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Emotion regulation and affective cognitive control: a multimodal approach investigation

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The paragraph 5.1 of Chapter 5 presents the following published open access paper that is under the Creative Commons Attribution License (CC BY) that allow to include the paper in a thesis:

Kelley NJ, Gallucci A, Riva P, Romero Lauro LJ and Schmeichel BJ (2019) Stimulating Self-Regulation: A Review of Non-invasive Brain Stimulation Studies of Goal-Directed Behavior. *Front. Behav. Neurosci.* 12:337. doi: 10.3389/fnbeh.2018.00337

The paragraph 6.1 of Chapter 6 presents the following published open access paper that is under the Creative Commons Attribution License (CC BY-NC-ND 4.0) that allow to include the paper in a thesis:

Gallucci A, Riva P, Romero Lauro LJ, Bushman BJ. Stimulating the ventrolateral prefrontal cortex (VLPFC) modulates frustration-induced aggression: A tDCS experiment. Brain Stimul. 2020 Mar-Apr;13(2):302-309. doi: 10.1016/j.brs.2019.10.015. Epub 2019 Oct 22. PMID: 31676301.

The paragraph 6.2 of Chapter 6 presents a manuscript in preparation of which I will be the co-first author. The manuscript has the following preliminary title “The regulation of emotions associated with social exclusion: modulating effects of tDCS over the rVLPFC in patients with borderline personality disorder” and list of authors: Gallucci A, Lisco A., Fabietti C., Preti E., Riva P., De Panfilis C. & Romero Lauro L. J.

Abstract

In humans' mind emotional and cognitive processes merge to affect emotions' regulation, a multi component construct, that strongly contributes to individuals' wellbeing and abilities to cope with interpersonal relationships and environmental demands. Emotions' regulation has received growing attention by affective sciences that explored the behavioral and neurobiological mechanisms underlying emotions' regulation. However, some questions remained open, in particular regarding whether different emotions' regulation strategies result in contrasting effects and which processes mediate automatic emotions' regulation. This thesis, by reporting behavioral studies on explicit (or conscious) and implicit (or unconscious) emotions' regulation, provides experimental evidence on the comparable effects of distraction and reappraisal when individuals deal with social exclusion. Moreover, it sheds light on the implicit influence of emotional stimuli (i.e., facial experessions) on cognitive performance, even in clinical conditions (i.e., brain lesions) characterized by potentially altered regulation abilities. Neuroscientific research reviewed in this thesis has revealed that both conscious and unconsciuos emotions' regulation encompass the stable interplay between prefrontal areas and subcortical regions involved in emotions. Non-invasive brain stimulation techniques (NIBS), applied over the prefrontal cortex, paved the way for the modulation of regulation processes, but the NIBS effects are still not definitely robust. This thesis qualitatively and quantitatively reviews the literature in this field, showing promising, yet preliminary, results about the effectiveness of NIBS on both goal-direct behaviors and emotions' regulation. Moreover, through experimental applications, it illustrates the NIBS modulation effects on frustration-induced aggression in helthies and rejection-related emotions in borderline personality disorder patients, contributing to the attempts of combining NBS protocols to the standard therapies for patients with emotional disorders. Finally, several open issues and future directions are discussed.

Introduction

Emotions are one of the most important higher cognitive functions and are necessary for a successful functioning of the human mind. They allow the appraisal of relevant external and internal events, directing the information processing, our thoughts and memories (Brosch et al., 2013; Lazarus, 1991; Lerner, Han & Keltner, 2007; Barrett et al., 2007; LeDoux, 2012; LeDoux & Hofmann, 2018), not only immediately when the event occurs, but also in the long-term, when similar situations are encountered. Hence, emotions have a crucial adaptive value, as they facilitate the detection of environmental threats, in case of negative emotions, or opportunities, in case of positive emotions, bringing together motivations, interests, cognitive resources and attention capabilities to facilitate coping with the environment (Zeelenberg et al., 2008; Frijda, Kuipers & Ter Schure, 1989).

Thus, emotions shape decisions and orient behaviors (Brosch et al., 2008; Gross et al., 2015; Mauss et al., 2005). Based on different appraisal processes, emotions drive specific motivational patterns, from those needed to react to threating stimuli when humans are scared (Frijda, Kuipers & Ter Schure, 1989), to those that influence complex social and economic decision-making (Engelmann et al., 2018). For instance, a recent perspective study underlied the impact of emotions on sustainable behaviors at the social and envirormental level. Moreover, authors suggested how results of affective sciences can provide insights in the field of sustainability change and transition (see Brosch & Steg, 2021 for details)

Building on these premises, it goes without saying that the ability to regulate one's emotions is crucial for individuals' mental and physical wellbeing and to function adaptively in society (Mauss, Bunge & Gross, 2008; Gross & Jazaieri, 2014). Recently, the issue of emotions' regulation has become a priority among scholars, who have made great strides toward the behavioral research on emotions' regulation. These investigations lead to the development of several theoretical models attempting to explain the cognitive and affective processes underlying emotions' regulation. The Chapter 1 of the present thesis will present an overview of such models, describing first the commonalities and differences of emotions' regulation processes and then which aspect(s) of the emotions' regulation each model prioritized. For instance some of them focused on the time of the regulation occurring within the course of an emotional experience, while others focused on the type of the regulation strategy applied.

Interestingly, the investigation about emotions' regulation has not been only at a theoretical level, but researchers in the field of affective sciences extended the interest also to experimentally

explore the regulation strategies. My PhD forms part of this background. Indeed, by focusing on the widely studied distinction between explicit (or conscious) and implicit (or unconscious) emotions' regulation processes, the Chapter 2 of this thesis will present the experimental paradigms applied in the literature to study these processes.

Then, the results of a series of studies I run to test how explicit and implicit emotions' regulation can be experimentally manipulated are presented in Chapter 3. In particular, regarding conscious regulation, I compared the effects of reappraisal and distraction on emotional reactions to an experience of social exclusion of a group of healthy participants (see paragraph 3.1). Regarding unconscious regulation, I used an implicit paradigm to study whether and how emotional information implicitely interfere with the cognitive task performance first of a group of healthy participants and second of a group of brain damaged patients (see paragraph 3.2).

Extending my investigation to brain damaged patients had also the aim to provide evidence for that part of the literature interested in the neuroscience of emotions' regulation. Concerning this field of literature, the Chapter 4 goes more in detail by describing the neural correlates of emotion' regulation. First, the Chapter presents the models that expanded the theorization to neural underpinnings of emotions' regulation; second, it reports the results of studies investigating the neural networks and hubs that mediate explicit and implicit emotions' regulation.

Based on these studies' findings, another part of my PhD was dedicated to investigate whether and how the application of non-invasive brain stimulation techniques to the brain areas activated by emotions' regulation strategies can effectively modulate emotions' regulation abilities. Therefore, the Chapter 5 of the present thesis, after a methodological overview of the brain stimulation techniques, first will report a review I wrote, in collaboration with other members of an international team (published in 2019 in Frontiers in Behavioral Neuroscience journal; see paragraph 5.1), that narratively summarizes the results of studies that used neurostimulation techniques in the general field of self-regulation (cognitive, emotional and behavioral domain) and goal-direct behaviors. Second, the Chapter will focus on the emotional self-regulation domain by presenting the results of a preliminary systematic review and meta-analysis that tested the efficacy of non-invasive brain stimulation to modulate emotions while implicit (e.g. dealing with emotional stimuli and information while the performance to cognitive tasks is measured) or explicit (e.g., reappraising or directly rating the emotions felt after stimuli presentation) regulation strategies are applied by studies' participants (see paragraph 5.2).

Then, based on the qualitative and quantitative findings I collected through the two reviews and the meta-analysis, a part of my PhD was dedicated also to experimentally applied non-invasive brain stimulation to modulate processes of emotions' regulation. Therefore, the Chapter 6 presents a study conducted to explore whether and how brain stimulation of the prefrontal cortex affects frustration-induced aggression in a group on healthy participants (paper published in 2020 in Brain Stimulation journal; see paragraph 6.1) and negative emotional reactions to social exclusion in a group of patients with a diagnosis of borderline personality disorder (see paragraph 6.2). Finally, the thesis will present open issues and future directions for coming research interested in exploring emotions' regulation processes, how they impact on cognition, even when brain damages occur, and how they can be modulated by the use of non-invasive brain stimulation.

Chapter 1: Emotions' Regulation

1.1 Emotions' regulation: lack of a shared definition

Emotions' regulation is a broad topic, lacking of a shared definition (Gross & Feldman Barrett, 2011; Gross, 2015). For instance, emotions' regulation has been defined by Gross (1998) as the set of processes that individuals use to manage their emotions and to exert control over them. In other words, emotions' regulation can be considered as an evaluation of an evaluation (Gross, 2014). Emotion regulation allows individuals to initiate new emotional responses or to wholly or partially alter the nature, magnitude, and duration of ongoing emotional reactions (Ochsner, Silvers & Buhle, 2012). Alternatively, emotion regulation is defined as the set of processes employed to redirect the spontaneous flow of emotions or as the ability to maintain a given emotional state (Koole, 2010).

More in details, defining emotions' regulation prompt the question of "what does emotions' regulation is for". Emotions' regulation is necessary to achieve humans' hedonistic and instrumental motives (Tamir, 2009), both momentary and in the long term (Gyurak, Gross & Etkin, 2011). Hedonistic motives consist in wanting to pursuing pleasure and avoiding any form of pain. While, non-hedonic motives consist in accepting to experience negative emotions in order to avoid even more painful emotions in the future. Instrumental motives allow individuals to pursue their goals, for instance to perform better (e.g. a person may want to feel more aggressive before competing in a box match), to acquire knowledge about themselves or the external world (e.g. studying hard for an exam to feel proud of oneself), or to experience a sense of meaning related to the Self (Tamir, 2016). Also social motives influence emotions' regulation (Tamir, 2016). Indeed, there is a general agreement considering emotions' regulation crucial to adapt in society and to ensure appropriate affective states and behaviours based on social contexts (Phillips, Ladouceur & Dravets, 2008 Phillips et al., 2003). For instance, individuals may regulate their emotions to increase (or decrease) closeness with another person or feel empathy, to influence other people's behavior, to elicit positive social judgement, to show congruent emotions to those of their belonging group, to adapt their emotions to their cultural norms and values (Tamir, 2016).

More broadly, the motivation to regulate one's emotions can also be influenced by the way a specific culture frames the expression of emotions (Gross, 1998; 2014; Tamir, 2016). For instance, Asians tend to show stronger negative responses to ostracism than Western cultures (Kimel et al., 2017) as well as to dampen positive emotions in context requiring high cognitive effort (i.e.,

studying for en exam) as compared to European Americans (Ma, Tamir & Miyamoto, 2018). Furthermore, among the emotions' regulation strategies, distraction and cognitive reappraisal appear to be less influenced by the social context compared to suppression that seems to be mostly used when non-close others are present. Moreover, while suppression is often driven by non-hedonic motives, distraction and cognitive reappraisal are preferred when the goal is to reach hedonic needs (English et al., 2017).

As for emotions' regulation, there is a lack of agreement regarding the definition of problems in emotion regulation or emotion dysregulation. A first issue is whether the emotions' dysregulation arises from the emotion generation level, such as experiencing an emotional over reactivity, or from the emotion regulation level, such as experiencing difficulties in applying regulation strategies, or from both (Sheppes, Suri & Gross, 2015; D'Agostino et al., 2017). Indeed, the narrative review by D'Agostino et al. (2017) defines emotions' dysregulation according to five dimensions: decreased emotional awareness (i.e., low ability to recognize and verbalize emotions), inadequate emotional reactivity (i.e., inappropriate responses to emotions), intense experience of emotions, emotional rigidity (i.e., dominance of a particular emotion or difficulty to modulate emotional responses according to the context) and difficulties in cognitive reappraisal of emotions (D'Agostino et al., 2017).

Moreover, emotions' dysregulation is frequently defined based on the patterns of maladaptive thinking strategies, such as worry or rumination, defense mechanisms, such as denial, or emotional behaviours, such as avoidance, venting and aggression, that it contributes to generate (D'Agostino et al., 2017; Bonanno & Burton, 2013; Sheppes et al., 2014). As such, difficulties in emotions' regulation are pivotal in psychiatric disorders (Sheppes, Suri & Gross, 2015). Indeed, emotion dysregulation appears to be a transdiagnostic issue across different mental disorders going from attention deficit/hyperactive disorder, autism spectrum disorder, to schizophrenia, anxiety and mood disorders, and borderline personality disorder (Aldao et al., 2010; for a review see D'Agostino et al., 2017).

The lack of a common definition is also due to the fact that, over the years, many research groups have proposed several cognitive and neurocognitive models, adopting different terminology and addressing different aspects of emotions' regulation processes. The next paragraphs present a brief description of the main cognitive models suggested about emotions' regulation processes and strategies (for the neural models and research see the Chapter 4).

1.2 Cognitive models of emotions' regulation: a brief overview

As previously mentioned, different cognitive models addressed the concept of emotion regulation. In my opinion, these models should not be considered as antithetical, rather they focus on specific aspects of emotion regulation processes and strategies. They have described emotion regulation processes according to different criteria, e.g., at which time point the different regulation strategies occur (Gross, 2014), for which motivation emotions' regulation is carried on (e.g., to achieve hedonic motives or goals, or to perform a task; Koole, 2010), whether the strategies are explicit or implicit (Phillips et al., 2003; Phillips et al., 2008; Etkin et al., 2015; Gyurak et al., 2011) and which are their neurobiological underpinnings, or whether they are intrinsic or extrinsic (Gross, 2014).

The cognitive models described both common aspects and differences of emotions' regulation processes.

Regarding the commonalities, most of the models (Gross, 2014; Koole, 2010; Phillips et al., 2008; Etkin et al., 2015) identified cognitive and behavioral strategies of emotions' regulation. Cognitive emotions' regulation strategies usually encompass the modulation of attention and reappraisal. Attentional strategies mainly involve selective attention, that is focusing the attential focus on a specific task or thought, and distraction, that is shifting the attentional focus from a stimulus, that usually elicits an intense emotional activation, to another, that usually reduces the emotional activation (Gross, 2014; Koole, 2010; Phillips et al., 2008). Also reappraisal is referred as a cognitive strategy (Gross, 2014; Koole, 2010; Phillips et al., 2008; Etkin et al., 2015). It consists of giving a different explanation or cognitive evaluation of the situation or stimulus that caused the emotional reaction or of the emotion itself and can be declined in different ways, such as reinterpretation, rationalization or anticipation of events (Phillips et al., 2008). Behavioral emotion regulation strategies include concrete actions undertaken both to prevent experiencing an emotion, through situation selection and situation modification, and to modulate its expression, using suppression or a variety of adaptive or maladaptive behaviours, such as consuming psychotropic substances, doing physical activity, using relaxing techniques (Gross, 2014; Koole, 2010; Phillips et al., 2008).

Regarding the differences, two useful distinctions that can help framing the literature on emotions' regulation are the ones between explicit vs implicit emotions' regulation processes and between intrinsic versus extrinsic emotions' regulation processes.

A first distinction is then between explicit and implicit emotions' regulation. Explicit emotions' regulation is conscious, controlled and effortful, and requires cognitive control. It occurs when individuals are aware to modify their emotional state, applying specific process or strategies. On the other hand, implicit emotions' regulation is unconscious, effortless and automatic (Braunstein, Gross & Ochsner, 2017). It occurs when individuals are unaware of their emotions' regulating goal, process, or both. Although the definition of explicit and implicit emotional regulation is rather shared, there is less agreement about which specific strategies are implicit and which are explicit. Some authors (Phillips et al., 2008; Etkin et al., 2015) claimed that the difference between explicit and implicit emotion regulation strategies does not regard the type of strategy used, but the level of awareness, control, and intentionality. Some other authors theorized that explicit and implicit emotions' regulation processes can be conceived on a continuum rather than as opposite processes (Gross, 2014). Indeed, although historically research most focused on voluntary/explicit processes, some authors identified specific implicit strategies, such as emotional conflict adaptation, emotion regulatory goals, (Gyurak et al., 2011; Braunstein, Gross & Ochsner, 2017), extinction, reinforcer evaluation, placebo (Braunstein, Gross & Ochsner, 2017), affect labeling, emotional conflict adaptation, habitual emotion regulation, error-related regulation (Gyurak et al., 2011), trying to develop theoretical frameworks that integrate evidence of explicit and implicit strategies, which are both needed to individual well-being (Gyurak, Gross & Etkin, 2011; Braunstein, Gross & Ochsner, 2017). For instance, Braunstein et al. (2017), in their two-dimensional model, interestingly hypothesised that both the goal of the regulation process and the regulation process itself could be explicit or implicit.

Finally, a second distinction is between intrinsic and extrinsic emotions' regulation processes that relates to the fact that emotions' regulation strategies can be used to change the affective state of both the Self and/or another person: intrinsic emotions' regulation consists of regulating one's own emotions; extrinsic emotions' regulation consists of regulating someone else's feelings. According to some authors, intrinsic and extrinsic regulation strategies can be interrelated: for instance, a person can use extrinsic regulation, such as helping someone else to calm down, to change his/her emotional state (Gross, 2014).

In the next paragraphs details of the most known cognitive models of emotions' regulation will be presented.

1.2.1. The process model of emotion regulation

The *process model of emotion regulation*, originally postulated by Gross (1998) and updated over the years (Gross, 2014, 2015), develops from the *modal model of emotion* (Barrett, Ochsner, & Gross, 2007; Gross, 2014; see Figure 1), which focuses on the temporal steps sequence involved in emotion generation. According to the *modal model*, the generation of an emotional response typically involves the following steps: a) the presence of a psychologically relevant situation (an external or internal stimulus); b) the shifting of the attention toward the relevant situation; c) the appraisal of the situation; d) the generation of an emotional response, that can originate a new loop of emotion generation process.

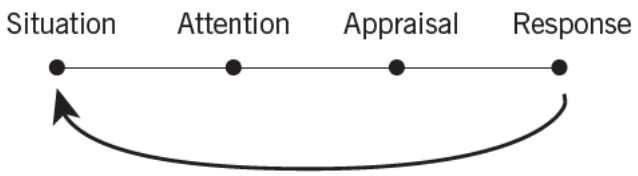


Figure 1. The figure shows the modal model of emotion (Gross, 2014).

Based on the *modal model*, the *process model of emotion regulation* (see Figure 2) focuses on when emotions' regulation strategies take place within the course of emotions' generation (Gross, 1998), before (*"antecedent-focused strategies"*) or after (*"response-focused strategies"*) experiencing an emotional activation (Figure 3).

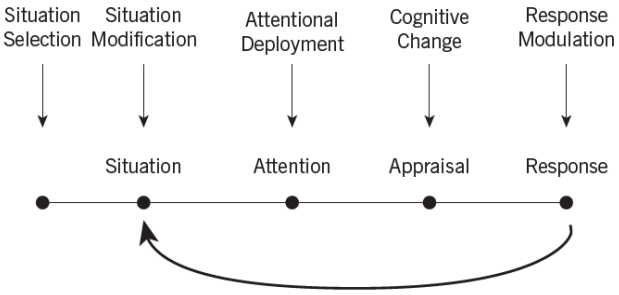


Figure 2. The figure shows the process model of emotion regulation (Gross, 2014).

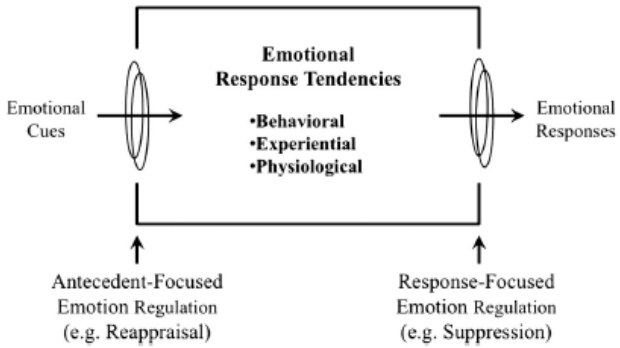


Figure 3. The figure shows the antecedent- and the response-focused strategies (Gross, 2014).

In details, *situation selection* consists in taking decisions that put the subject in a certain situation or not before that an emotionally relevant situation occurs (e.g., avoiding a dinner because it would be annoying), whereas *situation modification* consists in making direct changes on a specific situation, which has already occurred, to modify its emotional impact (e.g., leaving a room where two people are having an argument). *Attentional deployment*, such as rumination, distraction and concentration, consists in deliberately shifting the focus of attention toward a different and a more neutral stimulus/situation than the emotionally salient one (e.g., engaging in activities that absorb one's cognitive resources). *Cognitive change* consists in cognitively reframing the original appraisal of the emotional trigger, i.e. "reappraisal" (e.g., imaging a better outcome or thinking to a positive explanation for a situation; De Wit et al., 2015), or in modifying beliefs about own abilities to manage the situation, or in avoiding judging emotions when occur (i.e., acceptance). R*esponse modulation* consists in directly acting on behavioral or physiological or emotional reactions to the trigger with the aim to modify them (e.g., physical exercise, use of alcohol or drugs or food consumption) (see McRae & Gross, 2020 for a review).

With the *extended process model of emotion regulation* (see Figure 4) Gross (2015) postulates how a person decides to use a certain strategy instead of another to regulate his or her emotions. Indeed, according to the extended model, beyond the process that generates an emotional response, known as a first-level evaluation system, there is a second-level evaluation system that accounts for individuals' decision to regulate (or not regulate) emotions, based on a) the identification of the emotion(s) to regulate, b) the selection of a specific emotions' regulation strategy, and c) the implementation of the selected strategies. The model explains also why some individuals successfully use regulatory strategies, while others fail. For instance, the identification of the emotion(s) to regulate may fail because the subject lacks emotional awareness (Inzlicht, Schmeichel, & Macrae, 2014), shows psychological inertia or believes emotions are substantially immutable (Romero et al., 2014; Tamir, John, Srivastava, & Gross, 2007). The selection of the regulation strategy may fail because the person has few strategies in his or her repertoire or has a low emotions' regulation self-efficacy. The implementation of the regulation strategy may fail due to difficulties in perceiving and executing practical tactics.

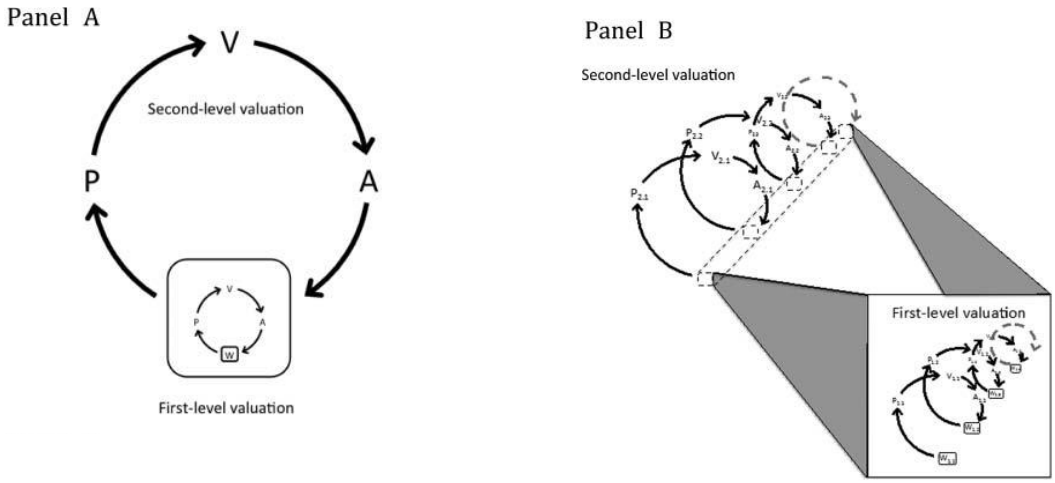


Figure 4. The figure shows the extended process model of emotion regulation (Gross, 2015).

1.2.2. Emotions' regulation model by Phillips (2003; 2008)

Phillips and colleagues (2003; 2008), in their model, for the first time, distinguished between voluntary (i.e., intentional) and automatic (i.e., unconscious), emotions' regulation, paving the way for successive models and research exploring and comparing effortful versus uncontrolled emotions' regulation processes.

Among the voluntary processes, authors included: "*voluntary behavioral control*" (i.e., suppression) that may consist in avoiding emotional facial expressions (Gross & Levenson, 1997; Hagemann, Levenson & Gross, 2006; Goldin, McRae, Ramel & Gross, 2007), or viewing emotional stimuli as a detached observer (Beauregard, Lévesque, & Bourgouin, 2001), or restraining from any emotional response (Ohira et al., 2006); "*voluntary attentional control*", such as selective attention (Goldstein et al., 2007); "v*oluntary cognitive change*" that consists in changing the cognitive meaning of an emotional stimulus by reappraisal, reinterpretation (Ochsner et al., 2002), rationalization (Phan et al., 2005), or anticipation of events and outcomes to be ready for future adverse events.

Among the automatic processes, authors included: "*automatic behavioral control*" that consists in behaviours extinction (e.g., fear extinction in a conditioned learning paradigm, Phelps et al., 2004) or stress response inhibition; "*automatic attentional control*" that consists in implicitly

turning the attention away from emotionally salient stimuli (Armony & Dolan, 2002; Pourtois et al., 2005); "*automatic cognitive change*" that consists in implicit appraisal and reappraisal of stimuli (e.g., , risk or rule learning that happens outside of subjective awareness).

The model by Phillips and colleagues has been developed also to explore neurobiological underpinnings of emotions' regulation. Therefore, more details of this model will be presented in Chapter 4.

1.2.3. The computational model by Etkin

Based on the existing literature on reinforcement learning, Etkin, Büchel & Gross (2015) postulated the emotions' regulation as a decision-making process, meaning that people decide to regulate (or not) emotions based on the value the emotions have for the Self, that in turn could positively (i.e., positive prediction error) or negatively (i.e., negative prediction error) change based on the effectiveness of the emotions' regulation strategy employed.

As Philips et al. (2003; 2008), also Etkin and colleagues distinguished between explicit and implicit processes of emotion regulation, with explicit emotions' regulation that is effortful and involves awareness, and implicit emotions' regulation that occurs without conscious monitoring. From a computational perspective, explicit emotions' regulation has been theorized as "model-based" emotions' regulation, that is strategies based on learned rules, while implicit emotions' regulation has been theorized as "model-free" emotion regulation, that is strategies depending on changes in the external environment.

1.2.4. The dual-process framework

Gyurak, Gross & Etkin (2011) integrated explicit and implicit emotions' regulation processes within a dual-process model. As shown in Figure 5, although explicit strategies occupy a central position in the model due to the involvement of awareness, cognitive efforts and conscious monitoring, explicit and implicit regulation strategies are actually inter-related (see the double arrows in the figure). Focusing on implicit regulation, authors identified different strategies that are not mutually exclusive, but rather they can occur together within the same regulation process (see the dashed lines surrounding each implicit strategy-box).

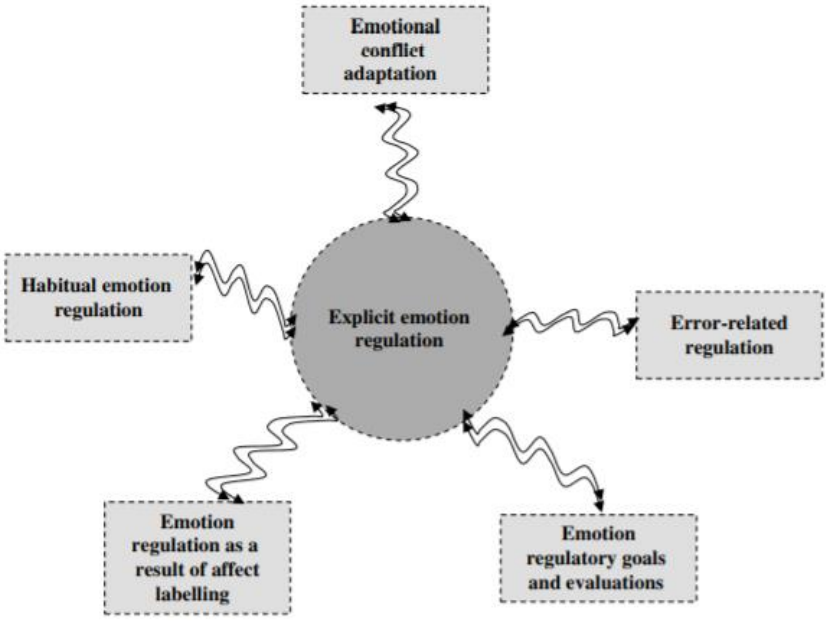


Figure 5. The figure shows the dual-process framework (Gyurak, Gross & Etkin, 2011).

The implicit strategies are the following: "*emotional conflict adaptation*" that requires to implicitly reduce (e.g., reduced reaction times) the emotional conflict elicited by a stimulus depicting an emotion and another stimulus depicting an opposite emotion (as happens in the incongruent trials of the emotional Stroop task; Egner et al., 2008);*"habitual emotion regulation*" that occurs when, due to the repeated emotions' regulation through an explicit strategy in a certain situation, individuals internalize the explicit strategy and transform it into an effortless/implicit strategy that can be generalized to different situations and contexts (Aarts & Dijksterhuis, 2000; Cohen, Berkman & Lieberman, 2012); "*emotion regulatory goals and values*" refers to the individuals' implicit goals of regulating emotions (Schweiger-Gallo et al., 2009);*"emotion regulation through affect labeling"* that consists in regulating emotions by labeling an affective event, for instance talking about affective sensations and events has been proved to effectively reduce emotional arousal, distress and physiological reactions, with both immediate and delayed effects on individuals' emotional responses (Torre & Lieberman, 2018); "*error-related regulation*" that occurs when individuals unconsciously reduce their reaction-times (Rabbitt, 1966) or increase the accuracy (Laming, 1979) to adjust their performance after committing an error when performing a cognitive task.

1.2.5. The multilevel framework

In a recent review, Braunstein, Gross & Ochsner (2017) proposed a multilevel framework that classifies emotion regulation according to two orthogonal dimensions: the nature of the emotions' regulation goal and the nature of the emotions' change process (Figure 6).

The goal dimension refers to how much the goal to regulate emotions is intentional and ranges from implicit to explicit: having an explicit goal means that a person is conscious and willing to achieve an emotional state, while being unconscious of the regulation goal occurs when it is incidental (e.g., walking can calm even if the goal of walking is going to the supermarket). The process dimension refers to the type of strategies implemented to achieve emotion regulation and ranges from automatic to controlled, based on how much top-down control, intentionality, and awareness are needed to apply the strategy. Accordingly, the multilevel framework results in four classes of emotion regulation strategies: "*explicit controlled emotion regulation*", i.e., the individual is conscious of both the goal to regulate and the process to use, for example selective attention, distraction, and reappraisal; "*explicit automatic emotion regulation*", i.e., the individual consciously regulates emotions but he/her acts in automatic ways, for example when individuals change their response to a painful stimulus based on the belief that they received a real treatment, whereas in reality they received a sham one, i.e., the placebo effect; "*implicit controlled emotion regulation*", i.e., the individual uses top-down processes but the goal to regulate one's emotions is incidental, for example responses to the emotional Stroop (Buhle, Wager & Smith, 2010) and go/no go (Berkeman, Burklund & Liebermann, 2009) tasks or to priming paradigms; "*implicit automatic emotion regulation*", i.e., the individual is unaware of both the goal to regulate emotions and the way this goal could be met, for example extinction - an association between a stimulus and an outcome is unlearned - and reinforcer revaluation - the association of a stimulus with an outcome is replaced with a different outcome) (Figure 6).

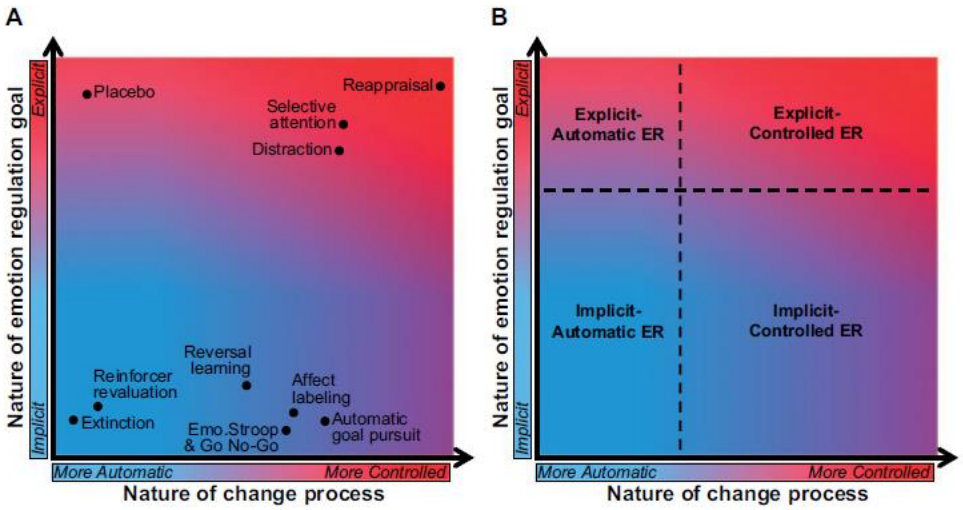


Figure 6. The figure shows the multilevel framework (Braunstein et al., 2017).

As shown by the brief overview of the cognitive models of emotions' regulation, the most actual dual models underlied that both explicit and implicit processes foster emotions' regulation. The studies that will be presented in this thesis support this point of view that, interestingly, is also shared by research exploring treatment strategies for deficits in the regulation of emotions. In this context, Grecucci and colleagues (2020) recently posits that not only the top-down and bottom-up emotions' generation mechanisms but also the descending cognitive and experiential treatment techniques should be integrated to effectively deal with emotions' dysregulation.

Chapter 2: Emotions' regulation in experimental research

2.1 Studying explicit emotions' regulation processes: paradigms in experimental research

Before presenting research paradigms usually used to test explicit and implicit emotions' regulation processes, it is worth noticing which are the methods applied to experimentally induce basic emotions (i.e., anger, disgust, surprise, happiness, fear and sadness). In this regard, Siedlecka & Denson (2019), in their review, identified five classes of experimental paradigms, namely visual stimuli presentation (e.g., Schofield, Youssef & Denson, 2017; Kragel & LaBar, 2013), music listening (e.g., Sharman & Dingle, 2015; Etzel et al., 2006), autobiographical recall (e.g. Schwartz & Davidson, 1997; Marci et al., 2007), situational procedures in which subjects are directly involved in emotion-eliciting situations (e.g. Lobbestael, Arntz & Wiers, 2008; Alaoui-Ismaïli et al., 1997), and imagery that requires participants to imagine specific emotionally relevant scenarios (e.g., Salerno & Peter-Hagene, 2013; Ottaviani et al., 2013).

Based on that, as regard explicit emotions' regulation, experimental literature explored several methods to facilitate the modulation of the induced emotions, as typically measured by rating scales (discrete or continuous). One of the most used consists in directly instructing participants to reappraise the negative affect they feel while looking at emotional visual stimuli. The aim is that, by using reappraisal (e.g., "reinterpret the stimulus such that it appears less stressful", or "imagine a more positive outcome or interpretation of the portrayed events", or "realise the stimulus is not real-life"), participants down-regulate their emotions, compared to control conditions in which participants are usually required to simply attend the visual stimuli to come (see McRae & Gross, 2020 for a review).

For instance, a series of studies tested this explicit emotion's regulation strategy by showing unpleasant picture from the International Affective Picture Set (IAPS; Lang, Bradley & Cuthbert, 1997) to healthy (Ochsner et al., 2002; Schutter & Van Honk, 2009) and clinical groups (e.g., patients with obsessive-compulsive disorder, OCD; Douw et al., 2020; De Wit et al., 2015). Results showed that reappraisal, compared to the no-regulation condition, was effective in reducing the images negative affects in healthy volunteers (Ochsner et al., 2002) and the impact of OCD-related images (washing, checking, symmetry) in OCD patients (De Wit et al., 2015). These results corroborate the findings by Ochsner et al. (2004) who demonstrated that both the self-focused

reappraisal, that is modulating the personal relevance of the presented images (e.g, increasing the sense of subjective closeness or the sense of objective distance to pictured events) and the situation-focused reappraisal, that is modulating the situational context of the presented images (e.g., thinking to a better or to a worse outcome or scenario) were effective in both decreasing and increasing negative emotional reactions.

Concerning pictures depicting social exclusion, He et al., (2019) showed that, compared to passively viewing, reappraisal (e.g., "image a better outcome or find a different explanation of the situation") significantly reduced negative emotions of participants with both high and low depressive symptoms. Interestingly, this result was consistent also when general negative pictures were presented. These findings were replicated by study by Zhang et al. (2019), in which the emotions' adjustment through cognitive reappraisal (e.g. "imagine that you are the one who is alone in the image, and please try to make your emotions less negative") reduced negative emotions induced by social exclusion and general negative pictures.

Interestingly, literature showed that while cognitive reappraisal entails different mechanism than other forms of explicit emotions' regulation, such as attentional deployment, it could be actually facilitated by directing gaze from emotional to neutral stimuli, that is a way of manipulating attentional deployment (Urry, 2010). Indeed, in a study by Van Reekum and colleagues (2007) participants were found to spend less time looking at emotional information of the images they reappraised to regulate their negative emotions.

Other studies further confirmed the regulation role of the attentional deployment by showing that shifting gaze towards neutral areas of unpleasant pictures enhanced brain event-related potentials that are sensitive to affective arousal (Dunning & Hajcak, 2009; Hajcak, Dunning & Foti, 2009).

Other forms of explicit emotions' manipulation include the imagery rescripting, a stepwise guided procedure that allows people to rescript a negative affect-evoking stimulus (e.g., image) into a positive one (Wild, Hackmann & Clark, 2008). The procedure first helps people entering the negative image and then changing the evoked emotions by perceiving the stimulus through all their senses (Fink et al., 2018). Two consecutive studies by the same research group showed that imagery rescripting and cognitive reappraisal equally reduced the negative impact of disgusting images on healthy participants and OCD patients, as compared to viewing neutral pictures (i.e., control condition; Fink et al., 2018; Fink & Exner, 2019).

Similar regulation effects were obtained by Kalisch et al. (2006), who tested the efficacy of using distraction as explicit emotions' regulation strategy. In their study, authors found that self-

distraction during an anxiety-inducing paradigm, in which participants were threatened to receive electric painful stimuli at variable time intervals, reduced anxiety as measured by heart rates levels. However, another study found that distraction was not more effective than cognitive reappraisal in down-regulate reactions to negative images (McRae et al., 2010). Differences in regulation efficacy between reappraisal and distraction were further confirmed by other studies that showed that, compared to distraction, reappraisal involves greater processing of stimuli affective meaning and memory for reappraised stimuli (Dillon et al., 2007; Sheppes & Meiran, 2007). Accordingly, reappraisal was found to be more effective then distraction when people have more time available to regulate their emotions (Kalokerinos et al., 2017) and when a lasting regulation is needed (e.g., instances in which people are repeatedly exposed to the emotion-inducing stimuli; Hermann, Kress & Stark, 2017; for a meta-analysis see Webb, Miles & Sheeran, 2012), while distraction seems to have more short-time effects (Kross & Ayduk, 2008). Therefore, it is not surprising that, compared to the other emotions' regulation strategies, reappraisal is associated with greater long-term physical (Appleton et al., 2014) and psychological well-being (Gross & John, 2003; Cludius, Mennin & Ehring, 2020) as well as social functioning (English et al., 2012).

Finally, studies investigating suppression, that is the conscious inhibition of emotional reactions (e.g., facial expressions, feelings, behaviours) to eliciting stimuli, showed that this effortful regulation strategy, compared the control condition, reduced arousal (i.e., heart rates, facial expression) after the presentation of disgusting-eliciting stimuli (Gross & Levenson, 1993, 1997; Hagemann et al., 2006). This result was confirmed by a more recent experiment (Lévesque et a., 2003) in which suppression, but not the simple viewing of sad films, decreased participants' sadness ratings. However, other studies pointed out that suppression could be also linked to weak regulation effects when compared to reappraisal (Goldin et al., 2008; Kalokerinos, Greenaway & Denson, 2015).

2.2 Studying implicit emotions' regulation processes: paradigms in experimental research

As theorised by more recent cognitive models (Phillips et al., 2003, 2008; Etkin, Büchel & Gross, 2015; Gyurak, Gross & Etkin, 2011; Braunstein, Gross & Ochsner, 2017; see paragraphs 1.2.2, 1.2.3, 1.2.4, 1.2.5), besides conscious emotions' regulation, people take advantage also from implicit processes of emotions' regulation that are based on unconscious and unaware mechanisms (Miyake & Friedman, 2012). Indeed, a review by Koole, Webb & Sheeran (2015) suggests that implicit processes determine the effectiveness of the emotions' regulation by affecting decisions about to regulate (or not) emotions and which regulation strategies (either habitual or contestualized) is selected and applied, based on automatic procedural skills and implementation intentions. This is similar to what happpens at the cognitive level where, as shown by a systematic review I run during my PhD, implicit attitudes and bias drive behaviors and phenotypic preferences (e.g., food behaviors and weight stigma; see Gallucci et al., 2021 for more details).

At the experimental level, different paradigms have been used to study unconscious regulation. Among them, implicit paradigms usually infer emotional reactivity as well as the ongoing regulation processes by measuring physiological indexes or the performance in behavioural tasks.

Regarding the assessment of physiological indexes, studies on both healthy participants and patients, for instance, recorded higher level of salivary cortisol (Brunoni et al., 2013) and heart rates (Berger et al., 2017; Brunoni et al., 2013), as well as variability in skin conductance (Herrmann et al., 2018) and facial electromyography activity (Hurlemann et al., 2015) as signals of less successful emotions' regulation. Although a detailed review and description of physiological indexes used by research on implicit emotions' regulation processes is beyond the scope of the present thesis, it is worth saying that there is a wide literature that theorised (e.g., Niedenthal et al., 2010; Goldman & Sripada, 2005; Fuchs & Koch, 2014) and tested (e.g., Harmon-Jones & Peterson, 2009; Niedenthal et al-. 2009; Havas, Glenberg & Rinck, 2007) the processes linked to the broad concept of "embodied emotion". In brief, several authors suggested that the somatosensory and motor components of emotional experience strongly impact on the higher order emotional processing, through continuous feedback cycles. For instance, according to Niedenthal et al. (2010), seeing facial expressions triggers a series of motor, somatosensory, affective and neural states (i.e., "embodied simulation") that represent the meaning that the perceiver attributes to the expressions,

thereby influencing the following regulation strategies (for reviews see Winkielman et al., 2015; Price, Peterson & Harmon-Jones, 2012).

Regarding the measurement of the tasks' performance, variations in the reaction times and accuracy are frequently considered as dependent variables. For example, a widely used paradigm is the emotional Stroop task, a modified version of the original task (Stroop, 1935), in which participants are required to ignore the stimuli emotional content (e.g., affective-related words or images) and to respond to not emotions-related characteristics of stimuli (e.g., color of the written words) as fast and accurate as possible (Williams, Mathews & MacLeod, 1996). Several studies applying the emotional Stroop task showed longer reaction times when more arousing stimuli (McKenna & Sharma, 2004; Frings et al., 2010) or stimuli with negative valence (Depperman et al., 2016) were presented to healthy participants. Similar results were found also by studies on clinical samples, such as patients with chronic pain (see Amaro-Díaz et al., 2022 for a review) or with remitted depression (Dai & Feng, 2011; Strand, Oram, & Hammar, 2013). Together, these findings suggest that changes in the cognitive performance due to the interference of emotional information (i.e., effective or ineffective inhibition of stimuli emotional arousal or valence) should be attributed to the occurrence of implicit emotions' regulation.

Another paradigm measuring task performance, in terms of reaction times, is the attentional engagement-disengagement task that assesses the ability to engage attention to and disengage attention from an emotional stimulus (e.g., emotional faces), as measured by the latency of the gaze shift. For instance, studies using this task combined with the eye-tracking demonstrated that healthy people are generally characterized by a positivity bias, that is the tendency to keep the attention longer (i.e., fixation latency) on positive stimuli (Kellough et al., 2008; Sears et al., 2010). However, the same studies did not find this bias in patients with major depression (Kellough et al., 2008; Sears et al., 2010), who showed difficulties in disengaging (i.e., shifting) their attention from negative stimuli, such as sad faces (Casera set al., 2007; Sanchez et al., 2013; De Raedt & Koster, 2010 for a review). Similar results were found also by Wolkenstein & Plewnia (2013). Indeed, in their study, depressed patients showed increased reaction times and reduced accuracy in a delayed response working memory task when affective, but not neutral, distractors were presented. Interestingly, these attentional difficulties negatively correlated with the ability of depressed patients to recovery from sadness caused by a stress induction task, administered later in the experimental procedure (Sanchez et al., 2013).

