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Criticism, self-esteem and the depressed brain: an experimental approach

Jonathan Remue

Promotor: Prof. dr. Rudi De Raedt

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CRITICISM, SELF-ESTEEM AND THE DEPRESSED BRAIN: AN EXPERIMENTAL APPROACH

Jonathan Remue

Guidance committee

Prof. Dr. Rudi De Raedt (promotor)
Department of Experimental Clinical and Health Psychology, Ghent University

Prof. Dr. Jill Hooley
Department of Psychology, Harvard University, Cambridge, MA, USA.

Prof. Dr. Chris Baeken
Department of Psychiatry and Medical Psychology, University Hospital Ghent (UZ Ghent), Ghent University

Prof. Dr. Marie-Anne Vanderhasselt
Department of Psychiatry and Medical Psychology, University Hospital Ghent (UZ Ghent), Ghent University

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Chase your dreams, cause they won't chase you, live your life, else it ain't living, dare to think and dreams will follow (Jonathan Remue, 2012, winning English poem, 'Dare To Think' campaign, UGent).

For a project on the impact of criticism and rumination on self-esteem, this quote is quit self-focused and (let's be honest) blatantly self-promotional to start with. Then again, the next pages will be all about how grateful I am to all the significant others (and who are we kidding also to the insignificant, like Igor for instance) in my journey through the academic wonderland… so why not start with a nice personal touch, slightly narcissistic, but mostly proud moment in these last few years at my alma mater!

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Jonathan
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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

PREFACE

Imagine two of my friends Tyler and Edward, who both just got scolded at by their respective bosses. Tyler reacts with an initial disappointment and mild discouragement, but quickly decides that the opinion of his boss is only one view, and feels determined that it shouldn’t affect his self-view or how he functions. Edward, however, feels personally criticized and starts worrying he is not the person he wants to, could or should be. Moreover, over time he becomes more and more self-critical, and feels stressed every time someone criticizes him, until finally, he cannot cope with it anymore and decides to see a clinical psychologist. Edward is diagnosed with depression. Now, why is it that Edward becomes depressed and Tyler does not? What are the underlying mechanisms of this vulnerability that might cause a different reaction of my two friends? Moreover, what is the relation between, being criticized, worrying and how Edward looks at himself? More importantly, could I have helped Edward if I had a better understanding of the underlying mechanisms that made him become depressed?

BACKGROUND: DEPRESSION

"*Depression is a prison where you are both the suffering prisoner and the cruel jailer*" (Dr. Dorothy Rowe, psychologist). In the last decades, the prevalence of mental illness has increased immensely, especially for mood disorders, such as depression (e.g., Wittchen et al., 2011). According to the World Health Organization (WHO, 2016) depression is worldwide a common illness, with an estimated 350 million people affected, and population estimates indicating a life-time prevalence of 19% in the United States (Kessler et al., 2009) and similar rates in Europe (Wittchen et al., 2011). This makes depression one of the most burdensome of mental disorders and the greatest single contributor of all disease burden in the European Union (Witcchen et al., 2011). It is not only associated with severe individual suffering, but also a heavy burden on the direct social environment, (mental) health services, and gives way to a substantial cost to society (Kessler et al., 2010; Gustavsson et al., 2011).

Depression is a mental disorder that not only affects our feelings, but also the way we perceive and think about ourselves and our environment. According to The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association [APA], 2013), a major depressive episode is characterized by the experience of negative mood and/or the loss of interest and pleasure in (almost) all activities most of the day and nearly every day. Additional symptoms described are, categorized as somatic, affective, and cognitive, including changes in sleeping and eating patterns, psychomotor agitation or retardation, fatigue or loss of energy, self-criticism, feelings of worthlessness, excessive or inappropriate guilt, concentration problems, indecisiveness, and recurrent thoughts of death or suicidal ideation (APA, 2013).

In spite of the correct use of pharmacological or psychotherapeutic approaches, a substantial number of patients become treatment resistant (up to 15%) (Burrows, Norman, & Judd, 1994; Fava, 2003). Although, pharmacological and psychological interventions show efficacy in the short term, there is a pressing need for improved long term effectiveness of treatments. This is especially true with regard to the prevention of recurrence. Many of these interventions have proven efficacy (Cuijpers et al., 2013) but relapse or recurrence rates are very high (Beshai, Dobson, Bockting, & Quigley, 2011). Numerous studies indicate that remitted patients have a 70% risk of developing new depressive episodes. Moreover, the risk of new episodes increases as a function of the number of previous episodes (Keller 2003). After multiple prior episodes of depression even minor stressors can become triggers for new depressive episodes (Monroe and Harkness 2005). Therefore, there is a dire need for a more comprehensive understanding of the underlying mechanisms that might lead to depression, and this by integrating both cognitive and neurobiological findings.

Hence, in facing the challenges of improving the understanding of depression it is clear that, given the heterogeneity of risk for depression (e.g., Kendler, Gatz, Gardner, & Pedersen, 2006), a wealth of different research strategies are required and need to be integrated in order to provide more solid answers on which pathogenic mechanisms should be targeted in order to more successfully treat depression (Koster et al., 2015).

CRITICISM AND DEPRESSION

Looking back at our protagonist Edward, it is clear that a strong trigger of his negative affect and negative self-referential thinking is interpersonal criticism. In everyday life this can be critique from your superior, getting negative feedback from a reviewer, or even harsh words in a fight with your girlfriend. Of course, the question is: "*did interpersonal criticism lead to depression in the case of Edward?*", and more specifically, "*which internal processes are involved?*".

Research has linked the coping with criticism to poor clinical outcomes in patients with such disorders as depression, alcohol dependence, post-traumatic stress disorder, and panic disorder and OCD (O'Farrell, Hooley, Fals-Stewart, Cutter, 1998; Tarrier, Sommerfield, Pilgrim, 1999; Chambless, Steketee, 1999). Although nobody likes to be criticized, for some people receiving criticism is especially problematic. Various studies have demonstrated the link between depression and sensitivity to criticism (e.g., Burcusa & Iacono, 2007; Hooley et al., 2009). Hooley and colleagues (2009) found that even after full recovery from an episode of major depression neural responses to criticism did not normalize. That is, when individuals who have recovered from depression are exposed to criticism, they specifically demonstrate decreased reactivity in the dorsolateral prefrontal cortex (DLPFC), which is a key region related to cognitive control processes, compared to never-depressed individuals (Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005; Hooley et al., 2009). Moreover, people who have had past episodes of depression are much more likely to relapse or show a recurrence of symptoms after recovery if they live in family environments that are characterized by high levels of criticism (Hooley, Orley & Teasdale, 1986; Vaughn & Leff, 1976).

Neuroimaging studies have indicated that a functional balance between ventral (ventral anterior cingulate cortex, ACC) and dorsal compartments in the brain (dorsal ACC and DLPFC) is necessary for maintaining homeostatic emotional control (Seminowicz et al., 2004; Johnstone et al., 2007; Ochsner and Gross, 2008; Wager et al., 2008). As such, many studies suggest that the DLPFC initiates emotion regulation by causing inhibition of the amygdala, a subcortical area involved in emotion processing (e.g., Siegle et al., 2007). Furthermore, being criticized is a distressing experience and activates self-conscious emotions (e.g., feeling hurt) and self-referential thinking (rumination), which need to be regulated to prevent maladaptive emotional responses to occur (e.g. Vanderhasselt, Remue, Ng, Mueller & De Raedt, 2015). Although these repetitive thoughts do not necessarily have unconstructive consequences (Watkins, 2008), depression vulnerable individuals have the tendency to focus their thoughts on negative information and self-referential content. It is therefore crucial to understand the mechanisms underlying the effects of critisism on self-evaluative ruminative thoughts, in order to prevent them from becoming unintentional and unconstructive, particularly in individuals who demonstrate a tendency to ruminate in everyday life.

LINK DEPRESSION AND CRITICISM: RUMINATION

Prior research has demonstrated that some of the most potent forms of stress are interpersonal and self-referential (Dickerson and Kemeny, 2004) - such as interpersonal criticism - a finding reflected in the self-focused content of rumination (Nolen-

Hoeksema, Wisco, & Lyubomirsky, 2008). Moreover, depression is associated with rumination about negative self-relevant information (Nolen-Hoeksema et al., 2008). According to the response styles theory (Nolen-Hoeksema, 1991; Nolen-Hoeksema et al., 2008), rumination is a mode of responding to distress that involves repetitively and passively focusing on symptoms of distress and on the possible causes and consequences of these symptoms. More specifically, it involves engaging in repetitive negative thinking about the self, emotions, and causes or consequences of emotions (Nolen-Hoeksema et al. 2008). Self-referential processing is the evaluation of information in relation to an individual's own mental concept of themselves (Christoff et al. 2011), while rumination is a form of self-referential processing, which is the process of relating information to the self (Nejad et al., 2013). The hypothesized mechanism is that individuals, when ruminating, focus on possible causes and consequences of their depressive feelings without engaging in active problem solving (Kuster et al., 2012). Thus, although the individual might assume he or she is getting closer to a solution by thoroughly thinking through his or her problem, rumination frequently impedes a solution because the individual remains passive (Nolen-Hoeksema et al., 2008). The content of ruminative thought in depressed people is typically negative in valence, similar to the automatic thoughts, schemas, and negative cognitive styles that have been studied extensively by cognitive theorists (e.g., Beck & Haigh, 2014). In addition, rumination is correlated with a variety of maladaptive cognitive styles, including negative inferential or attributional styles (Ciesla & Roberts, 2002), perfectionism (Flett, Madorsky, Hewitt, & Heisel, 2002), dysfunctional attitudes (Lyubomirsky, Tucker, Caldwell, & Berg, 1999), hopelessness (Robinson & Alloy, 2003), pessimism (Lyubomirsky & Nolen-Hoeksema, 1995), self-criticism (Lyubomirsky, Tucker, Caldwell, & Berg, 1999; Spasojevic & Alloy, 2001), low mastery (Nolen-Hoeksema & Jackson, 2001), dependency (Nolen-Hoeksema & Davis, 1999; Spasojevic & Alloy, 2001), sociotropy (Nolen-Hoeksema, Larson, & Grayson, 1999), neediness (Nolen-Hoeksema & Davis, 1999; Spasojevic & Alloy, 2001), and neuroticism (Lam, Smith, Checkley, Rijsdijk, & Sham, 2003) even after controlling for levels of depression (Lam et al., 2003; Nolen-Hoeksema et al., 1994; Nolen-Hoeksema, Parker, & Larson, 1999; Roberts, Gilboa, & Gotlib, 1998).

Importantly, rumination has been put forward as one of the most important underlying vulnerability factors for depression. Numerous prospective studies have documented that a ruminative response style predicts increases in depression (Abela, Brozina, & Haigh, 2002; Nolan, Roberts, & Gotlib, 1998; Nolen-Hoeksema, 1991, 2000; Nolen-Hoeksema, Larson, & Grayson, 1999; Nolen-Hoeksema, Morrow, & Fredrickson, 1993; Schwartz & Koenig, 1996; see also Rood, Roelofs, Bögels, Nolen-Hoeksema, & Schouten, 2009) and rumination is associated with depressive symptoms (Treynor et al. 2003) and prospectively with the onset (Nolen-Hoeksema 2000), severity (Just and Alloy 1997; Nolen-Hoeksema and Morrow 1991) and duration (Nolen-Hoeksema 2000) of depression. A meta-analysis by Mor and Winquist (2002), which summarized correlational and experimental data on the relation between self-focused attention and negative affect, confirmed the strong association between rumination and depression and suggested a reciprocal causal relation between the constructs. However, throughout the manuscript we will often refer to self-referential processing, thinking and thoughts as well as rumination. We clarify that we conceptualize rumination throughout this dissertation as self-referential thinking, that is, negatively thinking about oneself.

The ability to control ruminative thought is associated with recovery from depression (Kuehner and Weber 1999; Schmaling et al. 2002). Rumination is also associated with cognitive vulnerability, which is a central concept in cognitive theories of depression. This cognitive vulnerability idea suggests that negative cognitive factors emerge during stressful situations, and that cognitive reactivity, i.e., the ease with which particular patterns of negative thinking are reactivated in response to negative events, is critical for the onset, relapse, and recurrence of depression (Scher, Ingram, Segal, 2005). Moreover, rumination is also associated with cognitive reactivity, one of the crucial predictors of recurrent depression, even when depression levels were statistically controlled (Moulds et al. 2008). Even though most studies consider ruminative thinking as a trait characteristic, self-referent thoughts fluctuate continuously (especially in healthy individuals) and might provide valuable information to understand the development of a stable trait. To capture the effects of rumination, it may be crucial to include exposure to personally-relevant emotional stimuli that are consistent with the challenges an individual encounters in the real world (Davidson,

2010) and that are likely to evoke ruminative thoughts (self-referential thoughts). Prior research has demonstrated that the most potent forms of stress are interpersonal and self-referent (Dickerson and Kemeny, 2004), a finding reflected in the self-focused content of rumination (Nolen-Hoeksema et al., 2008).

LINK DEPRESSION AND CRITICISM: SELF-ESTEEM

With this in mind, with regard to our protagonist Edward we can ask the question: "*Can we link the interpersonal criticism to Edwards' self-views?*". Research has shown that the social context is an important aspect of the self as it relates to emotions (Hofmann, 2014). When you are criticized, the most common effect is that it can easily negatively self-views. Moreover, research has shown the detrimental impact of criticism on cognitive processing and thinking styles, such as rumination (e.g., Saffrey & Ehrenberg, 2007; Kaiser, Andrews-Hanna, Metcalf, & Dimidjian, 2015), and subsequently its effect on self-esteem (e.g. Weisbuch, Sinclair, Skorinko, & Eccleston, 2009). However, only cross-sectional evidence on the relation between rumination and self-esteem is available, suggesting that self-esteem is negatively correlated with rumination (Ciesla & Roberts, 2002, 2007; Joireman, 2004; Luyckx et al., 2008). Nonetheless, longitudinal or experimental study designs are required to draw conclusions about the direct link between rumination and self-esteem.

Although healthy individuals can regulate (i.e. cognitive control) criticism-induced thoughts and emotions to protect their self-esteem (and maintain emotional well-being), depressed patients, according to the cognitive theories of depression, show low self-esteem. Moreover, depression is associated with an increased attention to the self (Mor and Winquist, 2002), as well as with rumination about negative self-relevant information (Nolen-Hoeksema et al., 2008). Hence, when individuals are confronted with a stressor (e.g., criticism of their superior) this may lead to self-referential rumination and subsequently affect their self-esteem, which in turn, contributes to depressive affect (Oatley & Bolton, 1985; Roberts & Monroe, 1999). In addition, individuals with low self-esteem are likely to experience more negative affect when thinking about themselves (for the relation between self-esteem and negative affect, see Orth, Robins, & Widaman, 2011; Watson, Suls, & Haig, 2002) and consequently might be motivated to suppress self-related thoughts, which has the ironic effect of increasing ruminative tendencies (Wegner, Schneider, Carter, & White, 1987; Wenzlaff & Wegner, 2000).

Importantly, a growing body of research suggests that low self-esteem is a risk factor for the development of depression (e.g., Kernis et al., 1998; Orth, Robins, & Roberts, 2008; Orth, Robins, Trzesniewski, Maes, & Schmitt, 2009; Roberts & Monroe, 1992; Sowislo & Orth, 2013). In these studies, which used longitudinal designs and controlled for prior levels of the constructs, low self-esteem prospectively predicted changes in the level of depression. Overall, the evidence supports the vulnerability model, which states that low self-esteem is a diathesis exerting causal influence in the onset and maintenance of depression (e.g., Beck, 1967; Metalsky, Joiner, Hardin, & Abramson, 1993). An alternative model of the relation between self-esteem and depression is the scar model, which states that low self-esteem is an outcome rather than a cause of depression, because episodes of depression may leave permanent scars in the self-concept of the individual (cf. Coyne, Gallo, Klinkman, & Calarco, 1998; Rohde, Lewinsohn, & Seeley, 1990; Shahar & Davidson, 2003; for an overview of the scar and vulnerability model, see Zeigler-Hill, 2011). It is important to note that the vulnerability model and the scar model are not mutually exclusive because both processes (i.e., low self-esteem contributing to depression and depression eroding self-esteem) might operate simultaneously. Yet, in the extant literature – which is based on longitudinal studies, many of which used large samples and advanced statistical approaches (such as latent variable modeling), thereby increasing the validity of the conclusions (e.g., Orth et al., 2008; Orth, Robins, Trzesniewski, Maes, & Schmitt, 2009; Shahar & Henrich, 2010) - speaks against the scar model (cf. Ormel, Oldehinkel, & Vollebergh, 2004; Orth et al., 2008; Orth, Robins, & Meier, 2009; Orth, Robins, Trzesniewski, et al., 2009; Sowislo & Orth, 2013; but see Shahar & Davidson, 2003).

Although it is generally assumed that depressed individuals have lower positive self-esteem than non-depressed individuals, in recent years several studies have investigated the implicit positivity bias in (remitted) depressed patients and healthy controls (e.g. De Raedt, Schacht, Franck & De Houwer, 2006). Interestingly, although depressed and non-depressed people differ with respect to their explicit self-esteem they demonstrate surprisingly similar levels of (positive) implicit self-esteem (De Raedt et al., 2006; Greenwald et al., 2002; Risch et al., 2010; Yamaguchi et al., 2007). De Raedt and colleagues (De Raedt et al., 2006) compared implicit self-esteem in a group of depressed participants relative to healthy controls using three separate paradigms: the Implicit Association Test (IAT), Name Letter Preference Task (NLPT), and the Extrinsic Affective Simon Task (EAST). Across all three measures evidence for similar levels of positive implicit self-esteem was obtained for both groups. Some studies have even reported higher levels of (positive) implicit self-esteem in formerly depressed relative to never-depressed participants (Gemar et al., 2001; Franck, De Raedt, De Houwer, et al., 2008). In an attempt to explain these surprising findings, De Raedt and colleagues (De Raedt et al., 2006) argued that the IAT and other measures of implicit self-esteem may have captured actual self-esteem in non-depressed participants but ideal self-esteem in depressed participants. Whereas actual self-esteem refers to feelings of self-worth or the global evaluation of the current self (Buhrmeister, Blanton, & Swann, 2011), ideal self-esteem is considered to be a global representation of the attributes a person would like to possess (see Higgins, 1987). However, the question remains of how to accurately capture these concepts, i.e., both the actual and the ideal self?

HOW TO CAPTURE THE SELF: IMPLICIT MEASURE

Within the cognitive models of depression, negative self-schemas are thought to bias information processing in an automatic, repetitive and difficult to control manner (Clark, Beck, & Alford, 1999). Moreover, according to Beck's (1967) cognitive theory of depression, negative beliefs about the self are not just a symptom of depression but play a critical causal role in its etiology (see also Metalsky, Joiner, Hardin, & Abramson, 1993). These negative cognitions about the self are also argued to play a significant role in the maintenance and recurrence of depressive episodes (Ingram, Miranda, & Segal, 1998; Williams, 1997). Interestingly, however, much work on self-esteem and its relationship to depression has employed self-report measures which are susceptible to a variety of response biases such as social desirability and self-presentation. Many cognitive models of depression also assume that self-related schemata are not always consciously accessible and thus cannot always be verbally reported upon (Beck, Rush, Shaw, & Emery, 1979; Young, 1994). Consequently, it is questionable whether the use of self-report measures may provide meaningful information about such schemata. To overcome these limitations, a number of alternative procedures have recently emerged that reduce the participant’s ability to control their responses and operate in such a way that they do not depend on introspective access to the psychological content of interest. Whereas self-report measures of self-esteem can be classified as explicit measures that capture non-automatic instances of self-evaluation (e.g., self-evaluations that occur when participants have ample time and resources to reflect or have the intention to evaluate the self), implicit self-esteem measures can be thought of as measures that register more spontaneous, automatic self-evaluations (e.g., self-evaluations that occur quickly or when participants do not have the intention to evaluate the self; see De Houwer, Teige-Mocigemba, Spruyt, & Moors, 2009). For this reason, a distinction is drawn between the underlying schema processes that are not accessible and the products of such processes that are accessible within the conscious mind as opinions, inferences and interpretations (Ingram & Wisnicki, 1991). Hence, given recent research suggesting that implicit and explicit measures may assess different components of cognitive processes (Beevers, 2005; Haeffel et al., 2007), and that implicit measures may better predict distress and psychopathology than explicit measures (e.g., Nock & Banaji, 2007), it is important to investigate these underlying processes with implicit measures, and which tap into both actual and ideal-self constructs.

THE DEPRESSED BRAIN: NEUROBIOLOGICAL CIRCUITRY

In the last decade research into the neurobiological underpinnings of depression has accumulated an abundance of information consistently pointing to specific circuitries underlying deficient cognitive processes. Depression has been conceptualized as a failure to recruit prefrontal top-down cognitive control to regulate emotion producing subcortical limbic activity (Phillips, Ladouceur, & Drevets, 2008). In a meta-analysis of Fitzgerald, Laird, Maller, and Daskalakis (2008) evidence was found for the involvement of two neurocircuits in major depressive disorder. One network includes the dorsolateral prefrontal cortex (DLPFC) and dorsal (d) regions of the anterior cingulate cortex (ACC). These regions, among other regions which are implicated in attentional and cognitive control, are characterized by reduced activity during resting state, and return to normal after successful treatment. A second network is centered on the medial prefrontal cortex and ventral subcortical regions such as the amygdala, which is hyperactive to emotional stimuli during depressive episodes, and also returns to normal after treatment (Fitzgerald et al., 2008). The amygdala is activated when people are confronted with emotionally challenging events (Zald, 2003), and is tightly connected to the ventral ACC. The ACC can be conceived as a bridge between subcortical emotion processing and prefrontal cognitive control, because it integrates signals from its ventral and dorsal parts (Bush, Luu, & Posner, 2000). The dorsal ACC sends signals to the DLPFC to enhance cognitive control (Hopfinger, Buonocore, & Mangun, 2000; MacDonald, Cohen, Stenger, & Carter, 2000) and studies suggest that the DLPFC initiates control over emotions by inhibition of the amygdala via other brain regions (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007).

In the framework of De Raedt and Koster (2010), the authors proposed that prolonged processing of self-referential material such as rumination, after the activation of negative schemas when confronted with stressors, is caused by impaired activity in dorsal prefrontal areas, mediated by the serotonergic system which is under control of the Hypothalamic Pituitary Adrenal (HPA) axis. The HPA axis – the hallmark of the stress response – stimulates the release of stress hormones (corticosteroids), and becomes increasingly impaired after periods of hypercortisolism during depressive episodes (Van Praag, De Kloet & van Os, 2004), which means that it becomes more reactive to stressors (De Raedt & Koster, 2010). Interestingly, it has been shown that mood repairing psychological processes such as reappraisal of negative information are related to recruitment of the same dorsal areas. Healthy individuals who tend to use reappraisal to overcome negative affect in daily life were behaviorally faster and exerted more dACC activity when inhibiting a response to negative in favor of positive information (compared to inhibiting a positive in favor of a negative response) (Vanderhasselt, Baeken, Van Schuerbeek, Luypaert, & De Raedt, 2013a).

Individuals with a history of depression react differently to negative interpersonal criticism as compared to healthy individuals. At the level of neural systems, in line with the abovementioned account, they show a stronger activation of the amygdala, and a reduced activation of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Hooley et al., 2009). These anomalies in the cortical-limbic system are related to difficulties in emotion regulation, and are associated with vulnerability to depression (De Raedt & Koster, 2010). It has even been demonstrated that the number of earlier depressive episodes correlates with decreased prefrontal control (Vanderhasselt & De Raedt, 2009), which is in accordance with the crucial role of the prefrontal cortex in the regulation of attentional control for negative stimuli (Leyman, De Raedt, Vanderhasselt & Baeken, 2009) and the inhibition of the amygdala (De Raedt et al., 2010).

Cognitive and neural phenomena can be modulated to increase the ability to regulate momentary ruminative self-referent thoughts during a period of idleness, a process closely linked to the ruminative thinking style. This interplay between biological and cognitive factors is in line with a theoretical framework of De Raedt & Koster (2010), which states that cognitive control processes play a central and causal role in the relation between prefrontal neural activation and rumination. By using an experimental method that involves neurostimulation of the DLPFC to temporarily enhance its activity, one goes beyond correlational deduction and moves on to causal inferences. This is an important next step for building and refining our understanding of the neural bases of rumination and self-referential thinking in depression.

THE DEPRESSED BRAIN: NON-INVASIVE BRAIN STIMULATION

Hence, in recent years the development and evolution of non-invasive brain stimulation (NIBS) techniques (e.g., repetitive Transcranial Magnetic Stimulation, rTMS; transcranial Direct Current Stimulation, tDCS) has substantially increased over the last decades. NIBS is a unique experimental tool that allow researchers to non-invasively study the cortex in healthy and diseased states (Barker et al., 1985). Multiple sessions of neurostimulation are frequently used in the treatment of psychiatric disorders such as depression (e.g., Burt et al., 2002; Mitchell & Loo, 2006; O'Reardon et al., 2007; Boggio et al., 2008; George et al., 2010). These techniques are also used to investigate neural conductions and connections in the human brain, and are of considerable interest for researchers interested in understanding the basic neurophysiology of mood disorders (Paus et al., 2001; Pascual-Leone et al., 2002). Importantly, stimulation of the DLPFC with rTMS and tDCS has been shown to produce similar effects in different neural circuitries (Fregni et al., 2008a), neurotransmitter systems (Keck et al., 2002; Nitsche et al., 2006; Strafella et al., 2001), and the treatment of psychiatric diseases (for a review see Miniussi et al., 2008; George et al., 2009; and George & Aston-Jones, 2010). However, in patient populations these treatment studies are based on multiple rTMS or tDCS sessions. Nonetheless, investigating the effects of a single session of rTMS and tDCS in experimental research holds important implications. Due to their rather easy application, both modalities have been used to experimentally examine prefrontal cognitive and emotional control. Given that effects on cognition (e.g. information processing) within a study could be (partly) explained by changes in mood it is crucial to scrutinize possible effects of neurostimulation on mood. In addition, it allows researchers to experimentally test hypotheses, and shift away from the correlational deduction, allowing them to non-invasively study the cortex in both healthy and diseased states.

Interestingly, in many previous studies it could already be demonstrated that neurostimulation of the left DLPFC enhances cognitive processes, both for non-emotional (e.g., Fregni et al., 2005; Leite, Carvalho, Fregni, & Goncalves, 2011; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011) as emotional processes (Boggio et al., 2007; Wolkenstein & Plewnia, 2013). More specifically, anodal tDCS of the prefrontal cortex has been found to reduce state rumination via a beneficial change in working memory processes for emotional information (Vanderhasselt et al., 2013b) and also causally reduce other depressive symptoms (e.g., Brunoni et al., 2013). Cognitive control, or the lack of it, seems to also be an important factor in determining the degree of rumination a healthy individual normally engages in (Nejad et al., 2013). Hence, by applying neurostimulation over the DLPFC we can experimentally manipulate cognitive control and investigate its possible beneficial effects on cognitive and neurobiological processes.

RESEARCH OBJECTIVES OF THE DISSERTATION

The aim of the current Ph.D. project was to unravel how the link between criticism and ruminative processes affects self-esteem, focusing on both behavioral and neurobiological processes. To investigate this mechanism, we explored whether the effect of an experimental manipulation of the prefrontal cortex on self-esteem is mediated by rumination before and after criticism. Although we start from the premise that these underlying mechanisms are important in depression, it was crucial to start testing our causal hypotheses in healthy individuals, without the possible interference of the depressed mood state on the mechanisms under study. We focused on three levels of measurement. First, we investigated the effects of neurostimulation on rumination and self-esteem using self-report. Second we used implicit measures to index actual and ideal self-esteem, and third, we assessed the neurobiological correlates of this process. However, in order to answer these questions, we started with developing and testing several methods and prerequisites. First, we started with the development of a task to measure self-esteem in an implicit way, focusing on both actual and ideal self. In a second study, we replicated the findings of this first study with more stringent criteria as well as a methodologically fine-tuned design. Next, we conducted a systematic review to elucidate whether a single neurostimulation session would have an effect on mood in healthy participants, since mood effects might confound any effects found on cognitive processes. Thereafter, we investigated if a single placebo controlled neurostimulation session can influence the physiological stress response (using heart rate variability) during criticism. Finally, we applied a placebo controlled session of transcranial direct current stimulation in the fMRI scanner, to test the possible impact of neurostimulation of the dorsolateral prefrontal cortex on the underlying neurobiological processes of rumination (regional brain activity and functional connectivity) before and after an experimental induction of criticism and subsequently their effect on implicit self-esteem (using the Implicit Relational Assessment Procedure). .

OVERVIEW OF THE CHAPTERS

As our aim was to investigate different levels of self-esteem, we first explored in **Chapter 2** the measurement of self-esteem in an implicit way. Building further on the implicit positivity bias towards the self in depression, and the idea forwarded by De Raedt et al. (2006) that the IAT effects and other implicit (associative) measures of self-esteem might not reflect *actual* self-esteem but *ideal* self-esteem, we aimed at differentiating self-esteem in two separate conceptualizations by introducing propositions: “*I am*” versus “*I want to be*”. Therefore, we developed a new self-esteem task (based on the Implicit Relational Assessment Procedure, IRAP, Barnes-Holmes et al., 2006) to measure both actual and ideal-self in an implicit way and analyzed if we can find differences in responding between participants with sub-clinical depression (dysphorics) and healthy participants (non-dyphorics).

In **Chapter 3**, we followed up on the robust findings of our first study and aimed to replicate these results with more stringent criteria, as well as a methodologically fine-tuned design. Whereas De Raedt et al. (2006) used different associative implicit measures (e.g. the IAT), and we (Chapter 2) used a propositional implicit measure (the IRAP), we chose to administer both measures in this follow up study. This allowed us to compare both implicit measures within different groups and analyze both within and between group effects.

In **Chapter 4**, in anticipation of the use of neurostimulation as an experimental tool in our next studies, we first focused on the accrued interest in non-invasive brain stimulation (i.e., rTMS and tDCS) research and conducted a systematic review of the impact of a single neurostimulation (i.e., rTMS & tDCS) on mood in healthy individuals. Given our interest in underlying cognitive processes (e.g., rumination, self-referential processing, and reactivity to stress and criticism), this review can help us exclude that a single neurostimulation session would have an effect on mood in healthy participants, since mood effects might confound any effects found on cognitive processes.

In **Chapter 5**, we investigated if a single, placebo-controlled neurostimulation session can influence the physiological stress response (using heart rate and heart rate variability) during criticism. We targeted both left and right DLPFC and compared both groups of healthy participants on their physiological response to criticism. The manipulation of both left and right DLPFC with rTMS allows us to experimentally investigate the causal role of the DLPFC in coping with criticism.

In **Chapter 6**, we looked at the underlying neurobiological processes of rumination and self-referential processing (regional brain activity and functional connectivity) when healthy participants are confronted with criticism. This could further our understanding on the underlying neurobiological correlates of reactivity to criticism and might guide us in improving the treatment of depression.

In **Chapter 7**, building on the findings of our previous studies and given the influence of tDCS on cognitive processes related to rumination (Vanderhasselt et al., 2013b), we explored (under fMRI – online design), the effects of a single tDCS session on rumination before and after criticism, and subsequently on self-esteem (actual and ideal) in healthy individuals, since the influence of clinical depression on the brain might not allow any conclusion with regard to the underlying mechanisms

Finally, **Chapter 8** provides an integrated overview and general discussion of our main findings. In addition, theoretical and clinical implications, limitations and guidelines for future research are outlined.

It should be noted that this dissertation consists of several research papers, which have been accepted or submitted for publication. Since each of the chapters is a self-contained manuscript, which should be able to stand on its own, the text of some of the chapters may partially overlap.

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CHAPTER 2

SELF-ESTEEM REVISITED: PERFORMANCE ON THE IMPLICIT RELATIONAL ASSESSMENT PROCEDURE AS A MEASURE OF SELF- VERSUS IDEAL SELF-RELATED COGNITIONS IN DYSPHORIA[1]

ABSTRACT

Although depression is characterised by low self-esteem as measured by questionnaires, research using implicit measures of self-esteem has failed to reveal the expected differences between depressed and non-depressed individuals. In this study, we used an implicit measure which enables the differentiation of ideal self- and actual self-esteem, through the introduction of propositions: ‘‘I am’’ versus ‘‘I want to be’’. We measured implicit relational associations about actual and ideal self in low (N27) versus high dysphoric (N29) undergraduates. Our data revealed that dysphoric individuals have a higher ideal self-esteem, and lower actual self-esteem in comparison to healthy participants. The results underscore the need to go beyond simple associations and suggest that the use of individualspecific propositions could enhance our understanding of the implicit measurement of self-esteem. Furthermore, these results underscore the importance of actual versus ideal self-discrepancy theories, which might guide the content of therapeutic interventions.

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[1] Based on Remue, J., De Houwer, J., Barnes-Holmes, D., Vanderhasselt, M.-A., & De Raedt, R. (2013). Self-esteem revisited: Performance on the implicit relational assessment procedure as a measure of self- versus ideal self-related cognitions in dysphoria. *Cognition & Emotion*, 1-9. doi: 10.1080/ 02699931.2013.786681

INTRODUCTION

Self-esteem is one of the most extensively investigated constructs across various areas of psychology. One area of investigation in which its relevance seems almost self-evident is research on depression. It is generally assumed that depressed individuals have less positive self-esteem than non-depressed individuals. Moreover, negative self-schemata are central to the cognitive theory of depression (Beck, Rush, Shaw & Emery, 1979; Clark, Beck, & Alford, 1999). Research with self-esteem questionnaires such as the Rosenberg Self-Esteem Questionnaire (Rosenberg, 1965) supports this idea (e.g., Ingram, Miranda, & Segal, 1998, for a review).

Recently, however, results with so-called implicit measures of self-esteem have failed to reveal the expected differences in self-esteem between depressed and non-depressed people (e.g., Risch et al., 2010). This research is of high importance for the analysis and treatment of human psychopathology because, within cognitive therapy models, it is assumed that crucial dysfunctional schemata are not always consciously accessible and thus cannot be reported per se (Beck et al., 1979; Young, 1994). Whereas questionnaire self-esteem measures typically register non-automatic (e.g., deliberative) evaluations of the self, implicit self-esteem measures are designed to capture more automatic (e.g., unintentional) evaluations of the self (De Houwer, Teige-Mocigemba, Spruyt, & Moors, 2009). For instance, De Raedt, Schacht, Franck, and De Houwer (2006) used the Implicit Association Test (IAT) as an implicit measure of self-esteem. They asked participants to categorize words that appeared on a computer screen as referring to “me” (e.g., own name), “not-me” (e.g., other name), “negative” (e.g., evil) or “positive” (e.g., happy) by pressing one of two keys. During a consistent block of trials, the same key was pressed for “me” and “positive” words and the other key was pressed for “not-me” and “negative” words. During an inconsistent block, the first key was assigned to “me” and “negative” words and the second key to “not-me” and “positive” words. Intriguingly, both depressed and non-depressed participants were faster in the consistent than in the inconsistent block, a result that is typically taken to reflect positive self-esteem (but see Blanton & Jaccard, 2006). Whereas De Raedt et al.

(2006) found a similar IAT effect in depressed and non-depressed participants, some studies even revealed a larger advantage on consistent versus inconsistent trials in formerly depressed than never-depressed participants (Gemar, Segal, Sagrati, & Kennedy, 2001, Franck, De Raedt & De Houwer, 2008). This suggests even more positive implicit self-esteem in individuals who are vulnerable to depression.

As a possible solution to this conundrum, De Raedt et al. (2006) proposed that IAT effects and other implicit measures of self-esteem might not reflect *actual* self-esteem but *ideal* self-esteem. The ideal self can be defined as a representation of the attributes a person would like to have. Zentner and Renaud (2007) have argued that (1) the ideal self functions as an incentive for future behavior, a self “to be approached or avoided” (Cross & Markus, 1991), and (2) that the ideal self is an evaluator of actual self-esteem. Moreover, numerous studies have provided compelling evidence for the role of discrepancies between ideal and actual views of the self in relation to depressive disorders (e.g., Moretti & Higgins, 1999; Tangney, Niedenthal, Covert & Hill-Barlow, 1998). Implicit self-esteem measures such as the IAT might not be able to distinguish between actual and ideal self-esteem. The self-esteem IAT and other currently available implicit self-esteem measures were designed to assess the association between the concepts “self” and “positive” or “negative” without taking into account the way in which those concepts are associated. Whereas actual and ideal self-esteem can both be conceptualized as involving an association between the concepts “self” and “positive” or “negative”, the way in which these concepts are related must differ for the representation of the actual self (e.g., I AM positive or negative) and ideal self (e.g., I WANT TO BE positive or negative). In other words, actual and ideal self involve the same associations but different propositions (i.e., informational units that also specify *how* concepts are related). Therefore, in order to distinguish actual and ideal self at the implicit level, we need an implicit measure that can capture propositional information.

For this purpose, we used a self-esteem variant of the Implicit Relational Assessment Procedure (IRAP; Vahey, Barnes-Holmes, Barnes-Holmes, & Stewart, 2009). The IRAP (Barnes-Holmes et al., 2006) is a relatively new measure that is specifically designed to capture how objects are related to each other. In our study we used two IRAPs, i.e. the actual self IRAP (with the two sample stimuli: “I AM”, “I AM NOT”), and the ideal self IRAP (with the two sample stimuli: “I WANT TO BE” or “I DON’T WANT TO BE”).

Although these particular versions of the self-esteem IRAP have not been used before, many studies confirm that the IRAP provides a valid measure of how participants automatically relate various kinds of objects (see Drake et al., 2010, for a review). Assuming that the ease with which individuals automatically relate certain objects in certain ways is mediated by propositional knowledge in memory (see Hughes, Barnes-Holmes, & De Houwer, 2011, for an in depth discussion), one can thus argue that performance on the IRAP provides an implicit measure of propositional knowledge. Importantly, propositional knowledge, whether it is deemed to be consciously accessible or not, is the basic material targeted in cognitive therapies. The self-esteem IRAP that we used in this study may be able to differentiate between ideal self and actual self in that it does not merely capture the association between the concepts “self” and “positive” or “negative”, but the way in which these concepts are related (i.e., I AM versus I WANT TO BE). According to the ideas of De Raedt et al. (2006), one can therefore predict that depressed individuals would show higher implicit ideal self-esteem and lower actual self-esteem than non-depressed individuals. As a first test of this hypothesis, we examined dysphoric and non-dysphoric students. Dysphoric students have been shown to be prone to depression (e.g. Ingram & Siegle, 2009), and can thus be considered as a clinical analogue sample. In line with previous findings that depression might be related to discrepancies between ideal and actual views of the self (e.g., Moretti & Higgins, 1999; Tangney, Niedenthal, Covert & Hill-Barlow, 1998), we hypothesized that dysphoric students would display more positive ideal self-esteem than actual self-esteem whereas the reverse would be true for non-dysphoric students.

METHOD

Participants

In this experiment, 72 undergraduates participated in return for course credits. They were recruited by means of an on-line participant panel system after completing the BDI-II-NL (van der Does, 2002) as a screening measure. Upon invitation for the experiment, they completed the BDI-II-NL again. Based on the attrition data based on task requirements, our final sample consisted of 56 participants (see below for detailed information).

Using the cut-off score that is recommended in the BDI-II-NL manual, the final sample was divided into a low BDI group (≤13) consisting of 27 undergraduates (21 women and 6 men) aged between 18 and 30 years (*M* = 20.56, SD = 2.41) and a high BDI group (≥14) of 29 undergraduates (26 women and 3 men) aged between 18 and 30 years (*M* = 19.52, *SD* = 2.26). Assignment to BDI groups was based on the BDI score during the actual test session. By design, the high BDI group had significantly higher BDI-II-NL scores during test (*M* = 22,1 *SD* = 8,4) compared to the low BDI group (*M* = 5.8, *SD* = 4,2), *t*(54)=9.10, *p*<.001. Age did not differ significantly between groups (*t < 1)*. Note that BDI scores during test were not distributed normally (Shapiro-Wilk = .935; p< .005) simply because we invited participants with an extremely high or low BDI score during screening. We therefore used BDI as a dichotomous variable rather than a continuous variable in the analyses.

Materials

Questionnaire measures. The BDI-II, a 21 item self-report inventory, was used to measure the severity of depressive symptoms (Beck et al., 1996). The Dutch translation of the BDI-II has shown high internal consistency: Chronbach's α of .92 for a patient population and .88 for a healthy control group. Also, the validity index satisfies general psychometric criteria (van der Does, 2002).

IRAP Self-Esteem Measures. On each trial of our self-esteem IRAP, participants were presented with a sample stimulus on the top of a computer screen and a target stimulus in the middle of the screen (see Figure 1). The sample stimulus always referred to the self, the target stimulus was always a positive or negative word. Importantly, the self-related sample stimuli contained relational information. More specifically, in our study we used two almost similar IRAPs, that is, the actual self IRAP (with the two sample stimuli: "I AM", "I AM NOT"), and the ideal self IRAP (with the two sample stimuli: "I WANT TO BE" or "I DON'T WANT TO BE". For the explanation of the task specifics we will focus on the actual self IRAP, however the ideal self IRAP is exactly the same, except for the sample stimuli “I WANT TO BE” and “I DON’T WANT TO BE”.

In the actual self IRAP participants would, for instance, see the sample stimulus “I AM” together with the word “HAPPY”. Participants were asked to press a “correct” key or a “false” key based on the specific combination of sample and target stimuli. These response assignments were varied between blocks. In the consistent block, participants were asked to press “correct” whenever the sample-target combination expressed self-positivity (i.e., I AM + positive, I AM NOT + negative) and “false” whenever the sample-target combination expressed self-negativity (i.e., I AM + negative, IAM NOT + positive). In the inconsistent block, the correct response was required for sample-target combinations that expressed self-negativity whereas the false response was required for sample-target combinations that expressed self-positivity. The idea behind the IRAP is that participants will perform better when the required response assignments are in line with how participants typically relate the objects under investigation.

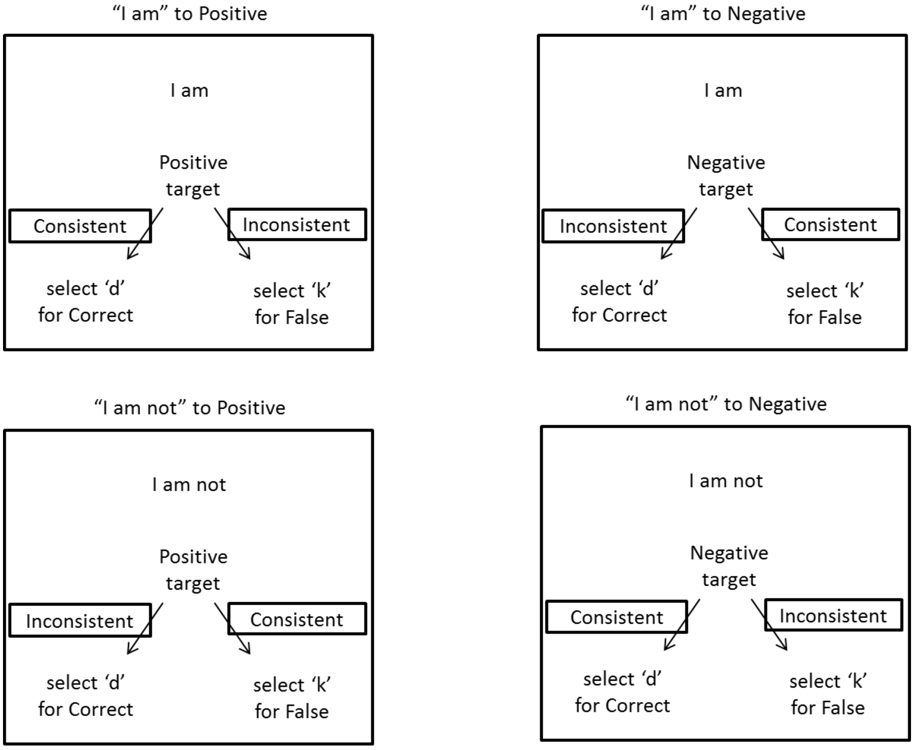

Figure 1. *Examples of the four trial types employed in the actual self-esteem IRAP: one for each combination of the two sample stimuli (“I am” or “ I am not”) with the two types of target stimuli (self-positive or self-negative evaluative words). The ideal self-esteem IRAP was similar except the two samples were “I want to be” versus “I don’t want to be”.*

The order of the two IRAP tasks was counterbalanced across participants. The task was implemented using the IRAP software provided by Barnes-Holmes (http://irapresearch.org/downloads-and-training, version 2008). In line with previous IRAP studies (for a review see Drake et al., 2010), participants were required to complete a maximum of four pairs of practice blocks and then two test blocks, with each block containing 24 trials. To rule out order effects, all participants commenced with a block of consistent trials (confirm self-positive and deny self-negative relations) and thereafter completed a block of inconsistent trials. Before starting the task, an instruction-screen was shown which explained these two blocks (i.e., consistent and inconsistent). Further, the key-assignment was explained. As in previous IRAP studies, the function of the keys changed randomly from trial to trial. Hence, on some trials, the left key was used to indicate “correct” and the right key to indicate “false” whereas the reverse was true on other trials. When a response was not in line with the instructions, a red X appeared and participants were asked to press the appropriate key as quickly as possible. In each block, the sample stimuli appeared once with each of the 12 target stimuli (see Table 1).

Table 1. *Stimulus response combinations (of the sample stimuli with the 12 self-evaluative words) deemed consistent in the self-esteem IRAP.*

Sample1	Positive targets	Sample 2	Negative targets	Sample 1	Negative targets	Sample2	Positive targets
I am/I want to be	Valuable Happy Tender Friendly Hopeful Competent	I am not/I don’t want to be	Helpless Guilty Desperate Sad Rejected Failed	I am/I want to be	Helpless Guilty Desperate Sad Rejected Failed	I am not/I don’t want to be	Valuable Happy Tender Friendly Hopeful Competent
Response option 1				Response option 2			
Correct				False			

Note. *By implication all other stimulus response combinations are deemed inconsistent.*

On each trial, all stimuli appeared simultaneously on screen. If the response was in line with the instructions, this response was followed by a blank screen for 400ms after which the next trial was presented. If the response was not in line with instructions, a red X appeared immediately under the target stimulus. To remove the red X and continue to the 400ms intertrial interval, the participant was required to emit the appropriate response. When the participant had completed all 24 IRAP trials, the screen cleared and two types of feedback were presented for that block: the percentage of correct responses and the median response latency. Between each block of trials the following instructions were presented on screen: “Important: during the next phase the previously correct and wrong answers are reversed. This is part of the experiment. Please try to make as few errors as possible – in other words, avoid the red X”. Before each test block, the following message also appeared: “This is a test. Go fast; making a few errors is okay.” In line with previous IRAP studies (e.g., Barnes-Holmes, Barnes-Holmes, Stewart, & Boles, 2010), the data from participants who failed to achieve at least 80% accuracy or a mean latency under 2500ms during the test blocks were excluded from the analyses. In our study, the data of 16 participants (9 with low BDI scores and 7 with high BDI scores) were ignored because of this reason, thus leading to a final sample of 56 participants.

