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Age-related changes in cortical connectivity influence the neuromodulatory effects of transcranial electrical stimulation

Anna Fertonani [a], Cornelia Pirulli [a], Alice Bollini [a,1], Carlo Miniussi [a,b], Marta Bortoletto [a,*]

[a] Cognitive Neuroscience Section, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Brescia, Italy
[b] Center for Mind/Brain Sciences - CIMeC, University of Trento, Rovereto, Trento, Italy

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ABSTRACT

Transcranial electrical stimulation (tES) is a potentially viable tool for boosting cognitive performance in aging. However, most knowledge on tES effects is based on studies involving young adults. Here, we applied tES (transcranial random noise stimulation [tRNS] as an effective stimulation and anodal transcranial direct current stimulation [atDCS] as a "control" stimulation) to the visual cortex during visual perceptual learning (VPL) in healthy young and older individuals. Moreover, we measured transcranial magnetic stimulation–evoked potentials to investigate the neurophysiological underpinnings of tES effects. We found that only the tRNS in the young, but not in the older, subjects modulated VPL, by decreasing performance. Transcranial magnetic stimulation–evoked potentials revealed age-related changes in connectivity, that is, a stronger activation of the prefrontal cortex after visual cortex stimulation, and a stronger modulation of the prefrontal cortex after VPL in the older subjects. These results may indicate that task performance in older adults relies on the recruitment of a wider network and a crucial contribution of the anterior portion of the brain, which may dramatically influence tES effects in aging.

1. Introduction

The interest in transcranial electrical stimulation (tES) to modulate and boost brain activity in healthy and pathological aging has increased in recent years as attested by the high number of published papers and reviews related to this topic (Gomes-Osman et al., 2018; Hsu et al., 2015; Perceval et al., 2016; Summers et al., 2016; Tatti et al., 2016). Evidence shows that tES can modulate neural activity with beneficial effects on behavioral performance in several cognitive domains (Berryhill and Martin, 2018; Simonsmeier et al., 2018). tES may indeed be a valuable and feasible tool for counteracting age-associated functional and cognitive impairment by increasing learning via current-induced supplementary neuromodulation.

Nevertheless, most knowledge regarding the effects of tES neuromodulation is derived from studies involving young subjects and cannot automatically be extended to different age populations (Fertonani and Miniussi, 2017; Li et al., 2015). The effects found in older adults are sometimes similar to those described in young subjects (e.g., Benwell et al., 2015; Martin et al., 2017; Meinzer et al., 2013; Penton et al., 2018), but there are also several reports of different effects between the 2 age groups, that is, the effects found in one group have not been found in the other group (Boggio et al., 2010; Fertonani et al., 2014; Fiori et al., 2017; Fujiyama et al., 2014; Heise et al., 2014; Mammarella et al., 2017; Penolazzi et al., 2010; Zimerman et al., 2013).

Currently, the mechanisms that underlie the behavioral differences in the effects of tES in aging are unknown, but we hypothesize that these mechanisms may be explained by age-related neurophysiological changes. This hypothesis is supported by evidence suggesting that the effects of tES are influenced by both the excitability (Benwell et al., 2015; Berryhill and Jones, 2012; Learmonth et al., 2015; but see, 2017) and the connectivity (Antonenko et al., 2018; Martin et al., 2017) of the stimulated area, and both of these properties of brain activity change with age.

A good model for exploring tES neuromodulation in aging is visual perceptual learning (VPL). VPL is a form of implicit memory that improves sensory discrimination after repeated exposure to visual stimuli (Fahle and Poggio, 2002; Thiele, 2004) and is considered a manifestation of neural plasticity in the adult brain

* Corresponding author at: Cognitive Neuroscience Section, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Via Pilastroni 4, 25125 Brescia, Brescia, Italy. Tel.: +390303501597; fax: +390303533513.
E-mail address: marta.bortoletto@cognitiveneuroscience.it (M. Bortoletto).
[1] Current address: U-VIP Unit for Visually Impaired People, Fondazione Istituto Italiano di Tecnologia, Genova, Italy.

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(Carmel and Carrasco, 2008; Gilbert et al., 2001; Li et al., 2004). Specifically, the orientation discrimination task (ODT) is a VPL paradigm that has been widely investigated. Many studies have demonstrated that it involves primary visual area (V1) neurons (Jehee et al., 2012; Shiu and Pashler, 1992; Vogels and Orban, 1985). Nevertheless, recent VPL literature (Maniglia and Seitz, 2018; Watanabe and Sasaki, 2015) noted the contribution of a broad network of brain regions, including parietal and frontal areas.

Several studies have investigated VPL in older adults and revealed a substantial preservation of plasticity mechanisms in an advanced age (Andersen et al., 2010; Chang et al., 2015, 2014). However, despite the similar rate of learning between young and older adults, substantial differences were observed in their visual system excitability and connectivity that may influence the mechanisms involved in learning dynamics and possibly the effect of an external aid, such as tES, on learning. Convergent neurophysiological evidence has revealed a loss of cortical inhibition and increased firing rates in visual cortex neurons in senescent animals (Hua et al., 2008; Leventhal et al., 2003; Schmolesky et al., 2000; Yang et al., 2008), conceivably resulting from decreased levels of the neurotransmitter GABA (Hua et al., 2008). This loss of cortical inhibition has been suggested to explain behavioral results in which a higher level of noise seems to worsen perceptual processing in older adults (Bennett et al., 2007; Betts et al., 2007; Bower and Andersen, 2012). Regarding visual system connectivity, recent studies using a graph-theory approach have highlighted age-related decreases in connectivity within the visual network (less modularity: Betzel et al., 2014; Chhatwal et al., 2018; less segregation: Chan et al., 2014) and enhanced connectivity between networks (higher participation coefficient: Betzel et al., 2014; Chan et al., 2014) with a greater proportion of connections directed outside the visual network (Geerligs et al., 2015). In summary, given all these findings, although VPL might be observed overall, there are widespread neurophysiological differences in the visual system throughout one's lifespan that may lead to different tES-induced neuromodulation effects across age groups.

In this study, we explore the neuromodulatory effects of tES on VPL in aging by assessing the changes in the excitability and connectivity of visual areas in the aged brain. We apply transcranial random noise stimulation (tRNS), anodal transcranial direct current stimulation (atDCS), and sham stimulation during an ODT (for recent reviews on tES, see Antal et al., 2017; Fertonani and Miniussi, 2017; Woods et al., 2016). tRNS was selected because it has shown specific effects in previous studies using the same task (Fertonani et al., 2011; Pirulli et al., 2013); atDCS was chosen as a control stimulation because it is the most applied type of tES used to improve learning (e.g., Berryhill and Jones, 2012; Flöel et al., 2012; Jones et al., 2015; Sandrini et al., 2014; Zimerman et al., 2013) but was not effective on ODTs in a previous study (Fertonani et al., 2011).

