



Right and left inferior frontal opercula are involved in discriminating angry and sad facial expressions

Igor Iarrobino^{a, b, 1}, Alessandro Bongiardina^{a, 1}, Olga Dal Monte^{a, c}, Pietro Sarasso^a, Irene Ronga^a, Marco Neppi-Modona^a, Rossana Actis-Grosso^{d, e}, Adriana Salatino^a, Raffaella Ricci^{a, *}

^a Psychology Department, University of Turin, Torino, Italy

^b Institute of Neuroscience, Université Catholique de Louvain, Woluwe-Saint-Lambert, Bruxelles, Belgium

^c Psychology Department, Yale University, New Haven, CT, USA

^d Psychology Department, University Milano-Bicocca, Milano, Italy

^e NeuroMi, Milan Center for Neuroscience, Milano, Italy

ARTICLE INFO

Article history:

Received 2 October 2020

Received in revised form

21 February 2021

Accepted 23 March 2021

Available online 27 March 2021

Keywords:

Emotion

Facial expressions

Emotion discrimination

Inferior frontal gyrus

Inferior frontal operculum

Transcranial direct current stimulation

Arousal hypothesis

Angry

Sadness

ABSTRACT

Background: Neuroimaging studies suggest that the inferior frontal operculum (IFO) is part of a neuronal network involved in facial expression processing, but the causal role of this region in emotional face discrimination remains elusive.

Objective: We used cathodal (inhibitory) tDCS to test whether right (r-IFO) and left (l-IFO) IFO play a role in discriminating basic facial emotions in healthy volunteers. Specifically, we tested if the two sites are selectively involved in the processing of facial expressions conveying high or low arousal emotions. Based on the Arousal Hypothesis we expected to find a modulation of high and low arousal emotions by cathodal tDCS of the r-IFO and the l-IFO, respectively.

Methods: First, we validated an Emotional Faces Discrimination Task (EFDt). Then, we targeted the r-IFO and the l-IFO with cathodal tDCS (i.e. the cathode was placed over the right or left IFO, while the anode was placed over the contralateral supraorbital area) during facial emotions discrimination on the EFDt. Non-active (i.e. sham) tDCS was a control condition.

Results: Overall, participants manifested the “happy face advantage”. Interestingly, tDCS to r-IFO enhanced discrimination of faces expressing anger (a high arousal emotion), whereas, tDCS to l-IFO decreased discrimination of faces expressing sadness (a low arousal emotion).

Conclusions: Our findings revealed a differential causal role of r-IFO and l-IFO in the discrimination of specific high and low arousal emotions. Crucially, these results suggest that cathodal tDCS might reduce the neural noise triggered by facial emotions, improving discrimination of high arousal emotions but disrupting discrimination of low arousal emotions. These findings offer new insights for treating clinical population with deficits in processing facial expressions.

© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The ability to recognize emotions in other people's faces is a complex process involving a bilateral fronto-temporo-limbic network [1,2]. Lesion studies have provided evidence that the inferior frontal gyrus (IFG), and particularly area 44, belongs to a

phylogenetically early emotional contagion system that operates on emotional empathy and emotion recognition [3–5]. Neuroimaging findings also suggested that the inferior frontal operculum (IFO) - i.e. a transition zone between the anterior insula and the frontal operculum - is part of a neuronal network subserving processing of emotional facial expressions [6–9]. Nonetheless, the causal role of IFO and putative hemispheric differences of this specific region in facial emotion recognition remain largely unknown.

Transcranial electrical stimulation has been recently used to probe the involvement of other frontal regions in emotional processing, although reporting partially contrasting results. Some

* Corresponding author. Via Verdi 10, 10124, Turin, Italy.

E-mail address: raffaella.ricci@unito.it (R. Ricci).

¹ Contributed equally to this work.

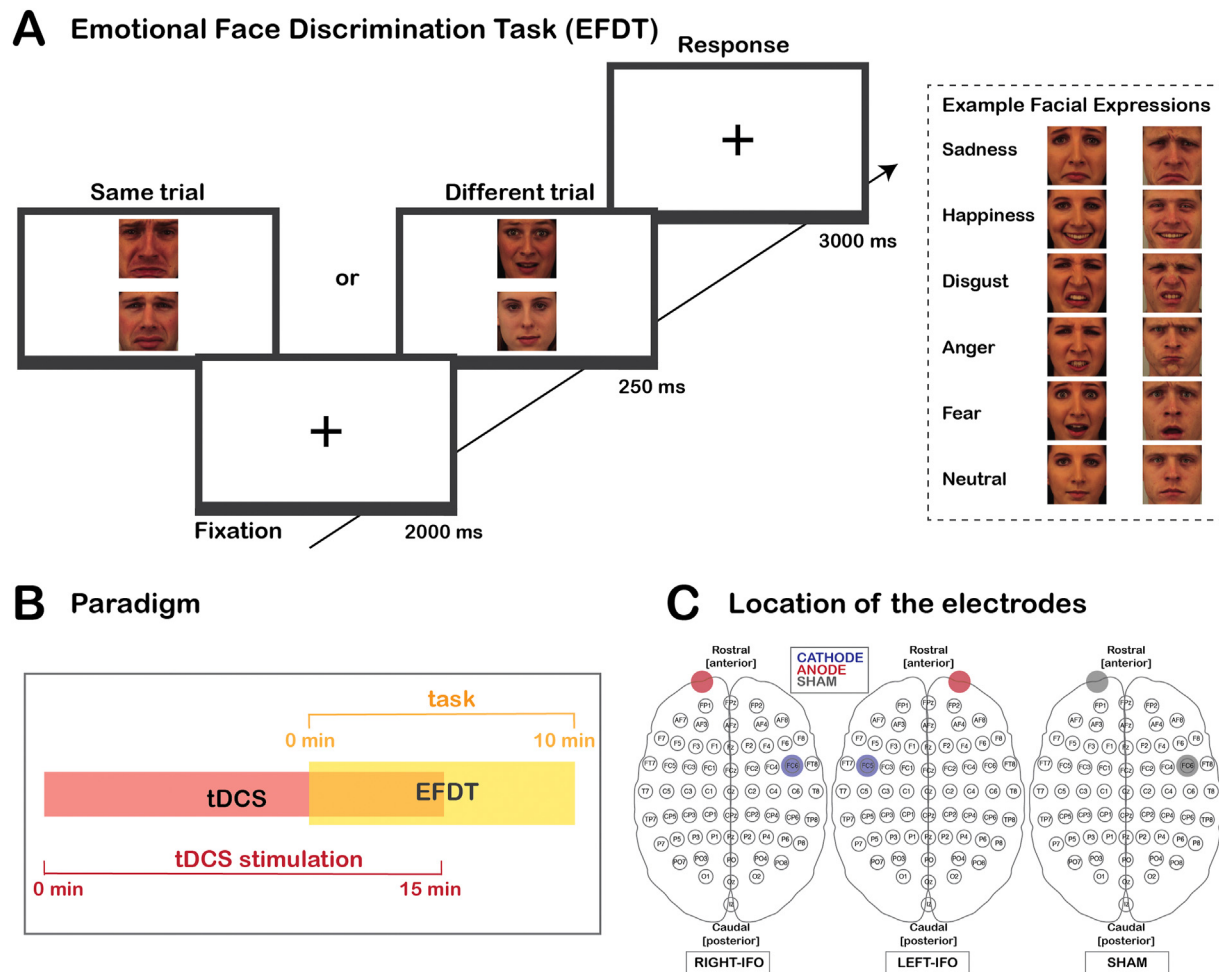


Fig. 1. Task and Paradigm. (A) Emotion Face Discrimination Task (EFDT). Participants faced a computer monitor on which fixation targets and facial expressions were shown. After holding central fixation for 2000 ms, two visual stimuli in a vertical position were presented for 250 ms followed by a 3000 ms fixation where subjects were asked to report, using the computer board, whether the two faces expressed the same or a different emotion. The EFDT had two types of trials: *same emotion and different emotion* condition. On the right are female and male examples of the six different expressions presented: sadness, happiness, disgust, anger, fear, neutral. Emotional face stimuli were taken from the K-DEF inventory. (B) Experiment 2 paradigm. TDCS was administered for 15 min. Participants started the EFDT task 10 min after the beginning of tDCS. The task was carried out for the first 5 min during brain stimulation and for the last 5 min without stimulation. (C) Location of the electrodes in the three transcranial direct current stimulation (tDCS) conditions; right-IFO (left panel), left-IFO (middle panel), and sham mode (right panel). The blue circle indicates a cathode. The red circle indicates an anode. The grey circle indicates sham stimulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

