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fMRI neurofeedback in emotion regulation: A literature review

Pavla Linhartová [a,*], Adéla Látalová [a], Barbora Kóša [a], Tomáš Kašpárek [a], Christian Schmahl [b], Christian Paret [b,**]

[a] Department of Psychiatry, University Hospital Brno and Faculty of Medicine, Masaryk University, Jihlavská 340/20, 62500, Brno, Czech Republic
[b] Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim, Heidelberg University, J5 68159, Mannheim, Germany

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ABSTRACT

Objectives: Emotion regulation is one of the most prevalent objectives for real-time fMRI neurofeedback (rt-fMRI-NF) studies. The existing studies differ in a number of methodological parameters. This study provides a literature review of the main parameters and results of studies using rt-fMRI-NF for emotion regulation enhancement.
Method: A search of the Web of Science database up through November 8, 2018, identified 144 articles written in English, 89 of which were excluded as irrelevant for this study. The remaining 51 original studies and four secondary analyses of previously published original studies were included in the literature review. The selection of target brain areas, target populations, emotion regulation protocols, NF presentation, control group types, and emotion regulation instructions were examined in relation to achieved brain regulation and changes in cognitive or clinical outcomes. Study results were evaluated in terms of their statistical robustness.
Results: The results show that healthy people are able to regulate their brain activity in the presence of rt-fMRI-NF from various brain regions related to emotion regulation, including the amygdala, anterior insula, and anterior cingulate cortex. The regulation of brain activity using rt-fMRI-NF from prefrontal-limbic connectivity or from individually navigated brain areas is feasible as well. Most studies that used a control group show that rt-fMRI-NF actually induces some effects on brain regulation, cognitive variables, and clinical variables. Generally, the success of ROI regulation during NF training is related to the combination of target brain region, the type of emotion regulation task, and the population undergoing the training. In terms of patient groups, the strongest support for the beneficial effects of rt-fMRI-NF has been shown in increased positive emotion experiencing in patients with depression and in decreased anxiety in patients with anxiety disorders. Symptom reduction following NF training has been also reported in patients with PTSD, BPD, and schizophrenia, but direct comparisons with control groups in these studies makes it impossible to evaluate the added value of NF. Studies often do not report all the relevant analyses for evaluating NF success and many studies lack statistical robustness.
Conclusions: Overall, rt-fMRI-NF seems a promising tool for emotion regulation enhancement with the potential to induce long-term symptom reduction in patients with various mental disorders. Preplanning of statistical analyses, careful interpretations of the results, and evaluations of the NF effect on symptom reduction in patient groups is recommended.

1. Introduction

Real-time fMRI neurofeedback (rt-fMRI-NF) is an innovative tool for learning brain self-regulation. In rt-fMRI-NF studies, the blood-oxygen-level dependent (BOLD) signal from a selected brain area is measured and presented back to a subject in an MRI scanner. The aim of rt-fMRI-NF is to promote the subject's learning self-control over the activity in a selected brain area and, consequently, over the mental state corresponding with the activity in the given brain area. One of the most broadly studied fields within rt-fMRI-NF is emotion regulation. Although a relatively high number of studies focus on this topic, they substantially

* Corresponding author. Department of Psychiatry, University Hospital Brno and Faculty of Medicine, Masaryk University, Jihlavská 20, 62500, Brno, Czech Republic.
** Corresponding author. Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim / Heidelberg University, J5 68159, Mannheim, Germany.
E-mail addresses: Linhartova.Pavla@fnbrno.cz (P. Linhartová), 393284@mail.muni.cz (A. Látalová), 397515@mail.muni.cz (B. Kóša), Kasparek.Tomas@fnbrno.cz (T. Kašpárek), christian.schmahl@zi-mannheim.de (C. Schmahl), christian.paret@zi-mannheim.de (C. Paret).

