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Does non-invasive brain stimulation modulate emotional stress reactivity?

Fenne M. Smits,[1,2] Dennis J.L.G. Schutter,[3] Jack van Honk,[3,4,5] and Elbert Geuze[1,2]

[1]Brain Research & Innovation Centre, Ministry of Defence, Lundlaan 1, 3584 EZ, Utrecht, The Netherlands, [2]Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands, [3]Experimental Psychology, Helmholtz Institute, Utrecht University, Heidelberglaan 1, 3584 CS, Utrecht, The Netherlands, [4]Department of Psychiatry and Mental Health, University of Cape Town, Observatory, 7925, Cape Town, South Africa, and [5]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Observatory, 7925, Cape Town, South Africa

Correspondence should be addressed to Fenne M. Smits, Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail: F.M.Smits-2@umcutrecht.nl

Abstract

Excessive emotional responses to stressful events can detrimentally affect psychological functioning and mental health. Recent studies have provided evidence that non-invasive brain stimulation (NBS) targeting the prefrontal cortex (PFC) can affect the regulation of stress-related emotional responses. However, the reliability and effect sizes have not been systematically analyzed. In the present study, we reviewed and meta-analyzed the effects of repetitive transcranial magnetic (rTMS) and transcranial direct current stimulation (tDCS) over the PFC on acute emotional stress reactivity in healthy individuals. Forty sham-controlled single-session rTMS and tDCS studies were included. Separate random effects models were performed to estimate the mean effect sizes of emotional reactivity. Twelve rTMS studies together showed no evidence that rTMS over the PFC influenced emotional reactivity. Twenty-six anodal tDCS studies yielded a weak beneficial effect on stress-related emotional reactivity (Hedges' $g = -0.16$, $CI_{95\%} = [-0.33, 0.00]$). These findings suggest that a single session of NBS is insufficient to induce reliable, clinically significant effects but also provide preliminary evidence that specific NBS methods can affect emotional reactivity. This may motivate further research into augmenting the efficacy of NBS protocols on stress-related processes.

Key words: stress; emotion; repetitive transcranial magnetic stimulation; transcranial direct current stimulation; review

Introduction

Stress is an integral part of life. It fundamentally serves to protect from danger and adapt to challenges. The adaptive stress response can, however, become detrimental when it is turned on too frequently or does not properly shut off (McEwen, 1998). Responses to stress include feelings of distress and negative emotions. Acute stress can impair executive functions (Shields *et al.*, 2016) and adversely affect performance and decision-making, such as during surgeries (Arora *et al.*, 2010; Chrouser *et al.*, 2018), emergency service operations (Regehr and LeBlanc, 2017) and military operations (Orasanu and Backer, 1996; Harris *et al.*, 2005). Moreover, chronically elevated emotional responses to stress increase long-term daily negative affect and the risk on developing affective disorders (McLaughlin *et al.*, 2010; Charles *et al.*, 2013; Swartz *et al.*, 2015). Finding ways to modulate acute emotional responses to stress, also called emotional stress reactivity, is therefore relevant for daily functioning and wellbeing.

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Emotional stress reactivity is associated with multiple brain regions, including the amygdala, hippocampus and frontal cortical areas. The prefrontal cortex (PFC) plays an important role in regulating acute stress responses on physiological, behavioral and affective levels (Radley *et al.*, 2015). Within the PFC, the ventromedial part (VMPFC) contains the major structural prefrontal–amygdala connections (Kim *et al.*, 2011) and modulates the hypothalamic–pituitary–adrenal (HPA) axis response to stress (Diorio *et al.*, 1993). Higher activation of the VMPFC is associated with reduced amygdala activity, diminished experience of negative emotions and better fear extinction learning (Diekhof *et al.*, 2011). The lateral parts of the PFC, the dorsolateral PFC (DLPFC) and the ventrolateral PFC (VLPFC) are associated with intentional or effortful emotion regulation by employing cognitive strategies, including (re)appraisal of emotional stimuli, response inhibition, attention regulation, and working memory (Phillips *et al.*, 2003; Steele and Lawrie, 2004; Wager *et al.*, 2008; Ochsner *et al.*, 2012; Buhle *et al.*, 2014; Kohn *et al.*, 2014; Etkin *et al.*, 2015; Morawetz *et al.*, 2017; Langner *et al.*, 2018). Yet, PFC structure and PFC functions are particularly vulnerable to the effects of acute and chronic stress (McEwen and Morrison, 2013; Arnsten, 2015; Radley *et al.*, 2015; Shields *et al.*, 2016). Moreover, stress and anxiety symptoms, characterized by exaggerated or context-inappropriate acute emotional response to stress, are clearly related to impaired PFC functioning (Bishop, 2007, 2009; Etkin and Wager, 2007; Basten *et al.*, 2011; Sylvester *et al.*, 2012; Grupe and Nitschke, 2013; Manber Ball *et al.*, 2013; Zilverstand *et al.*, 2017; Via *et al.*, 2018). Enhancing the regulatory function of the PFC could thus improve appropriate downregulation of stress-related emotions.

In addition to targeting PFC functioning with pharmacological (see, e.g. Harmer *et al.*, 2006; MacNamara *et al.*, 2016) and psychological treatments (see e.g. Browning *et al.*, 2010; Schweizer *et al.*, 2013; Goldin *et al.*, 2014; Carlisi and Robinson, 2018), non-invasive brain stimulation (NBS) may provide another means to modulate stress reactivity. Two widely used NBS techniques are repetitive transcranial magnetic (rTMS) and transcranial direct current stimulation (tDCS). With rTMS, magnetic pulses are delivered to the scalp that can increase or decrease neural excitability and shape synaptic plasticity in the underlying cortical areas. An increase in neural excitability is generally induced by high-frequency rTMS (pulse frequency ≥5 Hz), whereas a decrease in neural excitability is generally induced by low-frequency rTMS (pulse frequency 0.1–1 Hz) (Huang *et al.*, 2005; Fitzgerald *et al.*, 2006; Dayan *et al.*, 2013; Wischnewski and Schutter, 2015; Cirillo *et al.*, 2017). Theta burst stimulation (TBS) is a specific form of rTMS using trains of three 50 Hz pulses repeated every 200 ms. When delivery of these pulse trains is intermitted by 8-s pauses, neural excitability generally increases, while neural excitability generally decreases when the pulse trains are delivered continuously or prolonged (Gamboa *et al.*, 2010; Huang *et al.*, 2005). To control for placebo effects, active rTMS is compared to sham rTMS, where the rTMS coil is tilted or equipped with a magnetic shield to mimic the clicking sounds and, to some extent, the peripheral skin sensations without effective brain stimulation (Duecker and Sack, 2015). With tDCS, a weak electrical current (1–2.5 mA) is applied between two electrodes placed on the scalp that can change cortical excitability in a polarity-dependent fashion (Nitsche and Paulus, 2000). Anodal tDCS generally facilitates neural excitability and plasticity, while cathodal tDCS generally decreases neural excitability and plasticity (Liebetanz, 2002; Dayan *et al.*, 2013; Cirillo *et al.*, 2017). Active tDCS is commonly compared to sham tDCS, where the current is only ramped up and down at the beginning of the stimulation to mimic skin sensations without any effective stimulation of the brain (Ambrus *et al.*, 2012). When applied to the PFC, both rTMS and tDCS effects also influence brain regions that are distal but connected to the stimulated region, including contralateral prefrontal areas and limbic regions such as the amygdala (Shafi *et al.*, 2012). To illustrate the rTMS- and tDCS-induced electric field distributions over the cortical surface, Figure 1 depicts simulated images based on two examples of NBS montages that can be used for prefrontal NBS.

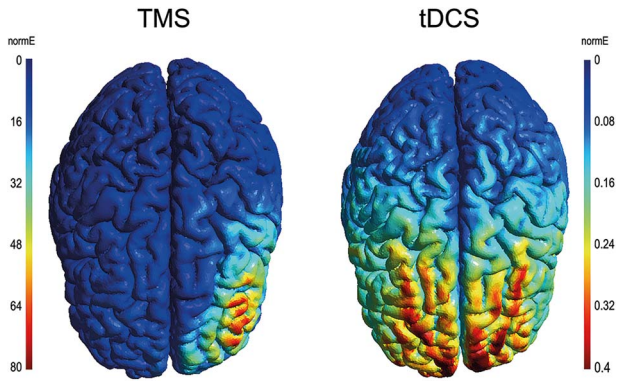

Fig. 1. Example of simulated images of induced electric fields by an rTMS and a tDCS montage (SimNIBS 2.1, Thielscher *et al.*, 2015). Note the difference in focality and magnitude of the electric fields induced by the two NBS techniques. The depicted rTMS-induced field simulation is based on a pulse with a current change of 40 A/µs, corresponding to 40% maximum stimulator output of a rapid rate stimulator, from a figure-of-eight double 70 mm coil placed over the 10–20 system electrode position F3 (left DLPFC). The depicted tDCS-induced field simulation is based on a direct current with an intensity of 2.0 mA flowing between a 5x7 cm anode and a 5x7 cm cathode, placed over electrode position F3 (left DLPFC) and Fp2, respectively.

Some evidence for the effectivity of rTMS and tDCS in modulating stress- and emotion-related processes comes from NBS interventions that have been carried out in the area of stress-related affective disorders. For example, applying rTMS over the DLPFC can reduce symptoms of depression (Schutter, 2010; Berlim *et al.*, 2013, 2014; Gaynes *et al.*, 2014), PTSD (Boggio *et al.*, 2010; Berlim and Van den Eynde, 2014; Philip *et al.*, 2016; Ahmadizadeh and Rezaei, 2018; Kozel *et al.*, 2018), and possibly also generalized anxiety and panic disorder (Mantovani *et al.*, 2013; Diefenbach *et al.*, 2016; Dilkov *et al.*, 2017; Assaf *et al.*, 2018; Vicario *et al.*, 2019). However, some studies showed no effects (Prasko *et al.*, 2007; Deppermann *et al.*, 2014), and uncertainties remain regarding the optimal rTMS settings, such as pulse frequency (Yan *et al.*, 2017) and target region (Ahmadizadeh and Rezaei, 2018). Effects of tDCS on stress-related symptoms have to date been investigated to a lesser extent than rTMS. Nonetheless, there is evidence that anodal tDCS over the left DLPFC reduces depressive symptoms (Shiozawa *et al.*, 2014). Moreover, two sham-controlled studies showed significantly reduced PTSD symptoms after interventions with bilateral tDCS over the DLPFC (Ahmadizadeh *et al.*, 2019) or anodal tDCS over the VMPFC during trauma exposure (van't Wout-Frank *et al.*, 2019). Further reports of tDCS effects on anxiety are summarized by Vicario *et al.* (2019).