The impact of failures of affective control on psychological well-being were demonstrated also by other experiments using the Emotional Picture Sorting Task (EPST; e.g., Aker & Landrø, 2014; Schweizer et al., 2020), that is the affective version of the Wisconsin Card Sort Task (WCST; Grant & Berg, 1948). The EPST typically presents emotional expressions instead of the traditional cards and requires participants to assign each card to one of the available deck based on randomly changing sorting rules: number, colour and shape of geometrical items in the classical version or of neutral versus emotional faces in the affective version. Studies showed correlations between lower affective control in the EPST and greater psychological problems as well as difficulties in emotion's regulation, especially in young adolescents (Schweizer et al., 2020).

Other studies pointed out the role of implicit emotions' regulation to manage the processing load of affective information and to guide the affective control elicited by behavioural tasks, such as the EPST. Indeed, Aker & Landrø (2014) showed that the performance of participants was better in the traditional than in the affective version of the WCST (Aker & Landrø, 2014). This result was corroborated also by studies (Mohammed, 2019; Veroude et al., 2013) reporting increased reaction times in the affective, but not in the traditional, versions of the n-back task and the letter-number task, that respectively require to decide about the similarity or the difference between target affective expressions and a reference expression presented n-times before in the trial and to focus on the faces' gender or affective valence according to where (e.g., upper or bottom quadrant) the stimuli appear.

In line with these studies, other works further focused on affective control by adopting the emotional go/no-go task (Schulz et al., 2007), that is the affective version of the traditional go/no-go task (Gomez, Ratcliff & Perea, 2007). Typically, in this task participants, according to changing instructions, have to respond or to not respond (i.e., inhibition) as fast and accurate as possible to emotional (e.g., facial expressions) or neutral stimuli that thus could be either go stimuli (i.e., the ones to respond to) or no-go stimuli (i.e., the ones to not respond to) (more details about the task will be presented in paragraph 3.2). By applying this task, Tottenham et al. (2011) demonstrated that emotional information interfered with the maintenance of cognitive control, as increased false alarm rates (i.e., failures in response inhibition) were recorded when emotional faces, regardless of their negative of positive valence, were no-go stimuli. Moreover, this result was more evident in children compared to adolescents, and in adolescents compared to adults. Thus, the affective control should be considered a complex ability slowly learned during the development. Indeed, looking at adolescents, while they are faster in responding to emotional faces as go stimuli (see also Steinberg

et al., 2008; Zhang et al., 2016), they slowed down when were required to inhibit responses to emotional faces.

Interestingly, a study measuring electroencephalography components during an emotional go/no-go task showed that inhibitions difficulties in adolescents were mediated by anhedonia and depressive symptoms (Zhang et al., 2016). Indeed, higher anhedonia correlated with increased automatic response inhibition (NoGO P3 amplitude) of positive faces. By contrast, higher depressive symptoms correlated with hypoactive automatic response inhibition of negative faces.

Similar results to Tottenham et al. (2011) were found also by Schel & Crone (2013). However, their findings contrast with previous literature (Brass et al., 2013) in showing that when affective stimuli are irrelevant for the task, as when participants had to respond (or not) to the faces' colours ignoring the emotional expressions, they did not influence the choice behaviour of children and adults, in terms of both reaction times and responses' accuracy.

Chapter 3: Experimental investigations of emotions' regulation processes

3.1 Explicit emotions' regulation processes: data from a healthy group

This paragraph reports the results of a study that tested the effects of different explicit emotions' regulation strategies on affective reactions of a group of healthy volunteers directly exposed to social exclusion. Indeed, as stated in the Chapter 2, experimental procedures in which subjects are directly involved in emotion-eliciting situations have been widely used in literature to induce emotional reactions and assess explicit modulation processes (e.g., Lobbestael, Arntz & Wiers, 2008; Alaoui-Ismaïli et al., 1997).

Before presenting the study methods and main results, it is worth noticing that a considerable body of literature attempted to shed light on emotional consequences of social exclusion. For instance, studies demonstrated that ostracism is associated with increased hurt feelings, anger, sadness, hostility (Gerber & Wheeler, 2009; Williams & Nida, 2011), humiliation (Dickerson, 2011) and worsened fundamental psychological needs, i.e., belonging, control, self-esteem, and meaningful existence, also during computer-based interactions (Williams & Zadro, 2001; Zadro et al., 2004). Crucially, distress has been recorded immediately following social exclusion (Zadro et al., 2004), but it could also last several minutes after exclusion episodes (Zwolinski, 2012, 2014; Zadro et al., 2006). This is particularly important considering the evidence that prolonged experiences of social ostracism, without the possibility to cope, cause depression, alienation and learned helplessness (Wesselmann et al., 2012; Zwolinski, 2012, 2014; Zadro et al., 2006; DeWall & Bushman, 2011). At a cognitive level, ostracism reduces cognitive performance (Baumeister, Twenge & Nuss, 2002) and increases readiness to interpret ambiguous behaviors as threats to self-concept (DeWall et al., 2009). Considering behaviors, being exposed to social exclusion affects self-regulation capabilities. In fact, excluded people tend to lose control on eating behavior (Oaten et al., 2008) or show increased aggression, for instance, by choosing unpleasant noises for their ostensible partner during a competitive task (Dambacher et al., 2015). At a group level, individuals exposed to prolonged exclusion or people belonging to minorities are more likely involved in mass-violence, such as terrorist attacks or mass-shootings (Leary et al., 2003; Wesselmann, Ren & Williams, 2015).

Building on these results, some authors theorized that an early detection system allows humans to immediately grasp signals of being exposed to possible experiences of social exclusion

(Williams, 2001; 2009). This system, in turn, motivates humans to take actions to regulate the social pain and recover functional relationships, preventing isolation (Gross & John, 2003). The ability to regulate emotional, cognitive, and behavioral reactions following ostracism is then crucial to avoid or modulate prolonged, and potentially chronic, consequences of social exclusion, such as loss in motivation, cognitive deconstruction, affective numbness, and depression (Williams, 2009; Twenge, Catanese & Baumeister, 2003). For instance, studies showed that focused attention on breathing before the exposure to an exclusion experience reduced the perceived threats to the fundamental psychological needs (Molet et al., 2013; Wesselmann & Williams, 2013). Moreover, changing own behavior, for example, by engaging in messaging, even with an unknown person (Gross, 2009), or by being included (Tang & Richardson, 2013), immediately after ostracism, were found to improve hurt feelings, self-esteem, mood as well as psychological needs.

However, how different explicit emotions' regulation effectively modulate reactions to exclusion is not fully understood. Therefore, this study tested whether distraction, emotion reinterpretation and situation reinterpretation applied after the exposure to social exclusion, compared to a no-regulation control condition, differently reduce negative emotions, as measured by the Rejected-Related Emotions Scale (RES; Buckley et al, 2004), threatened basic psychological needs, as measured by the Need-Threat Scale (NTS; Williams et al., 2009), temptation to act aggressively, as measurd by the Aggressive Temptation Scale (ATS; Allen & Leary, 2010), and social pain, as measured by the Pain Face Scale (Wong & Baker, 2001) and by asking participants to rate how much they feel ignored and excluded during the exclusion situation.[1] During my PhD, I had mainly a role in the data analysis and results' discussion rather than in the data collection.

[1] The RES is a 20-item questionnaire measuring anger, hurt, anxiety, rejection and sadness on a 7-point scale (ranging from 1= not at all to 7= very much). We averaged the scores across the 20 items to create an overall index of negative emotions (Cronbach α=.95), with higher scores indicating higher negative emotions.
The NTS is a 20-items questionnaire assessing how much basic psychological needs (belongingness, self-esteem, control, and meaningful existence) are threatened or satisfied on a 7-point scale (ranging from 1= not at all to 7= very much). We created an overall index by averaging the responses across the 20 items (Cronbach α=.95), with higher scores indicating that basic psychological needs were threatened during the game.
The ATS is a 17-item questionnaire evaluating temptation to engage in aggressive behaviors on a 7-point scale (ranging from 1= not at all to 7= extremely). We averaged the scores to obtain an overall index of antisocial behavior (Cronbach α=.64), with higher scores indicated greater temptation to act aggressively.
The Pain Face Scale is a single pictorial item presenting six faces expressing different levels of pain. Participants were asked to choose the face that mostly represented the level of pain felt during the Cyberball game (ranging from 0= not hurt to 5= worst hurt), with higher scores indicating higher social pain.

Methods

The study involved 387 healthy adults (153 males and 234 females, mean age = 30.22, sd = 10.64), recruited among students of University of Milano-Bicocca. All participants had normal or corrected to normal vision, and reported no history of neurological or psychiatric disorders. Written informed consent was obtained from all participants prior to the inclusion in the study, which was approved by the ethics committee of the University of Milano-Bicocca and conducted in accordance with the ethical standards of the revised Helsinki Declaration.

Participants volunteered to participate in a Cyberball experiment (Williams et al., 2000; Hartgerink et al., 2015). Cyberball is a widely used ball-tossing game, usually adopted to manipulate the short-term ostracism in a virtual computer setting. In the task participants think they are playing a ball game with other players, but the game is in fact controlled by the computer. Participants are only passed the ball on the first trials but not on subsequent trials, thus the task has been shown to simulate feelings of social exclusion similar to those experienced in real life. In particular, in the task version used in the present study, participants were randomly assigned to be included (i.e., receiving an equal number of tosses, roughlty the 33% of the tosses) or excluded (i.e., receiving the ball for the first few throws and then only the 10% of the tosse) by other two players, actually computer-controlled agent (see for instance Riva et al., 2015a).[2]

Right after the end of Cyberball, participants were randomized to get distracted (following the instruction *"We ask you to think to the route path from home to the building you are in right now. For example, you might think to the shops you passed along the way, the transports you used, or to how much traffic you encountered"*), or to positively reinterpret the emotions felt during the game (following the instruction *"We ask you to reinterpret the emotions you felt during the game in less negative way. For example, you might think to your emotions by adopting a detached, uninvolved perspective and unemotional attitude, as if you weren't one of the players"*), or to reinterpret the game experience (following the instruction *"We ask you to reinterpret what happened during the game in less negative way. For example, you might think that your co-players are not familiar with the use of the computer, or that they have not understood the instructions, or even that connection problems did not allow them to play properly"*), or to simply fix a white screen without further instructions (control condition). Next, the participants filled the self-report questionnaires and were debriefed about the experimental procedures.

[2] Analysis of the manipulation check showed that the manipulaton of the social exclusion was effective. Indeed, participants in the exclusion condition reported receiving the ball less often during the game than included participants, $F(1, 379)=1186.57$, $p=.00$, $\eta_p^2=.76$. Excluded participants felt more excluded and ignored than participants in the inclusion condition, $F(1, 379)=823.67$, $p=.00$, $\eta_p^2=.69$.

Data were analyzed using SPSS Statistics (27.0). The study employed a 2 (Cyberball condition: inclusion vs. exclusion) x 4 (regulatory strategy: distraction vs. emotion reinterpretation vs. situation reinterpretation vs. baseline) factorial design ANOVA, with Cyberball condition and regulatory strategy as between-subjects factors. Eight balanced experimental groups with 45-52 participants each were considered. Measures of negative emotions, basic psychological needs and social pain were entered as dependent variables. Fisher's LSD was used for post hoc comparisons.

Main Results

The ANOVA revealed a significant main effect of Cyberball condition for the set of dependent measures (negative emotions, overall index: $F(1, 379)=262.97$, $p<.001$, $\eta_p^2=.41$; basic psychological needs: $F(1, 379)=405.54$, $p<.001$, $\eta_p^2=.62$; social pain, Pain Face Scale: $F(1, 379)=127.91$, $p=.00$, $\eta_p^2=.025$; social pain, excluded/igniored: $F(1, 379)=823.67$, $p=.00$, $\eta p2=.69$; aggression: $F(1, 379)=204.98$, $p<.001$, $\eta_p^2=.35$), with participants in the exclusion condition, compared to those in the inclusion condition, reporting higher levels of negative emotions and social pain as well as feeling more threatened psychological needs and tempted to behave aggressively (see Table 1).

Analysis showed a significant main effect of the regulatory strategy for the overall index of negative emotions ($F(3, 379)=5.10$, $p=.001$, $\eta_p^2=.05$) and aggression ($F(3, 379)=5.35$, $p=.001$, $\eta_p^2=.04$). Indeed, distraction and emotion reinterpretation were associated with lower negative emotions and aggression than reinterpreting the situation and the control condition (see Table 1). The main effect of recovery strategy was also found for social pain ($F(3, 379)=4.73$, $p=.003$, $\eta_p^2=.036$). Indeed, lower painful feelings (i.e., feeling ignored and excluded) followed distraction and emotion reinterpretation compared to the control condition. Lower levels of social pain feelings resulted from emotion reinterpretation than reinterpreting the situation (see Table 1).

Regarding the negative emotions, the Cyberball condition x recovery strategy interaction was significant for "rejection" ($F(3, 379)=3.37$, $p=.02$, $\eta_p^2=.03$), and "anger" ($F(3, 379)=2.70$, $p=.046$, $\eta_p^2=.02$) subscales of the RES. As shown in Figure 7, included participants felt less rejected following distraction and reinterpreting the situation compared to emotion reinterpretation and control condition. Lower rejection feelings resulted from distraction and emotion reinterpretation than reinterpreting the situation and the control condition in the excluded participants (see Table 1 for means, standard deviations and significant pariwise comparisons). As shown in Figure 8, while

no differences in anger ratings were found between the recovery strategies for the included participants, lower anger followed distraction and emotion reinterpretation compared to reinterpreting the situation and the control condition in excluded participants (see Table 1 for means, standard deviations and significant pariwise comparisons).

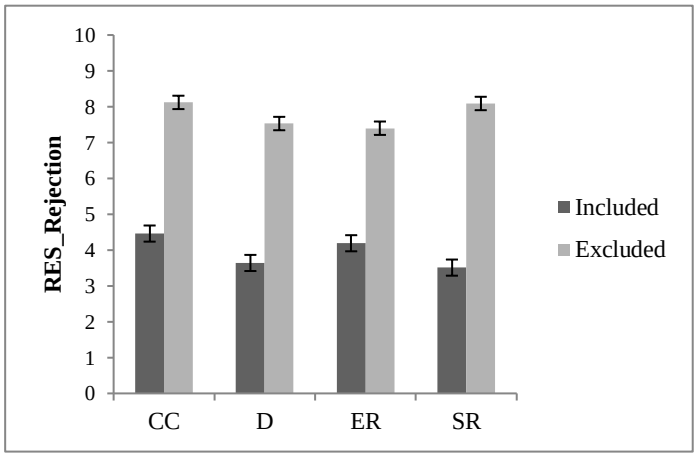


Figure 7. The figure shows the Cyberball x strategy interaction for "rejection" subscale of RES.

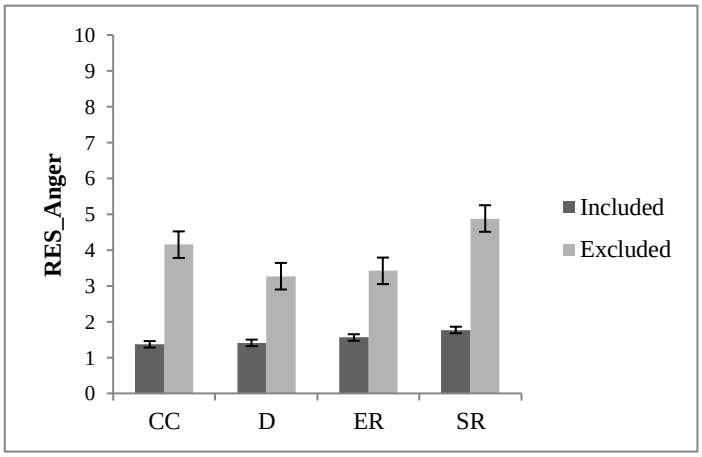


Figure 8. The figure shows the Cyberball x strategy interaction for "anger" subscale of RES.

Regarding aggression, the main effects were qualified by a significant Cyberball condition x recovery strategy interaction ($F(3, 379)=4.27$, $p=.006$, $\eta_{p^2}=.03$). Pairwise comparisons showed lower temptation to behave aggressively when ostracized participants got distracted or revaluated emotions than when they revaluated the situation or fixed the white scrren (Figure 9). Conversely, no difference was found among the regulation strategies in the inclusion condition (see Table 1 for means, standard deviations and significant pariwise comparisons).

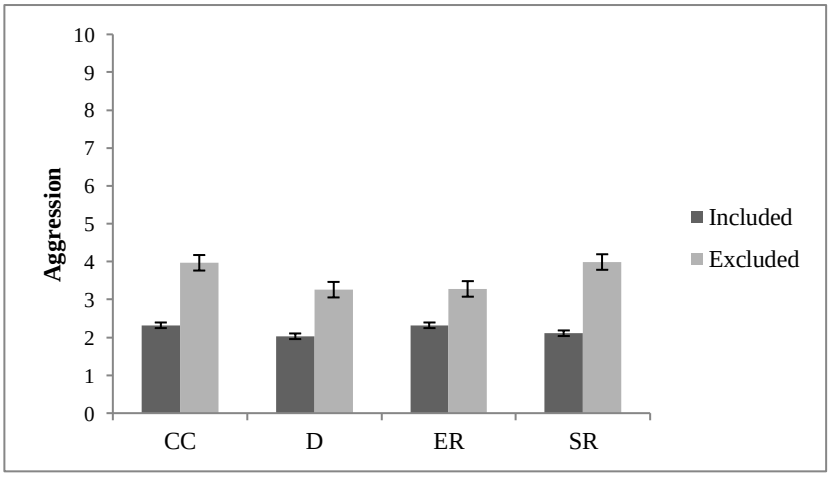


Figure 9. The figure shows the Cyberball x strategy interaction for behavioral aggression.

Regarding social pain, the main effects were qualified by a significant Cyberball condition x recovery strategy interaction ($F(3, 379)=5.35$, $p=.001$, $\eta_p^2=.04$). Pairwise comparisons showed that ostracized participants felt less excluded and ignored after emotion reinterpretation compared to the other regulatory strategies (Figure 10). No differences between the recovery strategies were found in included participants (see Table 1 for means, standard deviations and significant pariwise comparisons).

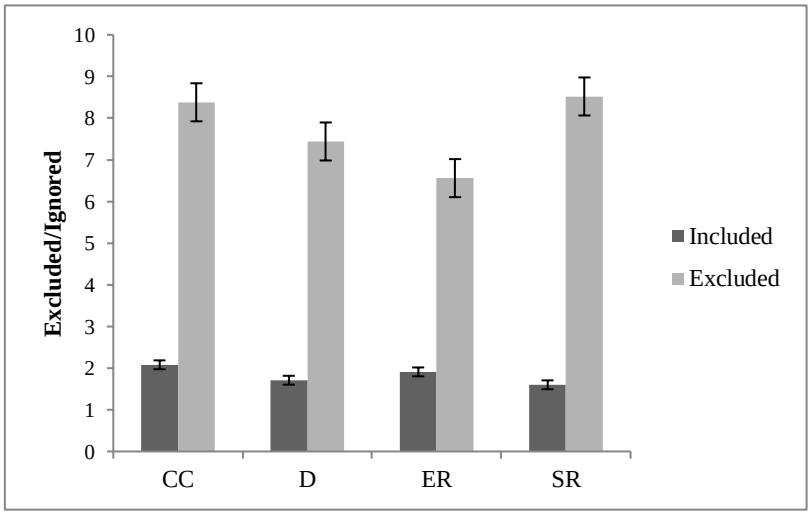


Figure 10. The figure shows the Cyberball x strategy interaction for social pain as measured by feeling excluded/ignored during Cyberball.

Table 1. Means, standard deviation, F values and their associated p-values.

	Inclusion				**Exclusion**						
	D (n=48)	**ER (n=45)**	**SR (n=51)**	**CC (n=52)**	**D (n=46)**	**ER (n=47)**	**SR (n=49)**	**CC (n=49)**	**Cyberball**	**Regulation strategy**	**Cyberball X regulation strategy**
RES Overall index	2.55 (.17)	2.76 (.18)	2.85 (.17)	2.93 (.17)	4.46 (.18)	4.55 (.17)	5.39 (.17)	5.36 (.17)	F=262.97 **p<.00**	F=7.07 **p<.00**	F=2.36 p<.07
RES rejection	3.64+ (.22)	4.19* (.23)	3.51°* (.22)	4.46+° (.21)	7.52 (.23)	7.40+° (.22)	8.10° (.22)	8.12+ (.22)	F=605.49 **p<.00**	F=3.81 **p<.01**	F=3.37 **p<.02**
RES anger	1.41 (.28)	1.56 (.29)	1.77 (.27)	1.37 (.27)	3.27+° (.28)	3.42* (.28)	4.88°* (.28)	4.15+ (.28)	F=150.25 **p<.00**	F=4.96 **p<.00**	F=2.70 **p<.05**
Excluded/ ignored	1.71 (.29)	1.91 (.30)	1.60 (.28)	2.08 (.28)	7.44+* ^ (.30)	6.59°* □ (.30)	8.52^□ (.30)	8.38+° (.30)	F=823.67 **p<.00**	F=4.73 **p<.00**	F=5.33 **p<.00**
Pain Face Scale	1.21 (.16)	1.36 (.17)	1.35 (.16)	1.29 (.15)	2.37 (.17)	2.30 (.16)	2.63 (.16)	3.06 (.16)	F=127.91 **p<.00**	F=2.42 p<.07	F=2.40 p<.07
ATS	2.03 (.14)	2.32 (.15)	2.11 (.14)	2.32 (.14)	3.26+* (.15)	3.28°^ (.14)	3.99*^ (.14)	3.97+° (.14)	F=204.98 **p<.00**	F=5.35 **p<.00**	F=4.27 **p<.01**
NTS	5.74 (.24)	5.21 (.25)	5.76 (.24)	5.34 (.23)	2.28 (.25)	2.29 (.25)	1.79 (.24)	1.86 (.24)	F=405.54 **p<.00**	F=0.98 p<.40	F=1.57 p=1

Notes. Degrees of freedom were 1, 379 for the main effect of Cyberball, and 3, 379 for the main of Regulaton strategy and for the Cyberball x Regulaton strategy interaction. P-values of significant effects and interactions are in bold. Black and red symbols

indicate significant pairwise comparison of Cyberball x regulatory strategy interaction for inclusion and exclusion condition, respectively.
List of acronyms: D, distraction; ER, emotion reinterpretation; SR, situation reinterpretation; CC, control condition; RES, Rejection Emotion Scale; ATS, Aggression Temptation Scale; NTS, Need-Threat Scale.

Discussion

The study aimed to extend the current knowledge on whether and how differently explicit emotions' regulation strategies, namely distraction, reinterpretation of emotions and reinterpretation of situation, affect negative emotions, threatened basic psychological needs, social pain feelings and behavioral aggression following ostracism, compared to a no-regulation condition.

Results mainly showed that distraction and emotion reinterpretation equally reduced participants' negative emotional reactions as compared to reinterpretating the situation and the control condition. Interestingly, this result was consistent across all the dependent measures.

On the one hand, the efficacy of distraction we found could reflect the results of previous studies that depicted distraction as a simple and short-lasting coping strategy compared to other strategies (e.g., reinterpretation) known to involve more complex cognitive processing and memory of stimuli affective meaning (Sheppes, Catran & Meiran, 2009; Sheppes & Levin, 2013; Dillon et al., 2007; Sheppes & Meiran, 2007; Kalokerinos et al., 2017; Hermann, Kress & Stark, 2017; Webb, Miles & Sheeran, 2012; Kross & Ayduk, 2008; see paragraph 2.1). Thus, it is not surprising that when people are exposed to trivial situations, such as the Cyberball short-term interactions, they may benefit from distraction. However, on the other hand, the lack of superiory of emotions' reinterpretation over distraction we observe from our data was unexpected.

In my opinion, one explanation for this finding could be that humans learned that social exclusion is qualitatively different from other factors known to elicit negative emotions. Accordingly, from an evolutionary point of view, humans may have become so hardwired to detect ostracism that their attempts to reinterpret episodes of social exclusion, even when are trivial, are partial, as we observed for reinterpretation of emotions, or easily fail, as we observed for reinterpretation of situation.

This hypothesis is in line with the theories about the presence in humans of an early detection system of social exclusion (Williams, 2001; 2009). Moreover, it accounts also for the evidence that people chronically exposed to social exclusion, compared to other kind of stimuli, continue to negatevely react to ostracism rather than show habituation (Schmid, Wilson & Rankin, 2015; Lloyd et al., 2014; Leavens et al., 2019; Sicard-Cras et al., 2022). For instance, children with

low interpersonal self-esteem and level of popularity among peers are more vulnerable to episodes of social exclusion (Tobia, Riva, & Caprin, 2017). Other works found that ostracism increases the likehood of problematic drug use among homeless people, leading to more extreme forms of social exclusion (Neale, 2006, 2008; Buchanan, 2004).

More broadly, these evidence, together with our findings, suggest that emotional consequences of being exposed to social exclusion could impair self-regulation (Baumeister et al., 2005). However, other studies found that regulation strategies devoted to improve more visceral reactions to ostracism rather than improving rejection-related cognitive contents, such as mindfulness and physical exercise, facilitated acceptance (Quaglia, Goodman, & Brown, 2014) and the ability to make social connections (Ramsey & Jones, 2015). These bottom-up regulation strategies also prevented physical inertia that often follows experiences of social exclusion (Twenge, Catanese, Baumeister, 2002). I think that, by finding that emotions' reinterpretation, compared to situation reinterpretation, was associated with lower levels of negative emotions, the present study look toward this direction. Indeed, one possibility is that reinterpretation of emotional, but not of situational, components of being excluded requires not only cognitive reappraisal processes, but also reviewing affective activation, arousal and physical reactions linked to emotions, thereby potentially overcoming the mere top-down cognitive reappraisal.

This study has some limitations. First, we used a between-subject design, in which participants were either included or excluded in the Cyberball game. Previous studies on Cyberball showed that responses to the paradigm mostly depend on the violation of involvement expectation rather than on probability of receiving the ball (Weschke & Niedeggen, 2015). Therefore, a within-subject design, in which participants are first included and then excluded, triggers a greater violation of sociality expectation compared to a between-subject design that elicits only the natural involvement expectation (Kawamoto et al., 2012). Accordingly, future studies using a within-subjects design should further explore our results.

Second, in our study, we used explicit measures (i.e., self-report questionnaires) to test effects of emotions' regulation strategies on reactions to ostracism. While it is a common procedure (Meneguzzo et al., 2021; Riva et al., 2017; Bernstein & Claypool, 2012; see also paragraph 2.1), also implicit mechanisms could have interfered with participants' emotional reactions to social exclusion and with effectiveness of regulation processes. Thus, the role of implicit emotions' regulation processes, also when dealing with social exclusion (Riva et al., 2014; Capellini et al., 2019; Sleegers, Proulx & van Beest, 2017), should be further explored.

3.2 Implicit emotions' regulation processes: data from healthy and clinical samples

The Chapter 2 described some of the experimental methods used in the literature to test implicit emotions' regulation processes. Among these, the emotional go/no-go task has received increasing attention in the last decades both by studies investigating behavioural responses to the task (Schulz et al., 2007; Tottenham et al., 2011; Steinberg et al., 2008; Zhang et al., 2016; Schel & Crone, 2013; Brass et al., 2013; see paragraph 2.2) and by studies that applied the emotional go/no-go task to investigate the neural correlates of unconscious processes of emotions' regulation (Berkman et al., 2009; Hare et al., 2005, 2008; Zhang et al., 2016; see paragraph 4.2).

In this paragraph I will present the results of two experiments I conducted during my PhD in which the emotional go/no-go task was employed to behaviourally explore the effect of implicit emotions' processing on cognitive performance as well as the ability of managing the impact of emotional information during the execution of a cognitive task. Indeed, in the context of the emotions' regolatory phenomena, some authors focused on the regulation of cognitive processes (e.g., attention, memory, etc.) by interfering emotional information (Campos, Frankel & Camras, 2004; Cole, Martin & Dennis, 2004). One experiment targeted healthy participants (Experiment 1), another involved patients with brain demages (Experiment 2) with the aim of exploring possible aberrant interplay between emotions and cognitive processing in the case of brain lesions. Indeed, although a detailed description of neural basis of emotions is beyond the scope of the present thesis, it is worth highlighting that in the field of affective neuroscience there is still a debate regarding the brain leteralization of emotional processes (see Gainotti, 2019a; Turnbull & Salas, 2021; Palomero-Gallagher & Amunts, 2021 for recent reviews). According to the traditional right-hemisferic dominance hypothesis the right hemisphere is dominant in the processing of emotions, regardless of the emotions' valence (Borod et al., 1998; Abbott et al., 2013). For instance, lesional studies demonstrated that the ability to discriminate and react to emotions was disrupted in right brain-damaged patients (Bowers et al., 1985; Heilman, Scholes & Watson, 1975; Heilman, Schwartz & Watson, 1978), who also showed worse performance than left-damaged patients and healthy participants in processing prosodic emotional stimuli, emotional content of sentences and gestural expressions (Blonder, Bowers & Heilman, 1991; Borod et al., 1998; for a review see Borod et al., 2002). Recently, a review found correlations between structural and functional alterations of the right hemisphere frontotemporal areas and emotional impairment (Gainotti, 2019b). Another recent study showed that the white matter pathway linking the temporo-amygdala-orbitofrontal network, that is larger in the right hemisphere correlated with the expression of both sd and happy faces

(Ioannucci et al., 2020). Moreover, this pathway was found to be commonly altered in psychiatric patients (Jenkins et al., 2016).

On the other hand, the valence lateralization hypothesis posits that the emotions' lateralization at the brain level is valence-dependent, with the righ hemisphere involved in the processing of negative emotions and the left hemisphere involved in the processing of positive emotions (Davidson, 1983; Berkman & Lieberman, 2009; Cohen et al., 2012; Kim & Hamann, 2007; Lieberman, 2007; Phillips et al., 2008; Wager et al., 2008). This hypothesis is supported by studies applying electroencephalography recordings (Zhao et al., 2018), but also by studies showing that the increased activation of the left amygdala in response to positive emotional stimuli observed in healthy subjects (Hamann et al., 2002; Lee et al., 2004) is impaired in psychiatric patients with emotional disturbances (Allen, Bobnar & Kolber, 2021). Interestingly, among studies in favour of the valence lateralization hypothesis, a line of research provided evidence that while the approach motivation, consisting of all the cognitive and affective states that tun the people towards the stimuli, is associated to a greater relative left frontal cortical activity, the avoidance motivation, that directs people away from negative stimuli, is associated to a greater relative right frontal cortical activity (see Kelley et al., 2017 for a review and paragraph 6.1 for more details).

Despite these two traditional hypotheses, recently authors suggested that large-scale, bilateral and interralated networks, rather than one specialized hemisphere, might underly the complexity of the emotional processes. These networks could dynamically change their left or right hemisphere lateralization based on whether the emotions are perceived, expressed or regulated (Morawetz et al., 2020), or based on the complexity of the environmental demands (Stanković, 2021). This latter argument could also explain interindividual differences observed in the emotions' procesess hemispheric lateralization as well as changes in the emotions' brain lateralization patterns under stress condtions (Frasnelli & Vallortigara, 2018).

Therefore, I think that exploring implicit emotions' regulation processes also of a sample of brain damaged patients, although does not end with data to definitely support the traditional or the most recent hypotheses on emotions' brain underpinnings, could provide interesting insights about how emotional information affects the cognitive task performance when a brain damage occurs.

The Emotional GO/NO-GO Task

The version of the emotional go/no-go task used in the two experiments I run during my PhD is similar to the one applied by Tottenham and colleagues (2011). In particular, the task required participants to press (or not) a button as fast and accurate as possible when a certain facial expression, either neutral or emotional, was presented. Therefore, following changing instuctions, neutral or emotional facial expressions were either "go stimuli" (targets), that are the ones to respond to by pressing a button, or "no-go stimuli" (distractors), that are the ones to not respond to by withholding pressing a button. Both the "go stimuli" and the "no-go stimuli" were presented within four different blocks that corresponded to as many emotions, namely happiness, sadness, fear, and anger. Each block consisted of a total of 60 stimuli. In order to induce a greater tendency to respond to "go stimuli" (targets) and make the response inhibition to "no-go stimuli" (distractors) more difficult, in each block, 42 facial expressions (70% of the stimuli) were "go stimuli" and 18 facial expressions (30% of the trials) were "no-go stimuli". Both the blocks and the stimuli (either "go stimuli" or "no-go stimuli") within each block were randomly presented to participants. Participants completed two different versions of the task. In the version named "EmotionalGO" the emotional facial expressions were the "go stimuli", while the neutral facial expression were the "no-go stimuli". On the contrary, in the version named "NeutralGO" the neutral facial expressions were the "go stimuli", while the emotional facial expression were the "no-go stimuli". The order of the two task's versions were counterbalanced among participants.

The facial expressions (both emotional and neutral) were taken from The Karolinska Directed Emotional Faces (KDEF) database (Lundqvist et al., 1998; for pictures validation study see Goeleven et al., 2008)[3]. All pictures were adjusted to the same size of 326×326 pixels. Moreover, the interference of background stimuli (hair and clothing) was eliminated so that only the

[3] The following pictures were selected selected for each of the four emotions plus their neutral pair: Caucasian females: AF01AFS, AF01ANS, AF01NES, AF01SAS, AF02AFS, AF02ANS, AF02HAS, AF02NES, AF02SAS, AF03AFS, AF03HAS, AF03NES, AF05ANS, AF05SAS, AF06HAS, AF07AFS, AF07ANS, AF07HAS, AF07NES, AF09HAS, AF09NES, AF11AFS, AF11ANS, AF11HAS, AF11SAS, AF13AFS, AF13ANS, AF13HAS, AF13SAS, AF14AFS, AF14ANS, AF14SAS, AF19AFS, AF19ANS, AF19NES, AF19SAS, AF20ANS, AF20HAS, AF22AFS, AF22ANS, AF22HAS, AF22SAS, AF23AFS, AF23ANS, AF23HAS, AF24AFS, AF24NES, AF24SAS, AF25ANS, AF25NES, AF26ANS, AF26HAS, AF29AFS, AF29ANS, AF29HAS, AF29NES, AF29SAS, AF30AFS, AF30ANS, AF30NES, AF31ANS, AF31SAS, AF32AFS, AF32ANS, AF32HAS, AF32NES, AF32SAS, BF01HAS, BF03ANS, BF03SAS, BF05AFS, BF05HAS, BF05NES, BF06AFS, BF06ANS, BF06NES, BF06SAS, BF07SAS, BF09AFS, BF09ANS, BF09SAS, BF11NES, BF13NES, BF14HAS, BF14NES, BF19HAS, BF20AFS, BF20NES, BF20SAS, BF22NES, BF23NES, BF23SAS, BF24ANS, BF24HAS, BF25AFS, BF25HAS, BF25SAS, BF26AFS, BF26NES, BF26SAS, BF30HAS, BF30SAS, BF31AFS, BF31HAS, BF31NES. Caucasian males: AM01ANS, AM01HAS, AM03ANS, AM04AFS, AM04HAS, AM04NES, AM05AFS, AM05ANS, AM05NES, AM05SAS, AM06AFS, AM06HAS, AM06NES, AM06SAS, AM08AFS, AM08ANS, AM08HAS, AM08NES, AM08SAS, AM09AFS, AM09ANS, AM09HAS, AM09NES, AM09SAS, AM10AFS, AM10ANS, AM10HAS, AM10NES, AM13ANS, AM13HAS, AM13NES, AM14AFS, AM14ANS, AM14HAS, AM14NES, AM14SAS, AM17ANS, AM17HAS, AM17NES, AM18ANS, AM18NES, AM18SAS, AM22ANS, AM22HAS, AM22NES, AM22SAS, AM23AFS, AM23ANS, AM24ANS, AM24SAS, AM25AFS, AM25ANS, AM27HAS, AM27SAS, AM28AFS, AM28ANS, AM28NES, AM31ANS, AM31NES, AM31SAS, AM34NES, AM35AFS, AM35ANS, AM35NES, AM35SAS, BM01AFS, BM01NES, BM01SAS, BM03AFS, BM03HAS, BM03NES, BM03SAS, BM04ANS, BM04SAS, BM05HAS, BM06ANS, BM10SAS, BM13AFS, BM13SAS, BM17AFS, BM17SAS, BM18AFS, BM18HAS, BM22AFS, BM23HAS, BM23NES, BM23SAS, BM24AFS, BM24HAS, BM24NES, BM25HAS, BM25NES, BM25SAS, BM27AFS, BM27ANS, BM27NES, BM28HAS, BM28SAS, BM31AFS, BM31HAS, BM34AFS, BM34ANS, BM34HAS, BM34SAS, BM35HAS.

facial expressions were presented (see also De Raedt et al., 2010). The task was preceded by a training phase in which participants had the possibility to familiarize with the task's procedure, instructions and stimuli. Then, the instructions of the "EmotionalGO" or of the "NeutralGO" task versions were presented based on the counterbalanced order and the task began. In both versions of the task, the stimuli were displayed at center of the computer screen with a duration of 500 ms; a fixation cross of 1000 ms was presented between each stimulus so that participants had enough time to respond (see Figure 11 for a representation of the task).

The task was run using the E-Prime 3.0 sofware. In particular, for Experiment 1, as the data were collected during the period of COVID-19 pandemic restrictions to access University laboratories, the E-Prime Go version of E-Prime 3.0, which allows researchers to collect data remotely, was used. Therefore, for this experiment, it was not possibile to control neither for the type and characteristics (contrast resolution and luminance) nor for the position of the monitor used by participants. Participants were only asked to seat in front of a personal computer being sure to run the esperiment in a quite and noice free place. For the Esperiment 2, as the data were collected in presence at the Dipartimento di Scienze Neuroriabilitative - Casa di Cura del Policlinico (Milano), the E-Prime 3.0 was used and for both brain demaged patients and orthopedic control patients the stimuli were displayed on a 14-inch HP laptop color monitor, with patients seating approximately 75 cm from the screen's center.

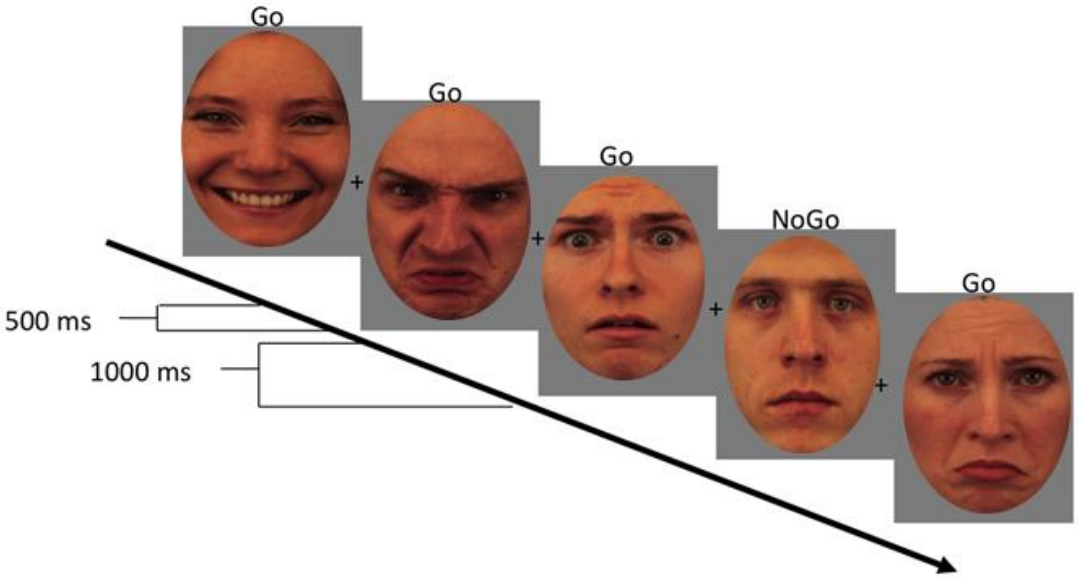


Figure 11. The figure shows the graphical representation of the emotional go/no-go task (EmotionalGO version) used both in the experiment on healthy participants and in the experiment on brain demaged patients.

Baseline measures

To explore whether baseline characteristics, in terms of emotions' regulation abilities and emotional state, could affect the task's performance, participants completed a series of self-report questionnaires right before the start of the go/no-go task. Emotions' regulation abilities were measured by the *Difficulties in Emotion Regulation Scale* (DERS; Gratz & Roemer, 2004), a 36-item self-report questionnaire (Likert scale, 1-5) designed to assess multiple aspects of emotional dysregulation, such as non-acceptance of emotional responses, difficulties engaging in goal directed behaviour, impulse control difficulties, lack of emotional awareness, limited access to emotion regulation strategies, lack of emotional clarity. Emotional state was measured by the *Positive and Negative Affect Schedule* (PANAS; Watson, Clark & Tellegen, 1988), a 20-items self-report questionnaire (Likert scale, 1-5) that asks participants to rate how they feel based on a series of 10 positive adjectives (e.g., interested, excited) and 10 negative adjectives (e.g., distressed, upset). Higher DERS scores indicate greater emotional dysregulation; higher PANAS-positive subscale and PANAS-negative subscale scores indicate higher levels of positive and negative emotions respecitively. In the Experiment 2 also the *Hospital Anxiety and Depression Scale* (HADS; Zigmond & Snaith, 1983) was administered. The HADS is a 14-items self-report questionnaire (Likert scale, 0-3) organized in two subscales measuring possible depression and anxiety symptoms due to hospedalization. For both subscales, scores ranging between 0 and 7 indicate absence of depression or anxiety symptoms, scores ranging between 8 and 10 indicate borderline conditions, and scores ranging between 11 and 21 indicate possibile pathological conditions.

Data analysis

For both experiments, the analyses of the emotional go/no-go task were separately run for response accuracy and reaction times by using the R software, version 3.4.3.

Analysis of response accuracy were run following the assumptions of the Signal Detection Theory (Stanislaw & Todorov, 1999), usually used to investigate decision-making under conditions of uncertainty, for instance the presence of ambiguous stimuli. In each trial of the classical signal detection experiments, participants are required to respond "yes" or "no" regarding the presence of signals among distractors. The classical and the emotional go/no-go tasks entail the Signal Detection Theory. In particular, in the emotional go/no-go task employed in the experiments of this PhD thesis the response "yes" corresponded to pressing the button, the response "no" corresponded to withholding pressing the button, the signals corresponded to the target stimuli, and the distractors

corresponded to the alternative, no target stimuli. Both emotional or neutral facial expressions could be the target stimuli or the distractors, based on the "EmotionalGO" or "NeutralGO" version of the task, respectively. Therefore, combining the stimulus type (target vs distractor) and the participants' choice (target present or absent) the following four categories were computed for each block (i.e., happiness, sadness, fear, and anger) and version (i.e., "EmotionalGO" vs "NeutralGO") of the emotional go/no-go task (see Figure 12):

- Hits: participants pressed the button when the "go stimuli" appeared;
- False alarms: participants pressed the button when the "no-go stimuli" appeared;
- Misses: participants withholded pressing the button when the "go stimuli" appeared;
- Correct rejections: participants withholded pressing the button when the "no-go stimuli" appeared.

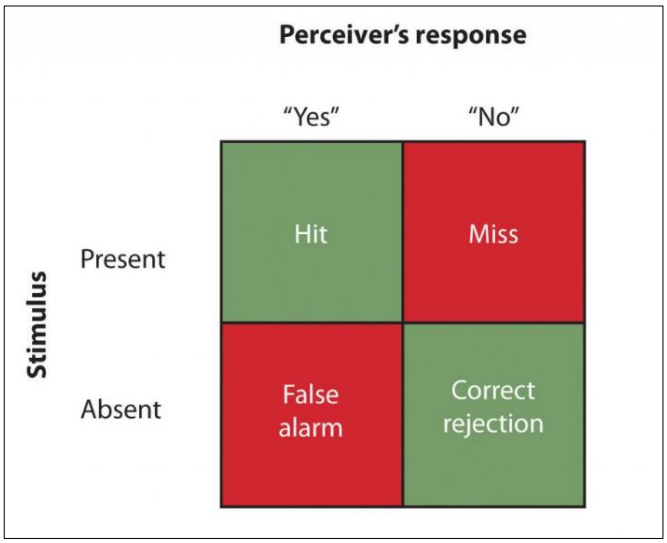


Figure 12. The figure shows the four possible categories deriving from type of stimulus and participants choice in the signal detection experiments and the emotional go/no-go task of this thesis.

