Social Cognitive and Affective Neuroscience, 2022, 4–14

doi: https://doi.org/10.1093/scan/nsaa099
Advance Access Publication Date: 5 August 2020
Original Manuscript

Neuromodulation Special Issue

Transcranial electric stimulation as a neural interface to gain insight on human brain functions: current knowledge and future perspective

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Abstract

The use of brain stimulation approaches in social and affective science has greatly increased over the last two decades. The interest in social factors has grown along with technological advances in brain research. Transcranial electric stimulation (tES) is a research tool that allows scientists to establish contributory causality between brain functioning and social behaviour, therefore deepening our understanding of the social mind. Preliminary evidence is also starting to demonstrate that tES, either alone or in combination with pharmacological or behavioural interventions, can alleviate the symptomatology of individuals with affective or social cognition disorders. This review offers an overview of the application of tES in the field of social and affective neuroscience. We discuss the issues and challenges related to this application and suggest an avenue for future basic and translational research.

Key words: neuromodulation; non-invasive brain stimulation; neuroenhancement; social cognition; transcranial direct current stimulation; tDCS; tES; NIBS

Introduction

Throughout life, the human mind is constantly engaged in the processing of affective experience and in the evaluation of the social effects of behaviour. Social and affective neuroscience is a growing cross-disciplinary field that aims to understand how the brain processes affective and social information. The field spans a wide range of topics, including embodied cognition, empathy, self-other processing, moral judgements, social beliefs, pro- and anti-social behaviour, emotion understanding and emotion regulation. Over the last few years, social and affective neuroscience reached beyond an academic audience and has started to attract clinical interest due to the possibility of improving the quality of life in individuals with social and affective disorders.

The development of non-invasive brain stimulation techniques allowed the investigation of the neurophysiological and behavioural correlates of social and affective functions using a causal approach. This technological advancement furthers our understanding of the neural substrates of social and affective processes, thus providing significant insights into the social mind. In particular, transcranial electrical stimulation (tES) has captured a broader scientific interest by offering a relatively inexpensive, safe and non-invasive method to detect brain–behaviour relations in the social and affective domains and to

Received: 10 January 2020; **Revised:** 12 May 2020; **Accepted:** 11 July 2020

alter these relations using a neuromodulatory approach. Among others, tES includes transcranial direct current stimulation (tDCS) and transcranial alternating current(s) stimulation (tACS). In general, these stimulation methods involve the application of two electrodes—such in a bipolar electrode configuration—or array of electrodes, such as in high definition (HD-)tDCS, that deliver low-intensity (1–3 mA) electrical currents in the brain, modulating cortical excitability (Woods *et al.,* 2016; Antal *et al.,* 2017; Fertonani and Miniussi, 2017). tES acts by modulating the resting membrane potential and the discharge rate of neurons in the stimulated area, although its effects are not confined to the stimulated region but may spread to functionally interconnected areas and anatomically adjacent regions (Luft *et al.,* 2014; Bergmann *et al.,* 2016). At the neuronal level, anodal stimulation leads to depolarisation and increases firing rates, whereas cathodal tDCS leads to hyperpolarisation and reductions of neuronal firing (Bindman *et al.,* 1964; Radman *et al.,* 2009). Furthermore, studies have shown that the rhythmic stimulation applied through tACS may modulate cortical brain oscillations (Thut *et al.,* 2017). Due to the low intensity of the applied currents, this mechanism likely consists of a modulation of endogenous frequencies of the stimulated cortical region rather than a frequency-specific change at the cortical level (Miniussi and Ruzzoli, 2013; Thut *et al.,* 2017). Hence to some extent, the effects of tACS in modulating existing activity may be similar to the effects induced by tDCS. The present work mainly covers tDCS since almost all studies in the social and affective domain use this approach.

tES offers many advantages for the field of social and affective neuroscience. As mentioned above, it is relatively inexpensive, safe, painless and portable, it can easily be used in association with a task or during interaction with other subjects, and it is supposedly easy to apply. Furthermore, tES does not generate any acoustic noise and consequently allows the implementation of a reliable sham condition (Fertonani *et al.,* 2015; Wallace *et al.,* 2016). These advantages have fuelled the rapid expansion of tES into the cognitive and social neuroscience domains and are unsurprisingly appealing to the novice. However, they should not lure the researcher into assuming that this technique is free from shortcomings or challenges. Although applying two or more electrodes on the scalp is in most cases an easy task, observing a reliable effect may not be as straightforward because, as clarified in the following paragraphs, the final outcome of tES application is affected by a wide range of variables. The non-trivial effects that follow the application of a weak electric field to a dynamic electrochemical system, such as the brain, preclude a simple extrapolation onto behaviour (Fertonani and Miniussi, 2017). Therefore, several methodological aspects should be considered before inferring causal relationships between brain regions and social or affective functions. Experimental designs should be based on a careful selection of features of the stimulation protocol as a function of specific hypotheses and research questions. Among these features, of particular relevance are the polarity of the electrical current (anodal *vs* cathodal), the timing of the stimulation (online or offline), the cortical target and its localization, the state and trait dependency with respect to the neurophysiological state of the brain in a given subject during stimulation, and the psychophysiological differences between subjects.

