Clinical Neurophysiology

Behavioural and electrophysiological modulations induced by transcranial direct current stimulation in healthy elderly and Alzheimer's disease patients: a pilot study

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Keywords: transcranial direct current stimulation; working memory; Alzheimer's disease, event-related potentials; compensatory mechanisms.

Research highlights:

1. tDCS modulated neural activity in healthy elderly and Alzheimer's disease patients.
2. Neural modulations may depend on the interaction between tDCS polarity and neural state.
3. Neural modulations induced by tDCS were related to working memory improvements.

Abstract

Objective: To investigate whether anodal and cathodal transcranial direct current stimulation (tDCS) can modify cognitive performance and neural activity in healthy elderly and Alzheimer's disease (AD) patients.

Methods: Fourteen healthy elderly and twelve AD patients performed a working memory task during an electroencephalogram recording before and after receiving anodal, cathodal, and sham tDCS over the left dorsolateral prefrontal cortex. Behavioural performance, event-related potentials (P200, P300) and evoked cortical oscillations were studied as correlates of working memory.

Results: Anodal tDCS increased P200 and P300 amplitudes in healthy elderly. Cathodal tDCS increased P200 amplitude and frontal theta activity between 150-300ms in AD patients. Improved working memory after anodal tDCS correlated with increased P300 in healthy elderly. In AD patients, slight tendencies between enhanced working memory and increased P200 after cathodal tDCS were observed.

Conclusions: Functional neural modulations were promoted by anodal tDCS in healthy elderly and by cathodal tDCS in AD patients.

Significance: Interaction between tDCS polarity and the neural state (e.g., hyper-excitability exhibited by AD patients) suggests that appropriate tDCS parameters (in terms of tDCS polarity) to induce behavioural improvements should be chosen based on the participant's characteristics. Future studies using higher sample sizes should confirm and extend the present findings.

1. Introduction

1.1. Cognitive impairment during physiological and pathological ageing

Ageing negatively influences many cognitive domains, and executive functions decline more than others in physiological (i.e., healthy elderly subjects) and pathological (e.g., Alzheimer's disease; AD) ageing (Baudic et al., 2006; Weintraub et al., 2012). Executive functions include a group of cognitive processes that are used in our daily life activities to execute goal-directed behaves and monitoring our actions (Chan et al., 2008; Diamond, 2013). In detail, as stated by Miyake and colleagues (Miyake et al., 2000; Miyake and Friedman, 2012), executive functions include three main cognitive processes: inhibition (i.e., ability to suppress irrelevant information), shifting (i.e., ability to switch attention between stimuli or set of features) and update (which, according to the mentioned authors, includes "constant monitoring and addition/deletion of working-memory contents"). Working memory is one of the most studied executive functions and comprises a group of cognitive processes that allow us to encode, store, maintain, retrieve and manipulate information in short-term memory (Baddeley, 2003). Beyond individual differences, working memory becomes less efficient during healthy ageing (Park et al., 2002; Peich et al., 2013), and it is drastically compromised in AD patients (Kirova et al., 2015). Interestingly, the brain of healthy elderly subjects deploys compensatory mechanisms (e.g., increased frontal activity and more bilateral patterns of activation during the performance of cognitive tasks) to maintain a good cognitive functioning (Davis et al., 2012) and the loss of this compensatory capacity is strongly related to cognitive impairment in AD patients (Cespón et al., 2018).

1.2. Cognitive enhancement by transcranial direct current stimulation: mixed findings

Transcranial direct current stimulation (tDCS) represents a potential rehabilitation tool that is thought to enhance cognitive functioning by boosting residual brain plasticity mechanisms in patients (Lefaucheur et al., 2017; Miniussi et al., 2008). tDCS involves the application of a constant

flow of current between two electrodes at a low intensity (1-3 mA) for a brief time period (around 10-20 minutes) (Antal et al., 2017; Woods et al., 2016). tDCS is capable of changing the neural state by modulating the spontaneous neurons firing rate (Creutzfeldt et al., 1962), which is increased by anodal tDCS and decreased by cathodal tDCS (Nitsche and Paulus, 2000). Such modulations persist after the cessation of the tDCS application for a time period that may last until 90 minutes (Nitsche and Paulus, 2000; 2001).

An early study reported that working memory abilities were improved by anodal tDCS and impaired by cathodal tDCS in healthy young subjects, who performed a 3-back task (Fregni et al., 2005). Recently, several studies have highlighted the potential capability of anodal tDCS to enhance a variety of cognitive functions in healthy elderly (Antonenko et al., 2018; Summers et al., 2016; Tatti et al., 2016). More specifically, research focusing on the improvement of working memory functions has typically delivered anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC), as this brain region plays a crucial role in working memory processes (Kumar et al., 2017; Levy and Goldman-Rakic, 2000). Some studies reported a working memory improvement after applying anodal tDCS in healthy elderly subjects (Berryhill and Jones, 2012; Jones et al., 2015; Park et al., 2014) and AD patients (Boggio et al., 2009); however, other studies reported the absence of any general cognitive benefit after anodal tDCS over the left DLPFC both in healthy elderly subjects (De Putter et al., 2015; Motohashi et al., 2013; Mylius et al., 2012; Sellers et al., 2015) and in AD patients (Bystad et al., 2016; Cotelli et al., 2014; Suemoto et al., 2014, for a review see Pellicciari and Miniussi 2018).

A limited number of studies used cathodal tDCS to modulate working memory. Evidence for working memory improvement after applying cathodal tDCS in healthy subjects was reported (Heinen et al., 2016) but other studies showed that cathodal tDCS disrupted working memory abilities in healthy young and elderly subjects (Cespón et al., 2017). Previous studies did not use tDCS to enhance working memory in AD patients even if cathodal tDCS improved the performance of AD patients in a neuropsychological assessment (Khedr et al., 2014). As stated in recent reviews,

the current evidence does not allow stating the efficacy of tDCS in cognitive rehabilitation of AD patients (Lefaucher et al., 2017; Pellicciari and Miniussi, 2018).

Inconsistent results about tDCS efficacy in healthy subjects (Horvath et al., 2014) or AD patients (Pellicciari and Miniussi, 2018) were attributed to differences in tDCS parameters such as duration and intensity of the applied stimulation, targeted site, montage of electrodes (e.g., return electrode in the arm vs. in the forehead) or underpowered studies. Nevertheless, it should be highlighted that inter-individual differences in tDCS-induced effects sometimes emerge even if a homogeneous sample of participants is used. For instance, neural activity induced by tDCS can be modulated by head anatomy (Kim et al., 2014) and the intrinsic neural state induced by the task (e.g., Bortoletto et al., 2015; Dockery et al., 2009); specifically, effects induced by anodal and cathodal tDCS will not only depend on excitation and inhibition induced by these currents but also on the neural state of the stimulated area (Fertonani and Miniussi, 2017).

Some characteristics inherent to the clinical populations, such as the neural hyper-excitability previously described in AD patients (Di Lazzaro et al., 2004; Ferreri et al., 2011; Pennisi et al., 2011), involve additional and important sources of complexity because these alterations may modulate the neural effects of the tDCS. Neural hyper-excitability was also reported using animal models of AD (Hall et al., 2015; Palop et al., 2007; Scala et al., 2015). This physiological characteristic is important because the effects of the tDCS in a given subject may be highly determined by differences in cortical excitability (Miniussi et al., 2013; Silvanto et al., 2008). Specifically, applying excitatory current to a highly excitable neural region could produce opposite effects by activating homeostatic mechanisms (Moliadze et al., 2012). In this respect, it is important to note that a very limited number of studies have evaluated how the neurophysiological state of the targeted patients determines the specific tDCS parameters that should be applied.

1.3. Electrophysiological correlates of working memory

Electrophysiological correlates of working memory processes have been previously investigated by means of electroencephalogram (EEG) and event-related potentials (ERP).