Although these effects of NBS interventions on stress-related symptoms look promising, the evidence remains inconclusive and leaves unclear how NBS is influencing stress- and emotion-related processes. Therefore, NBS effects on

underlying biological and cognitive mechanisms of stress and emotion have been further examined in many experimental studies in healthy volunteers that investigate how acute stress-related processes are affected directly after NBS. Such studies showed, for example, that a single session of prefrontal NBS does not directly change baseline mood in healthy individuals (Remue *et al.*, 2016a). On the other hand, some prefrontal NBS methods, such as high-frequency rTMS and anodal tDCS to the DLPFC, influence cognitive processes that support the regulation of acute emotional stress reactions; applying these prefrontal NBS methods in a single session already enhances working memory performance (Preston *et al.*, 2010; Brunoni *et al.*, 2013; Bagherzadeh *et al.*, 2016), may adjust attentional bias to threat (Zwanzger *et al.*, 2009; Mondino *et al.*, 2015) and can modulate identification and retrieval of emotional information, response inhibition and risky decision-making (Levasseur-Moreau and Fecteau, 2012; Nitsche *et al.*, 2012; Balconi, 2013; Kuo and Nitsche, 2015; Mondino *et al.*, 2015; Bell and DeWall, 2018). Furthermore, a recent meta-analysis showed that a single session of high-frequency rTMS and, to a lesser extent, anodal tDCS to the PFC attenuates activity of the autonomic nervous system (Makovac *et al.*, 2017), which plays an important role in the acute physiological stress response.

Together, this suggests that prefrontal NBS could modulate how one responds to stress. Several NBS studies on emotional stress reactivity have already been performed, where NBS is applied either directly before or during a stress manipulation. Laboratory stress manipulations are typically used, such as exposing participants to aversive visual material like arousing pictures or movie clips with emotionally negative content. Because aversive stimulus viewing paradigms use symbolic representations of a stressor (e.g. pictures of mutilated bodies), these paradigms can be considered passive stress inductions. Other studies use psychosocial stress manipulations, such as the Trier social stress test (TSST) (Kirschbaum *et al.*, 1993) or social exclusion in the Cyberball game (Williams *et al.*, 2000). Aversive physical or auditory stimuli can also be used to induce stress, such as cold, heat or pain or electrical shocks and loud noises in fear-conditioning paradigms. All these laboratory stress manipulations increase feelings of unpleasantness and arousal and elicit immediate stress responses at the level of the sympathetic nervous system (Lang *et al.*, 1993; Zadro *et al.*, 2004; Bernat *et al.*, 2006; Lipp, 2006; van Stegeren *et al.*, 2008; Boyes and French, 2009; Gerdes *et al.*, 2010; Sijtsema *et al.*, 2011; Kelly *et al.*, 2012; Maruyama *et al.*, 2012; Allen *et al.*, 2014; Storm *et al.*, 2019). Stress responses at the level of the HPA axis can also be elicited, particularly by psychosocial stressors (Allen *et al.*, 2014; Helpman *et al.*, 2017), prolonged physical stressors (van Stegeren *et al.*, 2008), cognitive challenge stressors (Dickerson and Kemeny, 2004) and, to some extent, negative mood inductions (Ottowitz *et al.*, 2004; Gadea *et al.*, 2005; Root *et al.*, 2009). Reactivity to these stressors can be assessed on different facets. Next to behavioral and physiological reactivity, the subjective experience of emotions represents another aspect of the stress response (Denson *et al.*, 2009; Mauss and Robinson, 2009). Emotional experiences in response to these stress manipulations are usually measured by self-report on negative emotional state scales or questionnaires, assessed during or directly after the stress manipulation. Emotional reactivity can also be assessed by rating the perceived emotional content of aversive stimuli used in the stress manipulation (Lang *et al.*, 1993). Such laboratory stressors and emotional measurements provide a controlled environment to assess the direct effects of NBS on subjective emotional stress reactivity.

Individual NBS studies on emotional reactivity may use diverse NBS techniques, diverse stress manipulations and diverse measurement methods. The findings across these different studies could collectively demonstrate the immediate effects of NBS on global emotional reactivity and thereby provide insights into the usefulness of a single session of NBS in modulating affective stress responses. Therefore, we assembled all measurements of self-reported emotional responses to stress after a single session of prefrontal NBS from previous studies. This systematic review aims to provide an interim overview and quantification of the effects of rTMS and tDCS studies with healthy participants. Since effectiveness of rTMS and tDCS may diverge (Brunoni and Vanderhasselt, 2014; Makovac *et al.*, 2017) and pulse frequency or current polarity may determine the direction of effects, results of low- and high-frequency rTMS and of anodal and cathodal tDCS were considered separately. Where the sample size of studies in the analyses allowed, we additionally examined the quantitative influence of targeted hemisphere (left PFC *vs* right PFC) and type of stress (passive stress induction, psychosocial stress or physical or auditory stress).

Method

Literature search

The electronic databases MEDLINE, Web of Science Core Collection and Scopus were systematically searched for rTMS and tDCS studies assessing self-reported emotional state in response to a stress induction. We retrieved articles up to October 2019.

Our search contained the following terms: *non-invasive brain/cortical stimulation*, *transcranial brain stimulation*, *transcranial electrical/direct current stimulation*, *repetitive transcranial magnetic stimulation*, *theta burst stimulation*, *stress/stressor*, *threat*, *fear*, *anxiety/anxious*, *emotion/emotional and aggression/aggressive*. To concentrate on adult human studies, we added *human*, *individuals*, *participants*, *subjects*, *men*, *women, NOT child* and *NOT infant*. Because we focused on the PFC, we added *prefrontal*, *frontal* and *PFC*. The exact search terms per database are provided in Supplementary Material 1.

Literature review

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher *et al.*, 2015) and Cochrane Handbook (Higgins and Green, 2011) guided this quantitative review. First, two authors (FS and EG) independently reviewed titles and abstracts on suitability. Second, full text copies of the remaining articles were evaluated for inclusion, and study references were screened for further relevant articles. Discrepancies in judgement of eligibility were resolved by consensus (FS, EG and DS).

Eligibility criteria

Retrieved studies were selected if they fulfilled the following criteria:

(i) The report is published in a peer-reviewed journal.
(ii) The study design includes a control condition. Eligible control conditions are restricted to the commonly used methods to apply sham stimulation as described in the Introduction.
(iii) The study procedure includes a stress induction. A stress induction was defined as any adverse or demanding

condition that exposes participants to physical, psychosocial, mental (cognitive) or emotional stress. Emotional stress involves stimuli inducing negative stress-related emotions such as fear, anxiety or anger. Studies with sadness-inducing manipulations were also included because they elicit responses that resemble other negative emotion inductions (e.g. fear) in terms of amygdala reactivity (Phan *et al.*, 2002), sympathetic nervous system reactivity (Kreibig, 2010), HPA axis reactivity (Ottowitz *et al.*, 2004; Gadea *et al.*, 2005) and feelings of unpleasantness and arousal (Kreibig *et al.*, 2007).

(iv) The study procedure includes the application of rTMS or tDCS over the PFC, with the aim to modulate the outcome measure.

(v) The study aims to test NBS effects on emotional responses to a stress induction.

(vi) The study reports data of subjective negative emotional state measured within the time frame of NBS (after) effects, in response to the stress induction. This involves all kinds of self-report measures of negative emotional reactivity, including experienced negative emotions and perceived emotional content of negative stimuli (i.e. stimulus ratings). Stimulus ratings differ from ratings of experienced emotions in terms of perspective or reference (stimulus ratings are 'world-focused' while emotional experience ratings are 'self-focused'), but both ratings share features of emotional reactivity (Lang *et al.*, 1993; Quigley *et al.*, 2013).

(vii) The study participants are healthy adults (18–70 years of age).

(viii) The study report is written in English.

Data extraction and processing

To evaluate the effect of prefrontal NBS on emotional reactivity, we focused on outcomes of self-report scores of emotional state questions or questionnaires. Of studies that reported such emotional stress reactivity scores, we examined which NBS methods were applied, which prefrontal region and hemisphere was targeted, what type of stress was induced, which task or context was used in the experiment, which state or trait factors influenced the NBS effects, which NBS settings were applied (pulse/current intensity and quantity, sham condition; tDCS, location of reference electrode) and how and when the outcome was measured.

For additional quantitative analyses, mean scores of emotional reactivity and corresponding standard deviations for the active NBS and sham conditions were extracted from each paper, its Supplementary Materials or data provided by authors on request. If these data were presented in graphs, we extracted the numerical scores and corresponding standard deviations in Plot Digitizer (plotdigitizer.sourceforge.net). The emotional state scores assessed during or after NBS (final emotional state scores) were used as the outcome variable in our analyses. If final scores were not available, we used the change from baseline scores instead ($n = 3$), which theoretically addresses the same underlying effect as the final scores in randomized controlled studies (Higgins and Green, 2011). Higher scores corresponded to stronger negative emotion in most studies. If a reversed scale was used in the original study (i.e. higher scores corresponded to weaker emotion), group mean values were transformed to get in line with the other data by subtracting the original group mean values from the maximum score of the applied scale. Finally, Hedges' g effect size (Hedges, 1981) was calculated for each separate experiment or outcome with the R package Metafor (Viechtbauer, 2012; R Core Team, 2019). The correction for overestimating effect sizes in small study samples was applied (Hedges and Olkin, 1985), resulting in a corrected Hedges' g (also known as Hedges' d). Negative effect sizes following from these computations indicate that active NBS lowered negative emotional stress reactivity relative to the sham condition.

We estimated the weighted mean effect sizes in separate random effects models for studies using (i) high-frequency rTMS and intermittent TBS protocols, (ii) low-frequency rTMS, prolonged intermittent TBS and continuous TBS protocols, (iii) anodal tDCS protocols, and (iv) cathodal tDCS protocols. The majority of studies reported more than one experiment or outcome of emotional reactivity. To be complete, we included all emotional reactivity outcomes from each study. We controlled for the dependence among effect sizes from the same study by applying robust variance estimation (RVE) (Hedges *et al.*, 2010; Moeyaert *et al.*, 2017) using the R package Robumeta (Fisher and Tipton, 2015), Metafor (Viechtbauer, 2012) and ClubSandwich (Pustejovsky, 2018). With RVE, a covariance matrix is estimated for correlated effects. Weighted mean effect sizes were also corrected for small samples of studies (Tipton, 2015). Second, we investigated if target hemisphere (left PFC *vs* right PFC) and type of stress induction (passive stress induction *vs* psychosocial stress *vs* aversive physical or auditory stress) influenced the effect of prefrontal NBS on emotional reactivity by adding these factors as categorical moderators to the model. The target hemisphere for tDCS was defined as the hemisphere that was the intended target of the original study, or, in case of a bipolar electrode montage, the hemisphere that was targeted by the anodal electrode. Moderator analyses were only carried out if each subgroup in the analysis contained data from at least four different studies.

Quality and risk of bias assessment

Methodological quality of each study was scored based on adequate reporting, external and internal validity and possible confounders, according to the study quality assessment tool for interventions in health care (Downs and Black, 1998). Additionally, risk of bias in the method and concealment of group allocation, blinding, selective outcome reporting and other sources of potential bias (e.g. conflicts of interest) were assessed according to the tool of Hartling *et al.* (2012). We assessed risk of publication bias by visually inspecting asymmetry in funnel plots of effect sizes against their standard errors for samples with at least 10 different studies. Funnel plot asymmetry was also formally tested by an Egger's regression test.

