only in the “baseline” block and in the high reward trials, arguably the most demanding task conditions for novelty and incentive reasons, the higher left PFC activity persisted for the entire duration of the task, perhaps reflecting a conjunction between the processing of verbal stimuli, and an approach motivation mindset (Ohmann et al., 2018; for a review see Kelley et al., 2017). Together, this pattern of behavioral performance and brain activation demonstrates that the experimental task designed for this study is a suitable one for testing in older adults, to examine the effects of reward motivation on cognitive performance.

4.2. Effects of reward motivation and anodal tDCS on hemodynamic activity and WM performance

The primary result of this study was the use of fNIRS to reveal an effect of anodal tDCS compared to sham, such that within bilateral PFC, specifically in channel F5, significantly higher activity was found during anodal relative to sham stimulation. The increased HbO activity due to anodal tDCS was localized in a posterior region of PFC near what has been termed the inferior frontal junction (Brodmann areas 6 and 44).

The effects appeared to be present both during the reward + tDCS block, but also continued after tDCS (and reward) stimulation ended, during the post-tDCS block. However, results confirmed that there were no effects during the pre-tDCS baseline condition, supporting the interpretation that the observed activation effects were a consequence of the differential stimulation.

This result is consistent with, but also significantly extends the results obtained by Jones and colleague (2015), as they also observed increased hemodynamic activity in left PFC due to the anodal tDCS. To the best of our knowledge, the study of Jones and colleague (2015) was the only previous evidence where WM + reward-related brain activity was monitored both before and after (but not during) anodal tDCS delivered over the PFC. In contrast, our study monitored the activity of right and left PFC, also during the reward + tDCS block and the pre/post-tDCS periods, finding that the increased hemodynamic activity was present bilaterally and occurred during the stimulation period itself. These results strengthen the conclusion that anodal tDCS stimulation, when combined with reward incentives, result in increased hemodynamic activity within PFC. The increased hemodynamic activity present also in the contralateral (with respect to stimulation) region suggests that tDCS might also modulate brain areas that are not necessarily located below the electrode itself. We speculate that anodal tDCS may have acted by both enhancing the activity of the stimulated region,

already activated by task demands, and increasing the activity of the less involved, but highly connected, homologous contralateral area. This interpretation is in line with recent neuroimaging evidence, which has shown that tDCS is able to induce functional changes in regions distal to the electrodes, also in the contralateral hemisphere, even without reflecting a significant effect on behavior (Mondini et al., 2018; Sallard et al., 2018; Vermeij et al., 2017; Weber et al., 2014).

A second result of this study is that anodal tDCS, combined with reward motivation, results in an improvement in older adults' WM performance, and that this improvement is modulated by the baseline WM capacity. Specifically, when adding the individual visuo-spatial WM capacity as a predictor of behavioral performance, a significant RT improvement emerged when anodal stimulation was applied, but not when reward motivation was combined with sham stimulation. This result is consistent with previous evidence, which showed the need of taking into account inter-individual differences, in terms of baseline cognitive functions, when assessing the effect of tDCS on cognitive performance (Arciniega et al., 2018; Berryhill and Jones, 2012; Li et al., 2015; Wiegand et al., 2016).

The results of between-subjects correlational analysis, which were conducted to understand the exact role of this predictor in our study, showed a negative relation between the effects of tDCS found on RTs and the visuo-spatial WM span. Our participants had a relatively high WM capacity (mode = 6; mean = 5.2; SD = 0.9) and this could explain the lack of an overall effect of tDCS. The correlation between WM span and anodal tDCS effects approached, but did not reach the level of statistical significance ($p = .056$), and this allowed us to only hypothesize that participants who benefited the most from the combination between anodal tDCS and reward manipulation were those with low WM capacity.

It is worth noticing that in our study anodal tDCS modulated RTs only, while in the study of Jones et al. (2015) anodal tDCS modulated accuracy rates. Despite this discrepancy, our findings are actually more in line with previous evidence, which has often shown that a single tDCS session often modulates RTs only (Dedoncker et al., 2016; Hill et al., 2016; Horvath et al., 2015; see also Brunoni and Vanderhasselt, 2014). We see two different but also related reasons that could explain this result. The first is the different experimental task employed respect to Jones et al. (2015), while the second is the different ages of the participant tested.

Despite participants in Jones and colleagues' study (2015) were young adults, and therefore could have had faster baseline RTs, their mean accuracy level was relatively lower when compared to the older adults in our study. This suggests that our task was probably comparatively easier than that employed in Jones and colleagues' study (2015) and, although not raising performance to a ceiling effect, it could have left less room for a possible tDCS (or reward motivation) related improvement. Alternatively, the better baseline performance of our participants, and the consequent lack of significant effect of anodal tDCS on accuracy rates, could be explained also by the age-related differences in motivation and in motivation-cognition interaction (Carstensen et al., 2006; Di Rosa et al., 2015; Ferdinand and Czernochowski, 2018; Samanez-Larkin and Knutson, 2015), which could presumably make

older adults differently, if not more, motivated to take part in research studies, when compared with the younger ones.

It is also worth considering that age-related changes in the brain structure and function could may have had an important influence on both tDCS effects and fNIRS findings.

As recently reviewed by Woods et al. (2019a), the reduced structural and functional connectivity, as well as atrophy, which typically characterizes the aging brain, can have a substantial influence on the conduction of electrical current, and therefore on the effect of tDCS on the underlying neuronal tissue. At the same time, atrophy seems to play a role also on the HbO levels measured with fNIRS. A recent study of Wagshul et al. (2019) reported a significant negative association between frontal grey matter volume and the increase in HbO levels showed by older adults performing a dual-task, in comparison to a single-task.

When taken together, these issues, despite mostly coming from few recent studies, speak to the necessity of carefully considering the complex set of psychological, cognitive and neural changes that occur during aging when assessing the effect of tDCS in older adults, and moreover when comparing results obtained by testing groups of different age ranges.

4.3. Limitations and future directions

Some limitations should be noted when considering our results. First of all, the experimental WM task designed for the present study did not allow us to clearly understand the effect of reward motivation on WM performance and hemodynamic activity. Indeed, although the time-on-task effects we observed are most intuitively interpreted as being due to practice, they could also reflect an “after-effect” of the reward motivation condition. By including no-reward control groups in future work, it might be possible to disentangle potential practiced from after-effects of reward motivation on task performance and fNIRS activation.

Secondly, and as previously mentioned, our experimental WM task might have been not challenging enough for the purposes of the present study. A more challenging task, possibly testing both recognition and recollection, may have elucidated further effects. Moreover, a task tailored on the individual baseline performance, and designed to allow a gradual difficulty increase after a certain number of correct trials, could better prevent practice effects and bring to larger behavioral/hemodynamic modulations. Future development of the present work should therefore take into account this aspect and overcome this limitation.

The imbalance between high and low WM span individuals also represents another limitation of the present study. Specifically, in measuring the WM span using the Backward Corsi Span task, only few subjects were classified as low WM span (i.e., with a score of 3 and 4), while the majority had a score of 5 and 6.

Although we believe that this limitation does not invalidate our results, a more balanced sample would have probably produced stronger and clearer individual differences findings, specifically in terms of the relationship between tDCS effects and baseline WM capacity.

Future studies should address this issue taking advantage of the neuropsychological assessment session, possibly planned before any experimental manipulation, to recruit a

more balanced sample of participants, or alternatively, to focus more directly on older adults with estimated low WM capacities, as our work suggests that these might be the population most likely to benefit from combined reward motivation and tDCS benefits.

Finally, regarding the fNIRS recording, we recognize that the inter-trial interval employed in the present study may not have been long enough to allow for a complete return to baseline of the hemodynamic response before the beginning of the next trial. It should be considered, however, that the time between the memory array of one trial and the memory array of the following one was on average 15 s. The choice of the inter-trial interval reflected a compromise that balanced the trade-off between providing enough time to the hemodynamic response to return almost to baseline while keeping participants engaged to the task. We are confident that our results have not been negatively influenced by the choice of inter-trial interval, since we used deconvolution to estimate the hemodynamic responses to the task. Deconvolution approaches have been found to be quite robust to confounding factors; when using deconvolution approaches event timing parameters have been shown to have negligible effects on the recovery of the hemodynamic response (Aarabi et al., 2017).