Previous ERP studies have related the P200 component to memory retrieval processes occurring during the performance of working memory tasks (Li et al., 2016; McEvoy et al., 2001). Interestingly, previous research demonstrated that the mentioned P200 component is increased by physiological ageing (Zhao et al., 2013) and decreased in cognitively declined subjects (Li et al., 2016). Additionally, the P300 ERP component is thought to be related to context information update (Polich, 2007), and it is also modulated by physiological (Friedman et al., 1997) and pathological (Polich and Corey-Bloom, 2005, Rossini et al., 2007) ageing. Specifically, P300 latency is delayed by physiological and pathological ageing whereas the frontal P300 amplitude is usually increased in healthy elderly (which is thought to reflect brain compensatory mechanisms) and decreased in AD patients (Polich and Corey-Bloom, 2005; Rossini et al., 2007), which may be reflecting a loss of the compensatory capabilities. Crucially, studying electrophysiological correlates of working memory processes before and after applying tDCS may provide important insights about the more appropriate parameters -such as polarity- to be used for "enhancing" the neural processes related to improved cognitive performance (Cespón et al., 2018). Improved working memory performance after anodal tDCS in healthy young (Keeser et al., 2011) and elderly subjects (Cespón et al., 2017) has been related to an increased frontal P300. Both of these studies (Cespón et al., 2017; Keeser et al., 2011) suggested that working memory improvement after tDCS may be mediated by the promotion of frontal activity related to attentional processes.

EEG studies also investigated the association between working memory processes and brain oscillatory activity. Encoding and retrieval of new information during the performance of working memory tasks were associated to increased theta oscillations (Hasselmo, 2006; Klimesch, 1999) whereas alpha oscillations were involved in encoding and reactivating long-term memory codes in working memory (Klimesch et al., 2005; Wang et al., 2017). Moreover, beta oscillations were related to the maintenance of the current cognitive set (Engel and Fries, 2010).

1.4. Objectives and hypotheses of the present study

In the present study, we investigated whether anodal and cathodal tDCS applied over the left DLPFC differently modulated working memory abilities -specifically, updating abilities according to the model of Miyake et al (2000)- in healthy elderly and AD patients, who performed a n-back task (for a graphical sketch of the cognitive tasks and experimental procedure, see Figure 1). In addition, we investigated the associated neural changes induced by tDCS (by analysing the P200 and P300 ERP components and the evoked oscillations in theta, alpha, and beta frequency bands within time windows corresponding to the studied ERPs). Considering the potential interaction between tDCS polarity and the neural state and the mentioned neural hyper-excitability related to AD (Di Lazzaro et al., 2004; Ferreri et al., 2011; Pennisi et al., 2011), we hypothesize that anodal and cathodal tDCS could induce differential behavioural and neurophysiological modulations during the n-back task in healthy elderly participants and AD patients. In detail, according to previous research, healthy elderly would improve after anodal tDCS but not after cathodal tDCS. However, in AD patients, cathodal tDCS may contribute to reduce the brain hyper-excitability. Thus, AD patients would improve after cathodal tDCS rather than after anodal tDCS.

2. Method

2.1. Participants

Fourteen healthy elderly subjects (9 females, 5 males; range age: 65-84 years old; mean age = 70.2, SD = 5.12; as in Cespón et al., 2017) and twelve AD patients (7 females, 5 males; range age: 68-84 years old; mean age = 76.0, SD = 5.9) participated in the present study. The Edinburgh handedness inventory test (Oldfield, 1971) was used to test that all the participants were right-handed. Moreover, all participants reported absence of previous neurological or psychiatric disorders and did not carry metal implants.

To estimate the achieved statistical power a post hoc analysis was carried out by calculating the Cohen's d (Cohen, 1988). Considering the d' index as primary outcome and assuming a mean effect size (0.5) for an alpha level of 0.05, the achieved power was 0.447 for between-within repeated

measures ANOVA. The relatively low power achieved is discussed as a limitation of the present study.

The inclusion criteria for AD patients were the following: a diagnosis of probable AD according to the National Institute of Neurology and Communication Disorder and Stroke-The Alzheimer's Disease and Related Disorders Association Criteria (NINCDS-ADRDA) (McKhann et al., 1984), a Mini-Mental State Examination (Folstein et al., 1975) score above 16 (mean = 20.3; standard deviation = 3.4), a stable treatment with cholinesterase inhibitors in the last 3 months, the ability to sign for the informed consent, the absence of any evidence of other central nervous system disorders that could explain the presence of dementia (i.e., structural anomalies, epilepsy, infective, degenerative or inflammatory/demyeliniting pathologies, such as Parkinson's disease and frontotemporal dementia), and the absence of a history of a significant psychiatric disease that could interfere with the participation in the study. All the experimental procedures were explained to participants, who voluntarily took part in the study, as well as to the caregivers of AD patients. Informed and written consent was obtained from all participants.

Experimental protocols for non-invasive brain stimulation were performed in accordance with safety guidelines procedures (Antal et al., 2017). The study, which received previous approval by "The Saint John of God Clinical Research Centre Ethical Committee", was carried out according to the ethical guidelines established by the Declaration of Helsinki.

2.2. Procedures

Participants took part in three experimental sessions, which were separated by (at least) five days. In each experimental session, each participant performed a working memory task (i.e., an n-back task, see Figure 1) before and after receiving tDCS. In each experimental session, participants received anodal, cathodal, or sham tDCS. As in the present research, a high number of previous studies (e.g. Keeser et al., 2011) that investigated the potential utility of tDCS to improve cognitive functions have applied the tDCS in an offline manner (i.e., participants performed the task before and after receiving tDCS). Other studies used online tDCS (i.e., participants performed the task to

obtain a baseline performance and then they receive tDCS while performing the task again). In the present study, we have decided to implement an offline design because online designs are more prone to produce artefacts in the EEG signal and we were strongly interested in obtaining an optimal EEG recording. Importantly, a recent meta-analysis (Summers et al., 2016) reported that cognitive improvements in elderly during the performance of cognitive tasks were higher in tDCS studies using offline than in tDCS studies using online experimental designs even if another meta-analytical study (including TMS and tDCS experiments) reported that online non-invasive brain stimulation would be more effective than offline protocols in AD patients (Hsu et al., 2015).

The order of the experimental sessions was counterbalanced among the participants. The tDCS was delivered by means of two rubber electrodes (active electrode = 16 cm^2; reference electrode = 50 cm^2) connected to a battery-driven constant current stimulator (BrainStim, EMS), following tDCS guidelines (Woods et al., 2016). The active electrode was placed over the F3 electrode (10-10 International System) in order to target the left DLPFC. The return electrode was placed over the right shoulder. With the terms anodal and cathodal, we refer to the polarity of the electrode placed over the left DLPFC. For anodal and cathodal tDCS, the current was delivered at 1.5 mA of intensity (current density = 0.09 mA/cm^2), for a duration of 13 minutes with a stimulation ramping period of 8 seconds at the start and at the end of the stimulation as in Cespón et al. (2017). Sham tDCS was delivered applying the current for 10 second at the beginning and at the end of the stimulation period. The experimental procedure is represented in Figure 1.

Figure 1 about here

2.3. Task

The mentioned n-back tasks consisted of 320 stimuli (80 targets and 240 non-targets), which were presented in two separated blocks. Therefore, the probability of target appearance was established at 25%. Each block lasted 6 minutes. The break between two blocks was approximately 90 seconds.

During the task, the letters A to L (in white colour against a black background) were presented in a random manner in the centre of the screen for 500 ms. Afterwards, the screen remained blank during a time interval between the stimuli that was jittered between 2000 and 2500 ms. Participants were instructed to direct their gaze to the centre of the screen (placed 100 cm in front of them) throughout the task and to respond to the stimulus matching the identity of the stimulus presented two trials before (2-back task, which was run for healthy elderly subjects) or one trial before (1-back task, which was run for AD patients), by pressing the space bar. These different versions of the task were designed to match the degree of difficulty for each group of participants. Each participant performed the n-back task before and after the application of the tDCS (anodal, cathodal and sham). In order to prevent learning of sequence in which the letters appeared; the order of the letters differed on each time the participant performed the task. A training block containing 20 targets and 60 non-targets (3 minutes long) was performed before the n-back task on each experimental session. All the participants achieved 60% of accuracy after three or less blocks of practice, on each experimental session, which was a requirement to proceed with the experiment.

2.4. EEG recordings

EEG was recorded using the following 31 electrodes (Easycap, GmbH, Brain Products): Fp1, Fp2, AF7, AF8, F7, F3, Fz, F4, F8, FC5, C1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO7, PO8, O1, and O2. Electrodes were placed according to 10-10 International System. The ground electrode was placed over Fpz. The electrode placed on the right mastoid was used as online reference for all electrodes. The electrode placed on the left mastoid was used offline to re-reference the scalp recordings to the average of the left and the right mastoid, i.e., including the implicit reference (right mastoid) into the calculation of the new reference. The EEG signal was acquired with a 0.1-1000 Hz bandpass filter and digitized at a sampling rate of 5000 Hz. A down sampling rate (1000 Hz) was obtained before EEG/ERP pre-processing. Vertical eye movements were recorded by means of two electrodes located above and below the right eye. Horizontal eye movements were recorded by using two electrodes located in the external canthi of each eye. The

EEG recording started after all the electrodes showed impedance below 5 kΩs. The ocular artefacts were eliminated by using independent component analysis. The EEG signal was filtered with a 0.1-80 Hz digital bandpass and a 50 Hz notch filter. A first artefact rejection was performed removing automatically the epochs exceeding ±100 μV. Subsequently, the remaining epochs were individually inspected and the trials still containing artefacts were eliminated from subsequent analysis. A baseline correction was applied by taking the mean voltage of the 200 ms pre-stimulus.