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List of abbreviations

rt	real-time
ACC	anterior cingulate cortex
AI	anterior insula
BOLD	blood-oxygen-level dependent
BPD	borderline personality disorder
BVS	best voxel selection
CBT	cognitive behavioral therapy
CG	control group
DLPFC	dorsolateral prefrontal cortex
DMPFC	dorsomedial prefrontal cortex
EG	experimental group
fMRI	functional magnetic resonance imaging
hIPS	horizontal intraparietal sulcus
IFG	inferior frontal gyrus
LPFC	lateral prefrontal cortex
MTL	middle temporal lobe
MVPA	multivariate voxel pattern analysis
NAcc	nucleus accumbens
NF	neurofeedback
OCD	obsessive-compulsive disorder
OFC	orbitofrontal cortex
PTSD	posttraumatic stress disorder
ROI	region of interest
SN/VTA	substantia nigra/ventral tegmental area
SVM	support vector machine
VLPFC	ventrolateral prefrontal cortex

differ in key methodological parameters, such as target brain areas, target populations, emotion regulation protocols, forms of neurofeedback presentation, control groups, and instructions for emotion regulation. The aim of this literature review is to describe the main methodological aspects that need to be considered when starting a new rt-fMRI-NF study in emotion regulation, and, consequently, to promote informed hypotheses generation in future studies in this important and rapidly developing field.

1.1. Brain targets and target populations for emotion regulation with rt-fMRI-NF

Various brain regions can be used for rt-fMRI-NF augmented emotion regulation training because of their differing involvement in emotion processing and emotion regulation (Morawetz et al., 2017). The activity of some regions is associated with the intensity of emotional experiencing; the activity of other regions is associated with the implementation of emotion regulation strategies (Kalisch, 2009; Paret et al., 2011). For example, the amygdala and anterior insula (AI) have been repeatedly found to be involved in experiencing both positive and negative emotions (Kurth et al., 2010; Sergerie et al., 2008). Thus, the amygdala or AI activity levels can be taken as correlates of emotional experiencing intensity, regardless of the emotional valence, i.e. regardless of whether the person experiences positive or negative emotions. On the other hand, lateral prefrontal cortex (LPFC) regions have been repeatedly found to be involved in cognitive emotion regulation (Kohn et al., 2014). Thus, LPFC activity levels can be taken as correlates of cognitive emotion regulation efforts.

NF-aided emotion regulation can be studied in healthy people, but the clinical goal of rt-fMRI-NF is to promote emotion regulation in patients whose ability to regulate emotions is impaired. Emotion regulation impairment is a frequently occurring challenge for patients with different mental disorders, including mood, anxiety, stress, and personality disorders (Kring, 2008). Thus, a focus on enhancing emotion regulation is a key feature in therapy for many psychiatric patients. At the same time, the type of emotion regulation impairment can differ among patient groups (i.e., different brain regions can be affected or the same regions can be affected in a different way). For example, patients with depression show an exaggerated amygdala response to negative stimuli and an attenuated amygdala response to positive stimuli (Groenewold et al., 2013). Accordingly, the goal of rt-fMRI-NF in patients with depression could be to decrease amygdala activity during the experience of negative emotions or to promote amygdala activity while experiencing positive emotions.

1.2. rt-fMRI-NF emotion regulation protocols

Subjects can be instructed to increase (i.e., upregulate) or decrease (i.e., downregulate) their negative or positive emotions by upregulating or downregulating their brain activity. Studies may or may not present additional emotion-evoking stimuli. For example, subjects can be presented with pictures or scripts with emotional content and, subsequently, subjects can be instructed to regulate the evoked emotions using NF information (e.g., Paret et al., 2014). In another approach, subjects can be instructed to regulate their brain activity by implementing an emotion regulation strategy that promotes or reduces the experience of emotions (such as contemplating emotional memories or relaxing) without the use of emotion-evoking stimuli (e.g., Zotev et al., 2011). The directions in which the emotions and the target brain area activity are regulated need to be distinguished. For example, the upregulation of the activity of a region that is not sensitive to emotional valence, such as the amygdala (Sergerie et al., 2008), can be achieved by upregulating either positive or negative emotions. In other regions, a BOLD signal increase may be related to specific emotional experiences. For example, activity in the reward-related brain areas, such as nucleus accumbens (NAcc), is associated with positive, but not negative emotions (Lang and Bradley, 2010).