studies showed improvement in emotion recognition when anodal (excitatory) transcranial direct current stimulation (tDCS) was applied to the right orbitofrontal cortex [10] or to the right dorsolateral prefrontal cortex (DLPFC) [10,11], whereas others showed emotion recognition improvement when anodal tDCS was applied to the left DLPFC [12]. On the contrary, both tDCS [13] and high-frequency transcranial random noise stimulation (which usually facilitates task performance) [14] applied to the bilateral DLPFC were not found to influence emotional processing. To the best of our knowledge, only two transcranial electrical stimulation studies investigated the causal role of IFG in facial expression processing. Penton and colleagues [15] found a general higher performance in facial emotion recognition when high-frequency transcranial random noise stimulation was applied to bilateral IFG, but they did not analyse the effect of brain stimulation on the different types of emotion (due to the low number of trials per type of emotion). On the other hand, Yang and Banissy [16] showed enhanced perception of anger but not happiness, after applying high-frequency transcranial random noise stimulation to bilateral IFG in older adults.

However, bilateral stimulation does not allow to disentangle the specific contribution of right and left IFG.

Previous findings have suggested possible hemispheric asymmetries in emotional processing [17]. Some theories have proposed a right hemisphere specialization for emotional processing (i.e., the Right Hemisphere Hypothesis) [17–19]. Others [20–22] have claimed that hemispheric lateralization depends on the emotional valence (i.e., the Valence Hypothesis), with the involvement of the right or left hemisphere in decoding unpleasant or pleasant emotions, respectively [23]. Along similar lines, the Arousal Hypothesis has classified emotions based on high (e.g., anger, fear and happiness) and low (e.g., sadness and disgust) arousal [17,24,25] proposing the involvement of the right hemisphere for processing high arousal emotions and of the left hemisphere for low arousal emotions. Consistent with this hypothesis, EEG findings have revealed that facial expressions are distinguished between 200 and 320 ms as a function of arousal or the degree of affective and motivational activation, as indexed by differences in N2 and EPN components

between happy and angry faces versus fearful, sad, and neutral faces [26].

In the current study, we directly investigated the causal role of IFO and putative hemispheric differences of this specific region in facial emotion recognition by applying cathodal tDCS to right (r-IFO) and left IFO (l-IFO) in different groups of healthy volunteers while they were performing an ad-hoc designed emotion discrimination protocol, the Emotional Faces Discrimination Task (EFDT). During this task participants were asked to judge whether pairs of faces expressed same or different emotions. Facial expressions comprised high and low arousal emotions. We used cathodal stimulation because, differently from anodal tDCS or high-frequency transcranial random noise stimulation (which enhance cortical excitability), it reduces cortical excitability [e.g., 27, 28] and inhibition of local activity can be used to test the causal involvement of a specific region in the execution of a cognitive task [29,30].

In experiment 1, we tested and validated the EFDT paradigm. In experiment 2, we used the EFDT to investigate the causal role of the r-IFO and the l-IFO in discriminating high and low arousal emotions. Based on the Arousal Hypothesis we expected to find a modulation in discriminating high arousal emotions, when tDCS was applied to the r-IFO and of low arousal emotions by tDCS to l-IFO. We critically aimed to investigate whether cathodal (inhibitory) tDCS applied to the r-IFO modulated discrimination of all high arousal emotions or instead it only affected specific expressions. Similarly, we wanted to understand the specific impact of cathodal tDCS applied to the l-IFO on low arousal emotions. Sham tDCS was also applied to r-IFO as control condition.

In relation to cathodal polarity, we expected different possible outcomes. Reduction of brain activity by inhibitory cathodal tDCS might disrupt discrimination of all facial expressions encoded by the stimulated site, as predicted by the 'virtual lesion' approach [29,30]. Alternatively, cathodal tDCS might diminish the neural noise triggered by the facial emotion, as suggested by previous findings [7,31]. For example, Klimm and colleagues [7] using Near Infrared Spectroscopy, showed that a reduction of excitability in the left IFG by cathodal tDCS facilitates emotion recognition on the 'Reading the Mind in the Eyes' test. The authors proposed that inhibitory tDCS might reduce the neural noise facilitating signal detection. In this case, the behavioural outcome might depend on the interaction between the tDCS inhibitory effect, and the arousal level triggered by a specific emotion. Cathodal tDCS reduction of neural activity might, on one hand, enhance discrimination of high arousal emotions and, on the other hand, disrupt the processing of low arousal emotions, by further reducing low-level neural excitability.

Finally, since the current evidence suggests that acute and after-effects of tDCS involve different mechanisms (i.e., the acute effects would derive from the modulation of membrane potential, while the after-effects would involve synaptic plasticity, see for example 28, 32, 33), we investigated tDCS effects during and after the application of brain stimulation. Despite neurophysiological studies have shown the persistence of tDCS effects when the current is switched off on cortical excitability (as measured, for example, by transcranial magnetic stimulation [27,28]), findings of tDCS after-effects on healthy individuals' performance are less consistent [29,34]. This difference is likely explained by greater sensitivity of neurophysiological assessment in detecting cortical excitability changes induced by tDCS compared to the sensitivity of behavioral measures in detecting cognitive changes consequent to modulation of cortical excitability. Based on this evidence, we expected to observe tDCS effects on the EFDT during brain stimulation and explored the putative presence of tDCS after-effects on this task.

Materials and methods

Experiment 1

Participants

Sixteen healthy graduate students (9 males; mean age = 24.6 ± 2.7), recruited from the University of Turin, participated in the study. All subjects gave their written informed consent to participate in this study, which was approved by the Ethics Committee of the University of Turin (#23996). Subjects did not receive any monetary compensation for their participation.

Emotional faces discrimination task

In the present experiment, the Emotional Faces Discrimination Task (EFDT) was implemented and tested (Fig. 1a). This new protocol was designed to allow modulation of healthy participants' ability to discriminate emotional facial expressions by non-invasive brain stimulation. On the basis of previous studies, using non-invasive brain stimulation techniques to assess the causal involvement of a specific brain region in a cognitive function [30,31,35], we designed and piloted a relatively challenging discrimination task that, by avoiding ceiling effects, allowed modulation of healthy young participants' performance [29,31]. To this end, pairs of male or female faces, expressing different or same emotions (Karolinska Directed Emotional Faces [37]), were briefly presented (Exposure Time: 250 ms) along the vertical axis in random order. Six different faces (3 females) depicted the five basic facial emotions: sadness, happiness, disgust, anger, fear. A neutral facial expression was also employed. Identities of the coupled faces came from different actors. Actors composing each pair could be only females (28.5%), only males (28.5%) or a female and a male (mixed, 43%). Each pair of faces was presented twice with inverted spatial position of faces (i.e. the face that was at the top in one stimulus was at the bottom in the second one). Each face image was 8.73 cm high and 6.44 cm wide. Faces were aligned along the vertical axis to avoid putative effect of lateralized brain stimulation on specific spatial locations along the horizontal axis [31; but also see 35, 36]. Before the beginning of data collection each participant went through a training session. We used 32 pairs of stimuli to familiarize the subject with the task. The EFDT had two conditions: *same emotion* and *different emotion*. In the *same emotion* condition two identical emotions were presented to the participant whereas in the *different emotion* condition a neutral face was paired with one of the five emotions. The experimental task comprised 192 pairs of faces: 72 pairs were used for the *same emotion* condition, and 120 pairs for the *different emotion* condition. Participants sat at 55 cm from the computer monitor and were asked to use a computer board, using the index and middle finger, to report as fast and as accurately as possible whether the two faces expressed the same or a different emotion. The two task conditions were presented in a random order. The EFDT was programmed and implemented in E-prime 2.0 software (Psychology Software Tools, Inc., Sharpsburg, PA). The experimental task lasted about 10 min.