2.5. Data analysis

Behavioural performance was assessed by studying the reaction time (RT) and accuracy (note that, the reported behavioural data in healthy elderly were used to contrast elderly subjects against young subjects in Cespón et al., 2017). Accuracy was calculated by using the d prime index (d'), which is obtained in the following way: $d' = Z_{(\text{hit rate})} - Z_{(\text{false alarm rate})}$, where Z denotes hit and false alarm rates transformed into z scores using the standard normalized probability distribution. The higher is the d′, the higher is the performance.

ERPs amplitudes and EEG power were calculated for hits. The epochs were set between -200 and 800 ms with respect to the onset of the target stimulus. P200 ERP was identified as the maximum positive polarity peak occurring between 150 and 300 ms, and it was analysed by computing the mean voltage value in a time window of 50 ms (i.e., ±25 ms around its peak latency). P300 ERP was identified as the maximum positive polarity peak occurring between 400 and 700 ms, and it was analysed by computing the mean voltage value in a time window of 100 ms (i.e., ±50 ms around its peak latency). Note that P200 and P300 mean amplitudes but not their peak latencies were studied in the present research. P300 analyses differ from those conducted in Cespón et al. (2017), where P300 amplitude was analysed by using fixed time windows for all subjects. The purpose of the present P300 analyses is studying possible differences between healthy elderly and AD patients induced by tDCS in the amplitude of P300. As AD patients show high inter-individual variability in P300 latency, we have opted by measuring the mean amplitude around the maximum

peak latency of each individual subject rather than by establishing fixed time windows. Therefore, we ensure that P300 analyses are carried out around P300 peak latency for all subjects.

For P200 and P300 ERP components, analyses were carried out within specific regions of interest (ROI), which included the frontal left region (i.e., the stimulated area) and the frontal right region (i.e., the homologous area regarding the stimulated site). In addition, P300 was analysed within the parietal left and right areas, in which this component normally achieves its maximum amplitude. These ROIs were calculated by making the following pooling of electrodes: frontal left (F3, F7, AF7, and FC5), frontal right (F4, F8, AF8, and FC6), parietal left (P3, P7, PO7, and CP5), and parietal right (P4, P8, PO8, and CP6). To shed light on the functional meaning of the ERP modulations observed after the application of the tDCS, correlation analyses were carried out between ERP changes and d' changes for each ROI and experimental condition.

Time-frequency analyses were carried out by using evoked wavelet transform in order to investigate whether cortical oscillatory activity in specific frequency bands was modulated by tDCS at the time windows related to the P200 and P300 ERP components. A Morlet continuous wavelet transform with Gabor normalization was implemented after averaging the hit trials for each subject. Epochs were established between -1000 ms and 1000 ms regarding the onset of the target stimulus. We extracted the power (in μV^2) in the theta (4.1-7.9 Hz), alpha (8.1-13.9 Hz) and beta (15.1-24.6 Hz) frequency bands, at 150-300 ms and at 400-700 ms time windows within the four ROIs {that is, frontal left (F3, F7, AF7, and FC5), frontal right (F4, F8, AF8, and FC6), parietal left (P3, P7, PO7, and CP5), and parietal right (P4, P8, PO8, and CP6)}. In detail, power modulations at 150-300 ms were studied in the left and right frontal ROIs whereas power modulations at 400-700 ms were studied in the four ROIs.

2.6. Statistical analysis

To assess whether or not tDCS modulated behavioural performance, separated repeated-measures ANOVAs for RTs and d' values were conducted with a between-subject factor, Group (2 levels:

healthy elderly and AD) and two within-subject factors, Stimulation (3 levels: anodal, cathodal, and sham) and Time (2 levels: before tDCS and after tDCS).

In line with a previous study (Cespón et al., 2017), the ERP components were analysed using repeated-measures ANOVA with a between-subject factor, Group (2 levels: healthy elderly and AD) and two within-subject factors, Stimulation (3 levels: anodal, cathodal, and sham) and Time (2 levels: before tDCS and after tDCS) for the corresponding ROIs (i.e., frontal left and frontal right for P200; and frontal left, frontal right, parietal left, and parietal right for P300). Pearson's correlation analysis was performed to investigate the correlations between increased d' values and increased ERP amplitudes observed after tDCS application (i.e., anodal, cathodal, and sham). Benjamini-Hochberg method was applied to control for false positives (Benjamini and Hochberg, 1995) by assuming a rate discovery value of 0.20, as suggested by previous studies (McDonald, 2014).

In order to investigate modulations induced by tDCS on cortical oscillatory activity for each frequency band, the extracted power was analysed by using repeated-measures ANOVA with a between-subject factor, Group (two levels: healthy elderly and AD) and two within-subject factors, Stimulation (three levels: anodal, cathodal, and sham) and Time (two levels: before tDCS and after tDCS).

When the condition of sphericity was not meet, the Greenhouse-Geisser correction for degrees of freedom was applied. The partial eta square (η2p) index—a measure of effect size —is reported for significant results. Additionally, when ANOVA showed significant effects due to the main factors or their interactions, Bonferroni correction was applied to the post hoc comparisons.

3. Results

3.1. Behavioural results

The repeated measures ANOVA for d' revealed a Time effect [$F(1, 24) = 6.58$, $p = 0.017$, $\eta^2p = 0.215$], as the d' index was higher after all the tDCS conditions (i.e., anodal, cathodal and sham

tDCS) ($p = 0.017$, $\eta^2p = 0.215$) (d' values are recapped in Table 1). However, the Stimulation x Time interaction did not reach a significant effect [$F (2, 48) = 2.13$, $p = 0.130$]. For RTs, the repeated-measures ANOVA did not show any significant effect for the factors Group, Stimulation or Time and neither for their interactions.

Table 1 about here

3.2. ERP results

For the left frontal P200 (see Figures 2 and 3), the repeated-measures ANOVA showed a significant Group x Stimulation x Time interaction effect [$F (2, 48) = 6.11$, $p = 0.004$, $\eta^2p = 0.203$]. Specifically, in the healthy elderly group, the P200 amplitude was larger after anodal tDCS was delivered ($p = 0.033$, $\eta^2p = 0.176$). Moreover, in AD patients, the P200 amplitude was larger after cathodal tDCS was delivered ($p = 0.001$, $\eta^2p = 0.350$).

For the right frontal P200, the repeated measures ANOVA showed a significant Group x Stimulation x Time interaction effect [$F (2, 48) = 4.88$, $p = 0.012$, $\eta^2p = 0.169$]. Specifically, in AD patients, the P200 was larger after cathodal tDCS was delivered ($p = 0.007$, $\eta^2p = 0.269$).

For the left frontal P300 (see Figures 2 and 3), the repeated-measures ANOVA showed a Time effect [$F (1, 24) = 6.12$, $p = 0.021$, $\eta^2p = 0.203$], as the P300 was larger after delivering any tDCS condition (i.e., anodal, cathodal and sham) ($p = 0.021$, $\eta^2p = 0.203$). Also, a Group x Stimulation x Time interaction effect was observed [$F (2, 48) = 5.98$, $p = 0.005$, $\eta^2p = 0.199$]. Specifically, in healthy elderly participants, the P300 was larger after anodal tDCS was applied ($p = 0.001$, $\eta^2p = 0.401$). Moreover, after the application of anodal tDCS, the P300 was larger in healthy elderly participants than in AD patients ($p = 0.029$, $\eta^2p = 0.184$).