Procedure

The procedure was identical for both groups. Upon arrival, participants read and signed a consent form and were randomly assigned an identification number to preserve their confidentiality and anonymity. Once the participants were seated, the experimenter stated that it was important to answer quickly and accurately throughout the procedure. Next the IRAP task was started. After the participants finished both IRAP tasks, each participant filled in the BDI. All participants were individually tested.

RESULTS

Data preparation

The raw IRAP data comprise of response latencies, defined as the time in milliseconds from the onset of a trial to the first emission of the appropriate response for that trial. These raw data were transformed using the D-IRAP algorithm (see Barnes-

Holmes, et al., 2010), which is derived from the D-algorithm developed by Greenwald, Nosek, and Banaji (2003) for the IAT. Important for our analysis, two compound D-IRAP scores were then calculated, that is, D-IRAP (pos) and D-IRAP (neg). The D-IRAP (pos) is calculated based on all trials with positive targets, and D-IRAP (neg) is calculated based on all trials with negative targets. Finally, a total D-IRAP score was calculated by averaging the D-IRAP (pos) and D-IRAP (neg) scores (see Vahey et al., 2009, for a detailed description of how such scores are calculated). A D-IRAP score reflects the difference in response latency between consistent and inconsistent blocks; therefore a D-IRAP score that is significantly different from zero indicates that there was, in fact, a significant difference between response latencies in consistent versus inconsistent blocks. A higher D-IRAP score indicates a higher (i.e., more positive) level of self-esteem (actual self-esteem on one IRAP and ideal self-esteem on the other IRAP). In the current study, the total D-IRAP score was the crucial dependent variable, but it was deemed important to start the analyses with D-IRAP (pos) and D-IRAP (neg) as a factor, to exclude the possibility that the valance of the words influenced the effects.

Split-Half Reliability.

To assess the internal consistency of the IRAP, two split-half reliability scores were calculated, one for Actual Self IRAP and one for the Ideal Self IRAP. In each case, two scores were calculated, one for odd trials and the second for even trials, and these were obtained in the same way as for the overall D-IRAP score, except that the D-algorithm was applied separately to all odd trials and even trials. Interestingly, while the split-half correlations between odd and even scores, applying Spearman-Brown corrections, proved significant for the Ideal-Self IRAP, $r = .492$, $n = 32$, $p < .001$, they were less so for the Actual-Self IRAP, $r = .221$, $n = 56$, $p < .10$. Given that a shortened version of the IRAP was used we refrain from making any strong conclusions about the difference between Ideal and Actual Self based on internal consistency scores.

Participant-type analyses.

The D-IRAP scores for each participant were entered into a 2 x 2 x 2 mixed ANOVA with Group (low versus high BDI) as the between-participants variable and D-IRAP Effect-Type (D-IRAP pos and D-IRAP neg) and Condition (Actual-Self versus Ideal-Self) as the within-participants variables. The results showed a main effect for the D-IRAP Effect-Type, $F(1, 54) = 4.71$, $p=.034$, but not for Condition, $F(1, 54) = .08$, $p=.778$. Most importantly, a highly significant interaction between Group and Condition was observed $F(1, 54) = 15.48$, $p <.001$. Because no significant interaction was found with Effect-Type, we continued all our analyses with the total D-IRAP score. To test our specific hypothesis on group differences between ideal self-esteem and actual self-esteem, we followed-up the Group X Condition interaction using independent one-tailed t-tests with the total D-IRAP effects. We found a significant group difference for both the Actual-Self-Condition, $t(54) = 3.07$, $p <.01$, $d =.82$, and the Ideal-Self-Condition, $t(54) = 1.68$, $p <.05$, $d =.45$, indicating lower actual self-esteem and higher ideal self-esteem in the dysphoric group relative to the non-dysphoric group. To test our hypothesis about possible differences between ideal and actual self-esteem within each group, we performed one-tailed paired sample t-tests for the total D-IRAP effects. For the Low BDI group the D-IRAP score for the Self-Condition was significantly higher than the D-IRAP score for the Ideal-Self-Condition, $t(26) = 3.65$, $p <.001$, $d =.72$ (actual self-esteem: $M =.45$, $SD =.39$; ideal self-esteem: $M =.16$, $SD =.41$). For the High BDI group the D-IRAP score for the Self-Condition was significantly lower than the D-IRAP score for the Ideal-Self-Condition, $t(28) = 2.17$, $p =.02$, $d =.54$ (actual self-esteem: $M =.12$, $SD =.41$; ideal self-esteem: $M =.35$, $SD =.44$) (see Table 2). The results of the current study were thus in accordance with our predictions.

Table 2. *Comparison of mean D-scores for both the Actual Self and Ideal Self IRAP between the low and high BDI group.*

Group	Low BDI Group	High BDI Group
Actual Self IRAP	*.45 (SD=.39)*	*.12 (SD=.41)*
Ideal Self IRAP	*.16 (SD=.41)*	*.35 (SD=.44)*

Note. *For Low BDI group N=27; for High BDI group N=29.*

DISCUSSION

The present study was designed to explore whether dysphoric and non-dysphoric individuals differ with regard to the valence of their ideal self and/or actual self. Based on the study by De Raedt et al. (2006), who proposed that higher self-esteem as measured with the IAT in depressed individuals could be indicative of associations related to ideal self instead of actual self-esteem, we used the IRAP procedure that allowed us to distinguish between ideal and actual self-esteem. In line with this idea, we found that the dysphoric (high BDI) group scored lower on actual self-esteem and higher on the index of ideal-self-esteem in comparison to the low BDI group. The D-IRAP total scores also showed that low dysphoric individuals have more positive actual self-esteem as compared to ideal self-esteem.

Hence, our results build further on previous research on self-esteem in depression (e.g. De Raedt et al., 2006), by demonstrating that dysphorics have more positive ideal self-esteem, while non-dysphorics have a higher actual self-esteem. The self-esteem IRAPs in this study differentiated between ideal self and actual self, by not simply capturing the association between the concepts “self” and “positive” or “negative”, but by elaborating on the way in which these concepts are related (i.e., I AM versus I WANT TO BE). By using the IRAP (and its use of propositions) we went beyond the results of De Raedt et al. (2006), with results suggesting that the IAT in their study might have measured ideal self-esteem in depressed, and actual self-esteem in non-depressed individuals.

This could explain why De Raedt and co-workers (2006) found similar positive self-esteem for depressed and non-depressed groups using the IAT. There is, however, still the question of why the IAT would measure different aspects of implicit self-esteem in depressed versus non-depressed individuals. A possible explanation is that the IAT does not restrict the way concepts or labels are interpreted, and that this interpretation varies across clinical conditions. More specifically, depressed individuals might conceptualize the IAT labels as “I WANT TO BE GOOD/BAD” whereas non-depressed individuals might interpret them as “I AM GOOD/BAD”. The idea that each individual might interpret – or proportionalize – concepts or labels in a different way is crucially important for future research using association tasks such as the IAT.

This study was the first to go beyond the unilateral associative character of the abundance of IAT-research, by differentiating between actual self-esteem and ideal self-esteem through the introduction of labels that specify the way in which concepts are to be related. The results underscore the need to go beyond simple associations and suggest that individual–specific propositions could be co-activated during implicit tasks. Because we showed that implicit measurements of propositions are possible, we argue that these automatically activated propositions should become a point of interest in future experimental and clinical research investigating self-esteem in depression. The use of propositions in implicit measures might be the start of a new avenue for future research, to further unravel how a concept is processed in different populations (e.g., “I HAVE TO BE” + “positive”/”negative”).

Further fine-graining the self-esteem concept may have clinical implications. Because implicit measures have been shown to predict distress and psychopathology (e.g. Franck, De Raedt & De Houwer, 2007), these results further clarify the importance of actual versus ideal self-discrepancy theories, which might hold promise to refine therapeutic interventions.

With regard to the modest split-half reliability measures of both IRAPs, a lower internal consistency might be an implication of using a shortened version of the IRAP with only two test blocks. Hence, in future research, more test blocks might be used to address this issue. Furthermore, as stated by Hughes & Barnes-Holmes (in press), future research should continue to benchmark the validity and reliability of the task against well-established alternatives such as the IAT. Thus, more conclusions about reliability could be drawn when future IRAP studies would consistently report these reliability measures.

A limitation to the present research is that we did not use a patient population. However, dysphoric students have been shown to be prone to depression (e.g. Ingram & Siegle, 2009), and can thus be considered as a clinical analogue sample. Nevertheless, our findings can stimulate further research to replicate these findings in different populations (e.g., remitted depressed, MDD, etc.), to further elucidate the role of self-esteem in depression. Secondly, given that 22% of the participants were excluded based on our criterion that they had to reach an accuracy of 80% before starting the actual task, it might be advisable in future studies to lower this threshold to 70%. Note, however, that an accuracy criterion of 80% has been used in most earlier IRAP studies in which healthy undergraduates participated (e.g., Barnes-Holmes et al., 2010).

To summarize, the results of this study suggest that dysphoric individuals, who are prone to depression, have a focus on ideal-self-esteem, and lower actual self-esteem, in comparison to healthy participants. Future research should take into account propositions in implicit measures of self-esteem, incorporating ideal self in the research of self-esteem and depression.

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CHAPTER 3

TO BE OR WANT TO BE: THE ROLE OF ACTUAL VERSUS IDEAL SELF IN IMPLICIT SELF-ESTEEM[1]

ABSTRACT

A growing body of work suggests that both depressed and non-depressed individuals display implicit positivity towards the self. In the current study, we examined whether this positivity can be underpinned by two qualitatively distinct propositions related to actual (‘*I am good*’) or ideal (‘*I want to be good*’) self-esteem. Dysphoric and non-dysphoric participants completed a self-esteem Implicit Association Test (IAT) as well an Implicit Relational Assessment Procedure (IRAP) targeting their actual self-esteem and an IRAP targeting ideal self-esteem. Both groups demonstrated similar and positive IAT effects. A more complex picture emerged with regard to the IRAP effects. Whereas non-dysphorics did not differ in their actual and ideal self-esteem, their dysphoric counterparts demonstrated lower actual than ideal self-esteem. Our results suggest that closer attention to the role of propositional processes in implicit measures may unlock novel insight into the relationship between implicit self-esteem and depression.

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[1] Based on Remue, J., Hughes, S., De Houwer, J., & De Raedt, R. (2014). To Be or Want to Be: Disentangling the Role of Actual versus Ideal Self in Implicit Self-Esteem. *PLoS One, 9*(9), e108837. doi: 10.1371/journal.pone.0108837 PONE-D-14-03121

INTRODUCTION

Self-esteem has been extensively investigated by researchers from a wide variety of theoretical persuasions and currently represents a key explanatory construct in many areas of psychological science, including health psychology (Taylor & Brown), 1988, social psychology (Baumeister, Campbell, Krueger & Vohs, 2003; Pyszczynski, Greenberg, Solomon, Arndt & Schimel, 2004) and clinical psychology (Crocker & Park, 2004). Within the latter domain, negative self-schemas are thought to bias information processing in an automatic, repetitive and difficult to control manner (Clark, Beck & Alford, 1999). These negative cognitions about the self are also argued to play a significant role in the maintenance and recurrence of depressive episodes (e.g., Ingram, Miranda, & Segal, 1998; Williams, 1997). Interestingly, however, much work on self-esteem and its relationship to depression has employed self-report measures which are susceptible to a variety of response biases such as social desirability and self-presentation. Many cognitive models of depression also assume that self-related schemata are not always consciously accessible and thus cannot always be verbally reported upon (Beck et al., 1979; Young, 1994). Consequently, it is questionable whether the use of self-report measures may provide meaningful information about such schemata. To overcome these limitations, a number of alternative procedures have recently emerged that reduce the participant's ability to control their responses and operate in such a way that they do not depend on introspective access to the psychological content of interest. Whereas self-report measures of self-esteem can be classified as explicit measures that capture non-automatic instances of self-evaluation (e.g., self-evaluations that occur when participants have ample time and resources to reflect or have the intention to evaluate the self), implicit self-esteem measures can be thought of as measures that register more spontaneous, automatic self-evaluations (e.g., self-evaluations that occur quickly or when participants do not have the intention to evaluate the self; see De Houwer, Teige-Mocigemba, Spruyt, & Moors, 2009).

Interestingly, a growing literature suggests that although depressed and non-depressed people differ with respect to their explicit self-esteem they demonstrate surprisingly similar levels of (positive) implicit self-esteem (De Raedt, Schacht, Franck & De Houwer, 2006; Greenwald et al., 2002; Risch, Buba, Birk, Morina, Steffens & Stangier, 2010; Yamaguchi et al., 2007). Consider, for example, the work of De Raedt and colleagues (2006) who compared implicit self-esteem in a group of depressed participants relative to healthy controls using three separate paradigms: the Implicit Association Test (IAT), Name Letter Preference Task (NLPT), and the Extrinsic Affective Simon Task (EAST). Across all three measures evidence for similar levels of positive implicit self-esteem was obtained for both groups. Some studies have even reported higher levels of (positive) implicit self-esteem in formerly depressed relative to never-depressed participants (Gemar, Segal, Sagrati, & Kennedy, 2001; Franck, De Raedt & De Houwer, 2008a).

In an attempt to explain these surprising findings, De Raedt and colleagues (2006) argued that the IAT and other measures of implicit self-esteem may have captured actual self-esteem in non-depressed participants but ideal self-esteem in depressed participants. Whereas actual self-esteem refers to feelings of self-worth or the global evaluation of the current self (Buhrmester, Blanton & Swann, 2011), ideal self-esteem is considered to be a global representation of the attributes a person would like to possess (see Remue, De Houwer, Barnes-Holmes, Vanderhasselt & De Raedt, 2013). Numerous studies have provided compelling evidence for the role of discrepancies between ideal and actual self in depressive disorders (e.g., Moretti & Higgins, 1999; Tangney, Niedenthal, Covert, & Barlow, 1998). One way to conceptualize actual and ideal self-esteem is in terms of the type of relation between the self and positive and negative valence. One could argue that both actual and ideal self-esteem involve such a relation but differ in the way that these concepts are related. Whereas actual self-esteem refers to current beliefs about the self (i.e., I am good / bad), ideal self-esteem would reflect beliefs about the desired future self (i.e., I want to be good / bad). These beliefs are propositional in nature because, unlike associations, they contain information about how concepts are related (see Lagnado et al., 2007, for an excellent discussion of the core differences between propositions and associations).

De Raedt and colleagues’ (2006) hypothesis certainly seems plausible given implicit measures are usually designed to assess whether one set of concepts (e.g., ‘self’ and ‘other’) is somehow related to a second set of concepts (e.g., ‘positive’ or ‘negative’) without regard to the way in which those concepts are related. To illustrate, consider a typical self-esteem IAT. During a first test phase, participants categorize items related to the self (e.g., the first name of the participant) and positive words (e.g., HAPPY) using one response key and items related to someone else (e.g., the first name of another participant) and negative words (e.g., INCOMPETENT) using another response key. During a second test phase, response mappings are reversed so that self-related items and negative words are assigned to the first key whereas other-related items and positive words are assigned to the second key. The difference in how well someone performs during the first relative to the second phase is considered to provide an overall measure of how readily this person associates the concept “self” with positive or negative valence. However, an IAT effect does not reveal how a person relates those concepts. For some individuals, the IAT score might reflect the extent to which someone believes that he or she is good (i.e., actual self-esteem) whereas for other individuals, the same score might reflect that he or she wants to be good (i.e., ideal self-esteem).

With this idea in mind, Remue and colleagues (2013) set out to distinguish actual and ideal implicit self-esteem using a relatively new procedure known as the Implicit Relational Assessment Procedure (IRAP; Barnes-Holmes et al., 2006). The IRAP stems from an intellectual tradition known as Contextual Behavioral Science (Hayes, Barnes-Holmes, & Wilson, 2012) and a functional account of human language and cognition known as Relational Frame Theory (RFT; Hayes, Barnes-Holmes, & Roche, 2001). Unlike many other implicit measures, the IRAP was specifically designed to capture how objects, stimuli and events are automatically related to one another (i.e., what RFT researchers refer to as ‘brief and immediate relational responses’; see Barnes-Holmes, Barnes-Holmes, Stewart, & Boles, 2010; Hughes, Barnes-Holmes, Vahey, 2012). If we assume that the ease with which people automatically relate stimuli is mediated by propositional knowledge in memory (see Hughes, Barnes-Holmes, & De Houwer, 2011 for an in-depth discussion), it could be argued that performance on the IRAP provides an implicit measure of propositional knowledge. In order to test this assumption, Remue et al. exposed a group of dysphoric and non-dysphoric participants to two separate IRAPs: one designed to assess actual and another to assess ideal self-esteem. Consistent with their predictions, two contrasting patterns of implicit self-esteem emerged, with dysphoric participants showing evidence of lower actual and higher ideal self-esteem relative to their non-dysphoric counterparts who showed evidence of higher actual and lower ideal self-esteem compared to the former group. These results tentatively suggest that the implicit measures used by De Raedt and colleagues (2006) may have assessed ideal self-esteem in the dysphoric group and actual self-esteem in the non-dysphoric group.

The present study set out to extend the work of De Raedt and colleagues (2006) and Remue and colleagues (2013) in several ways. Within the context of self-esteem, we examined whether implicit measures that are designed to capture associations may in fact reflect the operation of qualitatively distinct sets of propositions. Whereas De Raedt and colleagues only used an IAT and Remue et al. only used IRAPs, we asked our participants to complete both a self-esteem IAT and two separate IRAPs, one targeting actual ('I am') and another targeting ideal self-evaluations ('I want to be'). Moreover, we pre-selected participants who reported either high scores (i.e., dysphoric group) or low scores (i.e., non-dysphoric group) on an index of depressive symptoms during an earlier screening study. Based on the ideas of De Raedt and colleagues (2006), we expected contrasting patterns of implicit self-esteem as a function of the task employed and group tested. Although we expected dysphoric and non-dysphoric participants to produce similar (positive) scores on the self-esteem IAT, we anticipated that they would diverge in their respective IRAP performances, with the former group showing stronger ideal relative to the actual implicit self-esteem and the latter group showing stronger actual relative to ideal self-esteem. Furthermore, based on the idea the IAT might capture different aspects of self-esteem in dysphoric than in non-dysphoric participants, we expected that the IAT would correlate most strongly with the ideal self-esteem IRAP in the dysphoric group but with the actual self-esteem IRAP in the non-dysphoric group. In addition, we included a number of questionnaires to investigate whether a discrepancy between actual and ideal self-esteem would also emerge at the explicit level. Our goal here was to explore how implicit and explicit self-esteem interact within and between these two groups.

Finally, it is worth noting that the current study provided us with an opportunity to address three methodological issues that arose in our earlier work. First, Remue and colleagues (2013) employed a shortened version of the IRAP containing two (rather than the standard of six) test blocks which may have adversely affected the reliability of the observed effects (see Hughes & Barnes-Holmes, 2013). In order to circumvent this concern, and facilitate a direct comparison between our results and those observed elsewhere in the literature, the current study included a standard (six-block) version of the IRAP. Second, while Remue and colleagues (2013) required participants to respond with both speed (2500ms) and accuracy (80%) during the IRAP, recent evidence suggests that introducing even stricter mastery criteria could lead to more robust IRAP scores (Barnes-Holmes et al., 2010). Hence, we opted for a more stringent set of latency criteria than before. Third and finally, although many of the stimuli used in Remue and colleagues were related to self-esteem several were more directly relevant to depression in general (e.g., “Happy”, “Sad”). Unlike the IAT in which the definition of the categories (e.g. ‘Me” and ‘Worth’) appears to be more important than the individual stimuli used (e.g. ‘Peter’ and ‘Successful’) (De Houwer, 2001), it is crucial that stimuli directly relevant to the domain of interest be employed in the IRAP (see Nicholson, Dempsey & Barnes-Holmes, in press for a discussion). Therefore in the current study we only included items that were directly related to self-esteem.

METHOD

Ethics statement

Participants gave their written informed consent and received either credit or €10 for their participation. The study was approved by the ethics committee of Ghent University. The investigation was conducted in full accordance with the principles expressed in the Declaration of Helsinki.

Participants

Sixty-four students participated in the current study. Prior to the study, they were screened for depressive symptomatology using the BDI-II-NL (van der Does, 2002). These same participants completed the BDI-II-NL for a second time upon arriving at the laboratory for the actual test session. Both BDI-II-NL (pretest and test) scores correlated highly, and were based on the same high/low classifications. Using the recommended cut-off score from the BDI-II-NL manual, the final sample was divided into two groups: a low BDI group (≤ 13) consisting of 35 students (30 women and 5 men) ranging from 18 to 30 years (*M* = 21, *SD* = 2.84) and a high BDI group (≥ 14) consisting of 29 students (25 women and 4 men) ranging from 18 and 25 years (*M* = 19.38, *SD* = 2.06). Assignment to BDI groups was based on the BDI score during the second (test) session. By design, the high BDI group had significantly higher scores during test (*M* = 21.93, *SD* = 8.36) compared to the low group (*M* = 4.8, *SD* = 3.72), *t*(62) = 10.91, *p* < .001[2].

Materials

Beck depression inventory (BDI-II-NL). The BDI-II-NL, a 21 item self-report inventory, was used to measure the severity of depressive symptoms (Beck et al., 1996). The Dutch translation of the BDI-II has shown high internal consistency: Cronbach's α of .92 for a patient population and .88 for a healthy control group. Also, the validity index satisfies general psychometric criteria (van der Does, 2002).

Rosenberg self-esteem scale (RSES, Rosenberg, 1965; Dutch translation by Franck, De Raedt, Barbez, & Rosseel, 2008b**).** This self-report scale measures global feelings of self-worth or self-acceptance and is widely used because of its proven validity and test-retest reliability. It consists of 10 items where participants have to state whether they totally agree, agree, disagree or totally disagree with the presented statement. The overall score represents the degree of global self-esteem, with higher scores indicating higher self-esteem.

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[2] Note that, by design, BDI scores during the test session were not normally distributed (Shapiro-Wilk = .892; *p* < .001) due to the fact that we invited participants with extremely high or low BDI scores during initial screening. We therefore used BDI as a dichotomous rather than continuous variable in our analyses (however, for a critical discussion see MacCallum, Zhang, Preacher, & Rucker, 2002).

Semantic differentials. Participants were presented with the same twelve target stimuli as used in the IRAP and IAT (six positive and six negative) and asked to evaluate each of them using a five-point scale ranging from 0 (Totally Disagree) to 4 (Totally Agree). Each word was rated twice, once with respect to actual self-evaluations (e.g., '*I am successful*') and once with respect to ideal self-evaluations ('*I want to be successful*'). In this way we sought to acquire two broad measures of self-esteem, one related to self-reported actual (SR Actual) and a second related to self-reported ideal (SR Ideal) self-esteem. Finally, participants were given a number of additional questionnaires related to their psychological flexibility and rumination. However, all of these served exploratory purposes and will not be discussed further.

IAT. During the IAT, the words '*Me*' and '*Not Me*' served as the target category labels and the words '*Worth*' and '*Worthless*' served as the attribute category labels. Six positively valenced (the Dutch words for confident, nice, successful, important, intelligent, competent and pleasant) and six negatively valenced Dutch adjectives (insecure, inferior, failure, worthless, useless and stupid) served as attribute stimuli. The participant's first name and surname, place of residence and nationality were used as stimuli for the target category *'Me'*. The first name and surname of another participant were used as two items for the target category *'Not me'* while a fabricated (non-Belgian) place of residence and nationality were used as two additional items in that same category.

Prior to the onset of the IAT, participants were informed that a series of words would appear one-by-one in the middle of the screen and that their task was to categorize those stimuli as quickly and accurately as possible. They were also informed that the category labels 'Me' and 'Not Me' as well as 'Worth' and 'Worthless' would appear on the upper left and right sides of the screen and that stimuli presented in the middle of the screen should be assigned to these categories by pressing either the E (left response) or the I key (right response) on an AZERTY keyboard. Each trial started with the presentation of a fixation cross for 200ms in the middle of the screen followed immediately by a target or attribute stimulus. If the participant categorized a word correctly - by selecting the appropriate key for that block of trials - the stimulus disappeared from the screen and the next trial began. In contrast, an incorrect response resulted in the presentation of a red 'X' which remained on-screen until the correct key was pressed. Overall, each participant completed seven blocks of trials. During the first block of 20 practice trials they were requires to sort the self- or other-related words into their respective categories, with ‘Me’ assigned to the left (‘E’) key and ‘Not Me’ with the right (‘I’) key. On the second block of 20 practice trials participants had to assign positively valenced stimuli to the ‘Worth’ category using the left key and negative stimuli to the ‘Worthless’ category using the right key. Blocks 3 (20 trials) and 4 (40 trials) involved a combined assignment of target and attribute stimuli to their respective categories. Specifically, participants categorized ‘Me’ and positive words using the left key and ‘Not Me’ and negative words using the right key. The fifth block of 20 trials reversed the key assignments for self- and other-related items, with ‘Me’ now assigned to the right key and ‘Not Me’ with the left key. Finally, the sixth block (20 trials) and seventh block (40 trials) required participants to categorize ‘Me’ and negative words with the right key and ‘Not Me’ and positive words with the left key. The order of the critical test blocks was counterbalanced across participants.

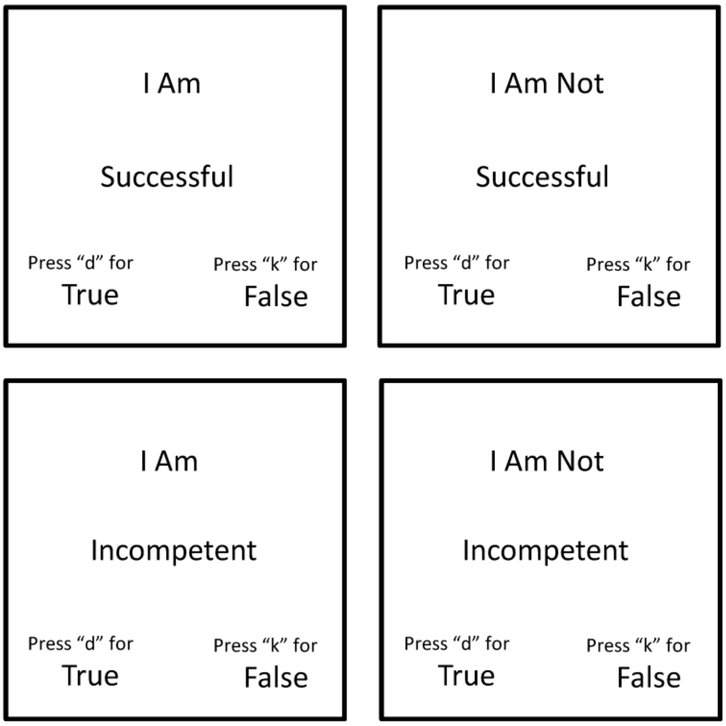
The location of the picture cued the location of the target correctly on 50% of the trials (valid trials) and incorrectly on the other 50% (invalid trials). Participants were informed that the location of the cue was not predictive for the target location. All the pictures were presented randomly with an equal number of presentations and trial type (valid versus invalid). Using long cue presentations, people can be faster at responding to invalid trials in comparison to valid trials. This effect is known as the inhibition of return (IOR) effect (Posner & Cohen, 1984) and results from inhibition of the previously attended location in favor of the unattended location.

To control for response strategies (for example focussing on only one fplaceholder during the experiment), 24 trials were inserted in which the fixation cross was briefly (150ms) replaced by an arrow. Participants had to indicate if this arrow pointed left or right. Three participants were removed from analysis due to their mistakes (more than 50%) on these arrow trials.

IRAP. The IRAP is a computerized latency-based measure which requires participants to respond quickly and accurately to stimuli in ways that are deemed consistent or inconsistent with their prior learning history. Specifically, half of the IRAP trials require participants to respond in ways that are consistent with their (assumed) history of learning, while the other half require participants to respond in ways that are inconsistent with that same history. For instance, participants might be asked to respond “True” to the statement “*I want to be Good*” on half of the trials but to respond “False” on the other half. The difference in time taken to respond on consistent relative to inconsistent trials - defined as the IRAP effect - is assumed to provide an index of the strength or probability of the targeted relations. Reliability estimates differ substantially between studies, ranging from values as low as .23 to values as high as .81 (for more on the measure and its psychometric properties see Golijani-Moghaddam, Hart, & Dawson, 2013; Gawronski, & De Houwer, 2014).

In the current study, each IRAP involved a minimum of two and a maximum of six practice blocks followed by a fixed set of six test blocks. Each block consisted of 24 trials that presented one of two self-related label stimuli (e.g., ‘*I Am*’ or ‘*I Am Not*’) in the presence of one of two types of target stimuli (positive or negative words drawn from the same set as the IAT) and required participants to emit one of two relational responses (‘True’ or ‘False’). In this way, the IRAP was comprised of four different types of trials (or “trial-types”: *Self-Positive*; *Self-Not Positive*, *Self-Negative* and *Self-Not Negative*; see Figure 1). Trials were presented in a quasi-random order so that each of the four trial-types appeared six times within each block in a random order.

Figure 1. *Examples of the four trial-types used in the actual self-esteem IRAP. On each trial, a label stimulus (e.g., 'I am' or 'I am not'), a target stimulus (e.g., 'Successful' or 'Incompetent') and two relational response options (True and False) were shown on the screen. Note: the ideal and actual self IRAPs were identical in all regards except for their respective label stimuli ('I want to be' and 'I don't want to be' versus 'I am' and 'I am not' respectively).*



Prior to the IRAP participants were informed that they would complete a word categorization procedure that required them to follow a general rule for responding. Specifically, on one set of blocks they were presented with the message "*Please respond AS IF I am positive and I am not negative*" (self-positive block), while on the alternative set of blocks they were presented with the message "*Please respond AS IF I am negative and I am not positive*" (self-negative block). Stated more precisely, a correct response during self-positive blocks required participants to select 'True' when 'I Am' appeared with a positive target stimulus (e.g., '*Intelligent*') or when 'I Am Not' appeared with a negative target (e.g., '*Stupid*'). At the same time, participants were also required to choose 'False' when 'I Am' appeared with a negative word or when 'I Am Not' appeared with a positive target stimulus. The opposite pattern of responding was required during self-negative blocks. The general rule for responding was alternated across each IRAP block to form three successive pairs of test blocks.

The IRAP commenced with a pair of practice blocks. Participants progressed from the practice to the test blocks when they met accuracy (at least 80% accuracy) and latency criteria (median latency of less than 2000ms) on a successive pair of practice blocks. Failure to meet these criteria resulted in re-exposure to another pair of practice blocks until participants either achieved the mastery criteria or a maximum of three pairs of practice block were completed. Failure to satisfy task requirements following three pairs of practice blocks resulted in participants being thanked, debriefed and dismissed (in the current study one participant failed to complete both IRAPs, another three failed the actual self IRAP while six more did not satisfy those same criteria during the ideal self IRAP). When the above criteria were met, a fixed set of three pairs of test blocks were then administered. Finally, it is worth noting that the actual and ideal self IRAPs differed only with respect to their self-related label stimuli. That is, while the actual self IRAP required participants to respond to valenced target stimuli using the terms '*I Am*' or '*I Am Not*' the ideal self IRAP required participants respond to the same stimuli in terms of '*I Want To Be*' or '*I Don't Want To Be*'.

Procedure

Upon arriving at the laboratory participants were welcomed by the researcher, asked to read and sign statements of consent and seated in front of a computer from which they received all instructions. They were informed that they would complete a number of questionnaires as well as computer based tasks - and given the sensitive nature of the study - that they would be randomly assigned an identification number in order to preserve their confidentiality and anonymity. Thereafter, participants completed the various self-report measures, an IAT and two IRAPs. The order of questionnaires and implicit measures as well as the order of the two IRAPs were counterbalanced across participants. The IAT was always administered prior to the two IRAPs. Overall, the experiment lasted about 60 minutes.

RESULTS

Data Preparation

Counterbalancing the order of the two IRAPs as well as evaluative measures (questionnaires and implicit measures) did not produce any main or interaction effects. Consequently, data were collapsed across both factors.

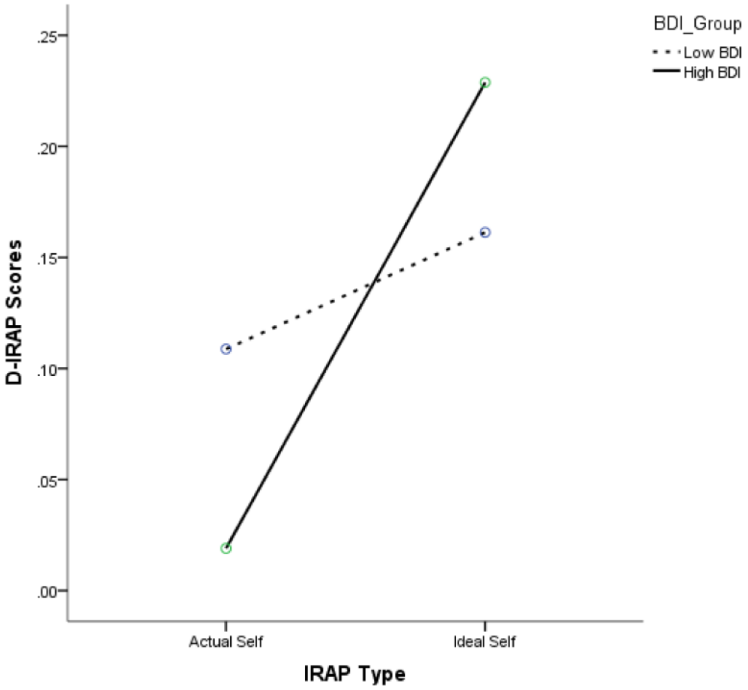
Implicit Measures

IAT. Following the recommendations of Greenwald and colleagues (2003), response latency data from the IAT was prepared using the D1 scoring algorithm. This transformation resulted in one IAT score for each participant, reflecting the difference in mean response latency between consistent and inconsistent blocks divided by the overall variation in those latencies. Scores were calculated so that positive values reflected a relatively higher positive self-esteem bias whereas negative values indicated the opposite. When IAT scores from the dysphoric and non-dysphoric groups were submitted to an independent samples t-test no significant difference emerged, $t(62) = .81$, $p = .42$. Consistent with our predictions, dysphoric ($M = .59$, $SD = .47$) and non-dysphoric groups ($M = .68$, $SD = .35$) both demonstrated similar and robust levels of positive implicit self-esteem.

IRAP. Response latency data were transformed into *D*-IRAP scores using an adaptation of Greenwald et al.'s (2003) *D* algorithm (for details of this data transformation see Barnes-Holmes et al., 2010). For each IRAP, we calculated a single overall *D*-IRAP score - one for the actual self IRAP and a second for the ideal self IRAP. These values were calculated so that higher scores reflected higher levels of (actual or ideal) self-esteem. When submitted to a 2 (*BDI Group*) x 2 (*IRAP-Type;* Actual vs. Ideal) mixed-models ANOVA, a main effect for IRAP-Type, $F(1, 52) = 14.72$, $p < .001$, $\eta^2_{partial} = .22$, as well as a two-way interaction between IRAP-Type and BDI Group was obtained, $F(1, 52) = 5.29$, $p = .03$, $\eta^2_{partial} = .09$. This crucial interaction effect reveals a stronger discrepancy between actual and ideal self-esteem IRAP scores in dysphoric participants

(*M* = .21, *SD* = .29) than in non-dysphoric participants (*M* = .05, *SD* = .19). To explore this interaction, we compared BDI groups for each IRAP separately as well as both IRAPs for each group separately. The first set of analyses did not reveal differences between the dysphoric and non-dysphoric groups in terms of their respective IRAP performances (all *ps* > .2). The second set of analysis did not reveal a difference between scores on the actual (*M* = .11, *SD* = .27) and ideal (*M* = .16, *SD* = .24) IRAPs for non-dysphorics (*p* > .2) but did reveal more positive scores on the ideal self (*M* = .23, *SD* = .24) relative to the actual self IRAP (*M* = .02, *SD* = .22) for dysphoric participants, *t*(25) = 3.6, *p* =.001*, d =* .93 (see Figure 2)[3].

Figure 2. *Mean D-IRAP scores as a function of IRAP-Type (actual vs. ideal) and BDI group (high vs. low). A positive value indicates a pro self-esteem bias and a negative score indicates the opposite.*



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[3] To assess the internal consistency of the IRAP, two split-half reliability scores were calculated, one for the actual self IRAP and one for the ideal self IRAP. In each case, two scores were calculated, one for odd trials and the second for even trials, and these were obtained in the same way as for the overall D-IRAP score, except that the D-algorithm was applied separately to all odd trials and even trials. The split-half correlations between odd and even scores, applying Spearman-Brown corrections, for the Actual-Self IRAP was (r = .53) and Ideal-Self IRAP was (r = .45). These split-half reliabilities were based on all participants who completed both IRAPs. The IAT's internal consistency (r = .96) was based on a Spearman-Brown corrected split-half correlation, the split-halves being derived from alternating pairs of trials in both critical blocks

Explicit Measures

Consistent with our predictions, we found that dysphoric participants (*M* = 13.0, *SD* = 3.0) showed significantly lower self-esteem scores on the Rosenberg scale relative to their non-dysphoric counterparts (*M* = 20.6, *SD* = 3.5), *t*(62) = 9.11 , *p* < .001, *d* = 2.29. When actual and ideal-self evaluations were submitted to a 2 (*Self*: Actual vs. Ideal) x 2 (*BDI Group*) mixed models ANOVA, a main effect for BDI Group, *F*(1, 62) = 48.13, *p* < .001, $\eta^2_{partial}$ = .44, and a two-way interaction between Self and BDI Group was obtained, *F*(1, 62) = 50.99, *p* < .001, $\eta^2_{partial}$ = .45. This reveals that dysphoric participants showed significantly higher self-discrepancy scores (*M* = 19.83, *SD* = 6.60) than their non-dysphoric counterparts (*M* = 9.91, *SD* = 4.45). To explore this interaction, we compared BDI groups for each self-evaluation separately as well as both self-evaluations for each group separately. The first set of analyses revealed that non-dysphoric participants (*M* = 35.14, *SD* = 4.72) reported significantly higher actual self-evaluations than their dysphoric counterparts (*M* = 24.24, *SD* = 6.03), *t*(62) = 8.11, *p* < .001. Dysphoric (*M* = 44.07, *SD* = .34) and non-dysphoric individuals (*M* = 45.06, *SD* = 2.89) showed similar and high levels of ideal-self evaluations (*p* = .22). The second set of analysis revealed a significant difference between actual and ideal self-evaluations for both dysphoric, *t*(28) = 16.18, *p* = .001, and non-dysphoric participants, *t*(35) = 13.17, *p* = .001.

Correlations.

Implicit-explicit correlations. In the non-dysphoric group, the IAT and ideal self-evaluations (SR Ideal) correlated positively, *r* = 0.43, n = 35, *p* = .009, while a marginally significant positive correlation appeared between the IAT and actual self-evaluations (SR Actual), *r* = 0.30, n = 35, *p* = .077. However, no significant correlations emerged between the actual and ideal IRAPs and any of the explicit measures. With respect to the dysphoric group, no significant correlations emerged between the IAT and the various explicit measures. However, the actual (but not the ideal self IRAP) correlated positively with self-esteem (RSES), *r* = 0.42, n = 28, *p* = .027, and actual self-evaluations (SR Actual), *r* = 0.53, n = 28, *p* = .004.

Implicit-Implicit correlations. A series of correlations within dysphoric and non-dysphoric participants were used to determine whether IAT and IRAP effects were related but none of the tests proved significant (see Tables 1 and 2): IAT with actual self IRAP (all *ps* > .3); IAT with ideal self IRAP, (all *ps* > .6). A significant correlation did emerge between the actual and ideal self IRAPs for the non-dysphoric, *r* = .70, n = 28, *p* < .001, but not the dysphoric group (*p* = .51)[4]

Explicits. In the non-dysphoric group, we found a significant positive correlation between self-esteem (RSES) and actual (SR Actual), *r* = 0.56, n = 35, *p* = .001. Finally, actual (SR Actual) and ideal (SR Ideal) self-esteem correlated positively, *r* = 0.40, n = 35, *p* = .019. With respect to the dysphoric group, self-esteem (RSES) and actual self-evaluations (SR Actual) correlated positively, *r* = 0.71, n = 29, *p* < .001 (see Tables 1 and 2).

Table 1. *Correlation matrix of explicit and implicit self-esteem scores for the low BDI group.*

	IAT	Actual IRAP	Ideal IRAP	RSES	SR Actual	SR Ideal
IAT						
Actual IRAP	.20					
Ideal IRAP	.10	.70**				
RSES	-.03	-.23	.05			
SR Actual	.30	.04	.05	.55**		
SR Ideal	.43*	.17	.20	.01	.40*	

Note. *RSES = Rosenberg Self-esteem Scale; SE Actual = Self-reported actual self-esteem; SR Ideal = Self-reported ideal self-esteem. * = p < .05 ** = p < .001.*

Table 2. *Correlation matrix of explicit and implicit self-esteem scores for the high BDI group*

	IAT	Actual IRAP	Ideal IRAP	RSES	SR Actual	SR Ideal
IAT						
Actual IRAP	.02					
Ideal IRAP	.03	.13				
RSES	.28	.42*	-.01			
SR Actual	.20	.53*	-.06	.71**		
SR Ideal	.09	-.31	.06	.00	.11	

Note. RSES = Rosenberg Self-esteem Scale; SE Actual = Self-reported actual self-esteem; SR Ideal = Self-reported ideal self-esteem. * = *p* < .05 ** = *p* < .001.

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[4] Although participants were pre-selected because they had high or low scores on the BDI during a screening study, a number of individuals nevertheless revealed BDI scores around the cut-off point during the actual test session. When a more stringent cut-off value was employed to create the non-dysphoric (scores from 0-9) and dysphoric groups (scores from 16-64) an almost identical set of findings emerged.

DISCUSSION

Accumulating evidence suggests that although depressed and non-depressed people differ with respect to their explicit self-esteem they demonstrate surprisingly similar levels of (positive) implicit self-esteem esteem (e.g., Gemar et al., 2001, Greenwald et al., 2002; Franck et al., 2008a; Risch et al., 2010; Yamaguchi et al., 2007). In an attempt to explain these surprising findings, it has been argued that the IAT and other implicit measures capture *actual* self-esteem in non-depressed participants but *ideal* self-esteem in depressed participants (De Raedt et al., 2006; Remue et al., 2013). In the current study we put this assumption to the test. In particular, we examined whether implicit measures designed to capture associations between the self and valenced stimuli (IAT) actually reflect the operation of qualitatively distinct sets of self-related propositions (IRAP). Whereas De Raedt and colleagues (2006) only used an IAT and Remue et al. (2013) only used IRAPs, we asked participants to complete both a self-esteem IAT and two separate IRAPs, one targeting actual ('*I am*') and another targeting ideal self-evaluations ('*I want to be*'). Based on previous work, we expected to observe three outcomes. First, dysphoric and non-dysphoric participants should produce similar (positive) scores on the self-esteem IAT. Second, those same participants should diverge in their respective IRAP performances, with dysphorics showing stronger ideal relative to the actual self-esteem and non-dysphorics stronger actual relative to ideal self-esteem. Third, performance on the actual-self IRAP (in the non-dysphoric group) and performance on the ideal-self IRAP (in the dysphoric group) should differentially correlate with the IAT.

Consistent with our first prediction, we found that dysphoric and non-dysphoric participants were relatively quicker to categorize self-related words with positive compared to negative stimuli on the IAT. This finding is also consistent with work elsewhere in the literature on the near universal positivity towards the self (Yamaguchi et al., 2007) that seems to emerge regardless of current or former depressive symptomatology (Gemar et al., 2001; Franck et al., 2008a). At the same time, our results extend beyond this early work. As indicated by the significant interaction between IRAP type and group, dysphoric participants showed a greater discrepancy between their (implicit) actual and ideal self-esteem than their non-dysphoric counterparts. This result replicates the crucial finding of Remue and colleagues (2013). However, several caveats should be noted. First, although the interaction between IRAP type and group was significant, several of the simple main effects involved in this interaction did not reach conventional levels of significance. Whereas dysphorics did show higher scores on the ideal self-esteem IRAP than on the actual self-esteem IRAP, non-dysphorics did not score differently on the two IRAPs. Hence, we did not replicate the finding of Remue et al. that non-dysphorics have a higher score on the actual self-esteem IRAP than on the ideal self-esteem IRAP. Unlike Remue et al., we also did not observe significant differences between groups in their performance on each of the IRAPs. Finally, and contrary to our third prediction, we did not observe a contrasting pattern of correlations between the IAT and IRAP as a function of depressive symptomatology.

Although our main goal was to investigate differences between different types of implicit self-esteem, we also included a number of questionnaires in order to investigate explicit self-esteem, and its relationship with implicit self-esteem. We found that dysphoric participants produced significantly lower scores on the Rosenberg scale relative to non-dysphoric participants. However, when actual and ideal-self evaluations were compared, a more complex picture emerged. Both groups displayed higher levels of ideal relative to actual-self evaluations, with the dysphoric group producing significantly lower actual-self scores than their non-dysphoric peers. Following the discrepancy theory of (Higgins, 1987) which states that the discrepancy between the actual and ideal self is a cognitive risk factor for depression, and consistent with previous work in this area (e.g., Stevens, Holmberg, Lovejoy, & Pittman, 2014), individuals suffering from higher levels of self-reported depressive symptomatology displayed greater discrepancies between their ideal and actual self-evaluations than those who did not report such symptoms. Note that discrepancy theory is supported not only by the effects that we observed on the explicit measures but also by the differences between groups in actual-ideal self-esteem discrepancy on the implicit measures.

We also found that implicit and explicit self-esteem correlated with one another in different ways as a function of depressive symptomatology. For instance, actual and ideal-self evaluations in the non-dysphoric condition tended to correlate regardless of the measure used. That is, explicit measures of ‘actual’ self-esteem correlated with explicit ‘ideal’ self-esteem while both explicit measures correlated with performance on the IAT in the non-dysphoric group. However, no correlations emerged between actual and ideal self-evaluations on either the explicit or implicit measures for participants in the dysphoric group.