In addition, we used transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) obtained by TMS-EEG coregistration to investigate the neurophysiological underpinnings of tES modulation of VPL during the task. The registration of EEG allows us to measure the direct activation of cortical neurons at the site of TMS and the spread of this activation over the cortex with great temporal resolution (Bortoletto et al., 2015; Ilmoniemi et al., 1997; Miniussi and Thut, 2010). Therefore, TEPs allow us to assess the impact of tES on both cortical excitability and connectivity. Recent studies have suggested that TEPs can be useful for describing the impact of tES on motor and parietal cortices (Pellicciari et al., 2013; Pisoni et al., 2018; Romero Lauro et al., 2014). Here, we used TEPs to investigate the tES-induced neuromodulation dynamics of VPL in young and older adults.

First, we expected that only tRNS, but not atDCS, would have a different behavioral effect on VPL compared with the sham condition. Moreover, we expected differences at baseline in the neurophysiological responses between the 2 age groups (young vs. older) as indexes of cortical excitability and connectivity changes. As a consequence of the latter prediction, we expected a different tES modulation of behavioral performance across age groups.

2. Materials and methods

2.1. Subjects

Young subjects—The final data set included data from 45 young participants (mean age 22.3 ± 3.1 years; 22 females). All subjects had normal or corrected-to-normal vision. Ten additional subjects were recruited but were then excluded from the analyses due to technical issues during the experiment or excessive artifacts in the EEG recordings (8 participants) or because their performance was 2 SD above the mean (2 participants).

Older subjects—The final data set included data from 36 older participants (mean age 66.1 ± 3.6 years; 21 females). All subjects had normal or corrected-to-normal vision. Moreover, 14 additional participants were recruited but did not participate in the study because they were unable to execute the behavioral task during the preliminary session (9 participants). In addition, 5 participants from this group were excluded from the analyses due to technical issues during the experiment or excessive artifacts in the EEG recordings.

Before being enrolled in the experiment, the older subjects visited the laboratory for a preliminary session to complete the Mini–Mental State Examination (Folstein et al., 1975), a detailed neuropsychological evaluation, and the Geriatric Depression Scale to confirm the absence of any cognitive deficits and depression. The neuropsychological test battery assessed nonverbal reasoning (Raven's Coloured Progressive Matrices), visuospatial ability (Rey-Osterrieth complex figure, copy), attention and executive function (Attentive matrices, Trail Making Test A and B), memory (Rey-Osterrieth complex figure recall, digit and spatial span, auditory verbal learning test immediate and delayed recall), and verbal fluency (phonemic and semantic). All tests were administered and scored according to standard procedures (Lezak et al., 2004). The Mini–Mental State Examination, neuropsychological tests, and Geriatric Depression Scale scores are reported in Table 1S–Supplementary Materials. A pathological score in one or more neuropsychological tests or the inability to execute the training block of the ODT above the chance level were considered exclusion criteria.

The young and older participants performed a training block of the task during their first visit to the laboratory to verify their understanding of the instructions.

The study was approved by the Ethics Committee of the IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Safety procedures were adopted based on noninvasive brain stimulation approaches (Antal et al., 2017; Rossi et al., 2009), and written informed consent was obtained from all participants before the beginning of the experiment.

2.2. Experimental design—procedures

tES was applied during the execution of an ODT. The subjects were randomly assigned to one of 3 stimulation condition groups (sham, tRNS, and atDCS). The characteristics of the subjects included in the different experimental groups are reported in Table 1. Eyes open EEG (data not analyzed here) and TMS-EEG coregistration preceded and followed the execution of ODT plus tES (see Fig. 1).

Table 1
Demographic data of the participants

		Sham	tRNS	atDCS
Young	N (female)	15 (8)	15 (7)	15 (7)
	Mean age (±SD)	22.7 (±3.2)	21.7 (±3.2)	22.3 (±3.2)
Older	N (female)	12 (7)	12 (7)	12 (7)
	Mean age (±SD)	66.0 (±2.7)	65.8 (±4.1)	66.3 (±4.1)

Key: atDCS, anodal transcranial direct current stimulation; tRNS, transcranial random noise stimulation.

2.3. EEG and TMS-EEG recording

EEG was recorded from 61 sintered scalp electrodes mounted in an elastic cap according to the international 10-10 system of EEG sensor placement. The electrical activity was acquired (BrainAmp MRplus, BrainProducts GmbH, Munich, Germany) using the right mastoid electrode as an online reference, the AFz electrode as the ground electrode, and 2 bipolar channels to record the horizontal and vertical electrooculograms. The impedance was set below 5 kΩ. The data were acquired at 5000 Hz and online bandpass filtered between 0.01 and 1000 Hz (Veniero et al., 2009).

TMS was delivered using a biphasic Super Rapid stimulator connected to a double 50-mm figure-eight custom coil (Magstim Company, Whitland, UK). At the beginning of the experiment, the resting motor threshold was calculated as the TMS intensity that elicited MEPs of at least 50 μV in amplitude in 5 of 10 trials during primary motor cortex stimulation. Then, 110% of the resting motor threshold was used to stimulate V1. TMS-EEG coregistration was performed by recording an EEG during the stimulation of the V1 area by placing the TMS coil parallel to the scalp over electrode Oz with the first peak of the induced current directed from anterior to posterior. The position of the coil was controlled using a TMS neuronavigation system (SofTaxic, EMS, Bologna, Italy). In total, 120 single TMS pulses were delivered before and after the application of electrical stimulation at random intervals (0.25–0.5 Hz). During TMS-EEG coregistration, the subjects wore earplugs to attenuate the "click" sound of the TMS.

2.4. Transcranial electrical stimulation

tES was delivered by a battery-driven stimulator (BrainStim, EMS, Bologna, Italy) through a pair of saline-soaked sponge electrodes for approximately 22 minutes from the second through the fifth block of the task (see Fig. 1 – Procedure). One electrode (area 16 cm^2) was applied over Oz under the EEG cap, and Ten20 conductive paste (Weaver and Company, Aurora, CO) was used to obtain a perfect adherence to the head. The reference electrode (area 60 cm^2) was fixed on the right shoulder by elastic bands. The intensity of the stimulation was 1.5 mA, and the current density was 0.094 and 0.025 mA/cm^2 for the Oz and reference electrodes, respectively. When atDCS was applied, the polarity of the Oz electrode was anodal, whereas the Oz and reference electrodes were not polarity dependent for tRNS.

tRNS consisted of an alternating current with a 0-mA offset applied at random frequencies (range 101–600 Hz). The stimulation did not induce any phosphene perception (Schwiedrzik, 2009). In the sham stimulation, the current was turned off 20 seconds after the stimulation began and turned on again during the final 20 seconds of the fifth block.