5. Conclusions

Taken together, the findings of the present study show that anodal tDCS over the left PFC, combined with reward motivation, can be beneficial for WM performance and can increase the hemodynamic activity of both left and right PFC in healthy older adults. These results represent an important extension of the study of Jones et al. (2015), who found that a similar experimental manipulation was able to cause an improvement in young adults' WM performance, and together with them encourage further investigations in this research field.

A potential future development of this study is the employment of the same innovative set-up with the aim to evaluate both the short- and long-term effects of a proper WM training on both cognitive performance and cortical activity.

Indeed, results of the present study demonstrate the feasibility of employing fNIRS and tDCS simultaneously and in repeated sessions, and confirm that fNIRS is an advantageous technique for measuring brain activity in the elderly, who can be tested in a more ecologically valid setting and with less physical and psychological discomfort than with other neuroimaging techniques.

Defining and evaluating the role of the moderating variables on the effects of non-invasive brain stimulation would be extremely useful not only for the basic research, but also for the clinical practice. The rapid aging of the worldwide population urgently requires the development of valid and reliable techniques to face the age-dependent cognitive decline. In our opinion, the combination of non-invasive brain stimulation and cognitive training represents a potentially promising interventional approach.

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References

Aarabi A, Osharina V, Wallois F, 2017 Effect of confounding variables on hemodynamic response function estimation using averaging and deconvolution analysis: an event-related NIRS study. Neuroimage 155, 25–49. [PubMed: 28450140]

Aasted CM, Yücel MA, Cooper RJ, Dubb J, Tsuzuki D, Becerra L, Petkov MP, Borsook D, Dan I, Boas DA, 2015 Anatomical guidance for functional near-infrared spectroscopy: AtlasViewer tutorial. Neurophotonics 2, 020801 10.1117/1.NPh.2.2.020801. [PubMed: 26157991]

Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB, 2011 Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 4, 84–89. 10.1016/j.brs.2010.06.004. [PubMed: 21511208]

Antonenko D, Nierhaus T, Meinzer M, Prehn K, Thielscher A, Ittermann B, Flöel A, 2018 Age-dependent effects of brain stimulation on network centrality. Neuroimage 176, 71–82. [PubMed: 29679735]

Appollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, Forapani E, Russo A, Nichelli P, 2005 The Frontal Assessment Battery (FAB): normative values in an Italian population sample. Neurol. Sci 26, 108–116. 10.1007/s10072-005-0443-4. [PubMed: 15995827]

Arciniega H, Gözenman F, Jones KT, Stephens JA, Berryhill ME, 2018 Frontoparietal tDCS benefits visual working memory in older adults with low working memory capacity. Front. Aging Neurosci 10 10.3389/fnagi.2018.00057.

Au J, Katz B, Buschkuehl M, Bunarjo K, Senger T, Zabel C, Jaeggi SM, Jonides J, 2016 Enhancing working memory training with transcranial direct current stimulation. J. Cogn. Neurosci 28, 1419–1432. 10.1162/jocn_a_00979. [PubMed: 27167403]

Bäckman L, Karlsson S, Fischer H, Karlsson P, Brehmer Y, Rieckmann A, MacDonald SWS, Farde L, Nyberg L, 2011 Dopamine D1 receptors and age differences in brain activation during working memory. Neurobiol. Aging 32, 1849–1856. 10.1016/j.neurobiolaging.2009.10.018. [PubMed: 19962789]

Bäckman L, Lindenberger U, Li S-C, Nyberg L, 2010 Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. Neurosci. Biobehav. Rev 34, 670–677. 10.1016/j.neubiorev.2009.12.008. [PubMed: 20026186]

Baddeley A, 2010 Working memory. Curr. Biol 20, R136–R140. 10.1016/j.cub.2009.12.014. [PubMed: 20178752]

Baddeley A, 2000 The episodic buffer: a new component of working memory? Trends Cogn. Sci 4, 417–423. 10.1016/S1364-6613(00)01538-2. [PubMed: 11058819]

Baddeley AD, 1992 Working memory. Science 255, 556–559. 10.1016/j.cub.2009.12.014. [PubMed: 1736359]

Barker JW, Aarabi A, Huppert TJ, 2013 Autoregressive model based algorithm for correcting motion and serially correlated errors in fNIRS. Biomed. Opt. Express 4, 1366 10.1364/BOE.4.001366. [PubMed: 24009999]

Belleville S, Gauthier S, Lepage É, Kergoat M-J, Gilbert B, 2014 Predicting decline in mild cognitive impairment: a prospective cognitive study. Neuropsychology 28, 643–652. 10.1037/neu0000063. [PubMed: 24588699]

Bennabi D, Nicolier M, Monnin J, Tio G, Pazart L, Vandel P, Haffen E, 2015 Pilot study of feasibility of the effect of treatment with tDCS in patients suffering from treatment-resistant depression treated with escitalopram. Clin. Neurophysiol 126, 1185–1189. 10.1016/j.clinph.2014.09.026. [PubMed: 25454337]

Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR, 2016 Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. Neuroimage 140, 4–19. [PubMed: 26883069]

Berryhill ME, Jones KT, 2012 tDCS selectively improves working memory in older adults with more education. Neurosci. Lett 521, 148–151. 10.1016/j.neulet.2012.05.074. [PubMed: 22684095]

Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, Mourdoukoutas AP, Kronberg G, Truong D, Boggio P, Brunoni AR, Charvet L, Fregni F, Fritsch B, Gillick B, Hamilton RH, Hampstead BM, Jankord R, Kirton A, Knotkova H, Liebetanz D, Liu A, Loo C, Nitsche MA, Reis J, Richardson JD, Rotenberg A, Turkeltaub PE, Woods AJ, 2016 Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 9, 641–661. 10.1016/j.brs.2016.06.004. [PubMed: 27372845]

Bopp KL, Verhaeghen P, 2005 Aging and verbal memory span: a meta-analysis. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci 60, P223–P233. 10.1093/geronb/60.5.P223. [PubMed: 16131616]

Botvinick M, Braver T, 2015 Motivation and cognitive control: from behavior to neural mechanism. Annu. Rev. Psychol 66, 83–113. 10.1146/annurev-psych-010814-015044. [PubMed: 25251491]

Braver TS, Barch DM, 2002 A theory of cognitive control, aging cognition, and neuromodulation. Neurosci. Biobehav. Rev 26, 809–817. 10.1016/S0149-7634(02)00067-2. [PubMed: 12470692]

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC, 1997 A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5, 49–62. 10.1006/nimg.1996.0247. [PubMed: 9038284]

Brigadoi S, Ceccherini L, Cutini S, Scarpa F, Scatturin P, Selb J, Gagnon L, Boas DA, Cooper RJ, 2014 Motion artifacts in functional near-infrared spectroscopy: a comparison of motion correction techniques applied to real cognitive data. Neuroimage 85 (Pt 1), 181–191. 10.1016/j.neuroimage.2013.04.082. [PubMed: 23639260]

Brigadoi S, Cooper RJ, 2015 How short is short? Optimum source–detector distance for short-separation channels in functional near-infrared spectroscopy. Neurophotonics 2, 025005 10.1117/1.NPh.2.2.025005. [PubMed: 26158009]

Brunoni AR, Vanderhasselt M-A, 2014 Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 86, 1–9. 10.1016/j.bandc.2014.01.008. [PubMed: 24514153]

Callan DE, Falcone B, Wada A, Parasuraman R, 2016 Simultaneous tDCS-fMRI identifies resting state networks correlated with visual search enhancement. Front. Hum. Neurosci 10, 72 10.3389/fnhum.2016.00072. [PubMed: 27014014]

Carstensen LL, Mikels JA, Mather M, 2006 Aging and the intersection of cognition, motivation, and emotion In: Handbook of the Psychology of Aging, pp. 343–362.

Carver CS, White TL, 1994 Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J. Personal. Soc. Psychol 67, 319–333. 10.1037/0022-3514.67.2.319.