Results

The systematic literature search yielded 419 studies (Figure 2). We added 10 studies identified from the references of the retrieved articles. After removing duplicate research, the titles and abstracts of 424 studies were screened for eligibility. Of these, 125 potentially relevant articles were selected for full text evaluation, including 50 studies that fulfilled the eligibility criteria. This final set contained 40 (80%) studies that reported or provided on request the numerical data of emotional state measures or emotional stimulus ratings, including 118 separate outcomes.

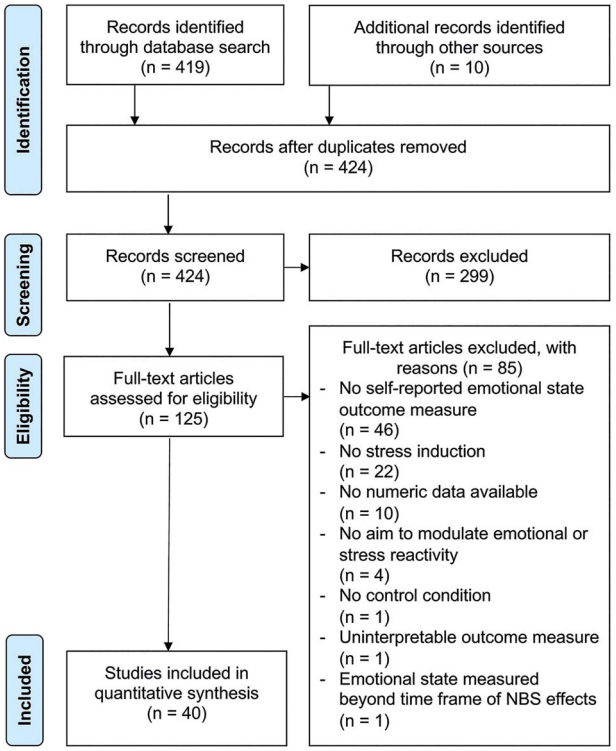

Fig. 2. PRISMA flow diagram.

Study characteristics

All included studies were performed in healthy young individuals who were free from current psychiatric or neurological conditions. The majority of studies used mixed gender samples, except for seven exclusively female study samples and four exclusively male study samples. Other study details can be found in Tables 1 and 2. All stimulation-related changes in emotional stress reactivity discussed below are described in comparison with results from sham conditions.

rTMS

High-frequency rTMS and intermittent TBS. We identified 5 high-frequency rTMS studies and 2 intermittent TBS studies that reported in total 12 different outcomes on emotional stress reactivity. The majority of these studies focused on the DLPFC. Two studies found no effect of 20 Hz rTMS or intermittent TBS over the left DLPFC on emotional responses to psychosocial stress (Baeken *et al.*, 2014; De Witte *et al.*, 2020), and two other studies found no effect of 10 Hz rTMS over the right DLPFC on ratings of perceived emotional content (Berger *et al.*, 2017) or experienced negative emotion (Jansen *et al.*, 2019) in response to aversive pictures. Two studies did find a significant effect of NBS over the DLPFC on emotional stress reactivity. Notzon *et al.* (2018), who targeted the right DLPFC, found a decrease in perceived negative valence and arousal of fearful face pictures after intermittent TBS. Möbius *et al.* (2017), who instead targeted the left DLPFC, found an *increase* in experienced sadness after watching sad movie clips following 10 Hz rTMS. Please note that, different from the other stress manipulations, this stress manipulation is limited to inducing sadness. The VMPFC was targeted in one study with 10 Hz rTMS (Guhn *et al.*, 2014) which effectively reduced emotional responses to fear-conditioned stimuli during extinction learning. For further details on stimulation parameters, type of stress and experimental context of each study (Table 1).

The data from this sample of studies ($k = 7$, $n = 251$) showed moderate heterogeneity ($I^2 = 49.0\%$), and the summary analysis estimated a weighted mean effect of $g = -0.06$, $CI_{95\%} = [-0.35, 0.24]$, $P = 0.70$. Based on these few studies, this analysis showed no significant main effect, and the low statistical power prevented further analysis of potential moderators.

Low-frequency rTMS, prolonged intermittent TBS and continuous TBS. We identified 4 low-frequency rTMS studies, 1 continuous TBS study and 1 prolonged intermittent TBS study that reported in total 14 different outcomes on emotional stress reactivity. All these studies focused on the DLPFC (see Table 1 for further study details). Three of the low-frequency rTMS studies targeting the right or left DLPFC found no effect on perceived emotional content of negative pictures or on biologically induced panic (Zwanzger *et al.*, 2007, 2014; Berger *et al.*, 2017). The fourth low-frequency rTMS study (Fitzgibbon *et al.*, 2017) also showed no group-level differences, but did find a link between a higher aversive impact of social exclusion in the Cyberball game and higher trait personal distress after active 1 Hz rTMS to the left DLPFC, but not after sham rTMS. The authors interpret this finding in terms of brain-state dependency of rTMS effects; rTMS may have amplified emotional reactivity only in those who are more sensitive to interpersonal stress.

Of the two studies using continuous or prolonged intermittent TBS, Hurlemann *et al.* (2015) found no effects of left DLPFC or left DMPFC stimulation on perceived emotional content of negative stimuli, while Keuper *et al.* (2018) showed that participants perceived negative pictures as less negative and less arousing after continuous TBS to the right DLPFC.

Together, the data from these studies ($k = 6$, $n = 207$) showed low heterogeneity ($I^2 = 14.3\%$). The summary analysis estimated a weighted mean effect of $g = -0.13$, ($CI_{95\%} = [-0.42, 0.16]$, $P = 0.39$). Also here, the low number of studies in this sample did not allow further moderator analyses.

tDCS

Anodal tDCS. We identified 26 anodal tDCS studies that reported in total 79 different outcomes on emotional stress reactivity (see Table 2 for study details). Of the studies focusing on the DLPFC, six studies targeting the left DLPFC (Brunoni *et al.*, 2013; Vierheilig *et al.*, 2016; Baeken *et al.*, 2018; Deldar *et al.*, 2018; Voss *et al.*, 2019) or right DLPFC (Brunoni *et al.*, 2013; Bogdanov and Schwabe, 2016; Vierheilig *et al.*, 2016) found no tDCS effects on emotional stress reactivity. This number includes the study of Baeken *et al.* (2018) who additionally reported no relationship between a measure of psychosocial stress sensitivity and psychosocial stress reactivity on the level of emotional experience (Dedoncker *et al.*, 2019). In contrast, six other studies targeting the left DLPFC (Boggio *et al.*, 2009; Peña-Gómez *et al.*, 2011; Maeoka *et al.*, 2012; Rêgo *et al.*, 2015; Carnevali *et al.*, 2019) or right DLPFC (Rêgo *et al.*, 2015) did find a significant decline in emotional stress reactivity after tDCS or at least in a subset of emotional outcomes (Plewnia *et al.*, 2015). Hence, in half of the studies targeting the DLPFC, anodal tDCS lowered emotional stress reactivity, while the other half of the studies showed no significant effects on similar outcomes. Focusing on the VLPFC, one study found no effect of anodal tDCS to the right VLPFC on emotional responses to threat of shock (Herrmann *et al.*, 2018),

Table 1. Characteristics of included rTMS studies

Reference	Design, sample size n(active) | n(control)	Coil position (localization method)	Stimulation frequency, quantity, intensity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
HF-rTMS							
Studies with passive stress induction							
Möbius *et al.* (2017)	Within-subjects, 23 | ~	Left DLPFC (F3, 10–20)	10 Hz, 3000 pulses, 110% rMT	Coil tilted 45°	Stress induction: 5 min after stimulation; measure: immediately after stress induction	Watching sad movie clips	Sadness (Likert: 1–10), PANAS-negative affect
Berger *et al.* (2017) (I)	Within-subjects (females only), 20 | ~	Right DLPFC (5 cm anterior to rMT region)	10 Hz, 900 pulses, 110% rMT	Sham coil	Stress induction: 10 min after stimulation; measure: during stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1–9)
Jansen *et al.* (2019)	Between-subjects, 18 | 18	Right DLPFC (neuronavigation to individual activation peak during emotion regulation)	10 Hz, 3000 pulses, 110% rMT	Coil tilted 90°	Stress induction: directly after stimulation; measure: during stress induction	Watching negative IAPS pictures	Negative emotional experience (VAS: 0–100)
Studies with psychosocial stress							
Baeken *et al.* (2014)	Within-subjects (females only), 31 | ~	Left DLPFC (middle frontal gyrus, neuronavigation)	20 Hz, 1560 pulses, 110% rMT	Coil tilted 90°	Stress induction: 5–10 min after stimulation; measure: immediately after stress induction	Mental counting task with bogus negative feedback	Anger and depression scales of POMS (VAS: 0–100)
Studies with aversive physical or auditory events							
Guhn *et al.* (2014)	Between-subjects, 32 | 30	Right VMPFC (NIRS channel 26)	10 Hz, 1560 pulses, 110% rMT	Sham coil	Fear acquisition before stimulation, fear extinction after stimulation; measure: 5–10 min after stimulation, during fear extinction	Fear extinction learning with 95 dB aversive screams	Subjective arousal and valence[b] in response to fear-conditioned stimulus (SAM: 1–9)
iTBS							
Studies with passive stress induction							
Notzon *et al.* (2018)	Between-subjects, 21 | 20	Right DLPFC (F4, 10–20)	iTBS, 600 pulses, 80% rMT	Coil tilted 90°	Stress induction: 5–10 min after stimulation; measure: 5 min after stress induction	Watching fearful face pictures	Perceived picture arousal and valence (SAM: 1–9)
Studies with psychosocial stress							
De Witte *et al.* (2020)	Within-subjects (females only), 38 | ~	Left DLPFC (middle frontal gyrus, neuronavigation)	iTBS, 1620 pulses, 110% rMT	Sham coil	Stress induction: before stimulation; measure: immediately after stimulation	TSST	Anger and depression scales of POMS (VAS: 0–100)

(Continued)