Then, based on the proportions of these types of categories (i.e., number of hits/number of target trials; number of miss/number of target trials; number of false alarms/number of distractors trials; number of correct rejections/number distractors trials), the *D-prime*[4] or perceptual sensitivity,

[4] To compute the *D-prime* first hit rates [hit/(hit + miss)] and the false alarm rates, [false alarm/(false alarm + correct rejectionr)] were calculated for each block (happiness, sadness, fear, and anger) and version ("EmotionalGO" vs "NeutralGO") of the emotional go/no-go task. Then, each

that indicates how much people discriminates targets from distractors, and the *response bias*, that indicates the degree to which people are biased to detect or not the targets, were independently calculated using the "psycho" package for R (Makowski, 2018). Regarding the *D-prime*, higher values correspond to higher sensitivity. Regarding the *response bias*, according to the Signal Detection Theory, people can use a more liberal or a more conservative criterion to detect targets. A liberal approach consists of a bias to respond to the target when uncertain (tendency toward "yes" responses or to press the button), while a conservative approach consist of a bias to reject targets when uncertain (tendency toward "no" responses or to withhold pressing the button) (see Figure 13). Consequentely, the liberal approach is associated to more hits and false alarms (and less correct rejections and misses), whereas the conservative approach is associated to more correct rejections and misses (and less hits and false alarms). Typically, the *response bias* is measured with β, but many authors have suggested to measure the *response bias* with *c* that is considered a more reliable measure (Macmillan & Creelman, 1990; Macmillan, 1993; Stanislaw & Todorov, 1999). Therefore, for the analysis of the experiments of the present thesis the *c* was used as measure of *response bias.* Negative values of *c* indicate a bias toward "yes" responses, whereas positive values indicate a bias toward "no" responses.

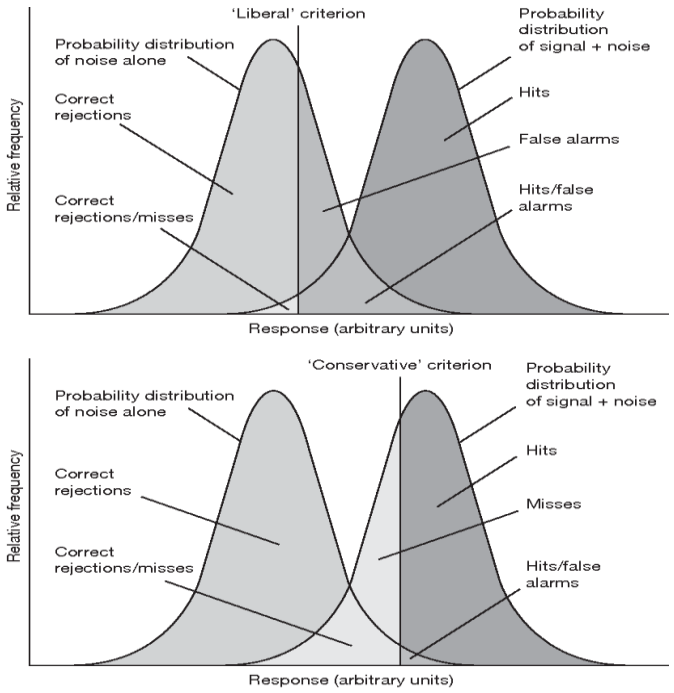


Figure 13. The figure shows the response bias according to the Signal Detection Theory.

probability was transformed in normal distribution z scores and the *D-prime* estimated by the difference of standardized hit rate and false alarms rate.The outliers were deleted via model criticism (2.5 sd of standardized residuals; Baayen, 2008) to ensure the normal distribution of the *D-prime*.

Regarding the reaction times, only the reaction times of the hits were selected: in the case of the "EmotionalGO" version the hits were the times in which participants pressed the button when an emotional facial expression (target) appeared, while in the case of the "NeutralGO" version the hits were the times in which participants pressed the button when a neutral facial expression (target) appeared. Then the mean reaction times were calculated for each block of the two versions of the task.

For the Experiment 1, the *D-prime*, the *c* and reaction times were finally entered as dependent variables in a 4 x 2 repeated measure ANOVA with block (4 levels: happiness, sadness, fear, and anger) and version (2 levels: "EmotionalGO" and "NeutralGO") as within-subjects factors. For the Experiment 2, the *D-prime* and the *c* were finally entered as dependent variables in a 4 x 2 x 2 repeated measure ANOVA with block (4 levels: happiness, sadness, fear, and anger) and version (2 levels: "EmotionalGO" and "NeutralGO") as within-subjects factors, and group (3 levels: right brain damaged patients, left brain damaged patients, and orthopedic control patients) as between-subjects factor. Reaction times were not included in the analysis of brain damaged patients experiment due to the high number of misses.

For the explorative analysis on the impact of baseline emotions' regulation abilities, emotional state and possible depression and anxiety symptoms (in the case of experiment on brain damaged patients), scores to the DERS, PANAS and HADS were analysed as covariates in the repeated measure ANOVAs.

3.2.1 Experiment 1: healthy participants

Participants

The experiment involved a total of 61 healthy participants (36 females and 25 males; mean age = 24.92, sd = 3.56) recruited among the students of University of Milano-Bicocca. All participants had normal or corrected to normal vision and reported no history of neurological or psychiatric disorders. Participants received credits for their voluntary participation. Written informed consent was obtained from all participants prior to the inclusion in the study, which was approved by the ethics committee of the University of Milano-Bicocca and conducted in accordance with the ethical standards of the revised Helsinki Declaration.

Results of Emotional GO/NO-GO Task performance

The 4 x 2 repeated measure ANOVA for the *D-prime* showed a main effect of block $F(3) = 39.47$, $p<.001$, with higher *D-prime* for happy faces (M = 1.79, sd = .80) as compared to negative expressions. Post-hoc analysis showed differences also among negative expressions, with higher *D-prime* for scared (M = 1.56, sd = .73) compared to angry (M = 1.17, sd = .66) and sad (M = 1.18, sd = .69) faces. *D-prime* scores did not differ between angry and sad expressions ($p > .05$) (Figure 14). Neither the main effect of version nor the block x version interaction were significant ($p > .05$).

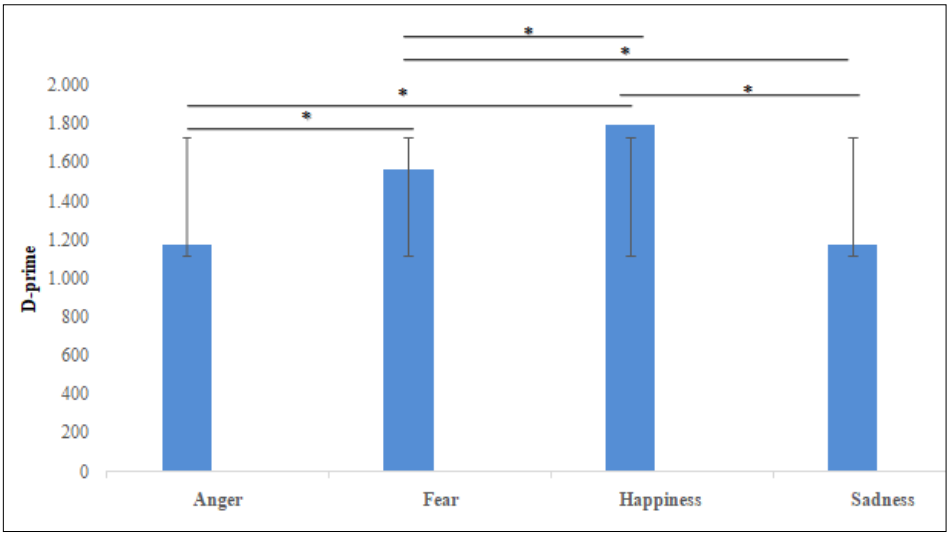


Figure 14. The figure shows the main effect of block for the *D-prime* 4x2 repeated measure ANOVA.

The 4 x 2 repeated measure ANOVA for the *response bias* showed a main effect of version $F(1) = 90.45$, $p < .00$. In both versions of the task *c* had negative values meaning that participants showed a liberal choice approach in both versions, i.e. they tended to provide "yes" responses by pressing the button even when the targets, either emotional or neutral facial expressions, were uncertain. Interestingly, the *c* values were more negative in the "EmotionalGO" version, that is when the targets were represented by emotional faces, as compared to the "NeutralGO" version. Thus, emotions seemed to significantly influence the *response bias* (Figure 15). Neither the main effect of emotion nor the block x version interaction were significant ($p > .05$).

Explorative analysis did not show differences related to DERS and PANAS scores neither for the analysis on *D-prime* nor for the analysis on *response bias* ($p > .001$).

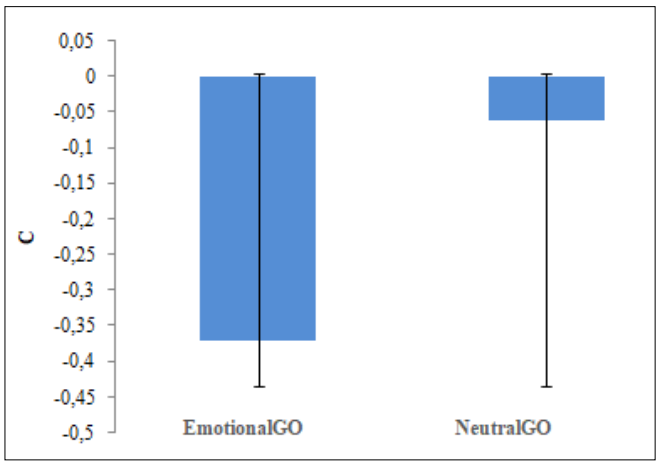


Figure 15. The figure shows the main effect of version for the *response bias* 4x2 repeated measure ANOVA.

The 4 x 2 repeated measure ANOVA for reaction times showed a main effect of block $F(3)=10.21$, $p<.001$, with lower reaction times when happy faces (M = 352.70 , sd = 46.60) appeared as compared to negative expressions. Post-hoc analysis showed differences also among negative expressions, with lower reaction times for scared (M = 362.27, sd = 43.77) compared to angry (M = 371.13 , sd = 42.36) faces. No differences were found neither between angry and sad expressions nor between scared and sad expressions ($p > .05$). Analysis showed also a main effect of version, with lower reaction times in the "EmotionalGO" version (M = 353.55, sd = 44.39) as compared to "NeutralGO" version (M = 373.07, sd = 43.72) of the task. The main effects were qualified by a significant block x version interaction $F(3)=2.65$, $p < .001$. Post-hoc analysis showed

that when the target stimuli were neutral faces the emotions of the 4 blocks did not affect the reaction times on neutral faces, while when the target stimuli were emotional faces reaction times were lower for happy faces (Figure 16).

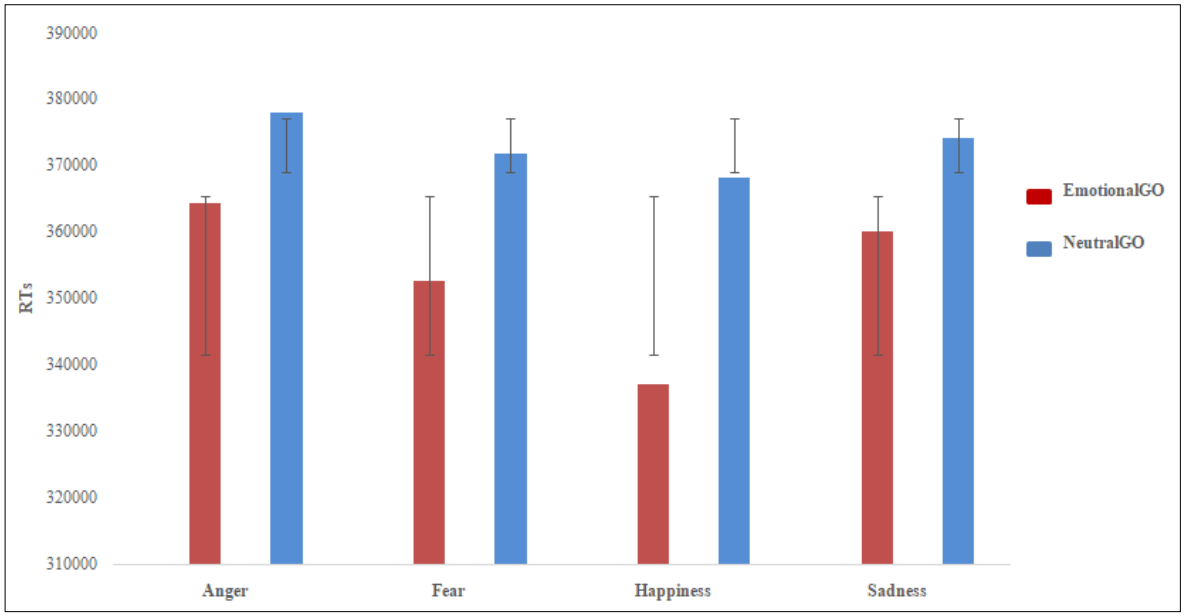


Figure 16. The figure shows the block x version interaction effect for the reaction times 4x2 repeated measure ANOVA.

Explorative 4 x 2 repeated measure ANOVA testing covariates on reaction times showed a significant version x DERS total score interaction $F(1)=5.95$, $p<.001$, indicating that when the target stimuli were emotional faces (i.e., "EmotionalGO" version) higher levels of emotional dysregulation correlated with higher hits' reactions times, conversely when the target stimuli were neutral faces (i.e., "NeutralGO" version), higher levels of emotional dysregulation correlated with lower hits' reactions times. No other significant differencesaccording to PANAS-positive or –negative subscales were found.

3.2.2 Experiment 2: brain damaged patients and orthopedic control patients

Participants

The experiment involved a total of 20 brain damaged patients (7 females and 13 males; mean age = 67.85, sd = 14.46) recruited at the inpatient service of the Dipartimento di Scienze Neuroriabilitative - Casa di Cura del Policlinico (Milano). Patients were included if they had a right or left hemispheric cortical, subcortical or cortico-subcortical brain lesion, ascertained by computed tomography or magnetic resonance, of various etiologies (vascular ischemic and hemorrhagic, traumatic, neoplastic). Exclusion criteria were: a) Mini-Mental State Examination (MMSE) score ≤ 10 (Magni et al., 1996); b) previous or current neurological diseases (e.g., Alzheimer's disease, Parkinson's disease, aphasia, Multiple Sclerosis), as assessed by the the referring neurologists, and/or psychiatric symptoms (e.g., depression, anxiety), as assesed by the administration of the HADS. Among the group of neurological patients, 10 were right brain damaged, while 10 were left brain damaged (see Table 3 for the details about the brain lesions).

Performance at the emotional go/no-go task of the brain damaged patients was compared with the one of a group of 20 orthopedic patients matched by age (16 females and 4 males; mean age = 68.5, sd = 17.25), used as control group, recruited at the inpatient service of the Dipartimento di Scienze Neuroriabilitative - Casa di Cura del Policlinico (Milano). Othopedic patients were excluded if they had previous or current neurological diseases (e.g., Alzheimer's disease, Parkinson's disease, aphasia, Multiple Sclerosis), as assessed by the the referring neurologists, and/or psychiatric symptoms (e.g., depression, anxiety), as assesed by the administration of the HADS.

As in the case of the healthy group, before the start of the emotional go/no-go experiment, both the group of neurological and orthopedic patients completed the baseline measures of emotions' dysregulation (through the DERS self-report questionnaire), emotional state (through the PANAS self-report questionnaire), and anxiety or depression symptoms (through the HADS self-report questionnaire). The Table 2 shows the means and standard deviations as well as the p-values of the analyses of variance and Fisher's exact tests comparing the baseline measures of the three patients' groups. Right brain damaged patients had more years of education (14.70 ± 3.43) than orthopedic patients (11.40 ± 3.71), $F(2,37) = 3.39$, $p = .05$, $\eta_p^2 = .16$. No other significant differences were found among the three groups.

Before the emotional go/no-go experiment, in addition to the baseline measures, the group of neurological patients completed also a brief neuropsychological assessment (see Table 3 for

details). In particular, the general cognitive status was assessed by the Mini-Mental State Examination (MMSE; for normative data we used Magni et al., 1996), while the executive functions were assessed by the verbal fluency test (for normative data we used Novelli et al., 1986), the Trail Making Test (TMT; for normative data we used Giovagnoli et al., 1996), the Stroop test (for normative data we used Caffarra et al., 2002), and the Frontal Assessment Battery (FAB; for normative data we used Appollonio et al., 2005). Written informed consent was obtained from all participants prior to the inclusion in the study, which was approved by the local ethics committee (Dipartimento di Scienze Neuroriabilitative - Casa di Cura del Policlinico - Milano) and conducted in accordance with the ethical standards of the revised Helsinki Declaration.

Table 2. Baseline characteristics of study groups

	Right Brain Damaged (n = 10)	**Left Brain Damaged (n = 10)**	**Orthopedic patients (n = 20)**	**p Value**
Age	63.7 (±15.99)	72 (±12.92)	68.5 (±17.25)	.51*
Male (n)	5	8	4	.32†
Female (n)	5	2	16	
Education (years)	14.7 (±3.43)	14.3 (±4.24)	11.4 (±3.70)	.05*
DERS (total)	2.03 (±.77)	1.99 (±.61)	2.11 (±.59)	.89*
PANAS_positive	34.2 (±6.55)	32 (±5.93)	32.55 (±6.87)	.73*
PANAS_negative	17 (±12.23)	12.9 (±3.57)	13.45 (±6.06)	.41*
HADS_anxiety	7 (±3.23)	5.6 (±2.41)	6.1 (±3.43)	.61*
HADS_depression	5.3 (±3.06)	5.3 (±2.91)	3.45 (±2.58)	.13*

Values are mean (SD) or n where specified.

*Univariate Analysis of Variance.

† Fisher's exact test.

List of acronyms: DERS (total), Difficulties in Emotion Regulation Scale (total score); PANAS_positive, Positive and Negative Affect Schedule_positive emotions; PANAS_negative, Positive and Negative Affect Schedule_negative emotions; HADS_anxiety, Hospital Anxiety and Depression Scale_anxiety subscale; HADS_depression, Hospital Anxiety and Depression Scale_depression subscale.

Table 3. Neuropsychological assessment of neurological patients

Left Brain Damage (n=10)							Right Brain Damage (n=10)						
P	**Lesion**	**MMSE**	**Verbal Fluency**	**TMT**	**Stroop Test**	**FAB**	**P**	**Lesion**	**MMSE**	**Verbal Fluency**	**TMT**	**Stroop Test**	**FAB**
P1	Ischemic stroke (posterior corona radiate)	28	36 (s) 39 (p)	33.66 (A) 128 (B) 95.34 (B-A)	27.2 (t) -2 (e)	18	**P3**	Ischemic stroke (anterior/posterior arm of internal capsule)	26	36 (s) 12 (p)+	76 (A) 193 (B) 117 (B-A)	10.78 (t) 14.5 (e)+	11.7+
P2	Ischemic stroke (thalamo-mesencephalic)	18.2*	15 (s)+ 18 (p)	131 (A) 217 (B) 86 (B-A)	-8.89 (t) 9 (e)+	4.3+	**P4**	Traumatic brain injury	27	40 (s) 36 (p)	42 (A) 87 (B) 45 (B-A)	15.60 (t) n.a. (e)	16.11
P6	Ischemic stroke (bulb)	28	41 (s) 26 (p)	30.23 (A) 139 (B) 108.77 (B-A)	33.42 (t) 0.25 (e)	15.4	**P5**	Minor stroke	27	39 (s) 24 (p)	28.32 (A) 50 (B) 21.68 (B-A)	22.12 (t) 5.25 (e)+	16.9
P7	Chronic subdural hematoma	27.3	51 (s) 29 (p)	36.08 (A) 124 (B) 88.92 (B-A)	26.96 (t) 3.75 (e)	15.4	**P8**	Post-traumatic ischemic stroke	27.2	46 (s) 29 (p)	36.3 (A) 120 (B) 83.7 (B-A)	26.21 (t) 1 (e)	16.4
P10	Ischemic stroke (internal capsule)	25	33 (s) 19 (p)	35 (A) 155 (B) 120 (B-A)	24.5 (t) n.a. (e)	15.7	**P9**	Cardioembolic stroke	28.1	28 (s) 30 (c)	n.a.	-6.87 (t) 21.25 (e)+	n.a.
P13	Ischemic (atheroembolic) stroke	24.7	39 (s) 38 (p)	44.76 (A) 188 (B) 143.24 (B-A)	10.17 (t) 4.5 (e)	15.4	**P11**	Ischemic stroke (middle cerebral artery thrombosis)	19.1*	23 (s) 30 (p)	101.07 (A) n.a. (B) n.a. (B-A)	65.17 (t)+ 5.5 (e)+	18.5
P14	Ischemic stroke	26	36 (s) 18 (p)	88 (A) 120 (B) 59 (B-A)	74.38 (t)+ 1 (e)	12+	**P12**	Ischemic stroke	26.2	28 (s) 24 (p)	47.09 (A) 170 (B) 122.91(B-A)	44.97 (t)+ 5.5 (e)+	15.7
P15	Ischemic stroke	22.7*	23 (s) n.a. (p)	43.46 (A) 205 (B) 161.54 (B-A)	n.a.	10.4+	**P16**	Frontal ischemic stroke	27.2	38 (s) 35 (p)	35 (A) 68 (B) 33 (B-A)	6.81 (t) .75 (e)	17
P17	Ischemic stroke (paramedial bulb)	23.2*	n.a.	46.21 (A) 164 (B) 117.79 (B-A)	n.a.	15.3	**P18**	Middle cerebral artery aneurysm	22.89*	n.a.	114 (A) n.a. (B) n.a. (B-A)	n.a.	10.37+

P19	Ischemic stroke	28.3	29 (s) 28 (p)	n.a.	n.a.	19	**P20**	Middle cerebral artery aneurysm	27	30 (s) 8 (p)+	120.01 (A) 227 (B) 106.99 (B-A)	27.85 (t) .50 (e)	13.01+

The table shows the scores corrected for patients age and education.
Asterisks (*) indicate MMSE scores < 24 cut-off.
Crosses (+) indicate 0 equivalent scores.
List of acronyms: P, patient; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; FAB, Frontal Assessment Battery; n, number; s, semantic; p, phonemic; t, time; e, errors; A, Trail Making Test – Part A; B, Trail Making Test – Part B; B-A, Trail Making Test – Part B - Part A; n.a., not administrated.

Results of Emotional GO/NO-GO Task performance

The 4 x 2 x 2 repeated measure ANOVA for the *D-prime* showed a main effect of block $F(3) = 13.61$, $p<.001$, with higher *D-prime* for happy faces (M = .95, sd = .94) as compared to angry (M = .55, sd = .68), scared (M = .63, sd = .79) and sad (M = .58, sd = .78) faces. Analysis showed also a main effect of version $F(1) = 7.99$, $p<.01$, with higher *D-prime* for the "EmotionalGO" task version (M = .74, sd = .85) then the "NeutralGO" task version (M = .62, sd = .77). There was also a main effect of group $F(2) = 8.87$, $p<.001$. Post hoc analysis showed that othopedic patients had higher *D-prime* (M = .97, sd = .84) than righ- (M = .48, sd = .72) and lef- (M = .29, sd = .59) brain damaged patients. The *D-prime* of the two brain damaged groups did not differ ($p > .05$).

The main effects of block and version were qualified by a significant block x version interaction $F(3) = 11.62$, $p<.001$. Post hoc analysis showed that while in the "NeutralGO" version the *D-prime* did not differ among the four emotions' blocks, in the "EmotionalGO" version the *D-prime* was higher for happy faces compared to negative emotions and for scared compared to sad faces (Figure 17).

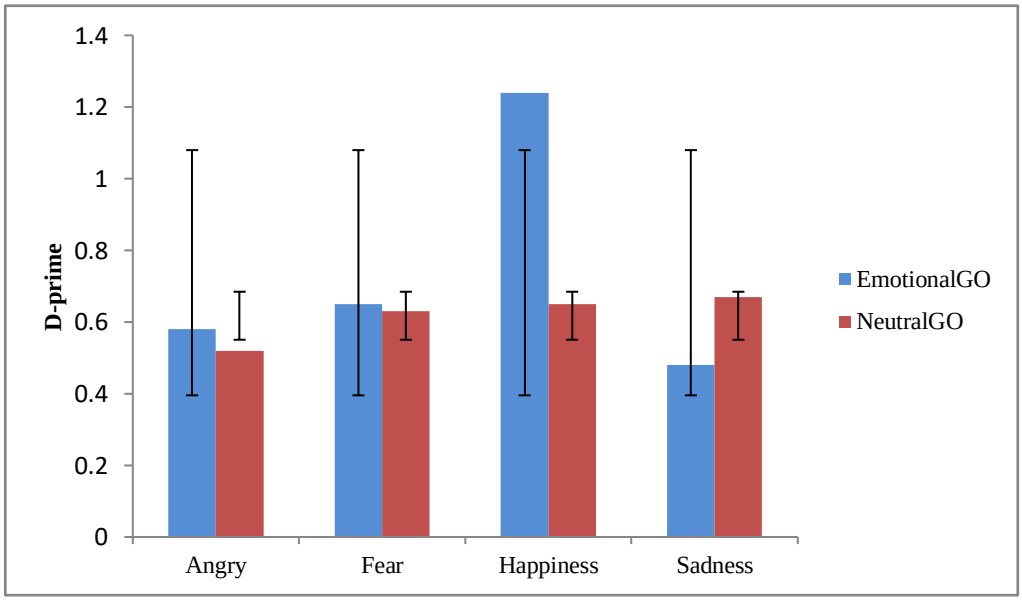


Figure 17. The figure shows the block x version interaction effect for the *D-prime* 4x2x2 repeated measure ANOVA.

The 4 x 2 x 2 repeated measure ANOVA for the *response bias* showed a main effect of version $F(1) = 72.47$, $p < .001$. In both versions of the task *c* had positive values meaning that participants showed a conservative choice approach in both versions, i.e. they tended to provide "no" responses by rejecting the targets, either emotional or neutral facial expressions, when uncertain. The *c* values were more positive in the "NeutralGO" version, that is when the targets were represented by neutral faces, as compared to the "EmotionalGO" version (Figure 18). There was also a main effect of group $F(2) = 9.23$, $p < .001$. Post hoc analysis showed that othopedic patients had lower *c* (M = .61, sd = .64) than righ- (M = 1.08, sd = .63) and lef- (M = 1.17, sd = .51) brain damaged patients. The *c* of the two brain damaged groups did not differ ($p > .05$). No other main or interaction effects were significant ($p > .05$).

Explorative analysis did not show differences related to DERS, PANAS, and HADS scores neither for the analysis on *D-prime* nor for the analysis on *response bias* ($p > .001$).

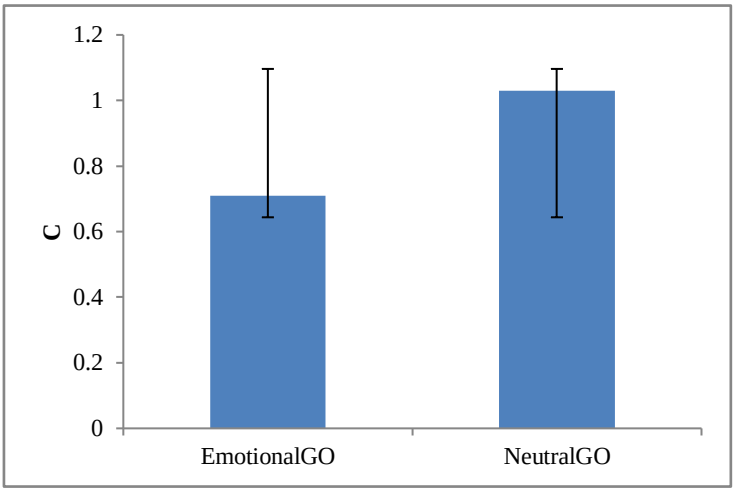


Figure 18. The figure shows the main effect of version for the *response bias* 4x2x2 repeated measure ANOVA.

3.2.3 Discussion of the Experiment 1 and Experiment 2

The two Experiments I conducted aimed at behaviourally exploring, by applying a cognitive task that is usually used to investigate implicit emotions' regulation, whether and how the processing of emotional information affects task performance, and whether such impact is different in particular in the presence of brain lesions. To this aim, an emotional version of the traditional go/no-go task, in which emotional or neutral faces are presented instead of the classical stimuli, was first administered to a group of 61 healthy participants in the Experiment 1, and second to a group of 20 righ- or left-brain damaged patients (10 righ- and 10 left-brain damaged) and 20 orthopedic control patients in the Experiment 2. Moreover, the experiments aimed at shedding light on whether baseline characteristics, in terms of emotions' dysregulation, affective state and depression and/or anxiety symptoms, could affect the ability of managing emotional stimuli during task's performance.

First, results showed that in both experiments the response sensitivity, that is the ability to discriminate the targets from distractors, as measured by the *D-prime*, was higher when happy, as compared to negative, faces were presented. In the Experiment 2 this effect was more evident in the "EmotionalGO" than in the "NeutralGO" version, where the *D-prime* did not differ among the four emotions' blocks. Crucially, healthy participants were even faster when happy faces were the stimuli to target, while the different emotional blocks did not affect reaction times when the targets were neutral faces.

The finding on the advantage of happy faces recognition over all negative facial expressions is consistent with the widely known evidence that happy expressions, probably due to their highly salient facial features, are more easily and accurately recognized compared to negative facial expressions (Leppänen & Hietanen, 2003; Palermo & Coltheart, 2004; Juth et al., 2005; Calvo & Lundqvist, 2008; Calvo, Nummenmaa & Avero, 2010; Tottenham et al., 2009; for a recent study see Vergallito et al., 2020).

Among negative facial expressions, healthy participants also showed a greater sensitivity and lower reaction times in discriminating scared than angry expressions. Similar results were found also in the Experiment 2, where the interaction between emotions' blocks and the "EmotionalGo"/"NeutralGO" task versions showed higher sensitivity for fearful compared to angry faces when emotional, but not neutral, expression were the target stimuli. However, these results contrast with the previous literature showing that the processing of threat-related stimuli negatively impact on the cognitive control and response inhibition abilities. For instance, a study found that

being exposed to images of spiders and snakes, compared to control images (e.g., flowers), in a n-back task increased reaction times as well as rates of response inhibition errors (Lindström & Bohlin, 2012). Similarly, in the study by Hartikainen and colleagues (2012) images of spiders in a go/no-go task increased failures in inhibitory control in contrast to neutral distractors. Based on this evidence, in our experiments, we expected that viewing fearful faces should cause the same negative effect on task's performance, but this was not the case.

Actually, in my opinion, another possibility is that fear could represent a particular salient stimulus for humans, leading to increased performance when they deal with fear-related stimuli. Consistently with this hypothesis, other scholars pointed out the adaptive role of fear that is supposed to mediate effective motivational processes and defensive behaviors via specific hard-wired fear neurobiological circuits (see Mobbs et al., 2019 for a recent review). In accordance with this hypothesis, altered fear basic processing and threat-related symptoms are core features of anxiety disorders. For instance, a meta-analysis on 963 anxiety disordered patients found that, compared to controls, patients showed fear inhibition deficits when safety cues were presented, as if anxiety lead patients to extend fear reactions also to safe stimuli. Moreover, fear extinction was reduced in anxiety disordered patients, compared to controls (Duits et al., 2015). Interestingly, in the search for possible underlying mechanisms of these impairments in fear stimuli processing, a huge body of literature has rapidly grown addressing the issue of fear conditioning, exploring both the related neural correlates (Dejean et al., 2015; Fullana et al., 2016) or possible treatments for clinical samples (Pittig, van den Berg & Vervliet, 2016; Raeder et al., 2020).

Regarding the results of *response bias*, in the Experiment 1 we found that, in both versions of the task, participants showed a liberal, rather than a conservative, choice approach, providing greater "yes" responses when the targets appeared. This was particularly true for the "EmotionalGO" version, thereby showing that emotions significantly influenced the *response bias*. This result is in line with the findings of Schulz and colleagues (2007), who demonstrated greater *response bias* in the emotional, but not in non-emotional, version of the go/no-go task.

However, the opposite result was found in the Experiment 2 where the three patients' groups, and in particular the group of brain damaged patients (either righ- or left-brain damaged), provided greater "no" responses when the targets appeared, regardless of their emotional or neutral valence. Actually, this result was not unexpected considering the high number of misses we found that prevented us also to calculate the patients' reaction times in the two versions of the task.

Finally, looking at the explorative analysis about baseline characteristics, no differences were found in Experiment 2 according to emotions' regulation abilities, emotional state and anxiety

and/or depression symptoms. However, in the Experiment 1 greater emotions' regulation abilities correlated with lower reaction times when emotional faces were presented as targets and higher reaction times when neutral faces were presented as targets. Conversely, greater emotions' dysregulation caused a worse performance in response to emotional targets and a better performance in response to neutral targets. In other words, people higher in emotions' regulation were faster in discriminating emotional than neutral faces, while people high in emotions' dysregulation showed greater latency in discriminating emotional than neutral expressions. This finding is in accordance with the evidence that patients with deficits in emotions' regulation, such as patients with borderline personality disorder, show a reduced ability to discriminate negative emotions (Jovev et al., 2011; Robin et al., 2012; Unoka et al., 2011) and an altered processing of positive emotions (Matzke et al., 2014). However, these results should be interpreted with caution. Indeed, the patterns of reactions to emotional faces shown by borderline personality disorder patients that emerge from studies are frequently unclear and inconsistent (Mitchell, Dickens & Picchioni, 2014).

The two Experiments have some limitations to be addressed by future studies. First, in our Experiments, we included only discrete facial expressions (e.g., angry vs sad vs happy vs fearful facial expressions). Therefore, although presenting emotional stimuli in a cognitive control task (e.g., go/no-go task) is widely used procedure to test (implicit) emotions' regulation processes (Tottenham et al., 2011), we cannot totally rule out that perceptual processing of faces could have affected the results we found. For instance, as previously described, the salient physical features of happy faces can explain, at least partially, the longlasting finding on the advantage observed in the task's performance when this kind of stimuli are presented. Thus, future studies could better disentangle between emotions' regulation and perception processes by using faces in which the emotional positive or negative valence is gradually represented.

Second, in the Experiment 2, the high number of missing responses prevented to account for patients' reaction times. Future studies with more row data available could overcome this limit, providing a complete investigation of the patients' task performance. Moreover, due to the small sample size, in particular as regard the group of brain damaged patients, we did not observe possible differences related to the side of the brain lesion as well as better explore the impact of baseline characteristics. Further research on greater samples could replicate our Experiments, providing more solid results.

Chapter 4: Neural correlates of emotions' regulation processes

In the previous Chapters, the main experimental paradigms to study explicit and implicit emotions' regulation processes were presented together with a detailed description of a series of experiments in which I explored the feasibility of some of these paradigms in healthy participants and clinical samples. However, besides investigating emotions' regulation from a bahavioral point of view, it is worth highlighting that a considerable body of neuroscientific evidence showed that emotions' regulation processes (either explict and implicit) involve specific brain networks.

First of all, at a theoretical level, Phillips et al. (2003) proposed a useful framework to understand how different brain areas may interact to support the cognitive control of emotions. Indeed, buinding on their cognitive model about the distinction between explicit and implicit emotions' regulation, the authors identified two neural systems underlying emotions' regulation, that can be also concurrently activated (e.g., Braunstein et al., 2017): a ventral and a dorsal system. The ventral system, involving subcortical - namely the amygdala, insula, ventral striatum, thalamus, brainstem nuclei - and cortical regions - as the ventral anterior cingulate gyrus (ACG), the orbitofrontal cortex (OFC), and the ventro-lateral prefrontal cortex (vlPFC) - is activated by automatic and unconscious regulation processes and mediates the generation of affective responses. Conversely, the dorsal system, involving the hippocampus, the dorsal anterior cingulate gyrus (dACG), the dorsomedial prefrontal cortex (dmPFC) and the dorsolateral prefrontal cortex (dlPFC), is activated by effortful voluntary regulation processes. In the updated version of the model (Phillips et al., 2008), authors postulated that the implicit emotions' regulation is mediated by a more medial (e.g., the OFC, subgenual and rostral ACG and dmPFC) rather than ventral system, while the explicit emotions' regulation is mediated by a more lateral (e.g., the dlPFC and vlPFC) rather than a dorsal system (Figure 19).

Other authors extended the models by Phillips et al. (2003, 2008), suggesting that the dorso-lateral system may exert a top-down control over the regions of the ventral-medial system (for a rview see Ochsner, Silvers & Buhle, 2012). For instance, studies looking at the modulation of reactions to negative photos showed that participants' amygdala responsens inversely correlated with responses of ventro-medial prefrontal cortex (vmPFC) (Urry et al., 2006; Johnstone et al., 2007). Further mediation analysis found that the vmPFC mediated the pathways between the left dmPFC (Urry et al., 2006) or the left vlPFC (Johnstone et al., 2007) and the amygdala. Similar results were found also by an experiment in which the down-regulation of negative emotions due to the activity of the left vlPFC was mediated by separate pathways through the amigdala and the

ventral striatum (Wager et al., 2006). Similarly, in a study exploring the modulation of craving elicited by photos of cigarettes or appetitive food the left dlPFC modulation of the ventral striatum underlied the reduction of the craving levels (Kober et al., 2010).

In the next two paragraphs a general description of the neural correlates of the explicit and implicit emotions' regulation processes will be presented.

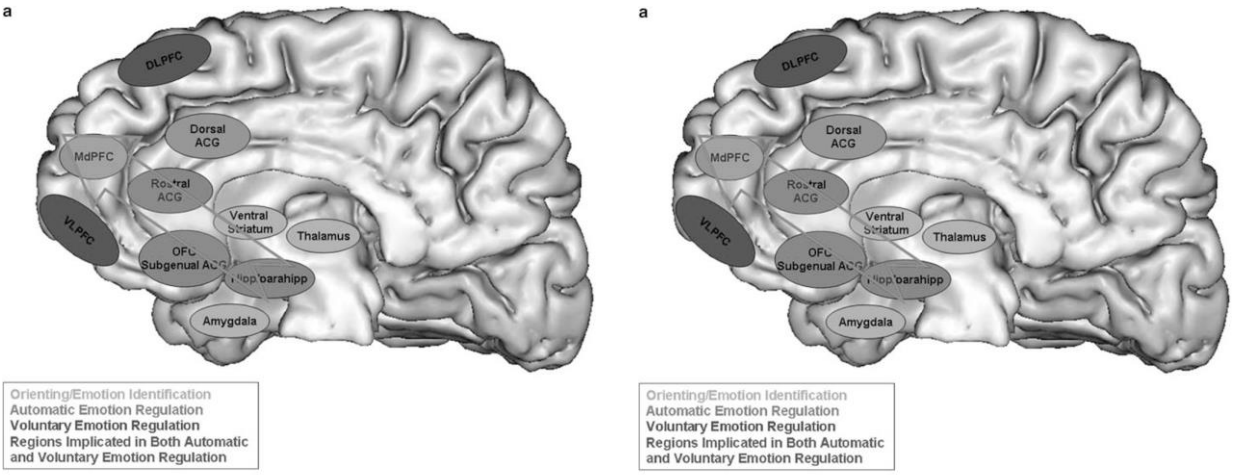


Figure 19. The figure shows the updated model by Phillips et al. (2008).

4.1. Neural correlates of explicit emotions' regulation strategies

Regading reappraisal, Kalisch (2009) found that it is associated with increased activity in the lateral (particularly in the superior, middle and inferior frontal gyri, the orbital gyri and the right anterior middle frontal gyrus) and in the medial frontal cortex (particularly in the superior frontal gyrus, with a peak of activity in the pre-supplemental motor area, and in the ACC). Moreover, Ochsner and colleagues (2012) suggested that using reappraisal to downregulate negative emotions activates the dlPFC, posterior prefrontal cortex, inferior parietal regions, dACC, vlPFC and dmPFC that modulate the activity of the amygdala and the ventral striatum and to a less extent the activity of the insula and the vmPFC. These findings are consistent with those of a meta-analysis by Buhle et al. (2014) who, in accordance with Ochsner et al. (2002), showed that reappraisal recruits posterior dmPFC, bilateral dlPFC and vlPFC, and bilateral posterior parietal cortex, while it is associated with a decreased activity of bilateral amygdala, left ventral striatum and pallidum (Figure 20).

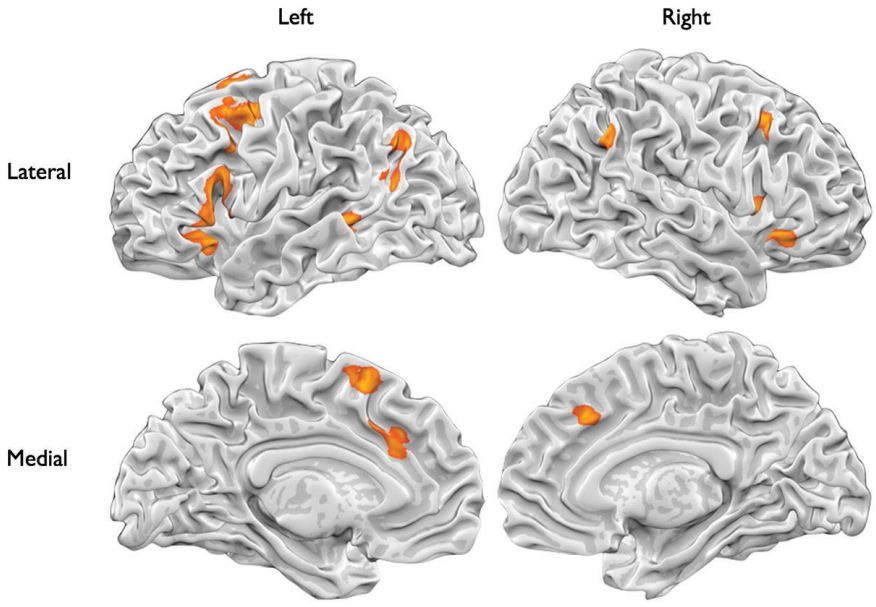


Figure 20. The figure shows the findings of the meta-analysis by Buhle et al., (2014).

Other studies demonstrated the top-down control of prefrontal cortices over the libic regions during reappraisal. For instance, an fMRI study by Banks et al. (2007), in accordance with the hypothesis of Ochsner et al. (2012), showed that a greater amygdala–OFC/dmPFC coupling correlated with a more effective reappraisal strategy, as noted by attenuated intensity of negative

affects following the presentation of highly arousing and aversive pictures. The interplay between the amygdala and the prefrontal areas was further explored by a study that investigated the neural activations of reappraisal used to up- and down-regulate reactions to threat-related stimuli (Eippert et al., 2007). The findings replicated the results by Ochsner et al. (2004) in showing that both regulation conditions were associated to the increased activation of ACC, dlPFC, and OFC. Crucially, the dlPFC was also found to mediate the role of amygdala that showed hyper or hypo-activation according to the up- or down-regulation, respectively. Interestingly, the result that prefrontal regions maintain their higher activations regardeless of the regulation instructions can be also explained by the findings of other studies showing that dlPFC activity is associated with keeping the regulatory goals (Braunstein et al., 2017; Kalisch, 2009) and that the dorsal ACC activity is associated with signalling when adjustments to the ongoing regulation strategies are needed (Ochsner et al., 2012; Braunstein et al., 2017).

Regarding attentional deployment, studies focusing on selective attention provided inconsistent results (Braunstein et al., 2017; Ochsner & Gross, 2005). For instance, some studies highlighted a decrease in amygdala activity when participants focused their attention on aversive (Taylor et al., 2003) or fearful visual stimuli (Hariri et al., 2003), while others found no change during the presentation of disgusted and happy faces (Gorno-Tempini et al., 2001) and of disgusted, fearful, happy and sad faces (Winston, O'Doherty & Dolan, 2003). Some authors suggested that these differences in results mainly depend on the hetogeneity in the stimuli and in the methods used by studies on selective attention to measure and control the focus and level of participants' attention (Ochsner & Gross, 2005; Ochsner et al., 2012; Buhle et al., 2010; Braunstein et al 2017).

Also studies on distraction showed some methodological limitations that prevent definite conclusions about the brain regions involved by this regulation strategy. For instance, some of them explored the neural basis of distraction by considering reactions to physical pain that, however, do not allow a clear distinction between the emotional and the physical unpleasantness of the reactions to painful stimuli (Tracey et al., 2012). Other neuroimaging studies on distraction used secondary tasks (e.g., the Stroop task) to investigate the brain areas that allow participants to shift their attention from emotional salient stimuli to the neutral stimuli of the secondary tasks (i.e., Valet et al., 2004). However, these paradigms prevent to distinguish the cases in which participants effectively use distraction from the salient stimuli to focus their attention on completing the secondary task from cases in which participants down-regulate their emotions, not necessarily by distraction, to be able to perform the secondary task (Ochsner & Gross, 2005).