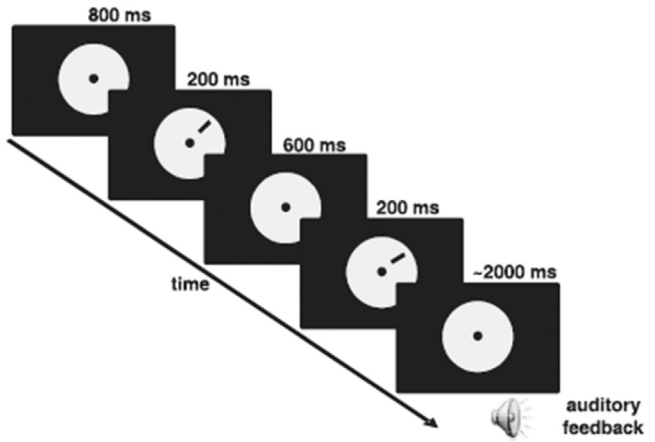

Fig. 2. A trial of the orientation discrimination task. After presenting the reference and target stimuli, the participants provided their response and received auditory feedback. Figure reproduced with permission from Fertonani et al. (2011).

2.5. Orientation discrimination task

The participants were seated in front of a computer screen in a quiet, semi-dark room. A chin rest kept the participant 57 cm from the screen. The subjects were asked to respond as quickly and accurately as possible after the second stimulus was presented by pressing 2 different keyboard buttons with their left (counterclockwise) or right (clockwise) index finger. During each trial of the ODT, the participants had to decide whether the presented stimulus was tilted clockwise or counterclockwise relative to the previously presented stimulus (see Fig. 2). Auditory feedback (duration: 50 ms; frequency following a correct response: 700 Hz; frequency following an incorrect response: 350 Hz) informed the subjects about the correctness of their responses. All stimuli were black lines, and each line stimulus was 2° long and 5′ wide (in visual

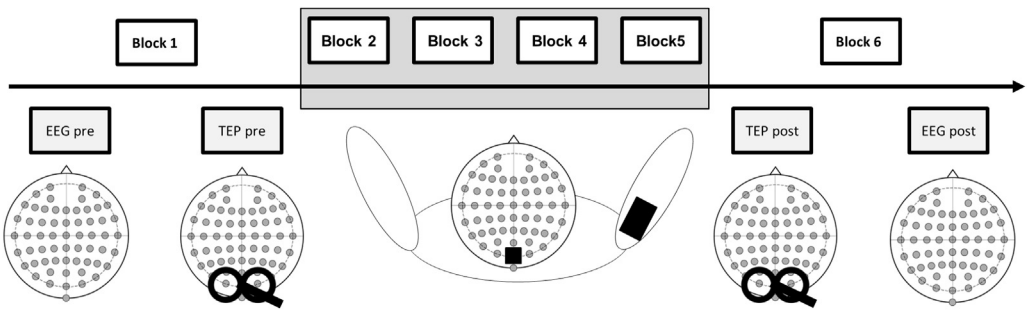

Fig. 1. Procedures. The experimental procedures were as follows: resting-state EEG recording; one block of the ODT; baseline TMS-EEG recording; 4 blocks of ODT with the online application of tES (sham, tRNS, or atDCS); post–TMS-EEG recording; one block of ODT; and resting-state EEG recording. Abbreviations: ODT, orientation discrimination task; tES, transcranial electrical stimulation; tRNS, transcranial random noise stimulation; atDCS, anodal transcranial direct current stimulation.

angles). The orientation of one of the 2 lines of the paired stimuli was fixed to 45° in the upper right and lower left hemifields and 135° in the upper left and lower right hemifields.

The line with a fixed orientation was presented first in half of the trials and second in the other half of the trials. The angular difference between the fixed orientation line and the other line was selected from 1.10, 1.21, 1.33, 1.46, and 1.61° for the young subjects and 1.33, 1.77, 2.36, 3.14, and 4.18° for the older subjects (modified from Fertonani et al., 2011; Matthews et al., 1999; Pirulli et al., 2013). The angular orientations were modified for the older participants to obtain a similar level of accuracy in the task execution between the 2 age groups. The aforementioned experimental parameters were balanced and randomized between blocks. The stimuli were presented on a computer screen using Presentation software v. 12.0 (www.neurobs.com) in each of the following 4 visual hemifields: upper left, upper right, lower left, and lower right. During each trial, the 2 stimuli were presented in the same hemifield.

The training block was similar to the experimental blocks but contained a different number of trials (only 8) and an increased rotation angle between the 2 stimuli (15° clockwise or counterclockwise). Each experimental block comprised 80 trials. The ODT consisted of 6 experimental blocks plus a training block.

2.6. Behavioral analysis

The average orientation sensitivity was calculated in terms of a d' value for each subject and each block separately for each stimulation condition and age group. Because the ODT is a two-alternative forced choice task, a value of d' = 1 corresponds to a 75% accuracy rate. To calculate the learning rate, we analyzed the relationship between the d' values and the block numbers using a linear regression analysis. This analysis allowed us to associate a slope value with each subject. The Kolmogorov-Smirnov test was applied to test for the normal distribution of all data (d' and slope values).

To exclude the presence of different ability levels in task execution at baseline, d' data from block 1 were entered into an age (young and older) * stimulation condition (sham, tRNS, and atDCS) ANOVA.

Then, to confirm the ability of the ODT to induce a learning effect, a repeated-measures ANOVA of the d' values of the 6 blocks of the task was performed in each group. Finally, the presence of a neuromodulation effect of tES on learning was evaluated by entering the slope values into an ANOVA with age (young and older) and stimulation condition (sham, tRNS, and atDCS) as the between-subjects factors.

Data related to the sensations induced by tES were analyzed with a nonparametric Kruskal-Wallis one-way analysis of variance to compare the different stimulation conditions (see the sensations results in the Supplemental materials; the raw data are reported in Tables 2S and 3S).

A p-value of 0.05 was considered significant in all statistical analyses. Regarding the post hoc tests, we applied the Tukey HSD correction or the unequal N HSD correction in the case of samples of different numerousness (i.e., young vs. older comparisons).

2.7. Neurophysiological analysis

2.7.1. TMS-EEG preprocessing

The EEG signal was processed with MATLAB (2016b, MathWorks) using custom scripts that combined the EEGlab (version 14.1.1, Delorme and Makeig, 2004) and Fieldtrip functions (Oostenveld et al., 2011). First, the TMS-induced artifact, which typically lasts up to 5 ms using our equipment (Veniero et al., 2009), was removed using cubic interpolation from −2 to 10 ms. Then, the continuous EEG and electrooculogram signals were high-pass filtered at 1 Hz (zero-phase Butterworth filter, second order), divided into epochs from −1000 ms to 1900 ms, down sampled to 1024 Hz, and demeaned using the whole epoch length. The segmented data were visually inspected to exclude epochs and channels contaminated by noncerebral source activity and then subjected to a restricted infomax independent component analysis to remove the artifacts. To identify the TMS-related artifactual components, we used a combination of criteria, including topography, latency, amplitude, and trial distribution. Subsequently, a 100 Hz low-pass filter and a 50-Hz notch filter were applied (zero-phase Butterworth filters, fourth order), and the noisy channels previously removed were interpolated. All data were re-referenced to the average of all scalp channels before performing a second artifact rejection to remove the reimaging artifacts. To obtain the TEPs, the epochs were reduced to −100 ms before and 400 ms after the TMS pulse, baseline corrected from −100 to −2 ms, and bandpass filtered at 45 Hz.