Statistical analysis

In this first experiment we examined whether the accuracy (dependent variable) was affected by the within-subjects factors *Task* (two levels: *same* and *different emotion* conditions) and *Emotion* (five levels: *sadness*, *happiness*, *disgust*, *anger*, and *fear*). Second, we investigated whether the reaction times (RTs) (dependent variable) were affected by the within-subjects factors *Task* and *Emotion*. We ran two independent ANOVAs, one for accuracy and one for RTs, and paired samples t-tests (with Bonferroni correction) were used for *post-hoc* comparisons.

Experiment 2

Participants

Fifty-four healthy graduate students were recruited from the University of Turin for this second experiment. Contraindications to a safe use of tDCS were assessed [38]. Participants were randomly assigned to one of three different tDCS conditions: cathodal tDCS to r-IFO (r-tDCS), cathodal tDCS to l-IFO (l-tDCS), sham tDCS to r-IFO (r-Sham). They were blind to the type of stimulation they received (i.e., active versus sham) and naïve to the tDCS technique. One participant assigned to the l-tDCS condition withdrew from the study because of personal time constraints. Hence, the final sample size of the three groups was as follows: r-tDCS group, $N = 18$ (9 males); l-tDCS group, $N = 17$ (7 males); r-Sham group, $N = 18$ (7 males). The three groups did not differ for age (r-tDCS group: mean = 25.4 ± 1.5 ; l-tDCS group: mean = 24.5 ± 2.3 ; r-Sham group, mean = 25.2 ± 2.2) as assessed by a one-way ANOVA [$F_{2, 52} = 0.766$, $p = 0.470$]. All subjects gave their written informed consent to participate in the study, which was approved by the Ethics Committee of the University of Turin. They did not receive any monetary compensation for their participation.

Procedure

The procedures and the task (EFDT) were the same of Experiment 1 with the addition of tDCS. All participants underwent a training session before the beginning of the experimental session. The tDCS was administered for 15 min (min). After 10 min of tDCS, the participants started the EFDT that lasted about 10 min. Thus, the task was carried out for the first 5 min during brain stimulation and for the last 5 min without stimulation (Fig. 1b). This design allowed us to investigate whether there was an effect on EFDT during the stimulation and putative after-effects following the stimulation.

Transcranial direct current stimulation

Transcranial Direct Current Stimulation (tDCS) is a portable device which uses a constant low-intensity current (between 1 and 2 mA) delivered directly to the cortex via surface electrode pads with an anode and a cathode [38,39]. In this study, a battery-powered tDCS stimulator (HDC stim, HDC kit, Magstim Company Limited, Whitland, Wales, UK) delivered constant current at 2 mA for 15 min (30 s ramp-up time) through a pair of saline-soaked sponge electrodes ($5 \times 5 \text{ cm}^2$). Current density was therefore 0.08 mA/cm^2 . The sites of stimulation (Fig. 1c) corresponded to FC6 [40] in the right hemisphere (placed at 1/3 of the distance between F8 and C6, on the standard 10/20 system EEG system) and FC5 in left hemisphere (placed at 1/3 of the distance between F7 and C5). In the r-tDCS group and in the l-tDCS group, the cathode electrode was placed over the right or left IFO, respectively, while the anode electrode was placed over the contralateral supraorbital area. In the r-Sham group, the cathode electrode was placed over the right IFO, while the anode electrode was placed over the contralateral supraorbital area. For this group the current was turned off 30 s after the beginning of the stimulation. This procedure allowed subjects to feel the itching sensation below the electrodes at the beginning of the stimulation, making it difficult for naïve subjects to distinguish sham from real stimulation. Participants were blind to the experimental condition (i.e. active or sham), but the experimenter was not.

Statistical analysis

Given the evidence that primary acute effects of tDCS derive from a modulation of membrane potential, while the after-effects involve synaptic plasticity [32], we analyzed the influence of the type of stimulation during tDCS and then we explored the possible

presence of tDCS after-effects. For both online and offline performance we examined whether the accuracy and the RTs (dependent variables) were affected by the between-subjects factor *Stimulation* (three levels: *r-tDCS*, *l-tDCS*, *r-sham*) and the within-subjects factors *Task* (two levels: *same* and *different emotion* conditions) and *Emotion* (five levels: *sadness*, *happiness*, *disgust*, *anger*, and *fear*). We ran independent repeated measures ANOVAs for accuracy and for RTs. Paired samples t-tests (with Bonferroni correction) were used as post-hoc analyses. LSD was used for between-subjects post-hoc analyses.

Results

Experiment 1

We started by investigating whether *Emotion* (*sadness*, *happiness*, *disgust*, *anger* and *fear*) and *Task* (*same* or *different emotion* condition) influenced the accuracy of the EFDT. Overall, we found a main effect of *Emotion* ($F_{4, 60} = 10.173$, $p < 0.0001$, partial $\eta^2 = 0.404$, power = 1.000) and a significant interaction *Task* by *Emotion* ($F_{4, 60} = 7.495$, $p < 0.0001$, partial $\eta^2 = 0.333$, power = 0.995). Post-hoc analyses for the factor *Emotion* showed higher accuracy for *happiness* (Mean = $77\% \pm 11\%$) compared to *disgust* (Mean = $65\% \pm 16\%$; $p = 0.005$), *fear* (Mean = $62\% \pm 16\%$; $p = 0.001$), and *sadness* (Mean = $53\% \pm 13\%$; $p < 0.0001$), while the difference with *anger* (Mean = $62\% \pm 22\%$; $p = 0.008$), did not reach a significant value after Bonferroni correction. Additionally, our participants were more accurate to discriminate *disgust* compared to *sadness* ($p = 0.005$) (Fig. 2a). In order to analyse the interaction *Task* by *Emotion* we performed paired samples t-tests comparing the two types of *Task* (*same* and *different emotions* condition) for each of the five emotions. We found that participants were more accurate in discriminating *happiness* ($p = 0.002$) when both stimuli presented were happy faces (*same emotions* condition) compared to when one was a neutral expression (*different emotions* condition). We did not find any other significant comparisons among all the other emotions (all $p > 0.05$, Bonferroni corrected) (Fig. 2b).

We also investigated how quickly the participants discriminated emotions. Consistent with the effects reported for the accuracy we found a main effect of *Emotion* ($F_{4, 60} = 4.335$, $p = 0.004$, partial $\eta^2 = 0.224$, power = 0.912) and a significant interaction *Task* by *Emotion* ($F_{4, 60} = 10.194$, $p < 0.0001$, partial $\eta^2 = 0.405$, power = 1.000). Post-hoc analyses (paired-samples t-tests) for the factor *Emotion* showed faster RTs ($p = 0.003$) for *happiness* (Mean = 819.347 ± 212.699) compared to *sadness* (Mean = 940.412 ± 229.669) (Fig. 2c). No other comparisons were significant after Bonferroni correction (all $p > 0.05$). In order to analyse the interaction *Task* by *Emotion* we performed paired samples t-tests comparing *same* and *different emotions* conditions for each of the five emotions. We found that participants were faster in discriminating *happiness* ($p < 0.001$) when both stimuli presented were happy faces (*same emotions* condition) than when one of them was a neutral expression (*different emotions* condition) (Fig. 2d). We did not find any other significant difference among all the other emotions (all $p > 0.05$).