Chib VS, Yun K, Takahashi H, Shimojo S, 2013 Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. Transl. Psychiatry 3 e268–e268. 10.1038/tp.2013.44. [PubMed: 23756377]

Clemens B, Jung S, Zvyagintsev M, Domahs F, Willmes K, 2013 Modulating arithmetic fact retrieval: a single-blind, sham-controlled tDCS study with repeated fMRI measurements. Neuropsychologia 51, 1279–1286. 10.1016/j.neuropsychologia.2013.03.023. [PubMed: 23603021]

Collins DL, Zijdenbos AP, Kollokian V, Sled JG, Kabani NJ, Holmes CJ, Evans AC, 1998 Design and construction of a realistic digital brain phantom. IEEE Trans. Med. Imaging 17, 463–468. 10.1109/42.712135. [PubMed: 9735909]

Conway AR, Cowan N, Bunting MF, Therriault DJ, Minkoff SR, 2002 A latent variable analysis of working memory capacity, short-term memory capacity, processing speed, and general fluid intelligence. Intelligence 30, 163–183. 10.1016/S0160-2896(01)00096-4.

Corballis MC, Häberling IS, 2017 The many sides of hemispheric asymmetry: a selective review and outlook. J. Int. Neuropsychol. Soc 23, 710–718. 10.1017/S1355617717000376. [PubMed: 29198268]

Corsi P, 1972 Memory and the Medial Temporal Region of the Brain

Cruz Gonzalez P, Fong KN, Chung RC, Ting KH, Law LL, Brown T, 2018 Can transcranial direct-current stimulation be used as a clinical intervention to improve cognitive functioning in persons

with mild cognitive impairment and dementia? A systematic review and meta-analysis. Front. Hum. Neurosci 12, 416. [PubMed: 30386223]

Dahlin E, Nyberg L, Bäckman L, Neely AS, 2008 Plasticity of executive functioning in young and older adults: immediate training gains, transfer, and long-term maintenance. Psychol. Aging 23, 720–730. 10.1037/a0014296. [PubMed: 19140643]

Das S, Holland P, Frens MA, Donchin O, 2016 Impact of transcranial direct current stimulation (tDCS) on neuronal functions. Front. Neurosci 10, 550. [PubMed: 27965533]

Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt M-A, 2016 A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul 9, 501–517. 10.1016/j.brs.2016.04.006. [PubMed: 27160468]

Delignières D, 1993 La perception de l'effort et de la difficulté In: Cognition et Performance, pp. 183–218.

Delpy DT, Cope M, van der Zee P, Arridge S, Wray S, Wyatt J, 1988 Estimation of optical pathlength through tissue from direct time of flight measurement. Phys. Med. Biol 33, 1433–1442. [PubMed: 3237772]

Di Rosa E, Schiff S, Cagnolati F, Mapelli D, 2015 Motivation–cognition interaction: how feedback processing changes in healthy ageing and in Parkinson's disease. Aging Clin. Exp. Res 27 (6), 911–920. [PubMed: 25854302]

Ehlis A-C, Haeussinger FB, Gastel A, Fallgatter AJ, Plewnia C, 2016 Task-dependent and polarity-specific effects of prefrontal transcranial direct current stimulation on cortical activation during word fluency. Neuroimage 140, 134–140. 10.1016/j.neuroimage.2015.12.047. [PubMed: 26748077]

Etzel JA, Cole MW, Zacks JM, Kay KN, Braver TS, 2016 Reward motivation enhances task coding in frontoparietal cortex. Cerebr. Cortex 26, 1647–1659. 10.1093/cercor/bhu327.

Falcone B, Callan DE, 2019 Neuromodulatory effects of transcranial direct current stimulation revealed by functional magnetic resonance imaging In: Neuroergonomics. Academic Press, pp. 143–145.

Ferdinand NK, Czernochowski D, 2018 Motivational influences on performance monitoring and cognitive control across the adult lifespan. Front. Psychol 9, 1018. [PubMed: 29997541]

Filmer HL, Ehrhardt SE, Shaw TB, Mattingley JB, Dux PE, 2019 The efficacy of transcranial direct current stimulation to prefrontal areas is related to underlying cortical morphology. Neuroimage 196, 41–48. [PubMed: 30978491]

Folstein MF, Folstein SE, McHugh PR, 1975 Mini-mental state. J. Psychiatr. Res 12, 189–198. 10.1016/0022-3956(75)90026-6. [PubMed: 1202204]

Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MTA, Paulus W, Pascual-Leone A, 2005 Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp. Brain Res 166, 23–30. 10.1007/s00221-005-2334-6. [PubMed: 15999258]

Gagnon L, Perdue K, Greve DN, Goldenholz D, Kaskhedikar G, Boas DA, 2011 Improved recovery of the hemodynamic response in diffuse optical imaging using short optode separations and state-space modeling. Neuroimage 56, 1362–1371. 10.1016/j.neuroimage.2011.03.001. [PubMed: 21385616]

Gandiga PC, Hummel FC, Cohen LG, 2006 Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin. Neurophysiol 117, 845–850. 10.1016/j.clinph.2005.12.003. [PubMed: 16427357]

Gates NJ, Rutjes AW, Di Nisio M, Karim S, Chong LY, March E, et al., 2019a Computerised cognitive training for maintaining cognitive function in cognitively healthy people in midlife. Cochrane Database Syst. Rev (3).

Gates NJ, Rutjes AW, Di Nisio M, Karim S, Chong LY, March E, et al., 2019b Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life. Cochrane Database Syst. Rev (3).

Gates NJ, Vernooij RW, Di Nisio M, Karim S, March E, Martínez G, Rutjes AW, 2019c Computerised cognitive training for preventing dementia in people with mild cognitive impairment. Cochrane Database Syst. Rev (3).

Gill J, Shah-Basak PP, Hamilton R, 2015 It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul 8, 253–259. 10.1016/j.brs.2014.10.018. [PubMed: 25465291]

Hauser TU, Rütsche B, Wurmitzer K, Brem S, Ruff CC, Grabner RH, 2016 Neurocognitive effects of transcranial direct current stimulation in arithmetic learning and performance: a simultaneous tDCS-fMRI study. Brain Stimul 9, 850–858. 10.1016/j.brs.2016.07.007. [PubMed: 27522169]

Hill AT, Fitzgerald PB, Hoy KE, 2016 Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul 9, 197–208. 10.1016/j.brs.2015.10.006. [PubMed: 26597929]

Hone-Blanchet A, Edden RA, Fecteau S, 2016 Online effects of transcranial direct current stimulation in real time on human prefrontal and striatal metabolites. Biol. Psychiatry 80, 432–438. 10.1016/j.biopsych.2015.11.008. [PubMed: 26774968]

Horvath JC, Forte JD, Carter O, 2015 Quantitative review finds No evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul 8, 535–550. 10.1016/j.brs.2015.01.400. [PubMed: 25701175]

Hummel FC, Cohen LG, 2006 Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 5 (8), 708–712. [PubMed: 16857577]

Huppert TJ, Diamond SG, Franceschini MA, Boas DA, 2009 HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl. Opt 48, D280–D298. [PubMed: 19340120]

Jacobson L, Koslowsky M, Lavidor M, 2012 tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp. Brain Res 216 (1), 1–10. [PubMed: 21989847]

Jantz TK, Katz B, Reuter-Lorenz PA, 2016 Uncertainty and promise: the effects of transcranial direct current stimulation on working memory. Curr. Behav. Neurosci. Rep 3, 109–121. 10.1007/s40473-016-0071-8.

Jasper HH, 1958 Report of the committee on methods of clinical examination in electroencephalography. Electroencephalogr. Clin. Neurophysiol 10, 370–375. 10.1016/0013-4694(58)90053-1.

Jones KT, Gözenman F, Berryhill ME, 2015 The strategy and motivational influences on the beneficial effect of neurostimulation: a tDCS and fNIRS study. Neuroimage 105, 238–247. 10.1016/j.neuroimage.2014.11.012. [PubMed: 25462798]

Jones KT, Peterson DJ, Blacker KJ, Berryhill ME, 2017 Frontoparietal neurostimulation modulates working memory training benefits and oscillatory synchronization. Brain Res 1667, 28–40. 10.1016/j.brainres.2017.05.005. [PubMed: 28502585]

Katsoulaki M, Kastrinis A, Tsekoura M, 2017 The Effects of Anodal Transcranial Direct Current Stimulation on Working Memory Springer, Cham, pp. 283–289. 10.1007/978-3-319-57379-3_25.

Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Moller H-J, Reiser M, Padberg F, 2011 Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J. Neurosci 31, 15284–15293. 10.1523/JNEUROSCI.0542-11.2011. [PubMed: 22031874]

Kelley NJ, Hortensius R, Schutter DJLG, Harmon-Jones E, 2017 The relationship of approach/avoidance motivation and asymmetric frontal cortical activity: a review of studies manipulating frontal asymmetry. Int. J. Psychophysiol 119, 19–30. 10.1016/j.ijpsycho.2017.03.001. [PubMed: 28288803]

Kropotov JD, 2016 Functional Neuromarkers for Psychiatry: Applications for Diagnosis and Treatment Academic Press.

Li LM, Uehara K, Hanakawa T, 2015 The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front. Cell. Neurosci 9, 181 10.3389/fncel.2015.00181. [PubMed: 26029052]

Logie RH, Morris RG, 2015 Working memory and ageing. Work. Mem. Ageing 1–49.

Mahdavi S, Towhidkhah F, Alzheimer's Disease Neuroimaging Initiative, 2018 Computational human head models of tDCS: influence of brain atrophy on current density distribution. Brain stimul 11 (1), 104–107. [PubMed: 29056365]

Mancuso LE, Ilieva IP, Hamilton RH, Farah MJ, 2016 Does transcranial direct current stimulation improve healthy working memory?: a meta-analytic review. J. Cogn. Neurosci 28, 1063–1089. 10.1162/jocn_a_00956. [PubMed: 27054400]

Martin DM, Liu R, Alonzo A, Green M, Loo CK, 2014 Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Exp. Brain Res 232, 3345–3351. 10.1007/s00221-014-4022-x. [PubMed: 24992897]

Melby-Lervåg M, Redick TS, Hulme C, 2016 Working memory training does not improve performance on measures of intelligence or other measures of "far transfer. Perspect. Psychol. Sci 11, 512–534. 10.1177/1745691616635612. [PubMed: 27474138]

Merzagora AC, Foffani G, Panyavin I, Mordillo-Mateos L, Aguilar J, Onaral B, Oliviero A, 2010 Prefrontal hemodynamic changes produced by anodal direct current stimulation. Neuroimage 49, 2304–2310. 10.1016/j.neuroimage.2009.10.044. [PubMed: 19853048]

Miyake A, Shah P, 1999 Models of Working Memory : Mechanisms of Active Maintenance and Executive Control Cambridge University Press.

Molavi B, Dumont GA, 2012 Wavelet-based motion artifact removal for functional near-infrared spectroscopy. Physiol. Meas 33, 259–270. 10.1088/0967-3334/33/2/259. [PubMed: 22273765]

Molero-Chamizo A, Alameda Bailén JR, Garrido Béjar T, García López M, Jaén Rodríguez I, Gutiérrez Lérida C, Pérez Panal S, González Ángel G, Lemus Corchero L, Ruiz Vega MJ, Nitsche MA, Rivera-Urbina GN, 2018 Poststimulation time interval-dependent effects of motor cortex anodal tDCS on reaction-time task performance. Cognit. Affect Behav. Neurosci 18, 167–175. 10.3758/s13415-018-0561-0. [PubMed: 29330825]

Mondini S, Mapelli D, Vestri A, Arcara G, Bisiacchi PS, 2011 Esame neuropsicologico breve 2: una batteria di test per lo screening neuropsicologico Cortina.

Mondini V, Mangia AL, Cappello A, 2018 Single-session tDCS over the dominant hemisphere affects contralateral spectral EEG power, but does not enhance neurofeedback-guided event-related desynchronization of the non-dominant hemisphere's sensorimotor rhythm. PLoS One 13, e0193004 10.1371/journal.pone.0193004. [PubMed: 29513682]

Nilsson J, Lebedev AV, Rydström A, Lövdén M, 2017 Direct-current stimulation does little to improve the outcome of working memory training in older adults. Psychol. Sci 28, 907–920. 10.1177/0956797617698139. [PubMed: 28509625]

Nitsche MA, Paulus W, 2001 Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57 (10), 1899–1901. [PubMed: 11723286]

Nitsche MA, Paulus W, 2011 Transcranial direct current stimulation–update 2011. Restor. Neurol. Neurosci 29, 463–492. 10.3233/RNN-2011-0618. [PubMed: 22085959]

Nucci M, Mapelli D, Mondini S, 2012 Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. Aging Clin. Exp. Res 24, 218–226. 10.3275/7800. [PubMed: 21691143]

Ohmann HA, Kuper N, Wacker J, 2018 Left frontal anodal tDCS increases approach motivation depending on reward attributes. Neuropsychologia 119, 417–423. 10.1016/j.neuropsychologia.2018.09.002. [PubMed: 30193845]

Oldfield RC, 1971 The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113. 10.1016/0028-3932(71)90067-4. [PubMed: 5146491]

Oldrati V, Colombo B, Antonietti A, 2018 Combination of a short cognitive training and tDCS to enhance visuospatial skills: a comparison between online and offline neuromodulation. Brain Res 1678, 32–39. 10.1016/j.brainres.2017.10.002. [PubMed: 29017911]

Osterrieth PA, 1944 Le test de copie d'une figure complexe: contribution à l' étude de la perception et de la mémoire. Arch. Psychol. (Geneve)

Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK, 2002 Models of visuospatial and verbal memory across the adult life span. Psychol. Aging 17, 299–320. 10.1037/0882-7974.17.2.299. [PubMed: 12061414]

Passow S, Thurm F, Li S-C, 2017 Activating developmental reserve capacity via cognitive training or non-invasive brain stimulation: potentials for promoting frontoparietal and hippocampal-striatal network functions in old age. Front. Aging Neurosci 9, 33 10.3389/fnagi.2017.00033. [PubMed: 28280465]

Pelletier SJ, Cicchetti F, 2015 Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. Int. J. Neuropsychopharmacol 18 (2), pyu047.

Peña-Gómez C, Sala-Lonch R, Junqué C, Clemente IC, Vidal D, Bargalló N, Falcón C, Valls-Solé J, Pascual-Leone Á, Bartrés-Faz D, 2012 Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. Brain Stimul 5, 252–263. 10.1016/j.brs.2011.08.006. [PubMed: 21962981]

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B, 2001 Current concepts in mild cognitive impairment. Arch. Neurol 58, 1985 10.1001/archneur.58.12.1985. [PubMed: 11735772]

Rey A, 1941 L'examen psychologique dans les cas d'encéphalopathie traumatique. Arch. Psychol. (Geneve)

Ruf SP, Fallgatter AJ, Plewnia C, 2017 Augmentation of working memory training by transcranial direct current stimulation (tDCS). Sci. Rep 7, 876 10.1038/s41598-017-01055-1. [PubMed: 28432349]

Sallard E, Mouthon M, De Pretto M, Spierer L, 2018 Modulation of inhibitory control by prefrontal anodal tDCS: a crossover double-blind sham-controlled fMRI study. PLoS One 13, e0194936 10.1371/journal.pone.0194936. [PubMed: 29590181]

Samanez-Larkin GR, Knutson B, 2015 Decision making in the ageing brain: changes in affective and motivational circuits. Nat. Rev. Neurosci 16 (5), 278. [PubMed: 25873038]

Santarnecchi E, Brem AK, Levenbaum E, Thompson T, Kadosh RC, Pascual-Leone A, 2015 Enhancing cognition using transcranial electrical stimulation. Curr. Opin. Behav. Sci 4, 171–178.