Based on the above, an important next step is to develop a more sophisticated understanding of how self-related cognitions impact implicit and explicit self-esteem. In conducting this work several points are worth noting. First, the research presented here (as well as in Remue et al., 2013) utilized a normative sample of students that varied in their respective levels of self-reported depressive symptomatology. It remains to be seen whether a sample of clinically depressed, remitted or recovered participants would also show evidence of elevated ideal and diminished actual self-evaluations. Second, it may be that other implicit propositions such as those related to people’s personal expectations (e.g., ‘*I should be*’ or ‘*I need to be*’), how they compare themselves to others (e.g., ‘*I am good but others are better*’) or perceived failures (e.g., ‘*I’m not good enough*’) are even more important for predicting behavior. With this in mind, research could examine whether IRAPs targeting other types of propositional knowledge provide even better diagnostic and predictive information about clinical and non-clinical populations. Third, while the current study assessed propositions related to actual and ideal self-esteem separately via two IRAPs, it may be that juxtaposing one set of propositions (e.g., ‘*I am good*’) with another (e.g., ‘*I need to be better*’) within a single IRAP would enable us to determine how the assessment context influences the activation of different propositions and their respective influence on one another. It may be that activating two sets of propositions within rather than across measurement contexts could magnify discrepancies between actual and ideal self-evaluations.

To the best of our knowledge, we are the first to test the idea that a single IAT might actually reflect different implicit beliefs in different people. More specifically, the fact that dysphoric and non-dysphoric individuals reveal similarly high scores on IAT it might be due to the fact that the IAT reflects (high) ideal self-esteem in dysphorics and (high) actual-self esteem in non-dysphorics. Based on this idea, we predicted that IAT scores should correlate primarily with ideal self-esteem IRAP scores in dysphorics but with actual self-esteem IRAP scores in non-dysphorics. Our data do not, however, reveal such pattern of correlations. Although these null findings might indicate that the IAT does not capture different beliefs in different groups, it is also possible other factors came into play. First, IRAPs scores were somewhat unreliable which reduces changes of finding meaningful correlations. Second, counterbalancing of the order of the three tasks and administrating those three task within a single session could have increased error variance.

Finally, in replicating the work of Remue and colleagues (2013), we implemented a number of methodological refinements that sought to strengthen the arguments forwarded in that earlier paper (e.g., we used a traditional six-block variant of the IRAP, more stringent mastery criteria and stimulus selection). In their paper, a number of dysphoric and non-dysphoric participants (22%) failed to complete an IRAP and they may have done so for entirely different reasons, with the former failing due to a lack of motivation and the latter due to an inability to respond quickly and accurately to certain propositions (or even vice-versa). The modifications implemented in the current study appear to be successful insofar attrition rates (14%) were lower than those reported by Remue et al. and other studies elsewhere in the IRAP literature (see Hughes & Barnes-Holmes, 2013). In addition, the split-half reliability estimates obtained in the current study proved to be relatively higher then to those seen in Remue et al. and elsewhere in the literature.

Although we did observe a significant interaction between group and IRAP type, other effects failed to reach significance (e.g., lack of group difference on the IAT and the two IRAPs). In part, these null effects could be due to a lack of power because of the relatively small sample. We therefore recommend that replications of our findings - especially those comparing clinical and healthy populations - incorporate power analyses to ensure that an adequate sample size is employed so that statistically reliable inferences can be drawn. The lack of power could also explain why we failed to replicate the observation of Remue et al. that non-dysphorics score higher on the actual self-esteem IRAP than on the ideal self-esteem IRAP, as well as the observation that both groups differed in their performance on each of the IRAPs. Nevertheless, future work could explore whether differences in the number of IRAP blocks, stimuli employed, mastery criteria used or other procedural properties contribute to the inconsistencies observed between the results of our study and the results of Remue et al. For instance, we always exposed participants to an IAT before the two IRAPs, which may have influenced the expression of self-related evaluations on the IRAP. Future work could counterbalance these measures to assess potential carry-over effects between measures.

To summarize, our results indicate that dysphoric and non-dysphoric individuals experience implicit positivity towards the self. Most importantly, dysphoric participants revealed a stronger discrepancy between actual and ideal self-esteem as indexed by IRAPs compared to non-dysphoric participants. This finding not only supports the theoretical position that the discrepancy between actual and ideal self-esteem is related to dysphoria but also demonstrates the added value of using implicit measures such as the IRAP that can capture different implicit beliefs.

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CHAPTER 4

DOES A SINGLE NEUROSTIMULATION SESSION REALLY AFFECT MOOD IN HEALTHY INDIVIDUALS? A SYSTEMATIC REVIEW [1]

ABSTRACT

Non-invasive neurostimulation or neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) were welcomed as promising tools for investigating cognitive and mood processes in healthy participants as well as in patients suffering from neuropsychiatric conditions. Due to their rather easy application, both modalities have been used to experimentally examine prefrontal cognitive and emotional control. However, it remains unclear whether a single session of such stimulation may affect the mood of participants in a healthy state. We provide a systematic review of studies reporting the effects of a single session of rTMS or tDCS (…-2014) on self-reported mood in healthy participants. Although early studies reported significant effects on self-reported mood in healthy participants, more recent work investigating mood effects after a single rTMS/tDCS session has failed to find any significant changes in self-reported mood. Therefore it appears that a single session of rTMS/tDCS has no impact on mood in the healthy state.

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TABLE 1. ABBREVIATIONS USED IN THIS REVIEW.

ABBREVIATIONS	
TMS	TRANSCRANIAL MAGNETIC STIMULATION
RTMS	REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION
TDCS	TRANSCRANIAL DIRECT CURRENT STIMULATION
(L/R) PFC	(LEFT/RIGHT) PREFRONTAL CORTEX
DLPFC	DORSOLATERAL PREFRONTAL CORTEX
LF/HF	LOW-FREQUENCY/HIGH-FREQUENCY
EEG	ELECTROENCEPHALOGRAM
HPA	HYPOTHALAMIC–PITUITARY–ADRENAL AXIS
M/F	MALE/FEMALE
APB	ABDUCTOR POLLICIS BREVIS
ADM	ABDUCTOR DIGITI MINIMI
MDLPFC	MID-DORSOLATERAL PREFRONTAL CORTEX
VAS	VISUAL ANALOG SCALE
PANAS	POSITIVE AND NEGATIVE AFFECT SCHEDULE
NIMH	NATIONAL INSTITUTE OF MENTAL HEALTH MOOD SCALE
POMS	PROFILE OF MOOD STATES
UMACL	UNIVERSITY OF WALES INSTITUTE OF SCIENCE AND TECHNOLOGY (UWIST) MOOD ADJECTIVE CHECKLIST
SACL	STRESS AROUSAL CHECKLIST
EWL	EIGENSCHAFTSWOERTLISTE
SUDS	SUBJECTIVE UNITS OF DISTRESS
(F)MRI	(FUNCTIONAL) MAGNETIC ESONANCE IMAGING

INTRODUCTION

Since the introduction of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) as non-invasive tools for examining motor cortex functioning, the application of neurostimulation has substantially increased over the last several decades. Multiple sessions of neurostimulation are frequently used in the treatment of psychiatric disorders such as depression (e.g., Burt et al., 2002; Mitchell & Loo, 2006; O'Reardon et al., 2007; Boggio et al., 2008; George et al., 2010). These techniques are also used to investigate neural conductions and connections in the human brain, and are of considerable interest for researchers interested in understanding the basic neurophysiology of mood in healthy participants (Paus et al., 2001; Pascual-Leone et al., 2002). Non-invasive neurostimulation techniques have also been used to investigate specific cognitive functions of the prefrontal cortex in healthy participants. The prefrontal cortex (PFC) plays an important role in the neuronal networks involved in emotion processing (which is lateralized in the PFC) and mood regulation (Nitsche et al., 2012). Given that prefrontal regions have been associated extensively with cognitive and emotional regulatory processes (Cerqueira et al., 2008; Damasio, 2000; Davidson et al., 2002), it is crucial to know whether the reported effects of neurostimulation cannot be attributed to mood changes. Therefore, in this review, we offer a systematic overview of studies reporting the effects of a single session of repetitive TMS and tDCS on self-reported mood in healthy participants (for a more elaborate review on the techniques, mechanisms of action, and safety of TMS and tDCS, see George & Aston-Jones, 2010).

TMS involves delivering a brief magnetic pulse to the scalp through a coil. The magnetic field penetrates the brain and induces an electric field in the underlying region of the cerebral cortex (Barker et al., 1985). An electrical field of sufficient intensity will depolarize cortical neurons generating action potentials and can either activate or suppress motor, sensory, or cognitive functions, depending on the brain location and parameters of its delivery (George & Belmaker, 2007). Several studies have shown that rTMS is a safe technique when recommended guidelines are followed (Rossi et al. 2009) and can produce neural and behavioral effects that last for up to 40 minutes (e.g., Tsuji & Rothwell, 2002; Peinemann et al., 2004). Importantly, it has been suggested that activation of the left DLPFC or deactivation of the right DLPFC might have a positive impact on mood and emotion in clinically depressed individuals (Mitchell & Loo, 2006). Indeed, rTMS has been shown to alter aspects of cortical excitability and cortical inhibition (Chen & Seitz, 2001). Low-frequency (LF)-rTMS (≤ 1 Hz) is considered to 'inhibit' cortical regional activity, while high-frequency (HF)-rTMS (≥ 1 Hz) 'activates' cortical areas (Chen et al., 1997; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000a). It should be acknowledged that there is inter-individual variability in these inhibitory/excitatory effects. Although, most research on inter-individual variability has focused on the motor cortex (e.g., Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000b). Future research should expand their focus on other stimulation target sites. Early research in this area found that HF-rTMS applied to the left prefrontal cortex had a negative effect on mood in healthy volunteers (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997). However, these studies were often characterized by small sample sizes while the effects obtained were limited and inconsistent, and perhaps most importantly, not sham-controlled. The presence of a sham (placebo) condition is used to try and ensure that changes in performance can be ascribed to TMS effects upon a specific brain area (for a more in depth discussion on the different sham conditions used in neurostimulation research, see Sandrini, Umilta, & Rusconi, 2011). Therefore, a more comprehensive overview is needed to establish whether a single session of rTMS affects mood in healthy participants.

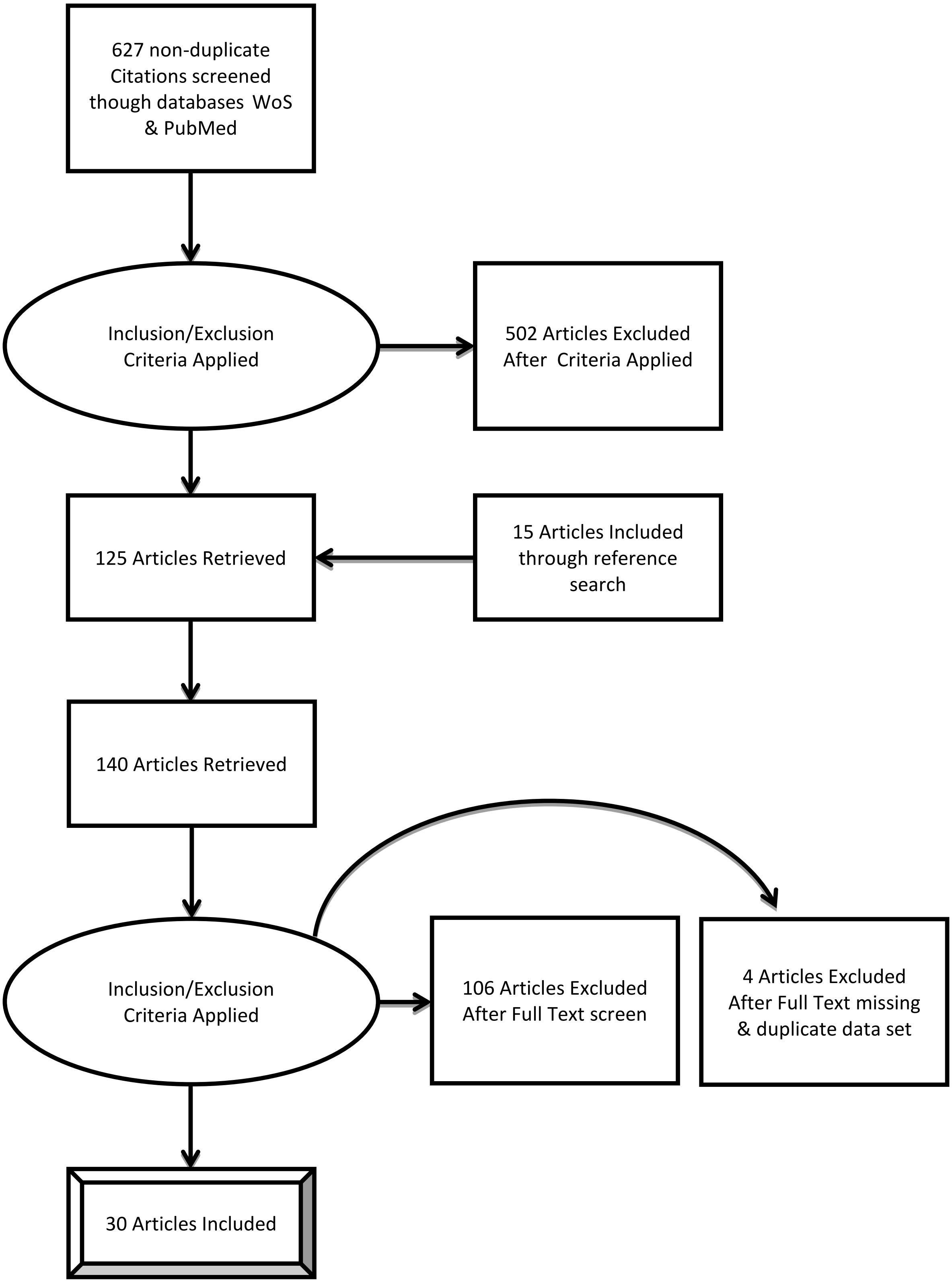
In recent years another neuromodulation tool (transcranial Direct Current Stimulation; tDCS), has received increased interest. tDCS is the application of a weak electrical direct current that flows between two electrodes (i.e. patches placed on the scalp). The current enters the brain from the anode, travels through the brain tissue towards the cathode, which has the ability to modulate spontaneous firing rates of the cortical neurons by depolarizing or hyperpolarizing the neural resting membrane potential. Anodal tDCS enhances while cathodal tDCS reduces cortical excitability (Priori, 2003; Nitsche et al., 2009). Research has shown that 10 minutes of stimulation can produce neural and behavioral effects that last for up to 40 minutes (Lang et al., 2004). Furthermore, tDCS modulates excitability in the motor, visual, and prefrontal cortex and differs from other noninvasive brain stimulation techniques such as TMS, since it does not induce neuronal firing by suprathreshold neuronal membrane depolarization, but rather modulates spontaneous neuronal network activity (Nitsche et al., 2008; Priori et al., 2009). Hence, the term Neuromodulation is often used. For the readability of this paper and given its common use in the literature we will refer to Neurostimulation for both techniques. The effects of tDCS depend on the polarity of the electric current such that anodal stimulation increases brain activity and excitability while cathodal stimulation reduces it. Although tDCS electrical fields are relatively non-focal, electrode positioning is critical. TDCS studies usually use one anode and one cathode electrode placed over the scalp to modulate a particular area of the central nervous system. However, a reference electrode is sometimes positioned on the shoulder, arm or leg. Electrode positioning is usually determined according to the International EEG 10-20 System (for a review of tDCS studies exploring different brain areas see Utz et al. 2010). In this review, several terms used to describe tDCS placements of the electrodes (i.e., “montages”) need to be discussed: next to the active electrode (which can be anodal or cathodal depending on the study question), researchers in the field also use the terms ‘‘reference’’ electrode to refer to the ‘‘neutral’’ electrode. However, the term ‘‘reference’’ electrode may also be problematic, because the ‘‘reference’’ electrode is not physiologically inert and can contribute to activity modulation as well. This could be a potential confound depending on the research question under investigation. Nonetheless, researchers use the above terms to highlight that they are operating based on the assumption that one electrode is being explored as the “stimulating” whereas the other is the “reference” (for a detailed discussion on the parameters of stimulation see Brunoni et al., 2012). The most applied montage of the electrodes used in research on depression is bilateral stimulation at frontolateral locations [F3 and F4 of the international EEG 10/20 system (Jasper, 1958)]. In anodal stimulation of the left prefrontal cortex, the anode placed over F3 (left prefrontal) and the cathode/anode over F4 (right prefrontal). This montage is often referred to as bifrontal tDCS or bilateral tDCS. However, this terminology is not always used consistently in the neurostimulation literature. Bifrontal refers to the positioning of two anodal electrodes on frontal regions (F3 & F4) and two cathode electrodes over the left and right mastoids, while bilateral refers to “anode and cathode on the same place contra lateral”. For reasons of clarity, in this review we will describe in detail the specific montages used in tDCS studies (for an overview on electrode placements and subsequent effects see Nitsche et al., 2008). TDCS is a safe method in humans as shown by neuro-psychological testing (e.g., Iyer et al., 2005; Fregni et al., 2006), electroencephalogram assessment (e.g., Iyer et al., 2005), neuroimaging studies (e.g., Nitsche et al., 2004) and brain metabolites evaluation (e.g. Nitsche & Paulus, 2001) (for a more elaborate review on the techniques, mechanisms of action, and safety, see George & Aston-Jones, 2010; or a state of the art overview, see Nitsche et al., 2008).

Importantly, although rTMS and tDCS are subject to different mechanisms of action – rTMS induces brief pulses of electric current of a relatively high intensity, whereas tDCS induces a continuous electric current of low intensity – stimulation of the PFC with rTMS and tDCS has been shown to produce similar effects in different neural circuitries (Fregni et al., 2008a), neurotransmitter systems (Keck et al., 2002; Nitsche et al., 2006; Strafella et al., 2001), and the treatment of psychiatric diseases (for a review see Miniussi et al., 2008; George et al., 2009; and George & Aston-Jones, 2010). However, in patient populations these treatment studies are based on multiple rTMS or tDCS sessions. Nonetheless, investigating the effects of a single session of rTMS and tDCS in experimental research holds important implications. Given that effects on cognition (e.g. information processing) within a study could be (partly) explained by changes in mood it is crucial to scrutinize possible effects of neurostimulation on mood. Since an abundance of research has shown the impact of mood on cognition (e.g., Ashby, Isen, & Turken, 1999; Pourtois, Schettino, & Vuilleumier, 2013), knowledge on the effect of neurostimulation on mood is crucial for understanding the effects on cognition in rTMS and tDCS research in healthy participants. Nevertheless, until now no unequivocal answer has been offered on this matter and the last review on this topic was conducted over 15 years ago (Mosimann, Rihs, Engeler, Fisch, & Schlaepfer, 2000). Based on the growing interest in and publication of rTMS and tDCS research (in healthy participants) over the last decade, an updated review on this topic seems warranted. Therefore, the aim of the present review is to provide a systematic overview of both rTMS and tDCS studies assessing the impact of one non-invasive stimulation session over the PFC on subjective self-reported mood of healthy participants. Moreover, we outline all possible stimulation sites and sides (left versus right (DL)PFC), as well as the frequency (HF vs LF), electrode placement, stimulation parameters, and mood measurement. Finally, it is important to note that the aim of this review is to not only focuse on studies which emphasize the possible impact of neurostimulation on mood as a primary hypothesis, but to also examine studies which reported mood effects as secondary to the main research question. Consequently, we can incorporate more easily null-findings, which otherwise might not have been published, to give a more conclusive overview and allow for a broader discussion on this topic.

METHOD

Articles for inclusion were identified by conducting a systematic literature search in the databases PubMed and Web of Science in the period between January 1955 and December 2014. The search criteria were 'transcranial', 'prefrontal', and 'healthy'. Based on this combination of terms we identified 627 hits. After careful consideration (title and abstract), we focused on studies with one session of stimulation targeting the prefrontal cortex, healthy participants, including all parameters and outcome measurements, which led to around 125 studies that appeared suitable. Review papers on topics related to neurostimulation and the references in the described studies were used for a renewed search for further inclusion in our systematic review. This led to further inclusions of 15 studies bringing the total to 140. We then refined (full text) this list further by only including studies that focused on the PFC as stimulation site, healthy participants, and that provided a clear description of all parameters and mood measurements. This resulted in the exclusion of 106 studies. The majority of these studies were excluded because of their different focus and their inadequate description of the mood measurements. Although we initially opted to only include studies which were sham-controlled, a review of all studies revealed that some of these non-sham-controlled studies were relevant to this particular question of mood effects in the past (e.g., George et al., 1996; Pascual-Leone et al., 1996). Of the 9 studies that are not sham-controlled, 4 of them showed mood effects after neurostimulation (Pascual-Leone et al., 1996; George et al., 1996; Padberg et al., 2001; Barrett et al., 2004). Because these studies may contribute to the understanding of the basic neurophysiology of mood generation and modulation, they have been frequently referenced and cited as evidence of possible effects. Therefore, we chose to also include non-sham-controlled studies in this review, even though sham-control is particularly important in rTMS/tDCS studies to control for the marked non-specific effects of the procedure, such as discomfort and noise. Furthermore, one study (Nedjat, Folkerts, Michael & Arolt, 1998) that has frequently been cited in many rTMS studies on mood in healthy participants is based on an abstract published in Electroencephalography and Clinical Neurophysiology (after 1999 known as Clinical Neurophysiology). After contact with one of the authors, it appeared the study was never published in full, however, the reference (of the abstract) was cited for the first time in the review of Mosimann, et al. (2000). Since then, Nedjat et al. (1998) has been frequently cited, but fails to address the stimulation parameters, sex of the participants and clear description of the experiment. Therefore, we chose to exclude this study. Finally, we took into account that some publications might (partially) use the same sample to test different hypotheses based on the identical authors and dates. Hence, we contacted all authors that might meet these criteria and excluded one study that used a sample which included participants who overlapped with another study (both studies tested different hypotheses but the absence of mood effects were reported in both). In conclusion, all studies (n = 30) fulfilling our predefined selection criteria were taken into account and evaluated according to their possible impact on mood. The study selection process was presented in a flow diagram (Figure 1).

FIGURE 1. A FLOWCHART OF LITERATURE SEARCH STRATEGY. A FLOWCHART OF THE INCLUSIONS AND EXCLUSIONS OF STUDIES IN THE CURRENT STUDY.



RESULTS

Description of the studies

The identified publications consisted of 30 studies, of which 13 were tDCS and 17 were rTMS studies. The studies comprise 16 papers which focused on mood effects of prefrontal non-invasive stimulation as a primary hypothesis, while in the other 14 studies mood changes were measured as a secondary outcome. Of these latter 14, two studies investigated the effect of HF-rTMS on sleep: Cohrs et al (1998) and Marshall et al. (2004). In two other studies, Fregni et al. (2008a; 2008b) looked into the effect of modulation of the prefrontal cortex with tDCS on food and smoking craving. In Iyer et al. (2004), the authors studied safety and cognitive effects of frontal tDCS. Brunoni and colleagues (2013) investigated polarity and valence dependent effect of tDCS on heart rate variability and salivary cortisol. Related to this, Baeken et al. (2014) looked at the effect of rTMS on the HPA-sensitivity after critical feedback. Vanderhasselt et al. (2013) and McIntire et al. (2014) studied cognitive effects of tDCS. The 5 other studies investigated the effects of prefrontal cortex stimulation on different emotional processing hypotheses, that is, on selective attention to threat (d'Alfonso et al., 2000), baseline state anxiety sensitivity (Baeken et al., 2011a), approach and withdrawal related emotional neuronal processes (Baeken et al., 2011b), negative emotional processing (Peña-Gómez et al., 2011), emotional state and processing (Nitsche et al., 2012). The characteristics of the included participants, stimulation protocols, mood ratings and outcomes of all identified studies assessing the influence of neurostimulation on mood are outlined in Table 2.

Table 2. Neuromodulation of the DLPFC and mood effects

Authors	Subjects (F) female (M) male	Sham controlled	Stimulation technique	Stimulation site	Frequency (LF) Low (HF) High	Train duration	Intertrain-interval	Pulses per session	Motor threshold	Mood Measure	Mean & SD	Mood effect
Pascual-Leone et al. (1996)	10 (4F)	NO	rTMS	L + R PFC & midfrontal	10 Hz (HF)	5s	25s	500	110%	VAS	*	rTMS over L PFC increases Sadness & decreases Happiness
George et al. (1996)	10 (4F)	NO	rTMS	L + R PFC & midfrontal/ occipital/ cerebellum	5 Hz (HF)	10s	120s	500	120%	VAS / PANAS / NIMH	*	rTMS over L PFC decreases Happiness (only with MINH)
Dearing et al. (1997)	9 (4F)	YES (45°/90° RPFC)	rTMS	L + R PFC	20 Hz (HF)	2s	58s	800	80%	VAS	*	rTMS over L PFC decreases Happiness
Cohrs et al. (1998)	12 (M)	YES (90° Vertex)	rTMS	L + R PFC & right left inferior parietal /	20 Hz (HF)	0.25s	8s	800	120%	VAS	*	No modulation effect of HF rTMS over L + R PFC on mood

				midoccipital								
D'Alfonso et al. (2000)	10 (F)	NO	rTMS	L + R PFC	0.6 Hz (LF)	*	*	*	130%	POMS	*	No modulation effect LF rTMS over L + R PFC on mood
Mosimann et al. (2000)	25 (M)	YES (90° LPFC)	rTMS	Left PFC	20 Hz (HF)	2s	30s	1600	100%	VAS	*	No modulation effect of HF rTMS over L PFC on mood
Habel et al. (2001)	18 (9F)	YES (?)	Single pulse TMS	L + R Frontal Cortex	0.5 Hz (LF)	*	*	60	130%	PANAS	*	No modulation effect of LF TMS over L + R FC on mood
Padberg et al. (2001)	9 (4F)	NO	rTMS	L + R DLPFC	10 Hz (HF)	5s	>30s	500	110%	VAS	YES	Mood decreased for both L + R DLPFC
Grisaru et al. (2001)	18 (11F)	YES	rTMS	L + R PFC	1 Hz (LF)	*	*	500	110%	VAS	*	No modulation effect LF rTMS over L + R PFC

												on mood
Jenkins et al. (2002)	19 (10F)	NO	rTMS	L + R DLPFC	1 Hz (LF)	60s	15s	*	*	PANAS / POMS / UMACL/ SACL/ BFS	YES	No modulation effect LF rTMS over L + R PFC on mood
Barrett et al. (2004)	10 Hz group 5 (F) & 1 Hz group 5 (F)	NO	rTMS	L + R DLPFC	10 Hz (HF) & 1 Hz (LF)	1s	10s	?150?	100%	Affect Q / PANAS / Vitality Scale	YES	10 Hz rTMS over L DLPFC decreased affect & vitality
Baeken et al. (2006)	28 (F)	YES	rTMS	L DLPFC	10 Hz (HF)	3.9s	26.1s	1560	110%	VAS / POMS	YES	No modulation effect HF rTMS over L DLPFC on mood

Baeken et al. (2008)	L: 20 (F) R: 27 (F)	YES	rTMS	L + R DLPFC	10 Hz (HF)	3.9s	26.1s	1560	110%	VAS / POMS / PANAS	YES	No modulation effect HF rTMS over L + R DLPFC on mood
Hoy et al. (2010)	10 (6F)	YES	rTMS	L DLPFC	5 Hz (HF)	10s	20s	900	120%	VAS	YES	No modulation effect HF rTMS over L DLPFC on mood after affective priming
Baeken et al. (2011)	24 (F)	YES	rTMS	R DLPFC	10 Hz (HF)	3.9s	26.1s	1560	110%	POMS	YES	No modulation effect HF rTMS over R DLPFC on mood
Baeken et al. (2011)	20 (F)	YES	rTMS	L DLPFC	10 Hz (HF)	3.9s	26.1s	1560	110%	POMS	YES	No modulation effect HF rTMS over L DLPFC on mood

Baeken et al. (2014)	30 (F)	YES	rTMS	L DLPFC	20 Hz (HF)	1.9s	12.1s	1560	110%	VAS	*	No modulation effect HF rTMS over L DLPFC on mood
Marshall et al. (2004)	30 (M)	YES	tDCS	Bifrontal (L + R PFC) (applied intermittently 15sec on, 15sec off)	0.26mA/cm² (equals .91 mA)	30min	NO task during tDCS	35 cm² electrodes size		PANAS / EWL	*	Mood improvement after tDCS???
Iyer et al. (2004)	103 (56F)	YES	tDCS	L PFC	1mA & 2mA	20min	During exp 2&3 a verbal fluency test	25 cm² electrodes size		VAS	*	No modulation effect tDCS over LPFC on mood
Fregni et al. (2008a)	24 (11F)	YES	tDCS	Bilateral (L + R PFC)	2 mA	20min	NO task during tDCS	35 cm² electrodes size		VAS	YES	No modulation effect tDCS over Bifrontal areas on mood

Fregni et al. (2008b)	23 (21F)	YES	tDCS	Bilateral (L + R PFC)	2 mA	20min	NO task during tDCS	35 cm^2 (anode) 100 cm^2 (cathode) electrodes size	VAS	*	No modulation effect tDCS over Bifrontal areas on mood
Koenings et al. (2009)	21 (9F)	YES	tDCS	Bilateral (L + R Orbitofrontal)	2.5mA	35min	NO task during tDCS	25 cm^2 electrodes size	POMS	YES (Mean change)	No modulation effect tDCS over Bifrontal areas on mood
Tadini et al. (2011)	82 (38F)	YES	tDCS	L DLPFC	1 & 2 mA	30 min	NO task during tDCS	35 cm^2 electrodes size	VAS	*	No modulation effect tDCS over L DLPFC on mood
Peña-Gómez et al. (2011)	16 (F)	YES	tDCS	L DLPFC	1 mA	20 min	An emotional processing task during both active and sham tDCS	35 cm^2 electrodes size	VAS / PANAS	YES	No modulation effect tDCS over L DLPFC on mood

Nitsche et al. (2012)	14 (5F) & 17 (8F)	YES	tDCS	L DLPFC	1 mA	20 min & 10 min	NO task during tDCS in exp1 A face recognition task during exp 2	35 cm² electrodes size	VAS /	*	No modulation effect tDCS over L DLPFC on mood
Plazier et al. (2012)	17 (M)	YES	tDCS	Bilateral (L + R DLPFC) & Bioccipital (L + R occipital area)	1 mA	20min	NO task during tDCS	35 cm² electrodes size	SUDS / POMS / PANAS	YES (M change % & SD)	No modulation effect tDCS over Bifrontal + Bioccipital areas on mood
Brunoni et al. (2013)	20 (17F)	YES	tDCS	Bilateral (L + R DLPFC)	1.5 mA	33min	IAPS pictures (negative & neutral) were shown during tDCS	35 cm² electrodes size	VAS	*	No modulation effect tDCS over Bifrontal areas on mood
Vanderhasselt et al. (2013)	25 (17F)	YES	tDCS	L DLPFC	2 mA	20min	NO task during tDCS	35 cm² electrodes size	PANAS	*	No modulation effect tDCS over L DLPFC on mood

Morgan et al. (2014)	18 (9F)	NO	tDCS	Bilateral (L + R DLPFC)	1 mA	12min	Filler task + retrieval phase of Memory Task	Circular electrodes with an area of 9 cm^2	PANAS	YES	Negative affect decreased after tDCS (due to “nervous” item)
McIntire et al. (2014)	30 (8F)	YES	tDCS	L DLPFC	2 mA	30min	NO task during tDCS	Custom set of electrodes (on each 5 separate EEG electrodes)	POMS + VAS	*	No modulation effect tDCS over L DLPFC on mood

*Notes.** not reported

Mood effects of non-invasive stimulation of the prefrontal cortex

In our review search only 6 studies reported changes in mood after stimulation, suggesting inconsistent results. Among these studies there are 5 rTMS and 1 tDCS studies. In their pilot study on the effects of HF- rTMS of the PFC on mood in 10 healthy volunteers, Pascual-Leone and colleagues (1996) found a significant increase in self-ratings of sadness and a significant decrease in self-ratings of happiness immediately after rTMS of the left DLPFC, as compared with right prefrontal and midfrontal stimulation. That same year George et al. (1996) investigated possible mood effects after HF-rTMS of the PFC in 10 healthy participants. Based on the comparison of five stimulation sites (left DLPFC, right DLPFC, midfrontal cortex, occipital cortex and cerebellum), results showed that the comparison of left and right DLPFC stimulation revealed significant differences between the hemispheres, with decreased happiness after left and decreased sadness after right prefrontal rTMS. However, both Pascual-Leone et al. and George et al. studies were not sham-controlled. One year later in the study of Dearing et al. (1997), a significant decrease of happiness and a non-significant increase of sadness was found after left compared with right prefrontal HF-rTMS in 9 healthy participants. However, these findings are based on comparison between left versus right side stimulation and not active versus sham stimulation. In Padberg et al. (2001) mood scores worsened for both left side as right side PFC stimulation and no significant differences were detected between left and right prefrontal HF-rTMS in 9 healthy participants. Finally, Barrett et al. (2004) found in a small sample of 10 female volunteers, a decreased negative affect after one session of active HF-rTMS applied over the left mid-dorsolateral prefrontal cortex. However, again no sham condition was included in the studies of Padberg et al. (2001) or Barrett et al. (2004).

The only study that found significant results of the effect of tDCS of the PFC on mood effects in healthy participants is Marshall et al. (2004). In this study the authors investigated in 30 healthy participants the effects of bifrontal anodal tDCS (electrodes were applied bilaterally at frontolateral locations (F3 and F4 of the international EEG 10/20 system) during a period of sleep, in order to look at the possible effects on declarative memory. Results showed signs of improved mood after tDCS in both the sleep as in the wake experiments. Importantly however, this result was never replicated in subsequent work (Kirov, Weiss, Siebner, Born, & Marshall, 2009; Marshall, Helgadóttir, Mölle, Born, 2006). In sum, of the 6 studies that found changes in mood, 5 of them found worsened mood after HF-rTMS over the left PFC (Pascual-Leone et al., 1996; George et al., 1996; Dearing et al., 1997; Padberg et al., 2001; Barrett et al., 2004), while Marshall et al. (2004) found an improvement in mood after bifrontal tDCS.

Overall effects of stimulation type on mood

Sample Size and Gender

The sample sizes in all studies varied greatly (for a detailed overview see Table 2). Small samples (≤12) were used in eight studies, medium samples (>12 & < 30) in 15 studies, and 7 studies used larger samples (≥30). Looking at the studies that recorded a significant effect of stimulation on mood (Pascual-Leone et al., 1996; George et al., 1996; Dearing et al., 1997; Padberg et al., 2001; Barrett et al., 2004; Marshall et al., 2004), all except Marshall et al. used small sample sizes, more specifically, 10 or 9 participants in total. Marshall et al. used a sample of 30 healthy participants.

Given the gender division in all of these studies, we can conclude that 12 studies used a homogenous sample. Of these 12 studies, four used an all-male (Cohrs et al., 1998; Mosimann et al., 2000; Marshall et al., 2004; Plazier et al., 2012) and eight an all-female sample (D'Alfonso et al., 2000; Barrett et al., 2004; Baeken et al., 2006; Baeken et al., 2008; Baeken et al., 2011a; Baeken et al., 2011b; Peña-Gómez et al., 2011; Baeken et al., 2014). In the other 18 studies a more heterogeneous sample was used (see Table 2). Looking at the studies that reported a mood effect, four out of six used a mixed sample (Pascual-Leone et al., 1996, 6M/4F; George et al., 1996, 6M/4F; Dearing et al., 1997, 5M/4F; Padberg et al., 2001, 5M/4F) while Barrett et al. (2004) and Marshall et al. (2004) used an all-female (10) and all-male (30) sample respectively. No gender effect has been found or described in any of the studies included in this review.

Table 3. Conditions, localization and stimulation timing

Authors	Conditions	Localization technique	Number/Time of sessions	Stimulation Order	Mood effect comparison
Pascual-Leone et al. (1996)	- R PFC (2X) - L PFC (2X) - Midfrontal (2X)	5cm rule	1 day (30min between different stimulations)	Crossover design: Random / Counterbalanced	Mood effect of Left vs Right / Midfrontal
George et al. (1996)	- L PFC - R PFC - Midfrontal - Occipital - Cerebellum	5cm rule	5 days (2 apart)	Crossover design: Random (except for Cerebellum stimulation, which was always last)	Mood effect of Left vs Right PFC
Dearing et al. (1997)	- L PFC - R PFC - Sham R PFC (45°)	5cm rule	1 day (20min between different stimulations)	Crossover design: Random	Mood effect Left vs Right PFC
Cohrs et al. (1998)	- L PFC - R PFC - L Inferior Parietal - R Inferior Parietal - Midoccipital - Vertex-sham (90°)	International EEG 10/20 system	6 days (5 to 7 days apart)	Crossover design: Random	No mood effects active vs sham

D’Alfonso et al. (2000)	- L PFC - R PFC	5cm rule	*	Crossover design: Random / Counterbalanced	No mood effects (pre vs post & active vs sham)
Mosimann et al. (2000)	- L PFC - sham (90°)	5cm rule	2 days (2 to 3 days apart)	Crossover design / Random	No mood effects (pre vs post & active vs sham)
Habel et al. (2001)	- R FC (F7) or - L FC (F8) or - sham (T1 – T2)	International EEG 10/20 system	1 day (3 different groups receive one stimulation)	Three different groups	No mood effects (pre vs post & active vs sham)
Padberg et al. (2001)	- L DLPFC - R DLPFC	5cm rule	1 day (30min between different stimulations)	Crossover design / Random	Mood effect pre vs post for both L and R DLPFC (no significant difference between L and R)
Grisaru et al. (2001)	- L PFC - R PFC - sham L PFC - sham R PFC	5cm rule	4 days (?)	Crossover design: Random	No mood effects (pre vs post & active vs sham)
Jenkins et al. (2002)	- L PFC - R PFC	5cm rule	2 days (7 days apart)	Crossover design: Random	No mood effects (pre vs post & active vs sham)
Barrett et al. (2004)	- L MDLFC (DLPFC) - R MDLFC (DLPFC)	5cm rule	2 days (consecutive)	Crossover design: Counterbalanced	Mood effect L MDLFC pre-post vs R MDLFC

Baeken et al. (2006)	- L DLPFC - sham (90°)	MRI non-stereotactic guidance	2 days (7 days apart)	Crossover design: Random	No mood effects (pre vs post & active vs sham)
Baeken et al. (2008)	- L DLPFC - R DLPFC - sham (90°)	MRI non-stereotactic guidance	2 days (7 days apart)	Crossover design: Counterbalanced	No mood effects (pre vs post & active vs sham)
Hoy et al. (2010)	- L DLPFC (F3) (twice) - sham	International EEG 10/20 system	3 days (7 days apart)	Crossover design: Counterbalanced	No mood effects (pre vs post & active vs sham)
Baeken et al. (2011)	- R DLPFC - sham	MRI non-stereotactic guidance	2 days (7 days apart)	Crossover design: Counterbalanced	No mood effects (pre vs post & active vs sham)
Baeken et al. (2011)	- L DLPFC - sham	MRI non-stereotactic guidance	2 days (7 days apart)	Crossover design: Counterbalanced	No mood effects (pre vs post & active vs sham)
Baeken et al. (2014)	- L DLPFC - sham	MRI non-stereotactic guidance	2 days (3 days apart)	Crossover design: Random	No mood effects (although increase of negative mood in both conditions, no difference active vs sham)
Marshall et al. (2004)	- Anode L DLPFC (F3) & R DLPFC (F4) / cathode L & R mastoids (4 electrodes) - sham	International EEG 10/20 system	2 days (7 days apart)	Crossover design	Mood effect pre vs post for active vs sham tDCS

Iyer et al. (2004)	- Anodal L DLPFC (F3) / cathode R Supraorbital - Cathodal L DLPFC (F3) / anodal R supraorbital - sham	International EEG 10/20 system	3 experiments (per experiment 3 different groups per condition)	Parallel design: Random	No mood effects (pre vs post & active vs sham)
Fregni et al. (2008a)	- Anodal L DLPFC / cathode R DLPFC - Cathodal L DLPFC / anode R DLPFC - sham	International EEG 10/20 system	3 days (2 days apart)	Crossover design: Random / Counterbalanced	No mood effects (pre vs post & active vs sham)
Fregni et al. (2008b)	- Anodal L DLPFC / cathode R DLPFC - Cathodal L DLPFC / anode R DLPFC - sham	International EEG 10/20 system	3 days (2 days apart)	Crossover design: Random / Counterbalanced	No mood effects (pre vs post & active vs sham)
Koenings et al. (2009)	- Anodal L Orbitofrontal (Fp1) / cathode R Orbitofrontal (Fp2) / reference electrode non-dominant arm - Cathodal L Orbitofrontal (Fp1) / anode R Orbitofrontal (Fp2) / reference electrode non-dominant arm - sham	International EEG 10/20 system	3 days (consecutive)	Crossover design	No mood effects (pre vs post & active vs sham)

Tadini et al. (2011)	- Anodal L DLPFC / cathode contralateral supraorbital - Cathodal L DLPFC / anode contralateral supraorbital - Intermittent Anodal L DLPFC / cathode contralateral supraorbital - sham	International EEG 10/20 system	3 experiments (three different groups)	Parallel design: Random	No mood effects (pre vs post & active vs sham)
Peña-Gómez et al. (2011)	- Anodal L DLPFC (F3) / Cathode R motor cortex (C4) - sham	International EEG 10/20 system	2 days (consecutive)	Crossover design: Random	No mood effects (pre vs post & active vs sham)
Nitsche et al. (2012)	- Anodal L DLPFC (F3) / cathode contralateral orbit - Cathodal L DLPFC (F3) / anode contralateral orbit - sham	International EEG 10/20 system	3 days (7 days apart)	Crossover design: Random	No mood effects (pre vs post & active vs sham)
Plazier et al. (2012)	- Andodal L DLPFC / cathode R DLPFC - Cathodal L DLPFC / anode R DLPFC	International EEG 10/20 system	6 days (>24h apart)	Crossover design: Random	No mood effects (pre vs post & active vs sham)

	- sham (+ bioccipital stimulation & sham)				
Brunoni et al. (2013)	- Andodal L DLPFC / cathode R DLPFC - Cathodal L DLPFC / anode R DLPFC - sham	International EEG 10/20 system	3 days (2 days apart)	Crossover design: Random / Counterbalanced	No mood effects (active vs sham)
Vanderhasselt et al. (2013)	- Anodal L DLPFC / cathode contralateral supraorbital - sham	International EEG 10/20 system	2 days (2 days apart)	Crossover design: counterbalanced	No mood effects (pre vs post & active vs sham)
Morgan et al. (2014)	- Andodal L DLPFC / cathode R DLPFC - Cathodal L DLPFC / anode R DLPFC	International EEG 10/20 system	2 days (7 days apart)	Crossover design: Counterbalanced	No mood effects (pre vs post & active vs sham)
McIntire et al. (2014)	- Anodal L DLPFC / cathode contralateral biceps + placebo coffee - sham + coffee - sham + placebo coffee	International EEG 10/20 system	1 day (3 different groups receive one stimulation)	Parallel design: Three different groups	No mood effects (active vs sham)

Notes. * not reported

Conditions and Stimulation timing

In Table 3 we provide an overview of all conditions, stimulation days and order, as well as the comparison of mood effects (e.g., left versus right PFC; or pre- versus post-stimulation). Looking at the conditions of the 6 studies that reported mood effects several conclusions can be drawn. First, only two studies were sham-controlled (Dearing et al., 1997; Marshall et al., 2004), but only in Marshall et al. the mood effects are based on a comparison of pre-post mood comparison for active tDCS versus sham tDCS. Although the study of Dearing and colleagues is sham-controlled, their mood effects are only based on left compared to right PFC stimulation, and not active versus sham. Second, although all 6 studies compare left versus right PFC stimulation, the location of the exact stimulation sites differ. In four studies (Pascual-Leone et al., 1996; George et al., 1996; Dearing et al., 1997; Padberg et al., 2001) the left and right PFC was targeted and located 5 cm anterior and in a parasagittal plane from the abductor pollicis brevis (APB) site. However in Barrett et al. (2004) the left and right mid-dorsolateral frontal cortex were targeted (importantly, according to Barrett et al. the MDLPFC refers to the dorsolateral prefrontal cortex). Marshall and colleagues are the first to use the international EEG 10/20 system that is F3 and F4. It is interesting to see that although all 6 studies target the same areas, opposite mood effects are found. In the rTMS-studies (where left versus right PFC stimulation is compared) a decrease in positive mood is reported after left versus right PFC. However, in Marshall et al. an increase in positive mood is found after anodal tDCS over left DLPFC, yet, this is based on comparison between active versus sham tDCS. The effects in the rTMS studies cannot be compared to a possible sham group, and therefore should be viewed in this light. With regard to Marshall et al., it is important to reiterate that this result was not replicated in subsequent work by the authors (Kirov, Weiss, Siebner, Born, & Marshall, 2009; Marshall, Helgadóttir, Mölle, Born, 2006). Several other tDCS studies in this review used the same stimulation sites (Fregni et al., 2008a; 2008b; Plazier et al., 2012; Brunoni et al., 2013; Morgan et al., 2014) and did not find any mood effect. Third, when looking at the stimulation days, three studies (Pascual-Leone et al., 1996; Dearing et al., 1997; Padberg et al., 2001) stimulated all different conditions on one day, with 20 to 30 min in between stimulation sessions. As such, possible carry-over effects may have interfered with the results.