State of the art and challenges

Stimulation protocols

It is now well established that tDCS induces polarity- and dose-dependent effects on cortical excitability as a function of stimulation parameters (e.g. Mosayebi Samani *et al.,* 2019). The stimulation-dependent model (Antal *et al.,* 2017) predicts that the behavioural results are based on changes in excitability induced by tDCS. As mentioned above, anodal tDCS induces depolarisation of the resting membrane potential and increases in cortical excitability, which is generally associated with facilitatory effects. On the other hand, cathodal tDCS induces hyperpolarisation and decreases in neuronal excitability which results in inhibitory effects (Antal *et al.,* 2017). These observations are based on neurophysiological data recorded from the motor cortex via amplitude modulation of motor evoked potentials (Nitsche and Paulus, 2000) or inferred via electroencephalograph recording from the stimulated area (e.g. Pellicciari *et al.,* 2013; Amadi *et al.,* 2014; Hill *et al.,* 2016; Pisoni *et al.,* 2018; Fertonani *et al.,* 2019) in terms of cortical spread of tDCS-induced excitability changes using combined TMS-EEG (Varoli *et al.,* 2018) or neurotransmitter concentration (Stagg *et al.,* 2009; Stagg and Nitsche, 2011). Although these methodological approaches can support the role of specific neural circuits involved in tDCS-induced effects, any association between the effects at the neural level and the behavioural level should be made with caution (Kuehne *et al.,* 2015) since the above observations cannot be easily extended to all domains. Therefore, the effect of the stimulation depends on the interaction between the stimulation parameters and the state of the stimulated system. For instance, in a study by Abend *et al.* (2016), tDCS over the medial prefrontal cortex (PFC) modulated the extinction of learned fear as hypothesised, but this effect overgeneralised to non-reinforced stimuli. This paradoxical behavioural effect was not anticipated and limits the potential clinical application of the protocol despite the promising effect of tDCS on fear extinction. Unexpected behavioural outcomes induced by tDCS are also showed in other studies. For instance, in the study by Iuculano and Cohen Kadosh (2013), the cognitive enhancement obtained with tDCS occurred at the expense of other cognitive functions, depending on the stimulated cortical target. Altogether, these findings suggest that any clinical translation of tDCS should be made with caution (e.g. Dedoncker *et al.,* 2016) and further research is needed to identify the most effective protocol parameters (e.g. intensity, timing, duration, polarity) to induce a targeted effect or to improve clinical conditions. In this respect, the inclusion of a broader range of cognitive and behavioural measurements to evaluate tES-induced effects may increase the likelihood of detecting unexpected outcomes, thereby enhancing the reliability of conclusions drawn from the data.

Timing of stimulation

One important decision to make upon designing the experimental protocol of a tES experiment is whether the stimulation should be administered before (offline) or during (online) task execution. Offline and online stimulation provide different yet relevant information on brain processes and cognitive functions. Therefore, a relevant decision is whether the system should be primed before or during the engagement of a given function. tES effects are not entirely unidirectional—they are not only dependent upon linear variations of stimulation parameters (e.g. polarity, intensity) but also, and above all, on the state of the brain during stimulation (Li *et al.,* 2019).

The online approach takes advantage of the additive effects of task- and stimulation-induced changes in cortical activity. For this reason, one could assume that online tES mainly affects the system activated by the task, thereby increasing the 'neural precision' of the stimulation in terms of conditional causality. Nevertheless, for the same reason in some cases, online tES could result in reduced or even reversed cognitive and behavioural changes. In this respect, the notion of state dependency of tES effects emphasises that the effects of the stimulation are proportional to the level of background neural activation during tES (Bortoletto *et al.*, 2015).

Offline stimulation involves neuronal activity changes that continue beyond the stimulation, the so-called neuroplastic aftereffects on cortical excitability, including the general homeostasis of the system (Müller-Dahlhaus and Ziemann, 2015). Moreover, based on the notion of state dependency of tES effects, the stimulation applied during a resting state should primarily affect the dynamics of resting-state networks. One limitation of offline stimulation is the lack of active engagement of a precise system during the stimulation. Therefore, homeostatic mechanisms may play a role in inducing a gain or loss of responsiveness to specific stimuli via a threshold modification and subsequently enhance or counteract tES-induced effects (Müller-Dahlhaus and Ziemann, 2015). Therefore, a relevant issue that should be considered to validate the finding of a tES study in parallel designs is the assessment of baseline-level responses in performance (Coll *et al.*, 2017). Without this information, one cannot rule out the possibility that the tES effects could be due to differences in baseline performance and related neural excitability between stimulation groups.