2.7.2. TEP statistical analysis

We did not have an a priori hypothesis regarding the spatial and temporal distributions of the effects on the TMS-evoked responses. Therefore, we analyzed the TEPs using nonparametric cluster-based permutation statistics (Maris and Oostenveld, 2007) using the time window between 10 ms and 400 ms after the TMS pulse and all EEG channels. This approach allows for a correction for multiple comparisons when computing statistics across multiple channels and time points. Two-tailed cluster-based permutation tests were performed with 1000 random sets of permutations and a cutoff p-value of 0.025 to both determine whether individual samples belong to a cluster and test the significance probability of the clusters.

To investigate the age-related changes in cortical excitability and connectivity, we compared the TEPs at baseline between the young and older subjects by clustering the t-values of independent samples. Using the same approach, we tested for task-related effects on TEPs by examining the main effect of time, that is, differences between TEPs before and after the stimulation independently from the stimulation condition, by clustering the dependent sample t-

Table 2
Average orientation sensitivity (d') and learning rate (slope) in the orientation discrimination task

Stimulation condition		B1	B2	B3	B4	B5	B6	Slope
Young	Sham[a]	0.418 ± 0.103	0.609 ± 0.105	0.646 ± 0.096	0.728 ± 0.072	0.891 ± 0.072	0.976 ± 0.116	0.106 ± 0.023
	tRNS	0.563 ± 0.087	0.597 ± 0.056	0.575 ± 0.076	0.640 ± 0.109	0.578 ± 0.091	0.652 ± 0.065	0.013 ± 0.017
	atDCS[a]	0.429 ± 0.099	0.739 ± 0.118	0.697 ± 0.072	0.693 ± 0.090	0.764 ± 0.102	1.008 ± 0.092	0.085 ± 0.024
Older	Sham[a]	0.469 ± 0.131	0.574 ± 0.127	0.588 ± 0.156	0.624 ± 0.113	0.666 ± 0.131	0.821 ± 0.137	0.059 ± 0.020
	tRNS[a]	0.565 ± 0.075	0.696 ± 0.117	0.879 ± 0.140	0.972 ± 0.115	0.882 ± 0.127	1.040 ± 0.142	0.086 ± 0.022
	atDCS[a]	0.536 ± 0.138	0.639 ± 0.164	0.758 ± 0.173	0.710 ± 0.185	0.740 ± 0.147	0.975 ± 0.156	0.070 ± 0.019

Data from blocks 1–6 are expressed as mean ± SEM.
Key: atDCS, anodal transcranial direct current stimulation; tRNS, transcranial random noise stimulation.
[a] Indicates a learning effect, that is, an increase of d' from block 1 to block 6. See also Fig. 1S–Supplemental materials.

values. Given that we found an age effect in the baseline TEPs, these analyses were also performed separately for the young and older groups. Finally, we examined the tES-related effects in the young and older groups separately. First, we tested for baseline differences among the 3 stimulation conditions within each age group by clustering the independent-sample F-values. Then, we examined the interaction between the stimulation condition and time by comparing the differences in the TEP amplitude between the delta value (TEP after - TEP before stimulation).

2.7.3. TEP localization

We obtained an estimate of the cortical sources of the TEP components in the young and old subjects separately. We calculated the standardized current source density distribution of the TEP average traces of each subject at baseline with the sLORETA method (sLORETA, Pascual-Marqui, 2002) using the parameter SNR = 100 and then calculated the grand average of the localized sources with the "average" function in sLORETA.

The same method was applied to the difference waveform (calculated as TEP pre − TEP post) in the time window of the significant effects to localize the neurophysiological changes associated with ODT execution.

3. Results

3.1. Behavioral results

The Kolmogorov-Smirnov test confirmed the normality of the distribution of the d' and slope data (raw data are reported in Table 2).

The performance at baseline, that is, d' in block 1, did not differ among the groups as indicated by the nonsignificant effects in the factorial ANOVA, including the main effect of age ($F(1,75) = 0.377$; $p = 0.541$), main effect of stimulation ($F(1,75) = 0.666$; $p = 0.517$), and age × stimulation interaction ($F(2,75) = 0.123$; $p = 0.884$).

Learning was observed in 5 of the 6 groups, and a significant difference was found in d' between the final and first blocks of the task as follows: the rmANOVAs of each single stimulation condition highlighted a difference among the sham-young ($F(5,70) = 8.595$; $p < 0.001$; $\eta_p^2 = 0.380$), atDCS-young ($F(5,70) = 7.895$; $p < 0.001$; $\eta_p^2 = 0.361$), sham-older ($F(5,55) = 2.975$; $p = 0.019$; $\eta_p^2 = 0.213$), tRNS-older ($F(5,55) = 6.913$; $p < 0.001$; $\eta_p^2 = 0.386$), and atDCS-older ($F(5,55) = 4.245$; $p = 0.002$; $\eta_p^2 = 0.279$) conditions. Specifically, the significant differences among the blocks were as follows (all comparisons $p < 0.05$): in sham-young, block 1 ≠ 4, 5 and 6 and blocks 2 and 3 ≠ 6; in atDCS-young, block 1 ≠ 2, 5, and 6 and blocks 3 and 4 ≠ 6; in sham-older, block 1 ≠ 6; in tRNS-older, block 1 ≠ 3, 4, 5, and 6 and block 2 ≠ 6; and in atDCS-older, blocks 1 and 2 ≠ 6. Only the tRNS-young condition did not show a significant learning effect ($F(5,70) = 0.386$; $p = 0.857$). This result indicates that performance improved during the task in young and older groups, except for the young group stimulated with tRNS, in which performance at the end of the task did not differ from baseline.

To compare the learning rate across the groups, we examined the slope values obtained from fitting the d' (see Fig. 1S—Supplementary materials). Interestingly, we found a statistically significant interaction between age and the stimulation condition ($F(2,75) = 4.262$; $p = 0.018$; $\eta_p^2 = 0.102$). The post hoc tests revealed a significant difference between the slope of the tRNS-young and sham-young conditions ($p = 0.019$) (see Fig. 3 and Table 4S—Supplementary materials). Both the main effects of age ($F(1,75) = 0.051$; $p = 0.823$) and stimulation condition ($F(2,75) = 1.386$; $p = 0.257$) were not statistically significant. The stimulation condition was not significant as a main effect as the only effect of stimulation was present for tRNS in the young group and not in the older group. In line with the previous analysis on the d' values, these results confirmed that the rate of visual perceptual learning (i.e., the slope) was modulated only in the young group by tRNS: indeed the slope in this condition was reduced compared to the slope in the sham condition in young subjects.

