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Baseline levels of alertness influence tES effects along different age-related directions

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ABSTRACT

Normal aging is usually accompanied by several structural and functional physiological changes of the brain, which are closely related to alterations of cognitive functions (e.g., visual short-term memory). As the average age of the population increases, it has become crucial to identify cognitive-behavioural interventions to maintain a healthy level of cognitive performance. Among a variety of approaches, the targeting of specific intrinsic alertness mechanisms has shown a solid rationale and beneficial effects in both healthy and pathological ageing. In a similar vein, the use of non-invasive transcranial electrical stimulation (tES) represents another promising approach to induce an alerting state that can produce advantages in the information processing in the brain and therefore behaviour. Here, we investigated whether time-locked bursts of tES (i.e., transcranial random noise stimulation) were effective in inducing behavioural and physiological changes, consistently with an alertness increase, in both young and older healthy adults. Namely, we expected to find a beneficial alerting effect on visual short-term memory performance as a function of stimulus perceptual salience and tES. The initial results showed that the performance of younger adults was not affected by tES, while older adults scored lower correct responses for high-salience stimuli during real tES with respect to sham stimulation. However, after including a baseline measure of subjective level of alertness in the analyses, a tES-induced memory improvement did emerge in the less alerted younger adults, while only the more alerted older adults were subject to the worsening effect by tES. We discuss these results in consideration of the evidence on critical age-related differences as well as the interaction between neurostimulation and baseline alerting mechanisms.

1. Introduction

Phasic alertness refers to the ability to increase response readiness for a short period of time following behaviourally relevant stimuli (Posner and Petersen, 1990). The underlying neural mechanisms of alertness can also be described under the notion of arousal (Aston-Jones and Cohen, 2005), however for the sake of consistency with the neuropsychological literature the term alertness will be used thereafter. Changes in alertness are known to lead to changes in cognitive performance. In healthy young adults, several studies suggest that task-induced increases of phasic alertness improve performance speed and accuracy (Hackley and Valle-Inclán, 2003; Petersen et al., 2017). Whether the same advantages induced by increased phasic alertness modulations are present also in physiological aging is still debated. Considering that physiological aging is usually accompanied by alterations of cognitive functions (Glisky, 2007), it becomes important to understand whether such variations in alertness can be modulated with the aim to improve individuals' performance. The age-related alteration in cognitive functions vary as a function of the cognitive domain. While some abilities, like crystallized intelligence or knowledge representations, are resistant to aging, others, such as processing speed and working memory, appear more susceptible to decline (Dennis et al., 2007). Existing investigations yield unclear results on how phasic alertness varies with aging. Some studies reported a preservation of alerting effects in physiological aging (Haupt et al., 2018), while others found a decrease or absence of alerting effects (Wiegand et al., 2017a).

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An efficient regulation of alertness is a crucial ability for the everyday activities. In older adults the failure to effectively react to the environmental requirements may determine frailty progression (O'Halloran et al., 2013), resulting in increased fall risk and accidents (Salthouse, 2012). Consistently with these reports, several cognitive intervention studies showed that targeting intrinsic alertness may improve executive functions and more generally cognition, both in healthy older adults (Van Vleet et al., 2016) and in patients with neurological diseases (DeGutis et al., 2016). In addition to the approaches based on cognitive/behavioural training, a novel line of research is exploring the possibility of using non-invasive brain stimulation techniques (e.g., transcranial electrical stimulation - tES) for enhancing alertness abilities to improve performance, in both clinical and non-clinical populations (Brosnan et al., 2018). In general, tES is an effective tool to modulate brain activity, insofar as state-dependent factors and participants' baseline levels are taken into account (e.g., task difficulty, anxiety levels, education) (for a review Fertonani and Miniussi, 2017). For example, Mauri et al. (2015) have shown that tES induces performance benefit in healthy young subjects, likely consistent with a modulation of phasic alertness, and crucially in accordance with initial levels of anxiety. In Mauri et al. (2015) bursts of high frequency transcranial random noise stimulation (tRNS, a type of tES), were administered through a fronto-occipital montage during a vigilance task concurrent to the presentation of the relevant stimuli, in order to exogenously increase the phasic alertness response. As expected by an enhancement of alertness, the results showed a speed-up of reaction times and a concurrent increase of skin conductance (Mauri et al., 2015) (skin conductance is a reliable physiological measure of arousal; see Dawson et al., 2016).

In the present study, we aimed at investigating whether the same tES protocol used in Mauri et al. (2015) was effective in inducing behavioural and physiological effects consistently with a phasic alertness increase across the lifespan. However, the evaluation of reaction times during a continuous performance test, like in Mauri et al. (2015), would not be an appropriate measure for a comparison between young and older adults, because such task is heavily reliant on motor components. Therefore, it is preferable to bypass the overall slowing of motor processes in aging using a nonresponse-related measure (Haupt et al., 2018). Given the accumulating evidence showing that alertness facilitation involves also the early perceptual/attentional levels (Petersen et al., 2017; Sturm and Willmes, 2001), we decided to use an adapted version of the visual short-term memory (VSTM) task proposed by Sutherland and Mather (2012). These authors provided compelling evidence supporting that alertness affects low level processing by enhancing the selectivity of attention in favour of perceptually salient stimuli and against non-salient stimuli (Mather and Sutherland, 2011). We have to take into account that, due to the limited processing capacity of the human brain, stimuli in the environment compete to gain access to advance processing in a winner-take-all fashion (Itti and Koch, 2001). Therefore, only stimuli with the highest saliency are selected at the expense of the non-salient items (Fecteau and Munoz, 2006). In their paradigm, Sutherland and Mather (2012) briefly presented arrays of letters with two types of contrast salience, high and low, requiring participants to report as many letters as they remembered regardless of the saliency. Researchers modulated alertness by presenting emotionally arousing sounds just before the presentation of letter arrays. Results showed that the increase of alertness biased competition in favour of high salience stimuli, in young (Sutherland and Mather, 2012) and marginally also in older (Sutherland and Mather, 2015) participants.