For the right frontal P300, the repeated-measures ANOVA showed a Time effect [$F (1, 24) = 5.39$, $p = 0.029$, $\eta^2p = 0.184$], as the P300 was larger after both active and sham tDCS conditions were applied ($p = 0.029$, $\eta^2p = 0.184$). Also, the analysis revealed a Group x Stimulation interaction

effect [F (2, 48) = 4.57, p = 0.015, η^2p = 0.160]; specifically, in the anodal tDCS condition, the P300 was larger in healthy elderly participants than in AD patients (p = 0.012, η^2p = 0.234). Moreover, a Group x Stimulation x Time interaction effect was observed [F (2, 48) = 3.85, p = 0.028, η^2p = 0.138]; specifically, in healthy elderly participants, the P300 was larger after anodal tDCS was applied (p = 0.004, η^2p = 0.294). Additionally, after applying the anodal tDCS, the P300 was larger in healthy elderly participants than in AD patients (p = 0.011, η^2p = 0.242). Moreover, in healthy elderly participants, the P300 was larger after applying anodal than after applying sham (p = 0.001, η^2p = 0.440) and cathodal (p = 0.002, η^2p = 0.440) tDCS.

For the left parietal P300, the repeated-measures ANOVA showed a Time effect [F (1, 24) = 11.8, p = 0.002, η^2p = 0.330], as the P300 was larger after the application of any stimulation condition, i.e. after both active and sham tDCS (p = 0.002, η^2p = 0.330). Additionally, a significant Stimulation x Time effect was observed [F (2, 48) = 4.54, p = 0.016, η^2p = 0.159]; specifically, the P300 was larger after anodal tDCS was applied (p < 0.001, η^2p = 0.568). In addition, after the application of tDCS, the P300 was larger in anodal tDCS than in sham (p = 0.005, η^2p = 0.472) and cathodal (p = 0.002, η^2p = 0.472) tDCS conditions.

For the right parietal P300, the repeated measures ANOVA showed a significant Time effect [F (1, 24) = 12.45, p = 0.002, η^2p = 0.34], as the amplitude of P300 was larger after applying any tDCS condition (i.e., both active tDCS and sham tDCS conditions) (p = 0.002, η^2p = 0.34).

Figures 2 and 3 about here

3.3. Correlations between working memory accuracy and ERP modulations

To shed light on the functional significance of the observed ERP modulations after applying tDCS, Pearson correlation coefficients between d' and ERP changes after tDCS were calculated (see Figure 4). In healthy elderly subjects, significant correlations were observed after anodal tDCS between enhanced d' and increased P300 within the left (rxy = 0.71, p = 0.005) and right frontal

regions (rxy = 0.54, p = 0.047) even if only the former survived after applying the Benjamini-Hochberg correction. For AD patients, non-significant tendencies were observed after cathodal tDCS between enhanced d' and increased P200 amplitude within the left (rxy = 0.53, p = 0.080) and right frontal regions (rxy = 0.41, p = 0.189).

Figure 4 about here

3.4. Evoked Wavelet results

For theta power at 150-300 ms time window, the repeated measures ANOVA revealed a Group x Stimulation x Time interaction effect within the left frontal region (F (2, 48) = 4.21, p = 0.021, η^2p = 0.149). In detail, whereas differences in theta power were not observed in healthy elderly subjects (see Figure 5), in AD patients, theta power was greater after cathodal tDCS than before cathodal tDCS (p = 0.017) (see Figure 6, middle panel). For the right frontal ROI, differences at 150-300 ms were not found. Differences at 400-700 ms were not found for any ROI (Figures 5 and 6 represent time-frequency results in the left frontal ROI for healthy elderly subjects and AD patients, respectively). No significant differences were observed in the power of alpha and beta frequency bands.

Figures 5 and 6 about here

4. Discussion

The present study investigated whether neural activity and associated working memory performance were differentially modulated in healthy elderly and AD patients by delivering anodal and cathodal tDCS over the left DLPFC. Electrophysiological changes were observed in frontal regions after anodal tDCS in healthy elderly (i.e., larger P200 in frontal left and larger P300 in

frontal left and right ROIs) and after cathodal tDCS in AD patients (i.e., larger P200 in frontal left and right ROIs). In healthy elderly participants, correlations between increased frontal P300 amplitude and enhanced accuracy in the performance were observed after anodal tDCS. In AD patients, correlations between increased frontal P200 amplitude and enhanced accuracy after cathodal tDCS were observed, even if as a trend. Also, time-frequency analyses revealed that theta power increased at 150-300 ms within the left frontal ROI after cathodal tDCS in AD patients. The main results of the present study are schematically summarized in Figure 7.

Figure 7 about here

4.1. Effects of tDCS on the working memory performance

Overall, the behavioural results showed that the level of accuracy (measured by using the d' index) was greater after the application of tDCS in all the experimental conditions. However, interaction effects were not significant, which indicates that both active tDCS conditions (i.e., anodal and cathodal tDCS) did not improve the working memory performance more than sham tDCS. A recent meta-analysis on tDCS effects in elderly showed that improvements in cognitive tasks were greater after offline tDCS (i.e., tDCS applied during resting state, as delivered in the present research) than after online tDCS (i.e., tDCS while the participant is performing a task) protocols (Summers et al., 2016). According to several studies (Hill et al., 2016; Jantz et al., 2016), we may point to high inter-individual variability of the tDCS effects and low sample size (Button et al., 2013) as plausible reasons to explain the lack of stronger cognitive improvements in any active tDCS condition compared to the sham condition at the group level. In fact, as showed by Figure 4, accuracy of some participants has clearly been improved after tDCS whereas in other participants the accuracy was impaired after tDCS. Nonetheless, on the basis of the obtained data, we cannot exclude that performance was improved by taking practise in the task (i.e., test-retest learning effect).

4.2. Electrophysiological changes induced by tDCS in working memory correlates

EEG and ERPs provide interesting information about the capability of tDCS to modulate neural correlates of working memory processes. In healthy elderly subjects, the P200 amplitude increased within the left frontal region after anodal tDCS, whereas in AD patients, the P200 amplitude increased within the left and right frontal regions after cathodal tDCS. Several studies linked the frontal P200 with memory retrieval processes, which occur during the performance of working memory tasks (Li et al., 2016; McEvoy et al., 2001). In line with these findings, the present results suggest that tDCS induced an increase of neural activity related to memory retrieval in healthy elderly and AD patients. This increased activity may be related to better working memory performance after tDCS. Indeed, slight tendencies were observed between increased P200 amplitude and enhanced performance in AD patients. Future studies with higher sample sizes should confirm the existence of a relationship between increased P200 and increased working memory performance.

In AD patients, time-frequency analyses revealed an increase of theta power in the left frontal region (i.e., in the stimulated area) at 150-300 ms after cathodal tDCS. This result aligns with previous findings about the potential capacity of tDCS to increase theta activity (Mangia et al., 2014; Miller et al., 2015). Thus, regardless of the applied type of current (i.e., anodal tDCS in these mentioned studies vs. cathodal tDCS in the present study), the increase of theta activity is related to better working memory performance. Importantly, considering the relationship between frontal theta and enhanced working memory (Itthipuripat et al., 2013; Klimesch et al., 2005; Pavlov and Kotchoubey, 2017; Zakrzewska et al., 2014), this result suggests that –alike the P200 enhancement- greater left frontal theta may represent a functional neural modulation induced by cathodal tDCS in AD patients. Interestingly, some studies suggested that theta oscillations are associated with retrieval of the information (Klimesch et al., 2005). Similarly, P200 was related to retrieval processes (Li et al., 2016; McEvoy et al., 2001). Future studies should investigate in a greater detail the relationship between frontal P200, frontal theta oscillations (note that modulation of theta oscillations and P200 occurred in the same site and time window) and the specific functional

meaning of both neural signatures. On the other hand, modulations of theta power in healthy elderly did not achieve statistical significance. Finally, the absence of differences in alpha and beta bands between healthy elderly and AD patients might be related to the different version of the task performed by AD patients and the less effort that 1-back task requires for maintaining the cognitive set and reactivating memory codes. Specifically, alpha oscillations were involved in reactivating long-term memory codes in working memory (Klimesch et al., 2005; Wang et al., 2017) and beta oscillations were related to the maintenance of the current cognitive set (Engel and Fries, 2010). Whereas the 1-back task performed by AD patients involves maintaining and retrieving the previous stimulus, the 2-back task involves a greater "neural involvement" for maintaining, manipulating and operating with the information stored in short-term memory.