3.2. Neurophysiological results

Under the baseline condition, we were able to identify the same TEP components in the young (see Fig. 4A and B) and older (see Fig. 4D and E) participants, namely the P20, N35, P50, N80, P110, N170, P270, and P370 components. In both age groups, the TEP source localization revealed that the cortical response was first generated in the visual areas, followed by the activation of prefrontal regions before 100 ms and frontocentral areas at later latencies, and then returned to the visual areas (see Table 3 and Fig. 4). No differences were found at baseline among the stimulation conditions within each age group in either the young (all clusters $p > 0.90$) or older (all clusters $p > 0.73$) participants.

However, notably, at baseline, the TEPs differed between the young and older participants in amplitude, suggesting a modulation in visual cortex excitability and connectivity with age. In 4 positive clusters, the amplitude in the older group was more positive than that in the young group, and in 3 negative clusters, the amplitude in the young group was more positive than that in the older group. The clusters were spread in time and space from approximately 35 ms–400 ms over the central parietal channels. The results of the cluster-level permutation test are shown in Fig. 5.

At the early latencies, we found that the TEP amplitude in the older subjects was greater than that in the young subjects as indicated by 2 overlapping clusters before 100 ms (positive cluster: t = 33–88 ms, $p = 0.0029$; negative cluster: t = 61–99 ms, $p = 0.04$; Fig. 5A). This effect indicates that effective connectivity from the visual cortex to prefrontal regions, where these early latency components have been localized, increases with age of participants. At the later latencies, we found the opposite pattern: TEP amplitude in the young subjects was greater than that in the older subjects in 3 positive (Fig. 5B.: t = 125–217 ms, $p < 0.0001$; Fig. 5C.: t = 247–300, ms, $p = 0.0029$; Fig. 5D.: t = 350–400 ms, $p = 0.019$) and 2 negative (Fig. 5B.: t = 129–214 ms, $p < 0.001$; Fig. 5C.: t = 242–305 ms, $p = 0.0019$) clusters. Therefore, effective connectivity from frontal to visual regions was reduced at these later latencies in the older group.

The comparison of the TEPs before and after the task revealed a reduction in amplitude that was independent of the stimulation condition in a frontocentral positive cluster between 87 and 161 ms ($p = 0.001$). Interestingly, this modulation was very similar in its temporal distribution between the young and older subjects. In the young group, this difference ($p = 0.001$) was significant in a

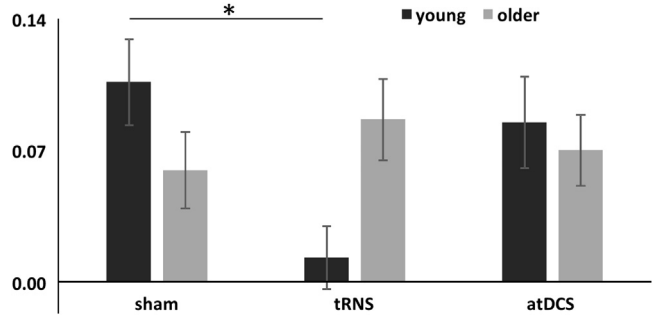

Fig. 3. Behavioral results. Learning rate (slope data) of the young (dark gray) and older (light gray) participants. The data are expressed as mean ± SEM. Higher values indicate higher learning in the 6 blocks of the task. Abbreviations: tRNS, transcranial random noise stimulation; atDCS, anodal transcranial direct current stimulation. Asterisk indicates significant effects ($p < 0.05$).

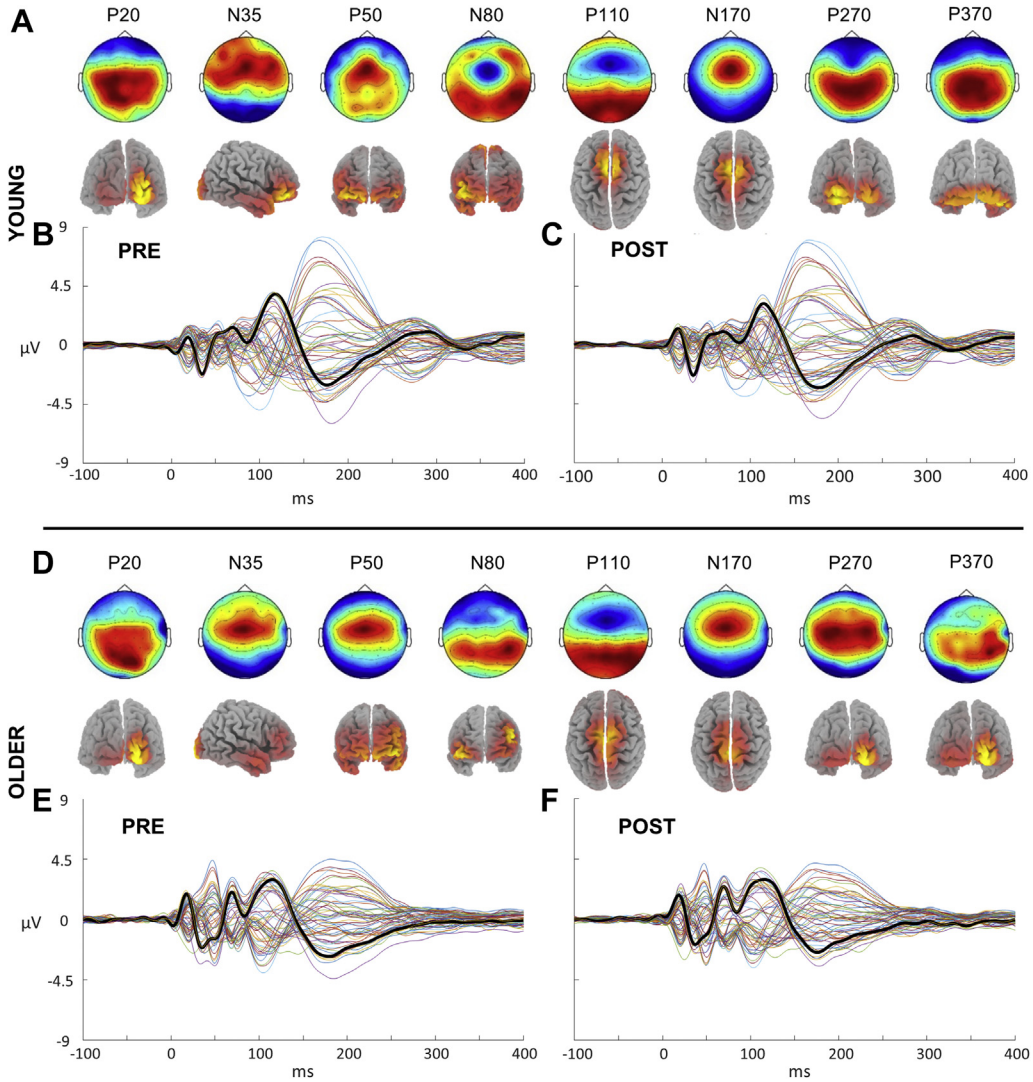

Fig. 4. TEP waveforms in young (Top) and older (Bottom) subjects. Topographies of the TEP components and their source localization in the young (A) and older (D) participants before (pre, B and E) and after (post, C and F) the tES stimulation. In the butterfly plots shown in B, C, E, and F, each line represents the grand average of an EEG channel. Oz is highlighted in bold black. The TEP amplitude is shown in μV (y-axis) and time in ms (x-axis). Abbreviations: tES, transcranial electrical stimulation; TEP, transcranial magnetic stimulation–evoked potential.