In the present study, we implemented the same VSTM task in young and older participants but used bursts of tES instead of auditory stimulation to modulate alertness. To capture possible consequences of the alertness enhancement induced by tES, we investigated behavioural accuracy as well as skin conductance response (SCR) during the VSTM task. We hypothesized to obtain an effect of tES-induced alertness biases in favour of high relevance stimuli. Should tES be as effective as the behavioural manipulation to enhance alertness, participants would report more high-salience letters in the real stimulation condition than in the sham condition. Crucially, we expected that different baseline characteristics within and between age groups could determine tES-induced effects on the VSTM task, in line with several evidence (e.g., Horvath et al., 2014; Krause and Kadosh, 2014; Li et al., 2015). We have recently reported that both baseline physiological and subjective levels of alertness at baseline significantly explained response speed during a prefrontal tDCS application in young participants (Esposito et al. submitted for revision).

2. Materials and methods

2.1. Participants

Twenty-three younger adults (YAs) and twenty-three older adults (OAs) were recruited in exchange for a small monetary reward. Data from three YAs and one OA were excluded from the analyses because they clearly discriminated tES conditions (real vs. sham), from one OA because he/she was an extreme outlier on the rate of false alarm in the baseline condition (more than 4 standard deviations of the group mean) and one OA dropped out after the first experimental session. The final sample was composed by 20 YAs (16 females, mean age = 23.5 years, SD = 2.8) and 20 OAs (12 females, mean age = 67.8 years, SD = 3.5).

All participants had normal or corrected-to-normal visual acuity, evaluated with the Lighthouse visual acuity charts (Lighthouse Enterprises, New York, NY) and reported normal values at the Pelli-Robson contrast sensitivity test (Pelli and Robson, 1988). All participants, but one YA, were right-handed according to the Edinburgh handedness inventory test (Oldfield, 1971), showed no risk factors for tES application, as assessed through a safety questionnaire (Fertonani et al., 2015), and reported being free of neurological and psychiatric disorders.

In all participants, we assessed the subjective levels of alertness experienced by participants with the State-Trait Anxiety Inventory (STAI-Y) (Spielberger et al., 1983). This self-report inventory is used to evaluate trait and state anxiety, this latter known to be closely related to the locus coeruleus activity i.e., the main neural underpinning of alertness (Eysenck, 1963; Mizuki et al., 1997; Robbins and Everitt, 1995). The STAI-Y was indeed predictive of the different tES effects observed in our previous study on alertness and tRNS (Mauri et al., 2015).

In addition, all OAs underwent a neuropsychological evaluation in order to assess the absence of any cognitive decline (Table 1). Written informed consent was obtained from all participants prior to the beginning of the experiment. All the procedures conformed to the Declaration of Helsinki for research involving human subjects and were approved by the ethics committee of the IRCCS San Giovanni di Dio Fatebenefratelli Scientific Institute of Brescia, Italy.

2.2. Behavioural task and procedure

All participants completed two experimental sessions during which they performed a VSTM task (adapted from Sutherland and Mather, 2012) combined with real or sham tES (i.e., within-subject design). At the beginning of each experimental session, all participants completed the STAI-Y questionnaire (Spielberger et al., 1983) to measure their trait anxiety level. Fig. 1 illustrates schematically the behavioural task. Each trial started with a fixation cross displayed at the centre of the screen for a variable interval of 750–3000 ms, after which a circular array of 8 letters was briefly presented (i.e., 200 ms for YAs and 300 ms for OAs, to obtain a comparable task difficulty). After a fixed interval of 200 ms, an acoustic neutral signal of 250 ms, followed by the appearance of a question mark, informed subjects to vocally report as many letters as they remembered. Participants were instructed to maintain fixation on the central cross during the whole trial. After the response, they had to press the spacebar to move to the next trial. Only accuracy, not speed of response, was emphasized.

Table 1
Neuropsychological evaluation of OAs reported as the mean scores (±SD). * Age- and education-adjusted neuropsychological results. **Cut-off scores according to Italian normative data are reported (all values falling within normal range).

	Raw score	*Adjusted score	**Cut-off
Mini mental state examination (MMSE)	28.54 ± 1.5	26.99 ± 2.0	≥24
Raven-colored progressive matrices	28.96 ± 3.7	31.8 ± 2.7	>18
Fluency-phonemic	34.83 ± 11.3	35.79 ± 9.9	>17
Digit span forward	5.83 ± 1.0	5.81 ± 1.0	>3.75
Digit span backward	3.75 ± 0.6	–	–
Story recall	14.85 ± 3.6	15.29 ± 2.8	>8
Spatial span	4.54 ± 0.9	4.71 ± 0.9	>3.75
Rey Auditory Verbal Learning Test (Immediate recall)	41 ± 8.4	44.05 ± 6.9	>28.52
Rey Auditory Verbal Learning Test (Delayed recall)	8.96 ± 2.1	10.01 ± 1.9	>4.68
Rey-Osterrieth complex figure-recall	13.77 ± 4.8	17.11 ± 4.5	>9.47
Trail making test-A	47.63 ± 17.9	31.42 ± 18.3	<93
Trail making test-B	117 ± 33.5	69.95 ± 31.8	<282
Trail making test-B-A	72.19 ± 24.4	40.95 ± 20.5	<186
Stroop test (errors)	0.54 ± 0.9	0.33 ± 0.7	<4.23
Stroop test (time)	3.70 ± 0.6	21.98 ± 8.9	<36.91
Attentional Matrices	46.58 ± 6.7	45.64 ± 7.1	>30
Rey-Osterrieth complex figure-copy	33.77 ± 3.4	34.92 ± 3.0	>28.88
Geriatric Depression Scale (GDS)	4.79	3.44	24/30

The letters were presented in uppercase with a dimension of ~0.87° x ~0.87° at a distance of 3.12° from the central fixation cross. All the Italian alphabet letters were used, except for the letter 'I' due to its high similarity with the lowercase letter 'L'. Each array of letters consisted of 3 high-salience letters (black stimuli, RGB value 102 102 102) and 5 low-salience letters (grey stimuli, RGB value 250 250 250). The letters and their salience were randomly selected on a trial-by-trial basis. Subjects were instructed to vocally report as many letters as they remembered, regardless of their colour. Stimuli were displayed on a light grey background using a Dell LED monitor, with a screen resolution of 1920 × 1080 pixels, located at a distance of 70 cm from the participants. The presentation was controlled by E-Prime software (Psychology Software Tools Inc, Sharpsburg, PA), while the vocal responses were recorded through a microphone and digitized with GoldWave software (GoldWave, Newfoundland, CA) with a sampling rate of 11 025 Hz.