An interesting finding was the increase of the P200 amplitude triggered by opposite tDCS polarity in healthy elderly subjects and AD patients. Namely, in healthy elderly participants, the P200 was larger after anodal tDCS, whereas in AD patients, the P200 was larger after cathodal tDCS. To explain these results, we should consider that, at the functional level, AD is characterized by neural hyper-excitability (Palop et al., 2007; Pennisi et al., 2011), which may be dysfunctional because it correlates with the degree of brain atrophy and learning ability (List et al., 2013). We suggest that cathodal tDCS reduced the brain hyper-excitability related to AD, allowing better "neuronal harmonization" to coordinate activity during task performance, as reflected by the enhanced P200 and accuracy. This interpretation aligns with the patterns of activity and excitability observed in previous studies with cognitively declined patients. For instance, transcranial magnetic stimulation studies reported increased motor cortex excitability in patients with cognitive decline related to AD (Bracco et al., 2009; Khedr et al., 2011), whereas ERP studies showed lower amplitudes of motor potentials during the performance of several cognitive tasks in patients at prodromal AD stages (Cespón et al., 2015; Cid-Fernández et al., 2017; Ramos-Goicoa et al., 2016; Zurrón et al., 2018). Overall, the increase of the P200 amplitude through the application of opposite tDCS polarity in healthy elderly subjects and AD patients illustrates how the tDCS effects may be

modulated by the functional neural state of the targeted subject (Bortoletto et al., 2015; Dockery et al., 2009; Fertonani and Miniussi, 2017; Miniussi et al., 2013).

Anodal tDCS increased the frontal P300 amplitude in healthy elderly subjects and the left parietal P300 amplitude in healthy elderly participants and AD patients. Whereas the parietal P300 is a correlate of neural activity related to context information update, the frontal P300 represents a correlate of neural activity related to allocation of attention to the stimulus (Daffner et al., 2011; Saliasi et al., 2013; Tusch et al., 2016; Wild-Wall et al., 2011). Thus, the results of the present study suggest that tDCS strengthened attentional processes in the healthy elderly subjects, as revealed by the larger frontal P300 amplitude after applying anodal tDCS, but not in AD patients. In addition, in healthy elderly participants, the frontal P300 increments correlated with the magnitude of the improved working memory performance, which allows interpreting the larger frontal P300 as compensatory activity to improve the task performance. Importantly, increased P300 after anodal tDCS was consistent with results from previous studies carried out in healthy young (Keeser et al., 2011, who used a 2-back task; note that Cespón et al 2017 did not find differences in young adults who performed a 3-back task) and elderly (Cespón et al., 2017) subjects. Additionally, previous studies reported a larger P300 after working memory training in an incremental difficulty level using 0-back, 1-back, and 2-back tasks (Tusch et al., 2016) and after other types of interventions, such as speed of processing (O'Brien et al., 2013) and aerobic exercise (Kamijo et al., 2009). The parietal P300 amplitude increased after anodal tDCS in healthy elderly subjects and AD patients, but correlations between the larger P300 and working memory performance were not observed. The existence of correlations in healthy elderly participants between enhanced working memory and increased frontal activity, but not parietal activity, supports the hypothesis that anodal tDCS might be strengthening attentional capacity, which declines during physiological ageing (Schneider-Garces et al., 2010).

4.3. Limitations and future directions

A limitation of the present study is the relatively small sample size (estimated power by using Cohen's d was 0.44), which may explain the weak tDCS effects observed at the behavioural level. This research provides a rationale for future investigations although the results of the present study should be taken carefully, as it represents a pilot study (for a review about the relationship between the "replication crisis" in neuroscience and underpowered studies see Button et al., 2013). In fact, we cannot entirely exclude that absence of significant differences between healthy elderly and AD patients in electrophysiological correlates is associated with the sample size used in the present study. Additionally, increased sample sizes would be useful to investigate the inter-individual variability of tDCS effects by studying high and low performers separately. This approach aligns with recent studies focusing on inter-individual variability of the tDCS effects (Benwell et al., 2015; Horvath et al., 2014; Hsu et al., 2016; Tseng et al., 2012). Moreover, other variables such as tDCS intensity, electrodes montage in relation to anatomical characteristics of brain and skull, baseline neurophysiological state, and neural changes related to physiological and pathological ageing (e.g., brain atrophy), may modulate the tDCS effects (Bergmann et al., 2016; Fertonani and Miniussi, 2017). Ultimately, investigation of variables related to individual differences in tDCS effects could lead to the use of individualised stimulation protocols in order to maximise the aimed cognitive improvements.

Another explanation for the lack of a net cognitive improvement at the group level is that a single tDCS session may be not enough to improve cognition. In this context, some studies reported promising cognitive improvements and transfer effects to untrained tasks after multi-day tDCS interventions (Antonenko et al., 2018; Au et al., 2017; Jones et al., 2015; Stephens and Berryhill, 2016) although null results have also been reported (Nilsson et al., 2017). Additionally, as previously mentioned, patients may benefit more by online than by offline tDCS protocols (Hsu et al., 2015). Therefore, the experimental design used in the present research, which involved the application of offline tDCS, could have contributed to the absence of a clear working memory improvement in AD patients at the group level.

Overall, follow-up neurophysiological studies with increased sample sizes and diverse cognitive tasks investigating different executive functions -i.e., working memory processes but also inhibitory control and / or attentional switching, which strongly depend also on prefrontal circuits (Miyake et al., 2000)- are needed to confirm to what extent there is an interaction between tDCS polarity and neural state in AD patients. Also, in order to avoid task-specific effects, previous studies indicated the convenience of using several tasks to assess working memory functioning (Wilhelm et al., 2013). Therefore, future studies should replicate and extent the findings about interaction between tDCS polarity and neural state by using diverse working memory tasks. Additionally, upcoming studies may focus on other ERP components such as N100, which is thought to reflect selective attentional mechanisms (Finnigan et al., 2011), and N200, which was associated with classification of stimuli (López-Zunini et al., 2016; Patel and Azzam, 2005). Altogether, the suggested future studies will be potentially useful to establish the appropriate parameters to improve executive functions in AD by properly modulating the underlying neural activity.

5. Conclusions

In summary, the results of the present study suggest that tDCS has the potential to improve working memory by modulating underlying frontal activity in healthy elderly subjects and AD patients. Crucially, the interaction between tDCS polarity and functional neural state suggests that tDCS parameters to improve working memory may be different (in terms of tDCS polarity) for AD patients –who shows brain hyper-excitability- and healthy elderly subjects –who usually benefit from increasing the spontaneous firing rate by anodal tDCS. Also, the successful translation of findings from proof-of concept studies in normal populations to clinical trials is frequently impeded by our current lack of understanding of the physiological mechanisms underlying the effects of tDCS and its interaction with intrinsic electrophysiological activity. The use of surrogate measures, such as ERPs, could be useful to evaluate clinical efficacy and better understanding the neural mechanisms related to changes induced by tDCS. Nevertheless, subsequent studies should provide

stronger evidence for the reported interaction between tDCS polarity and neural hyper-excitability in AD patients. Overall, future studies should exploit the advantages of neurophysiological techniques (e.g., optimal EEG/ERP temporal resolution, which adapts to the high speed of cognitive processes during the performance of a task) to design and perform tailored stimulation protocols for specific pathological conditions.

Funding

This study was funded by the Italian Ministry of Health GR-2011-02349998 to MCP and the European Commission Marie-Skłodowska Curie Actions, Individual Fellowships; 655423-NIBSAD to JC.

The authors declare no conflicts of interest.

Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

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Figure legends

Figure 1. Structure of the experimental sessions and representation of the cognitive tasks performed by healthy elderly subjects (2-back task) and AD patients (1-back task). The target letter (25% of trials) is represented within grey squares. Participants responded to the target letter by pressing the space bar. The letters were presented in the centre of the screen for 500 ms (inter-stimulus interval was jittered between 2000-2500 ms) in white colour against a black background.

Figure 2. Event-related potentials in healthy elderly subjects before and after tDCS. Each represented waveform results from averaging four electrodes that compounded the respective region of interest: frontal left (F3, F7, AF7, FC5), frontal right (F4, F8, AF8, FC6), parietal left (P3, P7, PO7, CP5), and parietal right (P4, P8, PO8, CP6). The P200 and P300 components were larger after anodal tDCS within the left frontal region. Moreover, the P300 was larger after anodal tDCS within the left parietal region.