Scholkmann F, Wolf M, 2013 General equation for the differential pathlength factor of the frontal human head depending on wavelength and age. J. Biomed. Opt 18, 105004 10.1117/1.JBO.18.10.105004. [PubMed: 24121731]

Soekadar SR, Herring JD, McGonigle D, 2016 Transcranial Electric Stimulation (tES) and NeuroImaging: the State-Of-The-Art, New Insights and Prospects in Basic and Clinical Neuroscience

Stephens JA, Berryhill ME, 2016 Older adults improve on everyday tasks after working memory training and neurostimulation. Brain Stimul 9, 553–559. 10.1016/j.brs.2016.04.001. [PubMed: 27178247]

Stephens JA, Jones KT, Berryhill ME, 2017 Task demands, tDCS intensity, and the COMT val158met polymorphism impact tDCS-linked working memory training gains. Sci. Rep 7, 13463 10.1038/s41598-017-14030-7. [PubMed: 29044248]

Summers MJ, Saunders NLJ, 2012 Neuropsychological measures predict decline to Alzheimer's dementia from mild cognitive impairment. Neuropsychology 26, 498–508. 10.1037/a0028576. [PubMed: 22612573]

Talsma LJ, Kroese HA, Slagter HA, 2017 Boosting cognition: effects of multiple-session transcranial direct current stimulation on working memory. J. Cogn. Neurosci 29, 755–768. 10.1162/jocn_a_01077. [PubMed: 27897670]

Turi Z, Paulus W, Antal A, 2012 Functional neuroimaging and transcranial electrical stimulation. Clin. EEG Neurosci 43, 200–208. 10.1177/1550059412444978. [PubMed: 22956648]

Unsworth N, Fukuda K, Awh E, Vogel EK, 2014 Working memory and fluid intelligence: capacity, attention control, and secondary memory retrieval. Cogn. Psychol 71, 1–26. 10.1016/j.cogpsych.2014.01.003. [PubMed: 24531497]

Vermeij A, Claassen JAHR, Dautzenberg PLJ, Kessels RPC, 2016 Transfer and maintenance effects of online working-memory training in normal ageing and mild cognitive impairment. Neuropsychol. Rehabil 26, 783–809. 10.1080/09602011.2015.1048694. [PubMed: 26010573]

Vermeij A, Kessels RPC, Heskamp L, Simons EMF, Dautzenberg PLJ, Claassen JAHR, 2017 Prefrontal activation may predict working-memory training gain in normal aging and mild

cognitive impairment. Brain Imaging Behav 11, 141–154. 10.1007/s11682-016-9508-7. [PubMed: 26843001]

Wagshul ME, Lucas M, Ye K, Izzetoglu M, Holtzer R, 2019 Multi-modal neuroimaging of dual-task walking: structural MRI and fNIRS analysis reveals prefrontal grey matter volume moderation of brain activation in older adults. Neuroimage 189, 745–754. [PubMed: 30710680]

Weber MJ, Messing SB, Rao H, Detre JA, Thompson-Schill SL, 2014 Prefrontal transcranial direct current stimulation alters activation and connectivity in cortical and subcortical reward systems: a tDCS-fMRI study. Hum. Brain Mapp 35, 3673–3686. 10.1002/hbm.22429. [PubMed: 24453107]

Westbrook A, Braver TS, 2016 Dopamine does double duty in motivating cognitive effort. Neuron 89, 695–710. 10.1016/j.neuron.2015.12.029. [PubMed: 26889810]

Wiegand A, Nieratschker V, Plewnia C, 2016 Genetic modulation of transcranial direct current stimulation effects on cognition. Front. Hum. Neurosci 10, 651 10.3389/fnhum.2016.00651. [PubMed: 28066217]

Wisniewski D, Reverberi C, Momennejad I, Kahnt T, Haynes J-D, 2015 The role of the parietal cortex in the representation of task-reward associations. J. Neurosci 35, 12355–12365. 10.1523/JNEUROSCI.4882-14.2015. [PubMed: 26354905]

Woods AJ, Antonenko D, Flöel A, Hampstead BM, Clark D, Knotkova H, 2019a Transcranial direct current stimulation in aging research In: Practical Guide to Transcranial Direct Current Stimulation Springer, Cham, pp. 569–595.

Woods AJ, Bikson M, Chelette K, Dmochowski J, Dutta A, Esmaeilpour Z, et al., 2019b Transcranial direct current stimulation integration with magnetic resonance imaging, magnetic resonance spectroscopy, near infrared spectroscopy imaging, and electroencephalography In: Practical Guide to Transcranial Direct Current Stimulation Springer, Cham, pp. 293–345.

Wörsching J, Padberg F, Ertl-Wagner B, Kumpf U, Kirsch B, Keeser D, 2016 Imaging transcranial direct current stimulation (tDCS) of the prefrontal cortex—correlation or causality in stimulation-mediated effects? Neurosci. Biobehav. Rev 69, 333–356. 10.1016/j.neubiorev.2016.08.001. [PubMed: 27496671]

Wörsching J, Padberg F, Goerigk S, Heinz I, Bauer C, Plewnia C, Hasan A, Ertl-Wagner B, Keeser D, 2018 Testing assumptions on prefrontal transcranial direct current stimulation: comparison of electrode montages using multimodal fMRI. Brain Stimul 11, 998–1007. 10.1016/j.brs.2018.05.001. [PubMed: 29759944]

Yee DM, Braver TS, 2018 Interactions of motivation and cognitive control. Curr. Opin. Behav. Sci 19, 83–90. 10.1016/j.cobeha.2017.11.009. [PubMed: 30035206]

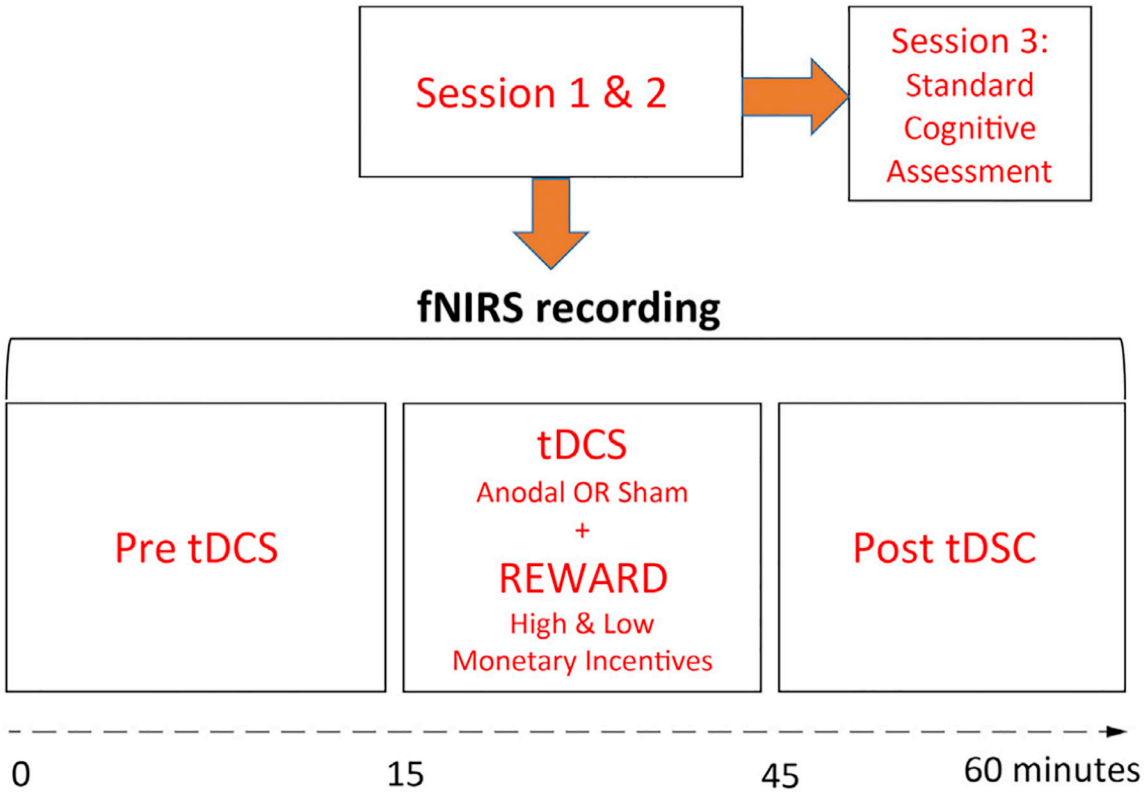

Fig. 1.