Table 1. Continued

Reference	Design, sample size n(active) | n(control)	Coil position (localization method)	Stimulation frequency, quantity, intensity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
LF-rTMS							
Studies with passive stress induction							
Zwanzger *et al.* (2014)	Between-subjects, 20 | 19	Right DLPFC (5 cm anterior to rMT region)	1 Hz, 1800 pulses, 120% rMT	Coil tilted 90°	Stress induction: 5–10 min after stimulation; measure: 5 min after stress induction	Watching fearful face pictures	Perceived picture arousal and valence (SAM: 1–9)
Berger *et al.* (2017) (II)	Within-subjects (females only), 20 | ~	Right DLPFC (5 cm anterior to rMT region)	1 Hz, 900 pulses, 110% rMT	Sham coil	Stress induction: 10 min after stimulation; measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1–9)
Studies with psychosocial stress							
Fitzgibbon *et al.* (2017)	Between-subjects, 16 | 13	Left DLPFC ('Beam F3')	1 Hz, 1200 pulses, 120% rMT	Coil tilted 90°	Stress induction: immediately after stimulation; measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Aversive impact scale
Studies with aversive physical or auditory events							
Zwanzger *et al.* (2007)	Within-subjects, 11 | ~	Right DLPFC (5 cm anterior to rMT region)	1 Hz, 1800 pulses, 120% rMT	Sham coil	Stress induction: immediately after stimulation; measure: immediately after stress induction	Panic attack induced by CCK-4 administration	Panic symptoms (API, PSS)
cTBS							
Studies with passive stress induction							
Keuper *et al.* (2018)	Between-subjects, 24 | 24	Right DLPFC (F4, 10–20)	cTBS, 600 pulses, 80% rMT	Control site stimulation (Cz, 10–20)	Stress induction: immediately after stimulation; measure: 5–10 min after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (VAS: 0–100)
Prolonged iTBS							
Studies with passive stress induction							
Hurlemann *et al.* (2015) (I)	Between-subjects (males only), 20 | 20[a]	Left DLPFC (middle frontal gyrus, neuronavigation)	iTBS, 1200 pulses, 80% rMT	Sham coil	Stress induction: immediately after stimulation; measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1–9)
Hurlemann *et al.* (2015) (II)	Between-subjects (males only), 20 | 20[a]	Left DMPFC (superior frontal gyrus, neuronavigation)	iTBS, 1200 pulses, 80% rMT	Sham coil	Stress induction: immediately after stimulation; measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1–9)

[a]Samples used for multiple experiments within a study. [b]Measures that are not included in the meta-analysis due to insufficient available numerical data. 10–20 = 10–20 system for localizing scalp electrodes; API = acute panic inventory (Fyer *et al.*, 2002); 'Beam F3' = freeware to determine location of DLPFC (Beam *et al.*, 2009); Cyberball = Cyberball game (Williams *et al.*, 2000); cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; IAPS = International Affective Picture System (Lang *et al.*, 1997); Likert = Likert scale; MDMQ = Multidimensional Mood State Questionnaire (Steyer *et al.*, 2004); NIRS = near infrared spectroscopy; PANAS = Positive and Negative Affect Schedule (Watson *et al.*, 1988); PMFC = posterior medial frontal cortex; POMS = Profile of Mood States (McNair *et al.*, 1971); PSS = Panic Symptom Scale (Argyle *et al.*, 1991); rMT = resting motor threshold; SAM = Self-Assessment Manikin.

Table 2. Characteristics of included tDCS studies

Reference	Design, sample size n(active) | n(control)	Electrode positions (localization method)	Current intensity, anode + cathode size, quantity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
A-tDCS							
Studies with passive stress induction							
Boggio *et al.* (2009)	Within-subjects, 23 | ~	Left DLPFC (anode, F3; cathode, Fp2, 10–20)	2 mA, 35 + 35 cm^2, 5 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching pictures of human pain	Perceived picture valence and emotional discomfort (Likert: 1–9)
Peña-Gómez *et al.* (2011) (I)	Within-subjects (females only), 16 | ~	Left DLPFC (anode, F3; cathode, C4, 10–20)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures	Perceived picture valence (Likert: 1–9)
Maeoka *et al.* (2012)	Within-subjects, 15 | ~	Left DLPFC (anode, F3; cathode, Fp2, 10–20)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: immediately after stimulation; measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal[b] and valence (SAM: 1–9)
Brunoni *et al.* (2013) (I)	Within-subjects, 20 | ~[a]	Left DLPFC (anode, F3; cathode, F4, 10–20)	1.5 mA, 35 + 35 cm^2, 33 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures	Negative mood and state anxiety (VAS: 0–100)
Brunoni *et al.* (2013) (II)	Within-subjects, 20 | ~[a]	Right DLPFC (anode, F4; cathode, F3, 10–20)	1.5 mA, 35 + 35 cm^2, 33 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures	Negative mood and state anxiety (VAS: 0–100)
Feeser *et al.* (2014)	Between-subjects, 21 | 21	Right DLPFC (anode, F4; cathode, Fp1, 10–20)	1.5 mA, 35 + 100 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective arousal in response to pictures (Likert: 1–9), depressed mood (MDMQ)
Rêgo *et al.* (2015) (I)	Between-subjects, 8 | 8[c]	Left DLPFC (anode, F3; cathode, F4, 10–20)	2 mA, 35 + 35 cm^2, 15 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during and immediately after stimulation	Watching videos of human pain	Subjective arousal and valence in response to videos (SAM: 1–9), mood scales: alert[b], confused[b], attentive[b], sad; hostile (VAS: 0–9)
Rêgo *et al.* (2015) (II)	Between-subjects, 8 | 8[c]	Right DLPFC (anode, F4; cathode, F3, 10–20)	2 mA, 35 + 35 cm^2, 15 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during and immediately after stimulation	Watching videos of human pain	Subjective arousal and valence in response to videos (SAM: 1–9), mood scales: alert[b], confused[b], attentive[b], sad; hostile (VAS: 0–9)

(Continued)

Table 2. Continued.

Reference	Design, sample size n(active) | n(control)	Electrode positions (localization method)	Current intensity, anode + cathode size, quantity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
Vierheilig *et al.* (2016) (I)	Between-subjects, 18 | 18[c]	Left DLPFC (anode, F3; cathode, F4, 10–20)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 20 s	Stress induction: during stimulation; measure: immediately after stress induction	Watching negative IAPS mutilation pictures	Perceived picture valence[b] and arousal (SAM: 1–9), PANAS-negative affect
Vierheilig *et al.* (2016) (II)	Between-subjects, 16 | 18[c]	Right DLPFC (anode, F4; cathode, F3, 10–20)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 20 s	Stress induction: during stimulation; measure: immediately after stress induction	Watching negative IAPS mutilation pictures	Perceived picture valence[b] and arousal (SAM: 1–9), PANAS-negative affect
Chen *et al.* (2017)	Between-subjects, 23 | 25	Left DLPFC (anode, F3, 10–20; cathode, left neck)	2 mA, 24 + 24 cm^2, 20 min	Current ramped down after 60 s	Stress induction: immediately after stimulation; measure: immediately after stress induction	Watching real-life threat and neutral videos	STAI-6
Voss *et al.* (2019) (I)	Between-subjects (females only), 40 | 40[c]	Left DLPFC (anode, F3, 10–20; cathode, right shoulder)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: immediately after stimulation; measure: 10 min after stress induction	Watching sexual and physical abuse video	Subjective arousal and negative mood in response to videos (SAM: 1–9)
Marques *et al.* (2018) (I)	Between-subjects, 30 | 30[c]	Left DLPFC (anode, F3; cathode, F4, 10–20)	1.5 mA, 16 + 16 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1–9), PANAS-negative affect[b]
Marques *et al.* (2018) (II)	Between-subjects, 30 | 30[c]	Right DLPFC (anode, F4; cathode, F3, 10–20)	1.5 mA, 16 + 16 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1–9), PANAS-negative affect[b]
He *et al.* (2018) (I)	Between-subjects, 23 | 21	Right VLPFC (anode, F6; cathode, Fp1, 10–20)	2.5 mA, 25 + 25 cm^2, 24 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching pictures of social exclusion, with and without downregulation instructions	Perceived negative emotion in picture (Likert: 1–9)
He *et al.* (2018) (II)	Between-subjects, 20 | 20	Right VLPFC (anode, F6; cathode, Fp1, 10–20)	2.5 mA, 25 + 25 cm^2, 24 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching pictures of social exclusion, with and without downregulation instructions	Perceived negative emotion in picture (Likert: 1–9)

(Continued)

Table 2. Continued.

Reference	Design, sample size n(active) | n(control)	Electrode positions (localization method)	Current intensity, anode + cathode size, quantity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
Marques *et al.* (2018) (III)	Between-subjects, 29 | 30[d]	Left VLPFC (anode, F7; cathode, F8, 10–20)	1.5 mA, 16 + 16 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1–9), PANAS-negative affect[b]
Marques *et al.* (2018) (IV)	Between-subjects, 30 | 30[d]	Right VLPFC (anode, F8; cathode, F7, 10–20)	1.5 mA, 16 + 16 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1–9), PANAS-negative affect[b]
Vergallito *et al.* (2018)	Between-subjects, 49 | 47	Right VLPFC (anode, F6; cathode, Fp1, 10–20)	1.5 mA, 25 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative emotion inducing videos	Five negative emotion DES (Likert: 1–10)
Koenigs *et al.* (2009) (I)	Within-subjects, 21 | ~[a]	Bilateral VMPFC (anodes, Fp1 + Fp2, 10–20; cathode, non-dominant arm)	2.5 mA, 25 + 25 cm^2, 35 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative and positive IAPS pictures	Subjective arousal in response to pictures (Likert: 1–7), anger and depression scales of POMS (Likert: 1–5) (change score relative to baseline)
Abend *et al.* (2018)	Within-subjects, 16 | ~	VMPFC (anode, above nasion; cathode, beneath inion)	1.5 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during and after stimulation	Watching frightening or violent videos	Subjective emotion intensity (Likert: 1–4), anxiety (VAS: 0–30)
Studies with psychosocial stress							
Hortensius *et al.* (2012) (I)	Between-subjects, 21 | 19[c]	Left DLPFC (anode, F3; cathode, F4, 10–20)	2 mA, 35 + 35 cm^2, 15 min	Current ramped down after 40 s	Stress induction: before stimulation; measure: 5–10 min after stimulation	Essay writing with negative social feedback	Anger (Likert: 1–5) (change score relative to baseline)
Hortensius *et al.* (2012) (II)	Between-subjects, 20 | 19[c]	Right DLPFC (anode, F4; cathode, F3, 10–20)	2 mA, 35 + 35 cm^2, 15 min	Current ramped down after 40 s	Stress induction: before stimulation; measure: 5–10 min after stimulation	Essay writing with negative social feedback	Anger (Likert: 1–5) (change score relative to baseline)
Riva *et al.* (2012)	Between-subjects, 19 | 19	Right VLPFC (anode, F8; cathode, Fp1, 10–20)	1.5 mA, 25 + 35 cm^2, 15 min	Current ramped down after 15 s	Stress induction: during stimulation; measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Unpleasantness (Likert: 1–10)

(Continued)

Table 2. Continued.