Experiment 2

To investigate whether the type of stimulation during online tDCS affected accuracy, we quantified the participants' performance on the EFDT based on the type of applied stimulation. The ANOVAs with *Task* (*same* and *different emotions* condition) and *Emotion* (*sadness*, *happiness*, *disgust*, *anger*, and *fear*) as within-subjects factors and *Stimulation* (*l-tDCS*; *r-tDCS*; *r-Sham*) as a between-subjects factor showed a significant main effect of

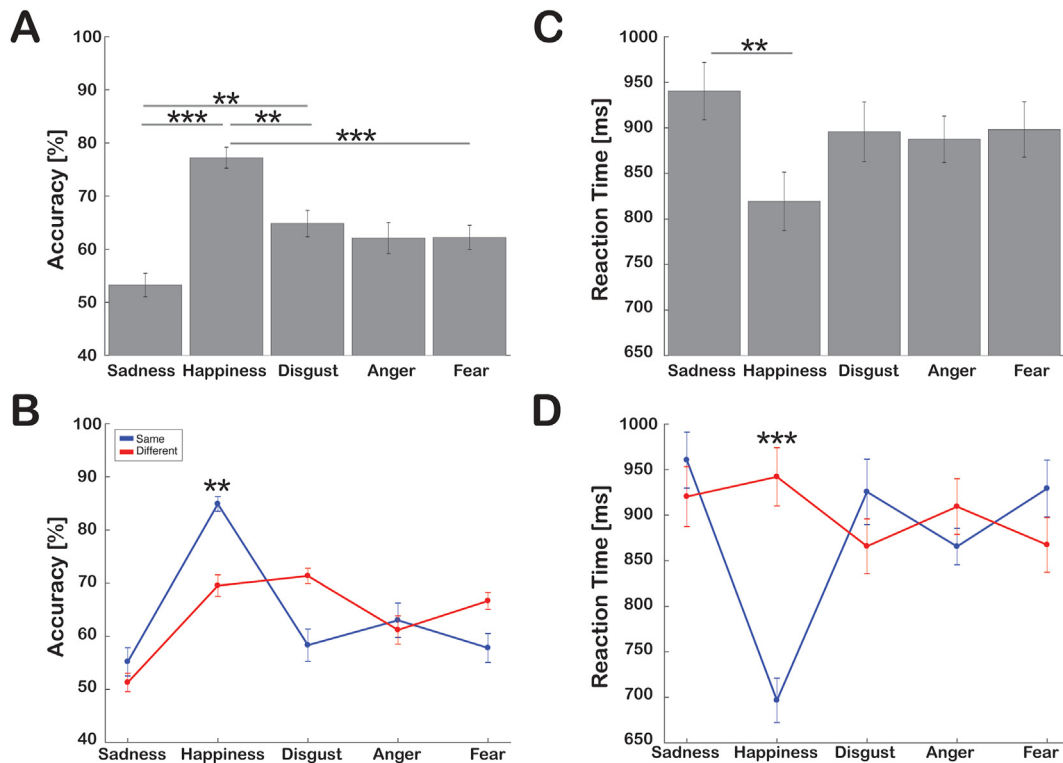


Fig. 2. EFDT Accuracy and Reaction Time. (A) Values shown are the mean percentage \pm SEM ($n = 16$) of successful emotion discrimination for Sadness, Happiness, Disgust, Anger, and Fear. (B) Emotion discrimination accuracy as a function of task condition (Same vs. Different condition). Values shown are the mean percentage \pm SEM. (C) Values shown are the mean reaction time \pm SEM of successful emotion discrimination for Sadness, Happiness, Disgust, Anger, and Fear. (D) Values shown are the mean reaction time \pm SEM of successful emotion discrimination for Sadness, Happiness, Disgust, Anger, and Fear as a function of task condition (Same vs. Different condition). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Emotion ($F_{4, 200} = 27.898$, $p < 0.0001$, partial $\eta^2 = 0.358$, power = 1.000), and a significant interaction *Emotion by Stimulation* ($F_{8, 200} = 2.006$; $p = 0.047$, partial $\eta^2 = 0.074$, power = 0.813).

In order to explore the interaction *Emotion by Stimulation* (Fig. 3), five separate one-way ANOVAs comparing differences between *Stimulation* (*l-tDCS*; *r-tDCS*; *r-Sham*) for each *Emotion* (*sadness*, *happiness*, *disgust*, *anger* and *fear*) were carried-out. Results showed a significant effect of *Stimulation* for *sadness* ($F_{2, 50} = 5.291$; $p = 0.008$) and *anger* ($F_{2, 50} = 4.797$; $p = 0.012$) (Fig. 3a and b). The *Stimulation* did not affect the performance for other emotions (all $p > 0.05$) (Fig. 3c–e). For *sadness* we found that stimulation of the left IFO (*l-tDCS*) compared to the sham condition (*r-Sham*; $p = 0.049$) significantly decreased participant's discrimination accuracy for sad expressions. Crucially, the *l-tDCS* reduced subjects' performance also compared to the *r-tDCS* ($p = 0.002$). On the other hand, stimulation of the right IFO (*r-tDCS*) significantly increased the participant's performance in discriminating *anger* compared to the sham condition (*r-Sham*; $p = 0.003$). Interestingly, also the *l-tDCS* resulted in a better accuracy for angry expressions compared to the sham (Fig. 3b). Although this difference was present numerically, it did not reach the significance level ($p = 0.064$).

To investigate possible after-effects of the different types of tDCS on accuracy, we quantified the participants' performance on the EFDT based on the type of stimulation they just received. The ANOVA with *Task* (*same and different emotions condition*) and *Emotion* (*sadness*, *happiness*, *disgust*, *anger*, and *fear*) as within-subjects factors and *Stimulation* (*l-tDCS*; *r-tDCS*; *r-Sham*) as a between-subjects factor showed a significant main effect of *Emotion* ($F_{4, 200} = 39.980$; $p < 0.0001$, partial $\eta^2 = 0.444$, power = 1.0) and interaction *Task by Emotion* ($F_{4, 200} = 17.294$; $p < 0.0001$, partial $\eta^2 = 0.257$, power = 1.0). However, the

interaction *Emotion by Stimulation* was not significant ($F_{8, 200} = 0.440$; $p = 0.896$, partial $\eta^2 = 0.017$, power = 0.203).

To summarize, the results showed that only online stimulation affected the participant's performance to the EFDT in line with previous findings in healthy individuals [29].

We also explored whether acute, online tDCS had any effect on how quickly the participants discriminated emotions. The ANOVA with *Task* (*same and different emotion conditions*) and *Emotion* (*sadness*, *happiness*, *disgust*, *anger*, *fear*) as within-subject factors and *Stimulation* (*l-tDCS*; *r-tDCS*; *r-Sham*) as a between-subjects factor did not show any significant result. When analyzing tDCS after-effects the ANOVA showed a significant effect of *Task* ($F_{1, 52} = 6.260$; $p = 0.016$, partial $\eta^2 = 0.111$, power = 0.689), *Emotion* ($F_{4, 208} = 2.820$; $p = 0.026$, partial $\eta^2 = 0.053$, power = 0.763), and a significant interaction *Task by Emotion* ($F_{4, 208} = 2.772$, $p = 0.028$, partial $\eta^2 = 0.053$, power = 0.755).

Discussion

Neuroimaging studies have been extremely helpful to inform our community about a wide fronto-temporo-parietal network [6–9,41] implicated in face processing and emotion recognition. Guided by these findings, in our study we aimed to investigate the causal contribution of the IFO in discriminating high and low arousal emotions. Here, we aimed to solve this puzzle by applying cathodal inhibitory tDCS to the right and left IFO while participants took part in an emotion discrimination task. Our study complements the functional neuroimaging evidence by suggesting a crucial role of the IFO in emotion discrimination.