Nonetheless, similarly to studies on reappraisal, also neuroimaging studies on distraction showed a coupled functioning of the amygdala with the vlPFC and inferior frontal cortex (IFC; Dolcos, Iordan & Dolcos, 2011). By contrast, other studies indicated that distraction while increases the activation of the OFC, ACC, the medial and lateral PFC (specifically the left inferolateral PFC and the right lateral PFC) and clusters in the superior parietal cortex, it also decreases activity in the midcingulate cortex, insula, thalamus, periacqueductal grey and amygdala (Ochsner & Gross, 2005; McRae et al., 2010).

Studies on situation selection showed that the increased activity of the striatum, when participants learned the needed action to end an unpleasant stimulation (i.e., a mild electric shock) in a conditioned learning paradigm, negatively correlated with the descreased activity of amygdala when levels of conditioned fear diminished (Delgado et al., 2009). In another study, Shimamura and colleagues (2013) noted that the emotion suppression during the presentation of disgusting film clips increased the activity of prefrontal regions (i.e., the dlPFC, vlPFC, OFC and ACC) and of medial and posterior parietal areas more than the suppression of arousal derived from the presentation of action film clips. By showing differences in the extend of brain activations between emotion suppression and suppression of more general negative stimuli (e.g., action films), this study provided evidence that suppression of emotions could be a specific strategy distinguishable from other forms of suppression.

Interestingly, a study comparing neural correlates of reappraisal and suppression in reducing negative emotions aroused by movie clips showed that while successful reappraisal entailed the later decrease in the activity of the left amygdala and left insula, suppression increased the activity in the amygdala and insula compared to reappraisal (Goldin et al., 2008). Crucially, the study also found that increased activations of the vlPFC, in particular the right portion, during reappraisal and suppression differed only for the timecourse of the right vlPFC involvement. Indeed, while reappraisal led to an early activation of rVLPFC, together with other regions associated with the cognitive control of emotions, namely the mPFC, dlPFC, and lateral OFC, suppression produced a later response of rVLPFC. This result is in line with the evidence that the rVLPFC consistently down-regulates negative emotions across different regulation strategies. For instance, a study showed that the rVLPFC was equally involved by both reappraisal and distraction (McRae et al., 2010). Furthermore, a series of studies (Harenski & Hamann, 2006; McRae et al., 2010; Wager et al., 2008; Ochsner et al., 2004; Phan et al., 2005) demonstrated the role of the rVlPFC in reducing (but not increasing; Kim & Hamann, 2007) negative emotions (e.g., anxiety following anticipation of painful stimuli) resulting from different stimuli.

4.2. Neural correlates of implicit emotions' regulation strategies

Studies investigating neural correlates of implicit emotions' regulation processes usually do not require participants to explicitly regulate their emotions, rather observe how they incidentally regulate their emotions (Hallam et al., 2015).

For instance, in a study using a modified version of the Stroop task, in which participants were required to respond to emotional faces ignoring the interference of congruent or incongruent and emotional or non-emotional distractors, showed the increased activity of the rostral ACC when participants regulated their attention toward emotional distractors in incogruent trials (for instance when the word 'fear' was shown as distractor over a male happy face). Moreover, the increased activation of the rostral ACC negatively correlated with the decreased activity of amygdala (Egner et al., 2008; Etkin et al., 2006). Crucially, the recruitment of the rostral ACC and the interplay between the rostral ACC and amygdala were totally incidental as participants were not excplicitely required to regulate their emotions, but they had to implicitely control the emotional information to deal with the conflict of the Stroop incongruent trials. These findings further confirm the role of the ACC, and in particular the rostral portion, in regulating reactions to emotional information during tasks requiring conflict monitoring and in mediating the adaptation to conflicting emotional stimuli (e.g., control of prepotent responses as those to label distractors in the emotional Stroop task) (Berkman & Lieberman, 2009). Interestingly, they also replicated the results of previous studies that consistently demostrated that the top-down ACC suppression of the amygdala activity is crucial for successful emotions' regulation (Etkin et al., 2015; Casey et al., 2019; Gee et al., 2013). Indeed, previous studies found that groups with impaired implicit emotions' regulation (e.g., patients with emotional distress disorders, such as depressive mood disorders, anxiety disorders – generalized anxiety disorder or social anxiety disorder - borderline personality disorder), compared to healthy controls, did neither show increased anterior ACC in conflicting emotional tasks nor show the typical activation pattern of increased anterior ACC and decreased amydgala (Hua et al., 2021; Etkin et al., 2010; Chechko et al., 2009; Etkin & Schatzberg, 2011).

Similar results were found by Maier & Di Pellegrino (2012), who investigated implicit emotions' regulation in individuals with cerebral lesions. In particular, reaction times and accuracy in an emotional Stroop task were compared between individuals with lesions of rostral ACC and patients with damages involving other brain areas, and healthy controls. Authors found that while clinical and healthy control group showed conflict adaptation to both neutral and emotional

distractors, individuals with lesions in the rostral ACC showed conflict adaptation when neutral, but not emotional, distractors were superimposed on faces stimuli.

A series of studies investigated the neural correlates associated to the affect labelling, a task used to measure implicit emotions' regulation processes based on the assumption that mental actions, such as reasoning, rationalizing and labelling, can effectively be used to control emotional reactions (Hariri, Bookheimer & Mazziotta, 2000). In particular, in the affect labelling task participants are instructed either to match an emotional face target to the emotional face that, out of the alternatives, is more similar to the target, or to match the verbal label that, compared to the alternative labels, better represents the emotion depicted by the face target. Interestingly, the study by Hariri, Bookheimer & Mazziotta (2000) showed that during an affective labeling task the activity of rVLPFC and amygdala were inversely related, with a greater activation of the rVLPFC during the label matching and a greater activation of amygdala during the face matching. These differences in the neural activations between the emotional (by the face-to-face matching) and the verbal (by the face-to-label matching) processing of stimuli may represent the modulatory top-down control of prefrontal regions over the subcortical processing of emotions mediated by the amygdala. Consistent results were found by Lieberman et al., 2007, who observed that increased activation of the rVLPFC inversely correlated with amygdala and mPFC activation during affective labeling. Based on these results, the authors suggested that the verbal reformulation of the feelings elicited by the emotional faces, through the labelling, implicitely regulate emotions by increasing the activity of the rVLPFC, which in turn reduces amygdala responses by way of connections with the mPFC.

Other studies further investigated the role of the vlPFC in the implicit emotions' regulation via other experimental paradigms to test incidental regulation of emotions, such as the go/no-go task. For instance, Berkman and colleagues (2009) applied a modified version of the go/no-go task in which participants were instructed to respond (i.e., go trials) or to not respond (no-go trials) to the gender of faces used as stimuli while ignoring their negative expressions. Results showed the increased activation of the rVLPFC in no-go trials compared to go-trials, suggesting that this area is crucially recruited when inhibition of emotional stimuli is required. Interestingly, the pattern of activation of the rVLPFC inversely correlated with the activity of amygdala that, by contrast, was found to be more active in go-trials, that is when free reactions to (emotional) stimuli were allowed, than no-go trials. These results were similar to those found by Hare et al. (2005), who showed that the suppression role of the rVLPFC in no-go trials mediated the increased and decreased amygdala activity in go- and no-go trials, respectively.

Another study showed that the strength of coupling between ventral PFC and the amygdala positively correlated with greater habituation of amygdala activity in response to repeated exposure to threats, fo instance fearful faces during an emotional go/no-go task (Hare et al., 2008). This seems crucial during adolescence when subcortical emotional processing, mediated by amygdala, is hyperactivated compared to childhood and adulthood. Moreover, authors found that amygdala habituation varied according to the trait anxiety levels, so that decreased amygdala habituation negatively correlated with increased trait anxiety both in adolescents and adults. This result is line with findings that less habituation of amygdala activity characterizes people with anxiety disorders (Wright et al., 2001; for a meta-analysis see Lissek et al., 2005). Other emotional go/no-go task experiments corroborated the role of emotional disorders in affecting neural responses to implicit emotions' regulation, as measured by electroencephalography components recorded at the prefrontal level. Indeed, depressive symptoms were found to negatively correlate with the NoGo P3 amplitudes elicided by inhibiting negative faces stimuli, while trait anhedonia was found to positively correlated with the NoGo P3 amplitudes elicided by inhibiting positive faces stimuli (Zhang et al., 2016).

Chapter 5: Use of non-invasive brain stimulation to regulate emotions

As previously mentioned, my PhD also aimed to further investigate emotions' regulation by applying non-invasive brain stimulation (NIBS) techniques. Therefore, in this Chapter, first I will briefly report some considerations about methodological aspects of these techniques. Second, I will present results from literature reviews (see paragraphs 5.1 and 5.2) I run during my PhD to revise studies on NIBS in self (in particular emotion) regulation field.

From a technical point of view, NIBS, compared to other instruments of cognitive neuroscience, presents several advantages. First, these techniques are usually used to temporarily modulate or interfere with cerebral activity in specific brain regions by applying external devices, not implanted in the brain (Boggio et., 2016; Brunoni et al., 2019). In particular, NIBS allows to transiently interfere with the activity of a certain cerebral regions or networks, directly activating or inhibiting the targeted areas or modulating their excitability (Nitsche & Paulus, 2000). This advantage of NIBS allows to draw causal conclusions about the relationship between cerebral activity and perceptual, cognitive and motor functions (Boggio et., 2016; Filmer et al., 2014; Walsh & Cowey, 2000; Shah-Basak et al., 2019). Second, compared to lesion studies, NIBS allows research on brains not altered by structural and functional changes linked to cerebral damages, that can add potential confounding effects (Boggio et., 2016; Pascual-Leone, Walsh & Rothwell, 2000). At the same time NIBS has been effectively used in the last twenty years to investigate their efficacy to treat a wide range of clinical conditions, either neurologica or psychiatric (e.g., see Fregni & Pascual-Leone, 2007; Kekic et al., 2016; Brunoni et al., 2019; Cantone et al., 2021; Vergallito et al., 2021 for reviews; for guidelines see Lefaucheur et al., 2020; Fregni et al., 2021).

Among NIBS, the Transcranial magnetic stimulation (TMS) and the transcranial direct current stimulation (tDCS) are the two more widely used techniques. Accordingly, the narrative review on self-regulation presented in paragraph 5.1 and the experimental studies presented in Chapter 6 will regard tDCS applications, while the systematic review and meta-analysis presented in paragraph 5.2 will provide data about both TMS an tDCS studies.

Briefly, TMS involves the delivery of a strong magnetic pulse though a coil held over the identified target area, inducing neuronal firing by suprathreshold neuronal membrane depolarization (Pascual-Leone, Walsh & Rothwell, 2000). Depending on the purpose of the stimulation, coils of different shapes and sizes can be used, for instance circular coils that produce a stronger magnetic field on the inner edges or figure-of-eight coils to achieve more focal stimulation. Moreover, single-

pulse stimulation protocols, typically applied to investigate corticospinal integrity (even in combination with other techniques, such as electroencephalography), or repetitive stimulation protocols (rTMS), typically applied to induce synaptic plasticity, can be used. In particular, high-frequency rTMS (> 5 HZ) and intermittent theta burst stimulation (iTBS) usually have excitatory effects, whereas low-frequency (< 1 Hz) or continuous theta burst stimulation (cTBS) usually have inhibitory outcomes. TMS intensity is usually determined as a percentage of the resting motor threshold (rMT), which is the minimum TMS intensity needed to generate a motor evoked potential (MEP) of at least 50 μV of amplitude in at least 5 out of 10 trials (see Brunoni et al., 2019; Klomjai, Katz & Lackmy-Vallée, 2015 for details).

In turn, transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that applies weak constant direct currents, through a pair of electrodes (an anode and a cathode), to modulate neurons' resting state membrane potentials in a polarity-dependent way: anodal tDCS is known to increase cortical excitability through neuron depolarization, and cathodal is known to decreaseit through hyperpolarization. When administering tDCS, several parameters must be considered: electrodes positioning and size, current intensity and density, duration of the stimulation, number of sessions delivered and time interval between sessions (e.g. Nitsche et al., 2008). Here I will not describe the details of the tDCS parameters that will be presented in deep in the narrative review of the next paragraph.

5.1 Results from a narrative review

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REVIEW
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Stimulating Self-Regulation: A Review of Non-invasive Brain Stimulation Studies of Goal-Directed Behavior

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Self-regulation enables individuals to guide their thoughts, feelings, and behaviors in a purposeful manner. Self-regulation is thus crucial for goal-directed behavior and contributes to many consequential outcomes in life including physical health, psychological well-being, ethical decision making, and strong interpersonal relationships. Neuroscientific research has revealed that the prefrontal cortex plays a central role in self-regulation, specifically by exerting top-down control over subcortical regions involved in reward (e.g., striatum) and emotion (e.g., amygdala). To orient readers, we first offer a methodological overview of tDCS and then review experiments using non-invasive brain stimulation techniques (especially transcranial direct current stimulation) to target prefrontal brain regions implicated in self-regulation. We focus on brain stimulation studies of self-regulatory behavior across three broad domains of response: persistence, delay behavior, and impulse control. We suggest that stimulating the prefrontal cortex promotes successful self-regulation by altering the balance in activity between the prefrontal cortex and subcortical regions involved in emotion and reward processing.

Keywords: transcranial direct current stimulation, self-regulation, emotion-regulation, goal-directed behavior, dorsolateral prefrontal cortex

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INTRODUCTION

At least since Walter Mischel's seminal work on delay of gratification (Mischel, 1958; Mischel et al., 1972), the practical and the theoretical implications of self-regulation have been important topics of study in psychological science (Carver and Scheier, 1982; Metcalfe and Mischel, 1999; Muraven and Baumeister, 2000). Self-regulation refers to the conscious and non-conscious processes that enable individuals to guide their thoughts, feelings, and behaviors in a purposeful manner. Self-regulation is crucial for goal-directed behavior and has been related to many consequential outcomes in life including physical and mental health, psychological well-being, ethical decision making, and strong interpersonal relationships. Likewise, failures at self-regulation are thought to contribute to alcohol and drug addiction, personal debt, obesity, and other outcomes that carry both personal and societal costs (for a review, see Vohs and Baumeister, 2016). Because of its consequences for so many crucial outcomes, the scientific study of self-regulation spans many of subfields in psychological science and frequently centers on a relatively simple question: How can we improve self-regulatory abilities?

One possible answer is by stimulating the brain with electrical current. Self-regulation is typically assessed with laboratory analogs of common challenges encountered in daily life, such as persisting at difficult tasks, choosing between immediate versus more delayed rewards, and managing emotional impulses. These examples represent paradigmatic forms of self-regulation, namely *persistence,* or the sustained performance of aversive behavior (e.g., tolerating pain, coping with failure); *delay behavior,* which refers to choices that favor more long-term investments at the expense of short-term gains; and *impulse control*, which involves the purposeful inhibition of emotive response tendencies. Below we focus on these three paradigmatic forms of self-regulation and review experiments that have used brain stimulation techniques to try to improve them. We then consider inconsistencies in findings, address unresolved questions, and point to new directions for future research.

Neural Correlates of Self-Regulation

Convergent evidence from social, cognitive, and affective neuroscience research reveals that the interplay between the prefrontal cortex and subcortical threat and reward processing is crucial for self-regulation (for a review see: Heatherton and Wagner, 2011; Kelley et al., 2015b; Berkman, 2017; Wagner and Heatherton, 2017). Numerous studies have associated successful self-regulation with top-down control from the prefrontal cortex over subcortical regions involved in reward and threat processing (e.g., Dambacher et al., 2014; Giuliani et al., 2014; Vijayakumar et al., 2014; Lopez et al., 2017). By contrast, self-regulatory failure occurs when top-down control is diminished or when the balance in activity favors threat and reward systems (e.g., Demos et al., 2012; Wagner and Heatherton, 2012; Wagner et al., 2013; Chester and DeWall, 2014; Lopez et al., 2014; Meyer and Bucci, 2016).

As an illustrative example, in a 40-year longitudinal follow-up with children who participated in Mischel's seminal delay of gratification work, children who successfully delayed gratification exhibited preferential recruitment of the prefrontal cortex (PFC) during a task requiring inhibitory control as adults. In contrast, children who were unsuccessful at delaying gratification showed preferential recruitment of the ventral striatum in a delay task as adults (Casey et al., 2011). These findings highlight the importance of the balance or relative activity levels in the prefrontal cortex and subcortical regions, respectively, and how shifts in this balance can tip the scales between short-term and long-term goal regulation.

Several models of emotion regulation similarly emphasize the balance in activity between prefrontal and subcortical brain regions. For example, Ochsner and Gross (2007) proposed a seminal model of emotion that distinguishes between bottom-up affective processing, mediated by limbic system structures such as amygdala, and top-down appraisal processes that involve prefrontal regions. Success at cognitive reappraisal, a form of emotion regulation that involves generating cool cognitive representations of affective states or changing the meaning of emotional events, is associated with increased activity in dorsomedial and dorsolateral prefrontal cortices, alongside corresponding decreases limbic system (i.e., amygdala) activity.

Another relevant model of emotion regulation highlighted the key role of a cortico-subcortical network consisting in a dorsal system and a ventral system (Phillips, 2003; Phillips et al., 2008). The dorsal system encompasses the hippocampus, the dorsal regions of anterior cingulate gyrus, and the DLPFC and is involved in executive functions, particularly planning, attention control, and effortful regulation of affective states. The ventral system includes the amygdala, the insula, the ventral striatum, the anterior cingulated cortex, the orbitofrontal cortex, and the ventrolateral prefrontal cortex (VLPFC) and is predominantly recruited for the automatic regulation of affective reactions and for the recognition of emotional valence of stimuli.

Consistent with and prior to these models of emotion regulation, Botvinick and colleagues (Cohen et al., 2000; Botvinick et al., 2001, 2004; Shenhav et al., 2013) discussed cortical-subcortical balance as it relates to cognitive control. Cognitive control refers to a constellation of functions that orient cognitive subsystems to perform difficult and novel tasks (Botvinick et al., 2004). Botvinick and colleagues' conflict monitoring hypothesis proposed that response conflict activates cortical brain regions (i.e., the dorsal ACC), thereby signaling the need for conflict resolution to facilitate effective behavior (see MacDonald et al., 2000; Botvinick et al., 2001; Ochsner et al., 2009). The theoretical models reviewed above suggest that regulation of both cognition and emotion is contingent upon the balance in activity between cortical and subcortical regions. Brain stimulation techniques targeting cortical regions may thus influence self-regulation by influencing cortical-subcortical balance.

Overview and Goals

We propose that non-invasive brain stimulation targeting the prefrontal cortex holds promise for improving human self-regulation. To orient the reader to neuromodulation, we first provide a methodological overview of transcranial direct current stimulation (tDCS) – one of the most popular brain stimulation techniques in psychological science. Then we review behavioral evidence that non-invasive brain stimulation targeting the PFC may enhance three paradigmatic forms of self-regulation: persistence, delay behavior, and impulse control (see **Table 1**). We conclude our review by highlighting inconsistencies in findings, unresolved questions, and new directions for future research.

A METHODOLOGICAL OVERVIEW OF tDCS

Effects of weak electrical currents on brain and neuronal function were first described more than two centuries ago (Priori, 2003; Nitsche et al., 2008; Zago et al., 2008). Systematic studies with animals showed the efficacy of inducing modifications, enhancements, or diminutions of cortical activity by delivering weak direct currents to the brains of laboratory rats. Specifically, passing currents through the scalp polarized the brain region beneath the electrodes and altered the firing rate of neurons. These effects were detected immediately after the stimulation and seemed to last beyond the stimulation period (Bindman et al.,

TABLE 1 | Study features, stimulation parameters, and key outcomes of all studies reviewed.

N	Time (min)	Size (cm^2)	Current (mA)	Montage	Design	Outcome
Persistence						
20	5	35	2	Sham, anode L DLPFC, M1, V1	W	Anode L DLPFC increased pain thresholds (Boggio et al., 2008)
12	20	35	2	Sham, anode and cathode tDCS over L and R DLPFC	W	Anode R DLPFC increased tolerance to heat (Mylius et al., 2012)
40	20	15	2	Anode and cathode tDCS over the L and R DLPFC	W	Anode L DLPFC decreased pain (Mariano et al., 2015)
79	20	16	2	Sham, anode L DLPFC, and cathode L DLPFC	B	Cathode L DFLPFC increased pain tolerance (Powers et al., 2018)
Delay behavior						
14	20	9	1.6	Sham, anode L DLPFC/cathode R DLPFC, cathode L DLPFC/anode R DLPFC	W	Anode L DLFPC increased preference for immediate rewards (Hecht et al., 2012)
24	20	35	1.5	Sham, anode L DLPFC/cathode R OFC, cathode L DLPFC/anode R OFC	W	Both types of active stimulation increased preference for larger-but-later rewards (Nejati et al., 2018)
23	20	35	2	Sham, anode L DLPFC/cathode R DLPFC, and cathode L DLPFC/anode R DLPFC	W	Anode R DLPFC decreased food cravings, visual attention toward desserts, and consumption (Fregni et al., 2008)
19	20	35	2	Sham and cathode L DLPFC/anode R DLPFC	W	Anode R DLPFC decreased food cravings but not consumption (Goldman et al., 2011)
10	20	35	2	Sham and cathode L DLPFC/anode R DLPFC	W	Anode R DLPFC reduced consumption and modulated the N2, P3a, and P3b ERP components (Lapenta et al., 2014)
17	20	25	2	Sham and cathode L DLPFC/anode R DLPFC	W	Anode R DLPFC reduced cravings for sweet but not savory foods or consumption (Kekic et al., 2014)
30	20	35	2	Daily sham or anode R DLPFC for 5 days	B	Anode R DLPFC reduced food cravings up to 30 days later (Ljubisavljevic et al., 2016)
30	20	25	2	Sham and cathode L DLPFC/anode R DLPFC	W	Anode R DLPFC reduced cravings and consumption (Burgess et al., 2016)
Impulse control						
20	15	5.3	0.45	Sham, anode L DLPFC, and anode R DLPFC	W	Anode R DLPFC combined with a cognitive reappraisal task reduced negative emotions (Pripfl and Lamm, 2015)
96	20	25/35	1.5	Sham or anode R VLPFC	B	Anode R VLPFC reduced the perceived intensity of negative emotions (Vergallito et al., 2018)
60	15	35	2	Sham, cathode L DLPFC/anode R DLPFC, or anode L DLPFC/cathode R DLPFC	B	Anode L DLPFC caused more aggression in angry participants (Hortensius et al., 2012)
32	12.5	35	2	Sham or anode R DLPFC	B	Anode R DLPFC reduced proactive aggression in men (Dambacher et al., 2014)
64	21.75	35	1.5	Sham, cathode L IFG/anode R IFG, and anode L IFG/cathode R IFG	B	No effect of IFG stimulation on response inhibition or aggression (Dambacher et al., 2015b)
90	15	35	2	Sham, cathode L DLPFC/anode R DLPFC, and anode L DLPFC/cathode R DLPFC	B	Anode R DLPFC increased rumination (Kelley et al., 2013)
202	15	35	2	Sham, cathode L DLPFC/anode R DLPFC, and anode L DLPFC/cathode R DLPFC	B	Anode R DLPFC sped up motive incongruent responses (Kelley and Schmeichel, 2016)
14	20	32	2	Five days of twice daily anode L DLPFC/cathode R DLPFC	N/A	Anode L DLPFC reduced sadness up to 30 days after treatment (Ferrucci et al., 2009)
10	20	35	1	Daily sham or anode L tDCS	B	Anode L DLPFC reduced depressive symptoms (Fregni et al., 2006)
23	5	35	2	Sham, anode L DLPFC, M1, V1	W	Anode L DLPFC increased accuracy in identifying positive pictures (Boggio et al., 2009)
80	20	35	2	Sham and anode R IFG	B	Anode R IFG decreased sustained fear and skin conductance levels to unpredictable threats (Herrmann et al., 2017)

(Continued)

TABLE 1 | Continued

N	Time (min)	Size (cm^2)	Current (mA)	Montage	Design	Outcome
45	30	25	1	Sham and either cathode L DLPFC/anode R DLPFC, or anode L DLPFC/cathode R DLPFC	W	Anode L DLPFC improved performance and decreased cortisol among participants high in ma anxiety (Sarkar et al., 2014)
47	20	25	1	Sham and anode L DLPFC	B	Anode L DLPFC enhanced fear memories (Mungee et al., 2014)
17	20	25	1	Sham and cathode R DLPFC	B	No effect of cathode R DLPFC on fear memories (Mungee et al., 2016)
80	20	25/35	1.5	Sham and anode R VLPFC	B	Anode R VLPFC reduced aggression after social exclusion (Riva et al., 2012)
79	15	25/35	1.5	Sham and anode R VLPFC	B	Anode R VLPFC reduced negative feelings after social exclusion (Riva et al., 2014a)
	20	25/50	1.5	Sham and anode R VLPFC	B	Anode R VLPFC reduced unproved aggression in violent-game players (Riva et al., 2017)
92	15	35	2	Sham, cathode L DLPFC/anode DLPFC, and anode L DLPFC/cathode R DLPFC	B	Anode L DLPFC increased jealousy after social exclusion (Kelley et al., 2015a)
16	20	35	1	Sham and anode L DLPFC	W	Negative pictures rated less negative after anode tDCS over the L DLPFC (Peña-Gómez et al., 2011)
48	20	35/100	1.5	Sham and anode R DLPFC	B	Anode R DLPFC enhanced cognitive control during emotion regulation (Feeser et al., 2014)
35/12	20	35	2	S1: Bilateral DLPFC S2: Unilateral DLPFC	B	Bilateral DLPFC tDCS modulated decision making (Fecteau et al., 2007b)
36		35	2	Sham, cathode L DLPFC/anode DLPFC, and anode L DLPFC/cathode R DLPFC	B	Anode R DLPFC reduced risk taking (Fecteau et al., 2007a)
16	19	35	2	Sham, cathode DLPFC/anode R DLPFC, and anode L DLPFC/cathode R DLPFC	W	Anode stimulation over the R DLPFC reduced risky decision-king (Cheng and Lee, 2016)
30	25	25	2	Twice daily sham or anode R DLPFC/cathode L DLPFC for 5 days	B	Active tDCS paired with the cognitive task reduced risk-taking This effects persisted 2 months (Gilmore et al., 2017)
20	15	25	1.5	Sham or anode R DLPFC/cathode L DLPFC	B	Anode R DLPFC caused greater R DLPFC-whole brain connectivity which was associated with reduced risk-taking (Wacker et al., 2008)
24	15	35	1	Anode and cathode R DLPFC or anode and cathode L DLPFC	W	Anode DLPFC (either L or R) led to reduced risk taking on a driving simulation (Beeli et al., 2008)

DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; L, left; R, right; B, between-subjects; W, within-subjects.

1964; Gartside, 1968; Hattori et al., 1990; Islam et al., 1995). Early research in human samples investigated the application of electrical currents in mood disorders treatment, with some evidence suggesting a reduction in symptoms of depression and mania (Costain et al., 1964; Carney, 1969). But subsequent studies and null findings contributed to skepticism in the efficacy of running weak electrical currents into the brain as an effective tool for symptom reduction (Lolas, 1977; Nitsche et al., 2003b). More recently, researchers have shed light on bidirectional, time, and polarity-dependent excitability changes following tDCS (Priori et al., 1998; Nitsche and Paulus, 2000).

How Does tDCS Work?

The tDCS device consists of an electric stimulator, which delivers a constant current and an isolation current, linked to a pair of electrodes positioned on the scalp over cortical regions of interest. The electrodes, namely an anode and a cathode, are typically covered by sponges soaked in NaCI solution (or electrode cream) to increase conductivity, reduce resistance, and improve the homogeneity of the electric field under the electrodes.

Transcranial direct current stimulation differs from other brain stimulation techniques, such as transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS), because tDCS does not induce action potentials in neuronal membrane. Instead, tDCS transiently modifies spontaneous neuronal excitability by depolarizing or hyperpolarizing neurons' resting membrane potentials, producing ionic concentration shifts within the extracellular fluid (Creutzfeldt et al., 1962; Purpura and McMurtry, 1965). Anodal stimulation typically depolarizes local neurons, which in turn will require less dendritic input to fire, whilst cathodal stimulation hyperpolarizes neurons' typical resting membrane potentials so that increasing dendritic input is required (Nitsche and Paulus, 2000). This mechanism of action generally occurs both during stimulation and for a short period of time (<5 min) thereafter.

Transcranial direct current stimulation has been found to involve more complex mechanisms including long-term potentiation (LTP) and long-term depression (LTD) mechanisms at the synaptic level, affecting hyper-communicative activity through the anode and hypo-communicative activity through the cathode. These tDCS-driven changes in LTP and LTD may

be mediated by a number of synaptic mechanisms including: NMDA (*N*-methyl-D-aspartate) receptors, GABAergic activity, glutamatergic activity, intracellular CA2+ concentration, brain-derived neurotrophic factor (BDNF) secretion, and tropomyosin-related kinase B (TrkB) activation (Liebetanz et al., 2002; Nitsche et al., 2003a, 2004; Stagg et al., 2009; Fritsch et al., 2010; Stagg and Nitsche, 2011). Also, non-synaptic mechanisms, such as changes in pH and transmembrane proteins, seem to be involved in long-term effects of tDCS (Ardolino et al., 2005).

Parameters Influencing Stimulation Efficacy

The efficacy of eliciting changes in brain activity using tDCS depends on several physical parameters including current density, stimulation duration, and the orientation and focality of the electrical field. These parameters constitute the tDCS dosage.

Current Density

Current density represents the ratio between current strength (normally up to 2 mA) and electrode size (normally reference electrode varies from 25 to 35 cm^2). Current density determines the delivered electrical field strength (Purpura and McMurtry, 1965).

Stimulation Duration

Stimulation duration refers to the amount of time participants undergo stimulation. It is based on LTP and LTD mechanisms and is related to the occurrence and length of aftereffects. Generally, keeping current density constant, brief exposure to tDCS stimulation (few seconds) does not induce long-lasting effects, whereas tDCS stimulations of about 10 min (up to 30 min) typically do elicit aftereffects (Nitsche et al., 2003c; Ardolino et al., 2005).

Orientation of the Electric Field

The orientation of the electric field normally depends on electrodes' polarity and position. As already described, tDCS produces polarity-dependent effects whereby anodal stimulation increases the activity of the stimulated area, whereas cathodal stimulation decreases it. Several studies of both the primary motor and visual cortices have found that different electrode positions modulate different neuronal groups and elicit different evoked potentials (Priori et al., 1998; Antal et al., 2004; Accornero et al., 2007) suggesting that electrode position is a crucial tDCS parameter.

Indeed, not only may electrode position affect the amount of current delivered to the brain and the direction of current flow, but also it may determine effects on the targeted brain region, due to electrical field interactions associated with neuronal geometry (Nitsche and Paulus, 2000; Nitsche et al., 2008). Whereas the coupling of anodal-excitatory and cathodal-inhibitory effects is well established in the sensorimotor domain, evidence gets more controversial when addressing higher cognitive functions (Jacobson et al., 2012). This lack of consistency between sensorimotor and cognitive functions is at this output level. It is not that the inconsistencies arise from differences in the effects of stimulation on sensorimotor cortices versus prefrontal cortices themselves. In other words, the inconsistency is not the result in differences in the effects of the stimulation protocol on activity or function but rather the consequence of those changes. Indeed, when dealing with more complex functions, likely represented by large and interconnected neural networks comprising both excitatory and inhibitory connections, it is more difficult to obtain a predictable outcome, hence it is not always the case that anodal tDCS leads to an enhancement (e.g., better performance in a task) and cathodal tDCS leads to a diminution of the assessed cognitive function (Fertonani and Miniussi, 2017).

Induced Electric Field Focality

Another important tDCS parameter is the induced electric field focality. Generally, large electrodes and bipolar scalp electrode arrangements limit tDCS focality (Gandiga et al., 2006), in part because large electrodes may alter activity in areas adjacent to the stimulated region. Moreover, with an intracephalic montage, the so-called reference electrode (the secondary electrode with regard to a specific experimental setting), being located on the scalp, is not entirely inert. The lack of spatial focality of tDCS effects suggests the need for arrangements to increase focality. For instance, to increase tDCS focality it is possible to use smaller target electrodes. Another option is to increase the reference electrode size so that, due to decreased current density, it becomes practically inert. Alternatively, using an extracephalic montage may increase stimulation focality (Nitsche et al., 2007, 2008; Ferrucci et al., 2008), although in this case the spread of current flow could be hardly traceable. In any case, widespread (non-focal) effects of tDCS should be taken into account, considering that functionally active cortical targets may be more susceptible to excitability changes induced by tDCS. Lack of spatial focality may undermine tDCS effectiveness in performing cortical mapping, but the idea that widespread cortical networks are affected by tDCS could explain the strength of the observed behavioral effects, in some cases lasting for months after several stimulation sessions are performed, thus supporting the possible benefits of this technique for clinical applications.

Underlying Neural Activity

Studies using fMRI to assess online and offline tDCS effects have found that anodal and cathodal stimulation elicit, respectively, an increment and a decrement of perfusion in a wide set of brain areas, including cortical and subcortical structures, even at some distance from the target area (e.g., Stagg et al., 2013). Similarly, computational models of current flow have indicated that strong electric fields occur not only underneath and near the stimulating electrodes but also in the regions between them (Miranda et al., 2013). Consistent with the computational modeling studies noted above, recent findings have observed tDCS effects on both structural and functional connectivity (Romero Lauro et al., 2014, 2016; Pisoni et al., 2017).

Practical Considerations

Sham Stimulation

Regarding its practical applications, tDCS, allows for more effective placebo stimulation-controlled studies compared to TMS where notable issues with placebo effects and limited

blinding success (Duecker and Sack, 2015). Placebo (sham) stimulation can be delivered for few seconds and subjects experience the same physical sensations as real stimulation (e.g., itching sensation), without substantial neural or behavioral effects (Gandiga et al., 2006; Nitsche et al., 2008).

Individual Differences

Another practical consideration concerns individual differences. Following seminal work in the tDCS literature (e.g., Nitsche et al., 2008) we recommend that participants be matched on individual differences like sex or age that can influence tDCS efficacy (Pitcher et al., 2003; Kuo et al., 2006; Quartarone et al., 2007; Chaieb et al., 2008). In addition to demographic factors, researchers should also consider whether participants respond to tDCS protocols. In two motor cortex studies, anodal stimulation increased cortical excitability in 50–64% of participants (Wiethoff et al., 2014; López-Alonso et al., 2015). These individual differences highlight the need to develop more robust stimulation protocols and well-powered studies which can systematically test for the moderating role of individual differences.

Safety

Transcranial direct current stimulation is a safe and non-invasive neuromodulatory technique. Several neuroimaging and EEG studies have demonstrated that tDCS does not cause adverse effects on the brain (Nitsche et al., 2004; Iyer et al., 2005). The most common side effects include mild tingling sensations, moderate fatigue and light itching sensations, especially at stimulation onset (e.g., Poreisz et al., 2007) and stimulation sessions up to 50 min do not cause serious consequences (Nitsche et al., 2008). Moreover, ramping up and ramping down current at the beginning and at the end of a stimulation session is useful to avoid brief retinal phosphenes or startle-like phenomenon caused by sudden neuronal firings.

To summarize, tDCS is a safe, inexpensive, well-tolerated, and easy to use. Its physiological consequences have led to an increasing interest in using tDCS to alter psychological processes. With an appreciation for the history and mechanics of tDCS, the next section will explore the consequences of prefrontal tDCS psychological processes in the domain of self-regulation.

TRANSCRANIAL DIRECTION CURRENT STIMULATION AND SELF-REGULATION

Persistence

Self-regulation enables individuals to guide their thoughts, feelings, and behaviors in a goal-directed fashion. Self-regulation can be aversive both physically and psychologically. Goal directed behavior often entails persistence, including the sustained performance of aversive behavior. For example, physical exercise sometimes elicits short-term pain or physical discomfort but also brings more long-term appearance- and health-related benefits. Individuals who are better able to endure the discomfort presumably exercise longer and more frequently. As a result, these same individuals may be more successful at achieving their fitness goals. Other situations may require individuals to endure psychologically aversive states in the interest of accomplishing one's goals. For example, academic and occupational successes may entail many failed attempts to solve complex problems. The ability to endure these aversive states seems likely to facilitate goal-directed behavior and thus may constitute an important facet of self-regulation.

Pain Tolerance

Research suggests that the DLPFC is a key brain region for various aspect of pain, including pain tolerance (see Seminowicz and Moayedi, 2017). Consistent with this viewpoint, several studies have used prefrontal tDCS to modulate the experience of pain in laboratory tasks. For example, Mylius et al. (2012) found that anodal tDCS over the right DLPFC increases tolerance to heat pain as measured by the temperature of a thermode applied to the forearm. Similar results were obtained by Boggio et al. (2008), who found that excitatory stimulation of the left DLPFC increases pain thresholds. Taken together, these findings suggest that stimulation to the prefrontal cortex in either hemisphere may increase pain tolerance – a classic form of self-regulation.

More recently, a study by Mariano et al. (2016) applied anodal versus sham tDCS during both a cold pressor task and a breath holding task (see also Mariano et al., 2015, for similar work probing the dorsal anterior cingulate cortex). These two tasks represent commonly used laboratory pain paradigms. Participants' pain ratings were assessed before and after stimulation using the Defense and Veterans Pain Rating Scale (DVPRS), which asks participants to rate their pain on an 11-point visual analog scale from 0 = *no pain* to 10 = *severe pain*. Ratings were obtained after the first 7 min of tDCS in each testing block and immediately after the cold pressor and breath holding tasks. Stimulation did not influence performance on the cold pressor task as measured by threshold, tolerance, or endurance, nor did it influence breath holding time. However, anodal stimulation over the left DLPFC decreased the experience of pain as measured by the DVPRS. This study suggests that excitatory stimulation of the DLPFC may influence pain perception.

Another relevant pilot study by Powers et al. (2018) paired anodal, cathodal, or sham stimulation over the left DLPFC with either pain education or a 3-min audio recording designed to mimic key components of Cognitive-Behavioral Therapy for pain. Afterward, participants completed five trials of a heat tolerance pain test. Regardless of which intervention was paired with tDCS, cathodal stimulation over the left DFLPFC increased pain tolerance. But several limitations in this study mar the interpretability of the results. First, the study included 6 experimental conditions with 79 total participants, resulting in small sample sizes in each condition and thus relatively low statistical power to detect anything but very large effects of tDCS. Second, the electrode montage involved placing the anode or cathode over the F3 region and the other electrode on the right shoulder. The study by Mariano et al. (2016) reviewed above, which found reduced pain experience but not increased pain tolerance, used the mastoid as a reference, whereas the study by Mylius and colleagues, which found increased pain tolerance, involved placing the reference electrode over the contralateral supraorbital area. Thus, inconsistencies in the

electrode montages used across studies of prefrontal tDCS and pain, along with differences in methods used to induce and measure pain, hamper our ability to draw clear conclusions about the effects of tDCS on pain experience and pain tolerance.

Delay Behavior

Often one's end goals are situated far in the future, and pursuing such goals comes at the cost of satisfying more immediate desires. Saving for the future comes at the cost of spending today. Maintaining a healthy physique comes at the expense of delicious desserts. Academic achievement often comes at the expense of fraternization. *Delay behavior* refers to choices that favor more long-term investments at the expense of short-term gains. To the extent that individuals stifle or subdue their immediate urges, the better they are in striving toward their long-term goals.

Delay Discounting

Delay discounting refers to the reduction in the present value of a reward with delayed receipt. The basic idea is that the valuation of rewards degrades over time. So, for example, gaining $10 today would typically be valued more than gaining $10 in a month from today. For each unit of time increase in the delay to receipt, the value of a reward decreases (or is discounted) by a non-fixed proportion. In other words, the effect of delay on value is not the same across the range of delays. At short delays value decreases less steeply, whereas at longer delays value degrades more steeply. A hyperbolic discounting function captures the pattern that at shorter delays reward valuation degrades less than it does at longer delay periods. The steepness of the slope within this hyperbolic model reflects the extent to which people prefer smaller-but-immediate (compared to larger-but-delayed) rewards. A steep slope (i.e., a larger hyperbolic k) reflects a stronger preference for smaller-but-immediate rewards. A less steep slope (i.e., a smaller hyperbolic k) reflects a stronger preference for larger-but-delayed rewards. Typically, a preference for smaller-but-immediate rewards is thought to reflect impulsivity (poor self-regulation) whereas a preference for larger-but-delayed rewards is thought to reflect self-control (good self-regulation).

Hecht et al. (2012) paired prefrontal tDCS with a delay discounting task. Specifically, participants received anodal right DLPFC/cathodal left DLPFC, cathodal right DLPFC/anodal left DLFPC, or sham stimulation. They observed a greater preference for smaller-but-sooner rewards when participants had received anodal stimulation over the left DLFPC, suggesting that this pattern of stimulation increased impulsivity or reduced self-regulation. Similar results have been obtained in TMS studies disrupting right DLPFC activity (Figner et al., 2010; Smittenaar et al., 2013). More recently, a study by Nejati et al. (2018) paired DLPFC stimulation with OFC stimulation prior to a delay discounting task. Specifically, participants received sham stimulation, anodal left DLPFC/cathodal right OFC, and cathodal left DLPFC/anodal right OFC. They observed that relative to sham stimulation, both active stimulation conditions caused a greater preference for delayed rewards as reflected in a smaller k value. The results of this study hinge upon the interaction between the DLPFC and OFC and as a result we cannot determine to what extent they were driven by the DLPFC (or OFC). Because of this, the study by Nejati and colleagues differs in a critical way from the discounting studies reviewed above as those studies speak moreso to the role of hemispheric asymmetry in discounting behavior. Thus, the majority of evidence here suggests that stimulation to shift the balance in neural activity toward the left prefrontal cortex increases delay discounting in a manner that suggests poorer self-regulation.

Food Choice

Food choice and eating entail delay behavior insofar as choosing nutritious foods (e.g., vegetables) over tempting ones (e.g., chocolate cake) represents a choice favoring long-term investments in health at the expense of a short-term hedonic gain. Fregni et al. (2008) compared excitatory right DLPFC stimulation (cathode over F3/anode over F4), excitatory left DLPFC stimulation (anode over F3/cathode over F4), and sham stimulation in the context of food. Self-report measures of food craving and craving in response to food in the laboratory were assessed before and after tDCS. Additionally, after tDCS, participants had their gaze patterns recorded while they viewed an array of nature scenes and images of tempting foods (e.g., desserts). Last, participants had the opportunity to ingest foods and the number of calories ingested was recorded. Results indicated that excitatory right DLPFC stimulation decreased food cravings, decreased visual attention toward tempting desserts, and decreased caloric consumption relative sham stimulation.

Goldman et al. (2011) conducted a similar experiment in a group of healthy individuals with frequent food cravings. Participants viewed food images from the International Affective Picture System (IAPS; Lang et al., 2008) before and after tDCS. Additionally, after stimulation, participants were free to eat a variety of tempting foods including chips, cookies, chocolate, and donuts. Consistent with the results of Fregni et al. (2008), Goldman and colleagues found that excitatory right DLPFC stimulation (cathode over F3/anode over F4) decreases food cravings, especially for sweets. Unlike the study by Fregni et al., however, the study by Goldman et al. did not find that tDCS influences food consumption. Thus, stimulation over the right prefrontal cortex appears to influence self-regulation in the context of desire for tempting foods but has seemingly inconsistent effects on consumption.

More recently, a study by Lapenta et al. (2014) found that excitatory stimulation over the right DLPFC reduces caloric ingestion and food intake (e.g., cakes and sweets). Additionally, after stimulation participants completed a GO/NO-GO task while EEG was recorded. Excitatory stimulation over the right DLPFC modulated the N2, P3a, and P3b ERP components. All three of these components have been implicated in successful inhibitory control during GO/NO-GO tasks (e.g., Albert et al., 2013). This study thus provides more direct evidence that tDCS over prefrontal cortex influences regulatory mechanisms, which in turn influence food choice behavior.

Kekic et al. (2014) compared excitatory right DLPFC stimulation (cathode over F3/anode over F4) to sham stimulation as participants completed both a food craving questionnaire and a food challenge task before and after stimulation. The food

challenge task consisted of two parts. First, participants watched two short videos of tempting foods (e.g., chocolate). Next, each of the foods from the videos was made available to participants in the laboratory. At this point participants rated their desire to eat and emotional reactions to each of the presented foods. After stimulation, participants were left alone with the foods and instructed to eat what they would like while the experimenter was out of the room. Consistent with past research (e.g., Fregni et al., 2008; Goldman et al., 2011), excitatory right DLPFC stimulation reduced cravings for sweet but not savory foods on the food challenge task. Much like the findings from Goldman et al. these effects did not extend to influence actual consumption during the free eating portion of the task. Kekic et al. further reported that the tDCS-driven reductions in cravings were more pronounced among participants with low (versus high) delay discounting tendencies. This pattern suggests that it was easier to modulate food-related cravings in individual relatively low in impulsivity (high in self-control).