Mood measurement

Most of the studies (18) used visual analog scales (VAS; McCormack et al., 1988) to measure mood changes. Five of these studies combined a VAS with another questionnaire, (George et al. (1996) also used a Positive and Negative Affect Schedule (PANAS; Watson & Clark, 1988) and the National Institute of Mental Health (NIMH) mood scale); Baeken et al. (2006) and McIntire et al. (2014) both used the VAS and the Profile of Mood States (POMS; Shacham, 1983); Baeken et al. (2008) and McIntire et al. (2014) used the VAS, POMS, and PANAS; Peña-Gomez et al. (2011) used a VAS and PANAS. The remaining studies (12) all used different questionnaires, either the PANAS (Watson & Clark, 1988), the UWIST Mood Adjective Checklist (UMACL) (Matthews, Jones & Chamberlain, 1990), the SAI (measure of stress and arousal) (MacKay, Cox, Burrows, & Lazzerini, 1978), the Befindlichkeitsskala (von Zerssen, Strian, & Schwarz, 1974), the Affect Questionnaire (in Barrett et al., 2004), the Vitality Scale (Ryan & Frederick, 1997), the Eigenschaftswoertliste (EWL, in Marshall et al., 2004), and finally the Subjective Units of Distress (SUDS, in Plazier et al., 2012) (for an overview see Table 2). Of the six studies who found mood effects, three studies (Pascual-Leone et al., 1996; Dearing et al., 1997; Padberg et al., 2001) found significant mood changes on a VAS by comparing left versus right PFC stimulation. In Dearing et al. (1997) a significant decrease in happiness and a non-significant increase in sadness were found after left compared with right prefrontal HF-rTMS. In Padberg et al. (2001) mood scores worsened for both left and right side PFC stimulation, and no significant differences were detected between left and right prefrontal HF-rTMS. In George et al. (1996), VAS assessed mood changes were not observed, and mood effects were apparent only with the modified version of the National Institute of Mental Health (NIMH) mood scale, which includes explicit questions about sadness and happiness. George et al. claimed the VAS not sensitive to mood change; however, he found significant effects with the self-rating scales (NIMH). In Pascual-Leone et al. (1996) the participants did not experience a clinically detectable mood change, although their analogue scale ratings differed. It is possible, in spite of the results in George et al. (1996) that scales designed to detect mood change do not usually capture the discrete changes caused by rTMS. In the two studies that found effects but did not use VAS, Barrett et al. (2004) found a decreased affect after 10 Hz rTMS over the left DLPFC, measured with the PANAS, and a decrease in vitality, measured with the Vitality scale. Marshall et al. (2004) investigated the effects of bifrontal anodal tDCS during a period of sleep, in order to look at the possible effects on declarative memory. Results measured with a PANAS showed signs of improved mood after tDCS in both the sleep as in the wake experiments.

In sum, in three studies mood changes were found with the VAS (Pascual-Leone et al., 1996; Dearing et al., 1997; Padberg et al., 2001), while three other studies found mood changes using the PANAS (George et al., 1996; Barrett et al., 2004; Marshall et al., 2004). No systematic differences between the two measures can be found.

Time of mood measurement

Regardless of what self-reported mood measurement was used, the time of administration differed across studies. Therefore a short outline clarifying possible differences in task administration seems warranted. In most studies mood measurement was administered immediately before (baseline) and after stimulation (rTMS/tDCS) sessions, that is, 19 studies applied this parsimonious setup (Pascual-Leone et al., 1996; d'Alfonso et al., 2000; Habel et al., 2001; Padberg et al., 2001; Jenkins et al., 2004; Marshall et al., 2004 Iyer et al., 2004; Baeken et al., 2006; Baeken et al., 2008; Koenings et al., 2009; Hoy et al., 2010; Baeken et al., 2011a; Baeken et al., 2011b; Peña-Gómez et al., 2011; Nitsche et al., 2012; Plazier et al., 2012; Vanderhasselt et al., 2013; Baeken et al., 2014). Of the other 11 studies, the majority (10) used protocols where mood measurements were not immediately administered before and/or after stimulation. In George et al. (1996) baseline mood measurement was performed between 7:00 and 9:00 A.M., while after stimulation participants reported their subjective mood at different rating points (30, 60, 90, and 180 min after stimulation). In Mosimann et al. (2000), the baseline VAS was administered just before and only 20min after stimulation. Grisaru and colleagues (2001) administered VASs 5min before and 5, 30 and 240 min after stimulation sessions. In both studies of Fregni et al. (2008a; 2008b) the procedure was different from previous studies, in that (1) mood evaluations were made at baseline, (2) next food (Fregni et al., 2008a) and smoking craving (Fregni et al., 2008b) exposure, (3) after which participants were assessed on food/smoking craving after exposure, (4) then tDCS treatment of 20 min., (5) followed by step 2 and finally step 1 again. In Tadini et al. (2012) both between baseline mood measurement and the start of tDCS, as well as, between the end of tDCS and the post-stimulation mood measurement, 15min of EEG recording was performed. In Brunoni et al. (2013) two mood measurements with the VAS were administered, however, only after tDCS was started, hence, no pre-post measurement was made, and the null-findings are thus based on comparing active vs. sham stimulation. In Morgan et al. (2014), the PANAS was used before and after stimulation, but between the measurement of mood and the stimulation session, participants received an encoding phase (pre-stimulation) and a retrieval phase (post-stimulation) for the memory task. Finally, McIntire et al. (2014) administered the VAS several times during the testing phase (two hours separated), and only before the last measurement participants receive their experimental treatment.

With regard to the remaining two studies a different approach was adopted. In the study of Dearing et al. (1998) only one post measurement of mood with a VAS was registered. As such, the inference that rTMS over the LPFC decreases happiness is based on the comparison between mood registrations of the L versus R PFC stimulation. Therefore, conclusions of mood effects in this study should take this aberrant measurement into account. Similar setups can be found in Cohrs et al. (1998), where a VAS was only registered immediately after stimulation of the different target locations (L PFC; R PFC; right inferior parietal; left inferior parietal; midoccipital), and possible mood effects were calculated by comparing the VAS after an active stimulation session with a VAS of the sham (vertex) stimulation session. However, in this study no mood effects could be registered. Furthermore, it seems important to note that in Habel et al. (2001) a learned helplessness task preceded the mood measurement before and after single pulse TMS. The authors report that a negative mood change was induced (based on the comparison of mood measurement before and after the learned helplessness), however, no variations in mood were found prior to and following TMS treatment.

To summarize, in the six studies that found mood effects, four studies used an immediate pre-post measurement of mood (Pascual-Leone, et al. 1996; Padberg et al., 2001; Barrett et al., 2004; Marshall et al., 2004), while in George et al. (1996) there was more time between mood measurements (baseline and 30, 60, 90, and 180 min after stimulation). Finally, in Dearing et al. (1997) only one mood measurement was used. However, no clear differential explanation related to the timing of mood measurement can be given that would explain these results. To specifically understand and describe the relevant parameters of the two neurostimulation techniques, we discuss them separately in the next part.

rTMS

Stimulation parameters

Apart from the previous excluded studies (Schaller et al., 2012; Motohashi et al., 2013; Gaudeau-Bosma et al., 2013) all studies used single session stimulation (for a full overview of the stimulation parameters see Table 2). For the frequencies, 5 studies used low frequencies ranging between 0.5 Hz and 1 Hz (d'Alfonso et al., 2000; Habel et al., 2001; Grisaru et al., 2001; Jenkins et al., 2002; Barrett et al., 2004), and 13 studies used high frequencies ranging between 5 Hz and 20 Hz (Pascual-Leone et al., 1996; George et al., 1996; Dearing et al., 1997; Cohrs et al., 1998; Mosimann et al., 2000; Padberg et al., 2001; Barrett et al., 2004; Baeken et al., 2006; Baeken et al., 2008; Hoy et al., 2010; Baeken et al., 2011a; 2011b; 2014). With regard to the motor threshold, the percentage applied ranged between 80% and 130%. Further, there is a notable difference between intertrain intervals used, ranging from 0.25s over 5-10s up to about 60s. Furthermore, with regard to studies using Low-Frequency (5), ranging from 0.5 Hz – 1 Hz, there were no registered mood changes (d'Alfonso et al., 2000; Habel et al., 2001; Grisaru et al., 2001; Jenkins et al., 2002; Barrett et al., 2004, which used both HF and LF).

To conclude, in consideration of all rTMS-studies which reported significant mood outcomes (5), the studies were all HF-studies, but varied in the frequencies used, that is, 5 Hz (George et al., 1996), 10 Hz (Pascual-Leone et al., 1996; Padberg et al., 2001; Barrett et al., 2004) and 20Hz (Dearing et al., 1997). Based on these same frequencies (5-20 Hz) 7 studies did not report any significant changes in mood (Cohrs et al., 1998; Mosimann et al., 2000; Baeken et al., 2006; Baeken et al., 2008; Hoy et al., 2010; Baeken et al., 2011a; Baeken et al., 2011b) (for a detailed overview see Table 2).

Localization of the stimulation site

The localization of the stimulation site is crucial to the montage of the rTMS session (for an overview of the localization parameters used across studies see Tabel 2).

To summarize, in 9 studies the localization parameters were based on the 5cm rule in combination with the motor cortex site (i.e., motor threshold of the APB and ADM). In 3 studies localization was based on 10/20 international system for EEG. Finally, in 5 studies (Baeken et al., 2006; 2008; 2011a; 2011b; 2014) the position of the coil was anatomically determined using MRI non-stereotactic guidance. Taking into account all TMS studies which reported significant mood changes, all of them used the 5cm rule in combination with the motor cortex site (i.e., motor threshold of the APB and ADM).

Left versus right side stimulation

Overall, 5 studies targeted only the left PFC (Mosimann et al., 2000; Baeken et al., 2006; Hoy et al., 2010; Baeken et al., 2011b; 2014), one study focused only on the right DLPFC (Baeken et al., 2011a), while 11 studies targeted both left and right (DL)PFC. As mentioned before of the 5 TMS studies that found changes in mood, 5 of them found a decrease in mood after HF-rTMS over the left PFC but not in right PFC (Pascual-Leone et al., 1996; George et al., 1996; Dearing et al., 1997; Padberg et al., 2001; Barrett et al., 2004). No significant results were found targeting the right PFC.

tDCS

Stimulation parameters & localization of electrodes

Of all tDCS studies (13), six stimulated bilateral (F3 and F4) (Fregni et al., 2008a; Fregni et al., 2008b; Koenings et al., 2009; Plazier et al., 2012; Brunoni et al., 2013; Morgan et al., 2014) with Koenings et al. (2009) using Fp1 and Fp2 for the active electrodes. Marshall et al., (2004) used a bifrontal stimulation setup. Six studies targeted only the left (DL)PFC (Iyer et al., 2004; Tadini et al., 2011; Peña-Gómez et al., 2011; Nitsche et al., 2012; Vanderhasselt et al., 2013; McIntire et al., 2014) (for an overview of all stimulation parameters (including electrode sizes) see Table 2; for all conditions and localization details see Table 3). Marshall et al. (2004) used electrodes of 35 cm^2 and applied bilateral stimulation at frontolateral locations [F3 and F4 of the international EEG 10/20 system and at the mastoids for the reference electrodes]. Anodal tDCS (i.e., positive polarity at both frontal sites) was applied intermittently (15sec on, 15sec off; current density, 0.26mA/cm^2) over a period of 30 min. In the placebo control session, the electrodes were applied as in the stimulation sessions, but the stimulator remained off. Stimulation was not felt by the subjects. Iyer et al. (2004) used electrodes of 25 cm² and applied frontal stimulation over the left prefrontal cortex, where the anodal electrode was placed over the left DLPFC (F3) and the cathode over the right supraorbital location and vice versa in the other condition. During three separate experiments, they stimulated with a current of 1mA (experiments 1 & 2) and 2mA (exp. 3) with 20min of stimulation. For sham, the electrodes were placed in the same locations and the current was delivered for 10sec, so that the participants felt the initial itching sensation associated with turning on the device, but received no current stimulation for the rest of the stimulation period. Fregni et al. (2008a) used electrodes of 35 cm². Three different types of setup were applied; (1) anodal left DLPFC (F3) and cathodal right DLPFC (F4) ; (2)) anodal right DLPFC (F4) and cathodal left DLPFC (F3) (3) sham stimulation of DLPFC, with the electrodes placed at the same positions as in active stimulation, but the stimulator turned off after 30sec of stimulation. Therefore, the participants felt the initial itching sensation associated with turning on the device, but received no current stimulation for the rest of the stimulation period. Research shows that this sham condition is a reliable blinding procedure (e.g. Gandiga, Hummel, & Cohen, 2006). A constant current of 2 mA intensity was applied for 20min. In Fregni et al. (2008b) the same setup was used as in Fregni et al. (2008a), with the only difference that for the cathode electrodes (for the anode electrode, the 35 cm² where used) a 100cm² electrode was used. This electrode montage was set to perform a functional monopolar anodal stimulation of the DLPFC without relevant shifting excitability of the contralateral DLPFC by the cathodal, reference electrode (Fregni et al., 2008b found that this large electrode induces fewer effects on cortical activity, M.A.N., unpublished data, 2005). Also here a constant current of 2 mA intensity was applied for 20min. Koenings et al. (2009) used electrodes of 25 cm². Participants underwent three sessions of tDCS (one anodal, one cathodal, and one sham). The two active electrodes were placed at positions Fp1 and Fp2 of the 10/20 International system. The reference electrode was placed on the non-dominant arm. For sham stimulation, the electrodes were placed at the same positions as for active stimulation, but stimulation was turned on for only 30sec. In Tadini et al. (2011) 35 cm² electrodes were used. Electrodes were held in place with an EEG cap, and were placed on the F3 DLPFC or on the contralateral supraorbital areas (10/20 International System). However, the parameters differed according to the experiment number. That is, in experiment 1, the anode electrode was placed on the left DLPFC and the cathode on the contralateral supraorbital area. tDCS was delivered in 3 trains of 10 minutes (with a 15min interval between each train when EEG was recorded). The intensity of stimulation was 1 mA (trains 1 and 3) and 2 mA (train 2). For Experiment 2 the electrodes were switched, while the other parameters were the same as Experiment 1. In Experiment 3 intermittent anodal DC stimulation was used, with a frequency of 1 Hz (current was 'ON' for 0.5sec and 'OFF' for 0.5sec), again all other parameters (including intensity) were the same as Experiment 1. For sham tDCS, the electrodes were placed at the same positions as for active stimulation but stimulation was turned on for only 30sec. Peña-Gómez et al. (2011) used electrodes of 35 cm^2. The anode electrode was positioned on F3 and the cathode electrode was positioned over the C4 (right motor cortex) using the 10/20 International system. Active tDCS consisted of a constant current of 1mA applied for 20min. For sham tDCS, the electrodes were placed at the same positions as for active stimulation but stimulation was turned on for only 30sec. Nitsche et al. (2012) used electrodes of 35 cm^2. In Experiment 1, tDCS of 1mA was delivered for 20min, in Experiment2 for 10min. The anode electrode was placed over the left DLPFC (F3) and the cathode electrode above the contralateral orbit in both experiments. In Experiment 2 the reason of the 10min stimulation duration, can be ascribed to the simultaneous use of a facial recognition task. Plazier et al. (2012) used electrodes of 35 cm^2. Participants underwent three sessions of bilateral stimulation (cathode left, anode right; cathode right, anode left; and sham stimulation) and three sessions of bioccipital stimulation (cathode left, anode right, cathode right/anode left, and sham stimulation). For the bilateral stimulation sets, the electrodes were positioned over the left and right DLPFC, consistent with F3 and F4 in the 10/20 International system. For the bioccipital stimulation, the electrodes were positioned over the left and right occipital area, 2cm lateral of the inion, consistent with O1 and O2 in the 10/20 International system. Finally, for the sham condition, the cathode was placed at the left side and the anode at the right side at the frontal or occipital area respectively. Active tDCS consisted of a current of 1.5mA for 20min. Sham stimulation only lasted 10sec before turning off. In Brunoni et al. (2013) 35 cm^2 electrodes were used. Participants underwent three sessions of bilateral stimulation (cathode left, anode right; cathode right; anode left; and sham stimulation), with the electrodes positioned over the left (F3) and right (F4) DLPFC. Active tDCS consisted of a current of 1.5mA for 33min. Sham stimulation only lasted 30sec before turning off. Vanderhasselt et al. (2013) used 35 cm² electrodes and used a single session of anodal tDCS (sham controlled), with the anode over the left DLPFC (F3) and the cathode over the contra lateral supraorbital area. A constant current of 2 mA with 20sec of ramp up was applied for 20min. For sham stimulation the same montage was used, however the current was ramped down after 20 sec. In Morgan et al. (2014) 35 cm² electrodes were used. Participants underwent two sessions of bilateral stimulation (cathode left, anode right; cathode right; anode left), with the electrodes positioned over the left (F3) and right (F4) DLPFC. tDCS was applied at an intensity of 1 mA for 12 minutes (with ramp up and down of 12 sec at beginning and end of stimulation). Finally, in McIntire et al. (2014) used a custom set of electrodes as described with both the anode and cathode consist of a separate array of 5 EEG electrodes (for detailed description see McIntire et al., 2014). Thirty participants were randomly assigned into the three stimulation sessions: anodal tDCS over the left DLPFC in combination with placebo caffeine chewing gum; sham tDCS with caffeine gum; and sham tDCS with placebo caffeine gum. For the active tDCS the anode was located at F3 while the cathode was placed over the contralateral bicep. tDCS was applied at 2 mA for 30min, while in the sham tDCS lasted only 30sec.

Summing up, stimulation intensity varied from 1 mA (Iyer et al., 2004; Tadini et al., 2011; Peña-Gómez et al., 2011; Nitsche et al., 2012; Plazier et al., 2012; Morgan et al., 2014) over 1.5 mA (Brunoni et al., 2013) and 2 mA (Iyer et al., 2004; Fregni et al., 2008a, 2008b; Tadini et al., 2011; Vanderhasselt et al., 2013; McIntire et al., 2014) to 2.5 mA (Koenings et al., 2009). Nine studies used 35 cm² electrodes (Marshall et al., 2004; Fregni et al., 2008a; Fregni et al., 2008b; Tadini et al., 2011; Peña-Gómez et al., 2011; Nitsche et al., 2012; Plazier et al., 2012 ; Brunoni et al., 2013 ; Vanderhasselt et al., 2013) while Iyer et al. (2004) and Koenings et al. (2009) used 25 cm² electrodes. Fregni et al. (2008b) used for the cathode electrodes a 100cm² electrode. Finally, Morgan et al. (2014) used circular electrodes with an area of 9 cm² and McIntire et al. (2014) used a custom set of electrodes with 5 separate EEG electrodes on each anodal, cathodal electrode.

When looking at the one study which reported a mood effect (Marshall et al., 2004), some differences from all other studies can be found. While Marshall targeted the same areas of the PFC (F3 and F4), the setup was different in that two anodal electrodes (one on F3 and one on F4) and two cathode electrodes (over the left and right mastoids) were used. Second, this study was the only one to apply intermittent stimulation (15sec on, 15sec off) over a period of 30 min. Importantly, however, this result was never replicated in subsequent work (Kirov et al., 2009; Marshall et al., 2006).

DISCUSSION

In the current review 30 studies were included, of which 24 reported no changes in mood. Based on our extensive review several points are worth noting. First, there is the crucial impact of localization when conducting neurostimulation research. All rTMS studies which reported significant mood changes used the 5cm rule in combination with the motor cortex site (i.e., motor threshold of the APB and ADM). In early studies this rule was used to place the TMS coil roughly over the prefrontal cortex (e.g., George et al., 1996; Cohrs et al., 1998; d'Alfonso et al., 2000). However, as the location of the motor strip and skull size varies between individuals, this simple rule results in a large variation of actual location on the scalp. Importantly, in the 5 studies of Baeken and colleagues (2006; 2008; 2011a; 2011b; 2014) the position of the coil was anatomically determined using MRI non-stereotactic guidance (Peleman et al., 2010), and no mood effects emerged. Hence, given the anatomical brain differences between participants, the importance of the localization of the stimulation site by determining the correct anatomical localization of the specific stimulation site under MRI guidance seems an important avenue for any rTMS or tDCS study. However, although there is an increased use of neuronavigation in neurostimulation research, no study has yet been able to clearly report a better outcome of stimulation after MRI guided localization (e.g. in the treatment of MDD). Future research is needed to investigate whether the effects of neurostimulation would be improved by using neuronavigation with MRI. Furthermore, there is a need for a correct localization method to target the DLPFC when MRI is not available (See Mir-Moghtadaei et al. 2015 and Rusjan et al 2010). Therefore, there might be a greater need for more individual localization, for instance, using MRI non-stereotactic guidance. It also seems important to highlight the study of Sparing et al. (2008) where the impact of different localization strategies was investigated by comparing the accuracy of five different localization strategies. Three approaches were based on information of either anatomical or functional MRI while the remaining two strategies relied either on standard cranial landmarks (i.e, the International 10-20 EEG system) or a standardized function guided procedure (i.e., the spatial relationship between the left and right M1-Hand). The findings suggest that highest precision can be achieved with fMRI-guided stimulation (accurate within millimeters) (for an in depth discussion see Sparing et al., 2008). In addition, in Herwig et al. (2001), the precision of the 5cm rule in combination with the motor cortex site has proven questionable. By using sterotaxy for evaluation, the final location of the coil relative to the underlying cortical structures was found to be quite variable (the coil was not placed over the DLPFC as intended in 7 out of 22 subjects). Therefore, in order to accurately target the (left or right) DLPFC, taking into account individual anatomical brain differences, the precise stimulation site and position of the coil should be determined using MRI non-stereotactic guidance (Peleman et al., 2010). In line with this and given that all studies with mood effects used the latter strategy, while all studies with fMRI-guided stimulation found no effects, the argument of specific localization might have interfered with the results.

Second, there is the possible difference in neurostimulation technique. Although they differ in their mechanisms, it has been shown that the stimulation of the PFC with rTMS and tDCS produces similar effects in different neural circuitries (Fregni et al., 2008a), neurotransmitter systems (Keck et al., 2002; Nitsche et al., 2006; Strafella et al., 2001), and the treatment of psychiatric diseases (for a review see Miniussi et al., 2008; George et al., 2009; and George & Aston-Jones, 2010). Furthermore, both have shown positive outcomes in the treatment of depression. However, in patient populations these treatment studies are based on multiple rTMS or tDCS sessions. With this in mind, two studies investigating mood effects as a primary objective (Motohashi et al., 2013; Schaller et al., 2011) and one study as a secondary objective (Gaudeau-Bosma et al., 2013), used multiple stimulation sessions over time. Schaller and colleagues (2011) used 9 sessions spread over 9 days of stimulation (HF-rTMS over left DLPFC), and claimed to find an effect on mood. In this study the authors found improved mood after left DLPFC rTMS, but only observed by changes in BDI scores and not in VAS scores. However, Wise and Streiner (2012) discussed in a Letter to the Editor many concerns on the relevance of the results in Schaller et al. (2011), based on expressed issues with the sample, methodology and presentation of the results (see Wise & Streiner, 2012). In contrast, Gaudeau-Bosma and colleagues (2013) used 10 sessions over 10 days of stimulation (HF-rTMS over left DLPFC) and did not find any effect of neurostimulation on mood (mood analyses based on delta scores – after rTMS minus before rTMS - of BDI and Hamilton Depression Rating Scale, HDRS). In Motohashi et al. (2013) the authors investigated mood and cognitive functioning following repeated tDCS that is 4 sessions a day, over 3 stimulation days. The results showed that repeated intervention with anodal tDCS over left DLPFC did not change mood (and cognitive function) in healthy subjects. Nonetheless, one could wonder whether multiple sessions in healthy participants might produce mood effects (as seen in rTMS treatment studies with depressed populations). In short, when looking at the question of influencing mood, nothing in this review indicates that the different neurostimulation techniques (tDCS versus rTMS) can corroborate the mood effects reported.

Five rTMS-studies found indications for a decrease in positive mood after HF-rTMS over the left PFC (Pascual-Leone et al., 1996; George et al., 1996; Dearing et al., 1997; Padberg et al., 2001; Barrett et al., 2004) and one tDCS study (Marshall et al., 2004) found an improvement in positive mood after bifrontal tDCS. However, taken all findings into account, the argument that a single neurostimulation session would affect mood is solely based on studies with several shortcomings. More specifically, in Pascal-Leone et al. (1996) a small sample size was used (10), there was no sham condition, all stimulation sessions where on one day (with 30min between them) and the mood results were based on left versus right side comparison (and not active versus sham). George et al. (1996) used only 10 participants, did not include a sham condition, only found mood changes with the MINH mood scale (but not with the VAS or PANAS), and based their results on comparing left versus right side mood comparison (and not active versus sham). Dearing et al. (1997) has a sample size of nine, stimulated all sites on one day (with 20min between them) and based their mood effects on comparison of left versus right PFC (and not active versus sham). In Padberg et al. (2001) only nine participants were used, there was no sham condition, all sites were stimulated on the same day (with 30min between them) and the mood effects were based on pre versus post mood measurement for both left and right PFC (with no significant difference between left and right). In the study of Barrett et al. (2004), the group that reported mood effects consisted only of five participants and these effects were based on pre-post left versus right comparison (and not active versus sham). Finally, Marshall et al. (2004) used a different setup of their electrode placements (with 4 electrodes, two anodal on the bifrontal areas and two on the mastoids) and in addition, stimulated intermittently (15sec on, 15sec off). Importantly however, this result was never replicated in subsequent work (Kirov, Weiss, Siebner, Born, & Marshall, 2009; Marshall, Helgadóttir, Mölle, Born, 2006).

Drawing upon these studies and the shortcomings described, we can conclude that when a study controls for them (Baeken et al., 2006; 2008; 2011a; 2011b; 2014), that is, by using a single blind sham controlled, counterbalanced, crossover design, a larger uniform sample, stimulation of one single region per session with a time interval of one week in order to exclude interaction effects with previous stimulation, brain imaging to determine the exact target of stimulation, and comparing pre versus post mood measurement (with several well validated mood scales, Baeken et al., 2008) between active and sham stimulation, these findings cannot be replicated. Hence, their non-finding underscores our claim that a single session of rTMS/tDCS does not influence subjective mood in healthy participants.

Although not the scope of the review, one can speculate on the underlying neurobiological brain mechanisms how stimulating the DLPFC can affect mood processes. When clinically depressed, neurobiological data support the choice of the DLPFC as a valid rTMS target site to intervene with the neuronal pathways deregulated in major depression. The observed changes in a depression related neurocircuitry seem to agree with other successful treatment modalities, such as pharmacological antidepressant treatment and electroconvulsive therapy (Baeken & De Raedt, 2011). Theoretically, also in healthy subjects the rTMS application is thought to result in changes in neuronal activity in the stimulated area (DLPFC), which through cortico-subcortical transsynaptic connections suppresses hypothalamic and/or indirectly amygdala hyperactivity, resulting in CRH decreases and ultimately in decreased salivary cortisol concentrations, returning to the initial homeostasis (Baeken et al., 2010, 2014). Importantly, these influences were only detectable in healthy individuals only when being stressed, or when individual anxiety levels were taken into account. But also in these studies no rTMS effects on subjective mood were detected (Baeken et al., 2009, 2011, 2014). Also in depressed patients no subjective mood effects were detected after one stimulation session, whereas neurobiological effects were already present (Baeken et al., 2009). It seems important to mention that, although studies using many different dosages are included in our overview, there are currently no studies directly examining whether different dosages of stimulation (i.e. pulses, frequencies, inter train interval etc.) could affect mood, which might be an interesting avenue for future research.

With regard to inter-individual variability, a recent study of Wiethoff and colleagues (2014) showed that after 2mA anodal tDCS over the motor cortex 75% of individuals showed the expected facilitation, while 25% showed inhibition. In the cathodal tDCS condition the proportions were 60:40 (facilitation: inhibition). Hence, it seems that the direction of the effects is more consistent after anodal than cathodal stimulation. However, it is important to mention that in this study 2 mA is used, with a large bipolar cephalic montage and the primary motor cortex as target size. Therefore, the results of this study may not apply equally to all paradigms. In addition, a recent study of Lopez-Alonso and colleagues (2015) investigated the intra-individual variability after anodal tDCS over the motor cortex in two separate sessions and found a fair reliability (60% responded in each of the two sessions) and 78% of the responders to the first tDCS session displayed the same response (increase in cortical excitability) in the second session. Although the studies included in our review all target the PFC and use anodal tDCS, there is need for more research on the inter-individual variability on cortical excitability after tDCS on the PFC (for a discussion on intra and inter-individual variability after tDCS see Horvath, Carter, & Forte, 2014).

Finally, it seems important to note that we did not perform a meta-analysis, even though this is the best way to answer the research question of this paper. However, after careful consideration the authors felt that the best approach with the current data was to perform a systematic review. This decision was based on the unresponsiveness of several authors to obtain crucial data, if excluding methodologically questionable studies our study pool would be too limited, and the large heterogeneity of the studies on several levels (stimulation parameters, time and mood measurement, etc.). In addition, and most importantly, no methodologically sound study reported significant effects, therefore the result of a meta-analysis would not be different from our findings.

In sum, by excluding the possible influence of mood effects after a single neurostimulation session, we can underscore that studies with cognitive/emotional effects in healthy subjects after a single neurostimulation session are not affected by mood changes. More than a decade ago Mosimann et al. (2000) pointed out that neurostimulation studies should fulfil several methodological requirements: a sham-controlled setup, larger sample sizes, and strictly one single stimulation region per session in order to exclude interaction effects with previous stimulation, to determine possible effects on mood in healthy participants. Fifteen years later, we reiterate these guidelines and feel confident that when we take the aforementioned methodological demands into account, mood in healthy participants is not affected by a single neurostimulation session.

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CHAPTER 5

THE EFFECT OF A SINGLE HF-rTMS SESSION OVER THE LEFT DLPFC ON THE PHYSIOLOGICAL STRESS RESPONSE AS MEASURED BY HEART RATE VARIABILITY[1]

ABSTRACT

Previous research has demonstrated that prefrontal activity is related to control over stress responses. However, the causal mechanisms are not well understood. In this study we investigated the possible influence of brain stimulation on the physiological stress response system. Since an increased stress response is known to precipitate psychiatric disorders, further inquiry can have important clinical implications. In 38 healthy, right-handed female participants, we examined the effects of a single sham-controlled high-frequency (HF) repetitive Transcranial Magnetic Stimulation (rTMS) session over the left (N=19) and right (N=19) dorsolateral prefrontal cortex (DLPFC) on the autonomic nervous system stress response, as measured by Heart Rate Variability (HRV). Stress was transiently induced through evaluative negative feedbacks. Although the induction procedure was efficient in increasing self-reported distress in all groups and conditions, only after real HF-rTMS over the left DLPFC the physiological stress response was diminished, as indicated by a significant increase in HRV. No effects were found in the sham or right side stimulation condition. These findings demonstrate that increasing brain activity by HF-rTMS over the left DLPFC can help attenuating physiological stress reactions. Our results are indicative of the positive effects of rTMS

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[1] Based on Remue, J., Vanderhasselt, M.A., Baeken, C., Rossi, V., Tullo, J., & De Raedt, R. (2015). The effect of a single HF-rTMS session over the left DLPFC on the physiological stress response as measured by heart rate variability. *Neuropsychology*

on stress resilience and underscore the possible benefit of HF-rTMS as a transdiagnostic intervention. Finally, the results also show that effects only occur when stimulating the left DLPFC, which is in line with the therapeutic effects of HF-rTMS in affective disorders.

INTRODUCTION

Stressful situations are part of everyday life, but only a select population of individuals develops stress-related pathologies. Although stress is a broad construct, in this study we define it as a state of apprehension, accompanied by negative affect and autonomic arousal, close to the concept of state anxiety (Spielberger et al., 1983). According to the reactivity hypothesis, frequent elevated physiological responses during stressful events lead to changes in physiological balance, triggering several pathogenic pathways (Pieper, Brosschot, van der Leeden, & Thayer, 2007). Previous research has shown that confrontation with stressful situations is known to precipitate psychiatric disorders such as major depressive disorder (MDD) (Wood, Walker, Valentino, & Bhatnagar, 2010). In Waugh and Koster (2015) the authors described resilience as a dynamic process that may be deficient in people in remission from depression, rather than as a static personal quality that is unattainable to people who have experienced psychopathology. Moreover, depression is associated with multiple indicators of physiological dysregulation, including potentially diminished levels of cardiac vagal control (Rottenberg, Clift, Bolden, & Salomon, 2007), affecting stress-related responses to environmental experiences (Disner, Beevers, Haigh, & Beck, 2011).

Anatomically, sympathetic and parasympathetic branches of the autonomic nervous system dually innervate the myocardium. Functionally, parasympathetic inputs provide constant, although fluctuating, inhibitory control of heart rate (HR) via direct innervation of the heart by the vagus nerve (for a more in depth discussion on cardiac vagal control see Cyranowski et al., 2011). Stressor-induced suppression of cardiac parasympathetic activity (Gianaros et al., 2005) has been documented in a growing number of studies investigating heart rate variability (HRV) as an indirect measure of parasympathetic (vagal) control over time-related variations in heart rate (e.g., Berntson et al., 1997). Heart rate variability is a noninvasive, simple, and frequently used measure of autonomic influences on heart rate. Evidence indicates that HRV indices of sympathetic and parasympathetic activation pattern reflect biomarkers not only for cardiovascular health, but also for complex patterns of brain activations (e.g., Sloan, Korten, & Myers, 1991). High HRV has been associated with greater behavioral adaptability and is related to adaptive recovery from stress (Thayer & Lane, 2009). Moreover, decreases of HRV have been related to worry (Pieper et al., 2007). Hence, we focus on HRV as a measure of stress responsiveness, which is one of the important physiological parameters in the context of the interplay between physiological and psychological phenomena (Wheat & Larkin, 2010). Interestingly, depression is associated with elevated heart rate and reduced heart rate variability, which are known risk factors for cardiac morbidity and mortality that may explain the increased risk associated with depression (Carney, Freedland, & Veith, 2005; Thayer & Lane, 2007; Tsuji et al., 1996). Interestingly, the ventral mPFC has been linked to higher-order contextual control over stress responses, providing a conceptual link with the cognitive generation and regulation of stress responses in humans (Wager et al., 2009). In human imaging studies, the dorsal cingulate/mPFC has been linked consistently with stress-induced increases in HR, blood pressure (e.g., Gianeros et al., 2004; 2008; Critchley et al., 2003) and cortisol (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007).

Thus, experimental manipulation is necessary to increase our insight in the possible causal relationship between brain functioning and the stress response. In contemporary brain research, repetitive transcranial magnetic stimulation (rTMS) has evolved as a well-established brain stimulation tool, becoming a mainstay of cognitive neuroscience in a variety of applications (for a review see Guse, Falkai, & Wobrock, 2010). rTMS is a non-invasive method of neuronal depolarization of specific areas of the human brain that can alter cortical excitability (George et al., 2003). “Low frequency” (LF) TMS is defined by rates ≤ 1Hz, and “high-frequency” (HF) by those ≥ 1Hz (up to 30 or more Hz). (Rossi & Rossini, 2004). Low-frequency rTMS is capable of temporally decreasing cortical excitability after stimulation, whereas high-frequency rTMS increases it (Post & Keck, 2001). It emerged as a new technology that holds promise for investigating the relationship between attentional control and emotion processing (Vanderhasselt, De Raedt, Leyman, & Baeken, 2009), insight into the pathophysiology of a variety of stress-related mental disorders (Akirav & Maroun, 2007). In addition, the effects of rTMS on neurophysiology is well understood (for an in depth discussion on neurostimulation and neurophysiological effects see Hoogendam et al., 2010; Rossi et al., 2009; Sandrini et al., 2011).

The left DLPFC has been implicated in the modulation of negative emotions and is a cortical target for rTMS treatment of depression (Borckardt et al., 2011), but it remains unclear whether HF-rTMS over this area can affect stress responsiveness. To test causal hypotheses, neurostimulation techniques might be very valuable. Unfortunately, with the currently used superficial coils it is impossible to directly target the vmPFC using rTMS. Previous research on the hypothalamic-pituitary-adrenal (HPA) system has shown that stimulating the left DLPFC indirectly influences cortisol secretion. Here, as well as in animal studies (Keck, 2003), it can be concluded that the neurobiological effects following DLPFC stimulation were established via indirect multimodal pathways (e.g., Baeken et al., 2009; 2010, 2014a), affecting implicated subcortical and vmPFC structures.

In the present study, we aimed to go beyond previous -although limited- stress response and brain stimulation research, by using a single sham controlled HF-rTMS session over the left and right DLPFC as a method to temporally influence stress responsiveness of healthy people. Although treatment protocols for psychiatric disorders such as depression typically involve HF-rTMS over the left DLPFC (De Raedt, Vanderhassent & Baeken, in press), given the absence of conclusive data on lateralization regarding the physiological stress response, we decided to include right and left stimulation groups. To induce stress, we used a performance feedback task, i.e. the Critical Feedback Task (adapted from Rossi & Pourtois, 2012a), which makes use of negative feedbacks referring to participants' task-performance. Moreover, difficult cognitive tasks have been shown in numerous studies to elicit cardio-acceleration (reduced HRV), which is often mediated by decreased parasympathetic cardiac activity (e.g., Berntson et al., 1994). Hence, we assessed whether the stress response after negative feedback can be decreased by means of a single HF-rTMS session over the DLPFC. We hypothesized that, compared to sham stimulation; participants would exhibit higher HRV, as sign of lower stress response, immediately after a single HF-rTMS session over the DLPFC. In line with the observation that decreased left DLPFC activity has been implicated in the modulation of negative emotions, and the beneficial effect of left-sided stimulation in depression, we mainly anticipated effects after real stimulation of the left DLPFC.

METHOD

Participants

The left side stimulation sample consisted of 23 healthy, right-handed females[2] recruited among undergraduates. This population may be particularly relevant because stress-related disorders such as depression occur twice as often in women as in men (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). We excluded one participant based on a high score on the BDI-II (> 30), and three participants were not included due to technical problems. The final left side stimulation sample had a mean age of 21.84 (*SD* = 2.95). The right side stimulation sample consisted of 19 healthy, right-handed females with a mean age of 21.74 (*SD* = 1.76). For both groups current and past psychiatric (both Axis I and Axis II) disorders were excluded using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). No drugs were allowed, except birth-control pills. The ethics committee of the University Hospital of the Vrije Universiteit Brussel (UZBrussel) approved the study. All participants gave written informed consent and were financially compensated. A part of the participants in this study also participated in a larger project investigating the influence of HF-rTMS on different neurocognitive (neuroimaging) and genetic markers, and on the Hypothalamic Pituitary Adrenal Axis (Baeken et al., 2014a).

Questionnaire measures.

The BDI-II, a 21 item self-report inventory, was used to measure the severity of depressive symptoms (Beck, Steer, Ball, & Ranieri, 1996). In addition, before and after the experiment anxiety was assessed using the state version of the STAI (Van der Ploeg, 1982). Mood state was further measured using six visual analogue scales (VAS) measuring how tired, energetic, angry, tension, depressed and cheerful participants were feeling “*at this moment*”. The VAS is a 10 cm line, with endpoints from “not at all”

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[2] For our study we chose to only included women because of the homogeneity of our data: including men would require doubling the sample size, to seriously consider gender as a factor in our design.

to “very much”. Total Mood scores[3] were measured for each time point, where all six VASs were compounded in one score (from 0 to 10, in mm). The logic for pulling together all of our VAS scores in one compound measure is based on the Total Mood Disturbance Score index (TMDS, NcNair, Lorr, & Droppleman, 1992), which is calculated by compounding the scales of the Profile of Mood States (POMS), including the Fatigue and the Vigor subscales (Vigor reverse-scored). We have explicitly chosen this strategy because in the literature it has been shown that this specific compound measure (TMDS) is highly correlated with State anxiety, capturing its fluctuations over time even better than the simple “tension” score (Bolmont & Abraini, 2013). Interestingly, this correlation with state anxiety is even higher during stress.

Critical Feedback Task (CFT).

The Critical Feedback Task is a mental counting task where participants receive bogus negative feedback on their performance at the completion of each test-block. This paradigm was successfully used before with the aim of inducing state anxiety and distress (for details, see Rossi & Pourtois, 2012a, 2013, 2014; Baeken et al., 2014a). The on-screen instructions told the participants that this task measured perceptual learning abilities and sustained attention, reflecting general intelligence. The task was divided into a practice block and three test blocks, in which participants were asked to covertly count the number of deviant lines in a stream of standard lines, reporting this number at the end of each block. The standard lines were always tilted 35°, while the target lines had a different in-plane orientation. The angular difference between standards

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[3] The logic for pulling together all of our VAS scores in one compound measure is based on the Total Mood Disturbance Score of the Profile Of Mood States (POMS) (TMDS, McNair, Lorr, & Droppleman, 1992), which is calculated by compounding the subscales including the Tired and the Vigor subscales (it is important to know that our VAS subscales are based on the POMS subscales). We have explicitly chosen this strategy because in the literature it has been shown that this specific compound measure (TMDS) is highly correlated with State anxiety, capturing its fluctuations over time even better than the simple “tension” score (Bolmont & Abraini, 2001). Interestingly, the correlation with state anxiety is even higher during stress. Therefore, being particularly interested in the concepts of stress and state anxiety, we preferred to stick to a validated procedure (that is, calculating the TMDS including fatigue and vigor), instead of creating a new compound score that had not been validated before in the literature. As a side note, given that anxiety has been related to processing efficiency impairments (see Derakshan & Eysenck, 2007), maintaining performance in the face of negative evaluations requires additional mental effort, which in turn can be expected to increase the perception of fatigue.

and targets was manipulated in order to create variation in perceptual load: one block was difficult (standard-target difference = 3° of angle), one was intermediate (standard-target difference = 5°) and one was easy (standard-target difference = 10°). Participants always started with the difficult block (unknown to them) and were informed by a cover story that after each block they would receive feedback on their performance, comparing them to a group of peers. Moreover, they were led to think that the difficulty of the subsequent block would depend on their performance on the current one (in a staircase design). However, the given feedback was in fact unrelated to performance (it was always negative), and the following block was always easier, to maintain motivation despite the elicitation of failure feelings and stress. Every feedback consisted of a neutral face with a text balloon, stating that they performed below average as compared to the other participants. A pseudo-randomly generated scatterplot showed their own performance against the scores of the previous (alleged) participants. Since the targets were difficult to notice during the task, this brought a high uncertainty on one's own performance, making it very likely for participants to believe that their performance was evaluated negatively. Moreover, the use of a direct comparison with other participants has been shown to be mostly effective in inducing stress/anxiety (Nummenmaa & Niemi, 2004).

Cardiac activity: Heart rate variability

Heart rate was measured per beat with a telemetric heart rate monitor (Polar S810). The heart rate data were transmitted to a personal computer. Measurement errors were filtered with the Polar Precision Performance Software for Windows. The filter was set at a moderate filter power and a minimum protection zone of 6 beats per minute (Cottyn, De Clerq, Pannier, Crombez, & Lenoir, 2006). The resolution of a POLAR Vantage NV heart rate monitor, which is analogous to the S810 but with lower memory capacity, was studied in Kinnunen and Heikkilä (1998). The data were further analyzed with software (Kubios; Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Kuipio, Finland) specifically designed for advanced HRV analysis. Artifacts were filtered on a medium level with the Kubios software (Tarvainen, Niskanen, Lipponen, Ranta-aho, & Karjalainen, 2014). HRV can be described either by frequency or time domain indices. We used RMSSD (the root mean square successive difference of normal-to-normal intervals, in ms) as an index of HRV. RMSSD primarily reflects parasympathetically mediated short-term changes in heart rate and is one of the time domain indices recommended by a task force report on HRV measurement (Task Force, 1996) and has demonstrated to decrease as an effect of stress as well as worry (Delaney & Brodie, 2000; Pieper et al., 2007), and to increase as an indicator of successful emotion regulation (Thayer, Ahs, Frederikson, Sollers, & Wager, 2012). For a detailed accounting of the other frequency bands see Thayer and colleagues (2010) for a recent review. HRV measurement started from the sixth minute after the start of the CFT, because the task only becomes stressful after the first negative feedback. The heart rate was recorded from the moment they entered the experimenter room, just before baseline, and stopped after the 15 minutes relax period at the end of the procedure.

HF-rTMS

A randomized sham-controlled, single blind, crossover design was used. To avoid carry-over effects from the previous stimulation, the second session was carried out after an interval of three days. The procedure of the second experiment day was exactly the same with the exception of the HF-rTMS session (real or sham), which was counterbalanced with random selection of order. HF-rTMS of the left and right DLPFC was performed using a MAGSTIM high-speed stimulator (Magstim Co., Whitland, UK) with a figure-of-eight shaped coil. In order to correct for individual anatomical differences and to avoid stimulation of other cortical areas besides the left or right DLPFC, all participants underwent a T1-weighted MRI (3D-TFE, voxel size 1 x 1 x 1 mm) of the brain using a 3-T Intera MR scanner (Philips, Best, The Netherlands). We located the left and right DLPFC visually in the 3D surface rendering of the brain based on the participant’s own gyral morphology and we marked the center of the middle frontal gyrus as the target site, which is anatomically localized in the center of the DLPFC (Brodmann area 9/46; Talairach coordinates – 50, 34, 34). The corresponding coil position was found by determining the perpendicular projection of this point on the scalp (Peleman et al., 2010). We used the following stimulation parameters: 110% of motor threshold of the right abductor pollicis brevis muscle (stimulation intensity), 20 HZ (stimulation frequency), 40 trains of 1.9s duration, separated by an inter-train interval of 12.1s, resulting in 1.560 pulses per session. The total stimulation time was approximately 10 min. The study was conducted according to double blind within-subjects design by randomized/counterbalanced crossover sham (placebo) and real HF-rTMS. Real and sham stimulation were performed at the same place on the skull, but for sham the figure-of-eight shaped coil was held at an angle of 90° only resting on the scalp with one edge. During stimulation, all participants wore earplugs and were blindfolded to ensure blindness of the stimulation procedure. The real and sham stimulation occurred immediately prior to the stress induction.

Procedure

Upon arrival on their first day the participants underwent an anatomical 3D MRI scan to define the exact stimulation point, which is based on a 10min scan. At the start of the experiment, the polar equipment was put on and the participants were subsequently asked to fill in the STAI-State. Then, they were asked to relax for 20 minutes. After the 15 minutes (which allowed for 5 minutes of adaptation) HRV recorded baseline (T1), participants filled in the first series of VASes. Next, each participant received a single (sham or real) stimulation session in another room. When they returned they filled in their second VASes. Next, they were asked to perform the Critical Feedback Task, which took approximately 8 minutes (T2). After the task, they were given the third series of VASes. Next, the participants were asked to relax again for 15 minutes (T3). The HRV registration was stopped and participants received their final (fourth) VASes, together with the second STAI-State and the BDI. The procedure of the second day was similar to the first, except for the rTMS session (depending on which type of stimulation they received on the first day, e.g. DAY 1 = Sham, DAY 2 = Real; or DAY 1 = Real, DAY 2 = Sham). During the experimental procedure all participants were in a seated position, as well as for the real and sham stimulation sessions. After the experiment, all participants were fully debriefed and asked if they were aware of the purpose of the critical feedback task. Some of the participants reported to be somewhat aware of the unsolvable nature of the task, but all said that they were stressed by the negative feedback they received. Furthermore, no significant differences were found when participants were asked to distinguish between real or sham HF-rTMS.