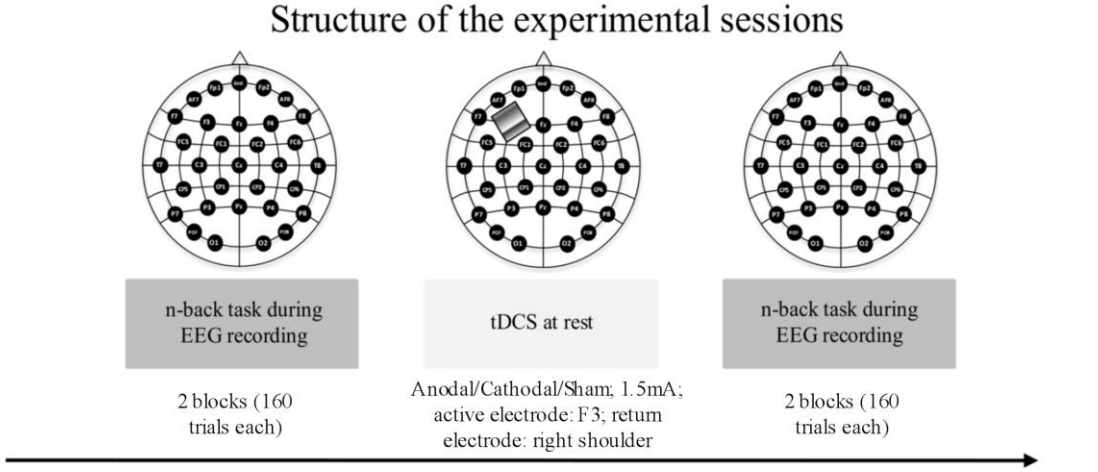
Figure 3. Event-related potentials in Alzheimer's disease patients before and after tDCS. As specified for healthy elderly subjects, each represented waveform results from averaging four electrodes that compounded the respective region of interest. The amplitude of the P200 increased after the application of cathodal tDCS within the left frontal region. Additionally, the amplitude of the P300 increased after the application of anodal tDCS within the left parietal region.

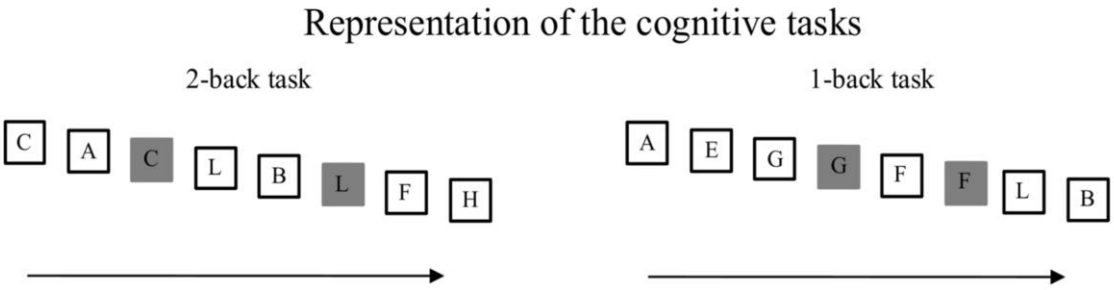
Figure 4. Pearson correlation analysis revealed significant correlations between the magnitude of the increased d' and the magnitude of the increased P200 and P300 components after the application of tDCS.

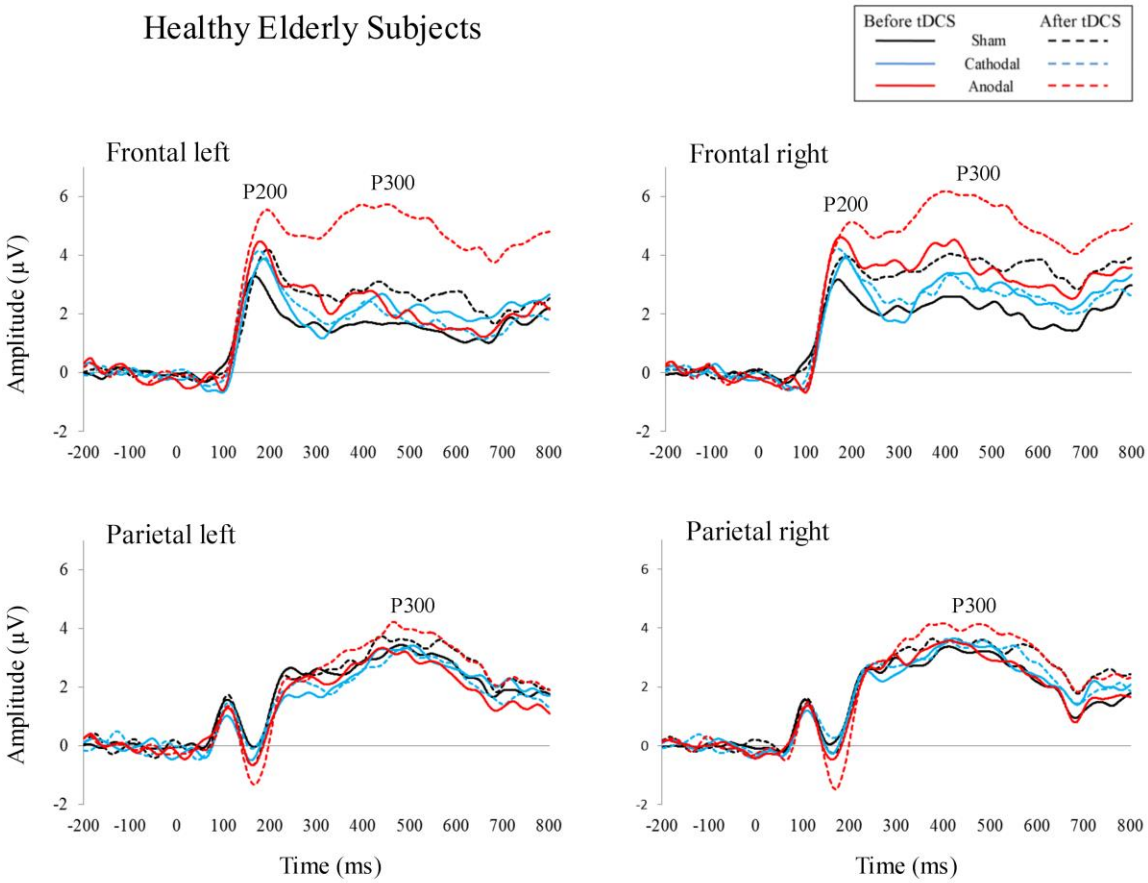
Figure 5. Spectral power in the time-frequency domain for elderly subjects within the left frontal ROI. Results showed the absence of significant changes after any tDCS condition for the studied frequency bands.

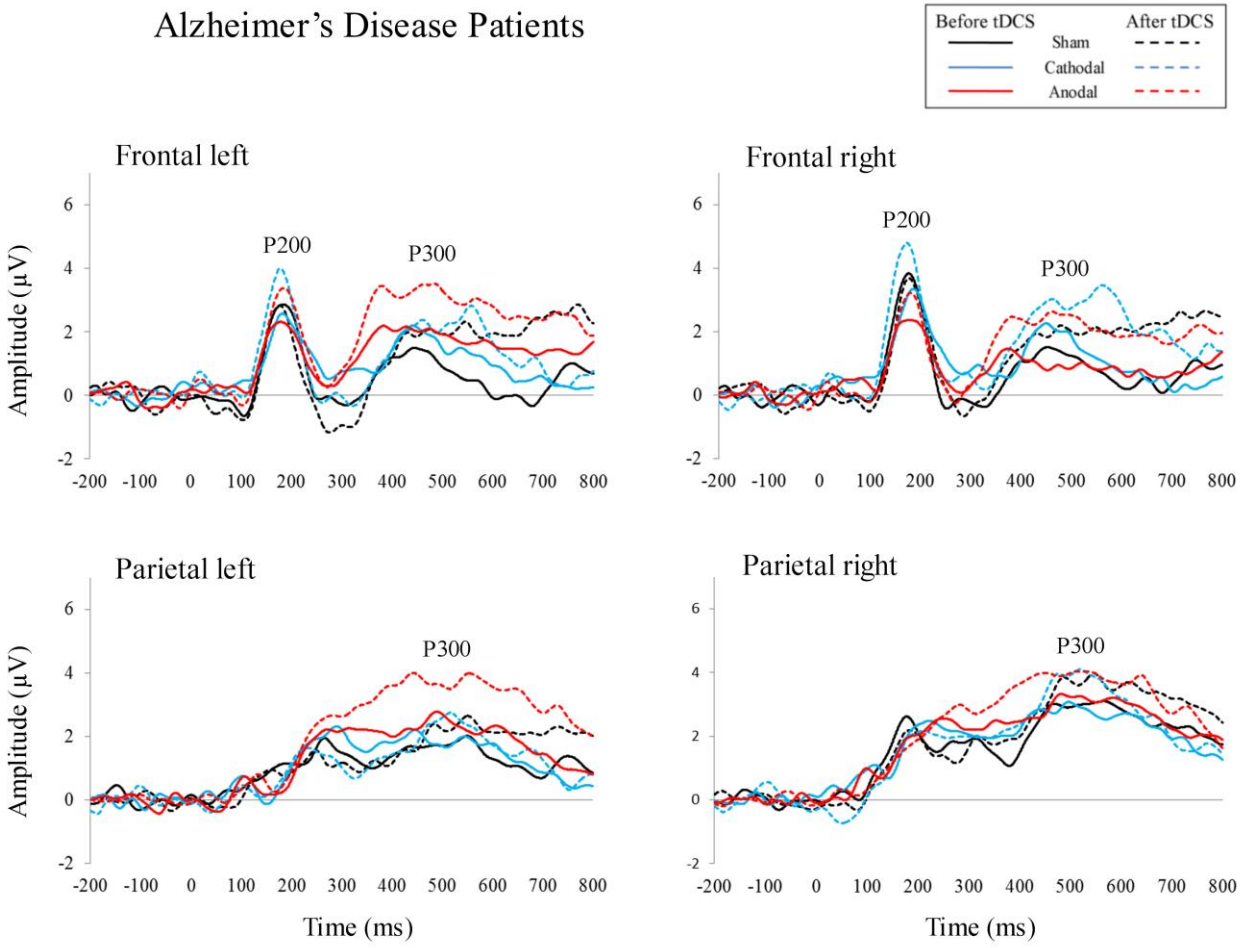
Figure 6. Spectral power in the time-frequency domain for Alzheimer's disease patients within the left frontal ROI. Results showed that, after applying cathodal tDCS (middle panel), theta power increased in 150-300 ms time window within the left frontal ROI.