Stimulation targeting

In several studies tDCS is used to explore the neural mechanisms of social or affective processing and the causal role of specific brain regions. Often the used method to target the brain regions of interest consists of using the international 10–20 EEG system to place the 'stimulation site/electrode' spatially over the area. This method is easy to implement but not entirely accurate and should be associated with a more informative approach. The choice of stimulation site is frequently informed by functional magnetic resonance imaging (fMRI) coordinates derived from previous studies on a different group of subjects. Localization of the target site and return electrode by means of fMRI-guided neuronavigation could result in a more accurate delivery of tES, especially when coupled with modelling. Recently, modelling methods have allowed identification of the optimal stimulation site by simulating the distribution of electric fields in the brain on a template head model using *ad hoc* software (Thielscher *et al.*, 2015) (e.g. the commercial finite element model (FEM) software or the Simulation of Non-invasive Brain Stimulation (SimNIBS software) or with individual head modelling (e.g. the most recent realistic volumetric approach to simulate transcranial electric simulation—ROAST). Although this methodological approach is time-consuming, it results in a more accurate localization of the target brain area at the individual level and in more precise delivery of tES. These approaches are useful to localize the stimulation target and evaluate the stimulation spread; however they involve issues with generalisation and accuracy of the estimated template. As mentioned already, tES effects are not limited to the stimulated target site but are spread over adjacent areas. Moreover, the effectiveness of the stimulation on a given cortical area will depend on the location of the electrodes with respect to the orientation of the applied electrical field and the neural populations engaged by the specific task (Karabanov *et al.*, 2019). These modelling approaches revealed that it is possible to use pseudo-unipolar or ring montages (Datta *et al.*, 2009; Bortoletto *et al.*, 2016) to focalize the stimulated area and reduce unwanted co-stimulation of other areas. In this respect a HD-tDCS montage, involving a central electrode surrounded by an array of return electrodes (e.g. 1x4) arranged in a circle, or a montage consisting of two concentric electrodes tDCS should improve stimulation focality and consequently the effectiveness of neuromodulation.

Another critical consideration is whether the left *vs* right hemisphere should be stimulated with respect to a specific social or affective domain. This is especially relevant for the affective domain considering the lateralization of emotion processing and left–right asymmetries in mood disorders (e.g. Bruder *et al.*, 2017). Several approaches have been used including bi-hemispheric and uni-hemispheric montages, although the rationale for using one approach over the other is not always stated in published studies. In a recent study, Brookshire and Casasanto (2018) showed that different lateralised tDCS (right-"excitatory" stimulation *vs* left-'excitatory' stimulation) modulated affective motivation, a basic dimension of human emotion, in right-handers and non-right-handers, highlighting individual differences in the neural organization of motivation and the need to consider hemispheric specialization to define tailored neuromodulation treatments. In this respect, we suggest that the ideal approach to localization should involve the use of neuroimaging to identify the cortical area involved in the specific social and affective process first and then the selection of the best protocol in terms of the current polarity and site of stimulation (both for active and return electrodes). While making this choice, it is important to consider the possible spread of the electrical current to a wider brain network, with possible secondary influences on other cortical and subcortical structures. In this respect, modelling data show that in bi-hemispheric montages, in which the anode and cathode are placed over homologous targets in each hemisphere, the highest current densities are close to the midline and not under the electrodes (Karabanov *et al.*, 2019). These data underlie the uncertainty in identifying the site of stimulation without an appropriate modelling of the electrode montage most suited for the purpose.

tES-induced changes: from performance measures to neural changes

Most studies in social and affective neuroscience test the effectiveness of tES using behavioural outcomes only, which is a major limitation because as mentioned earlier tES lacks focality and exerts an effect on both the stimulated area and distributed neural networks associated with it (Karabanov *et al.*, 2019). Therefore, the observed behavioural outcome does not necessarily depend on changes in brain activity in the targeted brain region. One advantage of combining tES with measures of brain activation is thus reducing the uncertainty about the neural substrate modulated by tES. This combination should be the ideal method to validate the neurobehavioral effects induced by a manipulative approach (Gilam *et al.*, 2018).