The temporal interval between the two experimental sessions was at least 7 days in order to avoid any long-term after-effect of the stimulation, and the order of the stimulation conditions was counterbalanced across participants. In each session, participants performed an initial short practice session, to become familiar with the task, and then 6 experimental blocks (30 trials each, 180 trials overall). tES was applied concurrently with the task execution only during blocks 3 and 4 (i.e., online-tES), whereas the other blocks were performed with tES stimulator in a stand-by state. Blocks 1 and 2 served as baseline (i.e., pre-tES), while blocks 5 and 6 were thought to capture possible short-term after-effects of tES (i.e., post-tES). Each experimental session lasted approximately 40 min.

2.3. tES procedure

Bursts of high frequency tRNS (100–640 Hz) were delivered using a battery-driven current stimulator (BrainStim, EMS, Bologna, Italy) through a pair of rectangular electrodes (35 cm^2) inserted in saline-soaked sponges prepared with a conductive gel solution. The electrodes were placed over FPz and Oz as determined by the International 10–20 EEG system. The stimulation was triggered during the two central blocks of the task (online-tES) with E-Prime software, for a total of 60 bursts of stimulation. Each burst of stimulation began 600 ms before the onset of the array of letters and lasted until 200 ms after its offset (duration = 1000 ms with YA and 1100 ms with OA). The stimulation parameters (current intensity = 2 mA; max current density = 0.057 mA/cm^2) are consistent with the safety limits (Antal et al., 2017). In the sham condition, the current was not delivered after the initial impedance check.

2.4. tES sensations

At the end of each experimental session, all participants completed a questionnaire to evaluate perceived discomfort (i.e., itching, pain, burning, heat, pinching, iron taste, fatigue) induced by tES (Fertonani et al., 2015). It was necessary that participants did not perceive any difference between real and sham stimulation, because the mere sensory stimulation could mimic the expected alertness effects. Data from three YAs and one OA were discarded from the analyses (as reported in 2.1

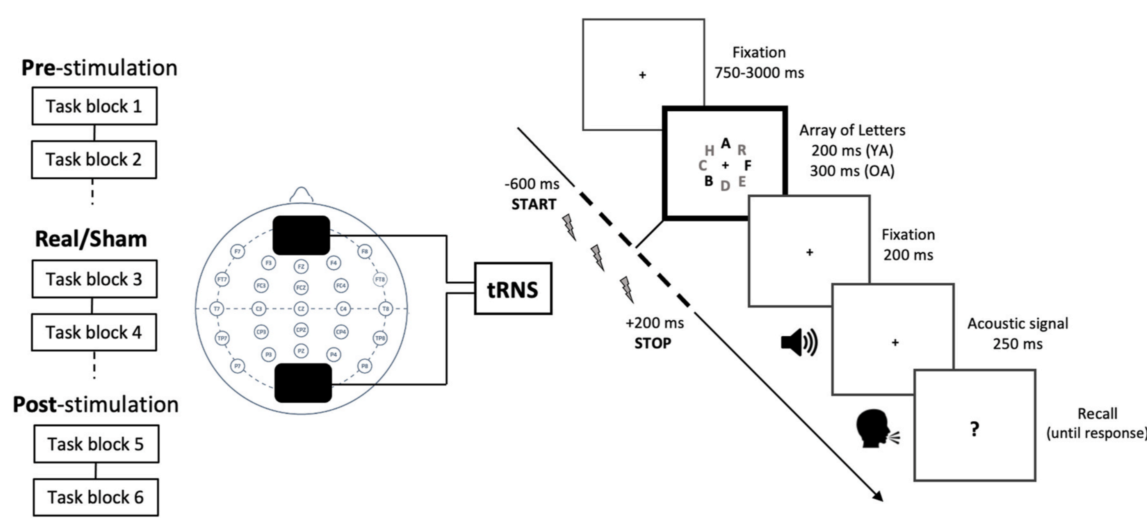

Fig. 1. A schematic illustration of the experimental paradigm and design. Bursts of tES were applied starting 600 ms before the onset of the array of letters and lasting until 200 ms after its offset. tES was applied only during the two central blocks of the task (i.e., Block 3 and Block 4).

Participants) because they clearly differentiated real from sham sessions. No participant of those included in the analyses reported any perceived sensation induced by tES application, except for one YA who reported itching at moderate level and fatigue at mild level during the real stimulation condition. These data are in line with our previous observations that bursts of stimulation do not evoke any sensations in most of the young individuals (Mauri et al., 2015) and extend them to older individuals.

2.5. Skin conductance response recording and processing

SCR was recorded from 1.3 cm of diameter Ag/AgCl electrodes placed on the distal phalanges of the second and third finger of the participant's non-dominant hand. The electrodes were prepared with an isotonic paste (Discount Disposables, St. Albans, Vermont), and the activity was recorded using a galvanic skin response module (BrainProducts GmbH, Munich, Germany) with a constant voltage applied across the electrodes. Electrodermal data were DC-recorded continuously with a resolution of 0.1 and digitized at a sampling rate of 5000 Hz (BrainAmp ExG MR 16 channels, BrainProducts GmbH, Munich, Germany).

The phasic SCR was estimated in relation to the bursts of stimulation. The SCR was measured in all blocks of real and sham tES conditions. According to Benedek and Kaernbach (2010), we considered the integrated SCR values as an indicator of response magnitude in an event-related design. Data within the temporal interval between 1 s before and 4 s after the onset of the bursts of stimulation were extracted from the raw data using BrainVision Analyzer v2 and then analysed using Ledalab software. The minimum amplitude criterion was set to 0.05 μS. A corresponding period of interest was analysed in those trials without bursts of stimulation (i.e., pre-tES and post-tES blocks in the real stimulation; all blocks in the sham stimulation).

2.6. Statistical analyses

Provided that the studies on aging reports divergent evidence on age-related cognitive changes (Bopp and Verhaeghen, 2005; Owsley, 2016), we firstly established differences in the behavioural and physiological responses at baseline between the two age groups (see 2.6.1). We then compared behavioural and physiological tES-induced differences in young and older participants during and immediately after tES application (see 2.6.2). Finally, we included our measure of subjective alertness in the analyses by performing a split on the STAI-Y State scale mean score of each age group.