Reference	Design, sample size n(active) | n(control)	Electrode positions (localization method)	Current intensity, anode + cathode size, quantity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
Kelley *et al.* (2015) (I)	Between-subjects, 14 | 16[c]	Left DLPFC (anode, F3; cathode, F4, 10–20)	2 mA, 35 + 35 cm^2, 15 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Jealousy (Likert: 1–9)
Kelley *et al.* (2015) (II)	Between-subjects, 15 | 16[c]	Right DLPFC (anode, F4; cathode, F3, 10–20)	2 mA, 35 + 35 cm^2, 15 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Jealousy (Likert: 1–9)
Plewnia *et al.* (2015)	Between-subjects (males only), 14 | 14	Left DLPFC (anode, F3, 10–20; cathode, right shoulder)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: 5 min after stimulation + 20 min after stimulation; measure: immediately after second stress induction	Frustrating mental counting task (PASAT)	PANAS-negative affect
Bogdanov and Schwabe (2016) (I)	Between-subjects, 20 | 20[c]	Right DLPFC (anode, F4; cathode, Cz, 10–20)	1.075 mA, 25 + 100 cm^2, 6–10 min	Current ramped down after 13 s	Stress induction: 20 min before stimulation; measure: immediately after stimulation	TSST	Depressed mood (MDMQ)
Baeken *et al.* (2018)	Within-subjects (females only), 28 | ~	Left DLPFC (anode, middle frontal gyrus, neuronavigation; cathode, Fp2, 10–20)	1.5 mA, 25 + 25 cm^2, 20 min	Current ramped down after 30 s	Stress induction: 5 min after stimulation; measure: immediately after stress induction	Hearing verbal criticism	Anger and depression scales of POMS (VAS: 0–100)
Carnevali *et al.* (2019)	Between-subjects (males only), 15 | 15	Left DLPFC (anode, F3, 10–20; cathode, F4)	2 mA, 35 + 35 cm^2, 15 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: 30 min after stress induction	Stressful interview and arithmetic task	STAI-state
Antal *et al.* (2014) (I)	Between-subjects (males only), 20 | 20[c]	Right VMPFC (anode, between F2-Fpz; cathode, between O2-P4, 10–20)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: immediately after stimulation; measure: immediately after stress induction	TSST	STAI-state (change score relative to baseline)
Studies with aversive physical or auditory events							
Deldar *et al.* (2018)	Within-subjects, 20 | ~	Left DLPFC (anode, F3, 10–20; cathode, right shoulder)	2 mA, 35 + 35 cm^2, 22 min	Current ramped down after 46 s	Stress induction: during stimulation; measure: during stimulation	Pain by electrical stimulation with and without concurrent cognitive (working memory) task	State anxiety (NRS: 0–100)
Herrmann *et al.* (2018)	Between-subjects, 31 | 49	Right VLPFC (anode, 1.5 cm posterior to F6; cathode, 1.5 cm from Fp1 towards Fpz, 10–20)	2 mA, 35 + 35 cm^2, 20 min	Current ramped down after 20 s	Stress induction: during stimulation; measure: immediately after stress induction	Sustained threat paradigm with 98 dB aversive screams	Subjective valence, arousal and anxiety in response to threat-associated stimulus (Likert: 1–9), STAI-state, PANAS-negative affect

(Continued)

Table 2. Continued.

Reference	Design, sample size n(active) | n(control)	Electrode positions (localization method)	Current intensity, anode + cathode size, quantity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
Abend *et al.* (2016)	Between-subjects, 15 | 14	VMPFC (anode, above nasion; cathode, beneath inion)	1.5 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Fear acquisition before stimulation, fear extinction during stimulation; measure: immediately after extinction	Fear extinction learning after conditioning with 80 dB aversive screams	Conditioned stimulus fear (Likert: 1–10)
Dittert *et al.* (2018) (I)	Between-subjects, 40 | 27	Right VMPFC (anode, beneath F8; cathode, beneath F7, 10–20)	1.5 mA, 16 + 16 cm^2, 20 min	Current ramped down after 60 s	Fear acquisition before stimulation, fear extinction during stimulation; measure: during stimulation, during extinction	Fear extinction learning after conditioning with 95 dB aversive screams	STAI-state, PANAS-negative affect, subjective valence[b] and arousal[b] in response to fear-conditioned stimulus (Likert: 1–9)
Dittert *et al.* (2018) (II)	Between-subjects, 37 | 26	Left VMPFC (anode, beneath F7; cathode, beneath F8, 10–20)	1.5 mA, 16 + 16 cm^2, 20 min	Current ramped down after 60 s	Fear acquisition before stimulation, fear extinction during stimulation; measure: during stimulation, during extinction	Fear extinction learning after conditioning with 95 dB aversive screams	STAI-state, PANAS-negative affect, subjective valence[b] and arousal[b] in response to fear-conditioned stimulus (Likert: 1–9)
C-tDCS							
Studies with passive stress induction							
Peña-Gómez *et al.* (2011) (II)	Within-subjects (females only), 9 | ~	Left DLPFC (cathode, F3; anode, C4, 10–20)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative IAPS pictures	Perceived picture valence (Likert: 1–9)
Voss *et al.* (2019) (II)	Between-subjects (females only), 38 | 40[c]	Left DLPFC (cathode, F3, 10–20; anode, right shoulder)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: immediately after stimulation; measure: 10 min after stress induction	Watching sexual and physical abuse video	Subjective arousal and negative mood in response to videos (SAM: 1–9)
Koenigs *et al.* (2009) (II)	Within-subjects, 21 | ~[a]	Bilateral VMPFC (cathodes, Fp1 + Fp2, 10–20; anode, non-dominant arm)	2.5 mA, 25 + 25 + 25 cm^2, 35 min	Current ramped down after 30 s	Stress induction: during stimulation; measure: during stimulation	Watching negative and positive IAPS pictures	Subjective arousal in response to pictures (Likert: 1–7), anger and depression scales of POMS (Likert: 1–5) (change score relative to baseline)

(Continued)

Table 2. Continued.

Reference	Design, sample size n(active) | n(control)	Electrode positions (localization method)	Current intensity, anode + cathode size, quantity	Control condition	Timing stress induction; timing outcome measure	Task/stress induction	Outcome measure
Studies with psychosocial stress							
Riva *et al.* (2015)	Between-subjects, 20 | 20	Right VLPFC (cathode, F6; anode, Fp1, 10–20)	1.5 mA, 25 + 35 cm^2, 20 min	Current ramped down after 15 s	Stress induction: during stimulation; measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Negative emotions (Likert: 1–10)
Bogdanov and Schwabe (2016) (II)	Between-subjects, 20 | 20[c]	Right DLPFC (cathode, F4; anode, Cz, 10–20)	1.075 mA, 25 + 100 cm^2, 6–10 min	Current ramped down after 13 s	Stress induction: 20 min before stimulation; measure: immediately after stimulation	TSST	Depressed mood (MDMQ)
Antal *et al.* (2014) (II)	Between-subjects (males only), 20 | 20[c]	Right VMPFC (cathode, between F2-Fpz; anode, between O2-P4, 10–20)	1 mA, 35 + 35 cm^2, 20 min	Current ramped down after 30 s	Stress induction: immediately after stimulation; measure: immediately after stress induction	TSST	STAI-state (change score relative to baseline)
Studies with aversive physical or auditory events							
Ganho-Ávila *et al.* (2019)	Between-subjects (females only), 27 | 16	Right DLPFC (cathode, F4; anode, left shoulder, 10–20)	1 mA, 24.75 + 24.75 cm^2, 20 min	Current ramped down after 30 s	Stress induction: fear acquisition 24 h before stimulation, fear reinstatement immediately before stimulation; measure: immediately after stimulation, before and after fear extinction learning.	Fear-conditioning and extinction learning with 95 dB aversive screams	Subjective valence and arousal in response to fear-conditioned stimulus (Likert: 1–9)

[a]Samples used for multiple experiments within a study. [b]Measures that are not included in the meta-analysis due to insufficient available numerical data. [c,d]Active stimulation conditions that are compared to the same placebo group. 10–20 = 10–20 system for localizing scalp electrodes; A-tDCS = anodal tDCS: tDCS with the anode placed over the target brain region; C-tDCS = cathodal tDCS: tDCS with the cathode placed over the target brain region; Cyberball = a virtual ball-toss game used to study social exclusion (Williams *et al.*, 2000); DES = Differential Emotions Scale (Schaefer *et al.*, 2010); IAPS = International Affective Picture System (Lang *et al.*, 1997); Likert = Likert scale; MDMQ = Multidimensional Mood State Questionnaire (Steyer *et al.*, 2004); NRS = Numerical Rating Scale; PANAS = Positive and Negative Affect Schedule (Watson *et al.*, 1988); PASAT = Paced Auditory Serial Addition Test (Lejuez *et al.*, 2003); POMS = Profile of Mood States (McNair *et al.*, 1971); SAM = Self-Assessment Manikin; STAI = State and Trait Anxiety Inventory (Spielberger *et al.*, 1970), STAI-6 is the 6-item short form of the STAI-State; VAS = visual analogue scale.

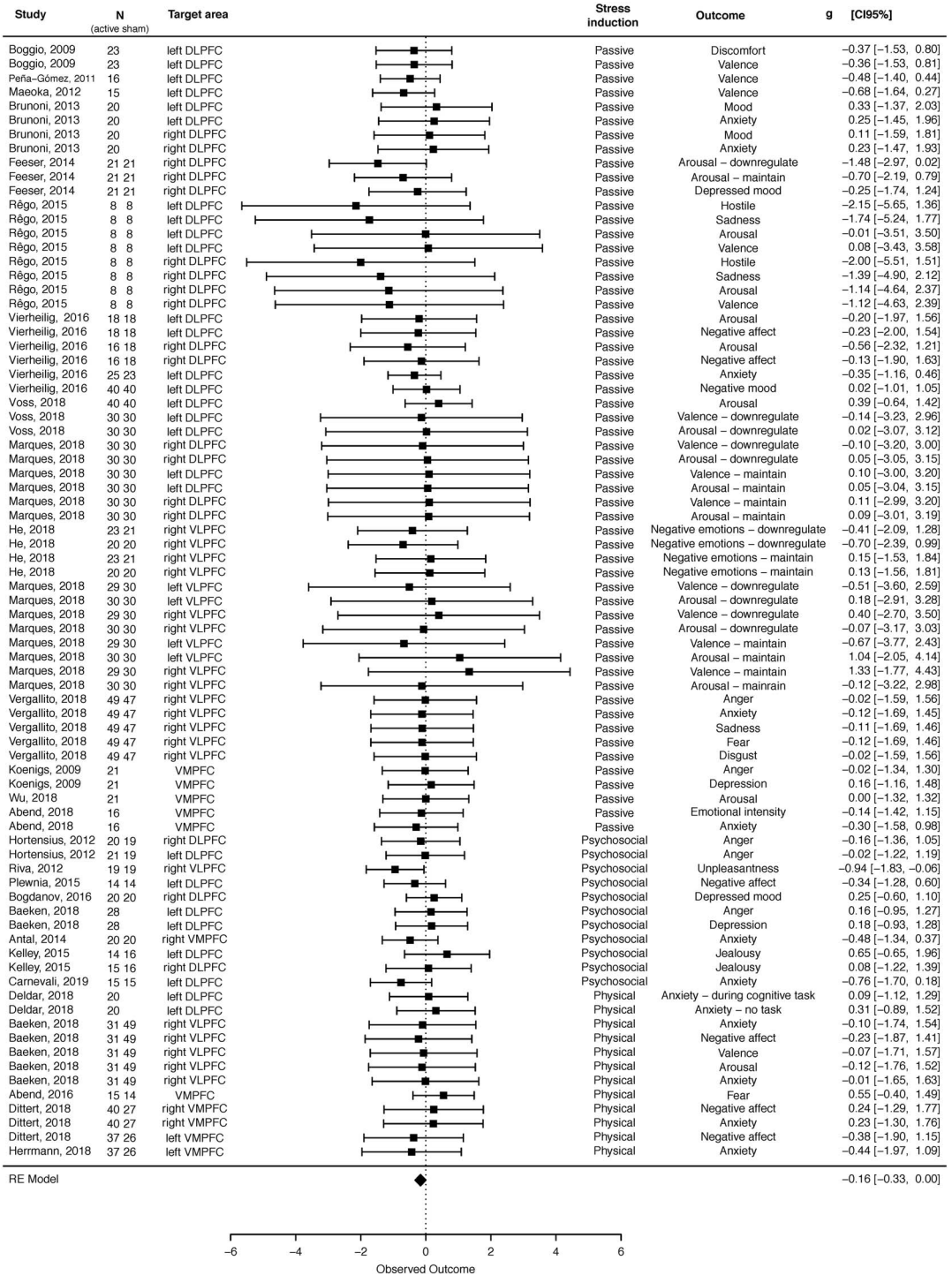

Fig. 3. Forest plot of the separate outcomes of anodal tDCS studies. The figure additionally depicts for each study the sample sizes of active tDCS and sham tDCS conditions (sham sample size is left blank for crossover studies), the target area for anodal stimulation, the type of stress induction in the experiment and the outcome measure.