Statistical Analysis

All collected data were analyzed with SPSS 19 (Statistical Package for the Social Sciences). First, for mood analysis we used a 2 (experimental Condition: rTMS and sham) X 4(Time: after T1, before T2, after T2, and after T3) mixed ANOVA with stimulation side (left vs. right) as between-subjects factor, followed-up by paired-samples t-tests. To yield a sensitive measure of global impact of the protocol and so the CFT on negative mood, as proposed by Rossi and Pourtois (2012a, 2012b), we collapsed the VAS scores into a compound VAS for mood, by adding up the scores of the six items (the two positive mood items were reverse-scored): the compound score ranges therefore from a minimum of 0 (minimum level of negative mood) to a maximum of 60 (maximum level of negative mood) (see table 1 for an overview of the separate VAS scales). Our HRV data were not normally distributed (Shapiro Wilk test). To address this, we log transformed the data, which resulted in a normally distributed dataset, with all p-values higher than *.11*. For the HRV data we performed a mixed 2 Condition (real vs. sham HF-rTMS) X 3 Time (T1 = baseline resting state HRV; T2 = stress induction HRV, and T3 = recovery resting state HRV) X 2 Stimulation Side (Left vs. Right) ANOVA, with time and condition as within-subjects factors, stimulation side as between-subjects factor, and HRV as dependent variable. To follow-up interaction effects, paired sample *t* tests were performed. Effect sizes were calculated as Cohen *d* (Cohen, 1988) for the HRV means (based on the observed means and standard deviations), for both within as between Condition comparisons.

RESULTS

Mood

The ANOVA yielded a marginally significant effect of time, *F*(3,35) = 2.54; *p = .060*. Given the absence of simulation side and condition interaction effects, as a follow-up we computed the means collapsed over condition and stimulation side of the total mood scores, to follow up the near significant main effect of time. As shown in Figure 1, negative mood increased significantly between T1 and T4 *t*(37) = 2.05; *p = .048*, with a marginally significant increase between T2 and T3 *t*(37) = 1.91; *p = .064*, i.e. before and after the CFT. This shows a global increase of negative mood throughout the whole procedure, while the increase between T2 and T3 shows an increase of negative mood, specifically during the CFT. Next, we also compared the possible mood effects on the STAI-State questionnaire before and after the protocol. In the left stimulation study one participant failed to complete the STAI questionnaire. The ANOVA with the STAI-State score as dependent variable showed no significant main or interaction effects (all *p*'s > .09).

Table 1. *Visual Analogue Scales descriptives (in cm).*

			Condition			
			rTMS condition			
VAS	Tired	Vigor	Angry	Tension	Depressed	Cheerful
T1	3.67 (2.56)	5.00 (1.87)	0.36 (0.51)	1.00 (1.21)	0.43 (0.87)	5.97 (2.04)
T2	2.94 (1.97)	5.05 (1.93)	0.54 (0.82)	1.58 (1.56)	0.32 (0.45)	5.43 (2.20)
T3	3.02 (1.94)	4.72 (1.99)	0.62 (0.93)	1.35 (1.54)	0.34 (0.62)	5.11 (2.11)
T4	3.40 (2.11)	4.72 (1.74)	0.46 (0.69)	0.96 (1.21)	0.44 (0.72)	4.99 (1.91)
			Sham condition			
VAS	Tired	Vigor	Angry	Tension	Depressed	Cheerful
T1	4.07 (2.56)	4.70 (2.00)	0.40 (0.58)	1.20 (1.19)	0.48 (0.88)	5.50 (1.85)
T2	3.60 (2.27)	4.73 (1.97)	0.36 (0.56)	1.14 (1.40)	0.47 (0.83)	5.55 (1.90)
T3	3.39 (2.20)	4.43 (2.04)	0.61 (0.96)	1.26 (1.69)	0.47 (0.86)	5.21 (1.98)
T4	3.86 (2.35)	4.31 (2.18)	0.51 (0.80)	0.95 (1.35)	0.43 (0.79)	5.02 (1.81)

Table 1. *Mean ratings and standard deviations for the VAS subscales before (T_1) and immediately after HF-rTMS/Sham (T_2). Immediately after the Critical Feedback Task (CFT) (T_3) and 15 min later (T_4) (see Figure 1 for graphical presentation of Total Mood Scores). VAS scales are used to capture mood states, and scores are expressed on scales going from 0 to 10 (cm) and range from 0 = absence of that emotion; tot 10 = max emotion.*

HRV

The 2X3X2 ANOVA showed a main effect of time, F(1,35) = 11.59; p < .001 and an interaction effect of time and condition, F(1,35) = 4.04; p = .026. The crucial three-way interaction effect between condition, time and stimulation side, F(1,35) = 4.63; p = .016 was also significant. To further follow-up this interaction effect, we performed separate 2X2 within-subjects ANOVA's for the left and the right side stimulation group.

For the left side stimulation group, no significant main effects for both condition, F(1,18) = 1.20; p = .29 and Time, F(1,17) = 2.16; p = .15 emerged. Most importantly, a highly significant interaction between condition and time was observed, F(1,17) = 8.75; p = .002. To follow-up this interaction effect, paired sample t tests were performed. At

T1 there was no significant difference in RMSSD between the real HF-rTMS and the sham condition, t(18) = .85; p = .41, d = .11. However, at T2 (during the stress task) we observed a significant higher RMSSD in the HF-rTMS-condition as compared to the sham condition, t(18) = 3.26; p = .004, d = .37. Finally, at T3 the significant difference in RMSSD between HF-rTMS-condition and sham-condition disappeared, t(18) = .69; p = .50, d = .08. When looking at the within condition differences, we found a significant increase in RMSSD in the rTMS condition from T1 to T2, t(18) = 3.05; p = .007, d = .30, which remained unchanged from T2 to T3, t(18) = .28; p = .78, d = .02. As such, a single rTMS session, successfully led to an increase of RMSSD during the stress induction. In the sham condition there was a marginally significant decrease in RMSSD from T1 to T2, t(18) = 1.97; p = .065, d = .18. Comparing T2 with T3, a significant increase in RMSSD was found in the sham condition, t(18) = 2.48; p = .023, d = .27. The pattern of results is shown in Figure 2. Finally, the order of presentation of rTMS versus sham conditions across sessions had no significant effect on the stress response, F(1,16) = .25; p = .78.

For the right side stimulation group, no significant interaction between condition and time was observed, F(1,17) = .99; p = .42. The order of presentation of rTMS versus sham conditions across sessions had also no significant effect on the stress response, F(1,16) = .48; p = .63. The pattern of results is shown in Figure 2[4].

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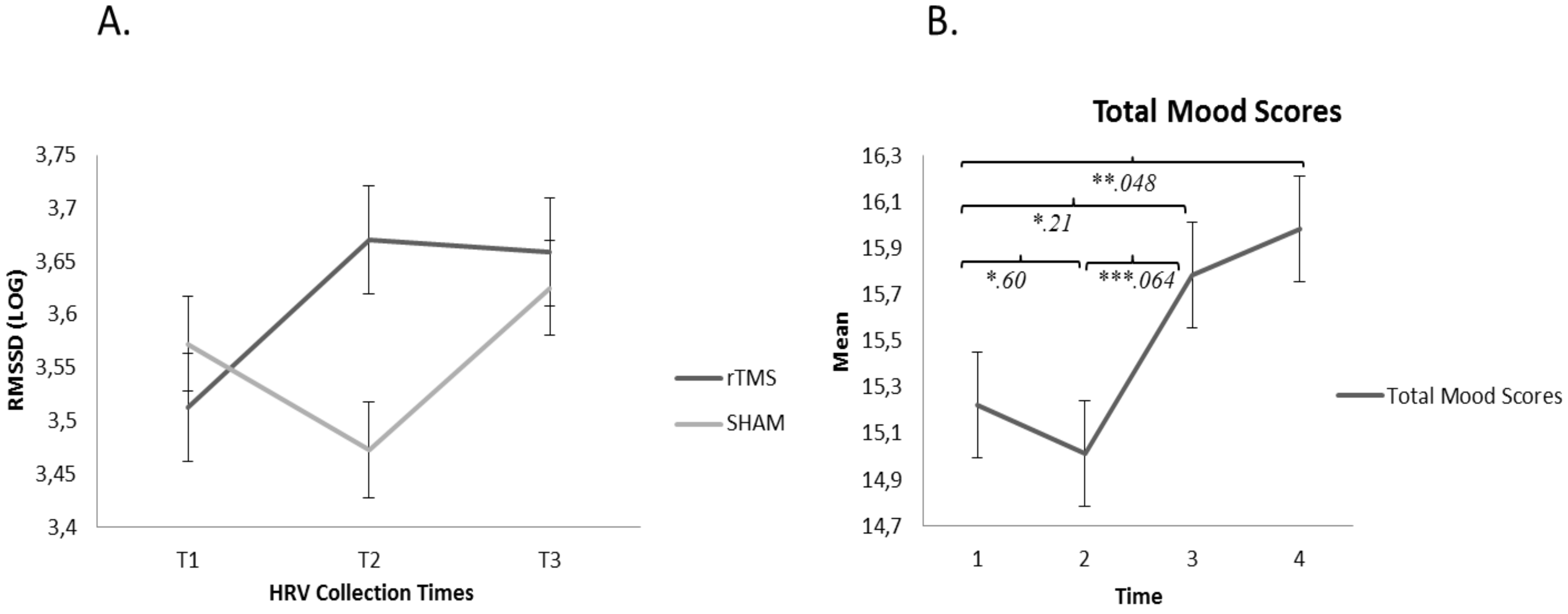
[4] Given that RMSSD, PNN50 and the high frequency component of the power spectrum (HF power) are closely related, and all reflect vagal cardiac influence, we included the HF-HRV (frequency domain methods) and PNN50 (time domain methods) in a similar mixed 2X3X2 ANOVA. The results show converging findings to the RMSSD data. Furthermore, all indices of HF-HRV, PNN50 and RMSSD correlated highly (all r >.800; p < .001)

Figure 1.

A. *Left side stimulation of the DLPFC. The stress response measured by HRV on T1, T2, and T3 in rTMS and sham conditions. Higher HRV = lower stress response.*

B. *Total Mood Scores at T1, T2, T3 and T4, which ranges from a minimum of 0 (minimum level of negative mood) to a maximum of 60 (maximum level of negative mood)*

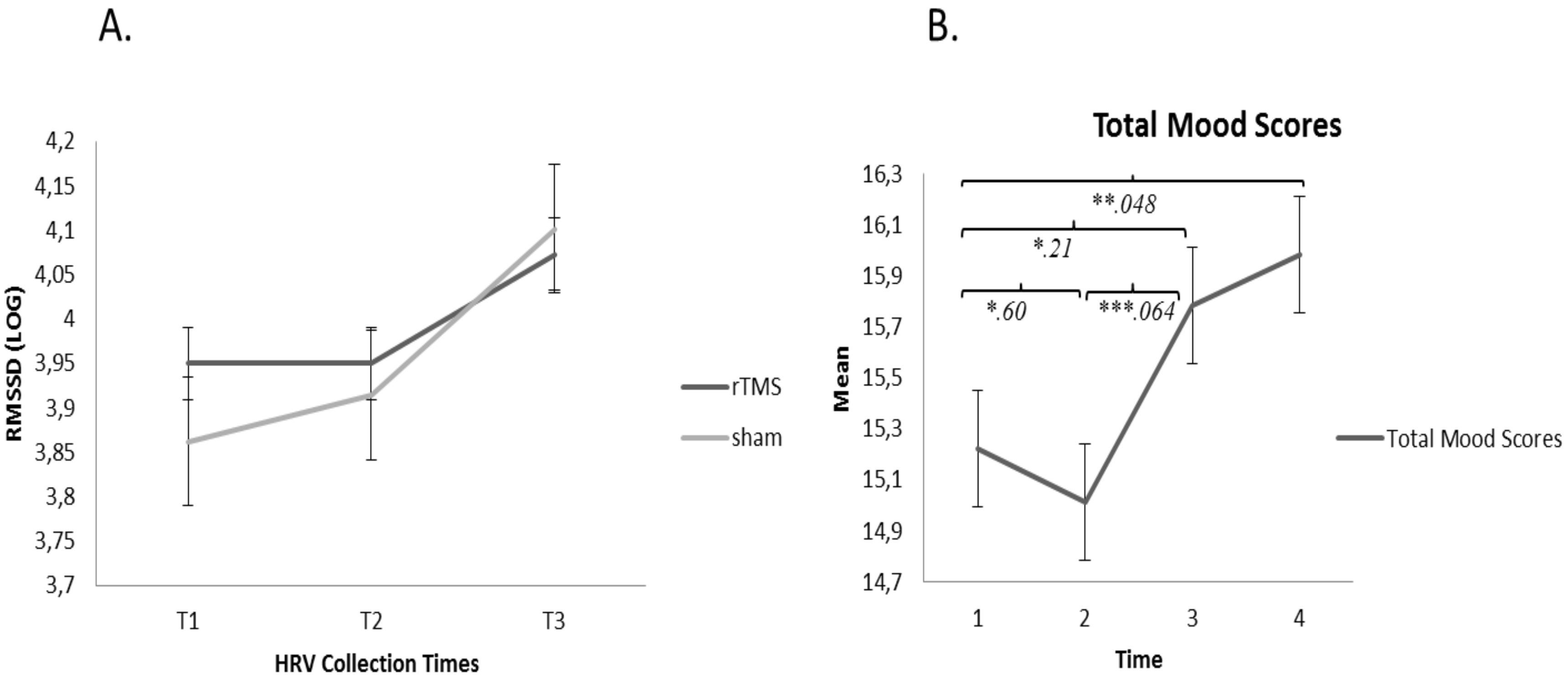


Note. *RMSSD (LOG): root mean square standard deviation (log transformed); HRV: heart rate variability; rTMS: repeated transcranial magnetic stimulation; *p > .05; ** p < .05; *** p = .064*

Figure 1.

A. *Right side stimulation of the DLPFC. The stress response measured by HRV on T1, T2, and T3 in rTMS and sham conditions. Higher HRV = lower stress response.*

B. *Total Mood Scores at T1, T2, T3 and T4, which ranges from a minimum of 0 (minimum level of negative mood) to a maximum of 60 (maximum level of negative mood)*



Note. *RMSSD (LOG): root mean square standard deviation (log transformed); HRV: heart rate variability; rTMS: repeated transcranial magnetic stimulation; *p > .05; ** p < .05; *** p = .064*

DISCUSSION

The present study was designed to investigate the effects of a single HF-rTMS session over the left and right DLPFC on the physiological stress response of healthy female participants. The results showed the expected significant increase of HRV during stress induction compared to baseline after left-sided stimulation, which was not observed in the sham condition. This increase was not registered in the right-sided stimulation group. Moreover, there was no difference between the real and sham condition. These effects are in line with the therapeutic effects of rTMS in affective disorders (for a review see George, 2010; Lefaucheur et al., 2014), and with models of emotion lateralization (Davidson & Irwin, 1999). The clear difference between real left sided stimulation and sham during the stressor is indicative of the positive influence of HF-rTMS.

During the recovery period after the whole left side stimulation procedure, the differences between sham and real stimulation disappeared, which means that our healthy participants showed normal stress recovery after the stressor has disappeared. In addition, although the mood analyses did not show a three-way interaction, the Time effect shows a general impact of the protocol, with an increase of the total negative mood score from before to after the stress induction task, indicative of the mood inducing effect of the CFT over Condition and Stimulation Side.

The present study was the first experimental study using HF-rTMS over the left DLPFC demonstrating an impact on parasympathetic modulation in humans. However, through which exact pathway left DLPFC HF-rTMS affects the ANS remains to be clarified and without concomitant neuroimaging techniques the interpretation of our psychophysiological results remains to some extent speculative. A possible working mechanism points to a DLPFC / anterior cingulate cortical (ACC) pathway. Indeed, in brain imaging studies examining negative affect, besides the dorsolateral prefrontal cortex, dorsal (d)ACC areas are often involved as well (Pizzagalli, 2011). Different brain imaging studies in MDD lend support to the assumption that left HF-rTMS affects and ‘normalizes’ DLPFC and ACC metabolic and functional neuronal activities (Baeken et al., 2009; Kito, Hasegawa, & Koga, 2012; Fox, Halko, Eldaief, & Pascual-Leone, 2012). The subgenual (sg)ACC, part of the ventromedial prefrontal cortex (Barbas et al., 2003; Ray & Zald, 2012), may be a critical region to be involved in the response to HF-rTMS. In addition, in Baeken et al. (2015) PET imaging was used to show the impact of HF-rTMS on the subgenual ACC in refractory unipolar major depression, while in Baeken et al. (2014b) the effect of rTMS on functional connectivity between prefrontal areas and the subgenual ACC was demonstrated. Furthermore, HF-rTMS treatment has been shown to affect deregulated sgACC neurocircuits in depressed patients (Baeken et al., 2014a, 2015; Fox, Buckner, White, Greicius, & Pascual-Leone, 2012). Given that cortical brain systems that are hypothesized to regulate cardiac autonomic activity during behavior include the medial-prefrontal regions of the cortex (Gianaros et al., 2004), our HRV findings are in line with the existing animal literature showing an attenuating effect of rTMS of frontal brain regions on HPA system function (Keck et al., 2001; Hong et al., 2002).

Our findings suggest that the left DLPFC may be a critical brain area in the neurocircuitry underlying stress reactivity on negative feedback, and suggests that the PFC plays a role in the modulation of stress responses in healthy participants. By modulating this specific brain region stress resilience may be positively affected, which is crucial for coping with stress inducing events. Indeed, the increase in HRV associated with emotion regulation has been related to cerebral blood flow changes in the PFC (Lane et al., 2009). Our results are consistent with the conclusions of Davidson et al. (2002) and Maier et al. (2006) that the PFC is implicated in affect regulating and is vital for the protective effects of behavioral and cognitive control over stress responsiveness. Moreover, these findings are indicative of the potential of rTMS to increase cognitive control to cope with stressful stimuli, which is highly relevant in the treatment of stress-related disorders such as major depression (Scher, Ingram, & Segal, 2005). Therefore, De Raedt et al. (in press) emphasize the importance of combining conventional therapy with neurostimulation such as rTMS is highlighted, given that there is a high relapse rate after conventional therapies, suggesting that resilience is not increased perse. Indeed combining both approaches might have a dual effect of reducing the distress and increasing HRV.

In conclusion, our findings underscore the potential of experimental procedures to influence stress responses and negative affect in laboratory settings evaluating the effects of HF-rTMS on the HPA-system and ANS (Nummenmaa & Niemi, 2004). Indeed, De Raedt and Koster (2010) concluded, based on a review on the cognitive and neurobiological correlates of vulnerability for depression that an important therapeutic aim would be to restore stress reactivity. HR reactivity and cardiovascular reactivity also predict other health-related effects of stressors on the body (Wager et al., 2009). However, further research using rTMS combined with the presentation of a stressor to probe the physiological stress system in MDD and other disorders is necessary. In line with the beneficial use of exposure in the treatment of various disorders, and the crucial role of the PFC in these effects (for a review see De Raedt, 2006), it might well be that the effects of rTMS can be boosted by combining it with exposure to a stressor. Furthermore, we believe that these results show the potential of rTMS to be an additional treatment protocol, next to the more conventional (therapeutic and medicinal) treatments of depression.

An important caveat is that the absence of a physiological stress response in the right side stimulation group during the sham session, which is difficult to explain. One possible reason might be that there was no randomization for group (first left stimulation group, then right). Given that high vagally mediated HRV is associated with cognitive, emotional, and autonomic self-regulatory capacity (Thayer et al., 2000, 2009), and people with high HRV cope better with stress, this might explain the absence of a decrease of HRV (and increase in HR) for the right stimulation group. Since the overall HRV was larger in the right stimulation group as compared to the left stimulation group, a ceiling effect might prevent the stress induction task to influence their physiological responses. However, we cannot formally exclude that this group, by coincidence, coped better with the induced stress, explaining the absence of the physiological stress response in the sham condition in the right stimulation group, compared to the left. That said, future research should focus on this randomization issue when conducting lateralization studies.

Some limitations should be noted when interpreting our results. First, in the present study only young (18-30 years) healthy women were tested. Although this had the advantage of selecting participants known for their higher emotion sensitivity, it limits generalizability. In addition, there is also evidence that men and women differ in their autonomic and cardiovascular responses to psychological stressors (Matthews & Stoney, 1988). Future work is thus needed to test whether the present results generalize to a male sample or to a sample with a larger variation in age and health (e.g., MDD). Second, the fact that HF-rTMS did not induce a subjective differential effect (sham versus real stimulation) on the mood scales might be considered as surprising. However, subjectively experienced mood gives only limited insight into the neurophysiology of emotion and physiological responses might operate independently of verbal reports (Buck, 1999; Campbell & Ehlert, 2012). Thus, this may be indicative of a difference between subjective experience of distress and physiological responses. Furthermore, the menstrual cycle phase could be another systematic inter-individual influence, which may have impact on HRV (e.g., Sato, Miyake, & Kumashiro, 1995) but was not controlled in the present study. We suggest that this issue should be addressed in future research. Moreover, other factors, such as respiratory rate, tidal volume, or momentary physical activity may influence a reliable estimation of cardiac vagal tone (for an extensive discussion, see Grossman & Taylor, 2007). However, given the consistency between our different measures (RMSSD, HF-HRV, PNN50), these factors seem to have played a minor role. Third, all analyses are based on RR interval data, no ECG signal data or respiratory data was collected. Given the influence of respiratory changes on HRV (Cyranoswki et al., 2011), these results should be replicated with proper respiratory (and ECG) data included, or this should be taken into account when interpreting and generalizing the findings.

To summarize, the results of this study suggest that the DLPFC plays a significant role in the modulation of stress responses in healthy participants. In addition, this study also shows that through the use of HF-rTMS over the left DLPFC we can possibly augment the cognitive control to cope with emotional stimuli, which is highly relevant in the treatment of stress-related disorders (Scher et al., 2005).

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CHAPTER 6

THE ROLE OF THE PRECUNEUS IN COPING WITH CRITICISM: A NEUROMODULATION STUDY DURING FMRI [1]

ABSTRACT

Being criticized is a distressing experience that activates self-referential ruminative thinking. The prefrontal cortex is implied in cognitive control over ruminative self-referential thoughts, which have been related to cortical midline structures such as the precuneus. To investigate the neurobiological processes underlying the link between criticism and self-referential thinking, we applied transcranial Direct Current Stimulation (tDCS) to increase dorsolateral prefrontal cortex activity in the scanner, and measured brain activity in real time before, during and after exposing healthy individuals to social evaluative comments. Thirty-two female participants received 20 minutes of anodal tDCS over the left DLPFC. Participants were then exposed to neutral, praising, and critical audio comments. This procedure was performed during functional magnetic resonance imaging (fMRI) to examine the relationship between exposure to self-referential stimuli and neural activity after both real and sham tDCS. Our behavioral data indicated a significant decrease in self-referential thoughts after real tDCS, but not sham. After a single sham-controlled tDCS session participants showed lower activation in the precuneus compared to sham, when listening to positive and negative audio comments. In addition, the decrease in neural activity after tDCS was significantly larger after negative than positive comments. Furthermore, functional connectivity analysis revealed that real tDCS resulted in a decreased functional connectivity between the

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[1] Based on Remue, J., Baeken, C., Wu, G-R, Duprat, R., Hooley, J., Vanderhasselt, M-A, Brunoni, A., & De Raedt, R. *The role of the precuneus in coping with criticism: a neuromodulation study during fMRI.* Manuscript in preparation.

precuneus/posterior cingulate cortex seed and the ventromedial PFC (while an increased functional connectivity was observed after sham tDCS). The results show that a single tDCS session decreases self-referential thinking when confronted with criticism. Moreover, only real tDCS decreases activity in the precuneus and decreases functional connectivity in areas related to self-referential processing. Our study was the first to apply neuromodulation during fMRI as an experimental manipulation to investigate the neural correlates underlying the link between criticism and self-referential processes, demonstrating that tDCS can alter behavioral and neural responses of self-referential processing.

INTRODUCTION

Being criticized is a distressing experience that activates self-conscious emotions (e.g., feeling hurt) and self-referential thinking (e.g., Davidson, 2010; Vanderhasselt, Remue, Muller, & De Raedt, 2015). It also has a detrimental impact on cognitive processing and thinking styles, such as rumination (e.g., Saffrey & Ehrenberg, 2007; Kaiser, Andrews-Hanna, Metcalf, & Dimidjian, 2015). Rumination is a form of self-referential processing, which is the process of relating information to the self (Nejad et al., 2013). Self-referential processing can be defined as the evaluation of information in relation to an individual’s own mental concept (Christoff et al. 2011). More specifically, it is a mode of processing requiring one to evaluate or judge some feature or attribute in relation to the perceptual image or mental concept one has about oneself. Criticism may be a trigger that leads to a reevaluation of a person’s perceptual image and provokes ruminative thoughts.

The importance of criticism as a source of psychosocial stress is well highlighted by research that has linked criticism to poor clinical outcomes in patients with mental disorders such as major depressive disorder (MDD), alcohol dependence, post-traumatic stress disorder (PTSD), panic disorder and obsessive compulsive disorder (OCD) (O’Farrell, Hooley, Fals-Stewart, Cutter, 1998; Tarrier, Sommerfield, Pilgrim, 1999; Chambless, Steketee, 1999). Moreover, various studies have demonstrated the link between depression and sensitivity to criticism (e.g., Burcusa & Iacono, 2007; Hooley et al., 2009). Of particular importance is the findings that even after full recovery from an MDD episode, neural responses to criticism do not appear to normalize (Hooley et al., 2009).

Neuroimaging studies have indicated that a functional balance between ventral (ventral anterior cingulate cortex, ACC) and dorsal compartments in the frontal cortex (dorsal ACC, dorsolateral prefrontal cortex, DLPFC) is necessary for maintaining homeostatic emotional emotional control (Seminowicz et al., 2004; Johnstone et al., 2007; Ochsner and Gross, 2005, 2008; Wager et al., 2008). As such, many studies suggest that the DLPFC initiates emotion regulation by causing inhibition of the amygdala (e.g., Siegle et al., 2007). Though the DLPFC appears to moderate limbic reactivity to emotional cues in healthy individuals (Davidson, 2000) its activity and modulatory role is decreased in depressed individuals (Siegle et al., 2007). Activation of the DLPFC has also been shown to be decreased when never depressed healthy controls are exposed to a sad mood induction (Gemar et al., 1996; Baker et al., 1997; Liotti et al., 2000).

Other affective challenges have also been used. In the abovementioned study of Hooley et al. (2009), participants were exposed to critical, praising, and neutral comments from their own mothers to examine the relationship between exposure to personally relevant emotional stimuli and neural activity in the DLPFC, ACC, and amygdala. These are regions known to be involved in MDD (Fitzgerald, Laird, Maller, & Daskalakis, 2008). Using functional magnetic resonance imaging (fMRI) Hooley and colleagues were able to demonstrate decreased reactivity in the DLPFC and an increased amygdala reactivity in fully recovered depressed patients versus never depressed healthy controls (Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005; Hooley et al., 2009, 2012).

An obvious next step is to go beyond correlational findings by using experimental manipulations. These permit causal inferences to be made. One approach attracting increased attention is transcranial Direct Current Stimulation (tDCS). This technique can be used to temporarily enhance neural activity and cognitive processes, both for non-emotional (e.g., Fregni et al., 2005; Leite, Carvalho, Fregni, & Goncalves, 2011; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Brunoni & Vanderhasselt, 2014; Dedoncker, Baeken, Brunoni, Vanderhasselt, 2016) as emotional information (Boggio et al., 2007; Wolkenstein & Plewnia, 2013). TDCS involves the application of a weak, direct electric current through electrodes positioned over the scalp. The resulting stimulation reaches the underlying neuronal tissue and induces polarization-shifts on the resting membrane potential (Brunoni et al., 2011). Moreover, tDCS elicits after-effects lasting for up to one hour (Nitsche & Paulus, 2001; Nitsche et al., 2003). Anodal stimulation generally facilitates cortical activity, whereas cathodal tDCS has opposite effects. Importantly, anodal tDCS of the prefrontal cortex has been found to reduce state rumination via a beneficial change in working memory processes (Vanderhasselt et al., 2013) and also causally reduce other depressive symptoms (e.g., Brunoni et al., 2013).

Hence, these results are indicative of a link between remediating the homeostasis in the neuro-circuits affected in depression (for a review see De Raedt et al., 2015) through experimental manipulation (tDCS), and a subsequent decrease in rumination (see also Vanderhasselt et al., 2013). Moreover the link between the DLPFC and rumination has also been established in fMRI research (e.g., Vanderhasselt, Kuhn, & De Raedt, 2011; 2013). As such, in this study we searched to investigate how that manipulating these neuro-circuits could affect ruminative processes. Prefrontal regions have been associated extensively with cognitive and emotional regulation processes (Cerqueira et al., 2008; Damasio, 2000; Davidson et al., 2002b). It is also the case that a single session of neurostimulation over the prefrontal cortex does not affect mood in healthy participants. From this it can be concluded that the cognitive effects of neurostimulation cannot be explained simply by mood changes (see Remue, Baeken & De Raedt, 2016).

Brain imaging studies show that rumination scores are positively correlated with functional connectivity (FC) within the default mode network at rest (including the anterior and posterior midline structures) (Siegle et al., 2002; Ray et al., 2005; Johnson et al., 2009; Berman et al., 2011a,b; Farb et al., 2011; Hamilton et al., 2011; Vanderhasselt et al., 2011; Zhu et al., 2012; Paul et al., (2013); Nejad et al., 2013). The resting state literature offers support for the idea that disrupted cognitive control leads to intrusive ruminative thoughts, and that rumination has been associated with increased connectivity and activity of the default mode network (Sheline et al., 2010; Hamilton et al., 2011; Davey et al., 2012; Marchetti et al., 2012). The dynamics between the cognitive network and the default mode network can also be considered from a bottom-up perspective where increased maladaptive self-focus and thereby hyperactive cortical midline regions interfere with normal cognitive function (Nedjat et al., 2013). Regarding social evaluations (e.g., interpersonal criticism), research in social cognitive neuroscience has emphasized the functions of the precuneus, which is a functional core of the default mode network (DMN) (Uteisky, Smith & Huettel, 2014) and the posterior cingulate cortex (PCC) which is involved in social inferential processing (Kuzmanovic et al., 2012). Cabanis et al. (2013) have further demonstrated that the precuneus and the PCC are involved in the evaluation of social events (based on positive and negative sentences describing socially relevant situations in everyday life: e.g., "*Your boss appreciates your work in the team*"; "*The waitress ignores you in the bar*"). Interestingly, Kuzmanovic et al. reported increased neural activation of the precuneus and PCC when participants were exposed to verbal interpersonal evaluations (based on positive and negative sentences describing a social action suitable to induce impression, e.g., "*she told the secrets of a colleague to the others*").

In the current study we sought to manipulate neural processes underlying rumination (self-referential processes) that occurred when people were confronted with different emotional stimuli (standardized emotional comments of positive, negative, and neutral comments). This was accomplished by applying simultaneous tDCS over the DLPFC while participants were undergoing fMRI scans. Our study was the first to apply neurostimulation during fMRI as an experimental manipulation to investigate the neural correlates underlying the link between criticism and self-referential processes. Given the importance of network analyses (e.g., cognitive network, default mode network) we began by investigating the neural activity in healthy participants when confronted with different emotional stimuli. This allowed us to explore the influence of a single sham controlled neuromodulation session over the DLPFC on regional brain activity. We subsequently used those results as a guide to define seeds in FC analyses. A first hypothesis is the positive influence of real tDCS on rumination, where we expect a decrease in self-referential thoughts (rumination) after real tDCS, but not after sham. Second, based on the existing literature on cognitive control and self-referential processing, we anticipated effects in the DLPFC and the precuneus/PCC.

METHOD

Ethics statement

Participants were provided with full details regarding the aims of the study and the procedure. All participants gave their written informed consent and received a financial compensation for their participation. The study was approved by the Ethical Committee of the University Hospital of Ghent University (UZGent), and carried out according to the Declaration of Helsinki. This study was part of a larger study on neurocognitive effects of tDCS on the brain.

Participants

Participants were 36 right-handed female students with a mean age of 22.61 (SD = 2.22, Min = 20, Max = 29). They were recruited through student forums of Ghent University as well as via social media. Each participant received €80 for participation. Right-handed female participants were selected because of sex-related influences on neural mechanisms underlying emotion processing (e.g. Cahill, 2003; Van Strien & Van Beek, 2000). Participants were screened before study entry, based on the following inclusion criteria: (a) no current/history of psychiatric disorder, using the International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998), (b) BDI score below 14, (c) no current/history of neurological problems or implanted metal objects over the head, and (d) no current psychotropic medications. Of the 36 participants, one chose not to return for the second session, three had to be cancelled due to technical problems during the scans. Before the start of the protocol, the remaining 32 participants were randomly allocated to a real-first (n=16) or sham-first (n=16) stimulation condition.

Materials

The Beck Depression Inventory (BDI-II-NL). A 21 item self-report inventory was used to measure the severity of depressive symptoms (Beck, Steer, Ball, & Ranieri, 1996). The Dutch translation of the BDI-II has shown high internal consistency: Cronbach’s α of .92 for a patients and .88 for healthy controls. Also, the validity index satisfies general psychometric criteria (van der Does, 2002). In our sample the mean of the BDI scores was M = 3.56 (SD = 3.44), which is within the normal range.

The Momentary Ruminative Self-focus Inventory (MRSI). To obtain a state measure of ruminative thoughts following the criticism paradigm, we used a questionnaire that measures momentary self-reflective rumination (Mor, Marchetti, & Koster, 2015). All six questions relate to self-referent, ruminative thoughts with a particular focus on feelings, reactions, and sensations. The statements are not inherently negative or positive, and are considered as a state measure of ruminative thinking (e.g. “Right now, I am thinking about how happy or sad I feel” and “Right now, I wonder why I react the way I do”). Participants were requested to indicate whether they were engaging in these thoughts during after each resting state (see Figure 1). They were asked to respond using a seven-point Likert scale ranging from 1 (totally disagree) to 7 (totally agree) in order to measure the intensity of momentary ruminative self-referential thoughts (MRST).

Visual Analogue Scale (VAS). Mood state was assessed using six visual analogue scales (VAS) measuring how fatigued, vigorous, angry, tense, depressed and cheerful participants were feeling “at this moment”. The VAS is a 10 cm line, with endpoints from “not at all” to “very much”.

Criticism Challenge

While inside the scanner, we exposed participants to critical, praising, and neutral comments. These comments were directly addressed at the participant (e.g., “*One of the things that bothers me about you is that you…*”) and made by a female voice. All comments were based on comments previously used and validated (Hooley et al., 2009; 2012) and were the same for each participant. The criticism paradigm was used to trigger self-referential processes in healthy participants. The content of the comments were of different emotional content (positive, negative, neutral). The paradigm always followed the same order: neutral, positive, neutral, and always finishing with negative. Negative was always last to avoid emotional contamination and to maximize the negative impact just before the resting state. Each scanning epoch began with a 30-sec rest period, followed by 30 sec of criticism (or praise or neutral), another rest period, another 30 sec of criticism (or praise or neutral), and then another rest period. Each participant underwent four scanning epochs; thus, each participant heard two 30-sec segments of critical and praising commentary and four 30-sec segments of neutral commentary (this was chosen so there would be a buffer between the praising and the critical comments). Only one type of emotional comment was included within a scanning epoch (i.e., two critical or two praise or two neutral remarks; no commingling of comment type occurred within an epoch). Participants heard each comment once only, and participants did not hear any of the comments before the scanning. The criticism paradigm lasted 8.30 minutes in total. Examples of neutral, praising, and critical comments are provided for illustration:

"*One of the things she did today was to go out to lunch. She decided to go out for a sandwich and a cup of coffee around noon. She got there before the place got busy so it was pretty easy for her to find an empty table. She was there for about half an hour. She ate her sandwich, drank her coffee and read the newspaper. By the time she left, the place was quite crowded.*"

"*One thing I really like about you is the way you pay attention to the people you are with. You really seem to be able to make the people around you feel good. Part of it is that you are a good listener. But you also have a really warm personality and a genuine interest in other people. It's a great combination and it makes people feel really happy to be around you.*"

"*One of the things that bothers me about you is how bad you are at dealing with negative feedback. If someone says anything even remotely critical of you, you tend to get very defensive. You are far from a perfect person -- even if that is how you like to see yourself. I really wish you would listen when other people tell you what bothers them rather than getting all hostile and trying to defend yourself.*".

tDCS

Direct electrical current was applied in the fMRI scanner using a saline-soaked pair of surface sponge electrodes (35 cm2) and delivered by a battery-driven stimulator, which was MRI-compatible. To localize the target stimulation areas (left DLPFC and right supraorbital), Brainsight neuronavigation system (Brainsight™, Rogue Research, Inc) was used to navigate into participant structural cerebral MRI and localize both left DLPFC as contralateral supraorbital area. Subsequently, the anode was placed over the individually located DLPFC, while the cathode was placed over the contralateral supraorbital area. A constant, direct current of 1.5 mA with 30 s of a ramp up was applied for 20 min. For sham, the electrodes were positioned in the same way as when administering tDCS stimulation; however, the current was ramped down after 30 seconds. This procedure is a reliable sham condition (Nitsche, et al. 2008). Most participants (26/32) could not distinguish real from sham tDCS (the 6 others answered correctly to which condition was real vs sham). To avoid carry-over effects from the previous stimulation, the second session was carried out after an interval of at least 48h.

fMRI Procedure

To obtain individual anatomical information, all participants first underwent a T1-weighted MRI (3D-TFE, TR/TE=2530/2.58; flip angle=7°; FOV=220x220mm^2; resolution=0.9x0.9x0.9mm^3; number of slices=176) of the brain using a Siemens 3T TrioTim MRI scanner (Siemens, Erlangen, Germany). These scans were performed with a 32 channel SENSE head coil.

Then, outside the scanner, using Brainsight neuronavigation (Brainsight™, Rogue Research, Inc), the anodal electrode was visually located over the left DLPFC. For every individual we located the left DLPFC visually on the 3D surface rendering of the brain based on the known gyral morphology, and marked the center part of the midprefrontal gyrus as the left DLPFC target (Brodmann 9/46). The cathodal electrode was placed on the right OFC (1 cm above the eyebrows).

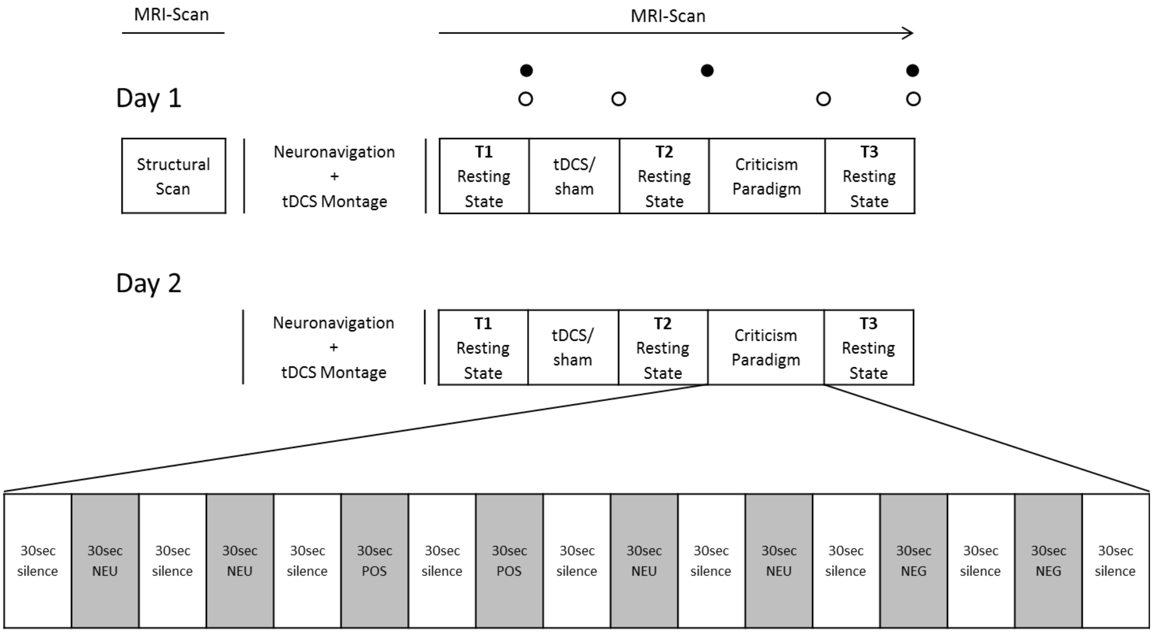
Next, the participants returned in the scanner. For the following fMRI measurements were performed using an EPI sequence (TR/TE=2000/29ms; flip angle=90°; FOV=192x192mm^2; resolution=3x3x3mm^3; slice thickness/ gap=3.00/1.00mm; number of slices=40). The images were corrected for the temporal difference in acquisition among different slices, and then the images were realigned to the first volume for head-motion correction. Participants were excluded from the dataset because either translation or rotation exceeded ±1.5 mm or ±1.5o, or mean frame wise displacement (FD) exceeded 0.3. The resulting volumes were then de-spiked using AFNI's 3dDespike algorithm to mitigate the impact of outliers. The mean BOLD image across all realigned volumes was co-registered with the structural image, and the resulting warps applied to all the de-spiked BOLD volumes. Finally, all the co-registered BOLD images were spatially normalized into MNI space and smoothed (8 mm full-width half-maximum).

Concerning the criticism paradigm, audiographic comments were presented over non-ferrous, gradient damping headphones, in a blocked design. More specifically, four separate blocks of 2 minutes each except the last was followed by 30 sec silence making the total paradigm lasting for total duration of 8.30 min (see Figure 1). During this criticism paradigm participants were instructed to keep their eyes open, focusing on a fixation cross projected on a plexiglas screen mounted at the end of the scanner bore.

During the resting-state measurements before tDCS, just after stimulation, and after the criticism paradigm, which involved each time 7.12 minutes of scanning (see Figure 1: T1: before tDCS, T2: after tDCS and before criticism, T3: after criticism), the participants were asked to stay awake with their eyes closed, as recommended for optimal resting state data (e.g., van den Heuvel & Pol, 2010; Patriat et al., 2013). To reduce sensory confounds as much as possible, the light in the room was dimmed during scanning. After the scan, participants confirmed that they had been awake throughout the scan and had complied with the instructions.

During the fMRI procedure two questionnaires were repeated several times (see details in Figure 1). To record any possible mood changes between the scanning blocks (which consisted of 3 resting state blocks, a real/sham tDCS stimulation block, and the criticism paradigm), mood was measured at five time points during the procedure: before the first resting state, after the first resting state, after the tDCS/sham session, after the criticism paradigm, and finally after the last resting state. The MRSI was administered three times during the fMRI procedure, after each of the three resting states. Both questionnaires were read out loud to the participants through the headphones to which they could respond through a built-in microphone.

Figure 1. Overview of the protocol during the two days of testing.



Note. NEU = neutral; POS = positive; NEG = negative audio script . ● = MRSI time point; ○ = VAS time point.

fMRI Analyses

The fMRI data were analyzed using both the AFNI and SPM12 package. For the criticism paradigm, the spm maps were submitted to an 2 x 2 x 3 ANOVA with comment type (neutral vs. positive vs. negative) as the within-subjects factor, order (first real then sham vs. first sham the real tDCS) and condition (real vs. sham tDCS) as the between subjects' factors. Significance was set at the cluster level FWE corrected with $p<0.001$ and k of 73 voxels. Post-hoc T-tests were performed for the significant interaction clusters for the 3 comment types (positive vs negative vs neutral).

For the seed FC analysis, several additional processing steps preceded the analysis of the voxel-based correlations. Several spurious or nonspecific sources of variance were removed from the data through linear regression: i) six head motion parameters obtained in the realigning step, ii) the averaged signals of no interest from subject-specific white matter (WM) and cerebrospinal fluid (CSF), iii) the whole-brain signal. Following this, the residual time series were linearly detrended and temporally band-pass filtered (0.008-0.1 Hz). Then the time series were further scrubbed with FD<0.3 (Power et al., 2012).

Correlation maps were obtained by extracting the BOLD time course from the seed region (precuneus) and computing the correlation coefficients between that time course and the time courses in all other brain voxels. The degrees of freedom for Pearson correlations were adjusted to keep it the same for all participants after censoring (i.e., movement artifact reduction).

To evaluate the effects of tDCS on functional connectivity before and after the criticism paradigm, we compared the rest fMRI before and after the criticism paradigm. We specifically focus on the precuneus/PCC as region of interest. This seed region was a 6-mm-diameter sphere centered on a point with MNI coordinates (x= -7, y= -45, z= 24), designed to encompass the precuneus/PCC. These MNI coordinates were selected following the recent paper of Berman et al. (2011), defining centroids of nodes within the default mode network, related to rumination. The seed for our FC analyses was selected anatomically and is similar in location to regions that other authors have used to define the default network (Greicius et al., 2003; Fox et al. 2005; Monk et al., 2009; Raichle, 2010). The precuneus/PCC has been argued to play a central role in the default mode network (Greicius et al., 2003), and has been found to reveal connectivity in the default network most effectively (Greicius et al., 2003) and is a reason why other authors have used the precuneus/PCC as a seed to define the default network (Monk et al., 2009). In addition, it is an area of greatest deactivation during off-task behavior (Shulman et al., 1997). To combine results across participants and compute statistical significance, Fisher's r-to-Z transformation was used to convert these correlation maps into Z-maps characterizing the rsFC of the seed region in each point.

These rsFC maps were used in a 2 x 2 x 2 analysis of variance using GLMFlex and SPM12 toolbox, with Time (pre-post criticism) as the within-subjects factor, and Condition (real vs. sham), and order (first real then sham vs. first sham then real tDCS) as the between subjects' factors, while correcting for age, and mean FD. Significance was set at the cluster level FWE corrected with $p<0.005$ and k of 257 voxels. Post hoc two-sample *T*-tests were performed to further investigate the characteristics of the significant interaction clusters. The significance threshold was set at $p< 0.05$, two tailed.