2.6.1. Baseline differences between age groups

Education and scores in STAI-Y State and Trait scales were compared between the two age groups using two tailed independent t-tests. In order to highlight any systematic difference between age groups independently from tES influence, we compared behavioural accuracy and SCR acquired in the baseline blocks of both sessions between YAs and OAs.

2.6.1.1. Behavioural accuracy. As a measure of behavioural accuracy, we evaluated the number of correctly reported letters. To account for the different number of high and low-salience letters, the raw number of the reported letters on each trial was adjusted to the total number of letters presented for both levels of *Salience* (i.e., number of reported high-salience letters/3; number of reported low-salience letters/5). This behavioural variable was normally distributed, as assessed with Kolmogorov-Smirnov test ($D = 0.058$, $p = .2$). Thus, a linear mixed model (LMM) was applied to the proportion of the remembered letters with *Age* (YA vs. OA) as a fixed factor and *Stimulation* (real vs. sham) and *Salience* (high vs. low) as random factors. Considering the number of subjects included in the studied sample, we choose the LMM, because it allows taking into consideration the subject variability, generalizing more the results to the population (degrees of freedom are not reported because they are estimated and thus not informative).

2.6.1.2. Skin conductance. A LMM with *Age* (YA vs. OA) and *Stimulation* (real vs. sham) was performed on SCR values.

2.6.2. tES-induced effects

We then investigated the effects induced by tES on behavioural and skin conductance measures in the two age groups, considering the values acquired during- and post-tES blocks normalized to the respective baselines (online-tES – pre-tES; post-tES – pre-tES). This strategy allows to emphasize tES-induced modulations, by minimizing between subject variability.

2.6.2.1. Behavioural accuracy. A LMM was applied to the baseline-normalized proportion of remembered letters with *Age* (YA vs. OA) as fixed factor and *Stimulation* (real vs. sham), *Salience* (high vs. low) and *Time* (online-tES vs. post-tES) as random factors.

2.6.2.2. Skin conductance. A LMM was applied to the baseline-normalized values of SCR with *Age* (YA vs. OA) as a fixed factor and *Stimulation* (real vs. sham) and *Time* (online-tES vs. post-tES) as random factors.

A comparison, in terms of goodness of fit of the LMMs performed on behavioural and skin conductance data, was evaluated through Akaike information criterion (AIC) and Bayesian information criterion (BIC) indices: the lower the indices are, the better the fit of the model is. Post hoc comparisons were adjusted with Sidak correction for multiple comparisons.

3. Results

3.1. Baseline differences between age groups

The age groups differed in education [$t\,(38) = 3.569$, $p = .001$], with YAs (13.7 ± 2.7 years) showing higher level of education than OAs (10.2 ± 3.4 years). No difference in STAI-Y scores was observed between the sham and real tES in either age group [paired *t*-test: all p's > 0.84], confirming the reliability of this test. We thus averaged the STAI-Y Trait and State scale values across the two experimental sessions for each subject. The comparisons between groups revealed that YAs (38.4 ± 8.5) and OAs (36.7 ± 9.1) showed an equal level of anxiety trait [$t\,(38) = 0.611$, $p = .54$], while they presumably reacted differently to the experimental setting, with OAs (33.5 ± 5.2) showing an higher anxiety state in comparison to YAs (30.0 ± 4.5) [$t\,(38) = -2.331$, $p = .025$].

Behavioural and skin conductance data collected at the baseline of the two tES sessions showed a reliable response stability in both groups, as no significant difference was observed between baseline blocks of real and sham stimulation (p's > 0.59).

3.1.1. Behavioural accuracy

Among the several LMMs performed on the proportion of correctly remembered letters, the model that best (lowest AIC and BIC) fitted the data was the one with *Age* and *Salience* as main effects and *Age* x *Salience* as interaction effect ($AIC = -111.88$, $BIC = -99.68$). The non-inclusion of the factor *Stimulation* in the model showed the robustness of the data as it proved irrelevant to determine any baseline difference. Instead, the analysis showed significant effects of the main factors *Age* [$F = 11.433$, $p = .001$] and *Salience* [$F = 126.133$, $p < .001$] revealing that, on the whole, YAs performed better than OAs and that both groups reported a greater number of high than low salience letters. Interestingly, results showed a significant interaction between *Age* and *Salience* [$F = 6.419$, $p = .012$]. Post-hoc comparisons revealed that the difference in performance between YAs and OAs concerned only low salience letters ($p <$

.001), whereas a similar amount of high salience letters was reported by the two groups ($p = .606$) (Fig. 2A).

As predicted, these results confirmed that (i) both YAs and OAs were subjected to the perceptual bias induced by contrast; (ii) OAs scored a lower number of low-salience letters along with the same report of early priority high-salience letters, hence indicating a lower span of visual short-term memory.

3.1.2. Skin conductance

Among the several LMMs performed, the model that best fit the SCR data was the one with only *Age* as main effect (AIC = 95.53, BIC = 100.24), which indicated a lower baseline levels of SCR for OAs [$F = 4.555$, $p = .037$]. No other effect reached significance ($p > .5$).

3.2. tES-induced effects

3.2.1. Behavioural accuracy

The model that best fit the data on tES-induced effects (AIC = −734.82, BIC = −704.88 with *Age*, *Salience* and *Stimulation* as the main effects and all the double and triple interactions between them) revealed that the factor *Age* interacted with *Salience* [$F = 4.283$, $p = .040$] and interestingly with *Salience* and *Stimulation* factors [$F = 5.159$, $p = .024$]. Post-hoc comparisons showed that tES did not affect the performance of YAs, neither for high- nor for low-salience letters (all p's > 0.51). In OAs, instead, real tES reduced significantly the amount of remembered high-salience letters in comparison to the sham condition ($p = .01$) (see Fig. 3A). No tES effect was found in the OA group for low-salience letters ($p = .79$), most likely because the amount of remembered low-salient letters was too low to be further reduced (i.e., floor effect). In addition, the three-way interaction revealed that YAs and OAs differed in the performance with high-salience letters during sham ($p = .014$). On the contrary, no difference in the performance was found between the groups during real stimulation (p = .49), indicating that the effect of real tES cancelled out the improvement shown by the OAs in the sham condition. Older participants, indeed, visibly improved their performance throughout the experimental blocks more than young participants did.