Ljubisavljevic et al. (2016) explored the consequences of repeated stimulation over the DLPFC on food craving. In their study, participants received excitatory right DLPFC stimulation for five consecutive days. Replicating past research, a single session of excitatory right DLPFC stimulation reduced the intensity of food craving. The effects of five consecutive days of stimulation reduced cravings both immediately and 30 days later. The craving reductions were most pronounced for fast foods and desserts. These effects were not moderated by participants' weight at the beginning of the study, nor did the stimulation protocol influence weight assessed 30 days later. Another study using a repeated stimulation design found that stimulation for 8 straight days reduced both self-reported appetite and caloric consumption during a free eating buffet on the last day of stimulation (Jauch-Chara et al., 2014).

Inspired by the evidence linking excitatory right DLPFC stimulation to reductions in food cravings, Burgess et al. (2016) extended this body of research by testing a sample of participants with clinical or subclinical binge eating disorder. They observed that excitatory right DLPFC stimulation not only reduced cravings across food categories but also decreased desire to binge eat and decreased food consumption. In summary, research using tDCS to influence delay behavior has occasionally tested delay discounting for monetary rewards, and the evidence suggests that a left lateralized pattern of prefrontal stimulation induces a more impulsive preference for immediate rewards. Even more studies have concentrated on the domain of food craving and food consumption. Much of this work has found that excitatory stimulation over the right DLPFC decreases cravings for unhealthy foods, and in some cases this stimulation pattern also decreased actual consumption.

Why does tDCS seem more likely to reduce craving but not consumption as the studies above suggest? It may be that cravings or subjective responses are easier to modulate with tDCS (and other interventions) than consumption or behavior. The fact that more of the studies reviewed above find craving effects than consumption effects is consistent with this view.

In the case of studies where cravings are reduced but not reduced consumption, in these studies it may be the case that craving was not reduced *enough* to reduce eating. Additional consumption without craving (or low levels of craving) may reflect a form of dysregulation suggesting more automatic/habitual factors may influence consumption independent of craving (e.g., mindless eating). These reasons suggest that many contextual factors may make detecting links between impulse and consumption more difficult.

Impulse Control

Impulse control involves the inhibition of emotive response tendencies. It plays a key role in diverse behavioral domains including emotion regulation, prosocial behavior, and risk taking.

Emotion Regulation

Emotions are not always functional. For example, emotions may work against one's goals when they are expressed at the wrong time or at an inappropriate level of intensity (Taylor and Liberzon, 2007). Emotion regulation refers to the conscious and non-conscious processes individuals use to influence the intensity, variety, and duration of their emotions (Gross, 1998, 2001). Antecedent-focused emotion regulation strategies aim to modulate emotional responses before they solidify, whereas response-focused strategies aim to modulate emotional responses that have already been initiated (Gross, 1998, 2001). Neurobiological models of emotion regulation distinguish between bottom-up emotion regulation (e.g., expressive suppression) mediated by limbic system structures, such as amygdala, and top-down emotion regulation (e.g., cognitive reappraisal), which involves prefrontal regions (e.g., Ochsner and Gross, 2007).

Current neural models of emotion regulation (e.g., Phillips, 2003; Phillips et al., 2008) further distinguish between deliberate, conscious emotion regulation processes, which involve specifically the DLPFC, and more automatic, implicit regulation, which predominantly recruits the VLPFC (Chaiken and Trope, 1999; Strack and Deutsch, 2004; Mauss et al., 2007). Although emotion regulation typically recruits a wide range of cortical and subcortical structures, the DLPFC and the VLPFC constitute two central hubs in emotion regulation processes. These two regions contribute also to other forms of self-control, including motor control, risk-taking behavior regulation, task switching, response inhibition, and conflict monitoring (Braver et al., 2003; Aron et al., 2004; Berkman et al., 2009).

Evidence from fMRI research regarding the contributions of VLPFC and DLPFC to emotion regulation paved the way for the application of non-invasive brain stimulation to these regions to investigate stimulation effects on both explicit and implicit control strategies. For instance, one study tested the hypothesis that a top-down form of antecedent-focused emotion regulation – cognitive reappraisal – involves DLPFC. Indeed, anodal tDCS over the right DLPFC combined with a cognitive reappraisal task reduced negative emotions (but not positive emotions or craving) compared to anodal tDCS over the left hemisphere and sham stimulation (Pripfl and Lamm, 2015). This pattern of finding corroborates the widely established role of the right hemisphere in painful or aversive feelings (Canli et al., 1998; Kalisch et al., 2006; Baek et al., 2012; Herrmann et al.,

2016, 2017; Salas et al., 2016; Mattavelli et al., 2017), but in this case stimulation to increase activity over right DLPFC reduced negative emotions. This perspective is further supported by the evidence that anodal tDCS over the right VLPFC, compared with sham stimulation, reduces the perceived intensity of negative (i.e., fear, anxiety, and sadness) but not positive or neutral emotions induced by film clips (Vergallito et al., 2018). In this study, participants were not explicitly instructed to apply any regulation strategy, suggesting a role for the VLPFC in incidental or implicit emotion regulation. In the next paragraphs we review tDCS effects on negative emotions, empathy, and social pain. Most of the reported studies have tested tDCS application on prefrontal cortex, mainly on DLPFC and VLPFC.

Anger and Aggression

Anger and aggression are associated with the activation of the behavioral approach system (Harmon-Jones and Sigelman, 2001; Harmon-Jones, 2003). The behavioral approach system is associated with greater left than right frontal cortical activity (Wacker et al., 2008; Zinner et al., 2008; Harmon-Jones et al., 2010). Using tDCS in laboratory aggression paradigms, several researchers have found additional support for a causal relationship between greater relative left frontal cortical activity and approach motivation.

Hortensius et al. (2012) asked participants to write a short essay on a controversial topic (e.g., abortion) before receiving insulting feedback on their essay from another ostensibly real participant. After writing the essay but before receiving the insulting feedback, participants received 15 min of tDCS. By random assignment some participants received stimulation to increase in relative left frontal cortical excitability (anodal over F3/cathode over the F4), increase in relative right frontal cortical excitability (cathode over F3/anode over F4), or sham stimulation. After tDCS, participants played a competitive reaction time game against the purported insulter. The game was based on the Taylor aggression paradigm (Taylor, 1967). Aggression was operationalized as the duration and intensity of a noxious noise blast given to the other participant. Participants also reported how much anger they felt both pre- and post-insult. Results indicated that after receiving tDCS to increase relative left frontal cortical activity, individuals behaved more aggressively toward the other participant, but only when they also reported high insult-related anger. In other words, stimulation to increase relative left frontal activity strengthened the link between anger and aggression.

Dambacher et al. (2015b) also combined tDCS over the DLFPC with the Taylor aggression paradigm. They found that stimulation to increase relative right frontal activity reduced aggression. Taken together with the results of Hortensius et al. (2012), these results suggest that manipulating frontal asymmetry with tDCS can modulate aggressive behaviors in a manner consistent with previous correlational work linking aggression to relative left frontal asymmetry: increasing relative left frontal activity increases aggression (especially among angry individuals; Hortensius et al., 2012) whereas increasing relative right frontal activity reduces aggression using the same Taylor aggression paradigm (Dambacher et al., 2015b). Unfortunately, Dambacher and colleagues did not include a condition to increase relative left frontal activity, so, they were unable to test whether increased left frontal activity increases aggressive behavior, as was the case for angry individuals in the study by Hortensius et al. (2012).

One difference between the results of Hortensius et al. (2012) and Dambacher et al. (2015b) is that the former found a main effect of tDCS on aggressive behavior whereas the latter did not. Rather, Hortensius et al. found a moderated pattern of results whereby anodal stimulation over the left DLPFC/cathodal stimulation over the right DLPFC increased aggression only for those high in insult-related anger. The studies differed insofar as Dambacher et al.'s study included two experimental conditions, whereas Hortensius study included three conditions. Moreover, another study (Dambacher et al., 2015a) did not find an effect of stimulation condition on aggressive behavior. Although this latter study did include all three stimulation conditions as in Hortensius et al. (2012), stimulation occurred over the F7/F8 prefrontal regions, whereas Hortensius et al. and Dambacher stimulated over the F3/F4 prefrontal regions. Thus, methodological differences preclude a direct comparison of these studies. Despite modest support for the effect of asymmetrical frontal cortical activity on aggressive behavior, further research is needed.

One common response to negative emotions, like anger, is rumination, which is an automatic cognitive process characterized by repetitive and distressful thoughts (Denson et al., 2006; Wade et al., 2008). Parallel literatures on depression (e.g., Heller et al., 1995; Nolen-Hoeksema, 2000) and anger (e.g., Bushman, 2002) have developed competing hypotheses about how rumination relates to lateralized patterns of prefrontal cortical activity. The depression literature links rumination to an increase in right frontal cortical activity, whereas the anger literature links rumination to an increase in left frontal cortical activity.

A study by Kelley et al. (2013) tested these two competing hypotheses by delivering anodal or cathodal tDCS over the right or left frontal cortex while participants received negative (insulting) ratings on their essay writing. Results supported the rumination-depression literature in showing that anodal stimulation over the right frontal cortex, compared with the other stimulation conditions, caused enhanced rumination. This study left open the question of what this increase in rumination means. One option flowing from the rumination-depression literature is that an increase in right lateralized frontal brain activity reflects an increase in avoidance motivation; the stronger the avoidance motivation, the greater the rumination. Another possibility, which may align with the rumination-aggression literature, is that the increase in right frontal activity reflects an increase in inhibition rather than avoidance motivation. Therefore, when considering the increasing of right frontal cortex activity, anger is still experienced, but inhibited; conversely left frontal cortex activation is linked to an approach-oriented motivation. Consistent with the latter interpretation, Kelley et al. observed an association between rumination and behavioral inhibition sensitivity (BIS; Carver and White, 1994), which is thought to reflect inhibition more so than avoidance (e.g., Neal and Gable, 2017).

A follow-up study further explored the consequences of excitatory tDCS over the right DLPFC for inhibitory processing. A meta-analysis of neuroimaging studies using a Go/No-Go task found a broad pattern of right frontal cortical activation during response inhibition (Swick et al., 2011). A separate EEG literature has often found that right lateralized frontal EEG alpha asymmetry is associated with exaggerated avoidance-motivated reactions to aversive events (Tomarken et al., 1990; Dawson et al., 1992; Wheeler et al., 1993; Kalin et al., 1998; Coan et al., 2001). These literatures suggest competing hypotheses regarding the psychological correlates of activity in the right frontal lobe.

Kelley and Schmeichel (2016) used tDCS to test the competing hypotheses. One hypothesis, flowing from the frontal EEG literature, is that excitatory stimulation over the right DLPFC should increase avoidance motivation. A second hypothesis, flowing from the neuroimaging findings, is that excitatory stimulation over the right DLPFC should increase response inhibition. The key to differentiating these two hypotheses is to test the effects of stimulation over right DLPFC on the inhibition of avoidance-oriented impulses. Kelley and Schmeichel paired tDCS with an approach-avoidance task whereby participants enacted motive incongruent motor responses to appetitive and aversive IAPS images. Specifically, participants in the positive emotion condition pushed away positive images whereas those in the negative emotion condition pulled negative images toward them. These responses require inhibitory control insofar as avoiding rewards and approaching threats requires one to override a predominant response tendency.

The results revealed that anodal stimulation over the right frontal cortex facilitates the inhibition of both approach-incongruent and avoidance-incongruent responding. These results are not readily explained by an increase in avoidance motivation. Indeed, an increase in avoidance motivation would have slowed the enactment of an avoidance-incongruent response. But Kelley and Schmeichel (2016) found that stimulation over the right DLPFC sped up both avoidance- and approach-incongruent responding. This study thus supported the hypothesis that increasing right frontal cortical activity increases response inhibition.

Sadness

Several studies have concentrated on testing tDCS efficacy in sadness regulation, which has important implications for considering tDCS as a treatment device for major depression. Indeed, it has been widely observed that major depression is associated with an asymmetry in prefrontal cortical activity, specifically hypoactivity in the left DLPFC and hyperactivity in the right DLPFC. For instance, one study found that five sessions of bilateral, twice-a-day tDCS over the DLFC (anode left/cathode right) decreased self-reported sadness in a group of patients with severe, drug-resistant major depression. These improvements lasted up to a month after the end of the treatment (Ferrucci et al., 2009). These findings are in line with a growing body of evidence that tDCS can be effective for treating the symptoms of major depression (for a review, see Nitsche et al., 2009). Indeed, a randomized, double-blinded, sham-controlled study found mood symptoms ameliorations after five session of active prefrontal tDCS in a group of newly diagnosed patients (Fregni et al., 2006b). Moreover, a study by Boggio et al. (2009) found that a single tDCS session over prefrontal cortex, but not occipital or sham tDCS, improved accuracy in identifying emotionally positive visual material in a sample of participants with major depression.

Fear

Another major, consequential negative emotion is fear. Fear plays a crucial role in the onset and maintenance of chronic pain (Riva et al., 2014b) and several mental disorders, including anxiety and post-traumatic stress disorder (Mungee et al., 2014). Regarding fear regulation, one study using an unpredictable threat paradigm found that anodal tDCS over right prefrontal cortex decreased sustained fear and skin conductance levels in the context of unpredictable threats (Herrmann et al., 2017). This finding lends additional support to the idea that right PFC activation increases response inhibition rather than avoidance motivation. Another study, this one using a bipolar montage over the DLPFC with the anode over the left DLPFC and cathode over the right DLPFC, found improved reaction times on simple arithmetic decisions and decreased cortisol concentrations among participants high in math anxiety (Sarkar et al., 2014).

On the other hand, a recent tDCS study on the consolidation of fear memories observed that greater right frontal cortical activity may enhance fear-related responding. Mungee et al. (2014) paired a fear-conditioning paradigm with either cathodal stimulation (i.e., stimulation to decrease activity) over the right dorsolateral prefrontal cortex, anodal stimulation (i.e., stimulation to increase activity) over the right dorsolateral prefrontal cortex, or sham stimulation. Fear was measured via skin conductance responses to the conditioned stimulus. Results revealed that anodal stimulation over the right dorsolateral prefrontal cortex increased memory for the conditioned feared stimulus as measured via skin conductance responses. These results suggested that increasing activation of the right dorsolateral prefrontal cortex increases fear memory consolidation (see also Mungee et al., 2016). However, this study did not simultaneously pair anodal stimulation to the right dorsolateral prefrontal cortex with cathodal stimulation to the left dorsolateral prefrontal cortex to create an asymmetric pattern of activity, as was done in the studies described in the previous paragraphs in this section. Given that the effects of anodal stimulation over the right dorsolateral prefrontal cortex in conjunction with cathodal stimulation over the left dorsolateral prefrontal cortex have yet to be tested in the study of fear memory consolidation, the causal relationship between greater relative right frontal cortical asymmetry and avoidance motivation remains unclear. Collectively, the evidence on prefrontal tDCS effects on the regulation of fear-related responses remains mixed. Future studies should clarify the extent to which excitatory stimulation over the right DLPFC helps or hinders fear regulation.

Social Pain

Social pain refers to the hurt feelings caused by rejection or ostracism from the group. These aversive social experiences

generally cause negative emotions and result in a loss of sense of belonging, control, and self-esteem (Williams, 2009). Some studies have found a role for the dorsal anterior cingulated cortex (dACC) and the right VLPFC in experienced and observed social exclusion conditions, suggesting the presence of a partially overlapping neural network involved both in physical and social pain (Eisenberger et al., 2003; Kross et al., 2007; Wager et al., 2008; Masten et al., 2009). The right VLPFC, in addition to being broadly involved in emotion regulation, has also been found to have a crucial role also in regulating the pain associated with social exclusion (Onoda et al., 2010).

These findings have lead researchers to test the effects of tDCS over brain regions involved in social pain regulation, mainly the right VLPFC. For example, participants in a study by Riva et al. (2012) received 15 min of anodal tDCS over the right VLPFC. At the end of the stimulation, participants were randomly assigned to be included or excluded in a virtual ball-tossing game called Cyberball (Williams et al., 2000). In the inclusion condition, subjects received a ball the same number of times as the other two players, whereas in the exclusion condition participants received the ball only on the first throws. Actually, participants did not play with real players; a computer program controlled the ball. Results revealed that anodal tDCS over right VLPFC, compared to sham stimulation, reduced levels of pain and hurt feelings among excluded subjects.

In a similar study, the same research group (Riva et al., 2014a) tasted the effects of tDCS on behavioral aggression following social inclusion or exclusion condition in the Cyberball paradigm. Participants received anodal or sham stimulation during the Cyberball game. At the end of the stimulation, subjects had to choose the amount of hot sauce for their ostensible partners to taste. This is the well-validated hot-sauce paradigm for studying aggression (e.g., Lieberman et al., 1999). Findings indicated that increasing right VLPFC cortical activity with tDCS reduced behavioral aggression among excluded participants, who were no more aggressive than included ones. These findings were replicated in a subsequent study (Riva et al., 2017), which found that brain polarization through anodal tDCS over the right VLPFC reduced unprovoked aggression as measured by the Taylor aggression paradigm (Taylor, 1967).

Similar results were obtained by Kelley et al. (2015a), who also paired a Cyberball game with prefrontal tDCS. In this modified version of the game, participants first chose a partner from a group of images of eight opposite-sex individuals. A third Cyberball player was assigned by the experimenter and was always the same sex as the participant. Harmon-Jones et al. (2009) had found that this Cyberball game evokes jealousy and that self-reported jealousy after being excluded by a desired partner correlates with relative left frontal cortical activity. Kelley et al. had participants choose a partner in the modified Cyberball paradigm and play a practice version of the game before receiving 15 min of tDCS in one of three conditions: excitatory left DLPFC stimulation (anode over F3/cathode over the F4), excitatory right DLPFC stimulation (cathode over F3/anode over F4), or sham stimulation. Stimulation to increase relative left frontal cortical activity increased self-reported jealousy. Because the direct manipulation of cortical excitability with tDCS produced the same outcome as the correlational finding reported Harmon-Jones et al. (2009), this study suggests that tDCS over the dorsolateral prefrontal cortex does indeed modulate emotive responses associated with social exclusion and asymmetric frontal cortical activity.

Collectively, these studies highlight the effects of tDCS over the prefrontal cortex on regulating responses to social exclusion. This work may have clinical implications for disorders characterized by maladaptive responses to social exclusion (e.g., borderline personality disorder). Future research should test the extent to which the increased negative affect and autonomic arousal (Kopala-Sibley et al., 2012) and inappropriate coping strategies and impulsive behaviors (Dixon-Gordon et al., 2011; Coifman et al., 2012) associated with these disorders can be modified by tDCS.

Empathy

Recently, some research has observed that personal physical suffering and empathy for the pain of others share the same neural network, involving prefrontal cortex as well as somatosensory cortex, anterior cingulate cortex, amygdala, and anterior insula (Eisenberger, 2012). To investigate the role of prefrontal cortex in empathic pain regulation, Boggio et al. (2009) conducted a study in which participants judged the unpleasantness of pictures showing human beings under painful conditions. Anodal tDCS was applied over the left DLPFC, the primary motor cortex, and the primary visual cortex (control site) in three experimental sessions. Findings revealed decreased unpleasantness and discomfort during anodal stimulation over left DLPFC compared to sham stimulation. Moreover, compared to a previous study in which tDCS was delivered together with an electrical peripheral stimulation (Boggio et al., 2008), no significant effects were found in the primary motor cortex stimulation condition, suggesting that DLPFC specifically contributes to the emotional processing of empathic pain.

These findings were expanded by a similar study comparing emotional reactions to negative, positive, and neutral human pictures (Peña-Gómez et al., 2011). This study found that anodal tDCS over the left DLPFC reduces only painful and not positive or neutral affects. Based on previously mentioned neural models (Phillips, 2003; Phillips et al., 2008; Kohn et al., 2014) and previous neuroimaging evidences regarding DLPFC involvement in more cognitive forms of emotion regulation (Blair et al., 2007; Boggio et al., 2007a; Ochsner et al., 2009; Peña-Gómez et al., 2012), the authors suggested that increasing activity in the DLPFC may enhance cognitive control of emotional reactions. Moreover, the tDCS effect was more noticeable for participants with higher subclinical scores on the introversion personality dimension, perhaps due to their enhanced ability to control emotion expression, which correlates with the increased cortical activity, compared with extraverts, especially in the frontal lobes (Suslow et al., 2010).

A similar finding was reported also by Feeser et al. (2014), who applied anodal tDCS over the right DLPFC while participants applied cognitive reappraisal strategies to down- or up-regulate the emotions elicited by negative or neutral pictures. Skin conductance responses were also assessed. Anodal

tDCS, compared to sham stimulation, increased emotional and autonomic reactions when the reappraisal instruction was to upregulate emotions and decreased emotional and autonomic responses when participants attempted down-regulation. Taken together, the studies reviewed here implicate DLPFC and VLPFC in emotion regulation when observing or experiencing painful situations, thereby highlighting the feasibility of tDCS application for the study of pain and empathy for pain.

Risk Taking

In addition to emotion and mood manipulations, another way researchers have explored the consequences of prefrontal brain stimulation on emotion regulation is by studying risk taking. Risk taking involves the possibility of punishment or potential harm in the pursuit of rewards or goal-relevant actions. From an emotion-regulation perspective, risk-taking involves managing the emotions associated with the anticipation of winning and losing. In a seminal tDCS study, Fecteau et al. (2007a) used tDCS over the DLPFC during a risk task (Rogers et al., 1999). Across 100 trials of a gambling task, participants viewed 6 horizontal boxes. Some boxes were blue, and some were pink, and the ratio of blue to pink boxes varied from trial to trial. The ratio could be 5:1, 4:2, or 3:3. Of the two options, the high likelihood option was always associated with a small reward whereas the low likelihood option was always associated with a large reward. Participants were to indicate which color box contained a token. Each trial selecting the winning color box earned a reward but selecting the incorrect color box incurred a penalty. Larger rewards were always paired with riskier decisions such that correctly choosing a pink box with a low win probability (1/6) would result in a large reward whereas making that same choice and losing was associated with same magnitude of a loss. Thus, participant's tendency to choose high-risk/unlikely rewards over low risk/likely rewards was the measure of risk-taking. Results indicated that excitatory right DLPFC stimulation increased the number of participants earned by decreasing risk taking on the task. These results suggest that excitatory stimulation over the right DLPFC tilted participants toward safer, less risky choices, as though they were less tempted by the larger, riskier rewards.

These findings have been partially replicated by Cheng and Lee (2016), who found that the excitatory stimulation over the right DLPFC influences performance on the Risky Gains Task (RGT; Paulus et al., 2003), but not on the Balloon Analogue Risk Task (BART; Lejuez et al., 2002). Regarding the RGT task, participant's goal was to win as many points as possible. To accomplish this goal, they made quick (1 s) decisions between taking a reward (i.e., points) now or waiting for a larger point value later. However, this later-but-larger reward also came with the risk of being punished (i.e., losing points equivalent to the later-but-larger reward). Risk-taking was quantified as the rate at which participants selected trials for which punishment was possible whereas safe decision-making was the rate at which participants chose point values with no possibility of punishment. The effect of excitatory right DLPFC stimulation on risky (but not safe) trials was moderated by individual differences in impulsivity, such that greater risk-taking was associated with greater (versus lower) impulsivity. More recently these results have recently been conceptually replicated in a clinically impulsive sample. Gilmore et al. (2017) paired excitatory stimulation over the right DLPFC (twice a day for 5 days) with a balloon analog risk taking (BART) task. They found that excitatory stimulation over the right DLPC reduced risk-taking by 46%. This diminished risk-taking persisted at a two-month follow-up.

Another study probed the underlying neurocircuitry that may be driving the changes in risk taking. Weber et al. (2014) used excitatory stimulation over the right DLPFC, prior to functional MRI during which participants completed the BART. They found that excitatory stimulation over the right DLPFC increased activity in the right DLPFC and the ACC as well. Additionally, this pattern of stimulation also influenced how these two regions connected with the rest of the brain. Specifically, greater right DLPFC-whole brain connectivity was associated with diminished risk-taking on the BART. These results suggest that the diminished risk-taking linked to excitatory right DLPF stimulation influences the neurocircuitry implicated in successful self-regulation.

In addition to laboratory risk-taking paradigms, an innovative study paired prefrontal tDCS with a more ecologically valid form of risk taking: driving behavior. In a driving simulator study, Beeli et al. (2008) observed that excitatory stimulation of the DLPFC (either left or right) led participants to keep a safer distance behind a lead driver and reduced the number of speeding errors. This pattern of stimulation did not influence average speed or revolutions per minute. These results are broadly consistent with reduced risk taking, but they differ from the risk-taking findings reviewed above in a crucial way: the electrode montage used. Whereas the risk-taking studies described above paired excitatory stimulation over the right DLPFC with inhibitory stimulation over the left DLPFC, the study be Beeli and colleagues placed the cathode over the ipsilateral mastoid. Because of this difference in electrode montages it is unclear to what extent these results are comparable to the risk-taking studies above. Future studies should explore the extent to which anodal right DLPFC/cathodal left DLPFC stimulation influences risk-taking in this domain.

In summary, numerous studies have observed enhanced self-regulation after anodal tDCS over right DLPFC (cathodal over left). Improved self-regulation manifested in a variety of ways including greater pain tolerance, healthier food choices, less impulsive decision-making, improved emotion regulation, reduced anger and aggression, less sadness and fear, more empathy, and less risk taking. Collectively, these results anodal tDCS over right DLPFC may be one tool that shows promise in helping individuals live happier, healthier lives.

Limitations and Future Directions

We have reviewed evidence suggesting that non-invasive brain stimulation over the prefrontal cortex may improve human self-regulation. First, we detailed a methodological review of tDCS highlighting that tDCS is a safe, inexpensive, and easy to use technique that can be used to study higher-order cognition, emotion, and clinical phenomena. We also reviewed stimulation parameters that may help or hinder tDCS efficacy including current density, stimulation duration, and the orientation and focality of the electrical field. Second, we reviewed findings

from experiments observing that non-invasive brain stimulation over the PFC can enhance three paradigmatic forms of self-regulation: persistence, delay behavior, and impulse control. Although the current review focused predominantly on tDCS, other techniques such as low energy neurofeedback (e.g., Ochs, 2006) and transcranial ultrasound (e.g., Tufail et al., 2011) also represent low-cost, non-invasive techniques for investigating the causal role of neural activation in various forms of self-regulation.

Although much of this review highlighted the ability of brain stimulation to promote self-regulation, under the right circumstances brain stimulation may also undermine self-regulation. For example, we highlighted studies wherein excitatory stimulation over the right DLPFC enhances inhibition (e.g., Kelley and Schmeichel, 2016) whereas excitatory stimulation over the left DLPFC increases approach motivated negative emotions like anger (e.g., Hortensius et al., 2012) and jealousy (e.g., Kelley et al., 2015a,b). These contrasting findings imply that excitatory tDCS is not an unmitigated good that improves self-regulation in all cases. In fact, these findings emphasize the need to identify precise stimulation parameters that help versus hinder self-regulation. Below, we discuss inconsistencies, unresolved questions, and new directions emanating from the above review.

tDCS Dosage

The efficacy of eliciting changes in brain activity using tDCS depends on several physical parameters including current density, stimulation duration, and the orientation and focality of the electrical field. These parameters constitute the tDCS dosage. As we noted above, different electrode positions modulate different neuronal groups and elicit different evoked potentials in the case of primary motor cortex and primary visual cortex stimulation, respectively (Priori et al., 1998; Antal et al., 2004; Accornero et al., 2007), and these different electrode positions may also determine effects on the targeted brain region due to electrical field interactions associated with neuronal geometry (Nitsche and Paulus, 2000; Nitsche et al., 2008).

Whereas the coupling of anodal-excitatory and cathodal-inhibitory effects is well established in the sensorimotor domain, the evidence pertaining to higher cognitive functions is more controversial (Jacobson et al., 2012). Indeed, when dealing with more complex functions represented by large and interconnected neural networks comprising both excitatory and inhibitory connections, it is more difficult to obtain predictable outcomes – especially when different electrode montages have been used across studies. Hence it is not always the case that anodal tDCS leads to an enhancement (e.g., better performance in a task) and cathodal tDCS leads to a diminution of the assessed cognitive function (Fertonani and Miniussi, 2017).

To illustrate this point, consider the studies above on physical pain tolerance. These studies found increased pain tolerance as the result of excitatory stimulation of the right DLPFC (Mylius et al., 2012), excitatory stimulation over the left DLPFC (Boggio et al., 2008; Mariano et al., 2016), and inhibitory stimulation over the left DLPFC (Powers et al., 2018). Of the four studies we reviewed, three difference electrode montages were used. Notably, the study by Powers and colleagues, unlike the other pain studies, paired tDCS with clinical interventions. These methodological differences likely contributed to the differences in results across studies and thus makes interpreting the effects of tDCS difficult. Future studies should more precisely optimize the stimulation protocols that accentuate versus undermine self-regulation for easier comparison across studies.

More broadly, however, the findings from the pain studies are congruent with the findings from studies of other self-regulatory domains in suggesting that stimulation over right DLPFC facilitates self-regulation. Whether such stimulation is most profitably paired with inhibitory (cathodal) stimulation over left DLPFC remains to be seen. And the effects of excitatory (anodal) stimulation over left DLPFC on self-regulation are even more uncertain, with some studies finding better and some finding worse self-regulation after excitatory stimulation over left DLPFC.

Individual Differences

Another inconsistency in past research concerns individual differences. Despite seminal work suggesting that participants should be matched on individual differences like sex or age that can influence tDCS efficacy (Pitcher et al., 2003; Kuo et al., 2006; Quartarone et al., 2007; Chaieb et al., 2008; Nitsche et al., 2008), many of the studies reviewed above did not use this strategy, and we recommend future studies implement matching procedures to reduce error variance and increase power to detect tDCS effects.

In addition to demographic factors, which may subtly influence tDCS efficacy, many of the studies we reviewed also did not consider the extent to which participants are responsive to tDCS. Previous research has found that between 50 and 64 percent of participants are responsive to tDCS protocols, which leaves a substantial proportion of individuals who are not particularly responsive to tDCS (Wiethoff et al., 2014; López-Alonso et al., 2015). Studies that include non-responders and studies that do not systematically test for differences between responders and non-responders many obscure effects of tDCS on regulatory behavior. Further, only few studies have considered individual differences traits, though these are also likely to moderate tDCS effects. For example, the study by Kekic et al. (2014) found that tDCS-driven reductions in food craving were more pronounced among participants with low (versus high) delay discounting tendencies. Evidence of this sort highlights the need to develop more robust stimulation protocols in well-powered studies that can systematically test for the moderating role of individual differences.

Impulse-Behavior Relationship

Another inconsistency in the research reviewed above concerns whether changes in emotive responding extend to changes in behavior. We summarized evidence that tDCS may alter food craving without altering food consumption (although sometime consumption changes, too; e.g., Fregni et al., 2008). Similarly, we summarized evidence that changes in emotional responses (e.g., anger) may occur in both the absence of and presence of corresponding changes in behavior.

The path from impulse to behavior entails multiple determinants, and thus impulses and behaviors may diverge for

several reasons. Practical considerations including variability in stimulation dosage may explain why tDCS sometimes does and sometimes does not influence behavior. For example, one important aspect of the tDCS dosage is electrode size. The study by Kekic et al. (2014) who did not find effects on food consumption used 25 cm^2 electrodes whereas Fregni et al. (2008) used 35 cm^2 electrodes. Smaller electrodes are more spatially precise compared to larger electrodes. The larger electrodes may affect distal brain regions that are less affected in studies using smaller electrodes possibly accounting for why the study by Fregni et al. founds effects on consumption, but Kekic did not. Beyond these practical considerations idiosyncratic food preferences may have played a role in the inconsistent results. The studies assessing compulsion offered actual food to participants, but those foods were not specifically tailored to the participant. Instead participants were offered foods that are generally (but not universally) well liked, such as chips, cookies, and chocolate. This may be problematic insofar as some participants may not prefer any of the food options offered by the experimenter. Future studies using more ecologically valid measures of food consumption and others types of regulatory behavior (e.g., naturalistic observation) may prove useful in clarifying the extent to which tDCS-induced changes in emotions/impulses influence subsequent behavior. However, we must also consider the possibility that cravings/subjective states are more readily influenced by tDCS, whereas behaviors may be harder to change as they have a multiple of determinates above and beyond the preceding subjective state.

How Does tDCS Effect Underlying Brain Activity?

The effects of tDCS on underlying brain activity are not well understood and subject to ongoing debate. It remains to be seen how tDCS affects brain activity and how these changes relate to changes in self-regulation. One way to advance research on this topic is to pair concurrent measures of brain function with electrical stimulation. Candidate neural processes mediating links between tDCS and self-regulation include changes in prefrontal EEG alpha and functional connectivity between the prefrontal cortex and subcortical regions.

Prefrontal Alpha

One potential mediator driving many of the effects reported in the current review is EEG alpha activity. Specifically, lateralized patterns of alpha activity may reflect a person's motivational orientation with left lateralized EEG alpha activity reflecting approach-motivation (Tomarken et al., 1992; Harmon-Jones and Allen, 1997, 1998; Sutton and Davidson, 1997; Harmon-Jones and Sigelman, 2001; Harmon-Jones et al., 2002, 2006; Coan and Allen, 2003; Harmon-Jones, 2007) and right lateralized pattern of EEG alpha activity has been linked to withdrawal or avoidance motivation (Davidson et al., 1990; Tomarken et al., 1990; Dawson et al., 1992; Kalin et al., 1998; Coan et al., 2001). Self-regulatory failure tends to occur when individuals have strong impulses such as strong impulses to engage in approach or avoidance motivated behavior. Likewise successful self-regulation tends to occur when impulses are weaker. To the extent that asymmetric patterns of alpha activity in the frontal cortex reflect the strength of appetitive and aversive impulses they may be a good candidate linking tDCS to changes in self-regulation.

Indirect support for the role of EEG alpha activity in tDCS effects comes from parallel findings using EEG and tDCS, respectively, to study the emotion of jealousy. Harmon-Jones et al. (2009) found that feelings of jealousy during a Cyberball game correlate with greater left frontal alpha activity, and Kelley et al. (2015a,b) found the same pattern by manipulating (rather than measuring) brain activity with tDCS. More specifically, Kelley et al. observed that excitatory stimulation of the right DLPFC paired with inhibitory stimulation of the left DLPFC increases feelings of jealousy during a Cyberball game. By finding the congruent effects with both measured and manipulated brain activity, the pair of results together suggest that EEG alpha activity may mediate the link between prefrontal tDCS and behavioral self-regulation.

In an innovative new study, Vöröslakos et al. (2018) developed an intersectional short-pulse (ISP) stimulation paradigm in cadaver and rodent studies. ISP delivers shorts bursts (less than 10 μs) of high intensity stimulation from multiple electrode pairs centered on a stimulation site of interest. ISP thus offers superior spatial focality plus higher current densities (7–9 MA) more easily tolerated than traditional tDCS paradigms (>2 MA), with relatively low charge densities and scalp sensations. Pairing Vöröslakos and colleagues then paired ISP with concurrent EEG measurement and observed that tDCS affects the amplitude of simultaneously recorded EEG alpha waves. This work provides an important example of how technical studies in mouse and cadaver models can be used to improve existing tDCS protocols. Future research should consider implementing innovate stimulation paradigms like ISP to increase the efficacy of existing stimulation paradigms and to trace the neural mediators of tDCS effects.

Functional Connectivity

The self-regulation findings we reviewed may also be mediated by frontal cortical-subcortical interactions. Due to its high spatial resolution, functional MRI is perhaps best suited to probe such possibilities. Research along these lines has already begun. Weber et al. (2014) administered excitatory stimulation over the right DLPFC prior to functional MRI of a risk-taking task. They found that excitatory stimulation over the right DLPFC influences how the right DLPFC connects to the rest of the brain. Specifically, stronger right DLPFC-whole brain connectivity and diminished risk-taking emerged in participants who had received excitatory stimulation over the right DLPFC. Although this study did not measure brain function during tDCS, the finding that tDCS administered immediately prior to a risk-taking task influences connectivity patterns revealed by fMRI does highlight that stimulation may influence communication among neural networks. Future studies should continue to probe the extent to which prefrontal stimulation influences connectivity to reward-relevant (e.g., ventral striatum) and threat-relevant (e.g., amygdala) subcortical regions.

Potential neural aftereffects of tDCS, such as changes in prefrontal alpha asymmetry or functional connectivity, may mediate the relationship between tDCS and regulatory behavior.

What remains to be established is the extent to which alpha asymmetry or functional connectivity carry the causal effects of tDCS on self-regulation, or whether they merely correlate with observed changes in regulatory behavior.

How Do Impulse and Control Strength Contribute to Regulatory Behavior?

Imagine a person who, when offered a chocolate treat, decides not to eat it. Does foregoing chocolate reflect the application of control to resist chocolate consumption, a low desire for chocolate, or some combination of both things? Social psychologists have traditionally viewed self-regulatory success as the consequence of applying self-regulatory strength (see Baumeister et al., 1994, 1998, 2007). In this view, a person forgoes chocolate by resisting the temptation to eat it. But impulse strength also contributes to self-regulatory outcomes. Presumably, weaker impulses are easier to control or hardly require control at all (e.g., Inzlicht and Schmeichel, 2012; Kelley et al., 2018). Successful self-regulation has been associated both with increased activity in areas associated with top-down control, including the prefrontal cortex, and reduced activity in subcortical regions involved in reward and threat processing. These patterns also implicate and potentially confound strong control and weak impulses. Thus, an unresolved issue concerns the relative contribution of control strength and impulse strength to self-regulatory outcomes. By paring tDCS with measures of concurrent brain function, it may be possible to compare the contributions of neural activity caused by (1) stimulation to areas associated with impulse strength, and (2) stimulation to increase activity in control regions.

What Are the Long-Term Consequent of Brain Stimulation on Regulatory Behavior?

In addition to limited understanding of the effects of tDCS on underlying neural processes, we also have a limited understanding of the long-term effects of tDCS. Most of the studies we reviewed involved just a single session of tDCS. Although some studies have involved the administration of tDCS once a day for multiple days (Fregni et al., 2006a; Boggio et al., 2007b), those studies have primarily been conducted with patients recovering from spiral cord injury or stroke. Pairing repeated stimulation with measures of self-regulation in non-patient samples may yield stronger, more consistent effects.

Self-regulation research touches on alcohol and drug addiction, personal debt, obesity, and a variety of other consequential outcomes. It is important to acknowledge that these outcomes are not the result of one decision or behavior but instead results from multiple patterns of behavior unfolding over long periods of time. Few studies have examined long-term downstream effects of stimulation. One notable exception was a study by Gilmore et al. (2017), who found that excitatory stimulation over the right DLPFC (twice a day for 5 days) reduced risk-taking at the end of the stimulation period and at a two-month follow-up. We encourage future studies to follow the example of Gilmore and colleagues and use both repeated stimulation paradigms and longitudinal designs to examine changes in behavior. Extend this work to include also concurrent changes in brain function would help to more precisely map the long-term consequences of tDCS on regulatory behavior.

CONCLUSION

Self-regulation is crucial for goal-directed behavior and contributes to many consequential outcomes in life including physical and mental health, decision making, and interpersonal functioning. Likewise, failure at self-regulation is thought to contribute to alcohol and drug addiction, personal debt, obesity, and other outcomes that carry both personal and societal costs. Based on the evidence reviewed here, we conclude that brain stimulation techniques hold promise for improving self-regulation across three broad domains of response: persistence, delay behavior, and impulse control. To maximize the utility of tDCS in future research, we encourage researchers be especially mindful of issues such as dosage and individual differences – issues that have been commonly been neglected in past research and have likely contributed to inconsistencies in past findings. Future research that takes these concerns into account and incorporates concurrent measures of brain activity will bring the promise of tDCS into sharper focus and help to reveal underlying neural mechanisms.

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5.2 Results from a primary systematic review and meta-analysis

Based on the data collected through the narrative review presented in the previous paragraph, to further explore the NIBS effects on emotions' regulation domain, here I report the results of a preliminary systematic review and meta-analysis I run during my PhD. The review and meta-analysis aimed at investigating whether NIBS can be effective in modulating emotion regulation in healthy participants and which specific variables could moderate such effects.

The rationale to conduct this systematic review and meta-analysis was twofold. First, systematically collecting data from studies applying NIBS in the field of emotions' regulation could contribute to shed light on the high heterogeneity, with respect to the cerebral areas stimulated, stimulation protocols used, emotion regulation strategies targeted and outcome measured, of studies of this literature domain.

Second, quantitatively testing the effects of NIBS when applied to the cerebral areas involved in explicit and implicit emotions' regulation processes (see Chapter 4), in combination with defined experimental paradigms, on the one hand could contribute to the knowledge on the neural networks underlying cognitive control of emotions, on the other could provide evidence for the use of NIBS as a potential adjuvant treatment for individuals with deficits in emotions' regulation. Indeed, while the first-line treatments for emotional disorders (e.g., anxiety disorders) comprise pharmacological or psychotherapeutic interventions, a consistent number of patients are resistant to the traditional treatments or are characterized by high rates of relapsing and drop-outs (Fernandez et al., 2015; Taylor, Abramowitz & McKay, 2012). Therefore, in the last thirty years, NIBS have been increasingly considered as alternative treatment (Brunoni et al., 2018; see Vergallito et al., 2021 for a recent systematic review and meta-analysis), also to be added to the classical therapies (Bose et al., 2014; Segrave et al., 2014; Sathappan, Luber & Lisanby, 2019). However, regarding the NIBS' efficicay, studies have provided promising yet preliminary and inconsistent results (Guo, Li & Wang, 2017; Kekic et al., 2016).

5.2.1 Methods

Literature search

The PRISMA guidelines (Moher et al., 2015; Shamseer et al., 2015) were used to screen PubMed, Web of Science, Scopus, PsychInfo and Embase considering papers published till the end of March 2020. The search query was build combining key words related to NIBS (using both the acronyms and the full-words) with "emotion regulation" (or "emotional regulation") and "affect regulation" (or "affective regulation"). The following NIBS keywords were used: "tDCS", "transcranial direct current stimulation", "TMS", "transcranial magnetic stimulation" "rTMS", "repetitive transcranial magnetic stimulation", "TBS", "theta burst stimulation", "NIBS" and "non invasive brain stimulation"

Records screening and data extraction

The records retrived by the search were screened by four independent and blinded researchers using Rayyan, a web and mobile systematic reviews manager (Ouzzani et al., 2016; https://rayyan.qcri.org/), and based on the following hierarchy of inclusion criteria: i) English written articles; ii) original peer-reviewed articles (reviews, meta-analysis, conference proceedings, case reports and conference abstracts were excluded); iii) studies on healthy humans (studies on clinical populations were excluded); iv) articles including NIBS application compared to placebo (sham) stimulation; v) studies administering behavioural tasks inducing emotions (studies reporting only neuroimaging and neurophysiological data were excluded).

The articles meeting the inclusion criteria at the first screening phase, based on the records' title/abstract, where screened a second time based on their full-text. In both screening phases conflicts were solved by consensus. Descriptive data wee extracted using a structured table (see Table 4).

Qualitative analysis

The quality of the articles was assessed through the Cochrane Collaboration's Risk-of-Bias Tool (Higgins et al., 2011) that allows to evaluate as "high risk" or "low risk" (or eventually "unclear risk" when the studies lack of useful information) the following sourses of bias: random sequence generation (i.e., randomization performed through a defined procedure, such as computer random number generator, random number table, coin toss, etc.), allocation concealment (i.e., randomization concealed till the participants' allocation to the study groups, such as real or sham

stimulation), blinding (i.e., single-, double-, triple-blind procedure), incomplete outcome data (i.e., attrition bias), and selective outcome reporting (i.e., complete reporting of results). Four independent and blinded researchers asssed the articles quality; conflict were solved by consensus.