1.3. Continuous vs. intermittent NF presentation

NF can be presented in either a continuous or intermittent form. Continuous rt-fMRI-NF means that NF is presented throughout the whole task (or respective experimental condition) with signal updates after each repetition time. Continuous NF can be presented e.g. as a continuously updated scale (e.g., Paret et al., 2014) or as a development curve (e.g., Scheinost et al., 2013). Intermittent (or end-of-block) NF is presented as a single outcome after the end of each trial or time interval, e.g. as a single outcome on a scale (e.g., Zilverstand et al., 2015) or as a number (e.g., Sarkheil et al., 2015) representing the level of target brain activity during the previous block. NF can also be presented in more complex ways, such as visual scenes (Lorenzetti et al., 2018). Whether the presentation of continuous or intermittent NF can be more advantageous in some situations remains uncertain. It can be argued that continuous NF provides subjects with more thorough information, and thus can theoretically lead to better training effects. On the other hand, if continuous NF is presented, the simultaneous use of visual emotion-evoking stimuli can possibly draw attention away from NF and diminish the training effects; alternately, it could produce emotion downregulation simply by drawing the subjects' attention away from these stimuli.

1.4. Control groups

Several types of control groups can be used in rt-fMRI-NF studies. Specifically, sham NF can be used; most frequently this is obtained from a different subject (further termed "yoked NF", e.g., Hamilton et al., 2011). Alternately, NF from a region other than the target brain region of a given subject can be presented in the control group (further termed the

"alternate region of interest (ROI) NF", e.g., Zotev et al., 2011). In yoked and alternate ROI NF control groups, the subjects are not aware that the signal they are receiving is not from their target brain area, and thus studies can be blinded. Finally, there can be an absence of NF presentation in the control group (further termed "no NF", e.g., Johnston et al., 2011). Because emotion regulation protocols involve emotion regulation training per se, the use of a control group is crucial for determining whether NF presentation provides an additional learning boost. However, the effect of control group manipulation remains a topic of ongoing debate. Using alternate ROI NF and yoked NF in control groups has the advantage of maintaining comparable motivational aspects as for subjects presented with genuine NF (Thibault et al., 2018). There are also studies showing that the presentation of any feedback is associated with brain activity increase (Emmert et al., 2016; Ninaus et al., 2013) and might produce specific effects that are different from those in control groups presented with no NF. Using control groups with no NF prevents blinding subjects and researchers, and likely increases psychosocial effects. On the other hand, feedback that is not contingent on the subject's target brain area activity has the potential to confuse and frustrate subjects (e.g., Sulzer et al., 2013), thus potentially negatively influencing their motivation and the success of their regulation. Cohen Kadosh et al. (2016) argue that the use of yoked or alternate ROI NF can raise ethical issues, since subjects could reject potentially successful strategies only because they do not correspond with the presented NF.

1.5. Instructions for NF regulation

Subjects may be instructed about strategies they should implement for ROI regulation in greater or lesser detail or not at all. If no specific instruction for emotion regulation is provided, subjects are only instructed to regulate their brain activity according to the NF presentation (Marxen et al., 2016), or subjects can be informed about the nature of the brain area (i.e., that it is related to emotions, e.g., Johnston et al., 2011). If specific instructions for emotion regulation are provided, several emotion regulation strategies may be suggested that subjects can use (e.g., Hamilton et al., 2016), or they may be asked to prepare the strategies before the experiment (e.g., Young et al., 2014), or they may even undergo emotion regulation training before the experiment (e.g., Sarkheil et al., 2015). It is unclear whether the emotion regulation instruction type and level of detail can influence the regulation success. While more detailed instructions or pre-experimental preparation can ensure greater focus on a specific emotion regulation strategy and longer time for training in this strategy during the experiment, providing subjects with space to find their own suitable strategy during the task can theoretically also be beneficial.