No other significant effects emerged from the analyses (all p's > 0.108). The factor *Time* worsened the goodness of fit of the model when included in the analysis, and it never reached significance, indicating that tES worsened the performance of OAs with high-salience letters during tES application but also afterward.

3.3. Correlation between tES-induced effects and sample characteristics

To investigate possible relationships between tES-induced effects on high-salience letters and any of the sample characteristics, we calculated Pearson's (r) two tailed correlation coefficients between the behavioural accuracy during or post-tES and i) education, ii) STAI-Y State score iii) baseline performance. As a measure of behavioural accuracy, we considered the proportion of high-salience letters reported for the on-line- and post-real tES condition (normalized to sham tES condition according to the following formula: high-salience letters in real tES – high-salience letters in sham tES).

Results showed that the **tES-induced effects on behavioural accuracy correlated only with the scores at the STAI-Y State scale**, both during- [$r(40) = -0.398$, $p = .01$] and post-tES [$r(40) = -0.336$, $p = .03$]. Although weak, these inverse correlations suggested that tES-induced worsening of the performance increased as the levels of anxiety state increased (Fig. 4).

3.4. Subjective alertness across age groups

In order to better explore how tES effects on behavioural performance were influenced by the subjective levels of alertness, we divided YAs and OAs participants in two subgroups (i.e., high and low alertness), by performing a split on the STAI-Y State scale mean score of each age group. Interestingly, all the four resulting groups differed on the STAI-Y State score in a progressive way: YA-low alertness (mean = 26.1 ± 2.2) < OA-low alertness (mean = 29.9 ± 3.1) < YA-high alertness (mean = 33.7 ± 2.2) < OA-high alertness (mean = 38.2 ± 3.4) (all p's < 0.005; t-tests corrected for the number of comparisons, $p = .017$).

We added the fixed factor *Alertness* (low vs. high) to the previous model. The model that best fit the data (AIC = −718.758, BIC = −688.969 with *Age*, *Salience*, *Stimulation* and *Alertness* as main effects, *Age* x *Salience*, *Stimulation* x *Salience*, *Age* x *Salience* x *Stimulation*, *Age* x *Salience* x *Alertness*, *Salience* x *Stimulation* x *Alertness* as interactions) revealed that the *Alertness* factor significantly interacted with *Age* and *Salience* [$F = 4.984$, $p = .008$] and also with *Stimulation* and *Salience* [$F = 5.176$, $p = .007$].

To better understand the influence of alertness in YAs and OAs distinctly, we run a LMM separately for each age group.

In YAs, the model that best fit the data (AIC = −371.92, BIC = −347.73 with *Salience*, *Stimulation* and *Alertness* as main effects and the triple interactions between them) revealed a trend toward significance of the main effect *Alertness* [$F = 3.358$, $p = .069$], with participants with low alertness performing better than those with high alertness did. A significant triple interaction between *Salience*, *Stimulation* and *Alertness* [$F = 3.242$, $p = .017$] revealed that real **tES induced a marginal memory improvement with respect to sham tES for high-salience letters only in YAs with low alertness** ($p = .08$), and no effect in participants with high alertness ($p = .6$).

In OAs, the model that best fit the data (AIC = −343.32, BIC = −319.13 with *Salience*, *Stimulation* and *Alertness* as main effects and interaction effects *Salience* x *Stimulation*, *Alertness* x *Stimulation*, and *Salience* x *Stimulation* x *Alertness*) corroborated the significant main

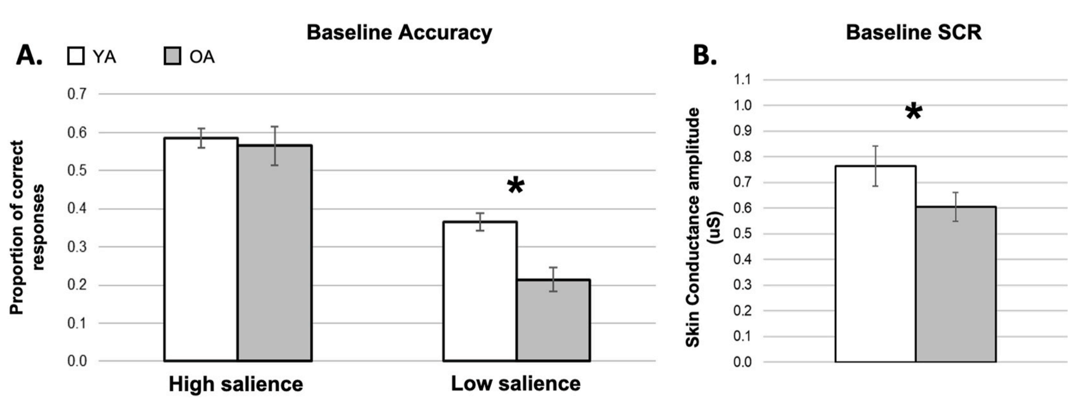

Fig. 2. (A) Behavioural accuracy for the high- and low-salience letters and (B) SCR at the baseline blocks in young (in white) and older (in grey) participants. * indicates p's < 0.05. Error bars represent the standard error of the mean (±SEM).