Schematic representation of the experimental design. In Sessions 1 and 2, anodal and sham tDCS were counterbalanced across participants and fNIRS was employed before, during and after the stimulation. In Session 3, standard neuropsychological tests were administered, together with questionnaires assessing cognitive reserve and reward sensitivity.

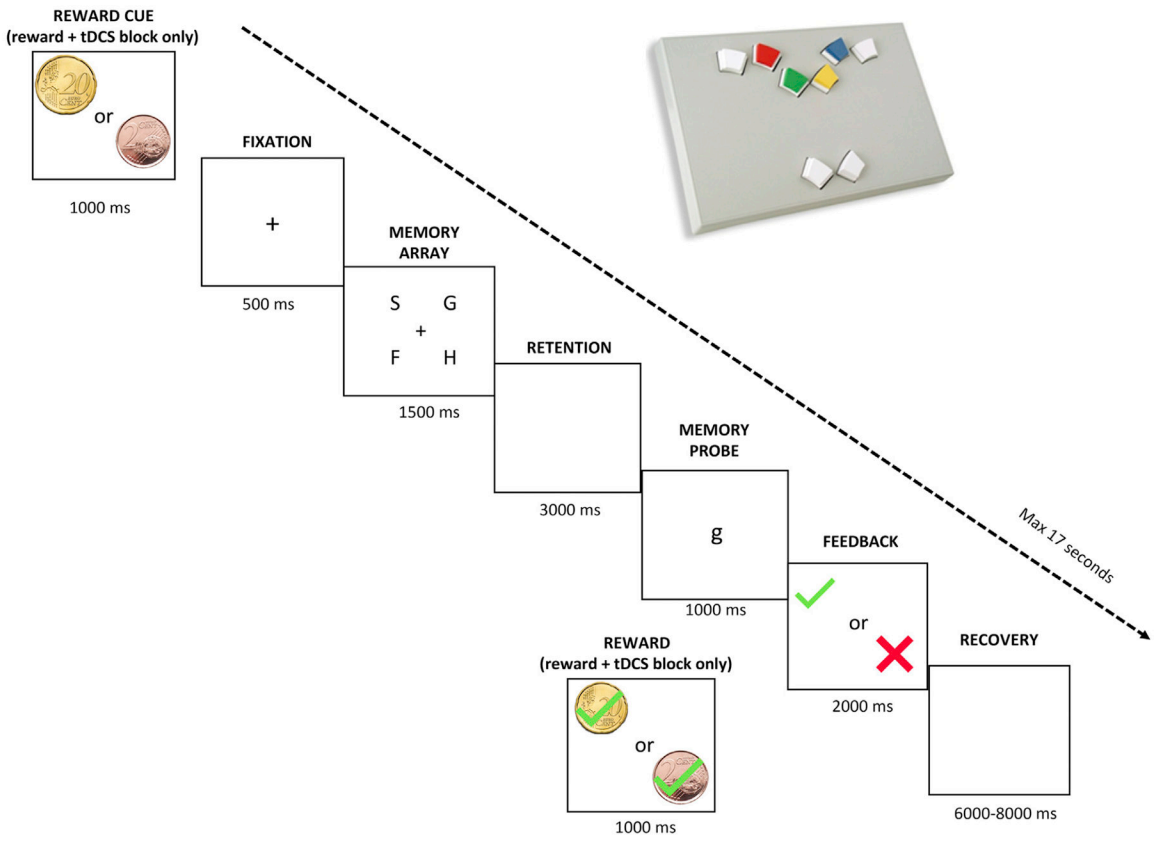

Fig. 2.

Details of the experimental working memory paradigm and the response box employed for the old-new judgment (Cedrus Response Pad RB-840).

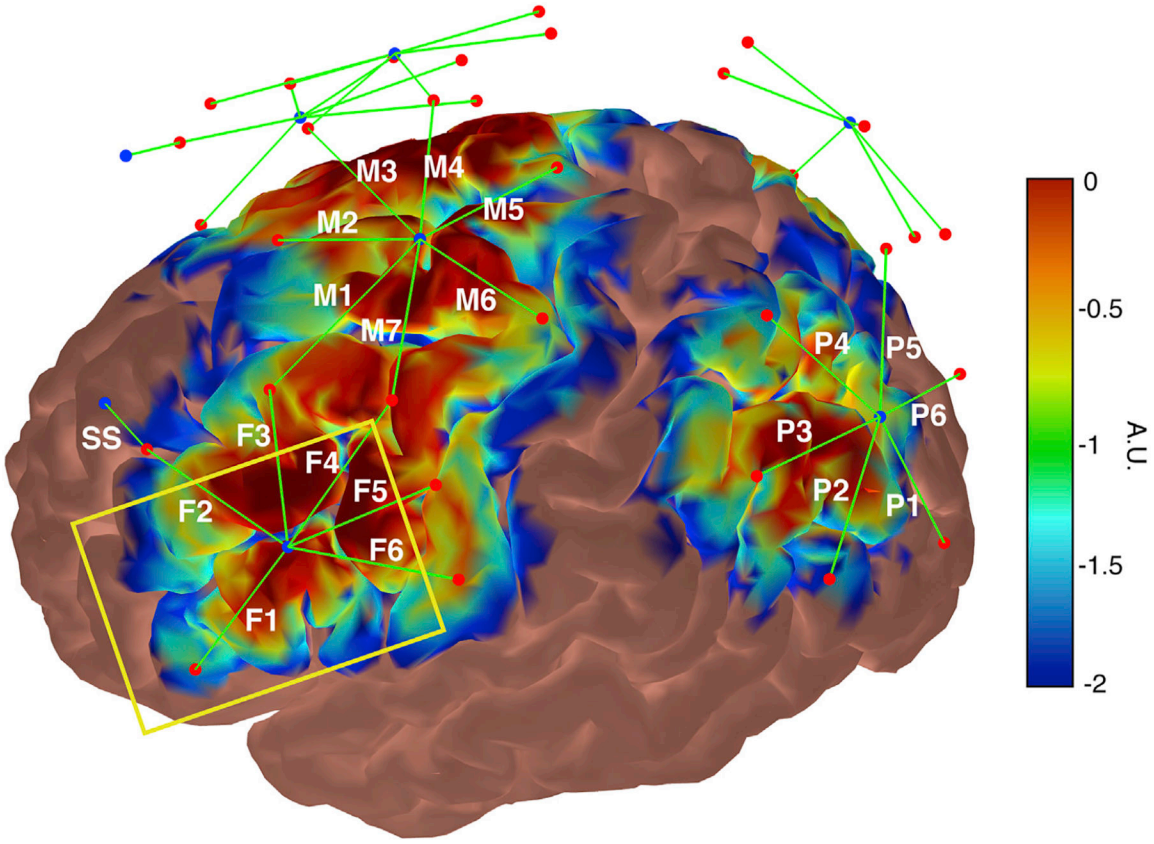

Fig. 3.

Probe placement. Sources are displayed with red dots, detectors with blue dots and channels with green lines. The putative brain areas more sensitive to the array are visualized in hot colours on a standard brain template (Colin27; Collins et al., 1998). These contain the bilateral inferior and middle frontal gyri, the supplementary motor areas and the IPS. Channels are named according to the ROI they cover: F for channels located over the frontal ROI, M for channels placed over the motor ROI and P for channels located over the parietal ROI. The channel named SS refers to the short-separation channel. Only the left hemisphere is shown for visualization purposes, but symmetric channels were placed in the right hemisphere. The yellow rectangle depicts the position of the tDCS anode electrode, placed only in the left hemisphere.