Quantitative analysis

Sampling variance, standardized mean difference (SMD), and summary analyses were computed for each included study, using the "escalc" function of "metafor" package (version 3.4.3, Viechtbauer, 2010) for R (4.0.2; R Core Team, 2019; https://www.R-project.org/). SMD was corrected for the positive bias for small group within the function, computing Hedge's g, which was used as a measure of the effect size. Then, the global effect of NIBS in modulating emotion regulation was measured using a random effects model. Heterogeneity was evaluated measuring the variation due to the sampling error (Q statistic). Potential outliers were graphically detected using the Baujatplot and statistically calculated using the analysis of influence (Polanin et al., 2016; Kovalchik, 2013; Del Re, 2015), which was implemented in the "inf" function of the "metafor" package. The random effects model was repeated after removal of the detected outliers. Publication bias was checked through the Egger's regression test (Egger et al., 1997) and the rank correlation test (Begg & Mazumdar, 1994) and was graphically represented using the funnel plot.

Moderation analysis was run using the "anova" function of "metafor" package to investigate whether the type of NIBS, the stimulation timing (i.e., online vs. offline) and protocol (i.e., excitatory vs. inhibitory) moderate the effects of non-invasive brain stimulation on emotions' regulation.

5.2.2 Results

Studies selection

The databases search retrieved a total of 2.768 records. After duplicates removal and separate screenings for acronyms and full-words searches, the full-text of 124 papers were entirely evaluated. Eighteen studies finally met our inclusion criteria and were included in the qualitative and quantitative analysis (see Figure 21 for a schematic representation of the screening process).

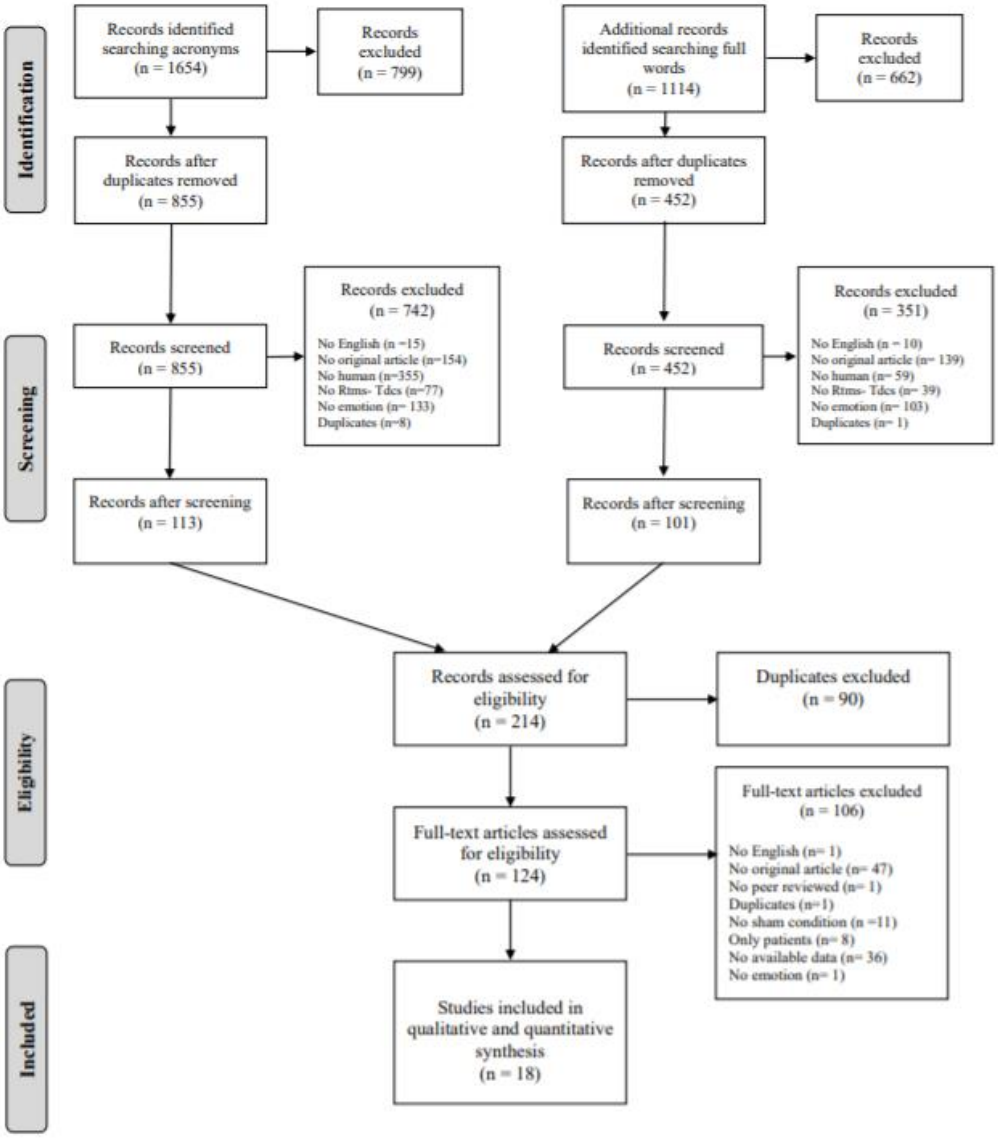


Figure 21. The Figure summarizes the selection procedure.

Results of quality evaluation

According to the Cochrane items, the randomization procedures were the main source of bias. In particular, also when authors just declared that they randomised their experimental participants, without consistently specifying the randomization strategy, was evaluated at low risk of bias. Actually, only one study (Fitzgibbon et al., 2017) described how the randomization was performed, namely through a computer generated random sequence. Yet, none of the included studies specified how the groups' allocation was concealed till performing the randomization.

The second source of bias regards the blinding strategy. Indeed, the majority of the studies (10/18) used a single-blind approach, in which only the study participants were anaware about the assigned experimental groups. Four studies (Balconi et al., 2014; Fitzgibbon et al., 2017; He et al., 2019; Hurlemann et al., 2015) did not report information about the blinding, while only four studies applied a double-blind strategy (Herrmann et al., 2016, 2018; Rêgo et al., 2015; Wolkstein & Plewnia, 2013). No study blinded the outcomes' assessors.

Concerning the attrition and the reporting bias, all studies received low risk assessment. Indeed, the missing data did not affect the studies validity across the articles and the authors did not avoid reporting significant and/or not significant results. However, it is worth saying that for the assessment of reporting bias, we did not check the studies' protocol when available. Therefore, we cannot rule out possible mismatch between what declared in the protocols and what finally reported in the studies (see Table 5 for details of quality assessment).

Table 5. The table shows the results of the quality assessment.

Study	Cochrane Items						
	Selection bias		Performance bias	Detection bias		Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Aboulafia-Brakhaa et al., 2016	●	●	□	●	●	□	□
Balconi et al., 2014	●	●	●	●	●	□	□
Berger et al., 2017	□	●	□	●	●	□	□
Brunoni et al., 2013	□	●	□	●	●	□	□
Chen, 2018	□	●	□	●	●	□	□
De Raedt et al., 2010	□	●	□	●	●	□	□
Depperman et al., 2016	□	●	□	●	●	□	□
Fitzgibbon et al., 2017	□	●	●	●	●	□	□
He et al., 2018	□	●	□	●	●	□	□
He et al., 2019	□	●	●	●	●	□	□
Herrmann et al., 2016	□	●	□	□	●	□	□
Herrmann et al., 2018	□	●	□	□	●	□	□
Hurlemann et al., 2015	□	●	●	●	●	□	□
Peña-Gómez et al., 2011	□	●	□	●	●	□	□
Rêgo et al., 2015	□	●	□	□	●	□	□
Sanchez et al., 2016	□	●	□	●	●	□	□
Sanchez-Lopez et al., 2018	□	●	□	●	●	□	□
Wolkstein & Plewnia, 2013	□	●	□	□	●	□	□

Emotion regulation strategies,experimental tasks and outcome measures

Most of the papers (12/18) explored unconscious emotions' regulation strategies by administering implicit paradigms in which participants dealt with emotional stimuli following cognitive task-related instructions. The papers of this group meanly measured reaction times and response accuracy by applying an emotional go/no-go task (Aboulafia-Brakhaa et al., 2016), or an attentional engagement-disengagement task (De Raedt et al., 2010; Sanchez et al., 2016; Sanchez-Lopez et al., 2018), or an emotional Stroop task (Depperman et al., 2016) (for a detailed description of characteristics of these task see paragraph 2.2). Actually, to better explore attention engagement and disengagement when emotional facial expressions are presented, Sanchez et al. (2016) and Sanchez-Lopez et al. (2018) paired the experimental task with the recording of eye movements as measured by an eye-tracking system. Two papers used a delay working memory task, measuring physiological indexes (i.e., skin conductance response and heart rate variability; Berger et al., 2017) or task performance (i.e., reaction times and accuracy; Wolkstein & Plewnia, 2013), respectively. In both papers, participants were instructed to delay recognise, among a group of interfering pictures – negative vs. positive (Wolkstein & Plewnia, 2013) or negative vs. positive vs. neutral (Berger et al., 2017) pictures used as distractors - a target stimulus – i.e., arousing pictures (Berger et al., 2017) or letters (Wolkstein & Plewnia, 2013) - that could be identical or different compared to one of the stimuli presented previously in the task. A pilot (Herrmann et al., 2016) and a more powered study (Herrmann et al., 2018) by the same research group measured participants' skin conductance response to investigate how they implicity regulate emotional reactions to neutral, unpredictable and predictable threats: unpredictable threats were preceded by a cue indicating that the threat could occur only during the cue presentation, while predictable threats were preceded by a cue indicating that the threat could occur at any time. Another study (Balconi et al., 2014) used a forced-choice response task, in which participans were required to focus on characteristics of emotional facial expressions to decide, as fast and accurate as possible, whether the expressions showed (or not) an emotion. Interestingly, authors explored differences related to the valence of facial expression and participants' anxiety levels, showing a greater negative-valence bias in high-anxiety subjects. Alternatively, Chen (2018) used the duration and intensity of noise blasts adminstered by study participants to other (dummy) players, during a competitive reaction time task (i.e., the Taylor Aggression Paradigm; see Giancola & Zeichner, 1995; Giancola & Parrott, 2008; Bernstein, Richardson & Hammock, 1987; Anderson, Lindsay & Bushman, 1999; Warburton & Bushman, 2019 and paragraph 6.1 for details), as indirect measures of aggression regulation. Onother paper of

this group (Fitzgibbon et al., 2017) experimentally involved participants in a task inducing social exclusion (i.e., the Cyberball task; see Williams, Cheung & Choi, 2000; Renneberg et al., 2012 and paragraphs 3.1 and 6.2 for details) to measure how participants regulate their reactions to ostracism.

Other papers explored conscious emotions' regulation strategies by explicitely requiring participants to regulate the emotions elicited by the presented stimuli. For instance, two consecutive studies by the same research group tested the effects of reappraisal on emotions caused by social exclusion images. In particular, He et al. (2018) measured pupul diameter and fixation duration while participants were instructed to objectively evaluate the social exclusion images by a third-person perspective or to imagine a better outcome of the scene. He et al. (2019) compared the effects of reappraisal used to dow-regulate emotions elicited by social exclusion or physical pain images, by measuring the late positive potential (LPP), an event-related potential component, known to reflect improved perception of and attention to emotional stimuli (Liu et al., 2012; Schupp et al., 2004). Accordingly, the decreased LPP after reappraisal is considered a signal of reduced emotional responses due to the downregulation of negative emotions (Liu et al., 2012; Schönfelder et al., 2013; Hajcak, MacNamara & Olvet, 2010; Dennis & Hajcak, 2009; Ochsner & Gross, 2005).

Alternatively, six papers tested explicit emotions' regulation strategies by directly asking participants to rate the valence (Peña-Gómez et al., 2011) or the valence and arousal (Rêgo et al., 2015) of emotional (either positive, or negative, or neutral) pictures (Peña-Gómez et al., 2011) or of arousing pain video clips (Rêgo et al., 2015).

Interestingly, two studies combined explicit and implicit measures of emions' regulation (Hurlemann et al., 2015; Brunoni et al., 2013). In particular, Hurlemann et al. (2015) administered a cognitive emotion judgment task and an emotion-modulated startle paradigm (both with presentation of negative, neutral and positive pictures). In the cognitive emotion judgment task, participants were simply asked to rate the pictures' valence and arousal. During the emotion-modulated startle paradigm, facial electromyographic activity was recorded while bursts of white noise, used as probes, were presented either alone or paired with an emotional picture. Smaller magnitude of the startle eyeblink reflex (i.e., calculated as the difference between the highest electromyographic activity after the startle probe onset and the average electromyographic activity immediately before the probe onset) was considered an indicator of successful emotion regulation. Moreover, the proportion of positive- or negative- pictures-startles relative to the number of all valid startle trials was calculated to investigate differences related to the pictures' valence.

Brunoni et al. (2013) presented negative and neutral pictures and asked participants to explicitely rate mood and anxiety levels elicited by the images. Moreover, authors measured variations in physiological indexes, e.g., electrocardiographic activity and salivary cortisol, while the pictures were presented. The Table 6 summarizes the details of descriptive data.

Characteristics of non-invasive brain stimulation

Most of the papers (11/18) applied tDCS protocols, while 5 out of 18 studies used repetitive TMS stimulation (rTMS: Balconi et al., 2014; Berger et al., 2017; De Raedt et al., 2010; Fitzgibbon et al., 2017; He et al., 2019) and 2 studies (Depperman et al., 2016; Hurlemann et al., 2015) intermittent theta burst stimulation.

Among the tDCS studies, most of the protocols (9/18) tested the effects of anodal tDCS, while two papers applied both anodal and cothodal tDCS (Rêgo et al., 2015; Brunoni et al., 2013). The dlPFC was the most targeted brain area. In particular, four studies stimulated both the left and righ dlPFC (Aboulafia-Brakhaa et al., 2016; Brunoni et al., 2013; Rêgo et al., 2015; Sanchez-Lopez et al., 2018), two studies the lDLPFC (Peña-Gómez et al., 2011; Wolkstein & Plewnia, 2013) and one study the rDLPFC (Sanchez et al., 2016). The rVLPFC (Chen, 2018; He et al., 2019) and the righ inferior frontal gyrus (Herrmann et al., 2016, 2018) were also targeted by the included studies.

The majority of the tDCS studies (10/18) used an online stimulation protocol, in which the stimulation was delivered while the studies' participants were involved in the experimental tasks or stimuli were presented. The stimulation intensity was 1mA in one study (Wolkstein & Plewnia, 2013), 1.5mA in three studies (Aboulafia-Brakhaa et al., 2016; Brunoni et al., 2013; Peña-Gómez et al., 2011), 2mA in six studies (Chen, 2018; Herrmann et al., 2016, 2018; Rêgo et al., 2015; Sanchez et al., 2016; Sanchez-Lopez et al., 2018), 2.5mA in one study (He et al., 2018;), and, across the articles, the current was delivered for a time ranging from 12 minutes (Chen, 2018) to 25 minutes (Aboulafia-Brakhaa et al., 2016).

All studies applied a variable number of sessions based on the type of stimulation to deliver and the study design. Thus, studies testing only anodal stimulation (Aboulafia-Brakhaa et al., 2016; Chen, 2018; He et al., 2018; Herrmann et al., 2016, 2018; Peña-Gómez et al., 2011) or anodal and cathodal tDCS (Rêgo et al., 2015) using a between-subject design run one session experiments, in which participants randomly received active or sham stimulation. The other tDCS studies that used a within-subject design run a number of sessions that varied based on the type of stimulation

delivered: two sessions in studies in which participants received anodal and sham tDCS (Sanchez et al., 2016; Sanchez-Lopez et al., 2018; Wolkstein & Plewnia, 2013); three sessions in a study in which participants received anodal, and cathode, and sham tDCS (Brunoni et al., 2013).

Among the rTMS studies, three studies explored the effects of eccitatory stimulation by applying high frequency rTMS at 10 Hz (Balconi et al., 2014; De Raedt et al., 2010; He et al., 2019), one study explored the effects of inhibitory stimulation by applying low frequency rTMS at 1 Hz (Fitzgibbon et al., 2017), while one study administered 10 Hz rTMS to one group of participants and 1 Hz rTMS to onother group of participants (Berger et al., 2017). Regarding the targeted area, rTMS studies stimulated the left primary motor cortex (Balconi et al., 2014), the lDLPFC (Fitzgibbon et al., 2017), the rVLPFC (Berger et al., 2017) or both (De Raedt et al., 2010), and the rVLPFC (He et al., 2019). All the rTMS studies used an offline stimulation protocol, except for Balconi et al. (2014).

Similarly to the tDCS studies, also in the rTMS studies the type of the stimulation delivered and the study design (either between- or within-subjects) determined the number of stimulation sessions. Indeed, studies investigating the effects of high or low frequency rTMS using a between-subjects design (Fitzgibbon et al., 2017; He et al., 2019) applied only one stimulation session, whereas in within-subjects designs as many sessions were used as the experimental and control sessions. For instance, in Balconi et al. (2014) rTMS was delivered across three sessions: active or sham stimulation over the left primary motor cortex, and active stimulation over another region used as further control condition. Finally, two papers (Depperman et al., 2016; Hurlemann et al., 2015) used the iTBS that is known to deliver eccitatory effects (see Chapter 5). Both papers used an offline protocol to stimulate the lDLPFC. Yet, Hurlemann et al. (2015) stimulated also the lDMPFC by using a within-subjects design. Based on the studies' designs, Depperman et al. (2016) and Hurlemann et al. (2015) used one and two stimulation sessions, respectively.

Regarding the control protocol, all tDCS studies included a sham condition in which the current was rampt up for a few seconds and turned down immediately after, such to produce the typical initial stimulation sensations without interfering with the cerebral activity (Gandiga et al., 2006). Considering the rTMS studies, one study used a shielded coil that reduced the magnetic field of approximately 90% (Berger et al., 2017). Another study (Balconi et al., 2014), as mentioned, used two control conditions: a no-stimulation condition and the stimulation of a control area (i.e., midline parietal cortex) (for consistency with the other studies, only the stimulation of the control area was included as control condition in the present quantitative analysis (see the next paragraph). Moreover, one study (Hurlemann et al., 2015) used a placebo coil that provided discharge

sensations and noise, however, without stimulating the targeted cortical area. Finally, to avoid inducing electrical currents, four studies placed the coil at an angle of 90° respect to the stimuated area (De Raedt et al., 2010; He et al., 2019; Depperman et al., 2016; Fitzgibbon et al., 2017). The Table 6 summarizes further details stimulations' characteristics.

Table 6. The table shows the studies' descriptive data.

Paper	Sample Size (mean age, sd)	NIBS	Target Area	Stimulation protocol	Study design	Emotions' Regulation Strategy	Experimental Task	Outcome measures
Aboulafia-Brakhaa et al., 2016	45 (27.16 ± 6.7)	atDCS	l/rDLPFC	Online, 1.5mA, 25 mins, 1 session	Between, single-blind	Implicit	Affective switch task	RTs
Balconi et al., 2014	29 (23.34 ± 0.11)	rTMS	lM1	Online, 100 trains of 10 Hz, 120% of rMT, 3 sessions	Within, blinding n.r.	Implicit	Forced-choice response task (with happy, angry, neutral faces)	RTs and accuracy
Berger et al., 2017	40 (24 ± 2.8)	rTMS	rDLPFC	Offline, one group 10 Hz/one group 1 Hz, 110% of rMT, 2 sessions	Within, single-blind	Implicit	Delay working memory task (with high/low valence negative pictures, or neutral pictures)	Physiological (SCR, heart rate) Ratings of valence and arousal
Brunoni et al., 2013	20 (24.9 ± 3.8)	a/ctDCS	r/lDLPFC	Online, 1.5mA, 15 mins, 3 sessions	Within, single-blind	Explicit/ Implicit	Picture presentation (negative and neutral)	Physiological (salivary cortisol levels, heart rate) Ratings of mood and anxiety
Chen, 2018	32 (20,41 ± 1.33)	atDCS	rVLPFC	Online, 2 mA, 12 mins, 1 session	Between, single-blind	Implicit	Taylor Aggression Paradigm	Ratings of punishment levels
De Raedt et al., 2010	37 (22.6 ± 2.6)	rTMS	r/lDLPFC	Offline, 40 trains at 10 Hz of 3.9 secs duration, 110% of rMT, 2 sessions	Within and Between, single-blind	Implicit	Attentional engagement – disengagement task (ECT: presentation of valid/invalid cues and target neutral and angry faces)	Attentional indices (i.e., latency – RTs - of gaze shifts)
Depperman et al., 2016	42 (25.43 ± 7.37)	iTBS	lDLPFC	Offline, 2 secs trains repeated every 10 secs for a total of 190 secs (600 pulses), 80% of rMT, 1 session	Between, single-blind	Implicit	Emotional Stroop task (positive, negative, neutral phobia-related words)	RTs and accuracy

Fitzgibbon et al., 2017	29 (24.17 ± 6.12)	rTMS	lDLPFC	Offline, 1200 1 Hz consecutive pulses, 20 mins, 120% of rMT, 1 session	Between, blinding n.r.	Implicit	Cyberball task	Ratings of feelings of social exclusion
He et al., 2018	Exp1: 44 (21 ± 1,35) Exp2: 40 (21.35 ± 1.3)	atDCS	rVLPFC	Online, 2.5mA, 24 mins, 1 session	Between, single-blind	Explicit	Reappraise reactions to presentation of social exclusion images	Physiological (pupil diameter, fixation duration) Ratings of emotion negativity
He et al., 2019	59 (21.4 ± 2)	rTMS	rVLPFC	Offline, 30 trains of a total of 1,170 pulses at 10 Hz, 120% of rMT, 1 session	Between, blinding n.r.	Explicit	Reappraise reactions to presentation of social exclusion images	Physiological (LPP amplitude) Ratings of valence and arousal
Herrmann et al., 2016	26 (24,05 ± 3,15)	atDCS	rIFG	Online, 2 mA, 20 mins, 1 session	Between, double-blind	Implicit	NPU task	Physiological (SCR, startle)
Herrmann et al., 2018	80 (23,55 ± 3,25)	atDCS	rIFG	Online, 2 mA, 20 mins, 1 session	Between, double-blind	Implicit	NPU task	Physiological (SCR) Ratings of valence and arousal
Hurlemann et al., 2015	41 (24.12 ± 3.66)	iTBS	lDLPFC lDMPFC	Offline, 1200 50 Hz pulses for 390 secs), 80% of rMT, 2 sessions	Within, blinding n.r.	Explicit/ Implicit	Cognitive emotion judgment task and Emotion-modulated startle paradigm (both with presentation of negative, neutral and positive picture)	Physiological (facial electromyographic recordings) Ratings of valence and arousal
Peña-Gómez et al., 2011	16 (22.93 ± 4.18)	atDCS	lDLPFC	Online, 1.5 mA, 20 mins, 1 session	Between, single-blind	Explicit	Picture presentation (positive, negative, neutral pictures)	Ratings of pictures' valence
Rêgo et al., 2015	24 (23±2.57)	a/ctDCS	r/lDLPFC	Online, 2 mA, 15 mins, 1 session	Between, double-blind	Explicit	Presentation of arousing pain video clips	Physiological (pupil dilation) Ratings of valence and arousal
Sanchez et al., 2016	30 (23.27 ±	atDCS	rDLPFC	Offline, 2 mA, 20 mins, 2 sessions	Within, single-blind	Implicit	Attentional engagement –	Physiological (eye movements)

	4.15)						disengagement task with presentation of happy, disgusted, and sad facial expressions	Attentional indices (i.e., latency – RTs - of gaze shifts)
Sanchez-Lopez et al., 2018	54 (23.15 ±sd n.r.)	atDCS	r/lDLPFC	Online, 2 mA, 20 mins 2 sessions	Within, , single-blind	Implicit	Attentional engagement – disengagement task with presentation of happy, disgusted, and sad facial expressions	Physiological/attentional indices (eye movements) Ratings of mood
Wolkstein & Plewnia, 2013	22 (31.91 ± 10.51)	atDCS	lDLPFC	Online, 1 mA, 20 mins, 2 sessions	Within, double-blind	Implicit	Delay working memory task	RTs and accuracy

List of acronyms: sd, standard deviation; NIBS, non-invasive brain stimulation; atDCS, anodal transcranial direct current stimulation; a/ctDCS, anodal and cathodal transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; l/rDLPFC, left and right dorso-lateral prefrontal cortex; lDLPFC, left dorso-lateral prefrontal cortex; rDLPFC, right dorso-lateral prefrontal cortex; lM1, left primary motor cortex; rVLPFC, right ventro-lateral prefrontal cortex; rIFG, right inferior frontal gyrus; lDMPFC, left dorso-medial prefrontal cortex; rMT, resting motor threshold; n.r., not reported; ECT, exogenous cueing task; NPU, neutral/predictable/unpredictable threat task; RTs, reaction times; SCR, skin conductance response; LPP, late positive potential.

Meta-analysis results

The random effects model revealed that the effect of NIBS on emotions' regulation measures had a tendency toward significance (overall SMD = -0.039; 95% CI[-0.085; 0.006], p = .088), preliminarily suggesting that NIBS might enhance emotion regulation. The studies' heterogeneity was low according to the test for heterogeneity $Q_{(175)} = 172.39$, p = .542. The Baujat plot (Baujat et al., 2002) suggested that He et al. (2019) – numbers 141 and 144 -, Sanchez et al. (2016) – number 151 -, and Sanchez-Lopez et al. (2018) – number 13 – were the main sources of variance (Figure 22). The influence test confirmed that He et al. (2019) – numbers 141 and 144 – and Sanchez et al. (2016) – number 151 – were outliers. Therefore, after removing these studies from the meta-analysis, the random effect model was re-run, but the global effect of NIBS over emotions' regulation scores remained tendent toward significance (overall SMD = -0.044; 95% CI=[-0.090, 0.002], p=.060; see Figure 23 for the forest plots).

Analysis on publication bias revealed no asymmetry (see the Figure 24 for the funnel plot) according to both Egger's regression test (z = -0.391; p=.696) and the Rank correlation analysis (Kendall's tau = -0.007; p =.896).

Analysis of moderators showed no effect for the NIBS technique used ($QM_{(1)}$ =.266, p = .606), for the protocol type (excitatory vs. inhibitory) ($QM_{(1)}$ = 1.469, p= .226) and for timing of the stimulation (online vs. offline) ($QM_{(1)}$ = 0.036, p =.849), suggesting that none of these factors significantly impacted on the overall NIBS effects on emotions' regulation processes.

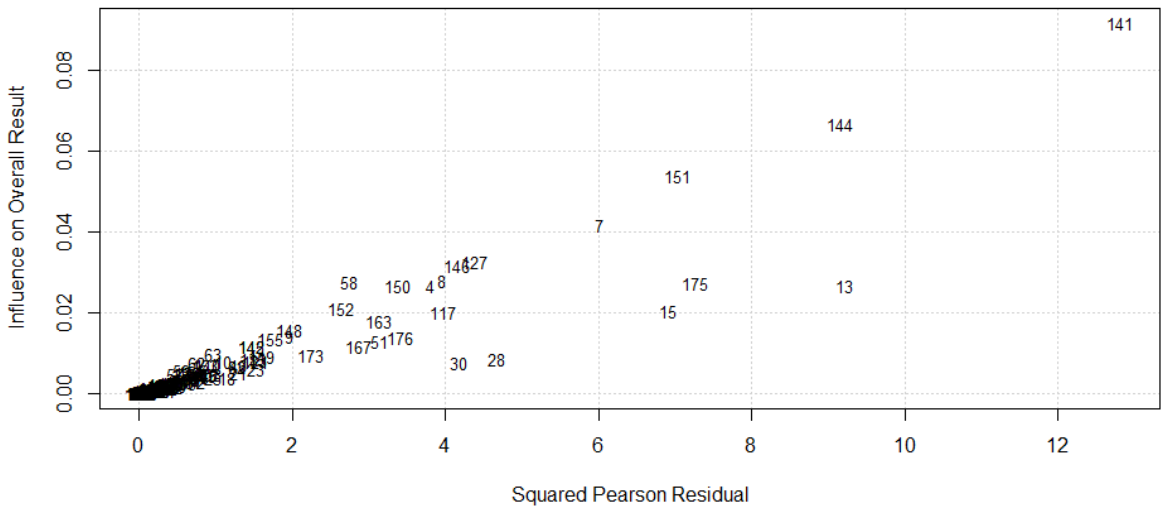
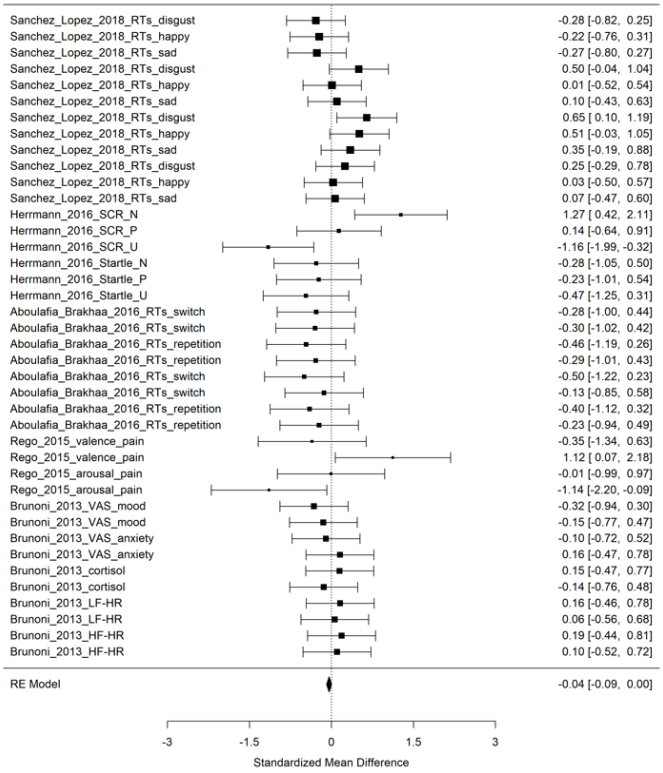
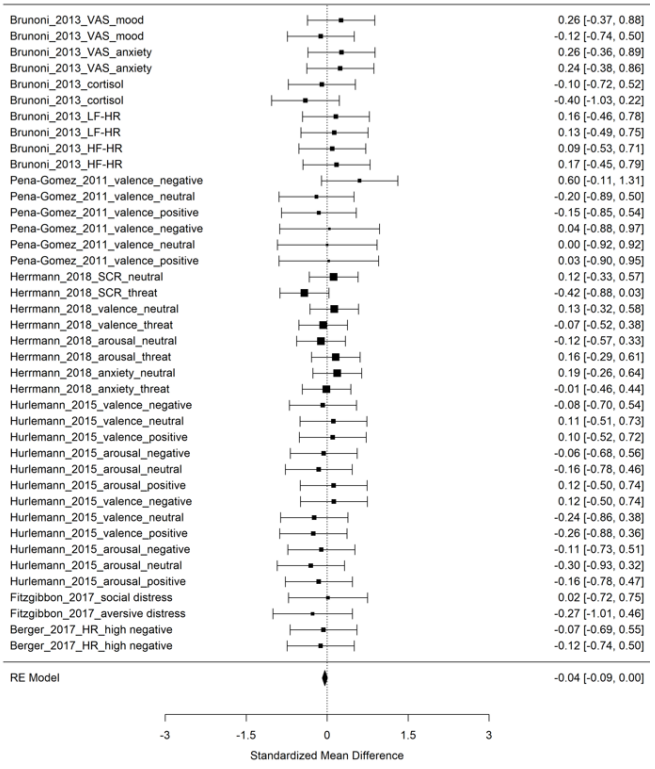


Figure 22. The figure shows the results of the Baujat plot inspection.

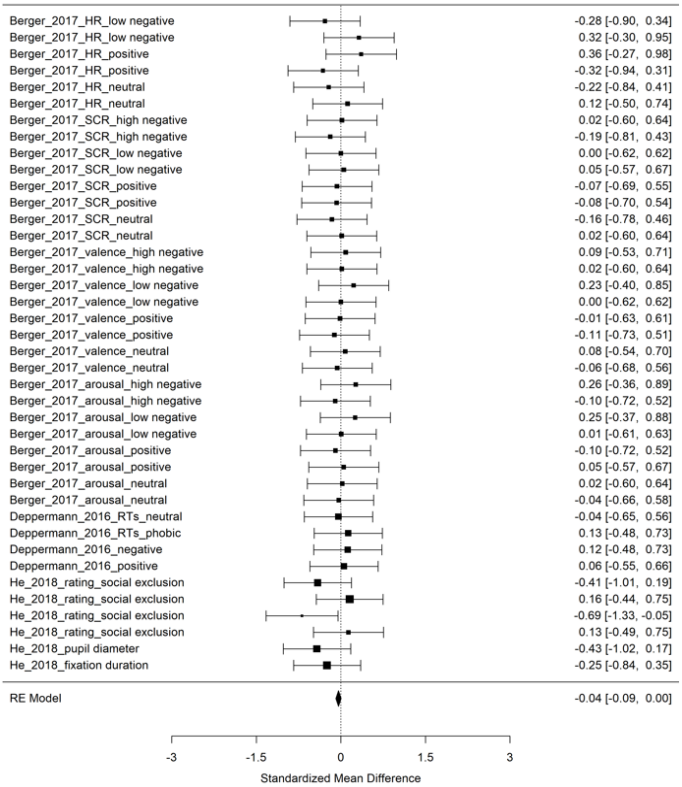
A


Sanchez_Lopez_2018_RTs_disgust -0.28 [-0.82, 0.25]
Sanchez_Lopez_2018_RTs_happy -0.22 [-0.76, 0.31]
Sanchez_Lopez_2018_RTs_sad -0.27 [-0.80, 0.27]
Sanchez_Lopez_2018_RTs_disgust 0.50 [-0.04, 1.04]
Sanchez_Lopez_2018_RTs_happy 0.01 [-0.52, 0.54]
Sanchez_Lopez_2018_RTs_sad 0.10 [-0.43, 0.63]
Sanchez_Lopez_2018_RTs_disgust 0.65 [0.10, 1.19]
Sanchez_Lopez_2018_RTs_happy 0.51 [-0.03, 1.05]
Sanchez_Lopez_2018_RTs_sad 0.35 [-0.19, 0.88]
Sanchez_Lopez_2018_RTs_disgust 0.25 [-0.29, 0.78]
Sanchez_Lopez_2018_RTs_happy 0.03 [-0.50, 0.57]
Sanchez_Lopez_2018_RTs_sad 0.07 [-0.47, 0.60]
Herrmann_2016_SCR_N 1.27 [0.42, 2.11]
Herrmann_2016_SCR_P 0.14 [-0.64, 0.91]
Herrmann_2016_SCR_U -1.16 [-1.99, -0.32]
Herrmann_2016_Startle_N -0.28 [-1.05, 0.50]
Herrmann_2016_Startle_P -0.23 [-1.01, 0.54]
Herrmann_2016_Startle_U -0.47 [-1.25, 0.31]
Aboulafia_Brakhaa_2016_RTs_switch -0.28 [-1.00, 0.44]
Aboulafia_Brakhaa_2016_RTs_switch -0.30 [-1.02, 0.42]
Aboulafia_Brakhaa_2016_RTs_repetition -0.46 [-1.19, 0.26]
Aboulafia_Brakhaa_2016_RTs_repetition -0.29 [-1.01, 0.43]
Aboulafia_Brakhaa_2016_RTs_switch -0.50 [-1.22, 0.23]
Aboulafia_Brakhaa_2016_RTs_switch -0.13 [-0.85, 0.58]
Aboulafia_Brakhaa_2016_RTs_repetition -0.40 [-1.12, 0.32]
Aboulafia_Brakhaa_2016_RTs_repetition -0.23 [-0.94, 0.49]
Rego_2015_valence_pain -0.35 [-1.34, 0.63]
Rego_2015_valence_pain 1.12 [0.07, 2.18]
Rego_2015_arousal_pain -0.01 [-0.99, 0.97]
Rego_2015_arousal_pain -1.14 [-2.20, -0.09]
Brunoni_2013_VAS_mood -0.32 [-0.94, 0.30]
Brunoni_2013_VAS_mood -0.15 [-0.77, 0.47]
Brunoni_2013_VAS_anxiety -0.10 [-0.72, 0.52]
Brunoni_2013_VAS_anxiety 0.16 [-0.47, 0.78]
Brunoni_2013_cortisol 0.15 [-0.47, 0.77]
Brunoni_2013_cortisol -0.14 [-0.76, 0.48]
Brunoni_2013_LF-HR 0.16 [-0.46, 0.78]
Brunoni_2013_LF-HR 0.06 [-0.56, 0.68]
Brunoni_2013_HF-HR 0.19 [-0.44, 0.81]
Brunoni_2013_HF-HR 0.10 [-0.52, 0.72]
RE Model -0.04 [-0.09, 0.00]
-3 -1.5 0 1.5 3
Standardized Mean Difference

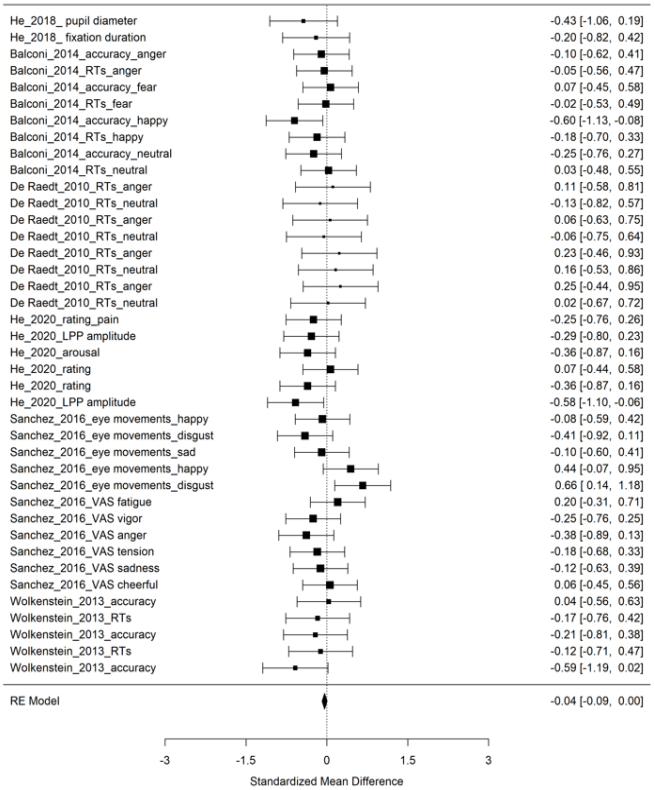
B


Brunoni_2013_VAS_mood 0.26 [-0.37, 0.88]
Brunoni_2013_VAS_mood -0.12 [-0.74, 0.50]
Brunoni_2013_VAS_anxiety 0.26 [-0.36, 0.89]
Brunoni_2013_VAS_anxiety 0.24 [-0.38, 0.86]
Brunoni_2013_cortisol -0.10 [-0.72, 0.52]
Brunoni_2013_cortisol -0.40 [-1.03, 0.22]
Brunoni_2013_LF-HR 0.16 [-0.46, 0.78]
Brunoni_2013_LF-HR 0.13 [-0.49, 0.75]
Brunoni_2013_HF-HR 0.09 [-0.53, 0.71]
Brunoni_2013_HF-HR 0.17 [-0.45, 0.79]
Pena-Gomez_2011_valence_negative 0.60 [-0.11, 1.31]
Pena-Gomez_2011_valence_neutral -0.20 [-0.89, 0.50]
Pena-Gomez_2011_valence_positive -0.15 [-0.85, 0.54]
Pena-Gomez_2011_valence_negative 0.04 [-0.88, 0.97]
Pena-Gomez_2011_valence_neutral 0.00 [-0.92, 0.92]
Pena-Gomez_2011_valence_positive 0.03 [-0.90, 0.95]
Herrmann_2018_SCR_neutral 0.12 [-0.33, 0.57]
Herrmann_2018_SCR_threat -0.42 [-0.88, 0.03]
Herrmann_2018_valence_neutral 0.13 [-0.32, 0.58]
Herrmann_2018_valence_threat -0.07 [-0.52, 0.38]
Herrmann_2018_arousal_neutral -0.12 [-0.57, 0.33]
Herrmann_2018_arousal_threat 0.16 [-0.29, 0.61]
Herrmann_2018_anxiety_neutral 0.19 [-0.26, 0.64]
Herrmann_2018_anxiety_threat -0.01 [-0.46, 0.44]
Hurlemann_2015_valence_negative -0.08 [-0.70, 0.54]
Hurlemann_2015_valence_neutral 0.11 [-0.51, 0.73]
Hurlemann_2015_valence_positive 0.10 [-0.52, 0.72]
Hurlemann_2015_arousal_negative -0.06 [-0.68, 0.56]
Hurlemann_2015_arousal_neutral -0.16 [-0.78, 0.46]
Hurlemann_2015_arousal_positive 0.12 [-0.50, 0.74]
Hurlemann_2015_valence_negative 0.12 [-0.50, 0.74]
Hurlemann_2015_valence_neutral -0.24 [-0.86, 0.38]
Hurlemann_2015_valence_positive -0.26 [-0.88, 0.36]
Hurlemann_2015_arousal_negative -0.11 [-0.73, 0.51]
Hurlemann_2015_arousal_neutral -0.30 [-0.93, 0.32]
Hurlemann_2015_arousal_positive -0.16 [-0.78, 0.47]
Fitzgibbon_2017_social distress 0.02 [-0.72, 0.75]
Fitzgibbon_2017_aversive distress -0.27 [-1.01, 0.46]
Berger_2017_HR_high negative -0.07 [-0.69, 0.55]
Berger_2017_HR_high negative -0.12 [-0.74, 0.50]
RE Model -0.04 [-0.09, 0.00]
-3 -1.5 0 1.5 3
Standardized Mean Difference

C


Berger_2017_HR_low negative -0.28 [-0.90, 0.34]
Berger_2017_HR_low negative 0.32 [-0.30, 0.95]
Berger_2017_HR_positive 0.36 [-0.27, 0.98]
Berger_2017_HR_positive -0.32 [-0.94, 0.31]
Berger_2017_HR_neutral -0.22 [-0.84, 0.41]
Berger_2017_HR_neutral 0.12 [-0.50, 0.74]
Berger_2017_SCR_high negative 0.02 [-0.60, 0.64]
Berger_2017_SCR_high negative -0.19 [-0.81, 0.43]
Berger_2017_SCR_low negative 0.00 [-0.62, 0.62]
Berger_2017_SCR_low negative 0.05 [-0.57, 0.67]
Berger_2017_SCR_positive -0.07 [-0.69, 0.55]
Berger_2017_SCR_positive -0.08 [-0.70, 0.54]
Berger_2017_SCR_neutral -0.16 [-0.78, 0.46]
Berger_2017_SCR_neutral 0.02 [-0.60, 0.64]
Berger_2017_valence_high negative 0.09 [-0.53, 0.71]
Berger_2017_valence_high negative 0.02 [-0.60, 0.64]
Berger_2017_valence_low negative 0.23 [-0.40, 0.85]
Berger_2017_valence_low negative 0.00 [-0.62, 0.62]
Berger_2017_valence_positive -0.01 [-0.63, 0.61]
Berger_2017_valence_positive -0.11 [-0.73, 0.51]
Berger_2017_valence_neutral 0.08 [-0.54, 0.70]
Berger_2017_valence_neutral -0.06 [-0.68, 0.56]
Berger_2017_arousal_high negative 0.26 [-0.36, 0.89]
Berger_2017_arousal_high negative -0.10 [-0.72, 0.52]
Berger_2017_arousal_low negative 0.25 [-0.37, 0.88]
Berger_2017_arousal_low negative 0.01 [-0.61, 0.63]
Berger_2017_arousal_positive -0.10 [-0.72, 0.52]
Berger_2017_arousal_positive 0.05 [-0.57, 0.67]
Berger_2017_arousal_neutral 0.02 [-0.60, 0.64]
Berger_2017_arousal_neutral -0.04 [-0.66, 0.58]
Deppermann_2016_RTs_neutral -0.04 [-0.65, 0.56]
Deppermann_2016_RTs_phobic 0.13 [-0.48, 0.73]
Deppermann_2016_negative 0.12 [-0.48, 0.73]
Deppermann_2016_positive 0.06 [-0.55, 0.66]
He_2018_rating_social exclusion -0.41 [-1.01, 0.19]
He_2018_rating_social exclusion 0.16 [-0.44, 0.75]
He_2018_rating_social exclusion -0.69 [-1.33, -0.05]
He_2018_rating_social exclusion 0.13 [-0.49, 0.75]
He_2018_pupil diameter -0.43 [-1.02, 0.17]
He_2018_fixation duration -0.25 [-0.84, 0.35]
RE Model -0.04 [-0.09, 0.00]
-3 -1.5 0 1.5 3
Standardized Mean Difference

D


He_2018_ pupil diameter -0.43 [-1.06, 0.19]
He_2018_ fixation duration -0.20 [-0.82, 0.42]
Balconi_2014_accuracy_anger -0.10 [-0.62, 0.41]
Balconi_2014_RTs_anger -0.05 [-0.56, 0.47]
Balconi_2014_accuracy_fear 0.07 [-0.45, 0.58]
Balconi_2014_RTs_fear -0.02 [-0.53, 0.49]
Balconi_2014_accuracy_happy -0.60 [-1.13, -0.08]
Balconi_2014_RTs_happy -0.18 [-0.70, 0.33]
Balconi_2014_accuracy_neutral -0.25 [-0.76, 0.27]
Balconi_2014_RTs_neutral 0.03 [-0.48, 0.55]
De Raedt_2010_RTs_anger 0.11 [-0.58, 0.81]
De Raedt_2010_RTs_neutral -0.13 [-0.82, 0.57]
De Raedt_2010_RTs_anger 0.06 [-0.63, 0.75]
De Raedt_2010_RTs_neutral -0.06 [-0.75, 0.64]
De Raedt_2010_RTs_anger 0.23 [-0.46, 0.93]
De Raedt_2010_RTs_neutral 0.16 [-0.53, 0.86]
De Raedt_2010_RTs_anger 0.25 [-0.44, 0.95]
De Raedt_2010_RTs_neutral 0.02 [-0.67, 0.72]
He_2020_rating_pain -0.25 [-0.76, 0.26]
He_2020_LPP amplitude -0.29 [-0.80, 0.23]
He_2020_arousal -0.36 [-0.87, 0.16]
He_2020_rating 0.07 [-0.44, 0.58]
He_2020_rating -0.36 [-0.87, 0.16]
He_2020_LPP amplitude -0.58 [-1.10, -0.06]
Sanchez_2016_eye movements_happy -0.08 [-0.59, 0.42]
Sanchez_2016_eye movements_disgust -0.41 [-0.92, 0.11]
Sanchez_2016_eye movements_sad -0.10 [-0.60, 0.41]
Sanchez_2016_eye movements_happy 0.44 [-0.07, 0.95]
Sanchez_2016_eye movements_disgust 0.66 [0.14, 1.18]
Sanchez_2016_VAS fatigue 0.20 [-0.31, 0.71]
Sanchez_2016_VAS vigor -0.25 [-0.76, 0.25]
Sanchez_2016_VAS anger -0.38 [-0.89, 0.13]
Sanchez_2016_VAS tension -0.18 [-0.68, 0.33]
Sanchez_2016_VAS sadness -0.12 [-0.63, 0.39]
Sanchez_2016_VAS cheerful 0.06 [-0.45, 0.56]
Wolkenstein_2013_accuracy 0.04 [-0.56, 0.63]
Wolkenstein_2013_RTs -0.17 [-0.76, 0.42]
Wolkenstein_2013_accuracy -0.21 [-0.81, 0.38]
Wolkenstein_2013_RTs -0.12 [-0.71, 0.47]
Wolkenstein_2013_accuracy -0.59 [-1.19, 0.02]
RE Model -0.04 [-0.09, 0.00]
-3 -1.5 0 1.5 3
Standardized Mean Difference

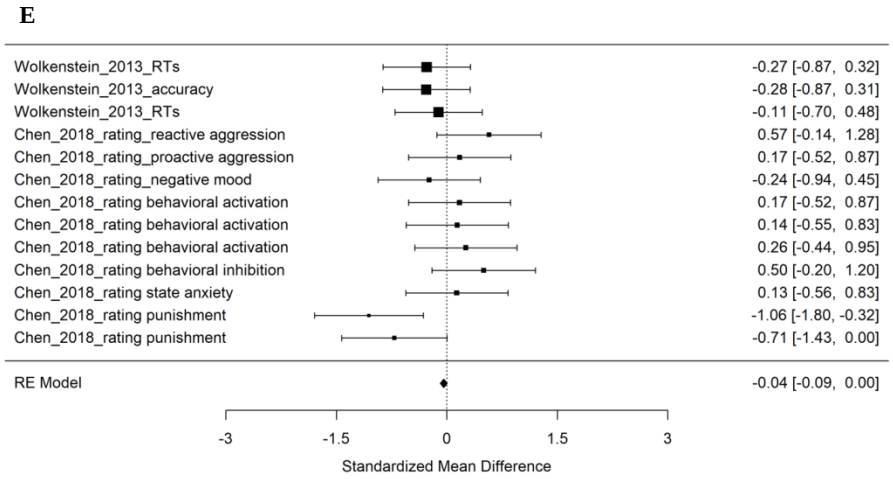


Figure 23. The figure (panels A to E) shows forest plots of the effect size of NIBS on measures of emotions' regulation.