1.6. Presentation of regulation success

Studies comprise one or several NF training runs within one or several fMRI sessions. Most often, the NF runs are composed of regulation and control conditions that can include a cognitive task, resting, or watching emotional stimuli without regulating. The success of ROI activity regulation is usually reported as a difference in achieved signal change during the task between the regulation and control conditions, and between the experimental group and the control group in studies that include control groups. In some studies, "transfer runs" are employed after the NF training that involve the same task as during NF training, but without NF presentation. Transfer runs serve to assess the sustainability of training effects after the removal of NF (e.g., Zotev et al., 2011). Some studies also evaluate self-reported cognitive effects or changes in clinical symptoms directly after the NF experiment (e.g., Hamilton et al., 2016) or in long-term aspects (e.g., Rance et al., 2018).

1.7. Objectives

Our objective in this literature review is to present a comprehensive overview of key design parameters of rt-fMRI-NF in emotion regulation studies and to explore the influence of these parameters on brain regulation success and cognitive or clinical changes after rt-fMRI-NF training. Specifically, the review addresses the following research questions:

1. In which *brain areas* has rt-fMRI-NF for emotion regulation been successfully used?
2. In which *populations* has rt-fMRI-NF for emotion regulation been successfully used?
3. Do studies with different *emotion regulation protocols* achieve similar results?
4. Is presentation of *continuous or intermittent* NF for emotion regulation more advantageous?
5. Is any type of *control group* superior to other types?
6. How does the presentation of *instructions for emotion regulation* influence the results?

2. Method

We searched the *Topic* (neurofeedback) AND (fMRI OR functional magnetic resonance imag* OR functional MRI) AND (emot* OR affect*) across all databases and all years in the Web of Science on November 8, 2018, with 125 results. Other potential studies (N = 20) were identified through an additional search. There were two eligibility criteria: 1. Original studies or secondary analyses derived from original studies using the rt-fMRI-NF method, and 2. The use of rt-fMRI-NF for voluntary emotion regulation enhancement. Both criteria needed to be met for the study to be included in the review. Voluntary emotion regulation was defined as the intentional modification of the subject's own present emotional experience. To keep the focus of the review, pain and craving regulation studies were not included, since they constitute more complex phenomena, with emotion regulation being only one possible part of the regulation process. Two authors of this review independently screened the titles and abstracts yielded by the search against the inclusion criteria. After duplicates were removed, 144 articles written in English were identified. We eliminated 52 articles not related to rt-fMRI-NF in the field of emotion regulation (e.g., studies using electroencephalography or functional near-infrared spectroscopy NF, or studies using rt-fMRI-NF not related to emotion regulation), 13 conference abstracts, 7 methodological articles, and 12 reviews or commentaries. The remaining 60 studies' full reports were screened. If any uncertainty about the eligibility of the article arose, it was discussed with the rest of the review authors. Based on this procedure, another five studies that did not meet both eligibility criteria were excluded. Studies that did not claim to be focused on emotion regulation directly, but that clearly instruct subjects to regulate their brain activity using emotion regulation strategies were included in the review (e.g., Caria et al., 2007; Ruiz et al., 2013; Yao et al., 2016). The final pool of papers includes 51 original studies (see Table 2 for the studies overview). Four studies presenting secondary analyses were also included (Paret et al., 2016b; Young et al., 2018, 2017a; Zotev et al., 2013).

2.1. Results presentation

First, the study characteristics were described for each study included in this literature review (Table 2). Second, study parameters were summarized according to our objectives (target brain areas, target populations, emotion regulation protocols, form of NF presentation, and emotion regulation instructions) and displayed, preferably, with figures. Third, study results were summarized. As the studies differ in the type of data analysis, related to differences in study designs, we developed an evaluation system that could be applied to a majority of the included studies (see Table 1 for criteria overview). Since only some studies used corrections for multiple comparisons, we considered the results to be significant if the relevant p value was less than 0.05 uncorrected; thus we maintained the same standard for all studies. If a study only presented

Table 1
Overview of criteria for studies results evaluation.