frontocentral positive cluster between 87 and 143 ms (see Fig. 6A, B and C.). In the aged group, the significant difference ($p = 0.019$) resulted in a central positive cluster between 89 and 143 ms (see Fig. 6D, E and F.). In an additional analysis, we compared the spatial distribution of these clusters between the young and older subjects with a cluster-based permutation test calculated over all channels that was restricted to the time window of the cluster (i.e., 90–140 ms). The results showed a significant negative cluster over the frontal electrodes ($p = 0.017$), indicating a subtle but consistent difference in the spatial distribution of TEP modulation after the task between the 2 age groups. Interestingly, the cortical localization of this effect revealed activation in the visual areas in both age groups and additional activation in the prefrontal regions in the older subjects. Therefore, the modulation of TEPs after task execution involved a different cortical pattern between the young and older subjects, with greater changes in anterior regions for the older than for the young subjects.

Finally, the cluster-based permutation analyses of the TEPs excluded an interaction between the pre-post effect and the type of stimulation in both the young (all $p > 0.21$) and older (all $p > 0.61$) subjects.

4. Discussion and conclusions

The present data reveal common effects but also differences between young and older subjects in both the tES-induced modulation of VPL and the effective connectivity of the visual system as evaluated by TEPs. Here, we argue that although plasticity

Table 3
MNI coordinates and corresponding Brodmann area (BA) of the TEP components

TEP component	Young	Older
P20	BA18: 20, −100, 0	BA18: 20, −100, −10
N35	BA18: 20, −100, 0	BA18: 20, −100, −10
	BA47: 50, 45, −10	
P50	BA11: 20, 65, −15	BA11: −35, 60, −10
N80	BA11: 40, 55, −10	BA11: 45, 55, −10
	BA6: 5, 0, 70	BA46: −40, 50, 20
P110	BA6: −5, 0, 70	BA6: 0, −20, 55
N170	BA6: −5, 0, 55	BA5: 0, −30, 55
P270	BA18: −20, −100, −10	BA18: 20, −100, −10
P370	BA18: −20, −100, 0	BA18: 20, −100, 0
		BA47: −50, 45, −10

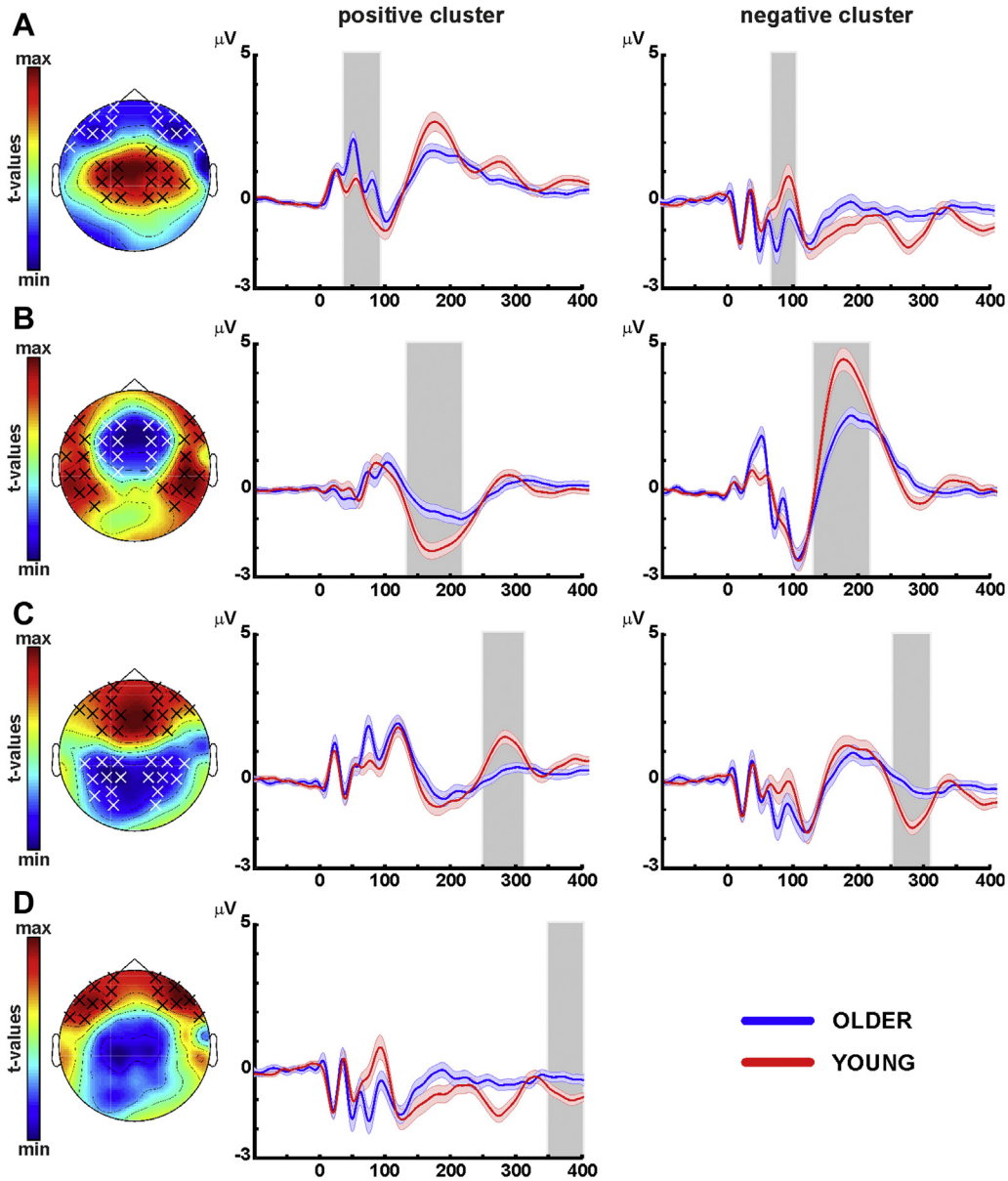

Fig. 5. Baseline TEPs differences between the young and older subjects in different time windows (A–D). On the left, the maps show the topographical distribution of the t-values in the comparison between the young and older subjects; the crosses represent the electrodes included in the significant positive (black) and negative (white) clusters as determined by the cluster-based permutation test. In the graphs, the TEP waveforms obtained by pooling the electrodes included in each significant cluster are shown for the older (blue lines) and young (red lines) participants. The bands represent the SE. The TEPs amplitude is shown in μV (y-axis) and time in ms (x-axis). The light gray areas highlight the time windows of the significant differences between the young and older subjects. Abbreviation: TEP, transcranial magnetic stimulation–evoked potential. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

mechanisms leading to learning are preserved in older adults, age-related changes in visual cortex connectivity may influence the circuitry functionally involved in VPL and the relative contribution of each node of the network, thus underlying the different effectiveness of tES in aging.