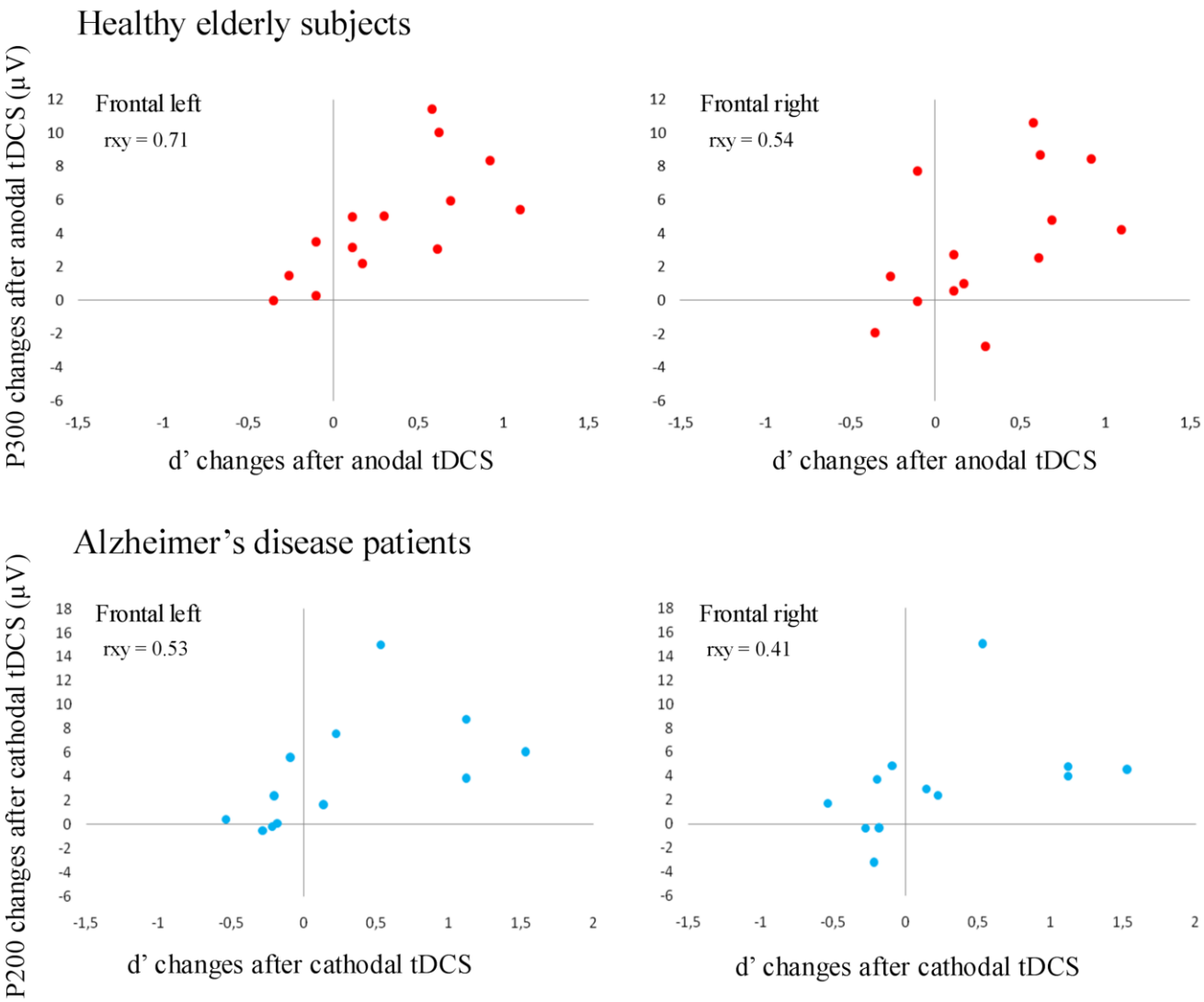
Figure 7. Summary of the significant behavioural, ERP, and time-frequency results. HE: healthy elderly subjects; AD: Alzheimer's disease patients.


Structure of the experimental sessions
n-back task during EEG recording
2 blocks (160 trials each)
tDCS at rest
Anodal/Cathodal/Sham; 1.5mA; active electrode: F3; return electrode: right shoulder
n-back task during EEG recording
2 blocks (160 trials each)


Representation of the cognitive tasks
2-back task
C A C L B L F H
1-back task
A E G G F F L B