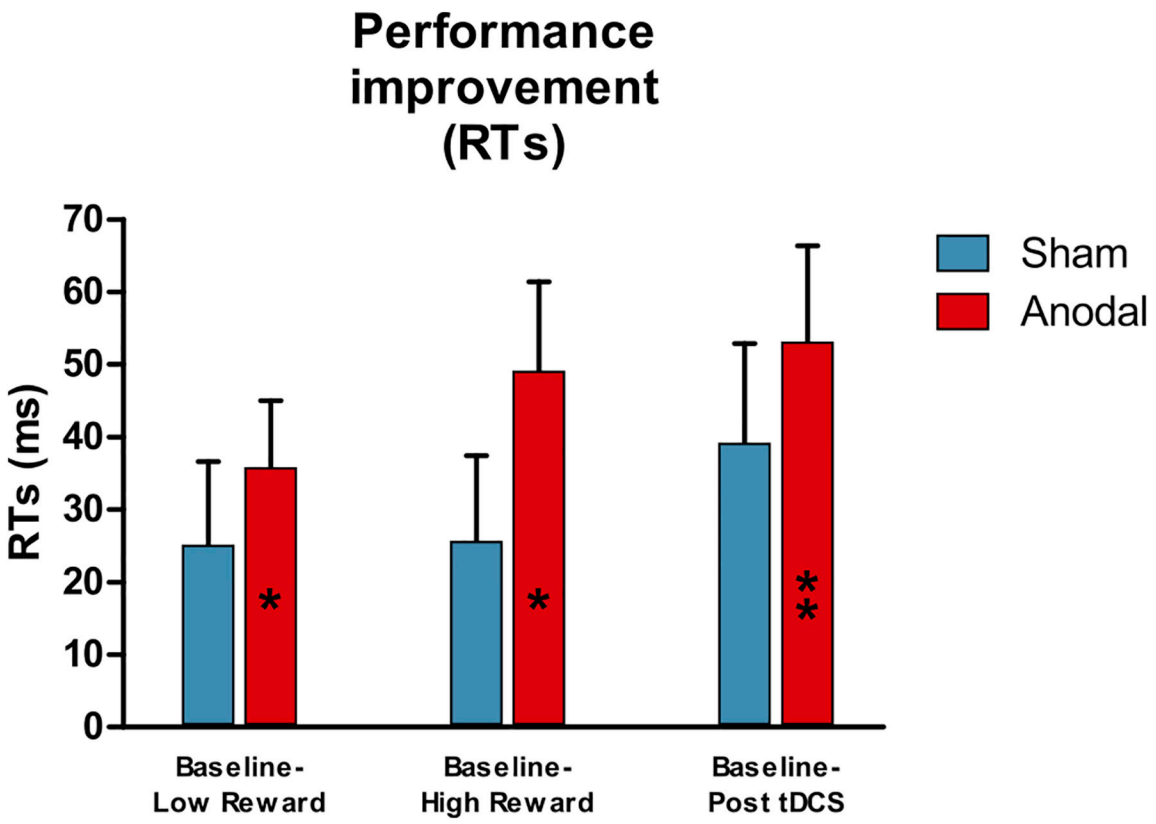

Fig. 4.

The graph represents the difference in RTs between baseline and low reward, baseline and high reward, and baseline and post tDCS. Post-hoc pairwise t-tests revealed that a significant difference was present only in the anodal stimulation session. Error bars represent standard errors of the mean; * refers to a p-value lower than 0.01; ** refers to a p-value lower than 0.005. Correction for multiple comparison (Bonferroni) was applied.

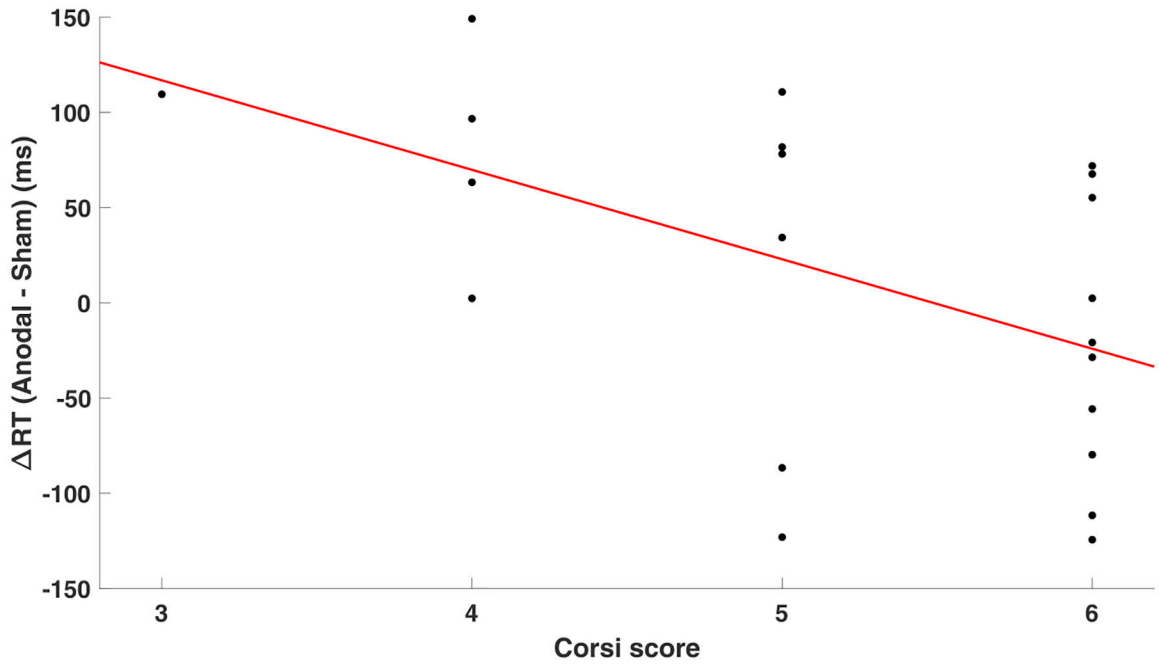

Fig. 5.

The scatterplot represents the significant interaction between WM span and the effect of tDCS on WM performance. In detail, the red line represents the significant negative correlation ($r = -0.461$, $p < .05$) present between the backward Corsi score (on the X axis) and the ΔRT (on the y axis) obtained comparing the RTs reduction, from Baseline to Post tDCS, in the anodal and the sham conditions. Precisely ΔRT = (RTs Baseline Anodal − RTs Post Anodal) − (RTs Baseline Sham − RTs Post Sham). Results suggest that participants with low WM span could benefit the most from the association between reward motivation and anodal tDCS.