In the first experiment we tested the ability to discriminate five basic facial emotions using the EFDT and, in agreement with the

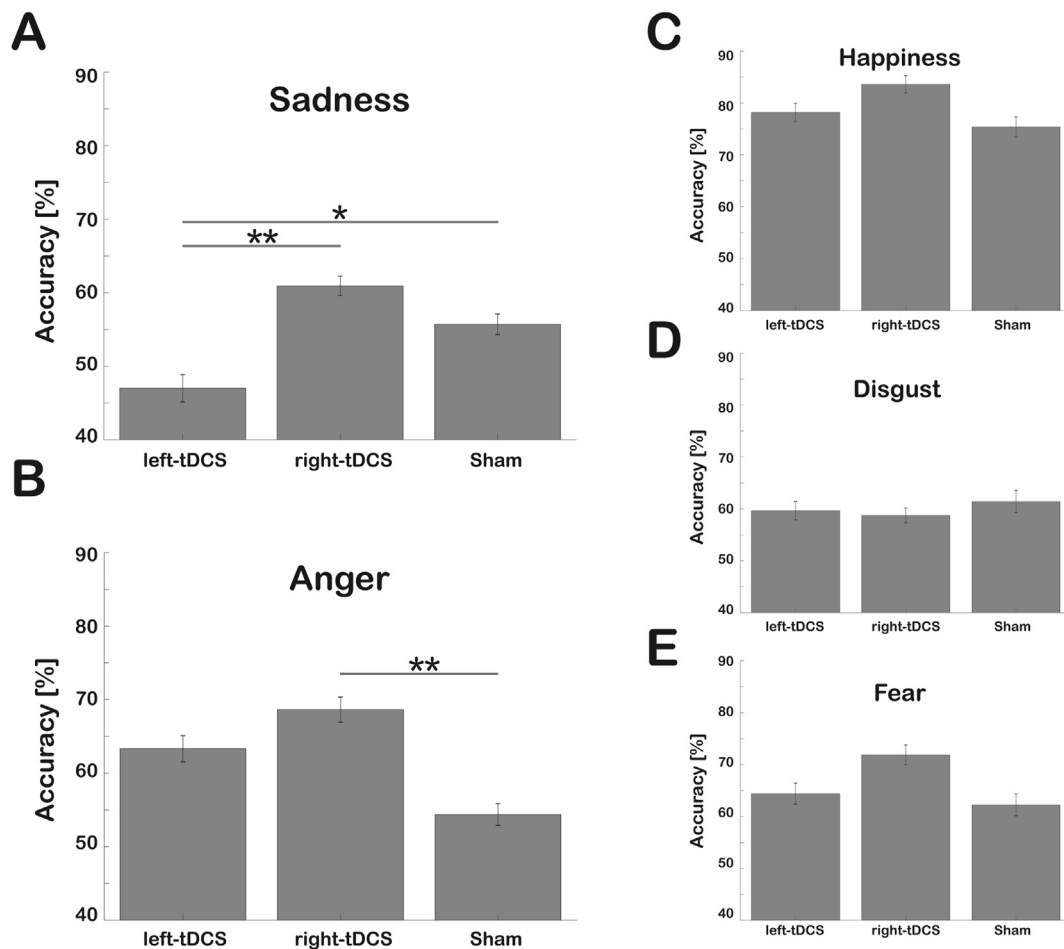


Fig. 3. Emotion discrimination accuracy as a function of (online) brain stimulation conditions. Values show the mean percentage \pm SEM of successful emotion discrimination for Sadness (A), Anger (B), Happiness (C), Disgust (D) and Fear (E). Participants were randomly assigned to one of three different tDCS conditions: left-tDCS ($n = 17$), right-tDCS ($n = 18$), and sham ($n = 18$). * $p < 0.05$, ** $p < 0.01$.

previous literature, we found a gradient in participants' discrimination accuracy [17,42–45]. They manifested the “happy face advantage” – i.e. happy faces were easier to discriminate than other expressions [42–45]. It has been proposed that happiness is easier to discriminate compared to the other emotions because it entails a superordinate category, while the other (negative valence) emotions would represent more subordinate categories of the superordinate category ‘unhappy’, resulting therefore more confusable with one another than with happiness [17].

In Experiment 2, participants showed an overall analogous performance (i.e. the ‘happy face advantage’). In relation to the main goal of this study, cathodal tDCS to both right and left IFO modulated EFDT performance in a direction that was consistent with the Arousal Hypothesis (high/low arousal emotions are processed by the right/left hemisphere, respectively). Cathodal tDCS applied to r-IFO affected recognition of a high arousal emotion (i.e. anger), while cathodal tDCS applied to l-IFO modulated recognition of a low arousal emotion (i.e. sadness). However, we also found a selective effect for distinct facial emotions. Brain stimulation of r-IFO only affected anger, while stimulation of l-IFO mainly affected sadness. Interestingly, cathodal (inhibitory) tDCS produced opposite outcomes on the two types of emotions, improving anger (when applied to r-IFO), while disrupting sadness (when applied to l-IFO).

These opposite outcomes might be interpreted in light of previous findings suggesting that cathodal tDCS may affect subjects'

performance via reduction of the neural noise triggered by the visual stimulus [7,31]. In particular a previous investigation [7], applying cathodal tDCS to left IFG using a protocol similar to ours, observed emotion recognition facilitation in association with reduced excitability at the site of stimulation, as measured through fNIRS. In our study, neural noise reduction may likely account for the opposite effects observed on high and low arousal emotions. Inhibitory tDCS might have reduced the arousal level induced by facial expressions specifically processed in right and/or left IFO, facilitating encoding of the high arousal emotion (i.e. anger) and, on the opposite, decreasing encoding of the low-arousal emotion (i.e. sadness). These findings indicate that the effects of cathodal tDCS applied to IFO not only depend on hemispheric lateralization but also on the arousal level triggered by the specific emotion encoded by the stimulated site.

Overall, the outcomes of our study are in line with the polarity of brain stimulation interventions targeting the DLPFC to treat mood disorders [46,47]. DLPFC is a region functionally connected to IFG [48]. It is well established that excitatory brain stimulation of left DLPFC and/or inhibitory brain stimulation of right DLPFC [49] are effective in treating depression and other mood disorders, manifesting among other symptoms, deficits in facial emotional perception [12]. However, these studies focus on dorsal regions of the prefrontal cortex. Our data are in line with previous findings [14,15] suggesting potential modulatory effects by transcranial electrical stimulation when targeting more ventral regions offering

therefore new possibilities for treatment of mood disorders manifesting specific deficits (i.e. anger and sadness) of facial emotion processing.

The ability to recognize other people's facial expressions is critical for effective social communication and behavioural regulation [50]. The devastating social consequences of a disruption of this ability have been observed in a wide range of clinical populations, including schizophrenia [51], psychopathy [52], autism spectrum disorder [53], and acquired brain injury [54]. In addition, impaired emotional faces perception is also observed in multiple [55,56] and amyotrophic lateral [57] sclerosis. Finally, the involvement of IFG has been reported in several brain pathologies, such as alexithymia [58], panic and post-traumatic stress [59], depression [60], eating [61] and anxiety [62] disorders.

Here we provide evidence that caudal regions of left and right IFG are specifically dedicated to sadness and anger encoding. Dysregulation of the activity of these specific regions might play a role in mediating encoding of anger and sadness from other people's face, in many of the above disorders. Neuromodulation possibilities offered by stimulation of this specific sites warrant further in-depth investigations. For example, future studies in healthy participants are necessary to understand whether the use of an opposite (anodal) tDCS polarity applied to right and left IFO might reverse the observed effects for anger and sadness and whether it might also affect other types of emotions. This information may be relevant to tailor tDCS treatments of brain disorders. Additionally, given the extensive literature about both the anatomical brain differences and the different ability between males and females to recognize and discriminate facial expressions [41,63] future studies should investigate whether the tDCS effects might vary as a function of gender. Research over the last years has also focused on age differences in facial emotion discrimination and recognition [64]. Given that older adults are worse at recognizing anger, sadness, and fear [65,66] it would be crucial to test our protocol in elderly population to investigate whether tDCS could impact especially the discrimination of those emotions. Finally, future studies should focus on targeting clinical populations such as patients with depression [67] and with frontotemporal dementia [68] given the well know impairment in emotion perception in these subjects.