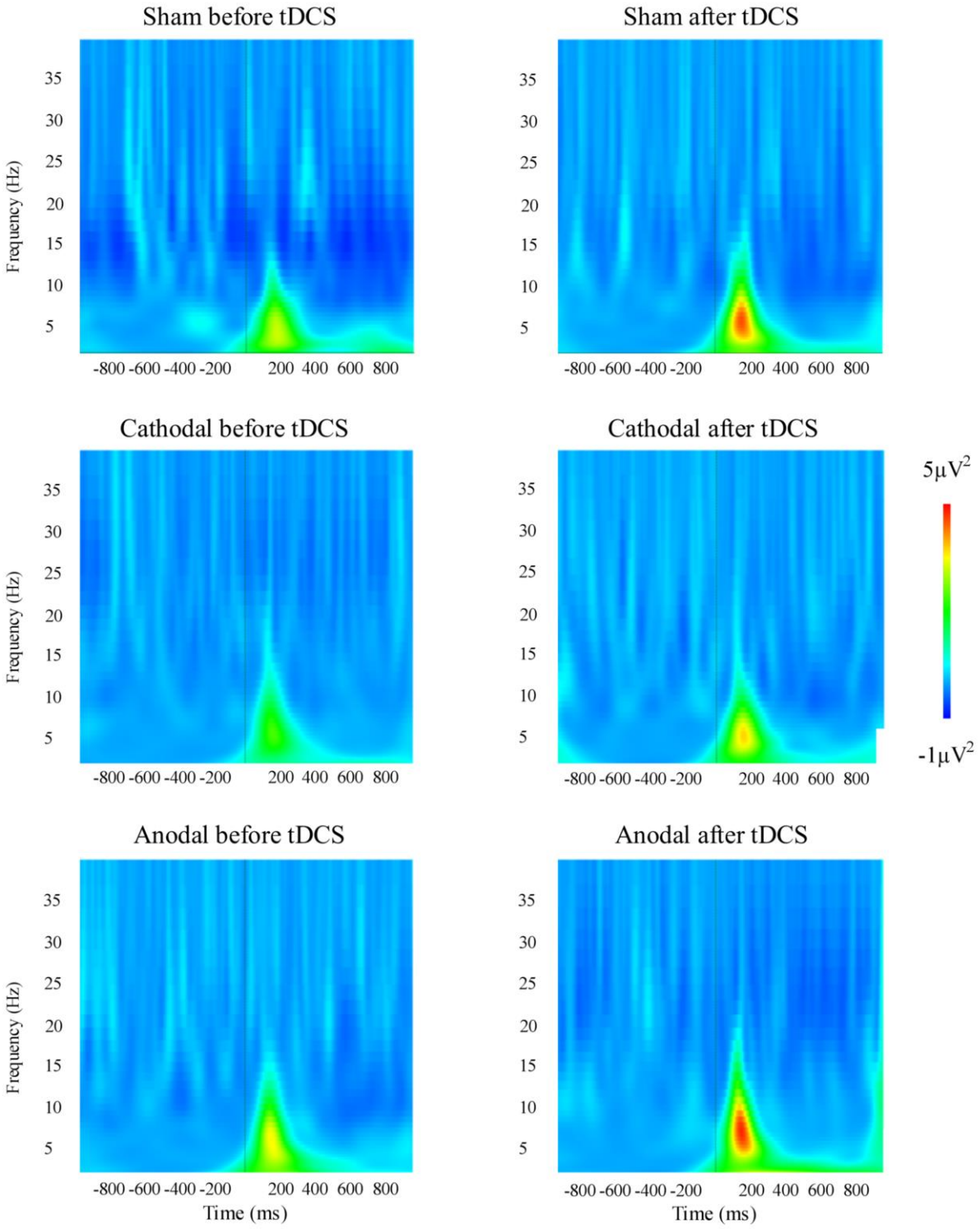

Healthy Elderly Subjects
Before tDCS
After tDCS
Sham
Cathodal
Anodal
Frontal left
P200
P300
Frontal right
P200
P300
Parietal left
P300
Parietal right
P300
Amplitude (μV)
Amplitude (μV)
Time (ms)
Time (ms)


Alzheimer's Disease Patients
Before tDCS
After tDCS
Sham
Cathodal
Anodal
Frontal left
Frontal right
Parietal left
Parietal right
P200
P300
Amplitude (μV)
Time (ms)
6
4
2
0
-2
-200 -100 0 100 200 300 400 500 600 700 800


Healthy elderly subjects
P300 changes after anodal tDCS (µV)
Frontal left
rxy = 0.71
Frontal right
rxy = 0.54
d' changes after anodal tDCS
d' changes after anodal tDCS
Alzheimer's disease patients
P200 changes after cathodal tDCS (µV)
Frontal left
rxy = 0.53
Frontal right
rxy = 0.41
d' changes after cathodal tDCS
d' changes after cathodal tDCS

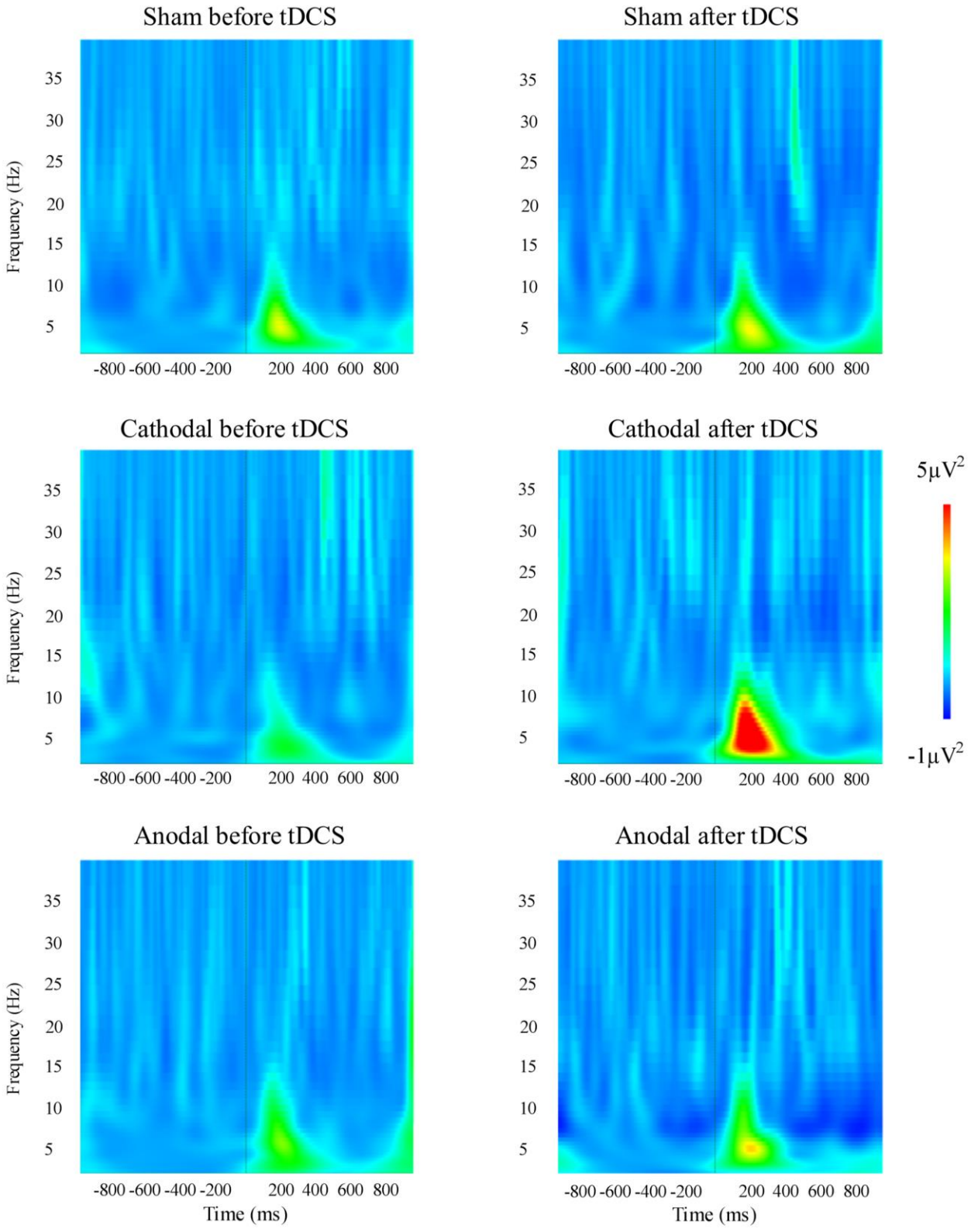
Healthy Elderly subjects

Frontal Left



Alzheimer's disease patients

Frontal Left



Summary of significant results for behavioural, ERP, and wavelet analyses

d prime	Time →	d' higher after tDCS (anodal, cathodal, sham)
Left Frontal P200	Group x Stimulation x Time →	HE: P200 larger after anodal tDCS AD: P200 larger after cathodal tDCS
Right Frontal P200	Group x Stimulation x Time →	AD: P200 larger after cathodal tDCS
Left Frontal P300	Time →	P300 larger after tDCS (anodal, cathodal, sham)
	Group x Stimulation x Time →	HE: P300 larger after anodal tDCS After anodal tDCS, larger P300 in HE than in AD
Right Frontal P300	Time →	P300 larger after tDCS (anodal, cathodal, sham)
	Group x Stimulation →	In anodal tDCS, larger P300 in HE than in AD
	Group x Stimulation x Time →	HE: P300 larger after anodal tDCS HE: P300 larger after anodal than after sham and cathodal tDCS After anodal tDCS, larger P300 in HE than in AD
Left Parietal P300	Time →	P300 larger after tDCS (anodal, cathodal, sham)
	Stimulation x Time →	P300 was larger after anodal tDCS was applied After tDCS, P300 was larger in anodal than in cathodal and sham
Right Parietal P300	Time →	P300 larger after tDCS (anodal, cathodal, sham)
Theta power	Group x Stimulation x Time within Left Frontal ROI (150-300ms) →	In AD patients, theta power was higher after applying cathodal tDCS

		Sham		Cathodal		Anodal	
		pre	**post**	**pre**	**post**	**pre**	**post**
Elderly	*RT*	878 (168)	855 (144)	854 (155)	857 (153)	863 (138)	845 (156)
	d'	2.3 (0.7)	2.4 (0.6)	2.2 (0.8)	2.3 (0.7)	2.3 (0.8)	2.6 (0.7)
AD patients	*RT*	743 (159)	784 (163)	737 (163)	739 (160)	796 (176)	796 (189)
	d'	2.9 (0.9)	2.7 (1.1)	2.0 (1.7)	2.3 (1.8)	2.1 (1.6)	2.3 (1.3)

Table 1. Means and standard deviations for RT (in milliseconds) and d' values in healthy elderly and Alzheimer's disease patients, before (pre) and after (post) tDCS, for all the experimental sessions (Sham, Cathodal, Anodal).