while two studies of anodal tDCS to the same region found significantly weaker negative emotional experience in response to psychosocial stress or aversive pictures (Riva *et al.*, 2012; Vergallito *et al.*, 2018). The VMPFC was targeted in three studies, of which two showed no tDCS effects on experienced emotions after psychosocial stress or watching aversive pictures (Koenigs *et al.*, 2009; Antal *et al.*, 2014). The third study did find support for tDCS being able to significantly reduce emotional experience in response to aversive pictures (Abend *et al.*, 2018). Furthermore, a number of studies found interesting indirect anodal tDCS effects on emotional reactivity. Three studies showed that anodal tDCS only reduced emotional reactivity when participants actively downregulated their emotions, but not when participants maintained their natural emotional responses (Feeser *et al.*, 2014; He *et al.*, 2018; Marques *et al.*, 2018). The first two studies showed these effects after placing the anode over the right DLFPC or

right VLPFC (Feeser *et al.*, 2014; He *et al.*, 2018), but the third study (Marques *et al.*, 2018) only found significant effects after anodal stimulation of the left VLPFC with the cathode placed on the contralateral VLPFC, but not with the reversed montage or when the bilateral montage was placed over the DLPFC. In addition, Chen *et al.* (2017) showed that anodal tDCS to the left DLPFC reduced attention bias towards threat videos, which was, in turn, associated with less emotional reactivity to these videos.

With regard to location of the reference electrode, the above described studies did not show a clear influence of cathode location on the effect of anodal stimulation (see Table 2 for cathode locations per study). Yet, a number of studies do show different effects of tDCS with different montages. For example, Dittert *et al.* (2018) found that bilateral VMPFC stimulation with the anode over the left VMPFC, but not the reversed montage, enhanced fear extinction learning, i.e. reduced fear for the conditioned stimulus when the unconditioned threat stimulus (aversive loud scream) was no longer presented. In contrast, Abend *et al.* (2016), who stimulated the VMPFC by placing the anode over the forehead and the cathode on the back of the head, found that tDCS *inhibited* fear extinction learning. Hortensius *et al.* (2012), who found no group-level differences in anger after negative social feedback, showed that a correlation between increased anger and more aggressive behavioral responses only appeared after bilateral DLPFC stimulation with the anode over the left DLPFC, but not after stimulation with the reversed montage. Similarly, Kelley *et al.* (2015) found that bilateral DLPFC stimulation with the anode over the left DLPFC, but not with the anode over the right DLPFC, increased jealousy after social exclusion in the Cyberball game.

Together, the data from these studies ($k = 26$, $n = 1284$) showed moderate heterogeneity ($I^2 = 48.59\%$). The full random effects model showed a statistically significant weighted mean effect size of $g = -0.16$, $CI_{95\%} = [-0.33, 0.00]$, $P = 0.05$ (Figure 3), indicating that anodal tDCS lowers emotional stress reactivity compared to sham tDCS. This effect was not significantly moderated by type of stress ($Q(3) = 5.56$, $P = 0.14$). The moderation of the effect by target hemisphere approached significance ($Q(2) = 4.95$, $P = 0.08$). Follow-up analyses showed a very small numerical difference between left- and right-sided effect sizes. Separate effects of left- and right-sided prefrontal tDCS were not statistically significant (right PFC: $g = -0.23$, $CI_{95\%} = [-0.48, 0.03]$, $P = 0.08$); left PFC: $g = -0.17$, $CI_{95\%} = [-0.41, 0.07]$, $P = 0.16$). The funnel plot of all anodal tDCS effects together did not show significant asymmetry (see Figure 4, Egger's regression test: $t(77) = -0.02$, $P = 0.99$).

Cathodal tDCS. We identified 7 cathodal tDCS studies that reported in total 13 different outcomes on emotional stress reactivity. Six of these studies found no effect on emotional reactivity to negative pictures or videos or to psychosocial stress after cathodal tDCS applied over the left or right DLPFC, the right VLPFC or the VMPFC (see Table 2 for other experimental settings) (Koenigs *et al.*, 2009; Peña-Gómez *et al.*, 2011; Antal *et al.*, 2014; Bogdanov and Schwabe, 2016; Ganho-Ávila *et al.*, 2019; Voss *et al.*, 2019). Only Riva *et al.* (2015), who applied cathodal tDCS over the right VLPFC and placed the anode over the contralateral orbitofrontal area, showed a significant amplification of emotional reactivity to social exclusion in a Cyberball game, which was not found when the cathode was placed over the parietal cortex.

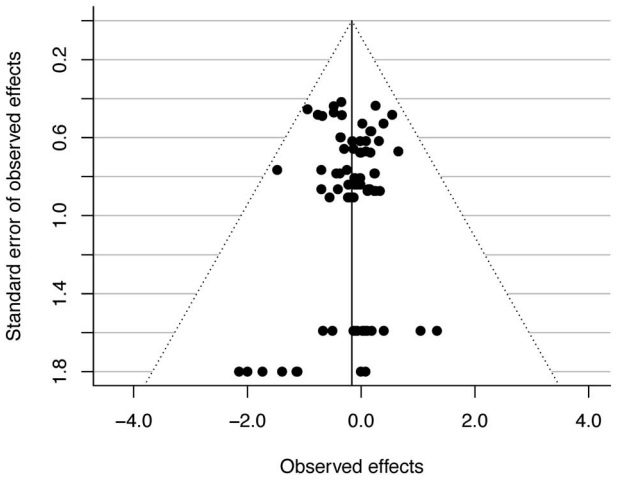

Fig. 4. Funnel plot of anodal tDCS studies. Note: because two studies reported many separate outcomes (Marques *et al.*, 2018; Rêgo *et al.*, 2015), the standard errors of their effects were increased by the RVE correction. These effects therefore appear at the bottom of the plot.

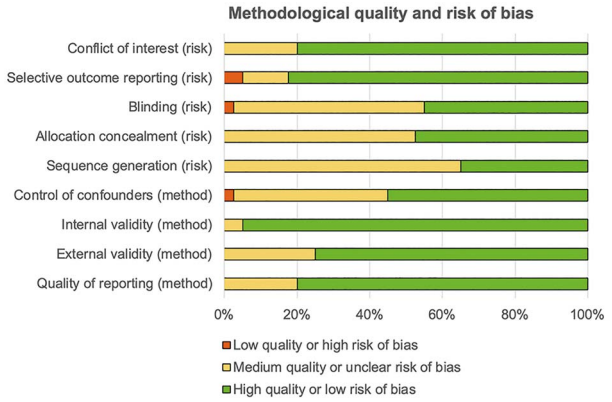

Fig. 5. Methodological quality and risk of bias of the included studies.

Together, the data from these studies ($k = 7$, $n = 271$) showed moderate heterogeneity ($I^2 = 43.9\%$), and the summary analysis estimated a mean effect of $g = -0.02$, $CI_{95\%} = [-0.22, 0.28]$, $P = 0.90$. As with the rTMS analyses, the low number of studies in this sample did not allow further quantitative analyses.

Quality and risk of bias

Figure 5 presents a graphical overview of methodological quality and risk of bias in the included studies. A common methodological weakness was incomplete reporting of experimental methods or results. Risk of bias in the included studies was strongest with regard to blinding: whether study personnel were blind to stimulation condition was often unclear, especially in rTMS studies where blinding procedures are more challenging than for tDCS. Additionally, although participants were typically randomized to conditions, many studies did not specify how the randomization sequence was generated, how groups were matched and if group allocation was concealed for study personnel, leaving it unclear if these studies dealt adequately with group-related confounders.

Discussion

Ongoing research efforts are dedicated to establish and understand NBS effects on stress-related processes. Experimental evidence is often derived from direct effects of single NBS sessions on acute stress. However, it has not been systematically analyzed if and how single sessions of prefrontal NBS affect stress reactivity on the level of subjective emotion in a normal-functioning stress system. We therefore systematically reviewed and quantified the immediate effects of prefrontal NBS on emotional stress reactivity in 40 sham-controlled healthy participant single-session NBS studies, including 12 rTMS studies and 28 tDCS studies.

The data from these studies show that the effects of a single session of prefrontal NBS may not be strong and stable enough to induce clinically relevant effects on emotional stress reactivity in all healthy individuals. On the other hand, some methods show promising effects that are worth further investigation. Acute effects of rTMS on emotional reactivity were investigated by relatively few studies, which showed effects in different directions. Acute effects of tDCS were more widely investigated, and quantitative results showed that applying anodal tDCS over the PFC overall slightly reduced negative stress-related emotions. However, effectivity of anodal tDCS varied between studies. Follow-up analyses suggested that the overall effect of anodal tDCS did not significantly depend on targeted hemisphere (left or right PFC) or on the type of stress that was induced (passive stress induction, psychosocial stress or aversive physical or auditory events). Several findings do suggest dependence of NBS effectivity on a number of other experimental and personal factors, including the NBS settings and the participant's psychological state.