Our first finding is that VPL occurred in both the young and older groups but was modulated by tES, namely, tRNS, only in the young group. This task has been shown to induce learning in young populations in several previous papers (Fertonani et al., 2011; Perini et al., 2016; Pirulli et al., 2013). The preservation of VPL in healthy aging, as an index of active plasticity mechanisms, is unsurprising and has been described in the literature. Li et al. (2017) reported similar patterns of learning between young and older participants in an ODT. Similar results have been described by Andersen et al. (2010) and Bower and Andersen (2012) using texture discrimination and motion discrimination tasks, respectively. Nevertheless, it is difficult to directly compare visual performance and learning in different age groups due to the decline in sensory and perceptual processing in aging, which may influence performance in behavioral tasks (Andersen, 2012; Betts et al., 2007). In our study, we have considered this issue and modified the difficulty of our task to obtain comparable baseline performances in our 2 age samples. With this adjustment, the learning rate in the older and young groups did not differ, suggesting that plasticity mechanisms may still be fully active in physiological aging (Andersen, 2012; Andersen et al., 2010; Li et al., 2017).

As shown in our previous studies (Fertonani et al., 2011; Pirulli et al., 2013), VPL in the young group was modulated by tRNS,

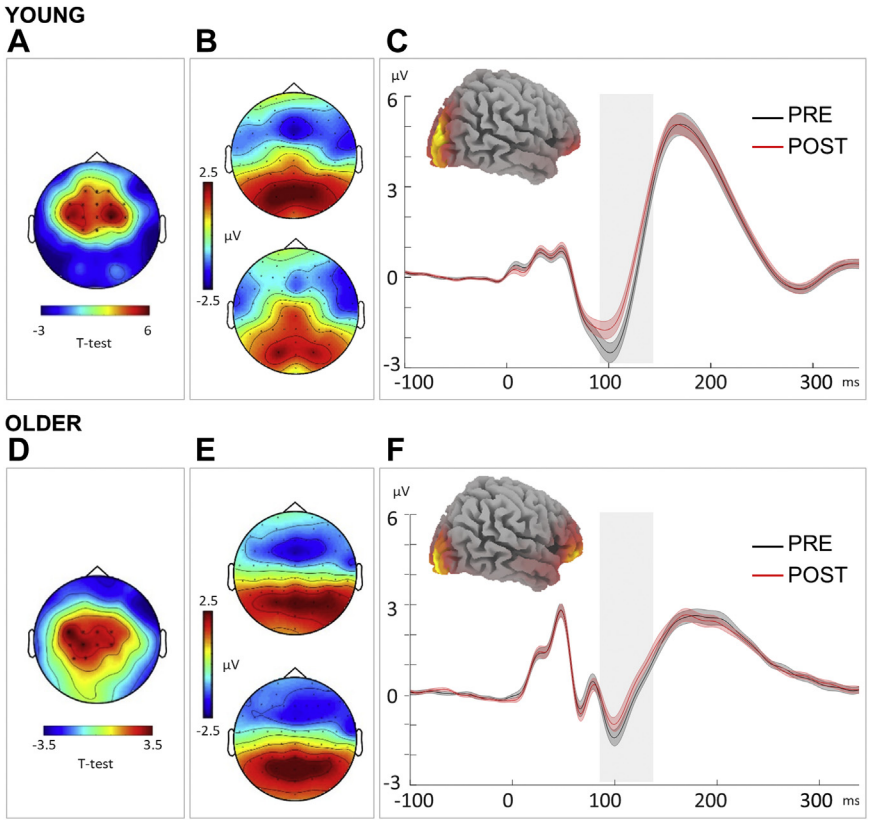

Fig. 6. Pre-post effect on TEPs in young (Top) and older (Bottom) subjects. On the left, the maps show the topographical distribution of the t-values in the comparison of post- and pre-tES stimulation in the young (A) and older (D) subjects. Asterisks represent electrodes included in the significant clusters as determined by the cluster-based permutation test. The middle panels show the TEP topographies pre- (Top) and post- (Bottom) tES stimulation in the time window of the significant clusters, that is, 87–143 ms in the young (B) and 89–143 ms in the older (E) subjects, and the source localization of the effect. On the right, the TEP waveforms obtained by pooling the electrodes included in the significant cluster are shown for pre- (black) and post- (red) stimulation in the young (C) and older (F) subjects. The bands represent the SE. The TEP amplitude is shown in μV (y-axis) and time in ms (x-axis). The light gray areas highlight the time windows of the significant differences between post- and pre-tES. Abbreviations: tES, transcranial electrical stimulation; TEP, transcranial magnetic stimulation–evoked potential. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

whereas no effect was found when applying atDCS. We hypothesize that the different effects of the 2 neurostimulation techniques are due to their different current waveforms and that only the repeated subthreshold random stimulation can prevent homeostasis in the neural system (Fertonani et al., 2011). We also found a reverse effect of tRNS in the young group compared to our previous studies (Fertonani et al., 2011; Pirulli et al., 2013), that is, a decrease in VPL rather than an improvement. This discrepancy may be explained by a few changes in the protocol parameters. A general inconsistency in tES effects is well known and explained by evidence showing that several technical variables seem to affect the final behavioral outcome (e.g., Fiori et al., 2017; Hsu et al., 2015; Pirulli et al., 2014, 2013). First, the task in this study was easier because a different set of orientations was used as follows: the subjects appear to start from higher baseline d' levels, and their learning rate in the sham condition seems steeper than that reported in Fertonani et al. (2011). The initial level of performance is a factor known to influence the subsequent tES effect (see, e.g., Benwell et al., 2015; Learmonth et al., 2015). Importantly, the baseline performance level may explain the differences in the young group in previous studies but not the differences between the groups in the present study because the young and older subjects had a comparable baseline level of performance.