In order to extend these research findings to clinical population the possibility to induce behavioral changes outlasting the period of stimulation becomes crucial. In our study, the absence of tDCS after-effects was likely due to the use of a single, relatively short, session of stimulation which was applied to young healthy individuals. Effective non-invasive brain stimulation treatments generally induce brain plasticity changes [33] leading to improved clinical outcomes when using long durations (up to 30 min) and repeated applications (a minimum of 5 applications in pilot experimental studies, to a minimum of 10 sessions in clinical trials). Future studies in patients with impairment in emotion perception are needed to verify whether repeated sessions (3–5) of cathodal tDCS applied to IFO for longer duration (20–30 min) might be suitable to produce beneficial after-effect outlasting the period of stimulation.

The present study has a series of limitations. The first limitation is the lack of a control active site of stimulation. However, we tested tDCS effects of right IFO on high arousal emotions and of left IFO on low arousal emotions, and findings were partially in line with our predictions. Furthermore, no changes occurred during sham stimulation. Other limitations consisted in the lack of procedures suitable to assess the level of arousal triggered by each emotion [69,70] and the lack of high and low arousal positive valence facial emotions [71]. Both aspects would have represented a valid test to unambiguously verify the Arousal Hypothesis. Indeed, they would have helped to disambiguate whether the observed effects are

purely accounted for by the *level* of the arousal triggered by the facial emotion independently of its negative or positive valence. As reported above, although our findings are in line with the Arousal Hypothesis, they clearly show selective effects by cathodal tDCS on specific negative valence emotions (i.e., only sadness and anger were modulated by cathodal tDCS of IFO), making unlikely the possibility that they are exclusively accounted for by the arousal level induced by a facial (negative valence) emotion. In line with this hypothesis, we did not observe any modulation of happiness by tDCS, although we cannot exclude that this result might be explained by ceiling effects, given the high accuracy demonstrated by participants in discriminating happy faces and the expectation of increased accuracy in correspondence of cathodal tDCS targeting the right IFO.

Future studies using the same or similar tasks shall be performed to investigate whether tDCS effects observed in this study are specific of left and right IFO or might also be induced by stimulation of anatomically contiguous or functionally connected areas, belonging to the same emotion network. In addition, the use of more (challenging) sensitive tasks (for example, using shorter exposure time or degraded visual stimuli) foreseeing procedures to assess the arousal level triggered by the specific emotion - for example, a subjective Lickert scale [69] or the skin conductance response [70] - and comprising high and low positive arousal emotions [71] might uncover subtle modulatory tDCS effects on the arousal level triggered by negative and positive emotions, that in our study might have been hidden by ceiling effects (see for example happiness).

Conclusions

This study provides evidence for the causal involvement of right and left IFO in discriminating angry and sad facial expressions. Importantly, here we demonstrated for the first time the relevance of the arousal level implicated by a specific emotion in determining the behavioural outcome of cathodal tDCS application. These findings are crucial for our understanding of the network and mechanisms underlying facial emotion discrimination, but also advocate the use of tDCS as a promising neurostimulation tool for addressing clinically significant emotion recognition deficits in a wide range of patients.

Credit author statement

I.I., A.B., A.S., R.R. coordinated the study. R.R., I.I., A.B., A.S., P.S., R.A.G. designed the study. I.I., A.B., P.S., I.R. performed the experiments. O.D.M., A.S., R.R. supervised data analyses. I.I., A.B., P.S., I.R. analyzed the data, R.R., O.D.M., I.I., A.B. wrote the manuscript, R.A.G., M.N.M., I.R., P.S., A.S. critically reviewed the manuscript; all authors approved the final version of the manuscript; R.R. obtained funding designed to the study.

Declaration of competing interest

None.

Acknowledgements

Funding source: This work was supported by MIUR (RICR_RILO_17_01, RICR_RILO_18_02) grants to RR.

References

- [1] Dal Monte O, Krueger F, Solomon JM, Schintu S, Knutson KM, Strenziok M, Pardini M, Leopold A, Raymont V, Grafman J. A voxel-based lesion study on

- facial emotion recognition after penetrating brain injury. *Soc Cognit Affect Neurosci* 2013;8(6):632–9. <https://doi.org/10.1093/scan/nns041>.
- [2] Sliwinski MW, Elson R, Pitcher D. Dual-site TMS demonstrates causal functional connectivity between the left and right posterior temporal sulci during facial expression recognition. *Brain Stimul* 2020;13(4):1008–13. <https://doi.org/10.1016/j.brs.2020.04.011>.
- [3] Adolphs R, Tranel D, Damasio AR. Dissociable neural systems for recognizing emotions. *Brain Cognit* 2003;52(1):61–9. [https://doi.org/10.1016/S0278-2626\(03\)00009-5](https://doi.org/10.1016/S0278-2626(03)00009-5).
- [4] Calder AJ, Keane J, Manes F, Antoun N, Young AW. Impaired recognition and experience of disgust following brain injury. *Nat Neurosci* 2000;3:1077–8. [https://doi.org/10.1016/S0896-6273\(03\)00679-2](https://doi.org/10.1016/S0896-6273(03)00679-2).
- [5] Dal Monte O, Schintu S, Pardini M, Berti A, Wassermann EM, Grafman J, Krueger F. The left inferior frontal gyrus is crucial for reading the mind in the eyes: brain lesion evidence. *Cortex* 2014;58:9–17.
- [6] Jabbi M, Keysers C. Inferior frontal gyrus activity triggers anterior insula response to emotional facial expressions. *Emotion* 2008;8(6):775–80. <https://doi.org/10.1037/a0014194>.
- [7] Klimm N, Ehlis AC, Plewnia C. Reduction of excitability in the left inferior frontal gyrus by cathodal tDCS facilitates emotion recognition. *Clin Neurophysiol* 2015;126(8):e142. <https://doi.org/10.1016/j.clinph.2015.04.229>.
- [8] Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G. Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. *Neuron* 2003;40(3):655–64. [https://doi.org/10.1016/S0896-6273\(03\)00679-2](https://doi.org/10.1016/S0896-6273(03)00679-2).
- [9] van der Gaag C, Minderaa RB, Keysers C. Facial expressions: what the mirror neuron system can and cannot tell us. *Soc Neurosci* 2007;2(3–4):179–222. <https://doi.org/10.1080/17470910701376878>. PMID: 18633816.
- [10] Willis ML, Murphy JM, Ridley NJ, Vercammen A. Anodal tDCS targeting the right orbitofrontal cortex enhances facial expression recognition. *Soc Cognit Affect Neurosci* 2015;10(12):1677–83. <https://doi.org/10.1093/scan/nsv057>.
- [11] Yang LC, Ren P, Ma YY. Anodal transcranial direct-current stimulation over the right dorsolateral prefrontal cortex influences emotional face perception. *Neurosci Bull* 2018;34(5):842–8. <https://doi.org/10.1007/s12264-018-0242-6>.
- [12] Brennan S, McLoughlin DM, O’Connell R, Bogue J, O’Connor S, McHugh C, Glennon M. Anodal transcranial direct current stimulation of the left dorsolateral prefrontal cortex enhances emotion recognition in depressed patients and controls. *J Clin Exp Neuropsychol* 2017;39(4):384–95. <https://doi.org/10.1080/13803395.2016.1230595>.
- [13] Vierheilig N, Mühlberger A, Polak T, Herrmann MJ. Transcranial direct current stimulation of the prefrontal cortex increases attention to visual target stimuli. *J Neural Transm* 2016;123(10):1195–203. <https://doi.org/10.1007/s00702-016-1542-5>.
- [14] Prete G, Laeng B, Tommasi L. Transcranial Random Noise stimulation (trNS) over prefrontal cortex does not influence the evaluation of facial emotions. *Soc Neurosci* 2018. <https://doi.org/10.1080/17470919.2018.1546226>.
- [15] Penton T, Dixon L, Evans LJ, et al. Emotion perception improvement following high frequency transcranial random noise stimulation of the inferior frontal cortex. *Sci Rep* 2017;7:11278. <https://doi.org/10.1038/s41598-017-11578-2>.
- [16] Yang T, Banissy MJ. Enhancing anger perception in older adults by stimulating inferior frontal cortex with high frequency transcranial random noise stimulation. *Neuropsychologia* 2017;102:163–9. <https://doi.org/10.1016/j.neuropsychologia.2017.06.017>.
- [17] Adolphs R. Recognizing emotion from facial expressions: psychological and neurological mechanisms. *Behav Cognit Neurosci Rev* 2002;1:21–61. <https://doi.org/10.1177/1534582302001001003>.
- [18] Benowitz LI, Bear DM, Rosenthal R. Hemispheric specialization in nonverbal communication. *Cortex* 1983;19(1):5–11. [https://doi.org/10.1016/S0010-9452\(83\)80046-X](https://doi.org/10.1016/S0010-9452(83)80046-X).
- [19] Borod JC, Obler LK, Erhan HM, Grunwald IS, Cicero BA, Welkowitz J, Santschi C, Agosti RM, Whalen JR. Right hemisphere emotional perception: evidence across multiple channels. *Neuropsychology* 1998;12(3):446–58. <https://doi.org/10.1037/0894-4105.12.3.446>.
- [20] Ahern GL, Schwartz GE. Differential lateralization for positive versus negative emotion. *Neuropsychologia* 1979;17(6):693–8. [https://doi.org/10.1016/0028-3932\(79\)90045-9](https://doi.org/10.1016/0028-3932(79)90045-9).
- [21] Tucker DM, Stenslie CE, Roth RS, Shearer SL. Right frontal lobe activation and right hemisphere performance. *Demerit during a depressed mood. Arch Gen Psychiatr* 1981;38(2):169–74. <https://doi.org/10.1001/archpsyc.1981.01780270055007>.
- [22] Davidson RJ, Fox NA. Asymmetrical brain activity discriminates between positive and negative affective stimuli in human infants. *Science* 1982;218(4578):1235–7. <https://doi.org/10.1126/science.7146906>.
- [23] Davidson RJ, Mednick D, Moss E, Saron C, Schaffer CE. Ratings of emotion in faces are influenced by the visual field to which stimuli are presented. *Brain Cognit* 1987;6(4):403–11. [https://doi.org/10.1016/0278-2626\(87\)90136-9](https://doi.org/10.1016/0278-2626(87)90136-9).
- [24] Russell JA. Affective space is bipolar. *J Pers Soc Psychol*. Author manuscript 1979;37:345–56. available in PMC 2006 Jan 25.
- [25] Russell JA. A circumplex model of affect. *J Pers Soc Psychol*. Author manuscript 1980;39(6):1161–78. <https://doi.org/10.1037/h0077714>. available in PMC 2006 Jan 25.
- [26] Calvo MG, Beltran D, Calvo MG, Beltrán D. Recognition advantage of happy faces: tracing the neurocognitive processes. *Neuropsychologia* 2013;51(11):2051–61. <https://doi.org/10.1016/j.neuropsychologia.2013.07.010>.
- [27] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527(Pt 3):633–9. <https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x>.
- [28] Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, Fricke K, Liebetanz D, Lang N, Antal A, Paulus W, Tergau F. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol* 2005 Oct 1;568(Pt 1):291–303. <https://doi.org/10.1113/jphysiol.2005.092429>.
- [29] Giglia G, Mattaliano P, Puma A, Rizzo S, Fierro B, Brighina F. Neglect-like effects induced by tDCS modulation of posterior parietal cortices in healthy subjects. *Brain Stimul* 2011;4(4):294–9. <https://doi.org/10.1016/j.brs.2011.01.003>.
- [30] Ricci R, Salatino A, Li X, Funk AP, Logan SL, Mu Q, Johnson KA, Bohning DE, George MS. Imaging the neural mechanisms of TMS neglect-like bias in healthy volunteers with the interleaved TMS/fMRI technique: preliminary evidence. *Front Hum Neurosci* 2012;6:326. <https://doi.org/10.3389/fnhum.2012.00326>.
- [31] Sarasso P, Ninghetto M, Salatino A, Ronga I, Bongiardina A, Iarrobino I, Neppi-Modona M, Ricci R. Everything is (still) illuminated: dual right cathodal-left anodal tDCS of PPC prevents fatigue on a visual detection task. *Brain Stimul* 2019;12(1):187–9. <https://doi.org/10.3389/fnhum.2012.00326>.
- [32] Horvath JC, Forte JD, Carter O. Quantitative review finds No evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain Stimul* 2015 May-Jun;8(3):535–50. <https://doi.org/10.1016/j.brs.2015.01.400>. Epub 2015 Jan 16. PMID: 25701175.
- [33] Bikson M, Paulus W, Esmaeilpour Z, Kronberg G, Nitsche MA. Mechanisms of acute and after effects of transcranial direct current stimulation. In: Knotkova H, Nitsche M, Bikson M, Woods A, editors. *Practical guide to transcranial direct current stimulation*. Cham: Springer; 2019. https://doi.org/10.1007/978-3-319-95948-1_3.
- [34] Vines BW, Cerruti C, Schlaug G. Dual-hemisphere tDCS facilitates greater improvements for healthy subjects’ non-dominant hand compared to uni-hemisphere stimulation. *BMC Neurosci* 2008 Oct 28;9:103. <https://doi.org/10.1186/1471-2202-9-103>. PMID: 18957075; PMCID: PMC2584652.
- [35] Salatino A, Poncini M, George MS, Ricci R. Hunting for right and left parietal hot spots using single-pulse TMS: modulation of visuospatial perception during line bisection judgment in the healthy brain. *Front Psychol* 2014 Oct 31;5:1238. <https://doi.org/10.3389/fpsyg.2014.01238>. PMID: 25400612; PMCID: PMC4215615.
- [36] Salatino A, Chillemi G, Gontero F, Poncini M, Pyasik M, Berti A, Ricci R. Transcranial magnetic stimulation of posterior parietal cortex modulates line-length estimation but not illusory depth perception. *Front Psychol* 2019 May 22;10:1169. <https://doi.org/10.3389/fpsyg.2019.01169>. PMID: 31191393; PMCID: PMC6540782.
- [37] Lundqvist D, Flykt A, Öhman A. *The karolinska directed emotional faces – KDEF, CD ROM from department of clinical neuroscience, Psychology section. Karolinska Institutet; 1998.*
- [38] Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull* 2007;72:208–14. <https://doi.org/10.1016/j.brainresbull.2007.01.004>.
- [39] Ricci R, Ghiggia A, La Rosa I, Milano A, Troni W, George MS, Borckardt JJ, Castelli L, Salatino A. Anodal Transcranial Direct Current Stimulation of the motor cortex reduces chronic pain in Alcock canal syndrome. *Brain Stimul* 2018. <https://doi.org/10.1016/j.brs.2018.02.006>. 2018; pii: S1935-861X(18)30069-X.
- [40] Zheng X, Dai W, Alsop DC, Schlaug G. Modulating transcallosal and inter-hemispheric brain activity using tDCS: implications for interventions in Aphasia. *Restor Neurol Neurosci* 2016;34(4):1–12. <https://doi.org/10.3233/RNN-150625>.
- [41] Wager TD, Phan KL, Liberzon I, Taylor SF. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage* 2003;3(3):513–31. [https://doi.org/10.1016/S1053-8119\(03\)00078-8](https://doi.org/10.1016/S1053-8119(03)00078-8). PMID: 12880784.
- [42] Calder AJ, Rhodes G, Johnson MH, Haxby JV, editors. *The oxford handbook of face perception*. Oxford: University Press; 2011.
- [43] Leppänen JM, Hietanen JK. Affect and face perception: odors modulate the recognition advantage of happy faces. *Emotion* 2003;3:315–26. <https://doi.org/10.1037/1528-3542.3.4.315>.
- [44] Shimamura AP, Ross JG, Bennett HD. Memory for facial expressions: the power of a smile. *Psychon Bull Rev* 2006;13:217–22. <https://doi.org/10.3758/bf03193833>.
- [45] Actis-Grosso R, Bossi F, Ricciardelli P. Emotion recognition through static faces and moving bodies: a comparison between typically developed adults and individuals with high level of autistic traits. *Front Psychol* 2015;6:1570. <https://doi.org/10.3389/fpsyg.2015.01570>.
- [46] Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neurosci Biobehav Rev* 2019;96:219–31. <https://doi.org/10.1016/j.neubiorev.2018.12.012>.
- [47] George MS, Nahas Z, Li X, Anderson B, Molnar C, Kose S, Borckardt J, Ricci R, Mu Q. Current status of daily repetitive transcranial magnetic stimulation for the treatment of depression. *Prim Psychiatr* 2005;12(10):51–8.
- [48] Li X, Ricci R, Large CH, Anderson B, Nahas Z, Bohning DE, George MS. Interleaved transcranial magnetic stimulation and fMRI suggests that lamotrigine and valproic acid have different effects on corticolimbic activity.

- Psychopharmacology 2010;209:233–44. ISSN 0033-3158 (print version) ISSN: 1432-2072 (electronic version).
- [49] Ninghetto M, Gammieri R, Miccolis R, Nobili M, Salatino A, Ricci R. Effects of repeated sessions of transcranial direct current stimulation on major depressive disorder and cognition. *J ECT* 2019;35(3):e32–3. <https://doi.org/10.1097/YCT.0000000000000611>.
- [50] Blair RJR. Facial expressions, their communicatory functions, and neuro-cognitive substrates. *Philos Trans R Soc Lond B Biol Sci* 2003;358(1431):561–72. <https://doi.org/10.1098/rstb.2002.1220>.
- [51] Kohler CG, Turner TH, Bilker WB, Brensinger CM, Siegel SJ, Kanes SJ, Gur RE, Gur RC. Facial emotion recognition in schizophrenia: intensity effects and error pattern. *Am J Psychiatr* 2003;160(10):1768–74. <https://doi.org/10.1176/appi.ajp.160.10.1768>.
- [52] Hastings ME, Tangney JP, Stuewig J. Psychopathy and identification of facial expressions of emotion. *Pers Individ Differ* 2008;44(7):1474–83. <https://doi.org/10.1016/j.paid.2008.01.004>.
- [53] Law Smith MJ, Montagne B, Perrett DI, Gill M, Gallagher L. Detecting subtle facial emotion recognition deficits in high-functioning Autism using dynamic stimuli of varying intensities. *Neuropsychologia* 2010;48(9):2777–81. <https://doi.org/10.1016/j.neuropsychologia.2010.03.008>.
- [54] Yim J, Neumann D, Tomita MR, Willer B. Meta-analysis of facial affect recognition difficulties after traumatic brain injury. *Neuropsychology* 2011;25(3):277–85. <https://doi.org/10.1037/a0021908>.
- [55] Phillips LH, Henry J, Cooper CL, Whyte M. Specific impairments of emotion perception in Multiple Sclerosis. *Neuropsychology* 2011;25(1):131–6. <https://doi.org/10.1037/a0020752>.
- [56] Lenne B, Barthelemy R, Nandrino JL, Sequeira H, Pinti A, Mecheri H, Kwiatowski A, Hautecoeur P. Impaired recognition of facial emotional expressions in Multiple Sclerosis. *Neuropsychol Trends* 2009. <https://doi.org/10.7358/neur-2014-015-lenn>.
- [57] Sedda A. Disorders of emotional processing in amyotrophic lateral sclerosis. *Curr Opin Neurol* 2014. <https://doi.org/10.1097/WCO.0000000000000147>.
- [58] Silani G, Bird G, Brindley R, Singer T, Frith C, Frith U. Levels of emotional awareness and autism: an fMRI study. *Soc Neurosci* 2008;3:97–112. <https://doi.org/10.1080/17470910701577020>.
- [59] Craig AD. How do you feel-now? The anterior insula and human awareness. *Nat Rev Neurosci* 2009;10:59–70. <https://doi.org/10.1038/nrn2555>.
- [60] Rolls E, Cheng W, Du J, Wei D, Qiu J, Dai D, Zhou Q, Xie P, Feng J. Functional connectivity of the right inferior frontal gyrus and orbitofrontal cortex in depression. *Soc Cognit Affect Neurosci* 2020;15(1):75–86. <https://doi.org/10.1093/scan/nsaa014>.
- [61] Oberndorfer T, Simmons A, McCurdy D. Greater anterior insula activation during anticipation of food images in women recovered from anorexia nervosa versus controls. *Psychiatr Res* 2014;214(2). <https://doi.org/10.1016/j.psychres.2013.06.010>.
- [62] Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatr* 2006;60:383–7. <https://doi.org/10.1016/j.biopsych.2006.03.042>.
- [63] Fischer AH, Kret ME, Broekens J. Gender differences in emotion perception and self-reported emotional intelligence: a test of the emotion sensitivity hypothesis. *PLoS One* 2018;13(1):e0190712. <https://doi.org/10.1371/journal.pone.0190712>.
- [64] Ruffman T, Henry JD, Livingstone V, Phillips LH. A meta-analytic review of emotion recognition and aging: implications for neuropsychological models of aging. *Neurosci Biobehav Rev* 2008;32(4):863–81. <https://doi.org/10.1016/j.neubiorev.2008.01.001>. Epub 2008 Jan 11. PMID: 18276008.
- [65] Sullivan S, Ruffman T. Emotion recognition deficits in the elderly. *Int J Neurosci* 2004 Mar;114(3):403–32. <https://doi.org/10.1080/00207450490270901>. PMID: 14754664.
- [66] Isaacowitz DM, Löckenhoff CE, Lane RD, Wright R, Sechrest L, Riedel R, Costa PT. Age differences in recognition of emotion in lexical stimuli and facial expressions. *Psychol Aging* 2007 Mar;22(1):147–59. <https://doi.org/10.1037/0882-7974.22.1.147>. PMID: 17385991.
- [67] Csukly G, Czobor P, Szily E, Takács B, Simon L. Facial expression recognition in depressed subjects: the impact of intensity level and arousal dimension. *J Nerv Ment Dis* 2009;197(2):98–103. <https://doi.org/10.1097/NMD.0b013e3181923f82>.
- [68] Van den Stock J, De Winter FL, de Gelder B, Rangarajan JR, Cypers G, Maes F, Sunaert S, Goffin K, Vandenberghe R, Vandenberghe M. Impaired recognition of body expressions in the behavioral variant of frontotemporal dementia. *Neuropsychologia* 2015;75:496–504. <https://doi.org/10.1016/j.neuropsychologia.2015.06.035>. ISSN 0028-3932.
- [69] Simon D, Craig KD, Gosselin F, Belin P, Rainville P. Recognition and discrimination of prototypical dynamic expressions of pain and emotions. *Pain* 2008 Mar;135(1–2):55–64. <https://doi.org/10.1016/j.pain.2007.05.008>. Epub 2007 Jun 20. PMID: 17583430.
- [70] Wang CA, Baird T, Huang J, Coutinho JD, Brien DC, Munoz DP. Arousal effects on pupil size, heart rate, and skin conductance in an emotional face task. *Front Neurol* 2018 Dec 3;9:1029. <https://doi.org/10.3389/fneur.2018.01029>. PMID: 30559707; PMCID: PMC6287044.
- [71] McManus MD, Siegel JT, Nakamura J. The predictive power of low-arousal positive affect. *Motiv Emot* 2019;43:130–44. <https://doi.org/10.1007/s11031-018-9719-x>.