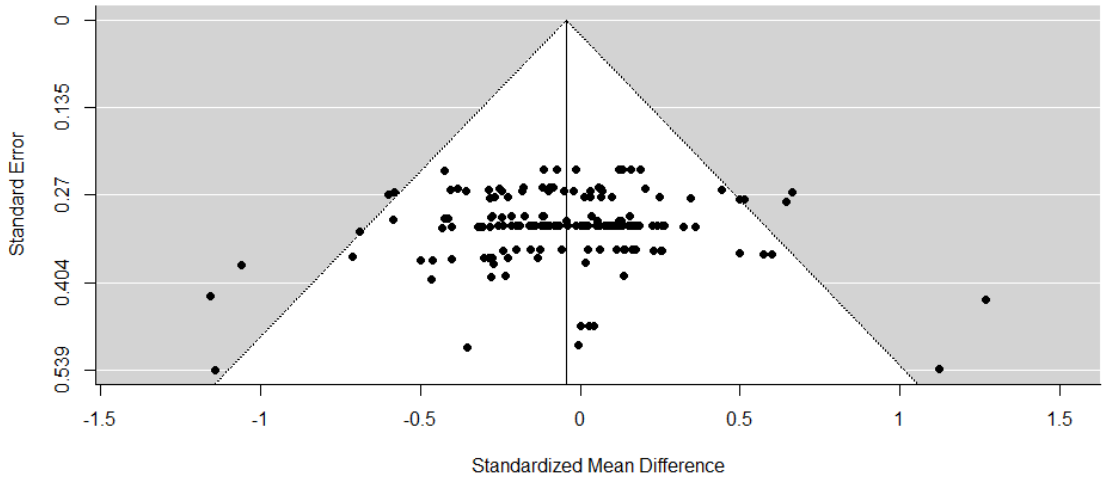


Figure 24. The figure shows publication bias assessed by the funnel plot.

5.2.3 Discussion

This systematic review and meta-analysis preliminary investigated whether non-invasive brain stimulation is effective in modulating emotions' regulation processes (either explicit or implicit) in healthy individuals. Therefore, the search strategy identified English original peer-reviewed articles appliying active, compared to placebo (sham), non-invasive brain stimulation on healthy individuals involved in behavioural tasks inducing emotions.

Overall, 18 articles were included following the inclusion criteria for both qualitative and quantitative analysis.

The included studies differed with respect to the emotions' regulation strategies investigated, the experimental tasks administered, the outcome measures considered and the stimulation protocols applied. Indeed, the majority of the included studies investigated implicit regulation processes (12 articles out of 18), while a minority explored explicit regulation processes, either by asking participants to reappraise their emotions (He et al., 2018, 2019) or to rate the valence and arousal of the emotions elicited by the stimuli (Peña-Gómez et al., 2011; Rêgo et al., 2015). Two articles explored the effects of NIBS on both explicit and implicit emotions' regulation (Hurlemann et al., 2015; Brunoni et al., 2013).

Across the included papers, the most used method to elicit emotions was the presentation of visual stimuli (e.g., emotional images) to measure emotions' effects in terms of valence/arousal (Peña-Gómez et al., 2011) and physiological indexes, including salivary cortisol levels, heart rate (Brunoni et al., 2013) and pupil dilatation (Rêgo et al., 2015), also following reappraisal of (He et al., 2018, 2019). Alternatively, emotional pictures were presented within experimental paradigms to measure participants performance (i.e., reaction times and accuracy), namely the go/no-go task (Aboulafia-Brakhaa et al., 2016), the forced-choice response task (Balconi et al., 2014), the delay working memory task (Berger et al., 2017; Wolkstein & Plewnia, 2013), the attentional engagement – disengagement task (De Raedt et al., 2010; Sanchez et al., 2016; Sanchez-Lopez et al., 2018), the emotional Stroop (Depperman et al., 2016), the neutral/predictable/unpredictable threats task (Herrmann et al., 2016, 2018), the cognitive emotion judgment task and the emotion-modulated startle paradigm (Hurlemann et al., 2015). Other studies used situational tasks, such as the Cyberball game (Fitzgibbon et al., 2017) and the Taylor Aggression Paradigm (Chen, 2018).

Concerning the stimulation protocol, the majority of the studies (11/18) were tDCS studies testing anodal stimulation (all but Brunoni et al., 2013 and Rêgo et al., 2015 that tested both anodal and cathodal stimulation), while seven out of 18 papers applied TMS. Among these, five studies

employed high frequency rTMS (all but Fitzgibbon et al., 2017 that tested low frequency rTMS) and two studies the iTBS (Depperman et al., 2016; Hurlemann et al., 2015) Almost all the studies targeted the prefrontal regions, mainly the left and right dlPFC, and in a minority of cases the rVLPFC (Chen, 2018; He et al., 2018, 2019) and IFG (Herrmann et al., 2016, 2018), and the lDMPFC (Hurlemann et al., 2015). Only in one study authors targeted the left premotor area (Balconi et al., 2014) (see Figure 25).

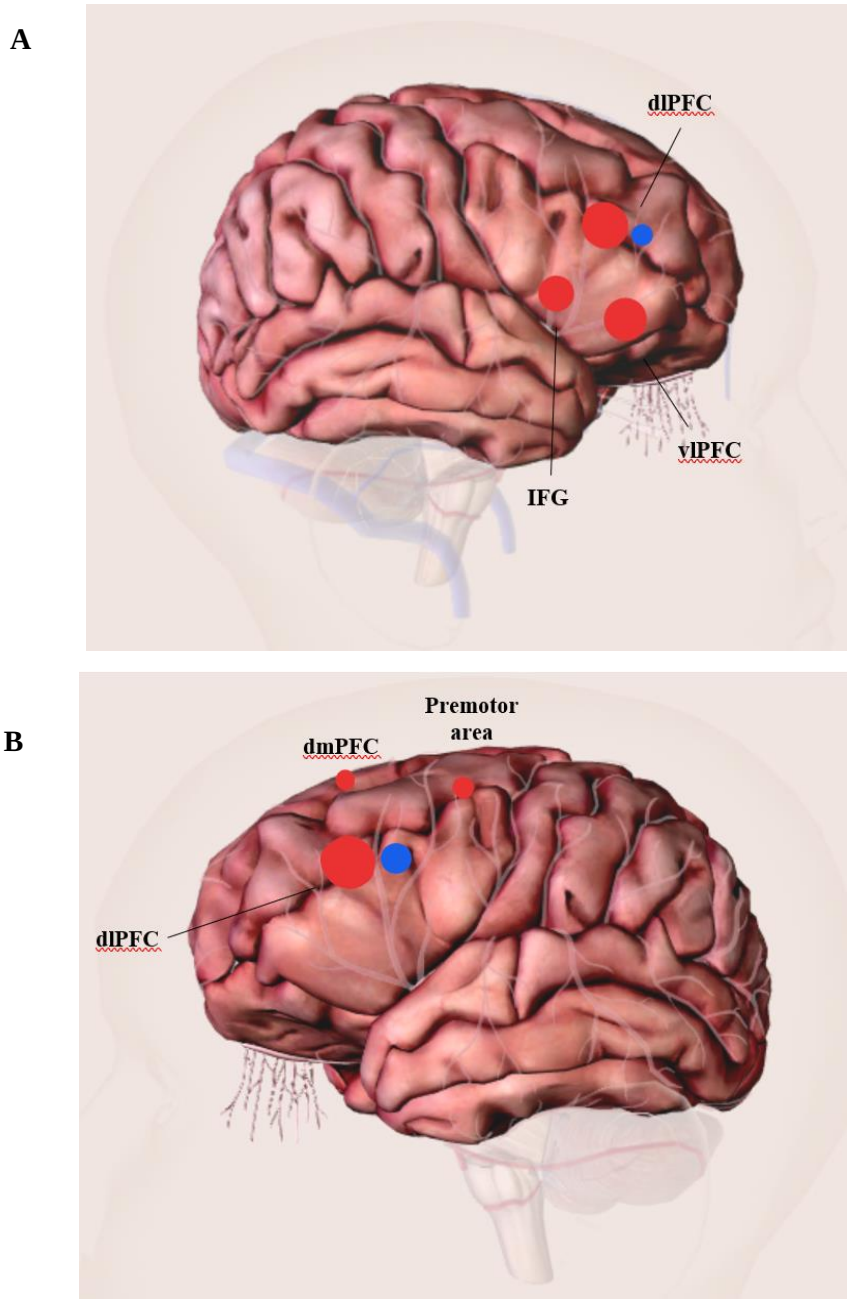


Figure 25. The figure shows the brain areas targeted by the included studies. Red circles indicate excitatory protocols, while blue circles indicate inhibitory protocols. Panel A represents the right emisphere, while Panel B represents the left emisphere. List of acronyms: dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; IFG, inferior frontal gyrus.

Overall, the meta-analysis highlighted an emotions' regulatory effect due to active non-invasive brain stimulation, compared to sham, that only tended to significance with a small effect size. In my opinion, one possibility is that when applied to healthy individuals, NIBS may only slightly improve the already functional emotions' regulation and that, instead, the application of NIBS could induce stronger effects in individuals with impaired emotions' regulation abilities, such as psychiatric patients (Berking et al., 2008). Indeed, these patients were found to be characterized by impairments in the cerebral areas underliying emotions' regulation processes that were targeted also by the experiments included in the present meta-analysis. For instance, in their review Zilverstand and colleagues (2017) showed reduced dlPFC and vlPFC activity while patients with mood, anxiety, personality, addiction and schizophrenic disorders downregulated negative emotions by reappraisal. Similar results were found also by a series of meta-analysis on fMRI studies on cognitive control across mood, anxiety and bipolar disorders (Wang et al., 2018), mood and anxiety disorders (Picó-Pérez et al., 2017), and bipolar disorder (Phillips & Swartz, 2014). Moreover, although preliminary, there are promising results about the efficacy of using TMS and tDCS as a novel treatment for several psychiatric diseases, such as major depressive disorder (Hui, Tremblay & Daskalakis, 2019), schizophrenia (Kostova et al., 2020), substance abuse (Trojak et al., 2017), and obsessive-compulsive disorders (Brunelin et al., 2018).

These evidence, together with the trend to significance of results of the present meta-analysis, suggest the need for future experiments and more complete meta-analysis to include a greater number of studies. Indeed, the findings provided by the present meta-analysis could be also explained by the few studies included that probably prevented us also to observe significant moderation effects of the NIBS type, protocol and timing of delivery and to test other potential moderators (e.g., experimental paradigm). This work should be therefore considered preliminary.

I think that future research, qualitative and quantitative synthesis on greater healthy and clinical samples and including other non-invasive brain stimulation techniques (e.g., transcranial alternating current stimulation) could for istance: a) test effects of different NIBS techniques when applied in a wide array of experimental paradigms to investigate emotions' regulation; b) clarify possible differences in efficacy due to characteristics of NIBS protocols (e.g., stimulation duration and intensity, number of sessions, online vs. offline application, target brain areas); c) shed light on possible moderator factors, such as the type of bahavioral task used, the emotions' regulation strategy stressed, or the outcome measures considered (e.g., physiological variances, task performance, emotions' ratings); d) evaluate differences in efficacy when healthy participants or individuals with impaired regulation abilities are included; e) assess the NIBS effects also when

positive (not only negative) emotions are considered and when both up- and downregulation processes of negative and positive emotions are targeted within the same study protocol; f) verify whether NIBS is more effective in modulating general emotional reactivity (i.e., autonomic spontaneous responses) than implicit or explicit emotions' regulation or viceversa.

Chapter 6: Efficacy of non-invasive brain stimulation to regulate emotions

6.1 Data from a healthy group

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Stimulating the ventrolateral prefrontal cortex (VLPFC) modulates frustration-induced aggression: A tDCS experiment

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ABSTRACT

Background: The prefrontal cortex is crucial for top-down regulation of aggression, but the neural underpinnings of aggression are still poorly understood. Past research showed the transcranial direct current stimulation (tDCS) over the ventrolateral prefrontal cortex (VLPFC) modulates aggression following exposure to risk factors for aggression (e.g., social exclusion, violent media). Although frustration is a key risk factor for aggression, no study to date has examined the modulatory role of tDCS on frustration-induced aggression.
Objectives: By exploring the VLPFC involvement in frustration-aggression link, we tested the hypothesis that the anodal tDCS over right and left VLPFC modulates frustration-induced aggression. We also explored whether tDCS interacts with gender to influence frustration-induced aggression.
Methods: 90 healthy participants (45 men) were randomly assigned to receive anodal or sham tDCS over the right or left VLPFC before being frustrated by an accomplice. To increase reliability, several tasks were used to measure aggression.
Results: We found that anodal tDCS over the left VLPFC, compared to sham stimulation, increased aggression. Unexpectedly, no main effect was found following tDCS of right VLPFC. However, we also found a significant interaction between gender and tDCS, showing that males were more aggressive than females following sham stimulation, but females became as aggressive as males following active tDCS.
Conclusion: Overall, these results shed light on the neural basis of frustration-induced aggression, providing further evidence for the involvement of VLPFC in modulating aggressive responses, and on gender differences in aggression. Future research should further investigate the role of stimulating the VLPFC on frustration-induced aggression.

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Stimulating the ventrolateral prefrontal cortex (VLPFC) modulates frustration-induced aggression: a tDCS experiment

"Frustration is the wet nurse of violence."

— David Abrahamsen, Norwegian forensic psychiatrist

One of the earliest proposed causes of aggression was frustration, defined as blocking or obstructing goal-directed behavior [1]. Despite the prominent role of frustration on aggression, no research has examined the neural mechanisms involved.

The regulatory role of the pre-frontal cortex on aggression

Past research has examined the role of the prefrontal cortex on aggression and violence [2–5]. The prefrontal network is crucial for a top-down control over subcortical regions involved in processing threatening stimuli, including frustrations [6–8]. Particularly, the ventrolateral prefrontal cortex (VLPFC) is critical for self-control and emotion regulation processes [9–13] including control over aggressive impulses.

Both hemispheres are involved. Studies of the right hemisphere show that the rVLPFC can play a role in decreasing a wide range of negative emotions that can trigger aggression [12,14–21]. Studies also show that the degree of rVLPFC activity, as well as the degree of

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negative interplay between the rVLPFC and the amygdala, significantly correlated with self-reported negative emotions [13,22–24]. The rVLPFC is also involved in controlling the impulses [25–30], which might include aggressive impulses.

Studies of the left hemisphere show that the lVLPFC is recruited especially in reappraisal-related emotion regulation strategies [16,31,32], and impulsivity control [29,30,33]. Moreover, it has been hypothesized that the rVLPFC is involved in both conscious and unconscious control, whereas the lVLPFC is only involved in conscious control [34]. Self-control is critical when it comes to inhibiting aggressive impulses. Indeed aggression often starts when self-control stops [35].

Anger is associated with approach motivation [64]. Approach motivational processes are associated with greater left than right fontal activity, whereas avoidance motivational processes are associated with greater right than left frontal activity. This asymmetric frontal cortical activity could affect the onset of aggressive responses. Thus, this experiment examines the role of both hemispheres on frustration-induced aggression.

Using tDCS over the pre-frontal cortex to study aggression

The neural mechanisms of aggression can be studied using non-invasive brain stimulation approach, such as Transcranial Direct Current Stimulation (tDCS). TDCS is a noninvasive neuromodulatory technique that delivers weak electrical currents through a pair of electrodes placed on the scalp. The electrical currents affect the excitability of cortical neurons beneath the electrodes in a polarity-dependent fashion: anodal stimulation typically enhances neural excitability, whereas cathodal stimulation reduces it [36].

Focusing on the modulation of aggression, past research has found that anodal tDCS applied over the rVLPFC decreases aggressive reactions elicited by several stimuli, including social rejection [38] and exposure to violent video games [39]. These results suggest that it is possible to influence the neurocircuitry implicated in successful self-regulation by modulating the cortical excitability of brain regions involved in the top-down regulation of aggression. However, to our knowledge, no study has tested whether tDCS applied over the VLPFC modulates frustration-induced aggression. This study attempts to fill this gap in the literature, exploring whether the effects of tDCS on aggression can be differently modulated by the type of aversive stimuli, in this case frustration, as compared to other stimuli investigated in past studies, such as social exclusion or video games [38,39].

Studies of the left hemisphere show that applying tDCS to increase relative left frontal cortical activity results in angry people behaving more aggressively [40,41]. Particularly, receiving a provocation after tDCS stimulation to left frontal cortex leads people to choose louder and longer noise blasts towards an ostensible partner [40], and reduces aggression inhibitions [41].

Gender differences in frustration-induced aggression

Previous research has shown that males are less tolerant of frustration than females [42,43]. However, no study has investigated whether tDCS can affect gender differences in frustration-induced aggression.

Previous research has found that tDCS interacts with gender to strengthen some crucial cognitive abilities. For instance, one study found that anodal tDCS over the medial prefrontal cortex enhanced performance on a theory of mind task in females more than males [44]. Another study found that anodal tDCS of the left temporal cortex improved emotion detection abilities in females more than males [45]. Still another study found that anodal stimulation applied over the VPFC increased utilitarian responses on a moral judgment task in females more than males [46]. In this study, we explored the possibility that tDCS stimulation might influence the gender differences in frustration-induced aggression.

Overview

This study investigated the modulatory role of the VLPFC on the link between frustration and aggression. Participants were first frustrated by means of an unsolvable task and were then randomly assigned to receive either anodal tDCS to the rVLPFC, anodal tDCS to the lVLPFC, or sham tDCS. Following stimulation, aggression was measured using three well-validated behavioral paradigms. In line with previous studies, we predicted a decrease in aggression following anodal stimulation of the rVLPFC [38,39]. Based on other studies, we also predicted that anodal tDCS to the lVLPFC would increase aggression [40,41,47,48]. Finally, we explored gender differences in the effects of tDCS onfrustration-induced aggression.

Method

Participants

Participants were 90 healthy adults from Milan, Italy (45 males and 45 females, mean age = 22.27, $SD = 2.46$). Of these, 73% were university students. However, we excluded psychology students who might be suspicious about procedures. Because results were similar for university students and non-students, data from the two groups were combined. All participants had normal or corrected to normal vision, and reported no history of neurological or psychiatric disorders, and no contraindications to tDCS [49]. Participants received 10€ (about $11) in exchange for their voluntary participation. The study was approved by the ethics committee of the University of Milano-Bicocca and conducted in accordance with the ethical standards of the revised Helsinki Declaration.

Frustration task

To induce frustration, participants were asked to solve number sequences that were unsolvable [50]. Specifically, participants were asked to complete 6 numerical sequences that an online partner of the same gender chose for them. The partner could select among 6 easy sequences (e.g. 16-14-12-10-8-6-4-?) and 6 difficult sequences (e.g. 9-6-18-19-7-5-10-?). The "difficult" sequences were actually unsolvable. The ostensible partner chose 6 difficult sequences and 0 easy sequences for the participant to solve. Participants had up to 30 s to solve each number sequence. To increase stress, a digital clock showed the time counting down. After 30 s, participants saw the message "incorrect response". To increase motivation, participants were told that they could earn an extra 1€ for each sequence they solved (in actually, all participants received 10€). Participants were given two easy training sequences to solve to make sure they understood the procedure. There actually was no partner; the task was controlled by a computer. To assess whether the frustrating task induced more negative emotions than positive emotions, participants completed an adjective checklist that contained 9 negative emotions (*angry*, *anxious*, *hurt*, *injured*, *irritated*, *mad*, *nervous*, *pained*, *tense*; Cronbach $\alpha = 0.91$) and 3 positive emotions (*cheerful*, *delighted*, *happy*; Cronbach $\alpha = .93$) on a scale ranging from 1 (*not at all*) to 7 (*extremely*).

TDCS

TDCS was delivered using a battery-driven, constant current stimulator (BrainStim, EMS, Bologna, Italy, http://brainstim.it),

through a pair of saline-soaked sponge electrodes. Participants were randomly assigned to one of three conditions: (a) anodal tDCS over the rVLPFC, (b) anodal tDCS over the lVLPFC, or (c) sham tDCS. In accordance with tDCS safety standards [49,51], the 20 min of stimulation was administered at 1.5 mA, with a 5 × 5 anode (0.06 mA/cm2 current density) and a 7 × 5 cathode (0.042 mA/cm2 current density). A fade-in/fade-out phase of 10 s was used at the beginning/end of the stimulation to diminish its perception. The 10–20 system was used to place electrodes. To stimulate the rVLPFC, the anode was placed over F6 (Montreal Neurological Institute coordinates: 58, 30, 8; 6); the contralateral homolog area (F5) was targeted for the stimulation of the lVLPFC. In both conditions, the cathodal reference electrode was placed over the contralateral supraorbital area. Fig. 1 shows a three-dimensional (3D) numerical computation of the electric field generated by tDCS according to the used montage, based on an MR-derived finite element model and computed using Comets Matlab toolbox ([52] http://www.COMETStool.com). For sham tDCS, the same electrode montage was used, placing the anode over one of the target areas, which was randomized across participants. However, the stimulation was active only for 10 s at the beginning and 10 s at the end of the 20 min stimulation period, which ensured that participants felt the initial itching sensation without any modulation of cortical excitability [53]. To keep both the experimenter and the participant blind to condition, condition codes were set through the BrainStim software, which controlled the tDCS device. At the end of the experimental session, participants were asked to rate how much pain they experienced (0 = *no pain* to 10 = *the maximum conceivable pain*).

Procedure

The experiment was conducted in two sessions (see Fig. 2). In the first session, participants completed online three self-report questionnaires thought to measure individual difference relevant to frustration-induced aggression: (a) the Physical Aggression subscale of the Buss Perry Aggression Questionnaire [54,55], which consists of 9-items (e.g. "Sometimes it happens to me that I am not able to control the desire to beat another person"; Cronbach α=.78); (b) the Negative Urgency subscale of the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale [56,57], which consists of 12-items (e.g. "I have difficulty controlling my impulses"; Cronbach α=.87); and (c) the Trait Anger Scale [58], which consists of 10-items (e.g. "I am a hot-heated person"; Cronbach α=.85). All items were scored using a 7-point scale (1 = *not at all* to 7 = *extremely*). We used these three questionnaires to ensure that the groups did not differ on these traits prior to receiving tDCS stimulation.

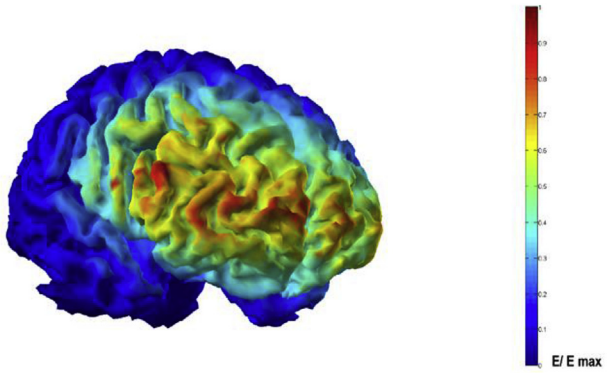


Fig. 1. Computational model of tDCS-induced electric field. A simulation of the electrical field induced by tDCS over the rVLPFC was computed using Comets. The anode (25 cm^2) was placed over the rVLPFC, corresponding to F6 electrode according to the 10–20 EEG system. The cathode (35 cm^2) was placed on the contralateral supraorbital area. Red parts indicate the strongest electrical field, occurring over the lateral and ventral portion of the right prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

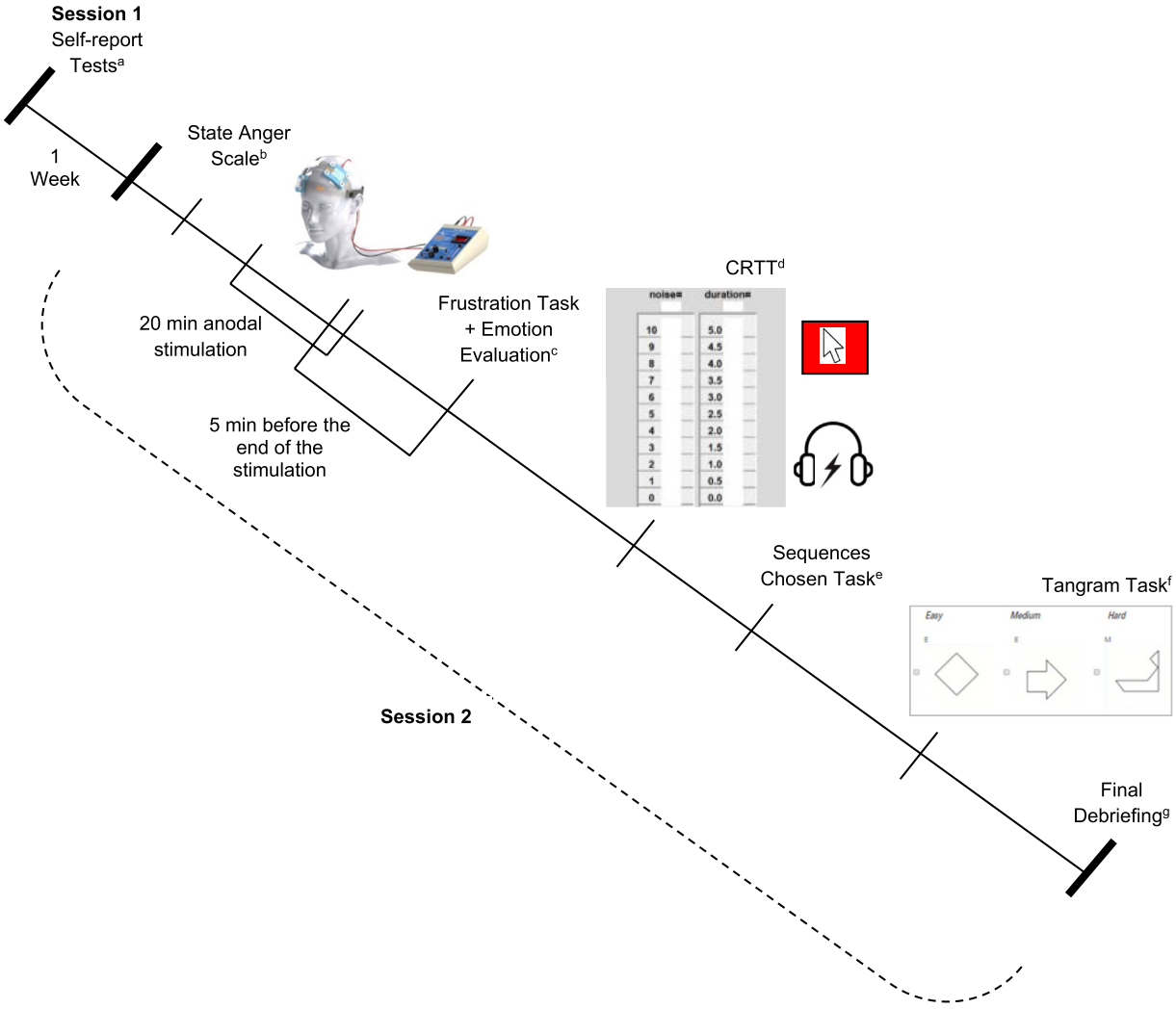
The second session occurred a week later in a laboratory at the Department of Psychology, University of Milano-Bicocca. To determine whether anger levels were similar before the frustration induction, participants first completed the State Anger Scale [58], which contains 7 items used to describe how they felt at that moment (e.g., "Angry"; 1 = *not at all* to 7 = *extremely*; Cronbach α=.92). Next, tDCS stimulation was administered. As a cover story, participants were told that the researchers were studying the effects of non-invasive stimulation on mental visualization on a series of tasks. Five minutes before the end of the tDCS stimulation, participants completed the frustration task. Following tDCS stimulation, three tasks were used to measure aggression. The first task was the competitive reaction-time task (CRTT; [59]), which was supposedly completed with an ostensible partner of the same gender. The task, which took about 8 min to complete, required the participant and the partner to press a button as fast as possible on each of 9 trials. The winner on each trial gave the loser noise blasts through headphones. The noise was a mixture of unpleasant noises (e.g., finger nails scratching on chalk boards, dentist drills, blow horns, sirens). Before each trial, participants set the level (ranging from 60 dB - level 1 – 105 dB - level 10) and the duration (from 0.5 to 5 s) of noise their partner would receive if their partner lost that trial. A non aggressive no-noise option (level 0) was also provided. At the end of each trial, participants saw the noise intensity and duration levels the partner set. Before the competition, participants received sample noise blasts at levels 2 (low noise) and 8 (high noise) to ensure they knew the noise was indeed unpleasant. The first trial was used to assess unprovoked aggression because participants had not received any noise blasts yet, and the following 8 trials were used to assess provoked aggressiveness. The partner set the maximum intensity and duration of noise on trial 1, and random noise levels on the remaining 8 trials. The participants lost trial 1, and half of the remaining 8 trials (randomly determined). The intensities and durations of noise participants set for their partner across all trials were the first aggression measure.

In the second task, participants chose 6 numerical sequences for their partner to solve among the 6 easy and 6 "difficult" (actually impossible) sequences. The number of "difficult" sequences participants chose for their partner was used as the second aggression measure.

In the third task, participants chose 11 Tangram puzzles for their partner to solve [60]. Participants could select the level of difficulty of the Tangram puzzles among 30 puzzles (10 easy, 10 medium, 10 difficult). Participants were informed that the partner could win 10€ if they successfully solved all 11 Tangram puzzles within 10 min. The number of difficult Tangram puzzles participants chose for their partner was the third aggression measure. A debriefing followed.

Statistical analyses

Data were analyzed using SPSS Statistics (Version 25.0). We considered three indices of aggressiveness (i.e., mean of intensities and durations across all 9 trials on the CRTT, number of impossible number sequences, number of difficult Tangram puzzles). The correlations between these aggression indices were quite strong (see Table 1). The three measures had good internal reliability (Cronbach α=.72). A principal component analysis also obtained a



[a] Physical Aggression subscale (Buss Perry Aggression Questionnaire [54,55]; Negative Urgency subscale (Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale [56,57]); Trait Anger Scale [58].

[b] The State Anger Scale [58] evaluates the anger levels from 1 (*not at all*) to 7 (*extremely*).

[c] The 6 impossible sequences chosen for participants by the ostensible partner. An evaluation of the positive and negative emotions caused by the task followed.

[d] The 9 trials of the CRTT [59].

[e] The 6 numerical sequences (easy versus impossible) chosen for the ostensible partner by participants.

[f] The 11 Tangram [60] puzzles (easy versus medium versus difficult) chosen for the ostensible partner by participants.

[g] Participants were debriefed about the experimental procedure and the mental visualization cover story.

Fig. 2. Schematic experimental procedure.

single factor of aggression, which explained 64% of the variance. To obtain a more reliable measure of aggression, the three indices were standardized and averaged (see Supplementary Materials for analyses of each aggression measure separately).

Data were analyzed using a 3 (stimulation condition: tDCS to the rVLPFC, tDCS to the lVLPFC, sham tDCS) x 2 (gender: male, female) between-subjects Analysis of Variance (ANOVA). Fisher's Least Significant Difference (LSD) was used for post hoc comparisons.

Table 1
Pearson correlations between aggression outcomes.

	Impossible sequences	Difficult Tangram puzzles	CRTT noise all trials
Impossible sequences	1	.54**	.48**
Difficult Tangram puzzles		1	.36**
CRTT noise all trials			1

Note. All outcomes were standardized. CRTT = competitive reaction time task. **$p < .01$ (2-tailed).

Results

Preliminary analyses

Individual differences

ANOVA found that trait anger [$F(2, 86) = 2.85$, $p = .06$], physical aggressiveness [$F(2, 86) = 0.32$, $p = .73$], and negative urgency scores [$F(2, 86) = 1.84$, $p = .17$] did not significantly differ across conditions. Thus, the groups were similar in their initial level of aggressiveness before the frustration induction.

State Anger Scale

ANOVA found that state anger levels did not differ across the three tDCS conditions [$F(2, 87) = 0.10$, $p = .90$]. Thus, initial anger levels were similar across conditions.

Frustration task

As expected, participants experienced more negative ($M = 3.44$, $SD = 1.51$) than positive emotions ($M = 1.70$, $SD = 1.03$) following the induction of frustration, $t(89) = 7.933$, $p < .001$,$d = 1.35$. Thus, it appears that the frustration task produced negative feelings.

Pain from electrodes

Similar to past research (Nitsche et al., 2008), participants reported experiencing slight pain from the electrodes ($M = 1.65$, $SD = 1.36$). Crucially, self-reported pain did not vary across the three experimental conditions, $\chi 2(2) = 0.86$, $p = .65$. Thus, the sham condition was successful.

Primary analyses

ANOVA found a main effect for stimulation condition, $F(2,84) = 3.57$, $p = .033$. Post hoc comparisons showed that participants who received anodal stimulation to the lVLPFC behaved more aggressively ($M = 0.24$, $SD = 0.14$) than participants who received sham stimulation ($M = -0.28$, $SD = 0.14$), $p = .009$, $d = 3.78$. Unexpectedly, we did not find differences between rVLPFC tDCS and sham stimulation ($p = .17$, $d = 1.98$), or between rVLPFC tDCS and lVLPFC tDCS ($p = .22$, $d = 1.80$). Analysis showed a significant main effect of gender, with higher levels of aggression in males ($M = 0.15$, $SD = 0.11$) than in females ($M = -0.18$, $SD = 0.11$), $F(1,84) = 4.24$, $p = .043$, $d = 3.03$. However, active stimulation seemed to reduce the gender difference, as indicated by a significant tDCS by gender interaction, $F(2,84) = 3.52$, $p = .034$ (Fig. 3). Males were more aggressive than females following sham stimulation ($p = .002$, $d = 4.82$), but females were not less aggressive than males following active tDCS, regardless of whether it was administered to the left ($p = .002$, $d = 4.61$) or right ($p = .007$, $d = 4.07$) hemisphere.

Discussion

Although past research has found that frustration increases aggression [1], the neural mechanisms of the frustration-aggression link have not been fully investigated. To our knowledge, this is the first study to test the effect of non-invasive brain stimulation effects on frustration-induced aggression. We explored the possible modulatory role of the anodal tDCS applied to the VLPFC, a cortical area involved in self-control [10,13,18,34], on frustration-induced aggression.

We found that increasing the cortical excitability of the lVLPFC significantly increased aggression following frustration. This result is consistent with the motivational direction model of frontal asymmetry [61], in which approach motivations are related to greater left than right frontal activity [47,48,62,63]. According to this model, because anger is associated with approach motivations, people are more likely to behave aggressively when angry [40,41,64]. In our study, we first exposed participants to frustration, which is known to be associated with anger, and then gave them a chance to aggress against the fictitious partner who had frustrated them on several standard laboratory aggression paradigms. Our results suggest that anodal stimulation over lVLPFC likely enhanced the approach motivations as shown by an increase in aggressive reactions.

Moreover, we found a significant interaction between gender and tDCS on frustration-induced aggression. Specifically, we replicated the finding that males are more aggressive than females in the sham (control) condition [42,43]. Importantly, our study is the first to show that left- and right-side stimulation eliminated this gender difference, because after tDCS males were no more aggressive than females. Different explanations might account for these null gender differences. One possibility is that the way females handle environmental demands becomes more similar to that of males after tDCS, even at the expense of socially acceptable behaviors. This explanation is consistent with the findings from a moral judgment study that found gender differences in utilitarian and socially desirable responses were eliminated after anodal stimulation of the ventral prefrontal cortex [46]. We can hypothesize that anodal tDCS drives females to adopt an “eye for an eye” strategy following frustration, overcoming their tendency to behave in a less aggressive and more socially desirable manner.

Second, it could be that tDCS is more effective for females than males. It is well known that there is high variability in the tDCS effects on cognition and behavior (for a review see Ref. [65]) and that many inter-individual factors moderate these effects, including gender (e.g. Refs. [66,67]). Previous research has found greater effects of tDCS on females than males across several tasks (e.g., go-no-go, Theory of Mind; [44,45]). However, the existence of a differential effect of tDCS on males versus females can be clearly inferred only when the outcome measures are the same at a baseline (i.e. are not influenced by gender). This was not the case in our study. Another possibility is that the strong difference between males and females' aggressive reactions we found at the baseline could conceivably be a possible ceiling effect for males, nullifying any modulatory effects of tDCS.

Regarding the right hemisphere, we expected to find that anodal stimulation decreases aggression. However, our current results are inconsistent with previous findings [37–39]. Two possible explanations could account for this unexpected result. First, previous studies focused on affective valence, such as by asking participants only to rate their negative emotions following the experimental task [37], whereas the present study focused on approach

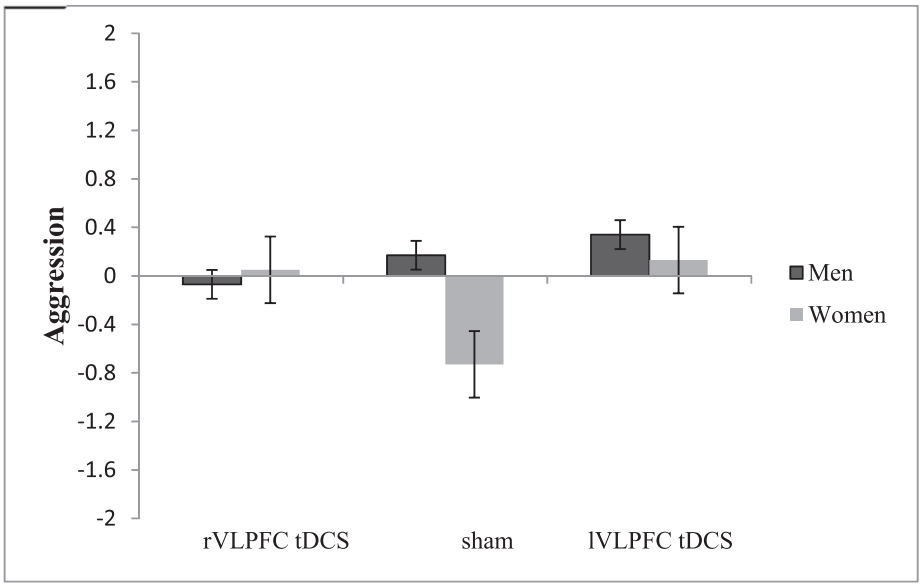


Fig. 3. Composite aggression index scores (i.e., mean of standardized aggression outcomes: CRTT all trials; the number of impossible sequences; the number of difficult Tangram puzzles) of males and females in the tDCS conditions. Capped vertical bars denote standard error.

motivation. When the focus is on affective valence, negative emotions are more likely related to greater right than left frontal activity. However, when the focus is on motivation direction (e.g., approach), negative emotions are more likely related to left than right frontal activity [64]. Several studies have demonstrated that the chance of tDCS long-lasting effects, likely affecting brain plasticity, relies upon ongoing brain activity [68,69]. TDCS stimulation depends upon the functional networks active while processing aversive stimuli. Therefore, applying tDCS over rVLPFC during tasks involving either affective valence or motivation direction could lead to different results. During tasks involving affective valence, tDCS over the rVLPFC did effectively decrease negative emotions evaluation (e.g. Refs. [21,37]). In our experiment, because the focus was on motivation direction (i.e., a "partner" first frustrated participants, and then we allowed them to aggress against their "partner"), consistent with the model of prefrontal asymmetry, we found a significant effect of anodal tDCS over lVLPFC on aggression, but no effect of anodal tDCS over rVLPFC on aggression.

A second explanation is that frustration is qualitatively different from other factors known to cause aggression (e.g., social exclusion, violent video games). Several fMRI studies reported specific abnormal activations in the prefrontal network in response to frustration [70]. However, results are still inconsistent. Indeed, some studies showed a decrease of activation in the frontal regions [71], whereas other studies showed an increase of activation in the right ventral prefrontal, medial prefrontal, anterior cingulate and dorsolateral prefrontal cortex in response to frustration [72,73]. Moreover, frustration-related neural responses are not linear, because several factors affect their variability, including trait aggressiveness [71] and susceptibility to frustration [73]. Thus, future research is needed to investigate the neural mechanisms involved in aggressive responses to frustration, compared to other factors linked to aggression. We believe that this will allow researchers to build more precise models of the neural underpinning of aggression when trigged by different factors.