Other changes in the paradigm that may have induced a different tRNS behavioral effect in the young subjects include changes in the experimental procedure, for example, a long preparation phase that may have led to changes in arousal and the application of a single-pulse TMS that may have interacted with tES (see Hurley and Machado, 2017 for a description of metaplasticity effects induced by the consecutive application of different neurostimulation protocols, although a TMS single-pulse paradigm may hardly induce metaplasticity phenomena). Therefore, it is difficult to determine the factors that may have induced a qualitatively different effect of tRNS in the young subjects in the present study, and further studies are needed to fully understand the effective parameters of tES.

Notably, tES had different effects on learning at the behavioral level between the 2 age groups as follows: we did not find any tES effect in the older group. This result is consistent with studies in which differential tES effects between young and older participants have been reported in different domains, including picture naming (Fertonani et al., 2014), motor learning (Heise et al., 2014; Zimerman et al., 2013), gambling tasks (Boggio et al., 2010; Fecteau et al., 2007), and reality monitoring tasks (Mammarella et al., 2017). Given that we applied the same protocol in both the young and older participants, it is likely that the different tES effects may be related to age-related changes in cortical activity rather than protocol-related changes.

Based on the present neurophysiological findings, we suggest that the differential behavioral effects of tES between young and older subjects may be due to intrinsic modifications in the connectivity of the aged brain. The age-dependent effects of tES may be explained by differences in the neural substrates underlying perception and in the connectivity patterns in young and older

individuals as also suggested by recent studies (Antonenko et al., 2018; Martin et al., 2017; Perceval et al., 2016). To support this conclusion, we provide the following evidence: first, we show that aging is associated with an altered effective connectivity in the visual cortex as measured by TEPs at baseline; second, we show that the cortical pattern of task-related changes as measured by the modulation of TEPs before and after VPL differs between the age groups.

TEPs at baseline provide information about cortical effective connectivity measured in a resting-state condition, that is, the influence of one area over the activity of another area, because their amplitude reflects the spreading of activation from the stimulated target to remote regions (Bortoletto et al., 2015; Hallett et al., 2017). In our data, the pattern of activation obtained with the source localization algorithm revealed that the initial response in the visual areas triggered the subsequent responses in the frontal regions to return to the visual areas. These results are difficult to compare with those of previous TMS-EEG studies analyzing TEPs after visual area stimulation (Bagattini et al., 2015; Herring et al., 2015; Taylor et al., 2010) due to methodological heterogeneity. Nevertheless, other studies have revealed similar results showing the relevance of anatomical and functional connections between the visual and prefrontal cortices. Several studies have reported that sufficiently strong visual stimuli lead to the activation of frontal areas even in simple visual perception (Panagiotaropoulos et al., 2012; Thorpe et al., 1983), including conscious visual detection (Lamme and Roelfsema, 2000; Ruhnau et al., 2014), and it has been shown that the prefrontal cortex is functionally linked to extrastriatal visual areas (Schall et al., 1995) with bidirectional communication. Frontal regions receive sensory inputs from visual areas (Chavis and Pandya, 1976; Thorpe et al., 1983) and, in turn, send feedback to these areas (Gottlieb, 2008), thus exerting their causal influence on visual activity (Morishima et al., 2009; Ruff et al., 2006; Taylor et al., 2007). Therefore, the activation induced by the TMS in the visual area may spread to frontal regions through active connections. Thus, the TEPs reveal a functional extended circuit that extends beyond the visual system and is causally activated by the stimulation of visual areas.

Importantly, the differences in the TEP amplitude at baseline indicate age-related modifications in the effective connectivity of these networks. Specifically, the aged brain was characterized by higher components generated in the prefrontal cortex between 40 and 100 ms, followed by smaller responses in central regions (approximately 125–215 ms), and subsequently absent feedback activation in the visual areas in later temporal windows (240–300 ms, and 350–400 ms). These results expand previous studies investigating the modified visual network connectivity in healthy aging (Betzel et al., 2014; Chan et al., 2014; Chhatwal et al., 2018; Geerligs et al., 2015). Importantly, the present data suggest that aging leads to increased effective connectivity from visual-to-prefrontal areas and decreased feedback effective connectivity in the opposite rostral-to-caudal direction.

In addition to the age-related connectivity changes measured at rest, a higher involvement of anterior regions may be present when visual areas are activated by visual stimuli during task execution. Support for this hypothesis is derived from the results of the task-related TEP modulation as follows: the TEPs were decreased after task performance in both age groups with a similar pattern, that is, in a central cluster in the same temporal interval (young 87–143 ms vs. older 89–143 ms). However, this change had a different spatial distribution over the EEG electrodes that corresponded to a different pattern in the source localization. Specifically, the changes were localized to visual areas in the young subjects and both visual areas and frontal regions in the older subjects. Therefore, the task-related changes in cortical activity in the older subjects involve anterior regions that are less involved in young adults. These results are interesting because they support recent models of VPL indicating the involvement of a visual-frontal network (Watanabe and Sasaki, 2015) in which learning is supported by changes in functional connectivity between the visual cortex and frontoparietal areas (Lewis et al., 2009). Moreover, these results are consistent with evidence suggesting that prefrontal regions contribute to decision making in visual discrimination tasks (Heekeren et al., 2006; Kahnt et al., 2011; Kim and Shadlen, 1999). Most importantly, our data suggest that the aged brain requires a higher contribution of frontal areas during visual learning tasks. These data are consistent with previous evidence of an age-related reduction in occipito-temporal activity coupled with an age-related increase in frontal activity (Grady et al., 1994; Huettel et al., 2001; Levine et al., 2000). The wider recruitment of the anterior portion of the brain has been proposed to have a compensation function by the PASA cognitive model (Davis et al., 2008).

In summary, our results suggest that aging entails functional changes in the brain that make it fundamentally different from the young brain and lead to divergent effects in regard to neuromodulation. Although both the young and older subjects were able to learn and improve their performance in the orientation discrimination task, tES induced a behavioral change of VPL in the young subjects, whereas no effects were found in the older subjects. Our neurophysiological data suggest that the differential effect of tES may be due to age-related changes in effective connectivity between visual areas and prefrontal regions. Specifically, the stronger activation of the prefrontal cortex after visual cortex stimulation and the stronger modulation of the prefrontal cortex after VPL in the older subjects may indicate that task performance relies on the recruitment of a wider network and a more crucial contribution of the anterior portion of the brain. We want to emphasize that the neurophysiological characteristics of the target population are fundamental to predicting the effects of stimulation protocols. The differences between young and aged brains may dramatically influence tES effects. Therefore, the young brain may not be appropriate as a model for developing efficacious tES protocols for aging. Models testing the effect of tES techniques should strictly correspond to their target, especially when the interest is in developing protocols for efficacious stimulation in pathological aging (Crosson et al., 2015).

Disclosure

The authors have no actual or potential conflicts of interest.

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The study was approved by the Ethics Committee of the IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Safety procedures were adopted based on noninvasive brain stimulation approaches (Antal et al., 2017; Rossi et al., 2009), and written informed consent was obtained from all participants before the beginning of the experiment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.07.009.

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