Three studies in the social and affective domain provide excellent examples of how a multimodal approach may benefit investigations of tES effects. Abend *et al.* (2019) stimulated the medial PFC with tDCS during the viewing of emotional video clips while simultaneously recording brain activity with fMRI. Compared to sham, anodal tDCS decreased the emotional response to negative clips. The fMRI results showed that the stimulation increased emotion-related activations in the ventromedial PFC and anterior cingulate cortex. Furthermore, tDCS altered functional connectivity between these regions and additional areas related to emotion processing, such as the insula and the amygdala. Coll *et al.* (2017) used a combination of tDCS, EEG and physiological recordings to examine the role of the right temporo-parietal junction (TPJ) in empathic responses. The authors showed that participants who received cathodal tDCS, compared to sham, perceived the pain in others as less intense and further showed decreased EEG responses to facial expressions to pain. Interestingly, tDCS did not affect skin conductivity and heart rate responses. Donaldson *et al.* (2019) showed performance changes in a social cognition task following tDCS over the right TPJ but did not find significant tDCS-induced changes in underlying neurophysiological processes, assessed with event-related potentials.

These observations raise a relevant question: what are the most appropriate neurophysiological measures to define the causal relationship between a brain area and its behavioural function by means of a neuromodulation approach? The modulation induced by tDCS in terms of inhibition/excitation ratios could subtend the involvement of several mechanisms of action, such as the ratio of excitatory glutamatergic cells and GABAergic interneurons that are not necessarily detected using neurophysiological methods. Increasing the evaluation of tDCS polarity-dependent effects in several cognitive domains in conjunction with electrophysiological and neuroimaging measures could more accurately validate hypotheses regarding behavioural/electrophysiological relationships relevant for testing the effects of stimulation in social and affective functions and assessing the causality between a brain area and its functional role. In this respect, the study by Gallo *et al.* (2018) provides an elegant example of how a multimodal approach may help isolate the contribution of a specific cortical area (i.e. somatosensory cortex) in prosocial decision-making. Specifically, in the first instance, the authors localized the cortical target involved in encoding experienced pain from fMRI signals. A region of interest was then defined to evaluate the cortical activity related to prosocial behaviour in an EEG experiment. Subsequently, to examine the causal contribution of this region to decision-making and pain perception, transcranial magnetic stimulation (TMS) and tDCS-based perturbational approaches were applied over the primary somatosensory cortex. The integration of different neuroimaging and neuromodulation methods used in this study could represent an ideal methodological approach to correlate a brain area to social and affective cognition.

One important approach to support the behavioural outcome in tES studies on affective processing is using physiological measurements that provide information on emotional arousal, such as pupillometry, heart rate and skin conductance. For example, a few studies have shown that tDCS to the lateral PFC increases the effectiveness of emotion regulation to negative stimuli (Feeser *et al.,* 2014; He *et al.,* 2018; Marques *et al.,* 2018), as indexed by a reduction of emotional ratings. This behavioural outcome was further supported by the reduction of the pupil diameter (He *et al.,* 2019), decreased skin conductivity (Feeser *et al.,* 2014) and decreased cardiac interbit interval (Marques *et al.,* 2018). Neuroimaging and physiological measures can also be helpful to reveal neurobiological effects of tES in the absence of a significant effect on behaviour or cognition. In a study by Antal *et al.* (2014), for instance, participants were exposed to the Trier Social Stress Test (TSST), a task that induces stress by asking participants to give a brief speech and perform mental arithmetic in front of an audience. Before the TSST, they received 20 min of real or sham stimulation to the medial PFC. Despite a lack of tDCS-induced differences in self-reported stress, anodal stimulation induced a decrease in cortisol levels and higher regional cerebral blood flow, as evaluated by means of fMRI, in the medial PFC. The lack of behavioural findings in tES studies on affective processing may arise because many studies involve self-evaluation of one's mood, emotional state or intensity of affective response. In these circumstances, participants may be unable to provide a self-report of their states or their responses may be biased by social desirability.

To conclude, measures of brain activation and psychophysiological measurements before and after administration of tES, or cFotoncurrently with it, provide a more accurate identification of the neural patterns and brain pathways affected by the neuromodulation, in addition to allowing the measurement of interindividual differences in the neural response to the stimulation. These measurements will be of paramount importance in future tES studies, especially when behavioural measurements are not sensitive enough to capture tES-induced effects.

The role of individual differences

Several factors influence the effects of tES on cognition, from the specifics of the stimulation protocol to intersubject variability in neuroanatomy, genetic polymorphisms and motivational factors (Dyke *et al.,* 2016; Sellaro *et al.,* 2016). In this paragraph, we consider additional sources of variability in the effects of tES on social cognition and affective processing, including gender and individual differences in personality traits and cultural background.