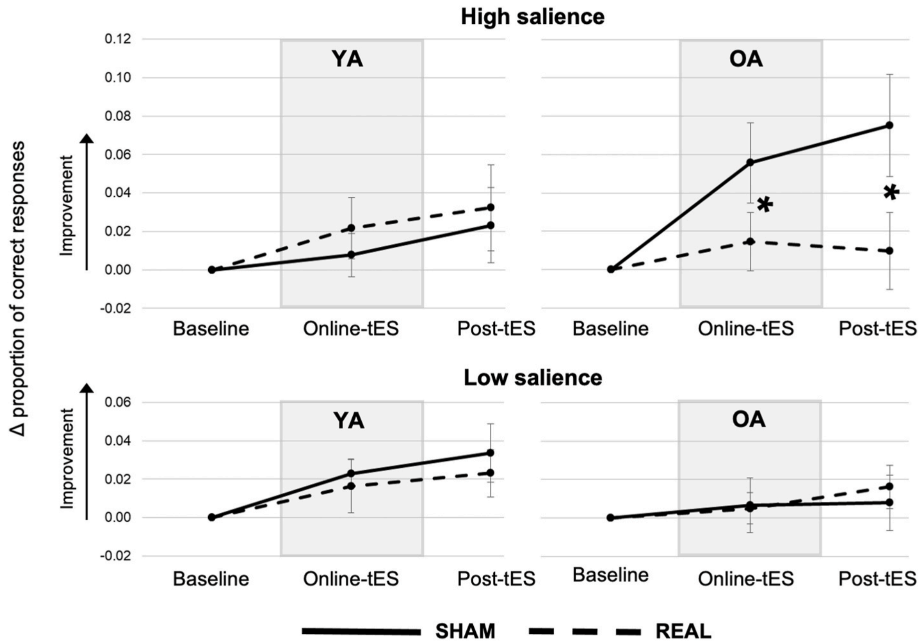

Fig. 3. Results relative to the behavioural accuracy for high- and low-salience letters, as a function of the blocks of the task, during sham and real tES, in younger (YA, on the left) and older (OA, on the right) participants. All data reported online- and post-tES blocks are normalized to the respective baseline blocks. * indicates p's < 0.05. Error bars represent the standard error of the mean (±SEM).

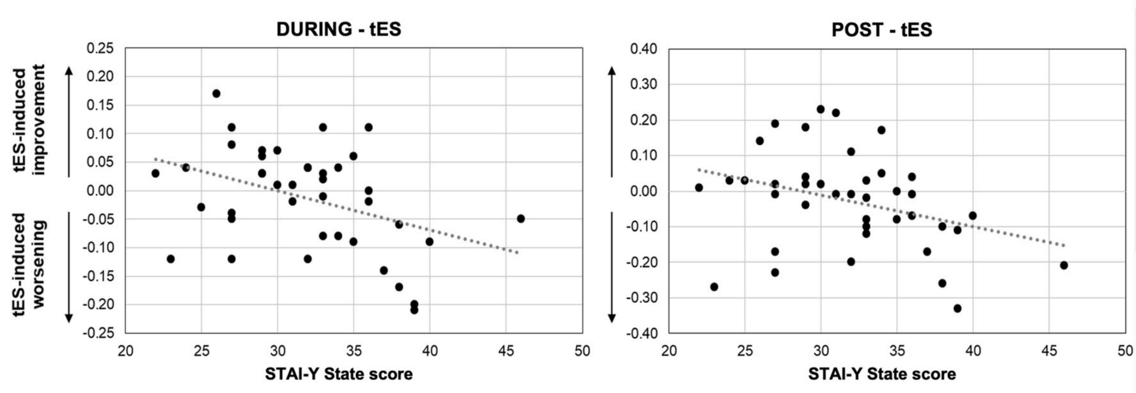

Fig. 4. Scatter plots showing the significant correlations between the behavioural accuracy (y-axis) of high-salience letters reported online- (on the left) and post-tES application (on the right) and the subjective levels of alertness (x-axis), as assessed with the STAI-Y State scale in both age groups such that higher scores reflect increasing anxiety. The behavioural accuracy is normalized to sham tES condition, so that positive values reflect a tES-induced improvement while negative values reflect a tES-induced worsening.

effects of *Salience* [$F = 7.186$, $p = .009$] and *Stimulation* [$F = 4.622$, $p = .034$]. Interestingly, the factor *Stimulation* also interacted with *Salience* [$F = 6.248$, $p = .014$] and with *Salience* and *Alertness* [$F = 4.966$, $p = .010$], revealing that the **real tES induced a memory worsening for high-salience letters only in OAs with high alertness** ($p = .001$), while no effect emerged with low levels of alertness ($p = .8$). In addition, during sham condition, OAs with high alertness remembered more high-salience letters ($p = .06$) and concurrently less low-salience letters ($p = .02$) than OAs with low alertness.

Overall, these results suggest that alertness affects behavioural performance in both groups, but according to different directions, which likely reflect age-related physiological changes in the brain (see Fig. 5A): The YA group showed better accuracy at low levels of subjective alertness, while the OA group performed better at high levels of subjective alertness. Alertness proved to be a crucial factor affecting the modulations induced by tES. At one extreme, we observed a tES-induced memory improvement in the YAs who reported the lowest level of alertness. At the other extreme, the highest level of alertness shown by the OAs was accompanied by a significant worsening of the performance.

3.5. Skin conductance

The model that best fit the SCR data (AIC = 51.49, BIC = 63.64 with *Age*, *Stimulation* and *Time* as main effects and *Stimulation* x *Time* and *Age* x *Stimulation* as interaction effects) showed a significant effect of the main factor *Stimulation* [$F = 4.492$, $p = .036$], according to which real stimulation was associated with a larger decrease of SCR with respect to sham stimulation (see Fig. 6). This effect was generalized to all participants, as the factor *Age* never approached significance (all p's > 0.7), and to both temporal intervals, as the interaction between *Stimulation* and *Time* did not reach significance [$F = 2.371$, $p = .126$].

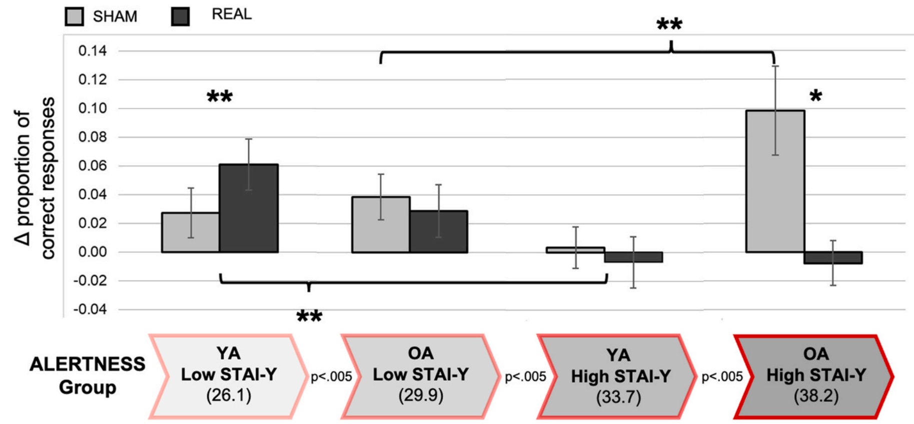

Fig. 5. Behavioural accuracy (normalized to baseline blocks) for high-salience letters online- and post-tES blocks (collapsed together) in the sham and real tES conditions, as a function of the subjective levels of alertness experienced by participants. From the left to the right subgroups with progressive subjective levels of alertness are reported for younger (YA) and older adults (OA).