In another review on prefrontal NBS, Remue *et al.* (2016a) concluded that a single session of prefrontal NBS does not affect mood. The present results, however, give an indication that a single session of prefrontal NBS may be able to modulate negative emotional state in response to stress, at least when using anodal tDCS. This suggests that prefrontal NBS could affect the emotional response to a threat or challenge rather than affecting emotional state by itself. Hence, prefrontal NBS may modify processes that are involved in changing the emotional state, rather than directly affecting 'static' emotional experience. Prefrontal NBS effects on emotional reactivity could be a result of effects on processes involved in emotion regulation. This is supported by a number of studies showing that anodal tDCS over the PFC mainly facilitates the cognitive modulation of emotions. For example, when participants were instructed to up- or downregulate emotional experience, anodal tDCS enhanced or reduced emotional reactions specifically in the instructed direction (Feeser *et al.*, 2014; He *et al.*, 2018; Marques *et al.*, 2018). In addition, tDCS may primarily affect attentional processes associated with the emotional experience (Chen *et al.*, 2017). Such results fit in with the previously proposed idea that prefrontal NBS modulates affective symptoms by improving the ability to self-regulate emotions through enhanced working memory and other cognitive control processes (Schmeichel *et al.*, 2008; Downar *et al.*, 2016; Lantrip *et al.*, 2017). However, this NBS effect on emotion regulation is not always found in single-session NBS studies (see, e.g. the study of Jansen *et al.*, 2019). Conclusions about the effect of NBS on emotion regulation are beyond the scope of the present results, and this hypothesis should be further tested in future studies.

Of the NBS techniques considered in the present article, rTMS and tDCS, it is relatively unexpected that rTMS shows the most uncertain effects. rTMS and tDCS differ in their primary neurophysiological effects, focality and other factors (Dayan *et al.*, 2013; Valero-Cabré *et al.*, 2017). Clinical effects in affective disorders such as depression are more established for rTMS (Schutter, 2010; Berlim *et al.*, 2013) than for tDCS (Shiozawa *et al.*, 2014), and effects on physiological stress reactivity are higher for prefrontal rTMS than for prefrontal tDCS (Makovac *et al.*, 2017). However, fewer rTMS studies than tDCS studies on emotional stress reactivity were available for the present analyses. Many single-session rTMS studies were not eligible for the current analyses because no experimental stress induction was applied or because emotions were not measured within the time frame of acute rTMS effects. Of the rTMS studies that did measure emotional reactivity, some findings suggest that the acute outcome of rTMS depends on task instructions, rTMS settings or psychological state (Fitzgibbon *et al.*, 2017; Möbius *et al.*, 2017; Notzon *et al.*, 2018). Other rTMS studies did not report any significant effects of a single rTMS session. Lack of acute rTMS effects on emotional reactivity may also be related to timing; tDCS studies often induced the stress or measured the emotional outcome during stimulation, whereas in rTMS studies these procedures usually take place after the stimulation is finished. Moreover, although the research objectives overlapped among the rTMS studies, the number of studies that used the same rTMS methods was limited. The heterogeneity in applied rTMS methods raises an issue concerning the aggregation of their results. The present results should therefore be considered as work in progress and indicative for the dependence of rTMS effects on various technical, contextual and task-related factors. The influence of such factors should be further investigated before drawing definitive conclusions about the overall effectiveness of rTMS in modulating emotional stress reactivity. On the other hand, the present results also suggest that anodal tDCS might complement rTMS as a technique to modulate stress-related processes. If rTMS and tDCS would eventually yield comparable results in clinical applications, tDCS might be preferred over rTMS for its easier use, portability and lower costs (Priori *et al.*, 2009; Valero-Cabré *et al.*, 2017).

The evidence for cathodal tDCS effects on subjective stress-related emotions is sparse. Perhaps, cathodal tDCS has low effectivity in general. Little support for significant effects of cathodal tDCS is in line with previous findings of tDCS effects on neural excitability (Lafon *et al.*, 2017) and on cognitive functions (Jacobson *et al.*, 2012). Yet, cathodal tDCS may affect neural excitability and plasticity in opposing ways depending on current intensity and stimulation time (Mosayebi Samani *et al.*, 2019). To provide clearer insight in cathodal tDCS, it could be interesting to investigate how these stimulation settings may moderate stimulation effects on emotion- and stress-related processes.

With regard to the optimal target hemisphere for prefrontal NBS, previous research showed that left-sided and right-sided PFC stimulation can have different effects on brain networks involved in emotion regulation and emotional state (Schutter *et al.*, 2001; Jansen *et al.*, 2017), but our results did not demonstrate a clear influence of target hemisphere (left PFC *vs* right PFC) on NBS effects at the level of emotional stress reactivity. This is somewhat surprising, since NBS should modulate neural activity primarily in the target hemisphere, and the data in this review were restricted to negative emotional states that have been associated with asymmetric prefrontal activation. Negative and predominantly withdrawal-related emotions, such as fear, nervousness and sadness, are associated with greater right- than left-sided PFC activity (Davidson, 1992; Wheeler *et al.*, 2007; Goodman *et al.*, 2013; Berkman *et al.*, 2014; Harmon-Jones and

Gable, 2018). In addition, greater right-sided PFC activity has been linked to stronger physiological reactivity to stress (Sullivan and Gratton, 2002; Koslov *et al.*, 2011; Goodman *et al.*, 2013; Quaedflieg *et al.*, 2015; Zhang *et al.*, 2018), anxiety and depression (Thibodeau *et al.*, 2006; Eidelman-Rothman *et al.*, 2016; Harmon-Jones and Gable, 2018). Greater left-sided PFC activity, on the other hand, is linked to stronger approach-related emotional reactions such as enthusiasm (Carletti *et al.*, 2009; Koslov *et al.*, 2011; Harmon-Jones and Gable, 2018), weaker physiological reactivity to stress (Goodman *et al.*, 2013) and reduced emotional reactivity to PTSD symptom provocation (Meyer *et al.*, 2018). However, greater relative left-sided PFC activity has also been associated with stronger feelings of anger and stronger aggressive responses to stress (Verona *et al.*, 2009; Hofman and Schutter, 2012; Harmon-Jones and Gable, 2018). In line with this latter effect of left-sided prefrontal dominance, the tDCS studies of Hortensius *et al.* (2012) and Kelley *et al.* (2015) report increased approach-related emotional reactivity (measured as feelings of anger and jealousy) specifically after applying anodal tDCS to the left PFC and cathodal tDCS to the right DLPFC, but not when the electrode montage was reversed. However, our quantitative results overall do not provide evidence supporting the acute influence of tDCS or rTMS on frontal asymmetry effects on global emotional stress reactivity. The optimal choice of target hemisphere for NBS protocols to modulate emotional processes may depend on other stimulation-related factors such as pulse frequency or current polarity (see also the discussion in Vicario *et al.*, 2019). Regarding specific PFC targets, the overview of included studies on emotional reactivity does not show a clear difference between effectivity of NBS over different PFC target regions, and the limited amount of data available per PFC target region prevented meaningful comparisons between target regions. Moreover, when aggregating across studies, the regional specificity of NBS can be low because different localizing methods to target a specific region are used, the electrical field distribution is influenced by individual anatomy, and, especially in case of tDCS, the induced electrical field is not very focal and depends on the electrode montage. Therefore, in the absence of simulations or other measurements of the peak location of the electrical field, we considered it more appropriate to collapse the outcomes from NBS studies targeting various PFC regions. However, targeting different PFC regions may affect different processes and thereby have different effects on stress responses and emotions. To determine the optimal target site for NBS effects on stress- and emotion-related outcomes, more specific comparisons between NBS target regions based on electrical field distributions are needed.

We also considered differences between NBS effects on emotional reactivity across three types of stress: passive stress inductions, psychosocial stress and aversive physical or auditory stress. Different types of stress can differently activate stress systems and differently affect stress regulation strategies (Hancock *et al.*, 2007; Bali and Jaggi, 2015; Lea *et al.*, 2019). However, both rTMS and tDCS studies did not demonstrate systematic different effects on emotional reactivity across types of stress. It could be that the influence of prefrontal NBS on emotional reactivity is independent of stressor category because some (medial) PFC regions are involved in general emotion regulation across different types of stress (Diekhof *et al.*, 2011). Alternatively, the variability in NBS effects on emotional reactivity may not depend on stress sources but on additional features of the stressor that partly determine stress response patterns. These include the unpredictability and uncontrollability of the stressor (Dickerson and Kemeny, 2004; Bali and Jaggi, 2015) and cognitive appraisals about the stressor (Denson *et al.*, 2009). Additionally, the type of emotion induced by the stressor makes a difference; stress responses associated with different types of negative emotions, like fear and sadness, show resemblance but also differ in intensity and specific activation patterns, such as shown for amygdala activation, sympathetic nervous system activations and feelings of pleasantness and arousal (Phan *et al.*, 2002; Kreibig *et al.*, 2007; Kreibig, 2010). Some included emotional outcomes reported in the studies may also be relatively specific to the stress manipulation. It could be difficult to generalize such outcomes to emotional stress reactivity in other situations or to stress-related clinical symptoms. For example, NBS effects on anger after psychosocial stress may say more about potential NBS effects on symptoms of interpersonal distress than on symptoms of panic. However, more research on this topic is needed to be able to zoom in on NBS effects on emotion- or stressor-specific processes. This review combines outcomes of different stress manipulations to give an indication of NBS effects on global emotional reactivity.

Our findings show preliminary evidence that prefrontal NBS, at least with anodal tDCS, lowers acute emotional stress reactivity. This motivates further research in the direction of using prefrontal NBS in enhancing resilience to acute effects of stress. Such protective effects of anodal tDCS have already been shown for acute stress interference on cognitive performance (Plewnia *et al.*, 2015; Bogdanov and Schwabe, 2016). If the efficacy of anodal tDCS on emotional reactivity would be further developed, it may be used to attenuate the tendency to strongly react with negative emotions to daily stressors (Charles *et al.*, 2013) and thereby reduce daily negative affect and the risk on anxiety, chronic stress complaints and PTSD (Steinhardt and Dolbier, 2008; Chiesa and Serretti, 2009; Galatzer-Levy *et al.*, 2013). Finally, although speculative, specifically targeting the PFC might improve resilience to the detrimental results of early-life adversity or life stress on PFC structure and function (Arnsten, 2009; Fisher *et al.*, 2016).

However, beside acute emotional stress reactions, a second important feature is the 'shutoff' or recovery of the stress response once a threat has passed (McEwen, 1998). Future NBS research should therefore continue measuring emotion for a prolonged time after the stress induction, to provide more insight in NBS effects in different stages of the emotional stress response, including the recovery of emotional stress responses.

Moreover, the presently estimated effect size of single NBS sessions in a non-clinical population is small (Cohen, 1988). An effect size of small magnitude in healthy samples agrees with NBS effects on working memory and autonomic nervous system functioning (Brunoni and Vanderhasselt, 2014; Makovac *et al.*, 2017). This may be due to a ceiling effect of NBS outcomes when performance on a function is already sufficient (Mottaghy *et al.*, 2003; Furuya *et al.*, 2014; Benwell *et al.*, 2015; McConathey *et al.*, 2017). Also, because prefrontal NBS effects show intraindividual variability as well as interindividual variability, NBS may not always affect emotional reactivity in the same manner in all individuals; factors that could influence the strength and direction of NBS effects on PFC-related processes include baseline neural activity (Antal *et al.*, 2007; Fertonani *et al.*, 2014), stress sensitivity (Peña-Gómez *et al.*, 2011; Fitzgibbon *et al.*, 2017), fatigue, task motivation and gender (Hurley and Machado, 2018). The different NBS methods, participants and experimental contexts that were used in the included studies could therefore have induced heterogeneous effects on emotional reactivity, which may diminish the summary effect.