tES could have differential effects in males and females due to differences in their brain structures (Ingalhalikar *et al.,* 2014), hormonal levels (Book *et al.,* 2001) or sociocultural differences in the stimulated cognitive function. Although recent research has shown that gender differences in emotion and cognitive processing are less pronounced than originally thought (Hyde, 2014), some tasks are particularly sensitive to gender differences, such as tasks involving empathy (Baron-Cohen and Wheelwright, 2004). Accordingly, gender-specific tES effects were observed in theory of mind abilities. Adenzato *et al.* (2017) delivered a short (6 min) 1 mA anodal and sham tDCS to the medial PFC while subjects performed an attribution of intentions task. The results showed that anodal stimulation increased attribution performance in females but not in males. This gender-specific tDCS effect was observed in other theory of mind tasks with longer stimulations to the medial PFC (Martin *et al.,* 2017). Another domain where males and females differ is aggressive behaviour (Archer, 2004). Dambacher *et al.* (2015) delivered 12 min of 2 mA anodal tDCS to the right dorsolateral PFC (DLPFC) while healthy subjects performed the Taylor Aggression Paradigm, in which participants' aggressive behaviour is measured as the amount of noxious stimulation administered to an ostensible opponent in a game (Taylor, 1967). The aim was to reduce left hemispheric frontal activity, which has been previously associated with aggressive behaviour (Peterson *et al.,* 2008). tDCS had no effects on females but reduced aggressive behaviour in males, who overall displayed a higher level of aggressiveness.

Several studies have demonstrated that brain responses during affective tasks (Canli *et al.,* 2001; Cremets *et al.,* 2010) and at rest (Wassermann *et al.,* 2001; Hoppenbrouwers *et al.,* 2010) are influenced by personality traits as defined by the five-factor model (extraversion, agreeableness, conscientiousness, neuroticism and openness, Widiger and Mullins-Sweatt, 2009). It is thus plausible that tES effects in affective tasks are modulated by trait-level variations. Peña-Gómez *et al.* (2011) examined whether individual differences in extroversion and neuroticism would influence emotional ratings during anodal tDCS to the left DLPFC, a brain region involved in emotion regulation (Ochsner *et al.,* 2002). The results showed that participants gave less negative ratings of the pictures during the anodal stimulation compared to the sham, and this effect was stronger in participants with high levels of introversion. In another study investigating whether psychopathic personality traits modulate tDCS effects on response inhibition, Weidacker *et al.* (2016) demonstrated that cathodal tDCS to the right DLPFC modulated response inhibition performance as a function of cold-heartedness scores, a psychopathic trait related to a lack of empathy and callousness in feelings. Furthermore, recent studies have consistently shown that the effects of tDCS in tasks involving the observation of social interactions or facial expressions are larger in participants with low levels of empathic capacity (Fini *et al.,* 2017; Jospe *et al.,* 2018; Peled-Avron *et al.,* 2019), raising the interesting possibility that tES in affective and social cognition is more effective in subjects with low levels of empathic capacity or when the task is demanding (Gill *et al.,* 2015).

In addition to gender and personality traits, cultural differences can also play a key role when considering tES effects in social and affective cognition. This is a relatively unexplored topic that deserves further consideration since affective and social cognition tasks frequently involve cultural differences and culture-related differences in their neural correlates (Mason and Morris, 2010; Han *et al.,* 2013; Lim, 2016). Individuals from different cultures may have baseline differences in tasks with a strong social or affective component or may approach these tasks using different strategies, which may, in turn, influence the tES effects and make the comparison of results across studies performed in different countries difficult. In a recent study supporting this view, Martin *et al.* (2019) tested 52 Caucasian and 52 Southeast Asian participants in a number of self-other processing tasks. The participants received 20 min of 1 mA anodal tDCS to the dorsomedial PFC or the right TPJ. The results revealed that the effects of tDCS were comparable when the baseline task performance of the two ethnic groups was similar. However, when the baseline task performance differed, differential effects of tDCS in the two groups emerged. Taking cultural differences into account in future tES studies may be one way to minimise the heterogeneity of results and improve replicability.

Altogether, the above studies show that the effects of tES on social and affective processes may differ depending on personality and cultural factors as well as gender. The vast heterogeneity in tES-induced effects, which is at the core of the growing scepticism regarding the reliability of the technique, could be partially reduced by taking these factors into account, especially in the realm of social and affective cognition where they may be a relevant source of variance. Interestingly, TMS studies showed that the outcome of non-invasive brain stimulation interventions on clinical populations with affective disorders is influenced by pretreatment personality traits (Berlim *et al.,* 2013). Individual differences in tES-induced effects could thus be particularly relevant when assessing the effects of tES interventions in those populations.

Limitations and future opportunities

Methodological limitations

Similar to tES studies in the cognitive domain and to the social sciences in general, affective and social tES studies struggle with issues of publication bias, small sample size and reproducibility.