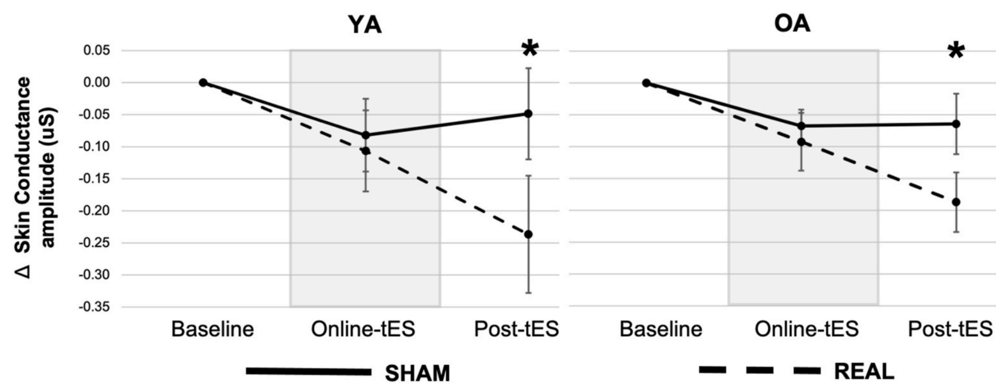

Fig. 6. Results relative to SCR, as a function of the blocks of the tasks, during sham and real tES, in younger (on the left) and older (on the right) adults, collapsed across stimuli saliency. All data reported online- and post-tES blocks are normalized to the respective baseline blocks. * indicates p's < 0.05. Error bars represent the standard error of the mean (±SEM).

3.6. *Correlation between tES-induced effects and sample characteristics*

Pearson's (r) two tailed correlation coefficients were calculated also between SCR and the sample characteristics (i.e., education, STAI-Y State score), but no significant correlation occurred (all p's > 0.19).

4. Discussion

In this study, we investigated changes in VSTM task performance following tES in both young and older participants. SCR was also measured to obtain an index of phasic alertness modulation. In light of the consistent alerting advantage on cognitive performance found in the literature, we expected a positive effect to be replicated by means of time-locked bursts of tES (i.e., tRNS) intended to mimic the sensory-driven endogenous phasic alertness (Mauri et al., 2015). In addition, we expected that the results would be highly contingent upon participants' age and subjective levels of alertness.

By focusing on the baseline state through the collection of subjective reports of alertness (i.e., STAI-Y State) from both age groups, we aimed at capturing some of the individual characteristics and state-dependent dynamics that may contribute to tES-induced effects (Fertonani and Miniussi, 2017; Krause and Kadosh, 2014). The topic of unaccounted individual differences generating heterogenous patterns of cognitive effects has taken centre stage in the field of tES, particularly for single session studies (Berryhill and Martin, 2018). Both brain anatomical (e.g., cortical surface topography, skull thickness, subcutaneous fat levels, cerebrospinal fluid density) and state-based factors (e.g., level of neural activation prior and during stimulation, performance rank, wakefulness, task priming or novelty) are considered crucial to the final behavioural outcome (Horvath et al., 2014; Krause and Kadosh, 2014; Li et al., 2015).

Phasic alerting has been traditionally found to increase response speed in a variety of task settings (Sturm and Willmes, 2001). However, there has been increasing evidence that phasic alerting may also exert its influence on the information processing as early as the encoding stage (Jepma et al., 2009; Wiegand et al., 2017b). This has given ground to investigating alertness effects not only on tasks with required fast motor responses but also on various accuracy-based measures (Matthias et al., 2010). For the purpose of our experimental paradigm, we built upon the arousal-biased competition model, which predicts an increased advantage in processing higher salience stimuli, that is featuring a prior attentional bias (Mather and Sutherland, 2011). We found that, on the whole, high contrast letters were indeed remembered more accurately and that baseline differences between the two age groups depended on the salience factor, with older participants reporting a lower proportion of low contrast letters than young participants. Thus, as far as our sample is concerned, a potential age-related decline in visual processing spared the high salience stimuli by exploiting a preserved ability to detect perceptual contrast (Fecteau and Munoz, 2006; Lee et al., 2012). In other words, older participants prioritized the processing of high salience stimuli while depleting attentional resources for further processing, consistently with their typical reduced memory span (Bopp and Verhaeghen, 2005).

The expectation that tRNS could effectively amplify this information-priority advantage was initially disconfirmed when analysing the sample on a group basis (YA vs. OA). However, a consistent effect was observed after including the STAI-Y State score in the analyses, with YA with low alertness showing an improved encoding of high-salience targets during real tRNS in comparison to sham.

Nevertheless, our tES protocol did not enhance the visual short-term memory performance of either groups; on the contrary, the OA showed a substantial drop in performance, precisely those with high alertness. tRNS seemed to prevent older participants from naturally improving their memory span for high salience letters over the experimental blocks. The explanation for tES not to have had the same impact on low salience letters could involve a floor effect. Several participants would have already scored the lowest possible proportion of low-salience letters at baseline (see Fig. 2A). While this is certainly a possibility for the older adults, under the arousal-biased competition model it was in fact expected that a phasic alerting effect would neglect lower-priority representations as well as information for perceptual suppression (Sutherland and Mather, 2012).

For the phasic arousal response to generate a prioritized selection of visual processing (e.g., encoding of high-contrast letters) some global and local neuronal events need to be in place: a temporary increase in the tonic activity of locus coeruleus (LC) causing a widespread release of norepinephrine which selectively interacts with high local glutamate levels (i.e., high-priority representations) in a positive feedback loop (see the GANE model, Mather et al., 2016). In our study, the assumption was that burst of tRNS entails a similar mechanism of action whose extent is hardly provable, although some explanations on the physiological impact of high frequency electrical bursts have been proposed, such as the stochastic resonance phenomenon (Benzi et al., 1981). In particular, the possibility that a signal-to-noise ratio of a non-linear system may increase or decrease depending on the level of injected noise has been extensively explored in several studies (Fertonani et al., 2011; Pavan et al., 2019; van der Groen and Wenderoth, 2016).