Data analytical plan: behavioral data

All collected data were analyzed with SPSS 23 (Statistical Package for the Social Sciences). First, to investigate if mood changes occurred throughout the study protocol, and if this was linked to any of the condition types, we performed a 2 (condition: tDCS vs sham) X 4 (time: $T^{vas}1$ = before tDCS/sham; $T^{vas}2$ = after tDCS/sham and before Criticism; $T^{vas}3$ = after criticism, before last resting state; $T^{vas}4$ = after last resting state) repeated measures MANOVA, with the mood scales as multiple dependent variables. To follow up on the significant changes in time, we compared each mood scale between blocks, which allowed us to register any mood change before and after a scanning block. As such, we could evaluate the impact of the resting states, stimulation block and criticism paradigm on mood separately. For this, we performed another MANOVA with 2 (condition) X 2 (time), with the mood scales as multiple dependent variables. To understand if there are any behavioral changes in self-referential thoughts, we looked at the three MRST questionnaires, which were measured after each resting state block. For the MRST data we used a 2 (condition: tDCS and sham) X 3 (time: $T^{MRST}1$ = after first resting state; $T^{MRST}2$ = after second resting state; $T^{MRST}3$ = after last resting state) repeated measures ANOVA.

RESULTS

Mood

The MANOVA revealed only an effect of time *F*(13, 18) = 5.45, *p* = .002 (not of Condition nor an interaction effect), that is over the whole study procedure. Univariate main effects of time were significant for fatigue, *F*(1, 30) = 3.72, *p* = .035; vigor, *F*(1, 30) = 12.33, *p* = .002; anger *F*(1, 30) = 3.48, *p* = .048; and cheerfulness, *F*(1, 30) = 6.40, *p* = .001., and there was a trend for depressed feelings: *F*(1, 30) = 2.85, *p* = .061; but no changes in tension, *F*(1, 30) = 0.93, *p* = .41.

Following up on the significant changes in time, we performed separate MANOVAs to compare the scores between each time point. First, we compared mood before ($T^{vas}1$) and after ($T^{vas}2$) tDCS/sham, which revealed that participants were more tired, *F*(1, 30) = 13.27, *p* = .001; less vigorous, *F*(1, 30) = 22.41, *p* < .001; and less cheerful *F*(1, 30) = 8.58, *p* = .006 (all other effects were *ns*).

For our manipulation check (before versus after the criticism paradigm = $T^{vas}2$ vs $T^{vas}3$) the MANOVA revealed differences in mood indicating that participants were more angry, *F*(1, 30) = 9.15, *p* = .005, more depressed, *F*(1, 30) = 5.55, *p* = .025, and (trend) less cheerful, *F*(1, 30) =4.05, *p* = .053. By comparison, there were no differences in feelings of fatigue, vigor, and tension (all other effects were *ns*). In summary, these data show an increase in feelings of anger, depression and a decrease in cheerfulness after criticism (although the criticism paradigm included neutral, praise and criticism, the last block was always criticism to maximize the effect on self-referential thinking before the last resting state).

Finally, we compared mood before ($T^{vas}3$) and after ($T^{vas}4$) the last resting state, which revealed only a significant decrease of vigor, *F*(1, 30) = 5.13, *p* = .031 (all other effects were *ns*).

MRST

The repeated measures ANOVA yielded no main effects of condition or time (all *p*'s > .09). However, a significant interaction effect of condition and time *F*(2,30) = 3.83; *p = .033*. In the real stimulation condition ruminative self-referential thoughts decreased from $T^{MRST}1$ to $T^{MRST}2$ *t*(31) = 2.63; *p = .013*, with no change between T2 and T3 *t*(31) = 0.30; *p = .767*, and an overall decrease from $T^{MRST}1$ to $T^{MRST}3$ *t*(31) = 2.24; *p = .033*., showing that the decrease in MRST after real tDCS stayed significant after the criticism paradigm. In the sham condition no significant changes over all time-points were observed. When comparing between conditions, no baseline differences were observed (*p* = .20), showing that the decrease in the real stimulation condition (and no changes in sham) cannot be ascribed to differences in baseline MRST.

fMRI results of the mixed ANOVA

In short, the 3 x 2 x 2 ANOVA whole brain analysis showed a significant three-way interaction effect for two clusters in the left and right temporal cortices, and one in the visual cortex. There was also a significant three-way interaction cluster observed in the posterior cingulate cortex (MNI coordinates: x= 3, y= -36, z= 42). The post hoc T tests

(See Table 1B) showed that both praise and criticism compared to neutral showed significant decrease of precuneus activity after real tDCS (not after sham), however more importantly the decrease after criticism was substantially larger when compared to praise. See for details in Table 1.

Finally, the 2 x 2 x 2 ANOVA seed FC analysis examining the effects of tDCS before and after criticism showed a significant interaction cluster in the left ventromedial prefrontal cortex (MNI coordinates: x= -6, y= 51, z= -15). Follow up T-Test revealed that real tDCS resulted in a decreased FC between the precuneus/PCC seed and the vmPFC. On the other hand, without stimulation, (sham) FC increase between these two areas after receiving criticism. See for details Table 2.

Table 1. A) Results of the 2 x 2 x 3 ANOVA whole brain analysis, showing the areas with significant interaction. Script (neutral vs. positive vs. negative) is the within-subjects factor, Order (first real then sham vs. first sham the real tDCS) and Condition (real vs. sham tDCS) the between subjects' factors. Significance was set at the cluster level FWE corrected with *p*<0.001 and k of 73 voxels. B) Post-hoc significant T-test clusters within the 2 x 2 x 3 ANOVA interaction mask for the 3 scripts. The significance threshold was set at *p*< 0.05 for all analyses. Only significant clusters with a threshold of k>50 are displayed.

(A) 2 X 2 X 3 ANOVA (CONDITION X ORDER X SCRIPT)

	Cluster size	**Anatomical region**	**Hemisphere**	**BA**	***F*-value**	**PEAK COORDINATES (X,Y,Z) (MM)**
	MAIN EFFECTS					
CONDITION	**NO SIGNIFICANT CLUSTERS EMERGED**					
ORDER	2247	Superior Temporal gyrus	Left	21	197.74	**-60 -21 0**
	1925	Superior Temporal gyrus	Right	22	182.66	**60 -15 0**
	4055	Lingual Gyrus	Right	18	26.45	**18 -87 -3**
	114	Cingulate Gyrus	Right	31	13.52	**6 -36 42**
SCRIPT	**NO SIGNIFICANT CLUSTERS EMERGED**					
	2-**WAY INTERACTION**					
CONDITION X ORDER	No significant clusters emerged					
ORDER X SCRIPT	No significant clusters emerged					
SCRIPT X CONDITION	No significant clusters emerged					
	3-WAY INTERACTION					
CONDITION X ORDER X SCRIPT	2038	Superior Temporal gyrus	Left	21	242.04	**-57 -21 3**
	1851	Superior Temporal gyrus	Right	22	241.85	**57 -15 0**
	4288	Middle Occipital Gyrus	Left	18	29.73	**-9 -96 9**
	103	Cingulate Gyrus	Right	31	12.15	**3 -36 42**

(B) Post-hoc T tests comparing real > sham tDCS

Contrasts	**Cluster size**	**Anatomical region**	**Hemisphere**	**BA**	**T-value**	**Peak coordinates (x,y,z) (mm)**
Neut > Pos	236	Precuneus	Right	19	2.65	**33 -84 36**
	218	Precuneus	Left	19	3.07	**-21 -75 30**
	58	Middle Occipital Gyrus	Left	37	3.00	**-54 -69 0**
	99	Precuneus	Left	7	3.71	**-27 -60 63**
Neut > Neg	78	Middle Temporal Gyrus	Left	21	2.39	**-54 3 -27**
	94	Precuneus	Right	7	2.74	**21 -57 30**
	80	Middle Temporal Gyrus	Left	37	2.28	**-45 -60 0**
	53	Middle Temporal Gyrus	Right	37	2.25	**45 -60 -3**
Pos > Neg	**77**	**Precuneus**	**Right**	**31**	**3.28**	**21 -45 12**

Table 2. A) Results of the 2 x 2 x 2 ANOVA seed analysis, showing the areas with significant interaction effects with the precuneus seed. Time (pre-post criticism) is the within-subjects factor, Order (first real then sham vs. first sham the real tDCS) and Condition (real vs. sham tDCS) the between subjects' factors. Significance was set at the cluster level FWE corrected with *p*<0.005 and k of 257 voxels. B) Post-hoc significant T-test clusters within the 2 x 2 x 2 ANOVA interaction mask. The significance threshold was set at *p*< 0.05 for all analyses.

(A) 2 X 2 X 2 ANOVA (TIME X CONDITION X ORDER)

	Cluster size	**Anatomical region**	**Hemisphere**	**BA**	***F*-value**	**PEAK COORDINATES (X,Y,Z) (MM)**
	MAIN EFFECTS					
TIME			No significant clusters emerged			
ORDER			No significant clusters emerged			
CONDITION			no significant clusters emerged			
	2-**WAY INTERACTION**					
CONDITION X ORDER			No significant clusters emerged			
ORDER X TIME			No significant clusters emerged			
TIME X CONDITION			No significant clusters emerged			
	3-WAY INTERACTION					
TIME X ORDER X CONDITION	257	Medial Frontal Gyrus	Left	11	49.053	**-6 51 -15**

(B) Post-hoc T tests comparing real > sham tDCS						
Contrasts	**Cluster size**	**Anatomical region**	**Hemisphere**	**BA**	**T-value**	**Peak coordinates (x,y,z) (mm)**
Pre > Post						
Sham	**No significant clusters emerged**					
Post > Pre						
Sham	204	Medial Frontal Gyrus	Left	11	-3.43	**-9 57 -6**
Pre > Post						
Real	161	Medial Frontal Gyrus	Left	11	3.63	**-6 51 -18**
Post > Pre						
Real	**No significant clusters emerged**					

DISCUSSION

In this innovative study we investigated the impact of a single sham controlled neuromodulation session in real time, on the underlying processes of rumination (self-referential processes), when confronted with online interpersonal criticism. Therefore, we exposed participants to different comment types (neutral, praise, and criticism) and measured neural activity related to each emotional condition. In a follow up we used the coordinates of the ROI that emerged from these initial results to create a seed for our FC analyses. This study is the first to use a ‘real time’ design to investigate the experimental manipulation of the underlying processes of rumination in response to interpersonal criticism. In sum, we examined three different issues (1) how does tDCS affect self-referential thinking (rumination), (2) how does tDCS affect neural activity during (a) praise and (b) criticism; and (3) what are the effects on functional connectivity with regard to self-referential processing, by comparing the resting states before and after the criticism paradigm.

We first focus on our neurobiological results. The data showed a differential pattern of neural activity in the precuneus during the criticism paradigm. More specifically, after real versus sham tDCS, both praise and criticism compared to neutral comments showed a significant decrease of precuneus activity. However, and more importantly, the decrease after criticism was substantially larger compared to the decrease after praise. In other words, when people are confronted with social evaluations (both praise and criticism), and only after real tDCS, they showed a decrease in activation of the precuneus, an area known for its crucial role in self-referential processing (Cavanna et al., 2006). This is indicative for less self-referential processing when confronted with social evaluations (both positive and negative). Moreover, the observation that the decrease of precuneus activity during criticism was larger than during praise after real tDCS, nicely demonstrates the impact of neuromodulation on negative self-referential processing (see also Vanderhasselt et al., 2013). The involvement of the precuneus is in line with several correlational studies (Cavanna & Trimble 2006; Summerfield et al. 2009, Freton et al., 2014) showing a possible role of this region in referential processing of socially relevant situations in everyday life.

Second, in a follow up we conducted functional connectivity analyses based on the regions of interest. Our data revealed that real tDCS resulted in a decreased FC between the precuneus/PCC seed and the vmPFC. On the other hand, sham resulted in a FC increase between these two areas. Importantly, the precuneus/PCC has been argued to play a central role in the default mode network (Greicius et al., 2003), and ruminative thought has been further associated with increased connectivity and activity of the DMN (Sheline et al., 2010; Hamilton et al., 2011; Davey et al., 2012; Marchetti et al., 2012). In addition, vmPFC–precuneus/PCC interactions are thought to underlie aspects of self-referential processing (Buckner et al., 2008; Qin and Northoff, 2011). Hence, our results are indicative of the beneficial effect of tDCS on the reduction (cognitive control) of self-referential thinking (rumination) after real tDCS. Moreover, after sham tDCS we see the expected increase of self-referential thinking (rumination) in two important nodes of the DMN, in response to criticism.

In line with our neurobiological results, our behavioral results showed a significant decrease in rumination (MRST) when comparing before versus after tDCS. Furthermore, we also observed such a decrease when comparing MRST scores at baseline with MRST scores after criticism. However, this was only observed in the real stimulation condition, but not in the sham condition. As such, we reestablish the beneficial effect of neuromodulation on cognitive control over negative information (e.g., Boggio et al., 2007; Wolkenstein & Plewnia, 2013) and specifically on rumination (Vanderhasselt et al., 2013).

Based on these results, several questions remain to be answered. First, what does the activation in the precuneus signify? In a meta-analysis of neuroimaging studies focused on self-referential processing, Northoff et al. (2006) found that commonly activated regions lie in dorsal and ventral areas of the medial prefrontal and anterior cingulate cortices, as well as the precuneus/PCC. These regions are cortical midline structures (Northoff and Bermpohl, 2004) and overlap with the intrinsic default mode network (Raichle et al., 2001; Spreng and Grady, 2010; Qin and Northoff, 2011). The default mode network is found to be activated during resting state functional imaging and deactivated during functional imaging of cognitive task performance (Fox et al., 2005; Smith et al., 2009). When the brain is at rest, i.e. not engaged in externally driven cognitive processing, self-referential processing is believed to predominate (Gusnard et al., 2001) and more activity in the DMN is observed. Importantly, when taking into account social evaluations, research in social cognitive neuroscience has demonstrated the particular functions of the precuneus/PCC in social inferential processing (Kuzmanovic et al., 2012). Moreover, there is increasing evidence that self-referential processing as well as the cortical midline structures (such as the precuneus/PCC) play a major role in the development, course, and treatment response of major depressive disorder (Nejad et al., 2013). Among the CMS, the precuneus may underlie the integration of self-relevant mental simulations with past experiences (Cavanna and Trimble 2006; Summerfield et al. 2009). Moreover, the results of Freton et al. (2014) are consistent with the role of the precuneus in higher order mental processes that are related to self-referential processing and self-consciousness. In addition, Freton et al. (2014) reported that negative correlations between rumination and the posterior CMS during self-focus could be interpreted as a difficulty for ruminators to disengage from spontaneous and unwanted thought during self-referential processing. Hence, our findings further underscore the existing social-cognitive neuroscience literature on the importance of the precuneus/PCC in self-referential processing when confronted with social evaluations.

A second question is, what can we conclude from the functional connectivity between the precuneus/PCC and the vmPFC? When looking at brain imaging studies, rumination scores are often positively correlated with FC within the default mode network at rest (including the anterior and posterior midline structures) (Siegle et al., 2002; Ray et al., 2005; Johnson et al., 2009; Berman et al., 2011a,b; Farb et al., 2011; Hamilton et al., 2011; Vanderhasselt et al., 2011; Zhu et al., 2012; Paul et al., 2013;

Nejad et al., 2013). The resting state literature offers support to the idea that disrupted cognitive control leads to intrusion of ruminative thought, and ruminative thought has been further associated with increased connectivity and activity of the default mode network (Sheline et al., 2010; Hamilton et al., 2011; Davey et al., 2012; Marchetti et al., 2012). The dynamics between the cognitive network and the DMN can also be seen from a bottom-up perspective where increased maladaptive self-focus and thereby hyperactive cortical midline regions interfere with normal cognitive function (Nedjat et al., 2013). Hence, drawing upon our FC results, we find support in the literature, emphasizing the role of the vmPFC as crucial ROI in processing emotional features during social cognition. Connectivity changes between the vmPFC and other DMN regions have been found in Theory of Mind (ToM) studies and morality studies (Li et al., 2014). Moreover, the vmPFC is engaged in identifying self-relevant information and assessing the salience of stimuli (Gusnard et al., 2001; Northoff and Bermpohl, 2004; Northoff et al., 2006). Both the amygdala and precuneus/PCC are densely and reciprocally connected with vmPFC (Price, 1999; Barbas, 2000; Raichle et al., 2001; Greicius et al., 2003), and vmPFC–precuneus/PCC interactions are thought to underlie aspects of self-referential processing (Buckner et al., 2008; Qin and Northoff, 2011). As such, the functional significance of the vmPFC–precuneus/PCC circuit suggests involvement in self-reflective cognition (Buckner et al., 2008; Qin and Northoff, 2011). Therefore, we can conclude that our results, which shows an decreased functional connectivity after real tDCS (not sham) between the precuneus/PCC and the vMPFC, are indicative of the beneficial effect of tDCS on the reduction (cognitive control) of self-referential thinking (rumination) after real tDCS.

A third question is how does tDCS over the DLPFC influences the activity of a distant region (precuneus/PCC)? A possible explanation might be found in the functionality of the regions observed in our study. There is sufficient evidence of the positive influence of tDCS over the left DLPFC on cognitive control over rumination (e.g., Vanderhasselt et al., 2013). In addition, The precuneus/PCC has been argued to play a central role in the default mode network (Greicius et al., 2003). Moreover, it has been found to reveal connectivity in the default network most effectively (Greicius et al., 2003), and ruminative thought has been further associated with increased connectivity and activity of the DMN (Sheline et al., 2010; Hamilton et al., 2011; Davey et al., 2012; Marchetti et al., 2012). As such, we can understand this link between anodal tDCS over the left DLPFC and activity in the precuneus/PCC as an effect of cognitive control over self-referential thoughts (rumination). Support for this explanation can be found in a study of Keeser et al. (2011), who could demonstrate that prefrontal tDCS changes connectivity of resting-state networks, for instance, in the DMN of which the precuneus plays a key role. Therefore, it can be concluded that prefrontal tDCS modulates resting state functional connectivity in distinct functional networks of the human brain (see also Park et al., 2013; Stagg, et al., 2013). Our findings are also in line with the idea that rumination could stem from a top-down control failure, where lack of inhibition from dorsolateral prefrontal regions to the anterior cingulate cortex allows free reign of ruminative thoughts (Nejad et al., 2013), as has been proposed by de Raedt & Koster (2010). On the other hand, a bottom-up process with overactive limbic regions could tag negative emotionality and salience to experiences leading to increased rumination and thereby to an interference with normal higher cognitive function and control (Nejad et al., 2013). Hence, targeting this neural circuitry - which is central in the conceptualization of depression, that is, a failure to recruit top-down control (e.g. PFC) to regulate limbic activity (e.g., amygdala; Davidson et al. 2002; Mayberg 1997; Ochsner et al. 2002; Phillips et al. 2003; Phan et al. 2004) - has already been shown to have a beneficial effect on rumination (Vanderhasselt et al., 2013) and on other depressive symptoms (e.g., Brunoni et al., 2013). Hence, this study is the first that investigated neural activity during (ROI analysis), as well as before and after criticism (resting state), following a single tDCS session in the scanner, revealing the beneficial effects of neuromodulation on the underlying processes of rumination (within the DMN).

Finally, what do the behavioral results tell us and how do they relate to our neurobiological results? Our behavioral data further corroborate the finding that tDCS has a beneficial effect on rumination, and as such, further supports our neurobiological data. Interestingly, when comparing the MRST scores before and after the criticism paradigm, no changes in the real tDCS condition are observed. Although this might seem puzzling, we feel that it is strong proof for the potent positive influence of tDCS on the cognitive control of rumination. More specifically, by applying tDCS over the DLPFC, self-referential thoughts are decreased in such a way that even criticism does not affect (increase again) these self-referential thoughts. Thus, our data further indicate the beneficial use of tDCS in coping with rumination, which holds promise for both experimental and clinical research. In addition, it also underscores the relevance of tDCS in clinical treatment, in particular in the treatment of depressed patients, since depression is strongly associated with rumination about negative self-relevant information (Nolen-Hoeksema et al., 2008).

Nonetheless, some limitations in this study need to be discussed. Because we were not aware of any other existing questionnaires to measure momentary ruminative self-referential thoughts, we used a short inventory that has only been used in a limited number of studies (Momentary Ruminative Self-focus Inventory; Mor et al., 2013; Vanderhasselt et al., 2013). Hence, further research is needed with this questionnaire. Secondly, we focused on women because rates of depression are higher in women than they are in men (Nolen-Hoeksema, 2002) and because we sought to minimize heterogeneity in our data due to gender effects. As such, this limits our generalizability towards a mixed/male population. Thirdly, and more importantly, further research with MDD population is needed to investigate the effects of criticism on rumination and the DMN activity within the depressed brain. This is especially important given that depressed patients, compared to healthy individuals, have been found to have difficulties disengaging from negative information (for an overview, see De Raedt & Koster, 2010). Moreover, depression has been conceptualized as a failure to recruit prefrontal top-down cognitive control to regulate emotion producing subcortical limbic activity (Phillips, Ladouceur, & Drevets, 2008). Thus, the reaction of MDD patients to interpersonal criticism might induce more and stronger effects than with healthy participants, challenging even more the underlying neuro-circuitry that was targeted in this study. However, it was crucial to start testing our causal hypotheses in healthy individuals, without the possible interference of the depressed mood state on the mechanisms under study.

In sum, we used a similar paradigm as Hooley et al. (2009; 2012) but added an experimental manipulation (while under fMRI) that allowed us to shift away from pure correlation research. By doing so we investigated the possible influence of tDCS on the processing of emotional stimuli (i.e., interpersonal criticism) and investigated FC during rest, to unravel the neurobiological basis of (ruminative) self-referential processing when confronted with interpersonal criticism. In doing so, we could further clarify the intricate relation between criticism, self-referential thoughts (rumination) and the underlying neurobiological processes (regional brain activity and FC). Our results further underscore the importance of the precuneus/PCC, as well as the FC with the vmPFC in self-referential processing and the impact of interpersonal criticism. Our study was the first to apply neurostimulation during fMRI as an experimental manipulation to investigate the neural correlates underlying the link between criticism and self-referential processes in real time, showing that tDCS can alter behavioral and neural responses of self-referential processing. With this novel design, we go beyond previous correlational research investigating the underlying processes of rumination, to increase our insights in the 'real time' neural correlates of these processes while confronted with social evaluations. In addition, our experimental manipulation is indicative of the importance to use non-invasive brain stimulation (NIBS) techniques to better understand underlying mechanisms of cognitive processes such as rumination, and the possible application for and transdiagnostic treatment focusing on underlying processes (see De Raedt, 2015).

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CHAPTER 7

ELECTRIFYING THE SELF: THE EFFECT OF tDCS ON THE LINK BETWEEN RUMINATION AND IMPLICIT SELF-ESTEEM AFTER CRITICISM[1]

ABSTRACT

Major Depressive Disorder (MDD) is characterized by negative self-esteem and ruminative self-referential thinking. Ruminative thinking has been related to decreased prefrontal control. In addition the link between MDD and criticism sensitivity has been demonstrated. However, how the relation between criticism and ruminative processes affects self-esteem is still unclear. In this study we explored whether the effect of neurostimulation of the prefrontal cortex on implicit self-esteem would be mediated by a decrease in momentary ruminative self-referential thoughts (MRST) before and after receiving criticism. We used a single, sham-controlled session of anodal transcranial Direct Current Stimulation (tDCS) to the left dorsolateral prefrontal cortex. After receiving tDCS/sham we exposed 32 healthy, right-handed female participants to critical audio scripts and subsequently asked them to complete two Implicit Relational Assessment Procedures (IRAPs), to implicitly measure actual and ideal self-esteem. First, our behavioral data indicated a significant decrease in momentary ruminative self-referential thinking (MRST) after real but not sham tDCS. Second, although there was no immediate effect on implicit self-esteem of tDCS, an indirect effect was found through a double mediation model, with the difference in MRST baseline-after stimulation and baseline-after criticism, as our two mediators. Hence the larger the

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[1] Based on Remue, J., Baeken, C., Loeys, T., Hooley, J., & De Raedt, R. *Electrifying the Self: the effect of tDCS on the link between rumination and implicit self-esteem after criticism.* Manuscript in preparation.

decrease of MRST of participants after real tDCS (and after receiving criticism), the higher their actual self-esteem. In line with the beneficial effects of neuromodulation in the treatment of MDD, these results further show how tDCS can influence cognitive processes, such as rumination, and subsequently, its effect on self-esteem. Given the significant role of rumination and negative self-esteem in MDD, these data expand our knowledge of the mechanisms of action of tDCS by showing its role in controlling self-referential processes and self-esteem as well as the important impact interpersonal criticism can have on this relation.

INTRODUCTION

Although nobody likes to be criticized, for some people receiving criticism is especially problematic. Various studies have demonstrated the link between depression and sensitivity to criticism (e.g., Burcusa & Iacono, 2007; Hooley et al., 2009). Hooley and colleagues (2009) found that even after full recovery from an major depressive disorder (MDD) episode, neural responses to criticism do not appear to normalize. That is, when individuals who have recovered from depression are exposed to criticism, they demonstrate decreased reactivity in the dorsolateral prefrontal cortex (DLPFC) compared to never-depressed individuals (Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005; Hooley et al., 2009). Neuroimaging studies have indicated that a functional balance between ventral (ventral anterior cingulate cortex, ACC) and dorsal compartments in the brain (dorsal ACC, dorsolateral prefrontal cortex-DLPFC) is necessary for maintaining homeostatic emotional control (Seminowicz et al., 2004; Johnstone et al., 2007; Ochsner and Gross, 2008; Wager et al., 2008). As such, many studies suggest that the DLPFC initiates emotion regulation by causing inhibition of the amygdala (e.g., Siegle et al., 2007).

Furthermore, research has shown that being criticized triggers self-referential thoughts and feelings that need to be regulated to prevent maladaptive emotional responses to occur (e.g. Vanderhasselt, Remue, Ng, Mueller & De Raedt, 2015). Being criticized is a distressing experience and activates self-conscious emotions (e.g., feeling hurt) and self-referential thinking (rumination). Importantly, rumination has been put forward as one of the most important underlying vulnerability factors for depression, and has been associated with onset, severity, as well as duration of depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Even though most studies consider ruminative thinking as a trait characteristic, self-referential thoughts fluctuate continuously (especially in healthy individuals) and might provide valuable information to understand the development of a stable trait. Therefore, we explored the occurrence of momentary ruminative self-referential thoughts during rest periods before and after criticism. Participants were asked to rest without any specific task – which is known to result in a stream of undirected thinking patterns – and momentary ruminative self-referential thinking (MRST) was assessed during this period using a short self-report questionnaire. MRST refers to a temporary cognitive thought pattern that is highly dependent on situational cues but that is independent of mood. Trait rumination, on the other hand, is defined as "*behaviors and thoughts that focus one's attention on one's depressive symptoms and on the implications of those symptoms*", and is measured as a habitual thinking response to sadness (Nolen-Hoeksema, 1991, p. 569).

The social context is an important aspect of the self as it relates to emotions (Hofmann, 2014). When you are criticized, the most common effect is that it can easily and negatively impact the self. Moreover, research has shown the detrimental impact of criticism on cognitive processing and thinking styles, such as rumination (e.g., Saffrey & Ehrenberg, 2007; Kaiser, Andrews-Hanna, Metcalf, & Dimidjian, 2015), and subsequently its effect on self-esteem (e.g. Weisbuch, Sinclair, Skorinko, & Eccleston, 2009); Although healthy individuals can regulate (i.e. cognitive control) criticism-induced thoughts and emotions to protect their self-esteem (and maintain emotional well-being), according to the cognitive theories of depression, depressed patients would show decreased self-esteem. Importantly, low self-esteem is not only a correlate but also a vulnerability factor for depression (Orth and Robins, 2013). Interestingly, however, much work on self-esteem and its relationship to depression has employed self-report measures which are susceptible to a variety of response biases such as social desirability and self-presentation. Many cognitive models of depression also assume that self-related schemata are not always consciously accessible and thus cannot always be verbally reported upon (Beck, Rush, Shaw, & Emery, 1979; Young, 1994). Consequently, it is questionable whether the use of self-report measures may provide meaningful information about such schemata. To overcome these limitations, a number of alternative procedures have recently emerged that reduce the participant's ability to control their responses and operate in such a way that they do not depend on introspective access to the psychological content of interest. Whereas self-report measures of self-esteem can be classified as explicit measures that capture non-automatic instances of self-evaluation (e.g., self-evaluations that occur when participants have ample time and resources to reflect or have the intention to evaluate the self), implicit self-esteem measures can be thought of as measures that register more spontaneous, automatic self-evaluations (e.g., self-evaluations that occur quickly or when participants do not have the intention to evaluate the self; see De Houwer, Teige-Mocigemba, Spruyt, & Moors, 2009). Interestingly, in recent years several studies have investigated the implicit positivity bias in (remitted) depressed patients and healthy controls (e.g. Gemar, Segal, Sagrati, & Kennedy, 2001; De Raedt, Schacht, Franck & De Houwer, 2006). Based on these findings Remue and colleagues (2013; 2014) investigated the premise that self-esteem might be broken down into actual and ideal self-esteem, with different patterns specifically related to depressive symptomatology (dysphorics versus non-dysphorics). Results showed higher levels of ideal self-esteem versus actual self-esteem in dysphorics, while a reversed pattern appeared in non-dyshporics (Remue, De Houwer, Barnes-Holmes, Vanderhasselt, & De Raedt, 2013).

Hence, in this study we investigated the impact of being criticized on MRST and how this affects a person’s self-esteem (both actual and ideal self). Moreover, in order to investigate the neurocognitive mechanisms behind this process, we manipulated cognitive control over these self-referential thoughts, by using neuromodulation over the dorsolateral prefrontal cortex (DLPFC), an area that is known for its regulatory function of coping with negative cognitions. The (dorsolateral) prefrontal cortex is implicated in regulating affective states, providing cognitive control over stress and emotion responsiveness (Davidson, et al., 2002a) and plays a crucial role in the integration of different aspects of cognition, memory, and emotional regulation by managing the cognitive control over emotional stimuli and emotional behavior (Hariri, Bookheimer, & Mazziotta, 2000; Kalish & Robins, 2006; Knight, Staines, Swick, & Chao, 1999; Miller & Cohen, 2001). Moreover, a variety of studies have shown that non-invasive brain stimulation (NIBS) over the left DLPFC can be effective in reducing depressive symptoms in the short term in clinically depressed populations (for an overview, see De Raedt, Vanderhasselt & Baeken, 2015).

To experimentally test if an experimental manipulation would lead to a greater control over these self-referential processes, and thus decrease rumination and negative self-esteem, we applied anodal transcranial Direct Current Stimulation (tDCS) to the DLPFC. TDCS consists of the application of a weak, direct electric current through electrodes positioned over one's scalp, which are able to reach the neuronal tissue and induce polarization-shifts on the resting membrane potential (Brunoni et al., 2011). It seems important to note that tDCS elicits after-effects lasting for up to one hour (Nitsche & Paulus, 2001; Nitsche et al., 2003). Anodal stimulation generally facilitates cortical activity, whereas cathodal tDCS has opposite effects. It is also the case that a single session of neurostimulation over the prefrontal cortex does not affect mood in healthy participants. From this it can be concluded that the cognitive effects of neurostimulation cannot be explained simply by mood changes (see Remue, Baeken & De Raedt, 2016). In many previous studies it could already be demonstrated that tDCS of the left DLPFC enhances cognitive processes, both for non-emotional (e.g., Fregni et al., 2005; Leite, Carvalho, Fregni, & Goncalves, 2011; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011) as emotional processes (Vanderhasselt et al., 2013a; Wolkenstein & Plewnia, 2013). Given that prefrontal regions have been associated extensively with cognitive and emotional regulatory processes (Cerqueira et al., 2008; Damasio, 2000; Davidson et al., 2002b). More interestingly, anodal tDCS of the prefrontal cortex has been found to reduce state rumination via a beneficial change in working memory processes (Vanderhasselt, Brunoni, Loeys, Boggio, & De Raedt, 2013) and also causally reduce other depressive symptoms (e.g., Brunoni et al., 2013).

Therefore, we hypothesized that healthy participants would show less ruminative self-referential thoughts after criticism during the real compared to the sham condition. Furthermore, given that no study to date has provided a clear effect of rumination on self-esteem we wanted to explore this link by investigating the correlations between (the change in) MRST and implicit self-esteem, i.e. actual and ideal self-esteem.

METHOD

Ethics statement

Participants were provided with full details regarding the aims of the study and the procedure. All participants gave their written informed consent and received a financial compensation for their participation. The study was approved by the Ethical Committee of the University Hospital of Ghent University (UZGent), and carried out according to the Declaration of Helsinki. This study was part of a larger study on neurocognitive effects of tDCS on the brain[2].

Participants

Participants were 36 right-handed female students with a mean age of 22.61 (SD = 2.22, Min = 20, Max = 29). They were recruited through student forums of Ghent University as well as via social media. Each participant received €80 for participation. Right-handed female participants were selected because of sex-related influences on neural mechanisms underlying emotion processing (e.g. Cahill, 2003; Van Strien & Van Beek, 2000). Participants were screened before study entry, based on the following inclusion criteria: (a) no current/history of psychiatric disorder, using the International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998), (b) BDI score below 14, (c) no current/history of neurological problems or implanted metal objects over the head, and (d) no current psychotropic medications. Of the 36 participants, one chose not to return for the second session, three had to be cancelled due to technical problems during the scans. Before the start of the protocol, the remaining 32 participants were randomly allocated to a real-first (n=16) or sham-first (n=16) stimulation condition.

Materials

Questionnaire measures To assess the presence of depressive symptoms, we used the self-report Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996; Van der Does, 2002). For explicit self-esteem we administered the Rosenberg Self-Esteem Scale (RSES; Rosenberg, 1965; Franck, De Raedt, Barbez, & Rosseel, 2008). Further, in order to assess trait tendencies to ruminate, the Rumination Response Scale was used (RRS, Treynor, Gonzalez, & Nolen-Hoeksema, 2003, Dutch translation by Raes & Hermans, 2007). However, to obtain a state measure of ruminative thoughts following the criticism paradigm, we used a questionnaire that measures momentary self-reflective rumination, that is, the Momentary Ruminative Self-focus Inventory (MRSI) (Mor,

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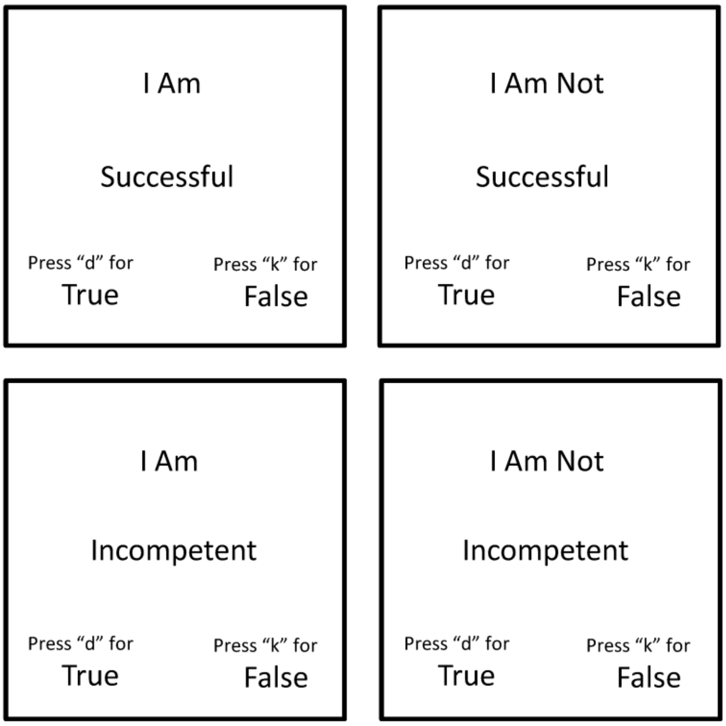
[2] The criticism induction was applied in an fMRI scanner, to measure the underlying neurobiological effects of the criticism induction as well as the online effects during tDCS stimulation.

Marchetti, & Koster, 2015). All six questions relate to self-referential, ruminative thoughts as a particular self-focus on feelings, reactions, and sensations without immediate environmental demands. The statements are not inherently negative or positive, and are considered as a state measure of ruminative thinking (e.g. “Right now, I am thinking about how happy or sad I feel” and “right now, I wonder why I react the way I do”). Participants were requested to indicate whether they were engaging in these thoughts during the 10 minutes of rest. They were asked to respond using a seven-point Likert scale ranging from 1 (totally disagree) to 7 (totally agree) in order to measure the intensity of self-referential thinking. Mood state was assessed using six visual analogue scales (VAS) measuring how fatigued, vigorous, angry, tense, depressed and cheerful participants were feeling “at this moment”. The VAS is a 10 cm line, with endpoints from “not at all” to “very much”. Finally, participants were presented with the same twelve target stimuli as used in the IRAP (see below) (six positive and six negative) and asked to evaluate each of them using a five-point scale ranging from 0 (Totally Disagree) to 4 (Totally Agree). Each word was rated twice, once with respect to their actual self (e.g., ‘I am successful’) and once with respect to their ideal self (‘I want to be successful’). In this way we sought to acquire two broad measures of self-esteem, one related to self-reported actual (SR Actual) and a second related to self-reported ideal (SR Ideal) self-esteem.

IRAP. The IRAP is a computerized latency-based measure which requires participants to respond quickly and accurately to stimuli in ways that are deemed consistent or inconsistent with their prior learning history. Specifically, half of the IRAP trials require participants to respond in ways that are consistent with their (assumed) history of learning, while the other half require participants to respond in ways that are inconsistent with that same history. For instance, participants might be asked to respond “True” to the statement “I want to be Good” on half of the trials but to respond “False” on the other half. The difference in time taken to respond on consistent relative to inconsistent trials - defined as the IRAP effect - is assumed to provide an index of the strength or probability of the targeted relations. In the current study, each IRAP involved a minimum of two and a maximum of six practice blocks followed by a fixed set of six test blocks. Each block consisted of 24 trials that presented one of two self-related label stimuli (e.g., ‘I Am’ or ‘I Am Not’) in the presence of one of two types of target stimuli (positive or negative words drawn from the same set as the IAT) and required participants to emit one of two relational responses (‘True’ or ‘False’). In this way, the IRAP was comprised of four different types of trials (or “trial-types”: Self-Positive; Self-Not Positive, Self-Negative and Self-Not Negative; see Figure 1). Trials were presented in a quasi-random order so that each of the four trial-types appeared six times within each block in a random order. Prior to the IRAP participants were informed that they would complete a word categorization procedure that required them to follow a general rule for responding. Specifically, on one set of blocks they were presented with the message “Please respond AS IF I am positive and I am not negative” (self-positive block), while on the alternative set of blocks they were presented with the message “Please respond AS IF I am negative and I am not positive” (self-negative block). Stated more precisely, a correct response during self-positive blocks required participants to select ‘True’ when ‘I Am’ appeared with a positive target stimulus (e.g., ‘Intelligent’) or when ‘I Am Not’ appeared with a negative target (e.g., ‘Stupid’). At the same time, participants were also required to choose ‘False’ when ‘I Am’ appeared with a negative word or when ‘I Am Not’ appeared with a positive target stimulus. The opposite pattern of responding was required during self-negative blocks. The general rule for responding was alternated across each IRAP block to form three successive pairs of test blocks. The IRAP commenced with a pair of practice blocks. Participants progressed from the practice to the test blocks when they met accuracy (at least 80% accuracy) and latency criteria (median latency of less than 2000ms) on a successive pair of practice blocks. Failure to meet these criteria resulted in re-exposure to another pair of practice blocks until participants either achieved the mastery criteria or a maximum of three pairs of practice block were completed. Failure to satisfy task requirements following three pairs of practice blocks resulted in participants being thanked, debriefed and dismissed (in the current study one participant failed to complete both IRAPs, another three failed the actual self IRAP while six more did not satisfy those same criteria during the ideal self IRAP). When the above criteria were met, a fixed set of three pairs of test blocks were then administered. Finally, it is worth noting that the actual and ideal self IRAPs differed only with respect to their self-related label stimuli. That is, while the actual self IRAP required participants to respond to valenced target stimuli using the terms 'I Am' or 'I Am Not' the ideal self IRAP required participants respond to the same stimuli in terms of 'I Want To Be' or 'I Don't Want To Be'.

Figure 1. *Examples of the four trial-types used in the actual self-esteem IRAP. On each trial, a label stimulus (e.g., 'I am' or 'I am not'), a target stimulus (e.g., 'Successful' or 'Incompetent') and two relational response options (True and False) were shown on the screen. Note: the ideal and actual self IRAPs were identical in all regards except for their respective label stimuli ('I want to be' and 'I don't want to be' versus 'I am' and 'I am not' respectively).*



Criticism Challenge

While inside the scanner, we exposed participants to critical, praising, and neutral comments. These comments were directly addressed at the participant (e.g., "*One of the things that bothers me about you is that you…*") and made by a female voice. All comments were based on comments previously used and validated (Hooley et al., 2009; 2012) and were the same for each participant. The criticism paradigm was used to trigger self-referential processes in healthy participants. The content of the comments were of different emotional content (positive, negative, neutral). The paradigm always followed the same order: neutral, positive, neutral, and always finishing with negative. Negative was always last to avoid emotional contamination and to maximize the negative impact just before the resting state. Each scanning epoch began with a 30-sec rest period, followed by 30 sec of criticism (or praise or neutral), another rest period, another 30 sec of criticism (or praise or neutral), and then another rest period. Each participant underwent four scanning epochs; thus, each participant heard two 30-sec segments of critical and praising commentary and four 30-sec segments of neutral commentary (this was chosen so there would be a buffer between the praising and the critical comments). Only one type of emotional comment was included within a scanning epoch (i.e., two critical or two praise or two neutral remarks; no commingling of comment type occurred within an epoch). Participants heard each comment once only, and participants did not hear any of the comments before the scanning. The criticism paradigm lasted 8.30 minutes in total.

tDCS

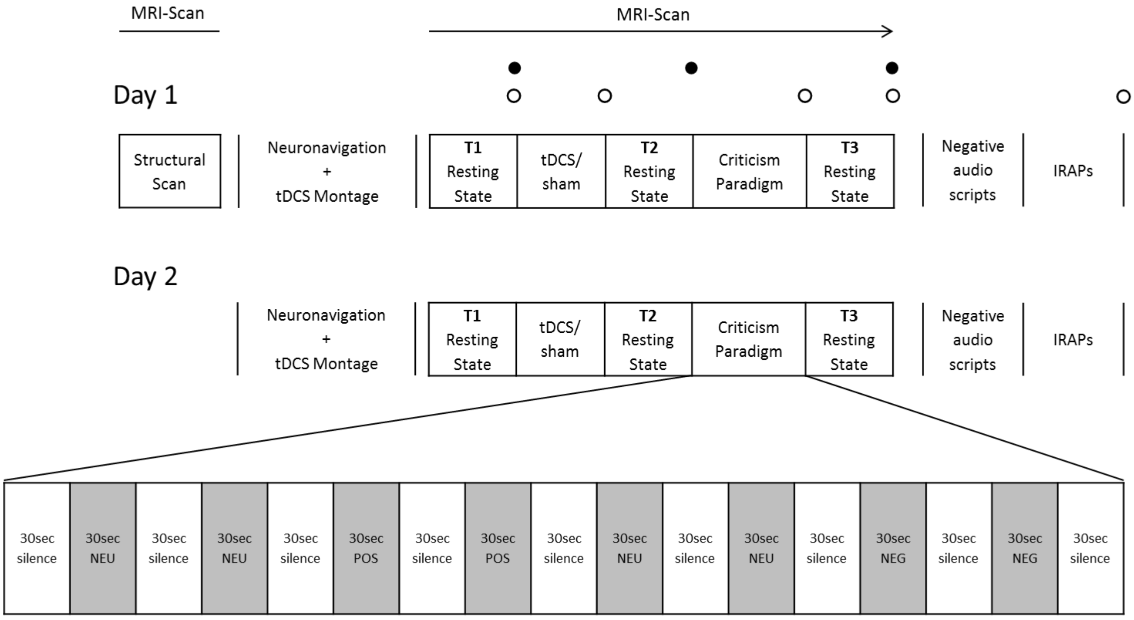
Direct electrical current was applied in the fMRI scanner using a saline-soaked pair of surface sponge electrodes (35 cm2) and delivered by a battery-driven stimulator, which was MRI-compatible. To localize the target stimulation areas (left DLPFC and right supraorbital), Brainsight neuronavigation system (Brainsight™, Rogue Research, Inc) was used to navigate into participant structural cerebral MRI and localize both left DLPFC as contralateral supraorbital area. Subsequently, the anode was placed over the individually located DLPFC, while the cathode was placed over the contralateral supraorbital area. A constant, direct current of 1.5 mA with 30 s of a ramp up was applied for 20 min. For sham, the electrodes were positioned in the same way as when administering tDCS stimulation; however, the current was ramped down after 30 seconds. This procedure is a reliable sham condition (Nitsche, et al. 2008). Most participants (26/32) could not distinguish real from sham tDCS (the 6 others answered correctly to which condition was real vs sham). To avoid carry-over effects from the previous stimulation, the second session was carried out after an interval of at least 48h.

Procedure

Upon arrival on their first day the participants were given an overall explanation of the studies protocol, signed the informed consent, and filled in the PCS. Next, each participant started with an anatomical 3D MRI scan. This scan was used to navigate into participants structural cerebral MRI and localize both left DLPFC as contra lateral supraorbital area, using Brainsight neuronavigation system (Brainsight™, Rogue Research, Inc). Subsequently, the tDCS montage was applied based on each participant's specific localization marks. Thereafter, the participants took place under the scanner and the tDCS wires were connected to the patches at the end of the scanner bore. During the scan period on different time points, participants were asked about their mood (VAS) and their momentary ruminative self-referential thoughts (MRST). For a full overview of these time points see Figure 2. The scan started with a 5min resting, after which the tDCS session was switched on for 20min in the real vs 30sec in the sham condition (each with a ramp up and down of 30sec). The tDCS-block was followed by another resting state. Next the criticism paradigm with the neutral, positive and negative audio scripts was administered. Each epoch, which lasted for 2:31, began with a 30 second rest period. This was followed by 30 seconds of commentary, another rest period, another 30 seconds of the same type of commentary, and then another rest period. Thus, in each epoch, participants heard two 30 second segments of each type of commentary. There was no commingling of comment type in the same scan epoch; participants heard either two critical, two neutral or two praising comments. For each scan-session participants heard different comments (of the same valence), so that they never heard the same (e.g. criticism, neutral or praise) comment twice. The order of the presented epochs was neutral-positive-neutral-negative. This order was chosen to always end with the criticism audio comments, to maximize the effect on the following resting state. Each individual comment was heard only once and participants did not hear any of the recorded comments prior to the scanning. Finally, a last resting state ended the scan period.