This study, like all studies, has limitations. Our design allowed us to test the effects of frustration on aggression above and beyond the effects of provocation, which was held constant across conditions (i.e., all participants were provoked on the first trial of the CRTT). However, the first limitation is that we did not include a no-frustration control condition. Because all participants were frustrated, we could not explore possible stimulation differences across our three stimulation groups between frustrated and non-frustrated participants. Including a no-frustration control condition would be key for future studies. Future studies could also take advantage of the possibility of assessing baseline levels of negative emotions and aggressiveness to detect changes over time linked with frustration and neuromodulation.

Another possible methodological limitation is that we did not consider a third group of participants comparing the stimulation of the VLPFC with stimulation of a control area. Future studies with larger samples could stimulate different cortical areas. For example, posterior regions, such as the temporoparietal junction, which is involved in the mentalizing network, could affect frustration-induced aggression [74]. In our study, we asked the participants to report previous neurological and psychiatric disorders. Although this procedure is common when testing healthy participants, we can not rule out the presence of anxiety or depressive disorders the participants were not aware of. Future research should also consider running a proper battery of tests screening for clinical, neurological and psychiatric disorders rather than relying on self-reports.

Another possible limitation is the well-known low spatial resolution of tDCS. Although in the present experiment a larger amount of current was caused by the small distance between the two electrodes, computational models of current flow have shown that tDCS usually results in a spread of electric fields that occur underneath the stimulating electrodes as well as in the regions between them [75]. Thus, we cannot rule out the possibility that the stimulation affected other areas within the prefrontal cortex, such as the dorsolateral prefrontal cortex, that have a key role for top-down monitoring [10,11,13]. Further research with more focal techniques (e.g., TMS) could specify our results. Future research should also considering adopting cathodal stimulation over the target regions to test for differential effects linked with tDCS polarity.

Conclusion

Our results show that modulating the cortical excitability of left and right VLPFC affects frustration-related aggression. Our experiment extends previous research on the modulatory role of VLPFC in a wide range of domains [9,11–13,76]. It also extends previous research on gender differences in aggression. More generally, our results support the feasibility of applying non-invasive brain stimulation techniques to study self-regulation processing and contribute to the growing knowledge about the neural underpinnings of aggression regulation. However, the lack of a reduction on aggressive tendencies in the context of frustration suggests that caution should be exercised when considering clinical or therapeutic uses of tDCS to address anger and aggression.

Author notes

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Declaration of competing interestCOI

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.10.015.

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6.2 Data from a clinical sample

6.2.1 Background

Borderline Personality Disorder (BPD) is a serious mental condition associated with high levels of functional impairment, not only compared to other psychiatric disorders such as major depressive disorder, but even compared to physical illnesses such as rheumatoid arthritis (Thadani et al., 2022; Ellison et al., 2018; Leichsenring et al., 2011).

Disturbed interpersonal relationships represent a core feature of BPD (Gunderson, 2007). Patients with BPD tend to establish unstable relationships, characterised by the unrealistic fear of abandonment (Gunderson et al., 2018) and difficulties in social adjustment (Soloff & Fabio, 2008). In BPD, experiences of rejection increase the risk of maladaptive emotional reactions, (Welch & Linehan, 2002), suicide attempts (Brodsky et al., 2006) and substance use (Seidl et al., 2020).

Increasing evidence suggests that BPD patients emotionally react as if they were rejected even in objectively-including social scenarios, thus exhibiting a biased view of the others as rejecting (Staebler et al., 2011a; 2011b; Renneberg et al., 2012). This social-cognitive pattern likely fosters the interpersonal difficulties associated with the disorder. For instance, studies using Cyberball, a virtual ball-tossing game that reproduces different levels of social inclusion by manipulating the percentage of passages the participants receive by two other co-players (Williams, Cheung & Choi, 2000; Williams & Jarvis, 2006; Renneberg et al., 2012; Staebler et al., 2011b; De Panfilis et al., 2015), showed that BPD patients, compared to healthy controls, feel more threatened in their need to belong not only when ostracized but also when fairly included (Gutz et al., 2015; Gratz et al., 2013; Jobst et al., 2014; Gerra et al, 2021). Furthermore, after both conditions, they report higher levels of negative affects (Domsalla et al., 2014; De Panfilis et al., 2015) and greater negative emotions toward others (Gutz et al., 2016) than non-BPD controls. Only a Cyberball overinclusion condition, where the participants are more-than-normally included by others, leads BPD patients to report levels of negative emotions that are comparable to those reported by healthy controls. However, even when overincluded BPD patients feel more socially disconnected than controls (De Panfilis et al., 2015; Weinbrecht et al., 2018).

Functional neuroimaging studies identified a specific cerebral network involved in the regulation of the individuals' emotional and behavioural responses to social exclusion (Eisenberger et al., 2003). Social exclusion determines a pattern of activation of cerebral areas that are also involved in the processing of physical pain, including the rVLPFC, that plays a major role in the

successful regulation of social pain and of rejection-related emotions, such as anxiety and affective instability (Berkman & Lieberman, 2009; Onoda et al., 2010; He et al 2018). Consistently, an enhanced activation of this area negatively correlates with the intensity of self-reported social pain (Masten et al., 2012), while a lower activation characterizes individuals high on rejection sensitivity (Kross et al., 2007). Non-invasive neurostimulation studies also demonstrated that, among non-clinical healthy subjects, augmenting the excitability of the rVLPFC by means of anodal tDCS decreases social pain and aggressive reactions following the Cyberball ostracism condition (Riva et al., 2012; 2015a). Conversely, the down-regulation of the rVLPFC by means of cathodal tDCS increases the levels of negative emotions experienced following ostracism (Riva et al., 2015b). Furthermore, anodal tDCS stimulation of the rVLPFC decreased negative emotions ratings when people reappraised emotions specifically elicited by seeing images of social exclusion, but not general negative images (He et al., 2018; 2020; Zhang et al., 2019; see also paragraph 2.1).

Overall, these findings suggest that tDCS stimulation of the rVLPFC might potentially lead to a better regulation of rejection-related emotions in BPD as well. In BPD samples, non-invasive brain stimulation over the dlPFC and dmPFC, either in single or multiple sessions, reduced other important symptoms of BPD psychopathology, such as impulsivity and emotional dysregulation (Lisoni et al., 2020; Schulze et al., 2019, Calderòn-Moctezuma et al., 2020; see Lisoni et al, 2022 for a systematic review). However, no study yet evaluated BPD patients' emotional responses to anodal tDCS on rVLPFC following social exclusion, inclusion and overinclusion.

This study evaluated whether, in a sample of BPD patients, the anodal tDCS of the rVLPFC, as compared to a sham stimulation, modulated rejection-related emotions, threats to fundamental needs, social pain and aggressive tendencies after the Cyberball conditions of social inclusion, exclusion and overinclusion. Buiding on previous evidence (De Panfilis et al., 2015; Weinbrecth et al., 2018), we hypothesised that the real tDCS stimulation would lead to a decrease in rejection-related emotions, threat to the need to belong, aggressive reactions and social pain not only after ostracism but also after fair social inclusion.

6.2.2 Methods

Participants

Participants were forty BDP patients (36 females, mean age = 33.35; sd = 13.24) recruited among outpatients seeking treatment at the Department of Mental Health and Pathological Dependencies of Parma Local Health Agency.

Included patients aged between 18 and 65 years and with a BPD diagnosis according to DSM-5 (APA, 2013) criteria, as established by the Structured Clinical Interview for DSM-5, Personality Disorders (SCID-5-PD; First et al., 2016). Patients were excluded if they a) had a diagnosis of psychosis, active bipolar disorder or substance dependence, assessed through the Structured Clinical Interview for DSM-5, Clinician version (SCID-5-CV; First et al., 2016); b) had a cognitive impairment, based on clinical judgement; c) met the exclusion criteria for tDCS stimulation (unstable medical conditions; neurologic or heart diseases; presence of metallic implants, pacemakers or acoustic prostheses) (Nitsche et al., 2008); d) participated to previous study using Cyberball. Potentially eligible participants participated in an assessment meeting in which received a formal screening to determine their eligibility for the study by a senior-level psychiatry resident, who was blind to the patients' randomization.

Written informed consent was obtained from all patients prior to inclusion in the study, which was approved by the local ethics committee (Department of Mental Health and Pathological Dependencies of Parma Local Health Agency) and conducted following the ethical standards of the revised Helsinki Declaration.

Baseline measures

At the end of the first meeting, the included patients filled demographic information (i.e., age, gender, educational level, work, and marital status) and the following self-report questionnaires assessing baseline characteristics:

The *Inventory of Personality Organization* (IPO; Lenzenweger et al., 2001; Prunas et al., 2012), a 57-item questionnaire (1 to 5 Likert scale), that measures instability of sense of Self and Other, instability of goals, instability of behaviors, and psychosis.

The *Effortful Control Scale* (ECS) of the *Adult Temperament* (Evans & Rothbart, 2007), a 19-item questionnaire (1 to 7 Likert scale), that measures effortful control.

The *Difficulties in Emotion Regulation Scale* (DERS; Gratz & Roemer, 2004), a 36-item questionnaire (1 to 5 Likert scale), that assesses multiple aspects of emotional dysregulation (see also paragraph 3.2).

The *Acceptance and Action Questionnaire* (AAQ-II; Bond et al., 2011), a 7-item questionnaire (1 to 7 Likert scale), that measures the willingness to experience unwanted private events in the pursuit of one's values and goals.

The *Justice Sensitivity Questionnaire* (JSQ; Schmitt et al., 2005; 2010), a 40-item questionnaire (1 to 5 Likert scale), that assesses victim sensitivity, beneficiary sensitivity, perpetrator sensitivity, and observer sensitivity.

The *Adult Rejection Sensitivity Questionnaire* (A-RSQ; Berenson et al., 2009), a 27-item questionnaire (1 to 6 Likert scale), that evaluates anxious and angry expectations about being accepted or rejected by significant others in social interactions.

In a separate appointment, patients participated in the tDCS protocol and then in a modified Cyberball experiment.

TDCS protocol

Participants were randomized in a 1:1 ratio to receive sham (20 patients) or active tDCS (20 patients) respectively. Randomization was performed based on the order of entrance in the study using a randomization list previously generated.

Transcranial direct current stimulation was delivered through a battery-driven stimulator (BrainStim, EMS, Bologna, Italy) by placing in the scalp a pair of electrodes covered by sponges soaked in saline solution and delivered. A constant current of 1,5 mA was applied to the rVLPFC (F6, 10-20 international system; MNI coordinates: 58, 30, 8; Onoda et al., 2010) for 20 minutes. An intracefalic montage was used with the anode (25 cm2, current density of 0.06 mA/cm2) placed on the target area and the cathode (35 cm2, current density of 0.042 mA/cm2) placed on the controlateral supraorbital region. In the anodal (active) stimulation the current remained constant for 20 minutes with 30 seconds of rump-in/out. In the sham stimulation the electrical current was applied only for 20 seconds at the beginning and at the end of the stimulation period expected for real tDCS. Therefore, to keep blinding about the group assignment, in both conditions, participants felt the same physical sensations (e.g., itching sensation) at the beginning and at the end of the

stimulation period, but in the sham condition the stimulation was substantially ineffective (Gandiga et al., 2006; Nitsche et al., 2008). TDCS was delivered by investigators, who were blind to the stimulation groups by specific numerical codes pre-programmed by researchers not directly involved in the experimental session.

Modified Cyberball experiment

Five minutes before the end of the stimulation, patients took part in a modified version of Cyberball, in which were invited to take turns throwing a ball with two other players, actually computer-controlled confederate players, told to be in another experimental room connected online with the Cyberball game. In this study, patients were first included, receiving the ball for roughly 33% of the total throws, then ostracized, receiving the ball for roughly 10% of the total throws, and finally over-included, receiving the ball for roughly 45% of the total throws, that is, more times than what would be expected in a fair game.

As a manipulation check, after each Cyberball condition, patients rated the percentage of throws (0 –100%) they received during the game as well as how they felt excluded and ignored (ranging from 1= *not at all* to 7= *extremely*) during Cyberball.

Measures of emotional reactions to Cyberball

Right after each Cyberball conditions, patients self-reported their negative emotions, filling the Rejected-Related Emotions Scale (RES; Buckley et al, 2004), their threatened basic psychological needs, by filling the Need-Threat Scale (NTS; Williams, 2009), their temptation to act aggressively, by filling the Aggressive Temptation Scale (ATS; Allen & Leary, 2010), and their perceived social pain, by filling the Pain Face Scale (Wong & Baker, 2001) (for a detailed description of the scales see paragraphs 3.1).

At the end of the experiment, patients were extensively debriefed about the study protocol and purposes.

Data Analysis

Data were analysed through the SPSS Statistics (Version 27.0). Baseline comparisons between the two study groups (real vs sham tDCS) were analysed using $\chi 2$, Fisher's exact, and Student's t tests. Changes in participants' reactions to the Cyberball game after either real or sham tDCS over rVLPFC were tested using a repeated-measure mixed model 2 X 3 analysis of variance (ANOVA), with stimulation condition (2 levels: real vs sham) as between-subject factor and Cyberball condition (3 levels: inclusion, exclusion and overinclusion) as within-subject factor. Fisher's Least Significant Difference (LSD) was used for post hoc comparisons.

6.2.3 Results

Preliminary analyses

Sample Characteristics

Regarding baseline measures, patients randomised to receive real tDCS showed less instability of behaviors (2.36 ± .97) at the baseline as compared with patients randomised to receive sham tDCS [(2.98 ± .84), t(35) = 2.08, p = .05]. No other significant differences were found between the two study groups (see Table 7).

Table 7. Descriptive characteristics of study groups			
	Real group (n = 20)	**Shamgroup(n = 20)**	**p Value**
Age	34.25 (±15.35)	32.45 (±11.05)	.67*
Male (n)	2	2	1†
Female (n)	18	18	
Occupational status			
Student (n)	7	7	.77ᵀ
Employed (n)	9	9	
Unemployed(n)	4	3	
Retired (n)	0	1	
Psychiatriccomorbilities			
Clinical disorders (n)	10	8	.38†
No clinical disorder (n)	10	12	
Personalitydisoders (n)	3	6	.23†
No personalitydisorders (n)	17	14	
Pharmacotherapy yes	18	19	1†
Pharmacotherapy no	2	1	
IPO			
Instability of sense of self/other	3.08 (± .89)	3.55 (± .78)	.10*
Instability of goals	3.16 (± 1.30)	3.44 (± 1.12)	.48*
Instability of behaviors	2.36 (± .97)	2.98 (± .84)	.05*
Psychosis	1.83 (± .56)	2.25 (± .81)	.09*
ECS (total)	4.07 (±1.11)	3.56 (±.82)	.12*
DERS (total)	55.89 (± 14.36)	61.39 (± 11.17)	.20*
AAQ-II (total)	33.58 (±11.30)	35.17 (±11.17)	.67*
JSQ			
victimsensitivity	3.08 (±1.09)	3.63 (±1.37)	.19*
beneficiarysensitivity	3.05 (±.97)	2.66 (±1.24)	.30*
perpetrator sensitivity	3.82 (± .91)	3.32 (±1.37)	.20*
observersensitivity	3.20 (±1.10)	3.11 (±1.46)	.84*
A-RSQ			
anxiousexpectations	11.73 (±5.29)	10.01 (±4.31)	.29*
angryexpectations	7.43 (±4.00)	7.77 (±2.93)	.76*

Values are mean (SD) or n where specified.

*Student's t test for independent samples.

† Fisher's exact test.

ᵀ $\chi 2$ test.

List of acronyms: IPO, Inventory of Personality Organization; ECS (total), Effortful Control Scale (total score); DERS (total), Difficulties in Emotion Regulation Scale (total score); AAQ-II (total), Acceptance and Action Questionnaire (total score); JSQ, Justice Sensitivity Questionnaire; A-RSQ, Adult Rejection Sensitivity Questionnaire.

Manipulation check

ANOVA found a significant effect of the Cyberball condition on ratings of percentage of throws received [F(2, 76) = 105.5, p = .00, ηp2 = .74] and on feelings of being ignored and excluded [F(2, 76) = 160.11, p = .00, ηp2 = .81]. As expected, patients reported different percentage of throws (ostracism 5.53 ± 2.35; inclusion 25.25 ± 1.89; overinclusion 62.20 ± 4,34; p > .001) as well as different ratings of feeling ignored and excluded (ostracism 6.23 ± .23; inclusion 2.7 ± .24; overinclusion 1.38 ± .16; p > .001) across all the three Cyberball conditions. Therefore, the Cyberball manipulation was successful.

Primary analysis

Rejection-related emotions

The ANOVA showed a significant main effect of Cyberball condition for the RES Overall index [F(2, 76) = 53.23, *p* = .00, ηp2 = .58], "anger" [*F*(2, 76) = 28.87, *p* = .00, η_{p^2}= .43], "anxiety" [F(2, 76) = 14.61, *p* = .00, η_{p^2} = .28], "sadness" [F(2, 76) = 20.32, *p* = .00, η_{p^2} = .35], "rejection" [F(2, 76) = 76.32, *p* = .00, η_{p^2} = .67], and "hurt" [F(2, 76) = 19.22, *p* = .00, η_{p^2} = .37] subscales of RES, with higher negative emotions following exclusion as compared to inclusion and overinclusion conditions (see Table 8).

There was also a significant main effect of tDCS condition for the RES Overall index [F(1, 38) = 5.63, *p* = .02, η_{p^2} = .13], "anger" [*F*(1, 38) = 6.35, *p* = .00, η_{p^2}= .14], "anxiety" [F(1, 38) = 3.99, *p* = .05, η_{p^2} = .10], and "sadness" [F(1, 38) = 5.19, *p* = .03, η_{p^2} = .12] subscales of RES, with patients who received real stimulation experiencing less negative emotions than patients who received sham stimulation (see Table 8). No main effect of tDCS was found for the "rejection" subscale of RES (*p* = .22).

For the RES Overall index, the ANOVA showed a significant Cyberball x tDCS interaction [F(2, 76) = 4.14, *p* = .02, η_{p^2} = .09]. As shown in Figure 26, patients in the real group, as compared to patients in the sham group, reported less negative emotions in both inclusion (*p* = .008) and exclusion (*p* = .024) conditions, while the two groups did not differ in the overinclusion condition (*p* = .66). The same results were found by the significant Cyberball x tDCS interaction for the "anger" subscale of the RES [F(2, 76) = 5.08, *p* = .01, η_{p^2} = .12] (see Figure 27).

Looking at the "rejection" subscale of the RES, the ANOVA showed a significant Cyberball x tDCS interaction [$F(2, 76) = 3.26$, $p = .04$, $\eta_{p^2} = .08$]. Pairwise comparisons showed that feelings of rejection were lower after the real, compared to sham, stimulation only in the inclusion condition, while patients of the two study groups reported comparable levels of rejection feeling when excluded and overincluded (Figure 28).

Considering scores of the "sadness" subscale of the RES, ANOVA unveiled a significant Cyberball x tDCS interaction [$F(2, 76) = 3.79$, $p = .03$, $\eta_{p^2} = .09$]. As shown in Figure 29, following social exclusion, patients in the real group reported lower levels of sadness than those in the sham group ($p = .012$). The two study groups did not differ for the Cyberball inclusion and overinclusion conditions.

No significant Cyberball x tDCS interaction was observed for scores of "hurt" and "anxiety" subscales of RES ($p > .05$) (see Table 8 for means and standard deviations).

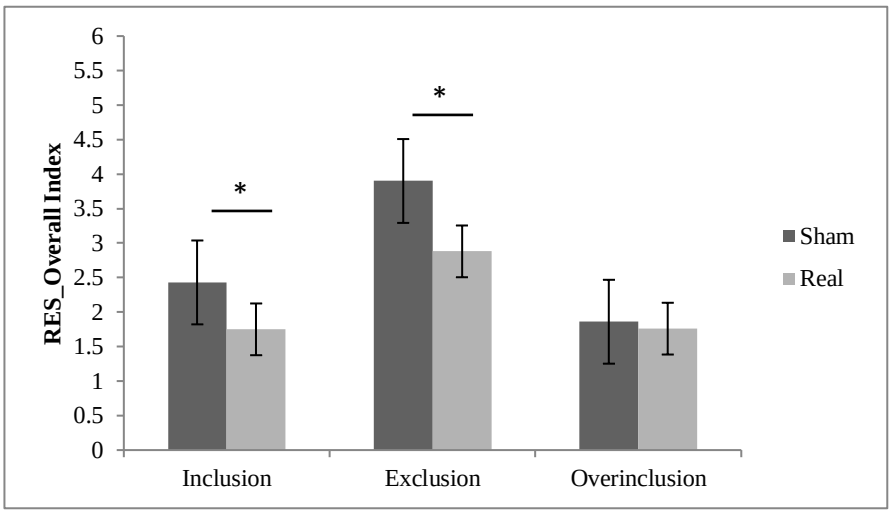


Figure 26. The figure shows the Cyberball x tDCS interaction for overall index of negative emotions as measured by the RES questionnaire.

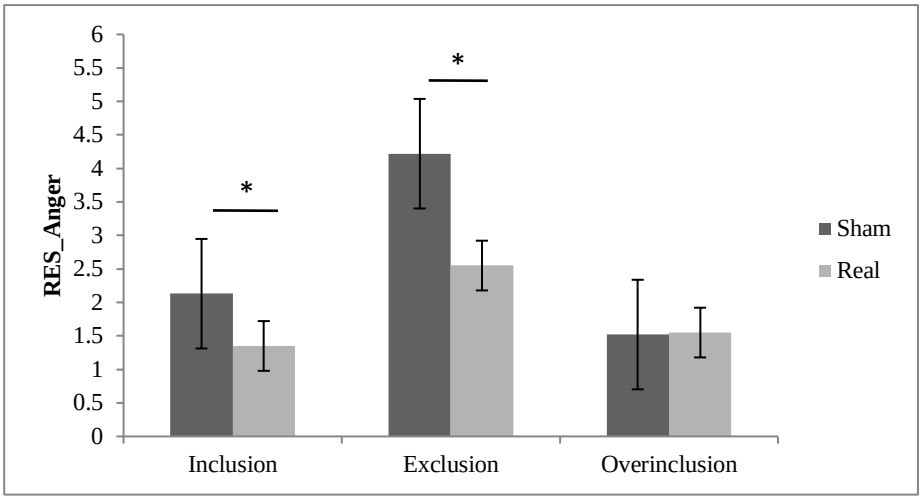


Figure 27. The figure shows the Cyberball x tDCS interaction for the "anger" subscale of the RES questionnaire.

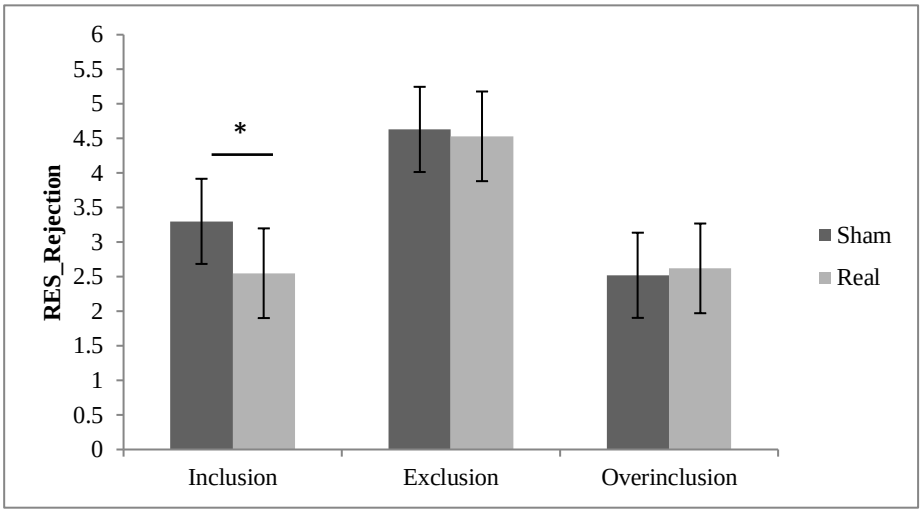


Figure 28. The figure shows the Cyberball x tDCS interaction for the "rejection" subscale of the RES questionnaire.

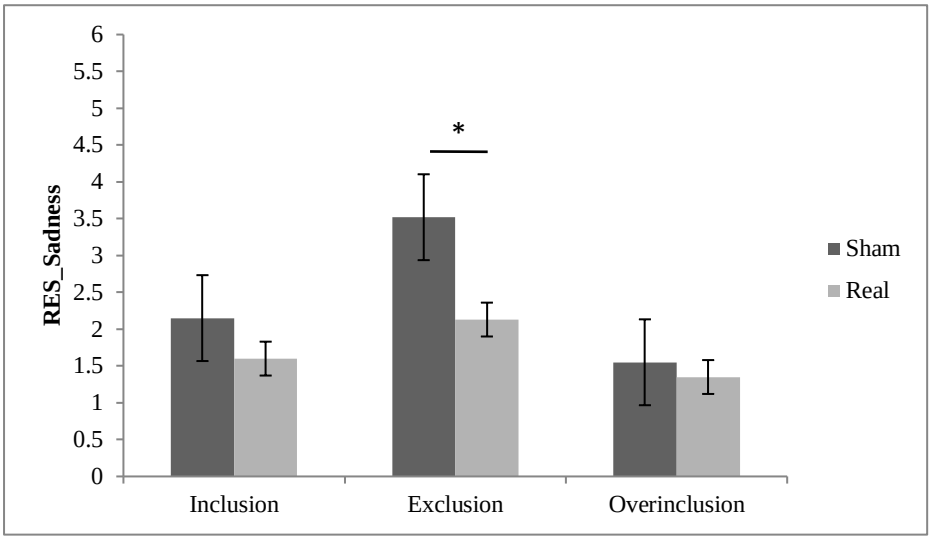


Figure 29. The figure shows the Cyberball x tDCS interaction for the "sadness" subscale of the RES questionnaire.

Threats to the needs to belong

For NTS scores, ANOVA found a main effect for Cyberball condition [$F(2, 76) = 84.43$, $p = .00$, $\eta_{p^2} = .69$]. Post hoc comparisons showed that the perceived threats to the needs to belong differed across all the three Cyberball conditions, with with overinclusion < inclusion < exclusion.

The main effect was qualified by a significant Cyberball x tDCS interaction [$F(2, 76) = 3.55$, $p = .03$, $\eta_{p^2} = .09$]. As shown in Figure 30, post hoc comparisons showed that the two study groups significantly differed in the exclusion condition, with real group reporting lower scores than the sham group ($p = .05$) (see Table 8). The real group reported lower scores as compared to the sham group also after inclusion condition, but the difference only tended to significance ($p = .06$).

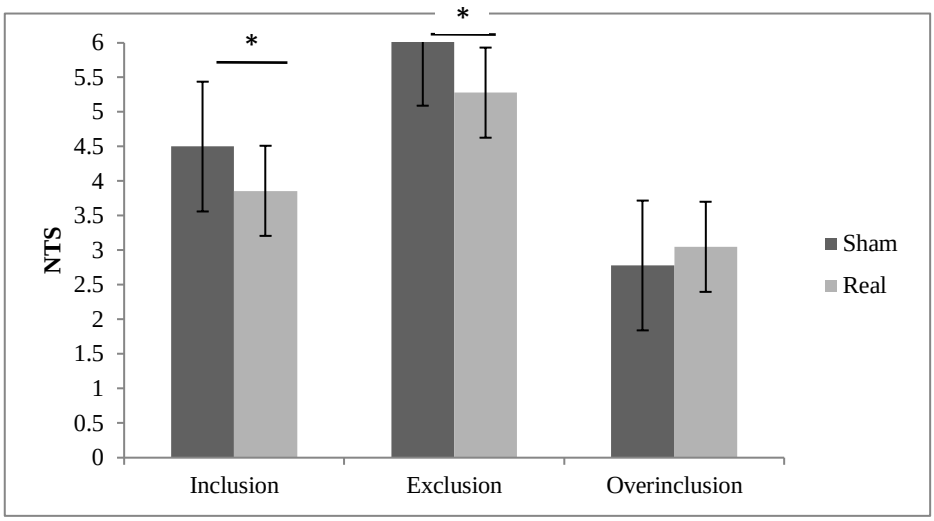


Figure 30. The figure shows the Cyberball x tDCS interaction for the NTS questionnaire.

Perceived pain

For Pain Face score, ANOVA found a main effect of Cyberball condition [$F(2, 76) = 21.39$, $p = .00$, $\eta_{p^2} = .36$], with pain scores that were higher in the ostracism condition as compared with the inclusion and overinclusion, but did not differ between the inclusion and the overinclusion conditions ($p = .17$). No other main or interaction effects were found ($p > .05$).

Aggressive temptations

For ATS scores, ANOVA found a main effect of Cyberball condition (ATS prosocial behaviors: [$F(2, 76) = 17.85$, $p = .00$, $\eta_{p^2} = .32$]; ATS aggressive behaviors [$F(2, 76) = 21.92$, $p = .00$, $\eta_{p^2} = .37$]), with prosocial behaviors scores that were lower in the ostracism condition as compared with the inclusion and overinclusion but did not differ between the inclusion and the overinclusion conditions ($p = .31$). Similarly, temptation to engage in aggressive behaviors was higher in the ostracism condition compared to the inclusion and overinclusion, while did not differ between the inclusion and the overinclusion conditions ($p = 1$). No other main or interaction effects were found ($p > .05$).

Table 8. Means, standard deviation, F values and their associated p-values.

	Real tDCS (n=20)			Sham tDCS (n=20)					
	Inclusion	**Exclusion**	**Overinclusion**	**Inclusion**	**Exclusion**	**Overinclusion**	**Cyberball**	**tDCS**	**Cyberball X tDCS**
RES Overall index	1.75 (.17)	2.88 (.31)	1.76 (.16)	2.43 (.17)	3.90 (.31)	1.86 (.16)	F=53.23 **p<.00**	F=5.63 **p=.02**	F=4.14 **p=.02**
RES Anger	1.35 (.21)	2.55 (.44)	1.55 (.25)	2.13 (.21)	4.22 (.44)	1.52 (.25)	F=28.87 **p<.00**	F=6.35 **p=.02**	F=5.08 **p=.01**
RES Rejection	2.55 (.23)	4.53 (.23)	2.62 (.12)	3.30 (.23)	4.63 (.23)	2.52 (.12)	F=76.32 **p<.00**	F=1.54 p=.22	F=3.26 **p=.04**
RES Sadness	1.60 (.26)	2.13 (.37)	1.35 (.19)	2.15 (.26)	3.52 (.37)	1.55 (.19)	F=20.32 **p<.00**	F=5.19 **p=.03**	F=3.79 **p=.03**
RES Anxiety	1.85 (.28)	3.02 (.40)	1.97 (.36)	2.85 (.28)	3.92 (.40)	2.45 (.36)	F=14.61 **p<.00**	F=3.99 **p=.05**	F=.58 p=.56
RES Hurt	1.38 (.21)	2.15 (.43)	1.32 (.15)	1.73 (.21)	3.23 (.43)	1.25 (.15)	F=19.22 **p<.00**	F=2.25 p=.14	F=2.92 p=.06
Pain Face Scale	1.45 (.24)	2.00 (.34)	0.85 (.23)	1.25 (.24)	2.85 (.34)	1.15 (.23)	F=21.39 **p<.00**	F=1.24 P=.27	F=2.68 P=.08
ATS Prosocial	4.52 (.43)	3.25 (.44)	4.95 (.47)	4.23 (.43)	2.55 (.44)	4.37 (.47)	F=17.85 **p<.00**	F=1.02 p=.32	F=.23 p=.79
ATS Aggressive	1.63 (.22)	2.47 (.39)	1.28 (.24)	1.58 (.22)	3.13 (.39)	1.63 (.24)	F=21.92 **p<.00**	F=.99 p=.33	F=1.21 p=.38
NTS	3.86 (.24)	5.28 (.26)	3.05 (.21)	4.50 (.24)	6.03 (.26)	2.78 (.21)	F=84.43 **p<.00**	F=2.63 P=.11	F=3.55 **p=.03**

Notes. Degrees of freedom were 1, 76 for the main effect of Cyberball and Cyberball x tDCS interaction, and 1, 38 for the main effect of tDCS. P-values of significant effects and interactions are in bold.
List of acronyms: RES, Rejection Emotion Scale; ATS, Aggression Temptation Scale; NTS, Need-Threat Scale.

6.2.4 Discussion

This study tested the modulatory effect of anodal tDCS applied to the rVLPFC on reactions to social exclusion of BPD patients. Forty BPD patients were exposed to 20 minutes of either anodal or sham stimulation and after stimulation rated rejection-related emotions, aggressive reactions, threats to the need to belong and social pain felt during a modified version of Cyberball paradigm involving an inclusion, exclusion and an overinclusion condition.

In line with the hypothesis, results showed that only patients receiving the anodal stimulation of the rVLPFC reported decreased overall level of rejection-related emotions, in particulal anger, not only following ostracism, but also following normal inclusion, which otherwise would lead them to report RES scores comparable to those experienced following ostracism. Indeed, the group receiving sham tDCS reported lower rejection-related emotions and anger only after overinclusion.

Our findings first confirm the specific role of the rVLPFC in mediating negative emotions. Indeed, in the present study, no effects were found in the overinclusion condition, that was associated to the lowest levels of reported negative emotions. Consistently, previous studies (see for instance Vergallito et al., 2018) showed the involvement of the rVLPFC when negative, but not positive, emotions were elicited by film video clips (see Berkman & Lieberman, 2009 for a review) or when negative facial expressions were presented in a go/no-go task (Berkman et al., 2009).

Furthermore, the findings of the present study corroborate the evidence that the regulatory function of rVLPFC over the negative emotions can be effectively modulated by the application of non-invasive brain stimulation, and in particular of the tDCS (see Vergallito et al., 2018). This is particularly important considering the possibility of applying tDCS in BPD patients with the same level of efficacy that was reported by previous studies on healthy groups (Riva et al., 2012; 2015a; 2015b). This, in turn, could pave the way for the use of tDCS protocols as adjuvant treatments to be added to the classical therapies for BPD patients. Interestingly, building on our findings, the neuromodulation protocols could target not only BPDs' negative emotions but also other and more complex reactions to social exclusion and inclusion, such as the perceived threats to the need to belong. Indeed, the results of this study showed that the real tDCS applied over the rVLPFC might improve the patients' need to belong following both exclusion and inclusion experiences, even though the finding about the inclusion condition only tended to significance.

Second, the result that also the inclusion condition increased patients' negative emotions corroborates previous studies (Weinbrecth et al., 2018, Gutz et al., 2015) showing enhanced P3

amplitude, an indicator for expectancy violation, in BPD patients, compared to healthy controls and patients with social anxiety disorder, even in the inclusion condition of the Cyberball game. These results, together with those of our study, support the hypothesis that patients with BPD are characterised by a biased perception and processing of social inclusion (Gutz et al., 2015; Renneberg et al., 2012; Lis & Bohus, 2013), so that their idealised expectations for fair levels of inclusion can be satisfied only by overinclusion conditions (De Panfilis et al, 2015).

Regarding aggressive reactions, patients of the present study reported a greater temptation to engage in aggressive behaviors following ostracism compared to the inclusion and overinclusion conditions. This result is consistent with studies that showed that BPD patients, compared to other psychiatric patients, are characterised by an increased tendency to aggression and verbal complaints following social exclusion (Gutz et al., 2016). However, unexpectedly, we did not find a tDCS effect on patients' aggressive tendencies.

In my opinion, different explanations might account for this null effect. One possibility is that one single tDCS session could be not enough to observe effects on aggression in BPD patients. Indeed, studies applying one session rVLPFC tDCS to modulate responses to images of social exclusion found that tDCS was ineffective in people high in depressive symptoms compared to people low in depressive symptoms (Zhang et al., 2019; He et al., 2019). It might be the case that the well known neural alterations of social interaction shared by patients with BPD and with major depression (Kupferberg et al., 2016; Liu et al., 2014; Malejko et al., 2018) limit the tDCS effects, especially with single delivery. Therefore, to investigate this point, further studies involving multiple stimulation sessions protocols are needed.

Second, it is well known that the brain regulatory functions are strongly asymmetrical at the prefrontal level, with the so called approach motivations, including behavioral aggression, related to greater left than right frontal activity (Sutton & Davidson, 1997; Harmon-Jones & Allen, 1997; Harmon-Jones et al., 2006; Peterson et al., 2011). Building on these evidence, in a study by our research group (published in 2020 in Brain Stimulation journal and presenred in paragraph 6.1 of the present thesis), we found that the anodal tDCS of the lVLPFC increased aggression when healthy subjects were required to aggressively behave after a frustration task (Gallucci et al., 2020). Therefore, future studies could explore effects on aggressive reactions to social exclusion when cathodal tDCS, known to reduce the neural excitability of cortical neurons, is applied on the left rather than the right VLPFC of BPD patients. Alternatively, studies could test modulatory effects of brain stimulation delivered to other prefrontal areas, such as the dorso-lateral prefrontal cortex,

that were found to be most involved in modulating cognitive control and impulsivity after ostracism (Phillips et al., 2003; Berkman & Lieberman, 2009).

Another possibility is that the strong temptation to engage in aggressive behaviors we found after ostracism could conceivably be a possible ceiling effect for patients, nullifying any modulatory tDCS effects. However, this hypothesis should be considered with caution. Indeed, in our study, we did not include a group of healthy controls, preventing us from comparing patients' and controls' aggressive reactions to ostracism. Future studies involving BPD patients and healthy volunteers could further explore this point.

Finally, considering our baseline measures, our study groups were not totally balanced. Indeed, patients in the real group, compared to those in the sham group, were characterised by less behaviors instability. Therefore, this could have influenced the modulatory effects we tested by means of tDCS.

This study has some limitations. First, we included BDP patients treated with psychotropic drugs, known to have possible confounding effects on tDCS outcomes (McLaren et al., 2018). In this study, comparisons between the two study groups showed no significant differences regarding the number of subjects who were or were not taking medications. However, it is not possible to totally rule out that medications somehow interfered with the tDCS effects.

Moreover, the tDCS modulating effect of reactions to both exclusion and inclusion conditions was not consistent neither for all the RES subscales nor for scores of perceived social pain and threats to the need to belong. One possible explanation could be related to the stimulation protocol used in the present study that included only one tDCS session. Indeed, the systematic review by Lisoni et al. (2022) underlied that, across studies applying rTMS and tDCS, improvements in BPD symptomatology became more evident and robust as the number of stimulation sessions increased (Sverak et al., 2018; Reyes-López et al., 2017; Molavi et al., 2020; Lisoni et al., 2020; Rachid, 2019). In particular, single stimulation sessions could be not enough to modulate the perceived threatened need to belong that, being reported also following experiences of extreme inclusion (Weinbrecth et al., 2018), might be a core and more stable feature of BPD psychopathology.

Despite the limits, the results of the present study suggest that tDCS applied to the rVLPFC specifically modulates negative emotional reactions of BPD patients to ostracisms and to fair including social environments. If confirmed, these findings may support the use of tDCS

as a targeted therapeutic approach in promoting appropriate regulation of emotions arising from social contexts in patients with BPD.

General conclusion and future directions

During the PhD I focused my research on studying emotions' regulation, which plays a critical role for the maintenance of mental health and well-being, and undergoes relevant changes across the lifespan. More in detail, my interest was directed to explore whether and how the cognitive control could be alterated in the context of potentially interfering emotional information, and how emotional and cognitive processes explicitely and implicitely interact to affect emotions' regulation.

Emotions' regulation is a complex and heterogeneous construct that encompasses several behavioral and neurobiological processes. This complexity has contributed to the first challenge of finding a shared difinition of emotions' regulation. Building on evidence emerging from the several cognitive and neurocognitive models of emotions' regulation, I think that future research in this field could first shed light on the common and nonspecific factors as well as motives (implicit, psychological, social) that mediate and drive emotions' regulation. Expanding this research could also provide interesting insights on the explicit and implicit strategies fostering effective emotions' regulation. Indeed, the main point supported by this thesis is that both these classes of strategies are important to prevent deficits in emotions' regulation. Second, research could clarify how to define and recognize cases of emotions' dysregulation. Indeed, considered as a transdiagnostic factor across different disorders, emotions' dysregulation can affect how the emotions are generated, or how they are hyper- or down-regulated by failures of effective regulation strategies, or even how they are expressed at neurophysiological, psychological and behavioural level. Third, future research could add evidence about the measurement of emotions' (dys)regulation processes. Indeed, despite in the last decades affective sciences have worked to explore the potential of experimental procedures for explicitely and/or implicitely studying emotions' regulation, more research toward this direction is needed.

Regarding this, during my PhD, I have directly tested the efficacy of explicit regulation strategies, namely reappraisal and distraction, on emotional reactions to an experience of social exclusion in a sample of healthy participants. The results were promising as they add evidence about the processing of social exclusion as a salient stimulus for survival and about the potential efficacy of bottom-up, less cognitive, regulation strategies. However, future research should deepen these findings by testing whether also implicit mechamisms could interfere with the processing of instances of social exclusion and with the people's abilities to regulate their emotional reactions to ostracism.

Actually, my PhD has also contributed to the study of implicit regulation. Indeed, part of my research was dedicated to the application of an implicit paradigm, that is an emotional version of the standard go/no-go task, to study whether and how emotional information, in particular facial expressions, implicitely interfere with the cognitive task performance. The results of the two experiments I conducted, the first on a group of healthy participants and the second on a group of righ- or left-brain damaged patients and their orthopedic controls, consistently converge with previous literature about the advantage of processing positive (i.e., happy) over negative facial expressions and opened new perspectives about how humans deal with fear-related stimuli. This, in turn, supports the body of literature that depicts fear as a general organizing principle of cognitive processes and behaviors. Moreover, the results I collected provide some suggestions about how emotions' regulation abilities interfere with the processing of emotional information during the execution of the cognitive task. However, this finding was not consistent across the two experiments, which also provide opposite results regarding the impact of dealing with emotional faces on cognitive *response bias*. Therefore, I think that these limits should be addressed by future studies on greater samples that, by using alternative versions of the emotional go/no-go task, could: a) better disentangle between emotions' regulation and perception processes elicited by the cognitive task; b) test possible differences related to the side of the brain lesion; c) deeply explore the role of abilities to regulate emotions and symptoms of emotions' dysregulation.

Based on the results I obtained from these behavioural experiments, another part of my PhD aimed at studying the neural correlates underlying explicit and implicit emotions' regulation processes and testing the feasibility of applying non-invasive brain stimulation techniques to modulate emotions' regulation abilities. Therefore, building on the findings of a narrative review I conducted on the use of NIBS for improving self-regulation (cognitive, emotional and behavioral domain) and goal-direct behaviours (published in 2019 in Frontiers in Behavioral Neuroscience journal), I run a systematic review and meta-analysis that provides promising results about the efficacy of NIBS in the specific filed of explicit and implicit emotions' regulation. However, due to the limited number of studies included, the results of the meta-analysis should be considerd preliminary. In my opinion, future works could further explore these findings, by clarifying the brain areas to target, the characteristics of effective NIBS protocols, the factors that moderate the NIBS effects, the findings of concurrent measures of brain activity and, last but not least, efficacy on emotions' regulation when NIBS is applied on healthy groups or clinical samples.

Regarding this latter point, the last part of this thesis presents the results of two experiments in which I tested whether and how the transcranial direct current stimulation of the ventrolateral

prefrontal cortex affects frustration-induced aggression in a group of healthy participants (paper published in 2020 in Brain Stimulation journal) and negative emotional reactions to social exclusion in a group of patients with a diagnosis of borderline personality disorder. The results of these two experiments extend previous research on the specific role of the vlPFC in the modulation of emotions' and self-regulation processes, contributing to the knowledge about their neural underpinnings. More in detail, the study on healthy participants reveals interesting insights about gender differences in the frustration-induced aggression. Regarding the study on borderline personality disorder patients, results showed that the stimulation of the right portion of the vlPFC reduces rejection-related emotions, including the perceived threat to the need to belong, that patients reported not only after exclusion but also after fair inclusion. This novel result suggests that the non-invasive brain stimulation of the rVLPFC effectively modulates the biased perception and processing of social inclusion that characterizes borderline personality disorder patients. I think that this finding crucially opens the way for the use of brain stimulation protocols as adjuvant treatments to be added to the classical therapies for borderline patients and, more in general, for patients with emotional regulation disorders.

However, despite these promising results, the possibility of using brain stimulation to target aggression with therapeutic purposes should be considered with caution. Indeed, both studies did not find a reduction of aggressive reactions neither to frustration nor to social exclusion when tDCS is applied on the rVLPFC. This null stimulation effect on the one hand underlines the importance to consider the asymmetry by which the regulatory functions are represented at the prefrontal level when building a stimulation protocol. On the other, it suggests the need for future studies testing different and multiple sessions stimulation protocols delivered to a wide range of prefrontal areas in controlled study conditions to gather more robust and consistent results.

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