Publication bias occurs when the results of published studies are systematically different from the results of unpublished studies. Since studies with null results are frequently unpublished, publication bias is generally associated with an overrepresentation of studies reporting statistically significant findings. Meta-analyses are relevant tools to address publication bias because in meta-analyses, publication bias can not only be analysed but also corrected for. Publication bias is a frequent observation in meta-analyses of tES effects in the cognitive domain (Mancuso *et al.,* 2016; Westwood and Romani, 2017; Galli *et al.,* 2019). However, publication bias might not have the same pressure in all research fields. For example, publication bias is more evident when clinical expectations are high, as in studies testing the effects of anodal stimulation on long-term memory (Galli *et al.,* 2019). Likewise, the reduction of undesirable social behaviours or negative affects following administration of tDCS can potentially translate into a clinical benefit, thus making the social and affective cognition domain particularly vulnerable to publication bias. Accordingly, publication bias was demonstrated in a recent meta-analysis of the effects of PFC tDCS on social cognition (Bell and DeWall, 2018). The results of this meta-analysis revealed that tDCS over the PFC significantly reduced risk-taking behaviour, overeating and bias. The average effect size for risk-taking and overeating, however, was considerably reduced after correcting for publication bias using the trim and fill procedure, which provides an estimate of how many unpublished studies are missing from the meta-analysis and uses this estimate to adjust the effect size.

In addition to publication bias, most tDCS studies in social and affective neuroscience do not have sufficient power to detect a reliable effect, with sample sizes as small as $N = 6$ (Esse Wilson *et al.,* 2018). Small sample sizes may result in a greater probability of detecting a large, spurious result by chance, which is especially relevant in the absence of clear experimental hypotheses because all experimental conditions could be tested without an *a priori* analysis plan and hypotheses could be generated based on the results (HARKing-Hypothesizing After the Results are Known; Kerr, 1998). If studies with statistically significant results obtained with small sample sizes and HARKing are overrepresented in the literature, the real effectiveness of tES will be hard to understand, and there may be issues with replicability. To date, direct replications of tES studies have generally failed to reproduce the significant effects of the original studies (Vannorsdall *et al.,* 2016; Boayue *et al.,* 2019). To reduce publication bias and improve the reproducibility of results, publication of null findings and preregistration of experimental hypotheses and procedures are warranted. Furthermore, more effort should be made in future studies to conduct systematic and replication studies on larger groups of participants to examine the circumstances under which tES does and does not exert its effects. At the moment, this understanding is limited by the vast heterogeneity of experimental protocols and variability of results.

Lack of functional specificity of tES effects

As mentioned above, tES lacks focality and exerts an effect on both the stimulated area and distributed neural networks (Karabanov *et al.,* 2019). In addition to challenging the involvement of the stimulated brain region in the specific function under examination, this may also lead to a lack of functional specificity of tES effects. In the field of social and affective neuroscience, the observation of changes in disparate social and affective functions following stimulation of the same brain region may be due to this lack of functional specificity (see also Sellaro *et al.*, 2016). For instance, stimulation of the DLPFC with tES induced changes in political beliefs (Chawke and Kanai, 2016), social norm compliance (Ruff *et al.*, 2013; Chen *et al.*, 2019), utilitarian judgements (Kuehne *et al.*, 2015; Zheng *et al.*, 2018), aggressiveness (Dambacher *et al.*, 2015), rule following (Gross *et al.*, 2018), honesty (Maréchal *et al.*, 2017; Gao *et al.*, 2018), emotion recognition (Nord *et al.*, 2017; Yang *et al.*, 2018), self-reported jealousy (Kelley *et al.*, 2015), cognitive appraisal of emotions (Peña-Gómez *et al.*, 2011; Feeser *et al.*, 2014), appreciation of beauty (Ferrari *et al.*, 2015), attentional bias for threat (Heeren *et al.*, 2017) and ratings of pain in others (Wang *et al.*, 2014). Although this observation casts doubt on the functional specificity of tES effects, it may also indicate that tES exerts its effects on mental functions that are shared across these behaviours and rely on the same neural substrates. For instance, the maintenance of attentional demands during the task and metacognitive control of one's responses are two processes that rely on the DLPFC (MacDonald *et al.*, 2000; Vaccaro and Fleming, 2018).

Alternatively, differences in relative electrode positioning and electrode size may have altered the current flow and induced differences in different functional areas within the DLPFC or more distantly. In this respect, the use of more sophisticated stimulation montages that deliver a more focused current flow, such as HD-tDCS, offers promise to improve the spatial and functional specificity of tES effects. Moreover, recent studies suggested that the current intensity used in conventional tES experiments might not be sufficient to affect brain neuronal circuits directly (Liu *et al.*, 2018). This notion is not new to the field (Miranda *et al.*, 2006), and we know that >60–80% of the current does not reach the grey matter because of shunting and the resistance of extra-cortical structures. Nevertheless, many neurophysiological studies show excitability changes after 1–2 mA tES (Antal *et al.*, 2017) suggesting that, albeit weak, an effect at the cortical level is present. Therefore, the absence of effects in some experiments should be explained with reference to the characteristics of the stimulation protocol (e.g. inappropriate montages, inadequate timing and intensity of stimulation) and brain nonlinearity as described above.