When participants left the scanner, they cleaned up the patches and the conduction gel before sitting in front of a computer. Before performing the two IRAPs, each participant listened to a repetition of the negative audio scripts they were exposed to in the criticism paradigm. Thereafter, they completed both IRAPs, which were counterbalanced, and finished with the explicit self-esteem questionnaire, i.e., semantic differentials. At the end of the first day participants received several trait questionnaires to be filled in before their next scan session. The second day of each participant was identical as the first, with the distinction of the pre-scan and neuronavigation. For an overview see Figure 2.

Figure 2. *Overview of the protocol during the two days of testing.*



Note. NEU = neutral; POS = positive; NEG = negative audio script . ● = MRSI time point; ○ = VAS time point.

Data analytic plan

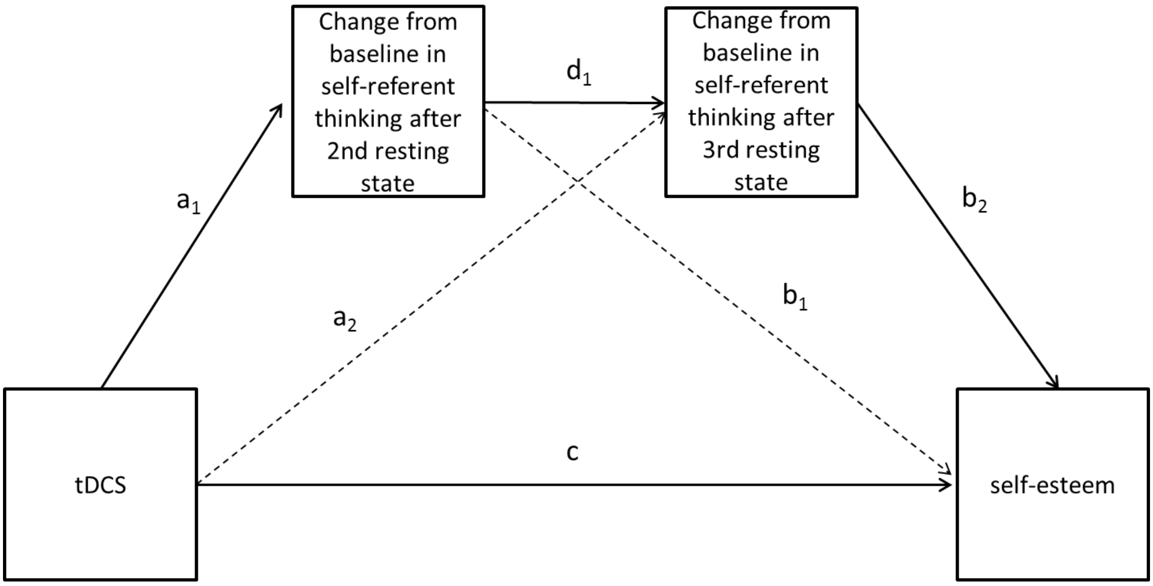
All collected data were analyzed with SPSS 23 (Statistical Package for the Social Sciences). First, for mood analysis we used a 2 (condition: tDCS vs sham) X 5 (time: $T^{vas}1$ = before tDCS/sham; $T^{vas}2$ = after tDCS/sham and before Criticism; $T^{vas}3$ = after criticism, before last resting state; $T^{vas}4$ = after last resting state and before IRAPs; $T^{vas}5$ = after

IRAPs) repeated measures MANOVA, with the mood scales as dependent variables. To follow up on the significant changes in time, we compared each mood scale between blocks, which allowed us to register any mood change before and after a scanning block. As such, we could evaluate the impact of the resting states, stimulation block and criticism paradigm on mood separately. For this, we performed another MANOVA with 2 (condition) X 2 (time), with the mood scales as multiple dependent variables.

For the MRST data we used a 2 (condition: tDCS and sham) X 3 (time: $T^{MRST}1$ = after first resting state; $T^{MRST}2$ = after second resting state; $T^{MRST}3$ = after last resting state) repeated measures ANOVA.

To unravel the mechanism of the effect of tDCS on actual self-esteem, we performed a mediation analysis. To this end, we considered the path analysis model presented in Figure 3. More specifically, we hypothesized that tDCS would decrease the MRST from baseline to after tDCS (the path coefficient a1), which in turn would lead to larger decrease in MRST from baseline to after the criticism paradigm (the path coefficient d1). Furthermore, it was hypothesized that a larger decrease in MRST from baseline to after the criticism paradigm would lead to a higher self-esteem (the path coefficient b2). To assess the absence of the direct effect of tDCS on change from baseline in self-referential thinking after the third resting state after controlling for the change from baseline in self-referential thinking after the second resting state (the coefficient a2) and the absence of an effect of change from baseline in self-referential thinking after the second resting state on self-esteem after controlling for the change from baseline in self-referential thinking after the third resting state (the coefficient b1), we performed a $\chi2$-difference test between the saturated model and the reduced model (with the path coefficients of the dashed arrows constrained to zero). In the absence of those effects, the mediated effect of tDCS on self-esteem through change from baseline in self-referent thinking is given by the product of coefficient a1 X d1 X b2. A 95% confidence interval for this mediated effect can be obtained using percentile-based bootstrap. Given the within-subject design of our study, the path coefficients were estimated by relying on the difference method (Judd, Kenny and McClelland, 2001 ; Josephy, Vansteelandt, Vanderhasselt and Loeys, 2015).

Figure 3. *The double mediation model.*



RESULTS

Mood

The MANOVA revealed only an effect of time F(7, 24) = 16.13, p < .001 (not of Condition or an interaction effect). Univariate main effects of time were significant for vigor, F(1, 29) = 4.19, p = .023; anger F(1, 29) = 3.95, p = .029; tension, F(1, 29) = 7.43, p = .001, and cheerfulness, F(1, 29) = 4.13, p = .016. By comparison, there was a trend for fatigue, F(1, 29) = 2.50, p = .071; and no differences in depressed feelings: F(1, 29) = 1.51, p = .23.

Following up on the significant changes in time, we compared all significant effects over the different time points. First, we compared mood before and after tDCS/sham ($T^{vas}1vsT^{vas}2$), which revealed that participants were more tired, F(1, 29) = 13.27, p = .001; less vigorous, F(1, 29) = 22.41, p < .001; and less cheerful F(1, 29) = 8.58, p = .006 (all other effects were ns). For our manipulation (before and after the criticism paradigm, $T^{vas}2vsT^{vas}3$) check the MANOVA revealed differences in mood before versus after the criticism paradigm indicating that participants were more angry, F(1, 29) = 9.15, p = .005, more depressed, F(1, 29) = 5.55, p = .025, and (trend) less cheerful, F(1, 29) =4.05, p = .053. By comparison, there were no differences in feelings of fatigued, vigorous, and tensed (all other effects were ns). In summary, these data show an increase in feelings of anger, depression and a decrease in cheerfulness after criticism (although the criticism paradigm included neutral, praise and criticism, the last block was always criticism to maximize the effect on self-referential thinking before the last resting state).

Next, we compared mood before and after the last resting state ($T^{vas}3vsT^{vas}4$), which reveals only a significant decrease of vigorous, F(1, 29) = 5.13, p = .031 (all other effects were ns). Finally, we compared mood before and after the IRAPs ($T^{vas}4vsT^{vas}5$), here participants showed only a significant decrease in tension, F(1, 29) = 12.84, p = .001 (all other effects were *ns*).

Momentary ruminative self-referential thoughts (MRST)

The repeated measures ANOVA yielded no main effects of condition or time (all *p*'s > .09). However, a significant interaction effect of condition and time *F*(2,30) = 3.83; *p = .033*. In the real stimulation condition ruminative self-referential thoughts decreased from $T^{MRST}1$ to $T^{MRST}2$ *t*(31) = 2.63; *p = .013*, with no change between T2 and T3 *t*(31) = 0.30; *p = .767*, and an overall decrease from $T^{MRST}1$ to $T^{MRST}3$ *t*(31) = 2.24; *p = .033*., showing that the decrease in MRST after real tDCS stayed significant after the criticism paradigm. In the sham condition no significant changes over all time-points were observed. When comparing between conditions, no baseline differences were observed (*p* = .20), showing that the decrease in the real stimulation condition (and no changes in sham) cannot be ascribed to differences in baseline MRST.

Implicit Measure: IRAP

Response latency data were transformed into D-IRAP scores using an adaptation of Greenwald et al.'s (2003) D algorithm (for details of this data transformation see Barnes-Holmes, Barnes-Holmes, Stewart I, & Boles, 2010). For each IRAP, we calculated a single overall D-IRAP score - one for the actual self IRAP and a second for the ideal self IRAP. These values were calculated so that higher scores reflected higher levels of (actual or ideal) self-esteem. When submitted to a 2 (Condition) x 2 (IRAP-Type; actual vs. ideal) ANOVA, a main effect for IRAP-Type, F(1,29) = 12.75, p <.001, with participants producing more positive scores on the ideal-self relative to the actual-self IRAP. However, no two-way interaction between IRAP-Type and Condition was obtained, F(1,29) < 1, p =.60.

Relation MRST and Self-Esteem

Although we did not find evidence of a total effect of tDCS on actual self-esteem, it is still worthwhile to further explore the presence of an indirect effect through changes in self-referential thinking. As noted by Loeys, Moerkerke and Vansteelandt (2015), the power to detect an indirect effect may be higher than the power to detect a total effect. The possible concern about unmeasured common causes of mediator and outcome, which would invalidate the estimated indirect effect, is limited here as subject-specific unmeasured common causes can be eliminated in within-subject designs (Josephy et al., 2015). We first compared the fit of the saturated model shown in Figure 3 with the fit of the reduced model (with the path coefficients of the dashed arrows set to zero), and found the reduced model to fit equally well (χ2(2)=4.059 ,p=.131). The estimated coefficients on the mediation path are all significant: a1=2.323 (95% CI: 0.548 to 4.065), d1=-0.929 (95% CI: -1.228 to -0.616) and b2=-0.025 (95% CI: -0.039 to -0.010). The estimated indirect effect thus equals 0.054, indicating that tDCS leads to higher self-esteem through changes in self-referential thinking. Since the 95% bootstrap CI (0.009 to 0.123) does not contain zero, we find evidence of an indirect effect

Implicit-Explicit correlations

Finally, we looked at the correlations between the implicit measures of self-esteem (i.e., IRAP) and the explicit measures (RSES, self-reported actual and ideal self-esteem). However, no significant correlations were found between implicit and explicit measures of self-esteem.

DISCUSSION

In this study we first investigated whether real versus sham tDCS would affect the change in momentary self-referential thinking by comparing baseline MRST scores with the scores after tDCS/sham and after criticism. Second, we investigated the influence of DLPFC neurostimulation on self-esteem. Results showed a significant decrease in MRST before and after tDCS as well as a decrease in MRST at baseline compared to after criticism in the real stimulation condition, but not in the sham condition. As such, reestablishing the beneficial effect of neurostimulation on cognitive control over negative information (e.g., Boggio et al., 2007; Wolkenstein & Plewnia, 2013) and specifically on rumination (Vanderhasselt et al., 2013b). Next, anodal tDCS of the left DLPFC (compared to sham) did not directly influence actual (or ideal) self-esteem. However, we observed that the influence of anodal tDCS (and not sham stimulation) on actual self-esteem was mediated by the decrease in MRST, but only after criticism (double mediation model). In other words, the larger the decrease of momentary self-referential thoughts of participants after DLPFC neuromodulation (and after receiving criticism), the higher their actual self-esteem. For the ideal self-esteem no significant results were found in either condition. Reports of mood after (as compared to before) the criticism paradigm confirmed increased emotional reactivity (feeling more angry, more depressed, and less cheerful) in response to criticism.

Given that neuroimaging studies have indicated that a functional balance between ventral (ventral anterior cingulate cortex, ACC) and dorsal compartments in the brain (dorsal ACC, dorsolateral prefrontal cortex-DLPFC) is necessary for maintaining homeostatic emotional control (Seminowicz et al., 2004; Johnstone et al., 2007; Ochsner and Gross, 2008; Wager et al., 2008), we sought to challenge the neural circuitry implicated in depression, not by inducing a sad mood, but by using a psychosocial stressor that has been empirically linked to the relapse process (Hooley et al., 2009). Our findings show that cognitive and phenomena can be modulated to increase the ability to regulate momentary ruminative self-referential thoughts during a period of idleness, a process closely linked to the ruminative thinking style. This interplay between biological and cognitive factors is in line with a theoretical framework of De Raedt & Koster (2010), which states that cognitive control processes play a central and causal role in the relation between prefrontal neural activation and rumination. Moreover, the current results go beyond correlational findings by using an experimental method that involves neurostimulation of the DLPFC to temporarily enhance its activity, thus allowing causal inferences. This is an important next step for building and refining our understanding of the neural bases of rumination within depression.

It seems important to mention that there are many ways to assess momentary self-rumination (see Smith & Alloy, 2009). In studies that have investigated momentary ruminative thoughts, participants are asked randomly during daily life to report the content of their thoughts (Killingsworth & Gilbert, 2010; Moberly & Watkins, 2008), or ruminative thoughts are induced by asking participants to focus their attention on a specific thought (presented by a statement) for some time (e.g., Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Whitmer & Gotlib, 2012). In line with the study of Vanderhasselt et al. (2013b) we asked individuals to rest without any specific task, which is known to result in a stream of undirected free thoughts (Filler & Giambra, 1973; Giambra, 1989; James, 1890). Because we did not interfere during this rest period and asked our questions immediately afterwards, we were able to assess naturally occurring self-focused thoughts without linking them to a precise emotional content or response to negative mood. Importantly, these self-referential thoughts do not necessarily have unconstructive consequences (Watkins, 2008), however, depression vulnerable individuals have the tendency to focus their thoughts on negative information and personal concerns. It is therefore crucial to understand how self-evaluative ruminative thoughts can be regulated in order to prevent them from becoming unintentional and unconstructive, particularly in individuals who demonstrate a tendency to ruminate in everyday life, such as patients with depression. Interestingly, strong criticism in the context of a generally supportive relationship may be less disruptive to cognitive functioning than even mild criticism in the context of a non-supportive relationship Kaiser et al. (2015). Alternately, individuals with non-supportive partners may become habituated to criticism, and therefore may be less sensitive to the disruptive effects of criticism. On a broader level, supportive relationships may be distinguished by social transactions that help the individual to regulate emotions, while non-supportive relationships may feature maladaptive transactions that exacerbate stress (Hofmann 2014).

This study is the first to find a link between rumination, criticism and a subsequent effect on (actual) self-esteem. Research has shown the detrimental impact of criticism on cognitive processing and thinking styles, such as rumination (e.g., Saffrey & Ehrenberg, 2007; Kaiser, Andrews-Hanna, Metcalf, & Dimidjian, 2015), and subsequently its effect on self-esteem (e.g. Weisbuch, Sinclair, Skorinko, & Eccleston, 2009). Moreover, people who have experienced depression are at risk of relapse or recurrence (Burcusa & Iacono, 2007) especially if they live in highly critical family environments (Butzlaff & Hooley, 1998). However, the process of how a critical environment could lead to depression remains unclear. This study might therefore shed a light on this intricate connection, by showing that the possibility to control rumination after receiving criticism is linked to a person’s (actual) self-esteem. In other words, the better a person deals with self-referential thoughts (rumination) after criticism, the more positive he or she perceives him/herself, and subsequently might prevent a negative self-esteem that can lead to depression. Therefore, it seems indispensable to disentangle the possible vulnerability factors that might lead to a low self-esteem. Importantly, in a meta-analysis of Sowislo and Orth (2013) the authors investigated the relation between self-esteem and depression. Whereas the vulnerability model states that low self-esteem contributes to depression, the scar model states that depression erodes self-esteem. Based on 77 studies on depression, the findings supported the vulnerability model. Therefore, understanding the influential causes of self-esteem (e.g. dealing with rumination, criticism/critical environment), interventions aimed at increasing self-esteem might be useful in reducing the risk of depression. Given that criticism might be linked to self-esteem, and our results show the possible beneficial impact of neurostimulation of the DLPFC on dealing with rumination after criticism, a first step might be taken in a better understanding of the development of low self-esteem and subsequently depression.

A puzzling finding in our study is related to our IRAP results when comparing them with previous self-esteem IRAP findings that showed higher actual and lower ideal self-esteem (Remue et al., 2013) or absence of any difference between actual and ideal self-esteem (Remue et al., 2014), in healthy participants. Here we see a somewhat reversed effect of lower actual versus higher ideal self-esteem. A first possible explanation for this reversed effect might be the time between the end of the stimulation and start of the IRAPs, which was about one hour. The after-effects of tDCS can last up to one hour (Nitsche & Paulus, 2001; Nitsche et al., 2003), however, there was no apparent difference between real and sham condition on implicit self-esteem, which might be explained by the fact that the after-effects of the tDCS had worn out. Nonetheless, we see a neuromodulation effect on the MRST and subsequently a link between the decrease in rumination after criticism and actual-self, so there is an effect of real tDCS on self-esteem to be noted, but more indirectly through MRST (after criticism). Another possible explanation might be the impact of the criticism on actual but less on ideal self-esteem. By receiving self-critical comments, participants might be affected in their current state and subsequently their state-oriented actual self. Moreover, this might also partly explain the absence of a relation between MRST decrease in the tDCS condition and the Ideal self IRAP. Namely, in this study we focused on state rumination, that is, how people feel about their momentary self-referential thoughts. Moreover, when implicitly measuring actual self, we also tap into a more state-oriented concept, how a person sees himself right now. However, when we look at the propositional nature of the ideal self, we are focusing more on a future oriented self, how a person would like to be. Hence, tapping into a more trait oriented concept. It is therefore plausible that the momentary nature of how we measure rumination as well as the way we exposed participant to interpersonal criticism in that moment, affects the state oriented part of self-esteem, i.e. actual but not ideal. Hence, leading to a decrease in actual but not ideal self-esteem for the IRAP performances.

Some limitations of the present study should be emphasized. Because we were not aware of any existing questionnaires to measure momentary ruminative self-referential thoughts, we used a short inventory that has only been used in a limited number of studies (Momentary Ruminative Self-focus Inventory; Mor et al., 2015; Vanderhasselt et al., 2013b). Secondly, we focused on women because rates of depression are higher in women than they are in men (Nolen-Hoeksema, 2002) and because we sought to minimize heterogeneity in our data due to gender effects. Another important limitation might be that although we describe the audio scripts paradigm as a criticism paradigm, the full block contains neutral, positive and negative audio blocks. This was done to investigate the differences in neural activity between the valences (see Remue et al., in preparation). However, given that every participant finished with the negative audio script and the mood scores indicated an increase of negative mood after the criticism paradigm (comparing before and after), we can assume that it does trigger the projected stress (criticism) induction. Finally, given the absence of a control condition for self-esteem after criticism (i.e., no condition where participants heard only neutral audio scripts), we cannot make any conclusion about the possible influence of criticism on the previously reported findings of actual and ideal self-esteem in healthy participants (see Remue et al., 2013; 2014).

In line with the beneficial effects of neuromodulation in the treatment of MDD, these results further show how tDCS can influence cognitive processes, such as rumination, and subsequently, its effect on self-esteem. Given the significant role of rumination and negative self-esteem in MDD, these data expand our knowledge of the mechanisms of action of tDCS by showing its role in controlling self-referential processes and self-esteem as well as the important impact interpersonal criticism can have on this relation. This study was the first to show a link between (state) rumination and self-esteem, showing a more positive actual self-esteem after a larger decrease in momentary ruminative self-referential thoughts, but only when following criticism, by means of a single tDCS session over the left DLPFC.

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CHAPTER 8

GENERAL DISCUSSION

RECAPITULATION OF THE RESEARCH GOALS

The general aim of this doctoral dissertation was to unravel how the link between criticism and ruminative processes affects self-esteem, focusing on both behavioral and neurobiological processes. To investigate this mechanism, we explored whether the effect of an experimental manipulation of the prefrontal cortex (PFC) on self-esteem is mediated by rumination before and after criticism. We focused on three levels of measurement. First, we investigated the effects of neuromodulation (transcranial Direct Current Stimulation, tDCS) on rumination and self-esteem using self-report measures. Second, we used implicit measures to index self-esteem. Third, we assessed the neurobiological correlates of this process. However, before we could begin to investigate this question, we needed to address some prerequisites by developing and testing new instruments. In a general introduction both the overarching theoretical framework of the dissertation and the key concepts were outlined. Then, we developed a task to measure self-esteem in an implicit way, focusing on both actual- and ideal-self (Chapter 2), which was made possible by the introduction of propositions (using the Implicit Relational Assessment Procedure, IRAP). In a second study, we replicated the findings of this first study with more stringent criteria as well as a methodologically fine-tuned design (Chapter 3). Thereafter, we conducted a systematic review to elucidate whether a single neurostimulation session would have an effect on mood in healthy participants, since mood effects might confound the effects found on cognitive processes (Chapter 4). In study four we investigated if a single placebo controlled neurostimulation[1] (repetitive Transcranial Magnetic Stimulation, rTMS) session can influence the physiological stress response (using heart rate variability, HRV) during criticism (Chapter 5). In the fifth study we applied a placebo controlled session of tDCS in the magnetic resonance imaging (MRI) scanner, to test the possible impact of neurostimulation of the dorsolateral prefrontal cortex (DLPFC) on the underlying neurobiological processes of rumination (regional brain activity and functional connectivity) before, during and after a social evaluative challenge (Chapter 6). Subsequently we tested whether the effect of neurostimulation of the dorsolateral prefrontal cortex (DLPFC) on implicit self-esteem is mediated by rumination before and after criticism (using the IRAP) (Chapter 7).

We start this general discussion with a summary of the main findings with regard to our main question: *what is the link between criticism and ruminative processes and how does it affect self-esteem, while focusing on both behavioral and neurobiological processes*. In chapter 2, 3, 4, and 5 we answer prerequisite questions that are needed to answer this overarching research question, which is tackled in chapter 6 and 7. We will also discuss the main findings from each of these chapters. Next, both theoretical and clinical implications will be discussed. Finally, several limitations of the present studies will be considered followed by directions and challenges for future research.

OVERVIEW OF THE MAIN FINDINGS

Self-esteem in depression: an implicit propositional perspective

Before we could investigate the influence of neurostimulation on rumination and self-esteem after receiving criticism, there was need for a more comprehensive understanding of the self, how to fully capture its conceptual meaning, and which would allow us to extend beyond the simple me-positive/negative associative character. Hence, in our first study we developed a self-esteem IRAP that introduced

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[1] Although the correct term for rTMS is neurostimulation and for tDCS neuromodulation. However, for the readability of this paper and given its common use in the literature we will refer to neurostimulation for both techniques

propositions in implicit measurement. More specifically, the introduction of labels that specify the way in which concepts are to be related allowed us to differentiate between actual and ideal self-esteem. In the first study (chapter 2) we explored whether dysphoric (scoring high on the Beck Depression Inventory, BDI) and non-dysphoric individuals differ with regard to their actual-self and/or ideal-self. Our results indicated that the dysphoric group scored lower on actual self-esteem and higher on ideal self-esteem in comparison to the low BDI group. The D-IRAP total scores also showed that low dysphoric individuals have more positive actual self-esteem as compared to ideal self-esteem. As such, the results indicated a differentiation in self-esteem scores based on the way it was measured, using propositions, and showed a more complex picture (as compared to associative measures literature) based on depressive symptomatology. The results of this study suggest that dysphoric individuals, who are prone to depression, have a higher ideal self-esteem, and lower actual self-esteem, in comparison to healthy participants. However, to fully test the aforementioned hypothesis whether positive self-esteem Implicit Association Task (IAT) scores would reflect different propositional relations, a direct comparison between the IRAP and the IAT scores is needed. Hence, in our follow up study (chapter 3) we administered a self-esteem IAT and the previously used self-esteem IRAPs to low and high BDI groups. In addition, we addressed three methodological issues that arose in our first study: first, in attempt to increase the reliability of the observed effects, we increased the number of test blocks compared to the IRAPs used in chapter 2 (increasing the number of test blocks from 2 to 6) (see Hughes & Barnes-Holmes, 2013); second, we introduced more strict mastery criteria (i.e., stringent set of latency criteria), which could lead to more robust IRAP scores (see Barnes-Holmes et al., 2010); third, we only included items that were directly related to self-esteem, rather than an overlap with stimuli more related to depression in general. As such, we made the implicit measurement more stringent, as well as more methodologically fine-tuned. Results revealed no difference in and similar positive IAT-scores between dysphorics and non-dysphorics. However, a slightly different picture emerged when we looked at the IRAP-scores. With regard to the dypshoric individuals a significant difference was observed between their actual and ideal-self, showing more positive ideal-self compared to their actual self, as such, replicating the main finding of our first study (chapter 2) with regard to depression prone individuals and self-esteem. However, our results also revealed no difference in actual versus ideal-self with regard to the non-dysphoric group.

In sum, our results of chapter 2 and 3 indicated that dysphoric and non-dysphoric individuals experience implicit positivity towards the self. Most importantly, dysphoric participants revealed a stronger discrepancy between actual and ideal self-esteem compared to non-dysphoric participants as indexed by IRAPs, with higher scores on ideal versus actual self-esteem. This finding not only supports the theoretical position that the discrepancy between actual and ideal self-esteem is related to depressive symptomatology but also demonstrates the added value of using implicit measures such as the IRAP that allow for the inclusion of propositions that can capture different implicit beliefs.

The importance of neurostimulation in healthy participants: a neuroscience perspective

Another prerequisite for our main research question revolved around the use of non-invasive brain stimulation (NIBS) in healthy participants. Given the accrued use of neurostimulation techniques in experimental studies, we wanted to thoroughly investigate the impact of a single session in healthy participants. Hence, we conducted a systematic review to identify whether a single neurostimulation session would have an effect on mood in healthy participants, since mood effects might confound any effects found on cognitive processes. In our review we included 30 studies, of which 13 tDCS and 17 rTMS studies. We concluded that when the various shortcomings of these studies are controlled for - by using a single blind sham controlled, counterbalanced, crossover design, a large uniform sample, stimulation of one single region per session with a consistently spread time interval in order to exclude interaction effects with previous stimulation, and comparing pre versus post mood measurement between active and sham stimulation – no significant mood effect of neurostimulation can be found. More than fifteen years ago, Mosimann et al. (2000) pointed out that neurostimulation studies should fulfill several methodological requirements: a sham-controlled setup, larger sample sizes, and strictly one single stimulation region per session in order to exclude interaction effects with previous stimulation, to determine possible effects on mood in healthy participants. Fifteen years later, we can reiterate these guidelines and feel confident that when we take the aforementioned methodological demands into account, mood in healthy participants is not affected by a single neurostimulation session.

The influence of rTMS on stress resilience: a physiological perspective

After establishing that a single neurostimulation session does not affect mood - which could confound any cognitive effects - we took the next step in our scientific endeavor: can neurostimulation influence a person's response when being criticized. Thus, we investigated if a single placebo controlled neurostimulation session could influence the physiological stress response (using heart rate variability) during criticism. Although the (criticism) induction procedure was efficient in increasing self-reported distress in all groups and conditions, only after real high frequency (HF)-rTMS over the left DLPFC was the physiological stress response diminished, as indicated by a significant increase in HRV. No effects were found in the sham or right side stimulation condition. As such, the present study was the first experimental study using HF-rTMS over the left DLPFC demonstrating an impact on parasympathetic modulation in humans. Furthermore, these findings demonstrate that increasing prefrontal brain activity by HF-rTMS can help attenuating physiological stress reactions in light of negative feedback (criticism). Moreover, these results suggest that the left DLPFC may be a critical brain area in the neuro-circuitry underlying stress reactivity (on negative feedback), and suggests that the PFC plays a role in the modulation of stress responses in healthy participants. By modulating this specific brain region stress resilience may be positively affected, which is crucial for coping with stress inducing events and dealing with negative feedback (criticism). Our results are indicative of the positive effects of rTMS on stress resilience and underscore the possible benefit of HF-rTMS as a transdiagnostic intervention. Finally, the results also show that effects only occur when stimulating the left DLPFC, which is in line with the therapeutic effects of HF-rTMS in affective disorders.

Criticism in the brain: a neurocognitive perspective

After focusing on how to conceptualize and measure self-esteem and investigating the possible impact of neurostimulation and its attenuating effect on coping with criticism, our next step was to tackle our main research question. As mentioned before, to answer this question we focused on different levels of measurement. In chapter 6 we assessed the neurobiological correlates of these processes. Finally, in chapter 7 we investigated the effects of neurostimulation on self-esteem, and evaluated its link with ruminative processes in relation to criticism. Hence, after fulfilling the necessary prerequisites to answer our general question, we first turn towards the underlying neurobiological processes (regional brain activity and functional connectivity) of prefrontal neurostimulation and its effect on ruminative processes before and after an experimental induction of criticism. To accomplish this, we performed the study under fMRI (both during the criticism paradigm and the different resting states before and after). As such, we were able to investigate exactly what happens during the administration of criticism as well as to analyze functional connectivity (FC) during this process.

Importantly, regarding social evaluation, research in social cognitive neuroscience has demonstrated the particular functions of the precuneus and the posterior cingulate cortex (PCC) in social inferential processing (Kuzmanovic et al., 2012). Moreover, Cabanis et al. (2012) revealed that the precuneus and the PCC are involved in the evaluation of social events. Interestingly, Kuzmanovic et al. reported increased neural activation of the precuneus and PCC when participants were exposed to verbal interpersonal evaluations. Hence, we expected an activation of these regions during the confrontation with the audio comments. Interestingly, our data showed neural activity in the precuneus/PCC. More specifically, after real versus sham tDCS, both praise and criticism compared to neutral expressions showed a significant decrease of precuneus activity. However, and more importantly, the decrease after criticism was substantially larger compared to the decrease after praise. In other words, when people are confronted with social evaluations (both positive and negative) only after real tDCS they showed a decrease in activation of the precuneus, an area known for its crucial role in self-referential processing (Cavanna & Trimble, 2006). This may mean that participants show less self-referential processing when confronted with social evaluations (both positive and negative). However, the beneficial effect of tDCS on coping with negative self-referential thinking (rumination) was larger than coping with praise, showing again the possible impact of neurostimulation on state rumination (see also Vanderhasselt et al., 2013). As such, in line with the literature, our results revealed activation in the precuneus was associated with the coping of positive and negative evaluations describing socially relevant situations in everyday life.

In a follow up of our neural activity data, we conducted FC analyses based on the regions that were implied, that is, the precuneus/PCC during resting state. Our data revealed that real tDCS resulted in a decreased FC between the precuneus/PCC seed and the vmPFC. On the other hand, sham stimulation resulted in a FC increase between these two areas. Given that the vmPFC is crucial in processing emotional features during social cognition, is engaged in identifying self-relevant information and assessing the salience of stimuli (Gusnard et al., 2001; Northoff and Bermpohl, 2004; Northoff et al., 2006), and vmPFC–precuneus/PCC interactions are thought to underlie aspects of self-referential processing (Buckner et al., 2008; Qin and Northoff, 2011), our results underscore these findings, showing an increase in FC (in the sham condition) between the precuneus/PCC-vmPFC when confronted with social evaluative material towards the self. However, and more importantly, after real tDCS we found a decrease in FC between the precuneus/PCC and the vmPFC, which might indicate an increase of cognitive control over the underlying ruminative processes that are triggered by interpersonal criticism. As such, this study is the first to investigate neural activity during criticism as well as during resting state before and after criticism, following a single tDCS session, while under fMRI. Both research questions reveal the beneficial effects of neurostimulation on the underlying processes of rumination. Furthermore, it gives a convincing proof of difference in neural activity with regard to negative and positive self-referential processes and further underscores the importance of NIBS techniques (e.g., rTMS, tDCS) as an experimental technique to understand the neurobiological processes underlying cognitive processes, such as rumination.

The link criticism, self-referential processes and self-esteem after tDCS

In our last study we tested the possible impact of a single neurostimulation of the DLPFC on the underlying ruminative processes before and after an experimental induction of criticism, and subsequently the effect on implicit self-esteem (Chapter 7). A first finding was the significant effect real (but not sham) tDCS had on momentary ruminative self-referential thoughts. When compared to baseline (i.e. measurement before real/sham tDCS) a significant decrease was observed in these momentary ruminative self-referential thoughts (MRST) after the real/sham tDCS as well as after the criticism paradigm. As such, these data reestablish the beneficial effect of NIBS on cognitive control over negative information (e.g., Boggio et al., 2007; Wolkenstein & Plewnia, 2013), and specifically on rumination (Vanderhasselt et al., 2013). A second finding was the effect of real tDCS on implicit (actual) self-esteem. Although there was no direct effect, a double mediation effect was observed with the decrease in MRST from baseline to after tDCS and, crucially, a decrease in MRST from baseline to after criticism as mediators. In other words, the larger the decrease in momentary self-referential thoughts of participants after prefrontal neurostimulation (and importantly after receiving criticism), the higher the participant’s actual self-esteem.

In this study we showed that neurostimulation is able to increase control over ruminative processes after receiving criticism and that this is linked to a person’s (actual) self-esteem. In other words, the better a person deals with self-referential thoughts (rumination) after criticism, the more positive he or she perceives him/herself. This process might prevent a negative self-esteem leading to depression. Hence, this study sheds a light on the intricate connection between ruminative processes, coping with criticism and self-esteem.

IMPLICATIONS OF THE RESEARCH RESULTS

Theoretical implications

Based on the summary of our findings, several theoretical implications can be put forward. Clinical implications will be discussed in the next section.

The Actual and Ideal Selves: Theoretical Implications for Research on Self-Esteem

Based on our findings that different propositional knowledge can provide a more elaborate view on the conceptualization of self-esteem, an important next step is to develop a more sophisticated understanding of how self-related cognitions impact implicit and explicit self-esteem. In conducting the work in this dissertation several points are worth noting with regard to understanding self-esteem and how to conceptualize it. First, based on our findings the relation between implicit and explicit measurements of self-esteem remain inconsistent. With this in mind, several authors argued that implicit and explicit measures may assess different components of cognitive processes (Beevers, 2005; Haeffel et al., 2007), and that implicit measures may better predict distress and psychopathology than explicit measures (e.g., Nock & Banaji, 2007). Moreover, in a recent study of Roberts and colleagues (2016) both implicit and explicit measures of self-esteem were administered among previously and never depressed individuals. Their results indicated higher implicit self-esteem, but lower explicit (trait) self-esteem compared to never depressed controls (in line with in line with Franck, De Raedt & De Houwer, 2007). As such, suggesting dissociations between implicit and explicit self-esteem. In addition, another possibility for the inconsistent correlations between implicit and explicit self-esteem, might be that implicit and explicit self-esteem are more strongly correlated when explicit measures are presented first (e.g., Bosson et al., 2000). Furthermore, Klavina and colleagues (2012), argued that one might wonder whether specific features of the construct of implicit self-esteem are responsible for the particularly low implicit–explicit correlations. Congruency versus discrepancy between implicit and explicit self-esteem seems to be a relevant personality characteristic in itself (e.g., Schröder-Abé et al., 2007a; b). Building further on the ideas of De Raedt et al. (2006) and the findings in this dissertation: a possible explanation for the recurrent finding of higher implicit compared to lower explicit self-esteem in (previously) depressed individuals, might be that their explicit self-esteem reflects a current state (e.g., how they feel quite poorly about themselves), while the implicit self-esteem might reflect more the underlying idea of how they want to be (or know how they would be if it wasn't for the their current mood). Hence, it might be that explicit measures tap in to a state concept while implicit measures tap more into a trait concept. Support for this assumption can be found in early cognitive theorizing that advocated a dispositional conceptualization of implicit attitudes as mental representations that are highly stable across time and context (e.g., Greenwald & Banaji, 1995; Wilson, Lindsey & Schooler, 2000). In the eyes of dispositional theorists, implicit and explicit attitudes represent two dissociated, non-interacting types of evaluation simultaneously held toward the same object (e.g., the self). Unlike explicit attitudes that develop in response to recent information, automatic evaluations were thought to reflect mental associations formed through early socialization experiences (e.g., De Hart, Pelham & Tennen, 2006; Rudman, 2004). Once formed, these associations are highly robust and resistant to change, as well as stable across both context and time (for a more elaborate explanation on implicit-explicit measurement differences see Hughes, Barnes-Holmes & De Houwer, 2011). However, in recent studies that support the dual-process models (e.g., Grumm, Nestler, & von Collani, 2009) the aforementioned findings that implicit attitudes measured implicitly are highly stable, are questioned. In Grumm et al. (2009) it is emphasized that implicit and explicit attitudes are the result of two distinct kinds of mental processes reacting to different manipulation methods. Furthermore, the results of our last study clearly showed that actual self-esteem (measured with the IRAP) was changed in function of our experimental manipulation, while the explicit measure of actual self-esteem did not. Therefore, our findings are inconsistent with the idea that implicit measures reflect a trait conceptualization, while explicit measures reflect a more state conceptualization.

Second, with the use of the IRAP, it feels important to at least briefly mention Relation Frame Theory (RFT), since this methodology emerged directly from RFT. RFT argues that language, rule-following, and stimulus equivalence are all instances of a type of operant behavior known as arbitrarily applicable relational responding (AARR; Barnes-Holmes, Luciano, & Barnes-Holmes, 2004a, b; Dymond & Roche, 2013; Hayes, Barnes-Holmes, & Roche, 2001; Rehfeldt & Barnes-Holmes, 2009). According to this perspective, ‘relating’ is a type of behavior and involves responding to one event in terms of another. While nonhumans and humans can both respond relationally to stimuli and events, the latter rapidly develop a more complex type of behavior (AARR) that fundamentally alters how they interact with the world around them (for a more detailed overview of the RFT see Hughes & Barnes-Holmes, 2016). Furthermore, drawing on a wealth of findings from the learning literature (e.g., De Houwer, 2009, Mitchell, De Houwer & Lovibond, 2009), which states that associative learning is due to the formation and truth evaluation of propositions about relations in the environment, we propose that the actual and ideal ‘selves’ are related to two qualitatively distinct propositions that can provide a more comprehensive understanding of the self. According to this perspective and building further on RFT, humans interact with the world around them and develop a rich and complex network of propositions based on and about those interactions. This network is continually updated and revised as contact with the environment continues and may be selectively activated in response to certain cues or contexts. An important sub-class of propositions within this network are related to the self (e.g., ‘I am good’, ‘I don’t want to be bad’, ‘Others always seem to do better than me’) and depending on the complexity of the proposition(s) involved, and the strength of that representation in memory, it may be activated automatically and guide how people respond during tasks such as the IAT and IRAP.

Given that it is generally assumed that propositional processes play a key role in more elaborate, non-automatic evaluations (Gawronski & Bodenhausen, 2011), the challenge for the above model is to explain how implicit self-esteem can be established. In fact, little is needed to formulate such an account (see Hughes, Barnes-Holmes & De Houwer, 2011). It suffices to assume that propositions about the self can be activated automatically from memory. For example, once the proposition “I am a good person” has been formed based on personal experiences (e.g., following charitable donations), deduction (e.g., recognizing that others give less to charity compared to one's self), inference or on any other basis, this proposition can be stored in memory. The memory representation is propositional in nature insofar as it not only contains information about a link between the self and positive valence but also specifies the nature of this link, namely, that I AM good. Once the proposition is stored in memory, it can be activated automatically (e.g., very quickly, without having the goal to retrieve that knowledge, or without being conscious of the retrieved information). While implicit self-esteem has largely been conceptualized as involving associations between stored representations (e.g., Dijksterhuis, 2004; Greenwald & Banaji, 1995), there is no a priori reason why propositional knowledge could not be activated automatically and lead to automatic evaluations as well - even those that are related to the self. Indeed, a rapidly growing body of work suggests that this may be the case (Gast & De Houwer, 2012; Hughes & Barnes-Holmes, 2013).

We believe that the above propositional model may unlock a better understanding of (implicit) self-esteem for several reasons. First, it highlights that the specific way in which people relate (rather than simply associate) the self with evaluative content matters - even under the various conditions of automaticity. The propositions 'I am good' and 'I want to be good' are associatively identical (the self is paired with positively valenced words) and yet they lead to different outcomes on the IRAP for highly dysphoric individuals, which can be explained because the way the self relates to positive content is different in both propositions. This finding introduces an interesting new possibility: there could be an entire spectrum of others propositions related to the self that (a) can also be activated automatically in order to guide behavior and (b) are potentially more predictive of clinically-relevant outcomes that those examined thus far. For example, it could be that propositions comparing the individual to others provide even more diagnostic information in dysphoric and non-dysphoric populations (e.g., 'I am good but others are better'). Importantly, this assumption extends beyond the current research area (depression) and may also apply to other clinical and non-clinical domains where automatically active propositions play a role (e.g., anxiety, obsessive-compulsions, phobias, chronic pain).

Second, by adopting this approach we may gain new insight into the development and change of self-esteem across time as well as how self-related propositions can be altered or eliminated when they become problematic (e.g., 'I always need to be the best in order to live a happy life'). A number of researchers have argued that propositions - including those related to the self - can be formed, modified or eliminated in a wide variety of ways, from direct experience to knowledge, instructions, intervention, and deductive reasoning (De Houwer, 2009). Given that existing attempts to manipulate implicit self-esteem have started from the position that this construct is associative in nature (Dijksterhuis, 2004; Grumm, Nestler & von Collani, 2008) it may be that a more effective strategy is one that directly attempts to enhance certain self-related propositions (actual) while reducing others (ideal) (e.g., Smith, De Houwer & Nosek, 2013). Third, by identifying problematic propositions within the laboratory we may provide clinicians with valuable information about mental content that needs to be modified (as in Cognitive-Behavioral Therapies; Beck, 2005) or how specific types of thoughts are experienced in order to promote desired behavior change and ultimately valued action (as in Acceptance and Commitment therapy; Hayes, Strosahl, & Wilson, 1999).

In short, we suggest that the actual and ideal selves should not be conceptualized as two fundamentally distinct constructs but simply as two sets of propositions about the self that can be automatically activated and guide behavior in different ways. This framework seems to accommodate existing findings within the literature in a parsimonious manner insofar as it draws upon a restricted set of concepts in order to account for a wide variety of outcomes (for related arguments at the functional level of analysis see Hughes, Barnes-Holmes & Vahey, 2012). It may also allow researchers to side-step emerging conceptual issues related to how the self should be 'carved up'. If new experimental evidence continues to implicate different 'selves' in (implicit) self-esteem then researchers may be tempted to treat them as fundamentally different from one another, create a taxonomy of these selves (e.g., actual, ideal, other-related) and attempt to specify their precise nature and interaction. We believe that a more economic approach would be to start from the position that people can form different propositions about the self and that - in certain instances – these propositions can be selectively activated and differentially impact behavior.

Importance of NIBS: are they relevant for experimental research and/or clinical treatment?

The advances in our understanding of the underlying mechanisms of depression, as well as the mechanisms of psychological interventions and treatment, have inspired translational efforts to develop highly intensive and targeted neurocognitive training interventions aimed at remediating cognitive impairments in depression (De Raedt et al., 2015). The use of NIBS techniques (such as rTMS and tDCS) in both experimental research and clinical treatment have substantially increased over the last decade(s). Multiple sessions of neurostimulation are frequently used in the treatment of psychiatric disorders such as depression (e.g., Burt et al., 2002; Mitchell & Loo, 2006; O'Reardon et al., 2007; Boggio et al., 2008; George et al., 2010), while experimental research often focuses on single neurostimulation sessions (chapters 5, 6, and 7 are examples). In the current project, we have used NIBS techniques to experimentally investigate underlying mechanisms related to depression (e.g., stress resilience, ruminative self-referential processing, self-esteem). Based on our findings we can conclude that neurostimulation can influence these processes, but more importantly, their application has helped us to better understand the underlying mechanisms that we have focused on throughout our research. First, we succeeded in demonstrating that the physiological stress response can be manipulated and attenuated in the face of a stressor (interpersonal criticism). Indeed, this is indicative of a possible beneficial effect of neurostimulation as a transdiagnostic intervention (applying multiple sessions of neurostimulation). De Raedt and Koster (2010) concluded, based on a review on the cognitive and neurobiological correlates of vulnerability for depression that an important therapeutic aim would be to restore stress reactivity. Second, our results indicated that a single neurostimulation session can influence (decrease) ruminative self-referential thoughts, as such, re-establishing the beneficial effect of NIBS on cognitive control over negative information (e.g., Boggio et al., 2007; Wolkenstein & Plewnia, 2013) and specifically on rumination, in line with the results of Vanderhasselt et al. (2013). In addition, through this decrease of rumination and only after receiving interpersonal criticism, NIBS had also an (indirect) influence on (actual) self-esteem.

Thus, underscoring the importance of criticism and rumination with regard to a person’s actual self-esteem. Furthermore, these findings underscore the use of NIBS techniques in the attenuating effect over ruminative self-referential processes and as such, reiterating the crucial importance of cognitive control with regard to rumination. Third, on the level of neural activity and functional connectivity, our findings are in line with previous physiological results. By demonstrating that when people are confronted with social evaluations (both positive and negative) they show a decrease in activation of the precuneus, an area known for its crucial role in self-referential processing (Cavanna et al., 2006), but only after real tDCS. However, the decrease in activity during self-referential thinking (rumination) was larger compared to the decrease in activity during praise, showing again the possible impact of neurostimulation on state rumination (see also Vanderhasselt et al., 2013). Furthermore, our data also revealed that real tDCS resulted in a decreased FC between the precuneus/PCC seed and the vmPFC. On the other hand, sham stimulation resulted in a FC increase between these two areas. These results are in line with an increase of cognitive control over the underlying ruminative processes that are triggered by interpersonal criticism.

That said, these results indicate that these mechanisms can be manipulated experimentally with effects at different levels of measurement (physiological, behavioural, neurocognitive). A central, common feature throughout our NIBS studies is the PFC as target site. Our findings suggest that the (left DL)PFC may be a critical brain area in the neuro-circuitry underlying stress and cognitive reactivity to interpersonal criticism, and suggest that the PFC plays a role in the modulation of stress and ruminative responses (in healthy participants). By modulating this specific brain region cognitive control and stress resilience may be positively affected, which is crucial for coping with negative life events. Our results are consistent with the conclusions of Davidson et al. (2002) and Maier et al. (2006) that the PFC is implicated in affect regulating and is vital for the protective effects of behavioural and cognitive control over stress responsiveness. Moreover, these findings are indicative of the potential of NIBS to increase cognitive control to cope with stressful stimuli, which is highly relevant in the treatment of stress-related disorders such as major depression (Scher, Ingram, & Segal, 2005). It seems important to note that this study was the first to investigate these underlying processes (neural correlates) in ‘real time’, that is, while under fMRI.

This novel approach opens up the possibility to accurately investigate what happens will these underlying processes are in play.