Still, across studies, the present findings show a weak effect of a single tDCS session on acute emotion stress reactivity. This effect stimulates to further investigate how the effectiveness of prefrontal tDCS, or NBS in general, can be augmented in order to establish clinically significant effects on emotional stress reactivity. The first and perhaps most obvious way to augment effectiveness is by giving a sequence of multiple stimulation sessions instead of relying on single stimulation sessions. Sequences of multiple stimulation sessions augment NBS effects on neurophysiology (Maeda *et al.*, 2000; Bäumer *et al.*, 2003; Pell *et al.*, 2011; Monte-Silva *et al.*, 2013; Bergmann *et al.*, 2016) as well as on behavior, including effects on working memory (Hill *et al.*, 2016) and cognitive control (Elmasry *et al.*, 2015). Moreover, for therapeutic use in affective disorders, a sequence of 20–30 sessions is recommended (McClintock *et al.*, 2018).

Furthermore, the NBS sessions should be combined with a task that activates or trains the targeted neural process. It has been proposed that the effects of tDCS are largest in neural networks and cognitive functions that are activated or trained during stimulation (Martin *et al.*, 2014; Gill *et al.*, 2015; Mancuso *et al.*, 2016; Pisoni *et al.*, 2018; Simonsmeier *et al.*, 2018), perhaps because synaptic activity could be a prerequisite for NBS effects to occur (Kronberg *et al.*, 2017). NBS effects may even be specific to the activated neural or cognitive process during stimulation. For example, prefrontal tDCS may not have one-directional effects on attentional bias for threat, but when participants are trained to direct attention either towards or away from threat, tDCS specifically increases the attentional bias convergent with the trained direction (Clarke *et al.*, 2014; Heeren *et al.*, 2015). Also for other cognitive functions, combining prefrontal tDCS with cognitive training amplifies stimulation effects (Martin *et al.*, 2013), resulting in cognitive benefits that can last for weeks or months and that can transfer to non-trained cognitive skills (Elmasry *et al.*, 2015; Berryhill and Martin, 2018). Likewise, combining prefrontal NBS with cognitive behavioral therapy (Bajbouj and Padberg, 2014) augments treatment response in depression, PTSD and anxiety disorders (Segrave *et al.*, 2014; Li *et al.*, 2016; Kozel *et al.*, 2018; Chalah and Ayache, 2019; van't Wout-Frank *et al.*, 2019), while prefrontal NBS in rest (i.e. NBS by itself) does not produce lasting improvements in cognitive performance in neuropsychiatric patients (Martin *et al.*, 2016, 2017). This suggests that NBS effects on emotion regulation processes can be augmented by applying prefrontal NBS during cognitive practice or cognitive therapy.

Finally, although the results of our study suggest that raising stress levels in an experiment may increase the sensitivity of emotional measures to prefrontal NBS effects, it remains unclear whether raising stress levels would also augment prefrontal NBS effects on stress- and emotion-related processes. Some studies showed improved PTSD symptom reduction when prefrontal NBS was combined with trauma exposure (Osuch *et al.*, 2009; Isserles *et al.*, 2013; van't Wout-Frank *et al.*, 2019), suggesting that NBS can act specifically on the activated fear memory processes. However, single-session NBS studies on fear extinction in healthy individuals (Asthana *et al.*, 2013; Guhn *et al.*, 2014; Mungee *et al.*, 2014, 2016; van't Wout *et al.*, 2016; Dittert *et al.*, 2018) and phobia patients (Notzon *et al.*, 2015) have shown null results or divergent effects of NBS. Further, the effects of a single session of prefrontal NBS on cognitive performance can be similar across neutral and emotionally arousing experimental contexts (Pripfl *et al.*, 2013; Faehling and Plewnia, 2016), both in depressed and healthy participants (Moreno *et al.*, 2015). Hence, single-session NBS studies do not clearly demonstrate whether or not prefrontal NBS effectivity depends on stress or arousal levels during NBS. In therapeutic uses of NBS, further studies are needed to discover if stress levels influence the effects of NBS on stress reactivity and stress-related symptomatology.

Future directions

This study presents an interim overview of the current evidence regarding the direct effects of a number of NBS methods on acute emotional stress reactivity. In this field of research, NBS is often applied with the objective to simply increase or decrease activity in a brain area in order to change stress- or emotion-related outcomes. Yet, our findings show that NBS effects on stress- and emotion-related processes vary. To further clarify the possibilities and limitations of NBS with regard to emotional stress reactivity, future research should focus on a number of important factors.

First of all, the stress processes that are most sensitive to prefrontal NBS should be identified. For instance, physiological measures, including heart rate variability and cortisol responses, appear more sensitive to the acute effects of NBS than self-reports of emotional state (Brunoni *et al.*, 2013; Antal *et al.*, 2014; Baeken *et al.*, 2014; Feeser *et al.*, 2014; Hurlemann *et al.*, 2015; Schroeder *et al.*, 2015; Herrmann *et al.*, 2016, 2018; Remue *et al.*, 2016b; Makovac *et al.*, 2017). Possibly, the physiological stress system mediates the effects of NBS on emotional state by lowering bodily arousal, thereby lowering the subjective experience of arousal (Barrett *et al.*, 2004; Dunn *et al.*, 2010), although the subjective arousal outcomes covered in this review did not clearly show stronger NBS effects than other outcomes. Emotional reactivity based on dimensions of valence, arousal or motivational direction also shows a stronger link to physiological stress reactivity than self-report data of discrete emotions (Mauss and Robinson, 2009). Self-reports of discrete emotions are subject to many other influences, including emotion vocabulary (Barrett, 2004) and personality characteristics (Austin *et al.*, 1998). On the other hand, some argue that self-reports of discrete emotion categories better capture emotional experiences, because they may have more semantic value (Cowen and Keltner, 2017). Different measures may thus capture different aspects of emotional experience. Yet, there are also substantial correlations between valence and arousal ratings on one hand and self-reports of discrete emotions on the other (Bradley and Lang, 1994; Hoffmann *et al.*, 2012; Cowen and Keltner, 2017), suggesting that these different measures capture similar aspects of emotion too. For this reason, different measures of emotional experience have been combined in the present study. To better understand how NBS affects different aspects of emotional experience, future studies should make more explicit distinctions between different measures of dimensional and discrete emotional categories. This difference between measures also demonstrates the need to use measurement instruments that are sensitive to the effects of NBS. For example, a single session of prefrontal NBS may have little effect on global mood after an experiment (Remue *et al.*, 2016a) but could at the same time change the acute emotional response to aversive pictures during the experiment (Feeser *et al.*, 2014; Rêgo *et al.*, 2015; Marques *et al.*, 2018). In addition, subjective experiences of emotion ('self-focused' emotions) share features with perceptions of emotional stimuli ('world-focused' emotions) (Quigley *et al.*, 2013) but also refer to distinct aspects of emotional processes. The prefrontal cortex, for example, seems more involved in self-focused emotional reactivity (Herbert *et al.*,

2011), suggesting that the focus of the emotional measure may influence sensitivity to prefrontal NBS effects. The use of insensitive measurement instruments or measurement timings may introduce heterogeneity in the outcomes and thereby obscure the direct effects of NBS.

Second, acute NBS effects seem to depend on task or experimental settings, such as task instructions (Feeser *et al.*, 2014; Möbius *et al.*, 2017; He *et al.*, 2018; Marques *et al.*, 2018), the time between the stress induction and measuring the emotional outcome (Feeser *et al.*, 2014; Rêgo *et al.*, 2015; Dittert *et al.*, 2018) and the relationship between the emotion and the behavior that is induced by the stressor (Hortensius *et al.*, 2012; Kelley *et al.*, 2015). Future NBS research should pay attention to experimental tasks and measurement protocols that are sensitive to the NBS effects, especially in single-session NBS experiments that produce very subtle effects.

Third, preferred cortical targets for NBS applications in stress and emotion may lie beyond the PFC. For example, stimulating the dorsal anterior cingulate cortex (dACC) could enhance emotional learning and memory for extinction of fear memories (Marin *et al.*, 2014; Downar *et al.*, 2016). Yet, the dACC may lie out of reach for tDCS and conventional rTMS and might therefore better be targeted by techniques such as deep TMS (Zangen *et al.*, 2005; Roth *et al.*, 2007; Isserles *et al.*, 2013). In addition, the occipital cortex (Janik *et al.*, 2015), the parietal cortex (Schutter *et al.*, 2009, 2010) and the cerebellum (Schutter and van Honk, 2009; Ferrucci *et al.*, 2012) may be suitable NBS targets to improve emotion regulation or restore emotional perception deficits in affective disorders (Kohler *et al.*, 2011).

Fourth, applying rTMS in certain rhythmic patterns or using transcranial alternate current stimulation (tACS) can induce interaction with other components of brain function than conventional rTMS and tDCS, e.g. by influencing ongoing oscillatory activity (Paulus, 2011; Schutter, 2014; Thut *et al.*, 2017). Such techniques may provide an alternative pathway to modulate cortical excitability (Paulus, 2011) and cognitive functions like working memory (Albouy *et al.*, 2018).

Finally, NBS effects are shaped by many technical (Jung *et al.*, 2008; Zaehle *et al.*, 2011; Jacobson *et al.*, 2012; Batsikadze *et al.*, 2013; Hoy *et al.*, 2013; Lage *et al.*, 2016), biological (Cheeran *et al.*, 2008; Ludwig *et al.*, 2010; Fertonani *et al.*, 2014; Teo *et al.*, 2014; Jannati *et al.*, 2017; Antonenko *et al.*, 2018), clinical (Guse *et al.*, 2010) and personal factors (Ridding and Ziemann, 2010; Hsu *et al.*, 2016; Huang *et al.*, 2017; Valero-Cabré *et al.*, 2017). However, the data in the present quantitative analysis did not allow analyses of all these factor-specific effects. Accordingly, the estimated effect sizes in this work might not be applicable to specific methods or populations. Future research should determine if and how moderating factors shape the scope of prefrontal NBS effects, particularly those moderating factors that are relevant to stress and emotion.

Conclusion

This review and quantitative analysis presents an overview of the direct effects of single-session prefrontal NBS on emotional stress reactivity as investigated with various NBS methods. These studies together do not provide evidence for a one-directional effect of prefrontal NBS on emotional stress reactivity in healthy individuals. However, the magnitude and direction of NBS effects on emotional reactivity may depend on various technical, experimental, neurobiological and mental state factors, which prevent drawing definite conclusions about the overall direct effects of prefrontal NBS on stress-related emotions. Effects of specific NBS methods demonstrate a small beneficial effect on emotional stress reactivity of anodal tDCS. These preliminary findings imply that prefrontal NBS can potentially be used to facilitate resilience against the detrimental impact of stress on cognitive functioning and mental health, but only if this technique is further investigated and developed.

Supplementary data

Supplementary data are available at *SCAN* online.

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Conflict of interest

The authors declare no conflicts of interest.

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