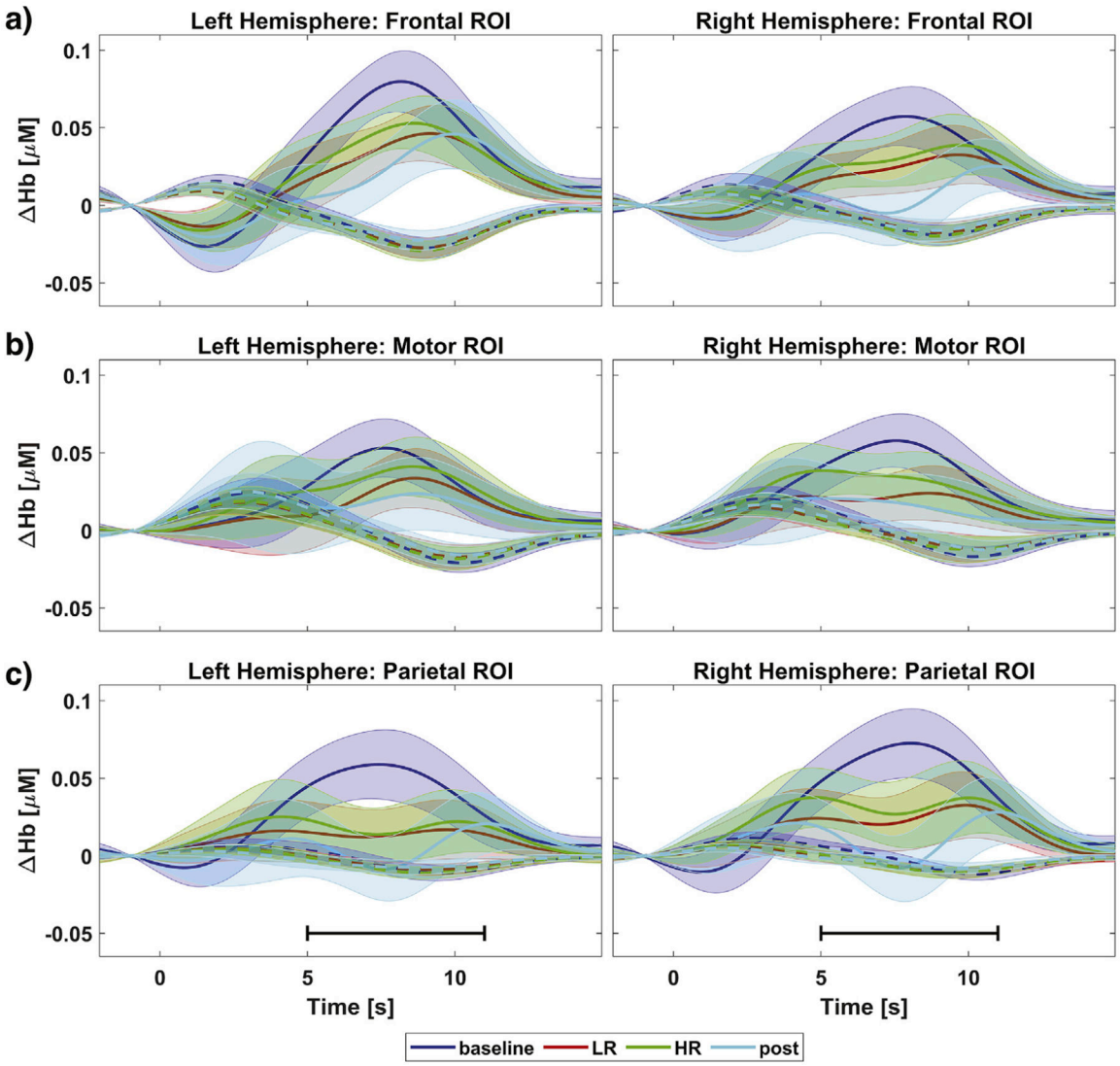

Fig. 6.

Effects of task condition and hemispheric (a)symmetry on the hemodynamic activity measured in all three bilateral ROIs. The frontal ROI is displayed in the top row (panel a); both the effect of task condition and hemispheric asymmetry, with the left hemisphere showing higher activation than the right one, are clearly visible. The motor ROI is displayed in the middle row (panel b); here only an effect of task condition was found. The parietal ROI is displayed in the bottom row (panel c); both the effect of task condition and hemispheric asymmetry, with the right hemisphere showing higher activation than the left one, are clearly visible. Baseline (blue), low reward (LR, red), high reward (HR, green) and post tDCS (light blue) task conditions. Data are averaged between anodal and sham stimulation sessions and across participants. Solid lines represent the HbO activity while the dashed lines the corresponding HbR activity (average between anodal and sham stimulation sessions). Shaded areas represent the standard error of the mean. The black line at the bottom of the figure represents the time interval averaged and submitted to statistical analyses.

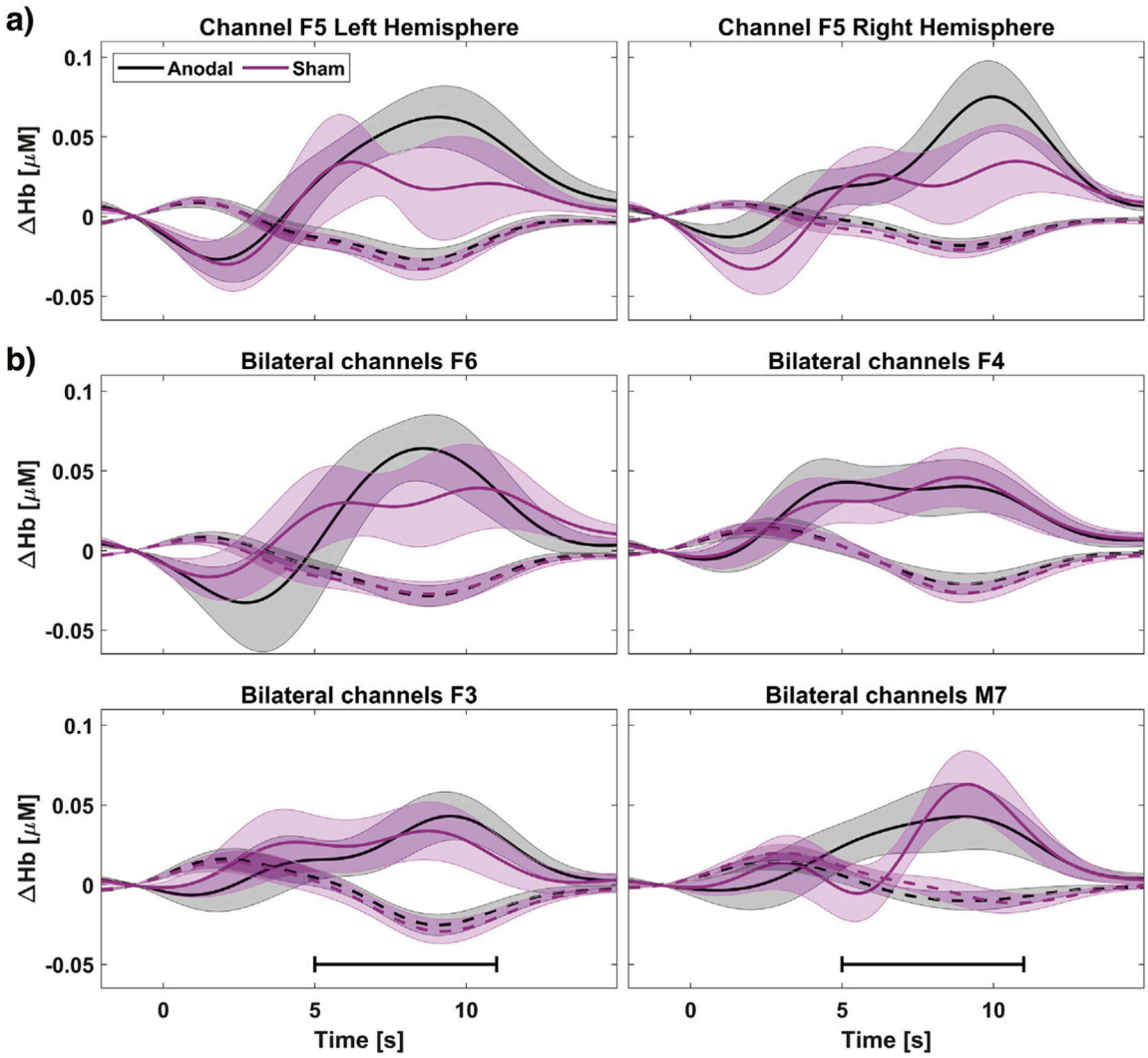

Fig. 7.

Top row (panel a): effects of tDCS on the hemodynamic activity measured in the left and right F5 channels of the frontal ROI during the “reward + tDCS” block. Only in this channel a statistically significant increase in hemodynamic activity during the anodal vs. sham stimulation was detected. Middle and bottom row (panel b): average hemodynamic activity during sham and anodal stimulation in four bilateral channels surrounding channel F5 (see Fig. 3 for the spatial localization of the channels). No statistically significant increase in hemodynamic activity due to anodal stimulation compared to sham was found in these channels, thus demonstrating the anatomical specificity of the anodal stimulation effect. The only channel showing a trend, although not statistically significant, similar to channel F5, is channel F6, which is located very close to channel F5. This closeness, combined with the spatial resolution of fNIRS, makes it likely that both channels are partially sampling some common areas of the brain. Data are averaged between high and low reward conditions. Solid lines represent the HbO activity while the dashed lines the corresponding HbR activity.

Shaded areas represent the standard error of the mean. The black line at the bottom of the figure represents the time interval averaged and submitted to statistical analyses.

Table 1

Mean correct RTs (ms) and accuracy rates, as a function of stimulation type (anodal vs sham) and the task condition. Standard deviations are reported in parentheses.

	BASELINE		LOW REWARD		HIGH REWARD		post tDCS	
	RTs	Accuracy	RTs	Accuracy	RTs	Accuracy	RTs	Accuracy
ANODAL	880 (81)	.78 (.11)	845 (71)	.81 (.10)	831 (80)	.83 (.10)	827 (72)	.85 (.09)
SHAM	857 (80)	.78 (.09)	832 (82)	.83 (.08)	832 (90)	.82 (.09)	818 (78)	.83 (.09)