In summary, the research in this dissertation showed the possible influence of (a single) NIBS session at the physiological (HRV), cognitive (rumination, criticism, implicit self-esteem) and neurobiological (neural activity and functional connectivity) level. In addition, the prefrontal cortex can be established as an important region of interest when investigating stress reactivity and cognitive control. Research has established the importance of stress resilience, rumination, coping with criticism and self-esteem within depression, as such, our findings tried to increase our understanding of the underlying mechanisms of these concepts and their intricate relation. Moreover, using NIBS techniques allowed us to experimentally and more directly scrutinize these underlying mechanisms in light of a better understanding of their relation. As postulated in Koster, Bockting, and De Raedt (2015) there are important advances in understanding and applying psychological interventions for depression. Integrating existing knowledge from psychological, physiological and neurocognitive research might hold promise for the development of combined interventions, allowing a personalized medicine approach for depression treatment, which has the potential to markedly change and improve the way depression is treated throughout all its stages. Below we highlight the clinical implications of our findings.

Clinical implications

The Self is just more than who I am!

Establishing a more fine-grained understanding of the self-esteem concept may have clinical implications. Because implicit measures have been shown to predict distress and psychopathology (e.g. Franck, et al., 2007), these results further highlight the importance of actual versus ideal self-discrepancy theories, which might hold promise to refine therapeutic interventions. Moreover, our findings of a more comprehensive view on self-esteem, based on the use of propositions, hold promise for clinical research. Following the discrepancy theory of (Higgins, 1987) which states that the discrepancy between the actual and ideal-self is a cognitive risk factor for depression, and consistent with previous work in this area (e.g., Stevens, Holmberg, Lovejoy, & Pittman, 2014), individuals suffering from higher levels of self-reported depressive symptomatology displayed greater discrepancies between their actual and ideal self-evaluations than those who did not report such symptoms. For instance, it is possible that a high ideal self in a (sub-clinical) depressed population could lead to self-discrepancy issues, that is, people experience and internal conflict between how they see themselves (actual-self) and how they want to be (ideal-self). Hence, a possible treatment strategy in therapy might be to directly focus on some specific sets of propositions related to the self. In our abovementioned self-discrepancy example, one can try to question the higher ideal-self and scrutinize it's "*high and/or unrealistic*" character, while at the same time focus on strengthening the actual-self through, for instance, competitive memory training (COMET - Korrelboom, 2011), which proved its efficacy in the treatment of low self-esteem for patients with a depressive disorder (for detail, see the randomized clinical trial study, Korrelboom, de Jong, Huijbrechts, and Daansen, 2009). As such, decreasing the discrepancy between what people think they are (actual-self) versus what they want to be (ideal-self), could be a new strategy in the clinical treatment of self-esteem issues within depression.

In addition, looking at the possibilities of propositional knowledge, it could be that propositions comparing the individual to *others* provide even more diagnostic information in (e.g., '*I am good but others are better'*). Importantly, this assumption may also apply to other clinical and non-clinical domains where automatically activated propositions may play a role (e.g., anxiety, obsessive-compulsions, phobias, chronic pain). As such, maybe a better way to understand the complex concept of self-esteem, is to conceptualize it as a combination of an entire spectrum of propositions related to the self that (a) can also be activated automatically in order to guide behavior and (b) are potentially more predictive of clinically-relevant outcomes that those examined thus far. Hence, by identifying problematic propositions within the laboratory we may provide clinicians with valuable information about mental content that needs to be modified (as in Cognitive-Behavioral therapies; Beck, 2005).

The importance of criticism and NIBS in the treatment of depression

Given the intricate relation between ruminative self-referential thoughts and interpersonal criticism, it seems important to integrate our current understanding of these concepts for the treatment of depression. An abundance of research has shown the importance of rumination within depression, but only limited research has focused on the effect of criticism on rumination and indirectly on self-esteem.

Our research builds further on the studies of Hooley and (2005; 2009; 2012) which investigated the sensitivity to criticism as an important factor in the recurrence of a depressive episode. These studies emphasized that people suffering a depressive episode had a higher risk of relapse after growing up in critical environments. More specifically, those people showed a lower activation of the DLPFC in response to criticism, thus, making them more vulnerable for relapse. As such, our research findings might have an added value with regard to a better coping for this population when confronted with criticism. Given the beneficial effects of NIBS, targeting the DLPFC, we can help augment cognitive control over these ruminative processes in dealing with criticism. However, (see next paragraph) the remediating effects of NIBS techniques will not suffice to prevent any relapse or provide a constructive coping with criticism in general. Moreover, the responsiveness to NIBS after criticism with regard to rumination is linked with a person's self-esteem. In other words, NIBS allows people to better cope with rumination that comes as a result of criticism and as such creates a buffer for one's actual self-esteem. This can be of high value in a population that is sensitive to criticism, has a high correlation with rumination, and is linked with lower levels of (actual) self-esteem. In light of these accounts, it feels important to emphasize that the underlying processes of *coping with criticism* should be given a more prominent focus in the treatment of depression. Especially given its link to ruminative responsiveness as well as to actual self-esteem (both rumination and self-esteem are concepts highly relevant for depression and its treatment).

In addition, since our research has shown that NIBS can have a positive impact on the reactivity to criticism-induced responses (physiological and cognitive), as well as decrease ruminative processing, this might hold promise for a combined application in the treatment of affective disorders. Our findings proved that NIBS can increase cognitive control to cope with stressful stimuli, which is highly relevant in the treatment of stress-related disorders such as major depression (Scher, Ingram, & Segal, 2005). Hence, we further corroborate the ideas of De Raedt and colleagues (2015), who propose combining conventional therapy with NIBS, given that there is a high relapse rate after conventional therapies, suggesting that resilience is not increased per se. In their review De Raedt and colleagues (2015) provided evidence that NIBS over the PFC influence neuro-circuits involved in rumination, cognitive control, attentional control and emotion regulation (De Raedt et al., 2015). Since NIBS techniques (such as rTMS and tDCS) are able to influence and modulate neuroplasticity (Kuo, Paulus, & Nitsche, 2014), the underlying neurobiological abnormalities can be remediated by these techniques. However, this remediation effect is not sufficient to permanently restore any pathophysiological abnormalities, and subsequently establish constructive, behavioural coping. Therefore, there is the need to revalidate the given re-establishing effect after NIBS, by combining it with CBT (e.g., emotion regulation training, cognitive restructuring). Hence, the effects of NIBS could thus be boosted by combining these techniques with training of cognitive strategies that foster new learning and thus facilitate plasticity, and ultimately increase resilience for (future) depressive episodes. This way of combining behavioral and neurocognitive findings with the actual treatment of psychopathology, might open up an array of possibilities (e.g., in OCD, anxiety disorders, addiction) and allow us to further optimize psychopathology interventions.

LIMITATIONS

The studies presented in this dissertation are not without limitations. A primary issue concerns the different possibilities of how rumination can be conceptualized and operationalized. In our studies, momentary self-referential ruminative thinking refers to a temporary cognitive thought pattern that is highly dependent on situational cues but that is independent of mood. Trait rumination, on the other hand, is defined as “behaviors and thoughts that focus one's attention on one's depressive symptoms and on the implications of those symptoms”, and is considered a habitual thinking response to sadness (Nolen-Hoeksema, 1991, p. 569). Even though most studies consider ruminative thinking as a trait characteristic, self-referent thoughts fluctuate continuously (especially in healthy individuals) and might provide valuable information to understand the development of a stable trait. Moreover, there are many ways to assess momentary self-rumination (see Smith & Alloy, 2009). In studies that have investigated momentary ruminative thoughts, participants are asked randomly during daily life to report the content of their thoughts (Killingsworth & Gilbert, 2010; Moberly & Watkins, 2008), or ruminative thoughts are induced by asking participants to focus their attention on a specific thought (presented by a statement) for some time (e.g., Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Whitmer & Gotlib, 2012). Since we did not use any behavioral measures, and we were not aware of any existing questionnaires to measure momentary ruminative self-referent thoughts, we used a short (so far unpublished) inventory that has only been used in a limited number of studies (Momentary Ruminative Self-focus Inventory; Mor et al.,2015; Vanderhasselt et al., 2013).

A second limitation to the present research is that we did not use patient populations. In chapters 2 and 3 a normative sample of students was used that varied in their respective levels of self-reported depressive symptomatology. It remains to be seen whether a sample of clinically depressed, remitted or recovered participants would also show evidence of elevated ideal and diminished actual self-evaluations. However, dysphoric students have been shown to be prone to depression (e.g. Ingram & Siegle, 2009), and can thus be considered as a clinical analogue sample. Nevertheless, our findings can stimulate future research aimed at investigating the role of self-esteem in depression in different populations. i (e.g., remitted depressed, MDD, etc.). This especially given that depressed patients, compared to healthy individuals, have difficulties to shift their attention away from negative stimuli (Williams et al., 1996). Moreover, depression has been conceptualized as a failure to recruit prefrontal top-down cognitive control to regulate emotion producing subcortical limbic activity (Phillips, Ladouceur, & Drevets, 2008). Thus, the reaction of MDD patients to interpersonal criticism might induce more and stronger effects than with healthy participants, challenging even more the underlying neuro-circuitry that was targeted in this study.

Finally, some general concerns can be highlighted, on which future research can focus in continuing this research line: the sample sizes on most included studies were of medium size, future studies should aim to replicate our findings in larger study samples; in almost all of our studies we focused on female participants because rates of depression are higher in women than they are in men (Nolen-Hoeksema, 2002) and because we sought to minimize heterogeneity in our data due to gender effects.

DIRECTIONS FOR FUTURE RESEARCH

The self in the eye of the beholder

First, as discussed before, it may be that other implicit propositions such as those related to people's personal expectations (e.g., '*I should be*' or '*I need to be*'), how they compare themselves to others (e.g., '*I am good but others are better*') or perceived failures (e.g., '*I'm not good enough*'), can be more important for predicting behaviour. With this in mind, future research could examine whether IRAPs targeting other types of propositional knowledge provide even better diagnostic and predictive information about clinical and non-clinical populations. With this in mind, a potential expansion of our research would be to focus more on the dimension of the *other*. For over a century, scholars have suggested that feelings about the self reflect beliefs about how one is evaluated by others (e.g., Cooley, 1902; Hardin & Higgins, 1996; James, 1890; Maslow, 1970; Mead, 1934; Pyszczynski, Greenberg, Solomon, Arndt, & Schimel, 2004; for a review, see Tice & Wallace, 2003). A classic example is the notion of the ''*looking-glass self*'' in which Cooley (1902) contends that people take the attitude toward the self that is assumed to be held by others. Cooley writes, ''*the character and weight of that other, in whose mind we see ourselves, makes all the difference with our feeling. . .We always imagine and in imagining share the judgments of the other mind*'' (p. 184). In line with this theory, Leary and Baumeister (2000) developed the sociometer model (Leary & Baumeister, 2000), which states that self-esteem is a gauge of perceived social value that fluctuates as a function of the degree to which one feels valued by those around him or her. Moreover, it indexes one's apparent value to others and is high to the extent that individuals feel accepted and appreciated, but low when they feel disapproved and rejected. Hence, again mirroring the importance to understand the possible impact of criticism on the self and subsequently stress resilience and depressive symptomology. Thus, by looking further than *actual* and *ideal* self-esteem, future studies could pinpoint the social dimension via the proposition of "*I ought to be*".

Drawing upon the results on actual and ideal self-esteem, another possible future avenue for this research lies in the use of social media, such as Facebook, Instagram, etc. These platforms are a widely used and might be interesting to researchers focused on self-esteem, especially in young adults. Some authors have hypothesized that heavy use of online social networks, e.g., Facebook, may contribute to an increased incidence of depression (Chou & Edge, 2012; Jelenchick, Eickhoff, & Moreno, 2013; Soo Jeong et al., 2013). Moreover, recent studies argued whether or not heavy Facebook use can lead to depression (Jelenchick et al., 2013; Moreno et al., 2012; Wright et al., 2012). One possible interpretation of our findings contributes to this argument. Specifically, the idea that people create an ideal version of themselves on Facebook (e.g., posting only happy thoughts, fun events and beautiful pictures), rather than a representative view of themselves (e.g., failures, less beautiful pictures, doubts about the self). As such, creating a possible discrepancy between how they actually view themselves versus how to would like to be, ideally. In addition, because of the "like" function, the social component is also included, and people can perceive this as an evaluation of the person they are. Therefore, it would be interesting to investigate self-esteem in relation to Facebook use and its influence on the perception of the self as well as the evaluative dimension of "liking" a comment, picture of status.

Towards combined interventions (psychological, pharmacological, neurocognitive treatments)

In facing the challenges of improving our understanding of depression it is clear that, given the heterogeneity of risk for depression (e.g., Kendler, Gatz, Gardner, & Pedersen, 2006), a wealth of different research strategies are required and need to be integrated in order to provide more solid answers on which pathogenic mechanisms should be targeted in order to more successfully treat depression (Koster et al., 2015). In this dissertation we focused on specific levels (physiological, behavioural, neurobiological) in order to integrate our findings and combine them in one large study that transcends the singular level. By doing so, we used different modalities to obtain a more comprehensive oversight into more innovative research in the field of experimental psychopathology. However, an important observation in this context is that given the divergence between different treatments strategies (e.g., psychotherapy, pharmacology, neurostimulation, etc.), with studies being frequently published in specialist journals, it is not always easy to obtain a comprehensive oversight into the most important innovations in this field or how they should be integrated. As such, integrating existing knowledge from psychological and neurocognitive research might hold promise for the development of combined interventions, allowing a personalized medicine approach for depression treatment, which has the potential to markedly change and improve the way depression is treated throughout all its stages (for an in depth discussing see Koster et al., 2015). In sum, there is a dire need for integration of psychological, pharmacological, and neurobiological findings to positively impact the treatment of depression on several levels of the etiology.

In this dissertation, there are several comments to be made, which could guide future research and further the understanding of the underlying mechanisms of depression. A first observation is that NIBS allows people to better cope with rumination due to interpersonal criticism and as such creates a buffer for one’s actual self-esteem. Thus, this can be of high value in a population that is sensitive to criticism, has a high correlation with rumination and linked with low levels of (actual) self-esteem, such as depression. Thus, several findings in our studies need to be conducted with clinical populations. In chapters 2 and 3 a normative sample of students was used that varied in their respective levels of self-reported depressive symptomatology. It remains to be seen whether a sample of clinically depressed, remitted or recovered participants would also show evidence of elevated ideal and diminished actual self-evaluations. Therefore, it is imperative that our findings are replicated in other affective disorder populations (e.g., remitted depressed, MDD, etc.), as wells as further elucidate the role of self-esteem in depression. A second observation is that most of our findings are confined to the use of an all-female population. Therefore future studies should replicate these results in a male population to identify the presence or absence of gender effects. Third, our study (Chapter 6 & 7) was the first to apply neurostimulation during fMRI as an experimental manipulation to investigate the neural correlates underlying the link between criticism and self-referential processes in real time, showing that tDCS can alter alter behavioral and neural responses of self-referential processing. With this novel design, we extend beyond previous correlational research investigating the underlying processes of rumination, to increase our insights in the ‘real time’ neural correlates of these processes while confronted with social evaluations. Hence, there is an important need for research that investigates these underlying mechanisms under fMRI. Moreover, given the accrued literature on the DMN, we need to further fine-grain the relationship between cognitive control over ruminative self-referential thoughts and the DMN. Furthermore, the beneficial use of NIBS in our studies, should stimulate researchers to combine these techniques while using fMRI, accurately pinpoint its effect on the *depressed brain*. Finally, with regard to the measurement of self-referential thoughts, and given that we were not aware of any existing questionnaires to measure momentary ruminative self-referent thoughts, we used a short (so far unpublished) inventory that has only been used in a limited number of studies (Momentary Ruminative Self-focus Inventory; Mor et al.,2013; Vanderhasselt et al., 2013). Therefore, future research should further proof the sufficient psychometric properties of this questionnaire.

FINAL CONCLUSION

This research project set out to investigate how the link between criticism and ruminative processes affects self-esteem, focusing on both behavioral and neurobiological processes. The work in this dissertation has unlocked some parts of the intricate relation between these underlying mechanisms as well as the role NIBS can play in unraveling their functioning. Yet much remains to be discovered about how the link between criticism and rumination influences self-esteem. Only by further improving our understanding of these processes and their complex relation, can we gain a more comprehensive understanding of the behavioral, cognitive and neurobiological foundations of the *depressed brain*.

Going back to the two friends at the start of my dissertation, Tyler and Edward, we might reevaluate their situation based on the findings of this dissertation. Hence, some deductions of their situation can be made based on our work. With regard to Edward, it is possible that the criticism originating from his boss lead to an increase in rumination, and has ultimately affected his actual self-view. But what does that tell us, and more importantly what could we do to help him? According to our results, it seems crucial to focus on how to deal with the increased ruminative thinking, following the interpersonal criticism, and investigate his possibly affected self-esteem. Before treating his depression with CBT, some NIBS techniques could be administered to increase his cognitive control to deal with ruminative self-referential thoughts as well as his stress reactivity when confronted with criticism. Either way, solely working on his depressive mood, would detract from the more complex relation of the underlying mechanisms involved in his story and this dissertation.

“*One's self-image may be criticized, vandalized and cruelly mocked, but it can never be broken unless it is surrendered*.”

— adapted quote from Michael J. Fox

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NEDERLANDSTALIGE SAMENVATTING

In de laatste decennia is de prevalentie van geestesziekten sterk toegenomen en dit vooral voor stemmingsstoornissen zoals depressie (e.g., Witcchen et al., 2011). Volgens de World Health Organization (WHO, 2016) is depressie een veel voorkomende ziekte, met op dit moment wereldwijd ongeveer 350 miljoen getroffen mensen. De geschatte life-time prevalentie bedraagt 19% in de Verenigde Staten (Kessler et al., 2009) en vertoont vergelijkbare cijfers in Europa (Witcchen et al., 2011). Hoewel farmacologische en psychologische interventies op korte termijn tot bevredigende effecten leiden, is er dringend nood aan een verbeterde effectiviteit van behandelingen op lange termijn. Bovendien wordt een deel van de patiënten therapieresistent (tot 15%) (Burrows, Norman, en Judd, 1994; Fava, 2003). Het is duidelijk dat een belangrijke uitdaging in het verbeteren van het begrijpen van de onderliggende mechanismen van depressie ligt in een integratie van verschillende onderzoeksstrategieën. Zo kunnen we meer omvattende antwoorden vinden die focussen op de pathogene mechanismen die aan de grondslag liggen van depressie en op die manier een betere behandeling mogelijk te maken (Koster, Bockting, & De Raedt, 2015). Echter, daarvoor is er dringend nood aan onderzoek waarbij een integratie gemaakt wordt van zowel cognitieve als neurobiologische bevindingen in verband met de onderliggende mechanismen van depressie. Een aantal van deze onderliggende mechanismen – waarvan uit onderzoek blijkt dat ze een grote impact hebben bij depressie – vormen de focus van dit doctoraatsproject: het omgaan met kritiek, ruminatieve, zelf refererende gedachten en zelfwaarde.

Onderzoeksdoelstellingen

Het algemene doel van dit doctoraatsproject was te onderzoeken hoe de link tussen kritiek en ruminatie van invloed is op zelfwaarde, waarbij we ons hebben gefocust op zowel gedrags- als neurobiologische processen. Om deze mechanismen te onderzoeken, gingen we na of het effect van een experimentele manipulatie van de prefrontale cortex op zelfbeeld wordt gemedieerd door ruminatie voor en na het krijgen van interpersoonlijke kritiek. Hoewel we vertrokken vanuit de opzet dat deze onderliggende mechanismen relevant zijn binnen depressie, was het cruciaal om met het testen van onze causale hypothesen te beginnen bij gezonde individuen. Op deze manier vermijden we een mogelijke vertekening van de te onderzoeken mechanismen in deze studie te wijten aan de depressieve stemming van de patiënt. In het onderzoek richtten we ons op drie meetniveaus. Ten eerste, onderzochten we de effecten van neurostimulatie op ruminatie en zelfwaarde door middel van zelfrapportagematen. Ten tweede, gebruikten we impliciete maten om zelfwaarde te meten. Ten derde, onderzochten we de neurobiologische correlaten van dit proces. Echter, vooraleer we deze vragen konden beantwoorden, moest er eerst aan een aantal vereisten worden voldaan door het ontwikkelen en testen van nieuwe meetinstrumenten. In de eerste plaats zijn we begonnen met de ontwikkeling van een taak om het gevoel van zelfwaarde te meten op een impliciete manier, met de nadruk op zowel het actuele als het ideale zelf (hoofdstuk 2). In een tweede studie, herhaalden we de resultaten van deze eerste studie met striktere criteria, evenals een methodologisch verfijnder design (hoofdstuk 3). Ten derde, voerden we een systematische review uit om te verduidelijken of één enkele neurostimulatie-sessie (repetitive transcranial magnetic stimulation, rTMS) een effect zou hebben op stemming bij gezonde deelnemers. Dit laatste, omdat stemmingseffecten de effecten op cognitieve processen zouden kunnen vertekenen (hoofdstuk 4). Ten vierde, onderzochten we of een placebo-gecontroleerde neurostimulatie-sessie de fysiologische reactie op stress (gemeten aan de hand van hartslagvariabiliteit) tijdens het krijgen van kritiek (hoofdstuk 5) kan beïnvloeden. Tot slot, combineerden we een placebo-gecontroleerde sessie van transcraniale direct current stimulation (tDCS) in de fMRI-scanner, om de mogelijke effecten na te gaan van neurostimulatie van de dorsolaterale prefrontale cortex op de onderliggende neurobiologische processen van ruminatie (hersenactiviteit en functionele connectiviteit) voor en na een experimentele inductie van kritiek (hoofdstuk 6). Vervolgens hebben we het effect op impliciete zelfwaarde bestudeerd (met behulp van de Implicit Relational Assessment Procedure, IRAP) (hoofdstuk 7).

Overzicht van de belangrijkste bevindingen

Zelfwaarde in depressie: een impliciet, propositioneel perspectief

In een eerste studie (**hoofdstuk 2**) ontwikkelden we een impliciete maat die ons toeliet om te differentiëren tussen actuele en ideale zelfwaarde. Via zelfwaarde IRAPs (Barnes-Holmes et al., 2006) onderzochten we of dysfore versus niet-dysfore (opdeling van hoge versus lage depressieve symptomatologie) individuen verschillen met betrekking tot hun actuele en ideale zelf. Op basis van onze resultaten konden we besluiten dat dysfore individuen een lagere actuele en een hogere ideale zelfwaarde vertoonden, en dit in vergelijking met de niet-dysfore groep. Daarnaast vertoonde deze laatste groep een meer positieve actuele zelfwaarde in vergelijking met hun ideale zelfwaarde. Op deze manier toonden de resultaten een differentiatie in zelfwaarde-scores op basis van een impliciete meting. Door proposities (i.p.v. associaties) te gebruiken, kwam er een meer complex beeld naar boven gerelateerd aan depressieve symptomatologie.

In onze tweede studie (**hoofdstuk 3**) bouwden we verder op deze bevindingen en includeerden we naast een propositionele, impliciete maat (IRAP) ook een associatieve, impliciete maat (IAT) in een vergelijkbaar opzet als onze eerste studie. Daarnaast pasten we in deze studie ook een aantal methodologische aanpassingen toe die de studie meer betrouwbaar, strikter en methodologisch verfijnder maakten. De resultaten toonden een vergelijkbaar positief, impliciete zelfwaarde (o.b.v. IAT scores) voor zowel laag als hoog dysfore individuen. Opnieuw verscheen er een meer gedifferentieerd beeld bij gebruik van de IRAPs. Ook hier vertoonden de dysfore groep een positievere ideale zelfwaarde in vergelijking met hun actuele zelfwaarde (herhaling eerste studie). Echter, voor de niet dysfore groep werden geen verschillen gevonden.

De resultaten uit deze twee studies toonden aan dat zowel dysfore als niet-dysfore individuen een impliciete positiviteit t.o.v. zichzelf ervaren. Daarnaast, vertoonden dysforen een grotere discrepantie tussen hun actuele en ideale zelfwaarde in vergelijking met niet-dysforen, met hogere ideale t.o.v. actuele zelfwaarde scores. Deze bevinding onderbouwt niet alleen de theoretische opvatting dat een discrepantie tussen actuele en ideale zelfwaarde gerelateerd is aan een depressieve symptomatologie, maar demonstreert ook de toegevoegde waarde van het gebruik van impliciete maten (o.b.v. proposities) die verschillende impliciete overtuigingen kunnen onderzoeken.

Zelfwaarde in depressie: een impliciet, propositioneel perspectief

Vervolgens (**hoofdstuk 4**) gingen we op zoek naar de mogelijke impact van niet-invasieve hersenstimulatie technieken op stemming bij gezonde individuen. Dit gezien de effecten op stemming de effecten op cognitieve processen kunnen vertekenen. In een systematische review includeerden we 30 studies, waarvan 13 tDCS en 17 rTMS studies. Op basis van onze bevindingen konden we concluderen dat door het controleren van bepaalde methodologische tekortkomingen (bvb. sham-gecontroleerd, gecounter-balanced, een grote steekproef, etc.) er geen stemmingseffecten worden gevonden na een eenmalige neurostimulatie-sessie.

De invloed van rTMS op stressweerbaarheid: een fysiologisch perspectief

Na de bevindingen uit studie 3, richtten we ons in een volgende studie (**hoofdstuk 5**) op de vraag of een eenmalige neurostimulatie sessie (rTMS) van de prefrontale cortex een invloed zou hebben op de fysiologische stress respons (gemeten via hartslagvariabiliteit) na het ontvangen van negatieve feedback (kritiek). Onze manipulatiecheck toonde aan dat onze kritiekinductie een zelf gerapporteerde stressverhoging teweegbracht, en dit over beide condities (actieve stimulatie en placebo). Echter, de hartslagvariabiliteit data toonden aan dat er enkel na een actieve stimulatiesessie een verminderde fysiologische stressrespons werd geregistreerd. In de placebo conditie was er geen significant effect op te merken. Deze studie was de eerste experimentele studie die neurostimulatie over de prefrontale cortex gebruikte die een impact op parasympatische modulatie aantoont. Bovendien tonen deze bevindingen hoe het verhogen van prefrontale activatie, via neurostimulatie, kan helpen om een fysiologische stressrespons te verminderen. Daarnaast kunnen we ook stellen dat door de prefrontale cortex te stimuleren we mogelijk de stressweerbaarheid positief kunnen beïnvloeden, wat cruciaal is voor het omgaan met stressvolle gebeurtenissen en negatieve feedback (kritiek). Deze bevindingen liggen in de lijn van de therapeutische effecten van neurostimulatie van de prefrontale cortex bij de behandeling van affectieve stoornissen (e.g., Boggio, 2008).

Kritiek in het brein: een neurocognitief perspectief

Na het op punt stellen van de conceptualisatie en meetwijze van zelfwaarde en het onderzoeken van de impact van neurostimulatie op de fysiologische stressrespons, kwam onze focus te liggen op de hoofdonderzoeksvraag in dit doctoraatsproject: wat is de link tussen kritiek en ruminatieprocessen en hoe heeft deze invloed op zelfwaarde? In hoofdstuk 6 onderzochten we de neurobiologische correlaten van deze onderliggende processen. Daarnaast analyseerden we de effecten van neurostimulatie op zelfwaarde en bekeken we de daar bijhorende link met ruminatieve processen alsook de relatie met kritiek (hoofdstuk 7).

In **hoofdstuk 6** voerde we de studie uit waarbij we tDCS (versus placebo) toepasten in de fMRI scanner, gevolgd door een sociale evaluatie-paradigma (luisteren naar neutrale, bekrachtigende en kritische commentaar). Door hersenactiviteit te meten tijdens rust voor en na het sociale evaluatie-paradigma, alsook tijdens het paradigma konden we in ‘real time’ onderzoeken wat het specifieke effect is van het krijgen van kritiek (in vergelijking met neutrale en bekrachtigende commentaar) op regionale hersenactiviteit en de functionele connectiviteit. In de sociale, cognitieve neuro-wetenschappelijke literatuur worden de precuneus en de posterior cingulate cortex (PCC) geassocieerd met sociaal evaluatieve verwerking (Kuzmanovic et al., 2012). Meer bepaald toonde Cabanis et al. (2013) aan dat de precuneus en PCC betrokken zijn bij de evaluatie van sociale gebeurtenissen. Ook Kuzmanovic et al. (2012) rapporteerden een toegenomen neurale activering van de precuneus/PCC wanneer gezonde individuen werden blootgesteld aan interpersoonlijke evaluaties. Uit de resultaten blijkt inderdaad een neurale activatie in de precuneus/PCC na het ontvangen van bekrachtiging en kritiek. Meer specifiek, observeerden we enkel na actieve tDCS een significante afname van activiteit in de precuneus bij zowel bekrachtiging als kritiek (in vergelijking met neutrale commentaar). Belangrijk om op te merken is dat de afname groter was na kritiek in vergelijking met de afname na bekrachtiging. Met andere woorden, wanneer mensen worden geconfronteerd met sociale evaluaties, ziet men na actieve tDCS een afname in activatie van de precuneus. Dit kan betekenen dat de participanten minder zelf refererende gedachten vertonen wanneer ze geconfronteerd worden met sociale evaluaties. Gezien de positieve impact van tDCS groter was bij het omgaan met kritiek (t.o.v. bekrachtiging), is dit indicatief voor de gunstige impact van neurostimulatie op negatieve zelf refererende gedachten (zoals ruminatie) (zie ook Vanderhasselt et al., 2013). In lijn met de literatuur tonen deze resultaten een associatie van de precuneus met het omgaan met positieve en negatieve evaluaties bij de confrontatie met sociaal relevante situaties in het alledaagse leven.

Daarna onderzochten we de functionele connectiviteit gebaseerd op de relevante hersenregio’s geïmpliceerd in de neuro-wetenschappelijke literatuur en de resultaten van onze regioanalyses (namelijk, precuneus/PCC). Onze resultaten toonden na actieve tDCS een afname in functionele connectiviteit tussen de precuneus/PCC en de ventromediale prefrontale cortex (vmPFC). Na placebo stimulatie zagen we een omgekeerd effect, namelijk een toename in activatie tussen deze twee regio’s. Gezien de vmPFC cruciaal is bij het verwerken van emotioneel stimuli tijdens sociale cognitie, en betrokken is bij het identificeren van zelf refererende informatie (Gusnard et al., 2001; Northoff and Bermpohl, 2004; Northoff et al., 2006), alsook dat interacties tussen de vmPFC en de precuneus/PCC aan de grondslag liggen van zelf relevante verwerking (Buckner et al., 2008; Qin and Northoff, 2011), ondersteunen onze resultaten de bevindingen in de literatuur. Ze toonden een toename in de functionele connectiviteit tussen de precuneus/PCC-vmPFC na blootstelling aan sociale evaluatieve stimuli. Meer bepaald, na actieve tDCS zien we een daling in functionele connectiviteit tussen de precuneus/PCC en de vmPFC, wat indicatief kan zijn voor een toegenomen cognitieve controle over de onderliggende ruminatieve processen die getriggerd worden door interpersoonlijke kritiek. Deze studie is de eerste die neurale activiteit gedurende kritiek onderzoekt alsook de functionele connectiviteit voor en na de kritiek, en dit onder fMRI. Beide bevindingen (regioanalyse en functionele connectiviteitsanalyse) tonen de gunstige effecten van neurostimulatie op het omgaan met ruminatie (na het ontvangen van sociale evaluatieve commentaar). Bovendien tonen onze resultaten dat het gebruik van neurostimulatie technieken als experimentele tools zinvol is bij het beter begrijpen van de neurobiologische processen onderliggend aan cognitieve processen.

De link tussen kritiek, zelf refererende processen en zelfwaarde na tDCS

In onze laatste studie (**hoofdstuk 7**) onderzochten we de mogelijke impact van neurostimulatie op ruminatieve processen voor en na kritiek, en vervolgens het effect op impliciete zelfwaarde. Een eerste bevinding was dat we een afname vaststelden in zelf refererende gedachten (ruminatie) na actieve tDCS. Daarnaast was er ook een afname in zelf refererende gedachten na kritiek in vergelijking met de baseline. Opnieuw toont dit de gunstige impact van neurostimulatie op de cognitieve controle over negatieve informatie (e.g., Boggio et al., 2007; Wolkenstein & Plewnia, 2013), en - meer specifiek - op ruminatie (Vanderhasselt et al., 2013). Een tweede bevinding was het effect van actieve tDCS op zelfwaarde. Hoewel er geen direct effect gevonden werd, vonden we een indirect effect via twee mediatoren, nl. de afname in zelf refererende gedachten baseline versus na tDCS én de afname in zelf refererende gedachten baseline versus na kritiek. Met andere woorden, hoe groter de afname in zelf refererende gedachten na actieve tDCS en na kritiek, hoe hoger de actuele zelfwaarde.

In dit doctoraatsproject toonden we aan dat neurostimulatie de cognitieve controle kan verhogen bij ruminatieve processen na het krijgen van kritiek én dat dit gelinkt is aan iemands actuele zelfwaarde. Dus, hoe beter een persoon omgaat met zelf refererende gedachten na kritiek, hoe positiever hij/zij zichzelf percipieert. Dit positieve proces kan een rol spelen bij het voorkomen van een lage zelfwaarde die op zich kan bijdragen tot het krijgen van een depressie. Op deze manier schept deze studie meer duidelijkheid over de ingewikkelde link tussen ruminatieve processen, omgaan met kritiek en zelfwaarde.

Implicaties van de onderzoeksbevindingen

Op basis van de bevindingen in dit doctoraatsproject kunnen we een aantal implicaties naar voor schuiven.

Het Actuele en het Ideale Zelf: Theoretische Implicaties voor Zelfwaarde Onderzoek

Met betrekking tot onze onderzoeksgegevens rond zelfwaarde, stellen we voor dat het actuele en het ideale zelf niet geconceptualiseerd moeten worden als twee fundamenteel verschillende constructen, maar als twee sets van proposities over het zelf die automatisch geactiveerd kunnen worden en gedrag in verschillende richtingen kunnen sturen. In lijn met de literatuur gebruikt dit raamwerk een beperkt aantal concepten om een verscheidenheid aan uitkomsten te verklaren (voor een uitgebreide beschrijving zie Hughes, Barnes-Holmes & Vahey, 2012). Het kan onderzoekers ook toelaten om conceptuele problemen, die gerelateerd zijn aan hoe het zelf zou moeten geconceptualiseerd worden, te omzeilen. Indien nieuw experimenteel bewijs verschillende “zelven” blijft betrekken in zelfwaarde, dan zouden onderzoekers er kunnen voor kiezen om hen te behandelen als fundamenteel verschillend van elkaar. Meer nog, zouden ze een taxonomie kunnen creëren van “zelven” (actuele, ideale, etc.) en proberen hun precieze aard en interactie te specifiëren. Wij vinden het meer correct om er vanuit te gaan dat mensen verschillende stellingen over het zelf kunnen vormen en dat - in sommige gevallen - deze stellingen selectief kunnen worden geactiveerd en op een gedifferentieerde manier gedrag kunnen kleuren. Bijvoorbeeld, iemand die de overtuiging over zichzelf heeft dat “ik ben goed”, “ik wil geen slechte persoon zijn”, en “anderen zijn slimmer dan mij”, kan in een specifieke situatie een vriend helpen (omdat het belangrijk is voor wie hij is, conform “ik ben goed”) en zo zijn gedrag ‘om te helpen’ laten bepalen door een specifieke stelling over zichzelf.

Het belang van neurostimulatie: zijn deze technieken relevant voor experimenteel onderzoek en/of klinische behandeling?

Het onderzoek in dit doctoraatsproject toont aan dat neurostimulatie een invloed kan hebben op een fysiologisch (hartslagvariabiliteit), cognitief (ruminatie, omgaan met kritiek, zelfwaarde) en neurobiologisch (neurale activiteit en functionele connectiviteit) niveau. Daarenboven kan de prefrontale cortex gezien worden als een cruciale hersenregio mbt stressreactiviteit en cognitieve controle. Onderzoek heeft reeds uitvoerig aangetoond hoe belangrijk stressweerbaarheid, ruminatie, omgaan met kritiek, en zelfwaarde is voor depressie. Daarom zijn we ervan overtuigd dat de resultaten in dit doctoraatsproject een duidelijker licht werpen op de onderliggende mechanismen en hun complexe relatie. Het gebruik van neurostimulatie technieken laat ons bovendien toe om experimenteel en meer nauwkeurig deze onderliggende mechanismen te onderzoeken. Zoals vooropgesteld door Koster, Bockting en De Raedt

(2015) is er een belangrijke vooruitgang in het begrijpen en toepassen van psychologische interventies voor depressie. Het integreren van bestaande kennis vanuit psychologisch, fysiologisch en neurocognitief onderzoek kan een rol van betekenis spelen bij het ontwikkelen van gecombineerde interventies. Deze interventies kunnen een meer gepersonaliseerde medicatie-aanpak voor de behandeling van depressie betekenen. Dit biedt bovendien potentieel om de behandeling van depressie sterk te veranderen en te verbeteren doorheen al zijn stadia.

Algemene Conclusie

Dit doctoraatsproject stelde zich tot doel om onderzoek te doen naar de link tussen kritiek en ruminatieve processen, en hoe deze zelfwaarde beïnvloedt. Daarbij focusten we ons op zowel gedragsmatige als neurobiologische processen. Het werk in dit onderzoeksproject heeft meer duidelijkheid geschept over verschillende delen van de complexe relatie tussen deze onderliggende mechanismen (ruminatie, kritiek, zelfwaarde). Daarnaast hebben de resultaten ook opnieuw het belang aangetoond van de rol die neurostimulatie kan spelen in het ontwarren van hun functioneren. Niettegenstaande deze conclusie blijft er nog veel te ontdekken over de link tussen omgaan met kritiek, ruminatie en zelfwaarde. Enkel door ons begrip van deze onderliggende processen en hun relatie verder te verbeteren, kunnen we een meer omvangrijk begrip van de gedragsmatige, cognitieve en neurobiologische basis van het *depressieve brein* bekomen.

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DATA STORAGE FACT SHEET Actual and Ideal Self-Esteem: Chapter 2

AUTHOR: Jonathan Remue

DATE: 14/06/2016

1. Contact
===
1a. Main researcher

-name: Jonathan Remue
-address:Henri Dunantlaan 2, 9000 Gent
-email: Jonathan.Remue@UGent.be
Jonathan.Remue@gmail.com

1b.Responsible ZAP

-name: Rudi De Raedt
-address:Henri Dunantlaan 2, 9000 Gent
-email: Rudi.DeRaedt@UGent.be

1c. Research group

- name: Psychopathology Affective Neuroscience Lab (PANLab)
- address: Henri Dunantlaan 2, 9000 Gent
- website: http://www.ugent.be/pp/ekgp/en/research/research-groups/panlab/

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DATA STORAGE FACT Actual and Ideal self-esteem: Revisited: Chapter 3

AUTHOR: Jonathan Remue

DATE: 14/06/2016

1. Contact
==

1a. Main researcher

-name: Jonathan Remue
-address:Henri Dunantlaan 2, 9000 Gent
-email: Jonathan.Remue@UGent.be
Jonathan.Remue@gmail.com

1b.Responsible ZAP

-name: Rudi De Raedt
-address:Henri Dunantlaan 2, 9000 Gent
-email: Rudi.DeRaedt@UGent.be

1c. Research group

- name: Psychopathology Affective Neuroscience Lab (PANLab)
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  - address: Henri Dunantlaan 2, 9000 Gent
  - affiliation: UGENT
  - e-mail: Maarten.DeSchryver@UGent.be

DATA STORAGE FACT SHEET Neurostimulation & Stress Reactivity: Chapter 5

AUTHOR: Jonathan Remue

DATE: 14/06/2016

1. Contact
==
1a. Main researcher

-name: Jonathan Remue
-address:Henri Dunantlaan 2, 9000 Gent
-email: Jonathan.Remue@UGent.be
Jonathan.Remue@gmail.com

1b.Responsible ZAP

-name: Rudi De Raedt
-address:Henri Dunantlaan 2, 9000 Gent
-email: Rudi.DeRaedt@UGent.be

1c. Research group

- name: Psychopathology Affective Neuroscience Lab (PANLab)
- address: Henri Dunantlaan 2, 9000 Gent
- website: http://www.ugent.be/pp/ekgp/en/research/research-groups/panlab/

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[x] other (specify): researcher's laptop, location C:\Users\jremue\JONATHAN\05 PhD - Research\Studie 3 - rTMS - Stress (ND)\RAW DATA

[x] other (specify): personal & research group hard drive back up

* Who has direct access to the raw data (i.e., without intervention of another person)?
[x] main researcher
[x] responsible ZAP
[ ] all members of the research group
[ ] all members of UGent

3b. Other files
----
* Which other files have been stored?
  - [X] file(s) describing the transition from raw data to reported results. Specify: see methodology section in the article
  - [X] file(s) containing processed data. Specify: SPSS files location: C:\Users\jremue\JONATHAN\05 PhD - Research\Studie 3 - rTMS - Stress (ND)\PROCESSED DATA
  - [X] file(s) containing analyses. Specify: see findings section in the article
  - [X] files(s) containing information about informed consent. Specify: a blank copy is saved on my PC
  - [X] a file specifying legal and ethical provisions. Specify: The documents that were submitted to the Ethical Commission are with co-author Prof. Dr. Chris Baeken, MD as well as a paper letter with the approval of the Ethical Commission.
  - [X] file(s) that describe the content of the stored files and how this content should be interpreted. Specify: see discussion section in the article
  - [ ] other files. Specify: ...

* On which platform are these other files stored?
  - [X] individual PC
  - [ ] research group file server
  - [X] other: personal & research group hard drive back up

* Who has direct access to these other files (i.e., without intervention of another person)?
  - [X] main researcher
  - [X] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent

4. Reproduction
==

* Have the results been reproduced independently?: [ ] YES / [X] NO

* If yes, by whom (add if multiple):
  - name:
  - address:
  - affiliation:
  - e-mail:

DATA STORAGE FACT SHEET Neurostimulation & Precuneus: Chapter 6

AUTHOR: Jonathan Remue

DATE: 14/06/2016

1. Contact
==
1a. Main researcher

-name: Jonathan Remue
-address:Henri Dunantlaan 2, 9000 Gent
-email: Jonathan.Remue@UGent.be
Jonathan.Remue@gmail.com

1b.Responsible ZAP

-name: Rudi De Raedt
-address:Henri Dunantlaan 2, 9000 Gent
-email: Rudi.DeRaedt@UGent.be

1c. Research group

- name: Psychopathology Affective Neuroscience Lab (PANLab)
- address: Henri Dunantlaan 2, 9000 Gent
- website: http://www.ugent.be/pp/ekgp/en/research/research-groups/panlab/

2. Information about the datasets to which this sheet applies
==
* Not published material.Publication in preperation in which the datasets are reported: Remue, J., Baeken, C., Wu, G-R, Duprat, R., Hooley, J., Vanderhasselt, M-A, Brunoni, A., & De Raedt, R. The role of the precuneus in coping with criticism: a neuromodulation study during fMRI. Manuscript in preparation.

* Which datasets in that publication does this sheet apply to?: all data

3. Information about the files that have been stored
==
3a. Raw data

---

* Have the raw data been stored by the researcher? YES
If not, please justify.
* On which platform are the raw data stored?
[x] paper version in researcher's office (questionnaires)
[ ] research group file server
[x] other (specify): researcher's laptop, location C:\Users\jremue\JONATHAN\05 PhD - Research\Studie 4 - tDCS\RAW DATA

[x] other (specify): fMRI DATA: personal & co-authors & research group hard drive back up

* Who has direct access to the raw data (i.e., without intervention of another person)?
[x] main researcher
[x] responsible ZAP
[ ] all members of the research group
[ ] all members of UGent
[x] other (specify): co-author Chris Baeken

3b. Other files
----
* Which other files have been stored?
  - [X] file(s) describing the transition from raw data to reported results. Specify: see methodology section in the article
  - [X] file(s) containing processed data. Specify: SPSS files location: C:\Users\jremue\JONATHAN\05 PhD - Research\Studie 4 - tDCS\PROCESSED DATA
  - [X] file(s) containing analyses. Specify: see findings section in the article
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  - [X] other: personal & co-authors & research group hard drive back up

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  - [X] main researcher
  - [X] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [x] other (specify): co-author Chris Baeken

4. Reproduction
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* Have the results been reproduced independently?: [ ] YES / [X] NO

* If yes, by whom (add if multiple):

- name:
- address:
- affiliation:
- e-mail:

DATA STORAGE FACT SHEET Neurostimulation & Self-Esteem: Chapter 7

AUTHOR: Jonathan Remue

DATE: 14/06/2016

1. Contact
==
1a. Main researcher

-name: Jonathan Remue
-address: Henri Dunantlaan 2, 9000 Gent
-email: Jonathan.Remue@UGent.be
Jonathan.Remue@gmail.com

1b.Responsible ZAP

-name: Rudi De Raedt
-address: Henri Dunantlaan 2, 9000 Gent
-email: Rudi.DeRaedt@UGent.be

1c. Research group

- name: Psychopathology Affective Neuroscience Lab (PANLab)
- address: Henri Dunantlaan 2, 9000 Gent
- website: http://www.ugent.be/pp/ekgp/en/research/research-groups/panlab/

2. Information about the datasets to which this sheet applies
==
* Not published material. Publication in preparation in which the datasets are reported: Based on Remue, J., Baeken, C., Loeys, T., Hooley, J., & De Raedt, R. *Electrifying the Self: the effect of tDCS on the link between rumination and implicit self-esteem after criticism.* Manuscript in preparation.

* Which datasets in that publication does this sheet apply to?: all data

3. Information about the files that have been stored
==
3a. Raw data
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* Have the raw data been stored by the researcher? YES
If not, please justify.
* On which platform are the raw data stored?
[x] paper version in researcher's office (questionnaires)
[ ] research group file server
[x] other (specify): IRAP DATA: researcher's laptop, location
C:\Users\jremue\JONATHAN\05 PhD - Research\Studie 4 - tDCS\RAW DATA

[x] other (specify): IRAP DATA: personal & research group hard drive back up
[x] other (specify): fMRI DATA: personal & co-authors & research group hard drive back up

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[x] responsible ZAP
[ ] all members of the research group
[ ] all members of UGent
[x] other (specify): co-author Chris Baeken

3b. Other files
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* Which other files have been stored?
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  - [X] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [x] other (specify): co-author Chris Baeken

4. Reproduction
==
* Have the results been reproduced independently?: [ ] YES / [X] NO

* If yes, by whom (add if multiple):
  - name:
  - address:
  - affiliation:
  - e-mail: