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

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1784253 since 2022-07-20T09:50:15Z

Published version:

DOI:10.1016/j.brs.2021.03.014

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12 October 2024

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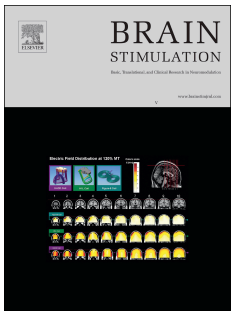

Right and left inferior frontal opercula are involved in discriminating angry and sad facial expressions

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PII: S1935-861X(21)00065-6

DOI: https://doi.org/10.1016/j.brs.2021.03.014

Reference: BRS 1933

To appear in: *Brain Stimulation*

Received Date: 2 October 2020

Revised Date: 21 February 2021

Accepted Date: 23 March 2021

Please cite this article as: Iarrobino I, Bongiardina A, Sarasso P, Monte OD, Ronga I, Neppi-Modona M, Actis-Grosso R, Salatino A, Ricci R, Right and left inferior frontal opercula are involved in discriminating angry and sad facial expressions, *Brain Stimulation*, https://doi.org/10.1016/j.brs.2021.03.014.

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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. analysed the data, R.R., ODM, 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.

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

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Declaration of interest: none

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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.

Keywords: Emotion; facial expressions; emotion discrimination; inferior frontal gyrus, inferior frontal operculum; transcranial Direct Current Stimulation; Arousal Hypothesis; angry; sadness.

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1. 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, 4, 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, 7, 8, 9]. Nonetheless, the causal role of IFO and putative hemispheric differences of this specific region in facial emotion recognition remain largely unknown.

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

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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, 18, 19]. Others [20, 21, 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

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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 [31, 7]. 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.

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2. Materials and methods

2.1. 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

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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 minutes.

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.

2.2. 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 [37]. 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

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(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 [$F_{2, 52}$ = .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 minutes (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]. 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 (5×5 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

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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.

Insert Figure 1 about here

3. Results

3.1. 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*

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(Mean = 77% ± 11%) compared to *disgust* (Mean = 65% ± 16%; p = 0.005), *fear* (Mean = 62% ± 16%; p = 0.001), and *sadness* (Mean = 53% ± 13%; p < 0.0001), while the difference with *anger* (Mean = 62% ± 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 analyze 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 η2 = 0.224, power= 0.912) and a significant interaction *Task by Emotion* ($F_{4, 60} = 10.194$, p< 0.0001, partial η2 = 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).

Insert Figure 2 about here

3.2. 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 *Emotion* ($F_{4,\ 200}$ = 27.898, $p < 0.0001$, partial η2 = 0.358, power = 1.000), and a significant interaction *Emotion by Stimulation* ($F_{8,\ 200}$ = 2.006; p = 0.047, partial η2 = 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 3b). 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 η2 = 0.444, power = 1.0) and interaction *Task by Emotion* ($F_{4,\ 200}$ = 17.294; p < 0.0001, partial η2 = 0.257, power = 1.0). However, the interaction *Emotion by Stimulation* was not significant ($F_{8,\ 200}$ = 0.440; p = 0.896, partial η2 = 0.017, power = 0.203).

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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 [28].

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 η2 = 0.111, power = 0.689), *Emotion* ($F_{4,208} = 2.820$; $p = 0.026$, partial η2 = 0.053, power = 0.763), and a significant interaction *Task by Emotion* ($F_{4, 208} = 2.772$, p =0.028, partial η2 = 0.053, power = 0.755).

Insert Figure 3 about here

Discussion

Neuroimaging studies have been extremely helpful to inform our community about a wide fronto-temporo-parietal network (6, 7, 8, 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 previous literature, we found a gradient in participants' discrimination accuracy [17, 42, 43, 44, 45]. They manifested the "happy face advantage" – i.e. happy faces were easier to discriminate than other expressions [42, 43, 44, 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 recognise 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 [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 minutes) 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 to 5) of cathodal tDCS applied to IFO for longer duration (20-30 minutes) 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

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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.

Acknowledgements

Funding source

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

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Figures Legend

Figure 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 2000ms, two visual stimuli in a vertical position were presented for 250ms followed by a 3000ms second 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 15min. Participants started the EFDT task 10min after the beginning of tDCS. The task was carried out for the first 5min during brain stimulation and for the last 5min 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.

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

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Figure 3. **Emotion discrimination accuracy as a function of (online) brain stimulation conditions.** Values show the mean percentage ± 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). * $p < 0.05$, ** $p < 0.01$.

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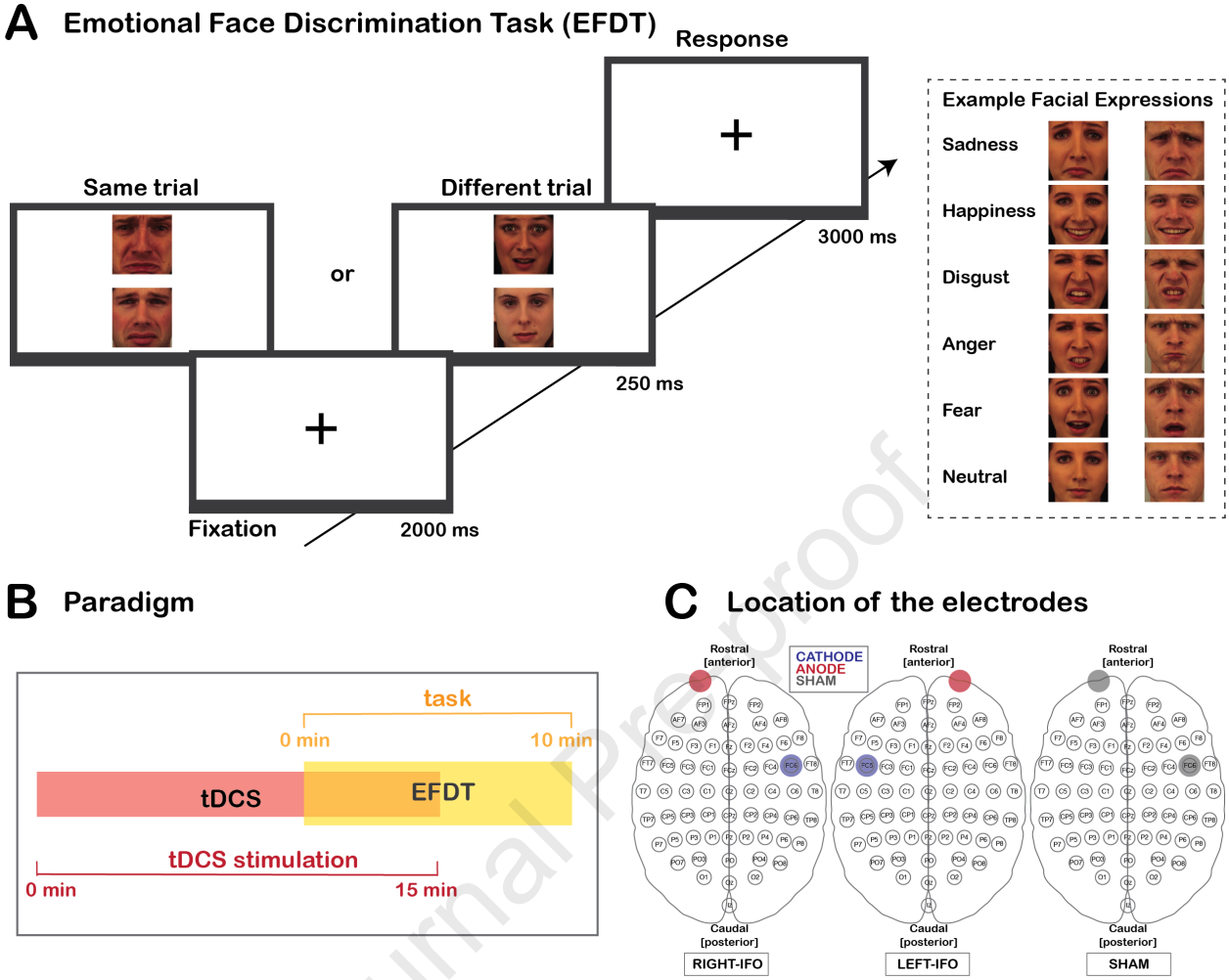

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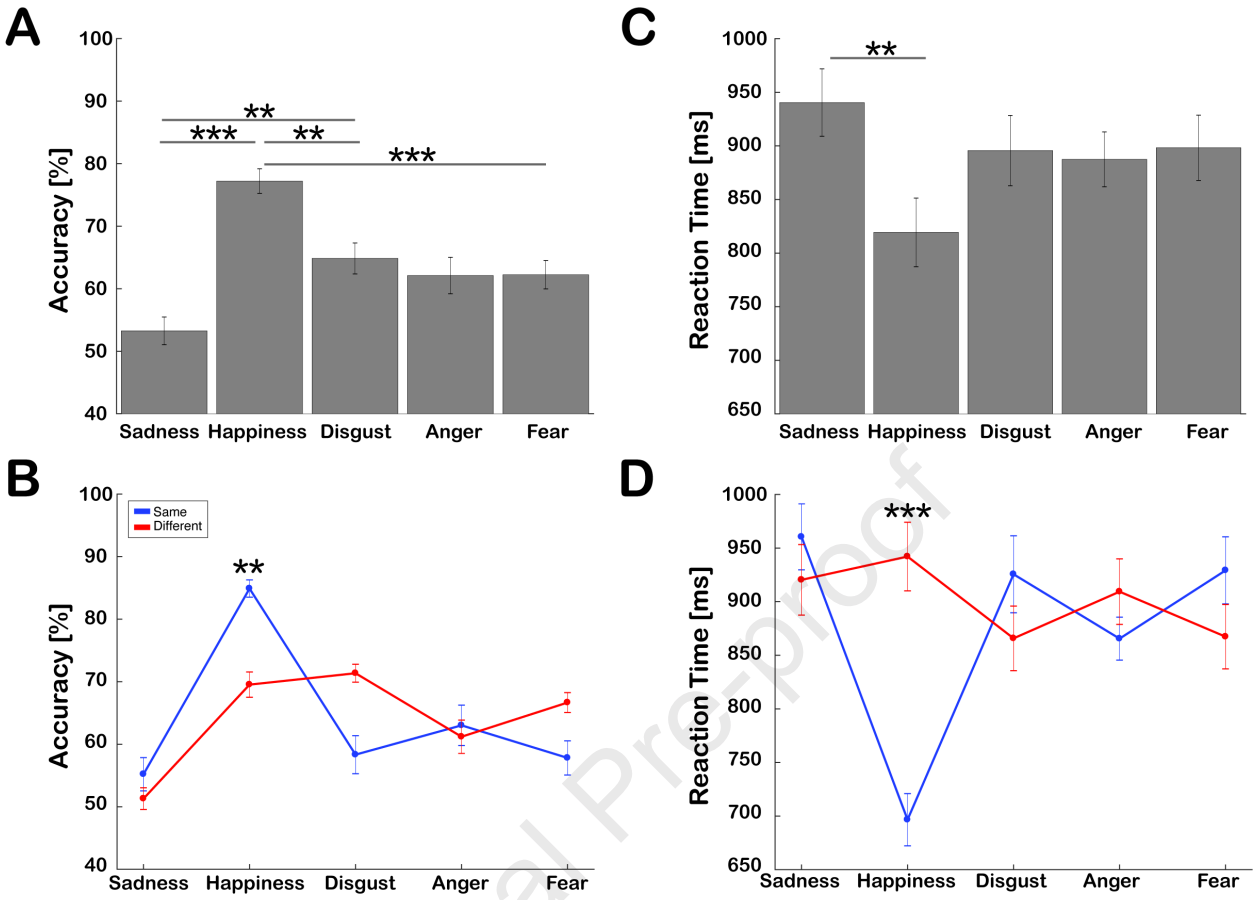

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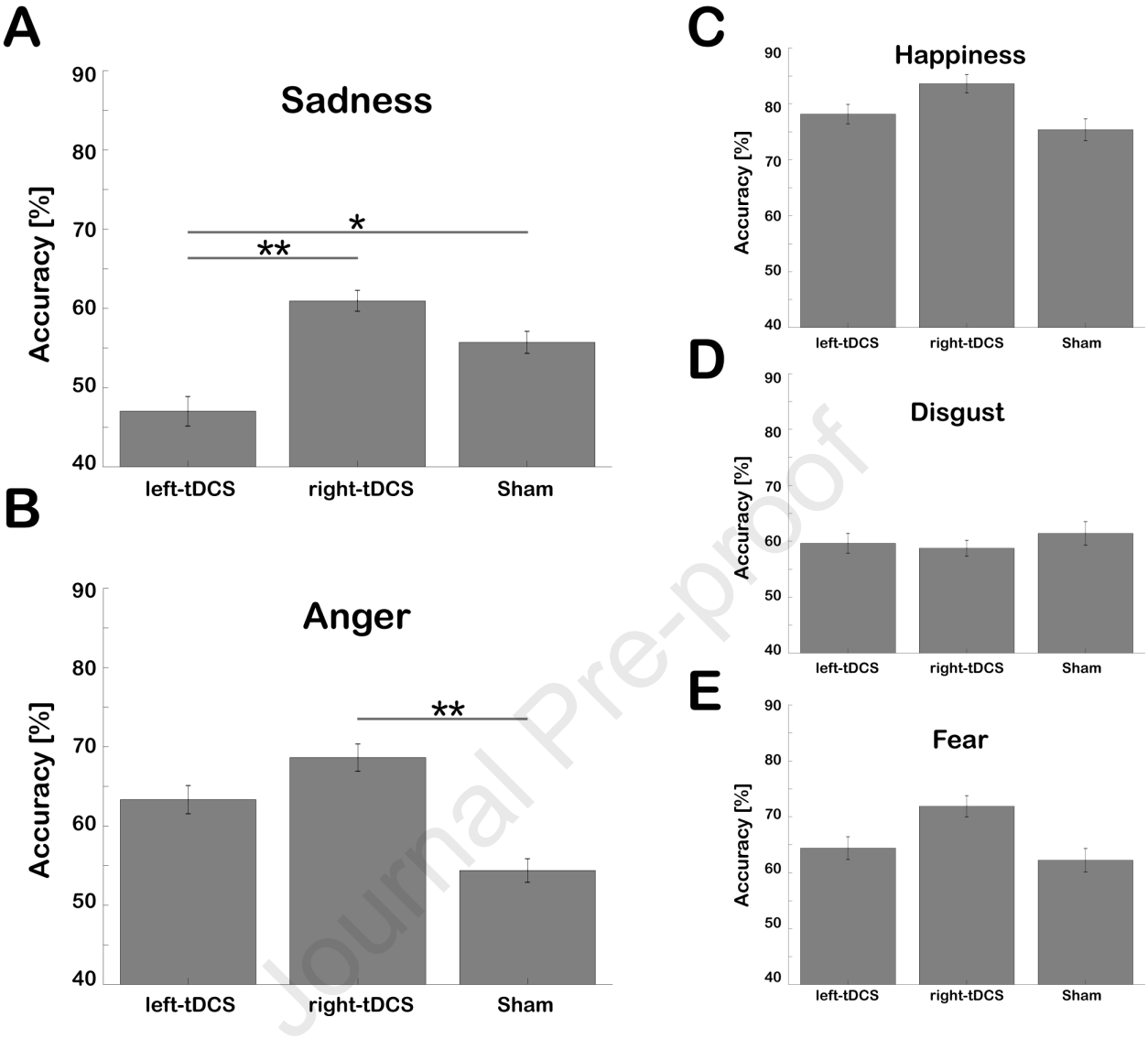

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Right and left inferior frontal opercula are involved in discriminating angry and sad facial expressions

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HIGHLIGHTS

- Cathodal tDCS was used to test the role of IFO in facial emotions discrimination
- TDCS of right IFO improved discrimination of anger, a high arousal emotion
- TDCS of left IFO impaired discrimination of sadness a low arousal emotion
- Cathodal polarity differentially modulated high and low arousal emotions
- These findings may have implications for emotion recognition deficits treatments.

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

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Declaration of interest: none

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