Multimodal interventions as an opportunity in affective tES studies

Several studies have examined whether tES induces effects in neuropsychiatric conditions with social cognition deficits or abnormal affective processing. These studies have produced mixed findings, as evidenced by recent reviews and meta-analyses (Boggio *et al.*, 2015; Brunoni *et al.*, 2016). One promising avenue for future research will be the combination of tES administration with psychopharmacological or cognitive behavioural interventions. This combined approach has the potential to produce therapeutic synergies and maximise the benefits of different interventions, especially in patients with drug-resistant psychopathological conditions. Successful combinations have already been described in neurorehabilitation. For instance, studies have demonstrated the benefits of combining tDCS with physical rehabilitation to facilitate motor recovery in patients with brain injury (Leśniak *et al.*, 2014). Studies that combine tES with cognitive interventions are still limited, but the available findings are promising. For instance, Heeren *et al.* (2015) used a combination of tDCS and Attention Bias Modification (ABM) training. ABM aims to reduce attentional bias towards negative information, a symptom that characterises several psychiatric conditions, such as depression and anxiety (Hertel and Mathews, 2011). Based on the evidence of dysfunctional hyper-/hypo-activation of the left DLPFC in anxious individuals, the authors administered anodal or cathodal tDCS to the left DLPFC in combination with ABM training in highly anxious females. The results showed that anodal tDCS reduced attentional bias towards emotionally negative facial expressions. Two recent studies used a combination of tDCS and cognitive and/or behavioural intervention in patients with major depressive disorder (Segrave *et al.*, 2014; Nord *et al.*, 2019). Segrave *et al.* (2014) delivered sham or active DLPFC tDCS associated with cognitive control training for 30 min for five consecutive days. Crucially, the inclusion of a sham cognitive training group, in addition to the sham tDCS and combined tDCS–cognitive training groups, allowed the comparison of the two interventions separately and in isolation. It was found that only the combined approach induced a reduction of depressive symptoms that lasted until the 5-week follow-up. The study of Nord *et al.* (2019) suggests that the effectiveness of a combined approach in depressed individuals may be dependent upon baseline activity in the stimulated brain region. In that study, left DLPFC tDCS or sham was delivered once a week for 8 weeks prior to cognitive behavioural therapy (CBT). The results showed no differences in clinical outcomes between sham and active tDCS, but participants with higher levels of activation in the left DLPFC, as evidenced by a pretreatment fMRI scan during a working memory task, showed larger tDCS effects.

Overall, these studies indicate that multimodal interventions combining neurostimulation with cognitive behavioural intervention could alleviate symptoms, possibly by counteracting dysregulated activity and maladaptive neuroplasticity in clinical populations. However, tES does not exert its effects on specific affects or disorders. Rather, it modulates mental functions that are associated with, or maintain, those affects or disorders. Anxiety, for instance, is characterised by negative affect, which in turn is maintained by attentional and learning biases towards negative information (Hertel and Mathews, 2011). These biases involve a number of brain regions, including the dorsomedial and ventrolateral PFC, anterior cingulate cortex, orbitofrontal cortex and hippocampus (Carlisi and Robinson, 2018). tES thus does not modulate anxiety or affect *per se* but modulates the underlying cognitive bias and associated brain networks. Therefore, when planning a tES treatment in populations with affective disorders, the choice of the target brain region should carefully consider the specific cognitive functions that are altered in those populations and their associated neural substrates.

tES studies with real-world interactions

To study human social cognition, studies should ideally use settings with real human interactions. However, social behaviours that guide human interactions in everyday settings can be difficult to elicit in a laboratory setting. Social cognition studies generally involve interactions with fictional participants or computers that may limit the ecological validity of the studies. tES studies are not an exception. Most studies investigate cooperation or prosocial behaviour using the prisoner's dilemma game or the ultimatum game, which involve rewards or points administered by a computer or a fictitious participant. In normal life though, cooperation is more complex. In addition, although some everyday behaviours are influenced by monetary incentives, much of our behaviour is enforced by social incentives, such as social disapproval. To translate real-world social behaviour into a laboratory setting, investigations of social cognition would ideally require a physical interaction between more participants. Two studies (Knoch *et al.,* 2008; Ruff *et al.,* 2013) provide an example of how this can be achieved. In the study conducted by Ruff *et al.* (2013), participants were randomly assigned to receive anodal, cathodal or sham stimulation to the right lateral PFC during a social norm compliance task. In each round of this task, one player received an amount of money and decided how much of it should be transferred to an anonymous opponent player as a function of whether this decision is punished by the opponent or not. Crucially, both players were real participants, and testing was simultaneously performed in the same room in groups of 12 participants who were randomly paired upon each round of the task. Knoch *et al.* (2008) also used a similar setting during an ultimatum game. In this game, a 'proposer' proposes how to split an amount of money with an anonymous 'responder', who can, in turn, either accept or reject the offer. In the case of a rejection, both players earn nothing, and therefore the proposer is punished; in the case of acceptance, the amount of money is split as proposed. As in the study by Ruff *et al.* (2013), participants were tested in groups in a large testing room, and a stimulation was delivered over the right lateral PFC but consisted of a cathodal and sham stimulation only. Both studies found that tDCS significantly increased altruistic behaviour, in that anodal tDCS increased social norm compliance in Ruff *et al.* (2013) and cathodal tDCS reduced propensity to punish unfair behaviour (see also Civai *et al.,* 2015). By using a setting that involved real social interactions, both studies increased the ecological validity of their findings. In this respect, an avenue for future social neuroscience research will involve the use of tES in virtual reality settings. Virtual reality allows the experimental control of laboratory measures while providing emotionally engaging environments that enhance affective experience and social interactions, thereby enhancing ecological validity without compromising internal validity. A recent pilot study on 12 veterans with warzone-related post-traumatic stress disorder (PTSD) delivered tDCS over the ventromedial PFC during six virtual reality sessions (van't Wout-Frank *et al.,* 2019). The virtual reality setting provided combat-related multisensory information, including visual, auditory, olfactory and haptic information. Results showed that active tDCS reduced the arousal in response to PTSD-related information compared to sham. This study showed that the application of tDCS in virtual reality settings is technically feasible and promising. Future studies should take advantage of the portability of tES and investigate the neural correlates of social cognition by immersing participants in settings that are as close as possible to real-life situations and social interactions.

Ethical issues

Ethical considerations regarding the application of tES in general have been described elsewhere (e.g. Antal *et al.,* 2017). One of the main ethical concerns is related to the consequences of the application of tES for home use. At the time of writing, tES devices can be purchased online for <€150, making them accessible to a wide audience. This, combined with its supposed ease of use, increased the proliferation of tDCS among lay individuals. These people are generally in their 20s–30s and use tDCS to enhance cognitive skills and improve negative effects (Jwa, 2015). In addition to issues related to the unlimited administration and long-term consequences of stimulation, specific concerns for the field of social and cognitive neuroscience are evident. If evidence accumulates that tES improves a number of social behaviours, individuals in this age range may start to view tES as a 'social enhancer', similar to psychostimulants and amphetamines, perhaps inducing addiction. Although this does not represent an immediate risk since evidence of long-term effects of tES on social and affective processing is still limited, viewing tES as a social enhancer in the future may pose distinctive ethical issues. A related ethical concern is whether the enhancements following tES constitute a form of cheating, possibly devaluing the act of putting in effort and discipline to achieve a goal and increasing social disadvantages (Lavazza, 2017, 2019).

We have highlighted that stimulation to one area can lead to changes in a number of different behaviours, which suggests that stimulation of one area might lead to undesired changes to behaviours other than the targeted one. For instance, what if a dorsolateral PFC stimulation aimed at reducing negative affect (Feeser *et al.,* 2014) concurrently induced an unintended conservative or liberal shift in political beliefs (Chawke and Kanai, 2016)? The lack of focality of tES could represent an ethical challenge in addition to a scientific one. One may even question whether changing people's political beliefs or making people more prosocial is ethical or desirable. How we relate to others and our ideas about how a country should be run are part of our identity, and altering these social processes involves changing aspects of our identity and distorting our own nature. In the field of moral enhancement—the enhancement of prosocial behaviour and morality (Harris and Savulescu, 2015)—ethical debate persists as to whether interventions to improve altruism may be desirable or whether moral enhancement limits the freedom to act immorally (Darby and Pascual-Leone, 2017). Finally, distinctive ethical considerations should be made for tES studies involving developmental populations. We know too little about the effects of tES on the developing brain and whether the enhancement of some functions may lead to the deterioration of others (Cohen Kadosh *et al.,* 2012). This fact, combined with the fact that children cannot make informed decisions on their own cognitive enhancement, makes ethical considerations particularly important when tES involves children.

Conclusion

The prospect of stimulating the brain and modifying social or affective behavioural output and defining the role of a given area is in line with the idea that we should be able to make the nervous system change congruously with the specific type of tES applied (i.e. tES can modify the brain based on the polarity used). In other words, tES is not sufficient to bring about the effect. Nevertheless, as detailed so far, a more up-to-date approach would consider that we should be able to make the applied current resonate congruously with the nervous system that we are willing to study, e.g. lurking factors that contribute to the effect should be considered in setting up the protocol. Therefore, future studies might be more focused on applying tES to the brain, guided (Bergmann, 2018) by a better-defined theoretical (e.g. the role of an area in a functional network that we are stimulating), technical (stimulation parameters) and computational (anatomical current distribution) modelling approach to obtain more precise evidence of the impact of tES on a given subject's brain state.

Conflicts of interest

The authors have no conflicts of interest.

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