In relation to the different age-related effects of alertness, STAI-Y state scores revealed that the older were significantly more alerted than the younger participants, despite they showed comparable trait scores. It is known that a sustained LC tonic activity generally leads to a suppression of the phasic response (Aston-Jones and Cohen, 2005). Thus, our data on baseline SCR aligns well with this arousal-based prediction, indicating that the older participants were on average less phasically responsive during the baseline task. This finding seems to reconcile with the general decline of the physiological arousal response in the aging population (Barontini et al., 1997; Kisley et al., 2007) and also with the notion that older adults are less likely to show measurable SCRs (Gavazzeni et al., 2007)– e.g., non-responders – as compared to the young (Neiss et al., 2009). This discrepancy could be due to a physiological reduction of skin hydration with aging that makes it more resistant to electrical current (Barontini et al., 1997). However, our best-fitting model revealed that SCR of both age groups were unchanged with sham and greatly reduced with real stimulation, which contrasts with what we found in a previous study (Mauri et al., 2015), hence our results on SCR should be treated with caution and not used to draw firm conclusions.

Interestingly, an inverse linear correlation with the STAI-Y state scores across groups revealed that higher levels of alertness were overall associated with a worsening effect of tES, which is akin to a previously reported relationship with RT performance in young individuals (Mauri et al., 2015). We were able to appreciate an almost opposing pattern of results after splitting the two age groups into low and high subjective alertness: tES substantially improved memory retrieval for the more salient letters in the younger participants with lower alertness, while no effect emerged in those with higher alertness. The older participants, by contrast, confirmed their unimproved performance only in those with high alertness and showed a negligible improvement that was no different from sham in those with low alertness. Incidentally, older participants with low alertness performed better than the counterpart at retrieving low salient letters during sham, suggesting that memory of background or otherwise non-salient perceptual information may still improve without an arousing context (Mather et al., 2009).

This more comprehensive analysis suggests that, given a relatively moderate level of subjective alertness, tES application may act as a beneficial phasic response in young individuals, but it becomes detrimental in older individuals with a higher level of subjective alertness. The notion of a better cognitive performance in association with a moderate level of activation is long-known in the literature (Aston-Jones et al., 1999; Yerkes and Dodson, 1908). For example, in a recent paper on the responsiveness to tDCS as a function of STAI-Y scores we showed that performance improvement during real stimulation was more hindered as baseline alertness increased (Esposito et al. submitted for revision). It should be noted, though, that age-related differences in the neural substrate and motivational attitude could imply a different interpretation of subjective alertness measures. This is especially true in consideration of all the neurofunctional compensative models describing the specific neural recruitment necessary for different task loads and its finite resources as age advances and one's "cognitive reserve" (i.e., neuroprotection factors) diminishes (Martins et al., 2015). For example, older adults are known to willingly engage more resources than younger adults in the presence of a relatively demanding cognitive task (Ennis et al., 2013; Hess et al., 2016). This likely increased effort expenditure proved to be successful in the sham condition of the older but not in the younger participants. Moreover, assuming a functional integrity of the arousal system in the young population, the same might not be true for the older population whose neurotransmission mechanisms undergo critical changes (Robertson, 2013), which are also related to a variety of learning and memory performances (e.g., Rey Auditory Verbal Learning Test, Visual Face-Profession Encoding Task, Dahl et al., 2019; Reversal Learning Task, Hämmerer et al., 2018).

Apart from alertness, the effect of tES, and particularly tRNS, may vary between young and older individuals for several neurophysiological reasons, such as their different cortical connectivity and reactivity profiles (Fertonani et al., 2019). Notably, having used a fronto-occipital montage may have caused the high frequency bursts to interact predominantly with those frontal areas that undergo critical reorganizations through aging. According to the posterior-anterior shift in aging (PASA) model, healthy aging is accompanied by a higher activation of the prefrontal cortex to compensate for a decrease in occipital activity (Davis et al., 2008). Thus, a decreased performance may be partly due to the interference with frontal hyper activation which is distinctive of the older adults.

5. Conclusions

In conclusion, the overall objective of this study was to take into account the importance of alertness in cognition along with the normal aging process (Berridge and Waterhouse, 2003) while exploring the possibility of inducing alerting effects by means of tES so as to strengthen memory performance. The actual benefit of targeting specific alertness mechanisms is that of adding on other types of cognitive training in older adults (Van Vleet et al., 2016). Normal aging is affected by a decline in multiple areas of cognition and everyday activities, such as memory and skill learning (Salthouse, 2012), which likely depend on a decreasingly efficacious modulation of intrinsic alertness (McAvinue et al., 2012). While the end goal is to find viable tES protocols that ameliorate or otherwise reverse nonbeneficial effects of aging on cognition, it is also crucial to know why and in what cases tES-induced effects might worsen a given cognitive ability (Meinzer et al., 2013; Sandrini et al., 2020). We argue that baseline and ongoing levels of alertness is a major factor that should have more weight in future studies on healthy and pathological aging. This might be achieved by including more reliable physiological predictors e.g., pupillometry (Zhao et al., 2019) as well as measurements of distinctive connectivity changes (Fertonani et al., 2019) that are key to understand the neural mechanisms underlying the effects of any tES protocol.

Author contribution

Marco Esposito: Writing – original draft; Piercarlo Mauri: Methodology, Investigation, Formal analysis; Laura Panizza: Conceptualization, Methodology; Investigation, Formal analysis; Veronica Mazza: Supervision, Writing – review & editing; Carlo Miniussi: Supervision, Writing – review & editing, Visualization; Debora Brignani: Conceptualization, Methodology, Writing – original draft, Project administration.

Data statement

Raw data from this study will be available in anonymized form upon request from qualified investigators subject to the approval by the ethics committee of the IRCCS San Giovanni di Dio Fatebenefratelli Scientific Institute of Brescia, Italy.

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Declaration of competing interest

None.

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