	ROI regulation (vs. CG)	Training time effect	ROI regulation in transfer task	Cogn./clin. effects vs. baseline (vs. CG)
Y	Sig. diff. between exp. and control condition in: • session average • the last block • the last block of the last session	• Sig. effect of training time on ROI regulation in regression analysis • Sig. diff. between first and last block/session in ROI regulation	Sig. ROI regulation in transfer task	Sig. diff. in cogn./clin. variables in EG after NF training vs. baseline (before NF training)
N	No sig. diff. between exp. and control condition	No sig. effect of training time on ROI regulation AND no sig. diff. between first and last block/session	No sig. ROI regulation in transfer task	No sig. diff. in cogn./clin. variables in EG after NF training vs. baseline (before NF training)
CG++	• Sig. effect of group on ROI regulation in regression analysis • Sig. diff. in ROI regulation between EG and CG (in average or in last block/session)	–	Sig. diff. in ROI regulation in transfer task between EG and CG	Sig. diff. in change in cogn./clin. variables between EG and CG
CG+	Sig. ROI regulation in EG, no sig. ROI regulation in CG	–	Sig. ROI regulation in transfer task in EG, no sig. ROI regulation in transfer task in CG	Sig. change in cogn./clin. variables in EG, no sig. change in cogn./clin. variables in CG
CG-	• No sig. diff. in ROI regulation between EG and CG • Sig. diff. in ROI regulation in both EG and CG	–	• No sig. diff. in ROI regulation in transfer task between EG and CG • Sig. diff. in ROI regulation in transfer task in both EG and CG	• No sig. diff. in change in cogn./clin. variables between EG and CG • Sig. change in cogn./clin. variables in both EG and CG
no CG	no CG used	–	no CG used	no CG used
NR	• results of ROI regulation are not reported	Study presents data for multiple blocks/session, but does not report the effect of training time on ROI regulation	Study involves a transfer task, but does not present results of ROI regulation in transfer task	Cogn./clin. changes were assessed but are not reported
NA	–	only block average analyzed/no time analysis	Study does not involve a transfer task	Cogn./clin. changes were not assessed

Note: Y = yes, N = no, EG = control group, CG = control group, NR = not reported, NA = not assessed, ROI = region of interest, sig. = significant, diff. = difference, exp. = experimental, cogn. = cognitive, clin. = clinical.

results with a correction for multiple comparisons, this is mentioned in a footnote. The study evaluation was performed according to the following criteria (see Table 1 for overview):

- *ROI regulation vs. control condition* describes whether the target ROI activity was significantly different in the regulation condition as compared to the control condition in the desired direction (i.e., higher in upregulation and lower in downregulation). ROI activity regulation in comparison to the control condition was reported as positive if either (1) the subjects significantly regulated the target ROI activity in the desired direction in comparison to the control condition on average for the whole session in studies comprising one session without an analysis of separate blocks within the session, or (2) the subjects significantly regulated the target ROI activity in the desired direction in comparison to the control condition in the last training block in studies with one session comprising multiple blocks, or (3) the subjects significantly regulated the target ROI activity in the desired direction in comparison to the control condition in the last session on average or in the last block of the last session in studies comprising multiple sessions.
- *ROI regulation vs. control group* describes whether the subjects in the experimental group regulated the target ROI activity significantly better than the subjects in the control group (under the condition that the experimental group did regulate the ROI activity successfully). ROI regulation vs. control group was reported as positive if either (1) there was a significant effect of group on ROI activity regulation in regression analysis, or (2) ROI activity regulation was significantly more successful in the experimental group than in the control group on average in studies without analysis of separate blocks/sessions, or (3) ROI activity regulation was significantly more successful in the experimental group than in the control group in the last block/session in studies analyzing separate blocks/sessions. Because a number of studies do not provide a direct comparison of experimental and control groups, we rated the ROI regulation vs. control group as positive also if (4) there was significant ROI activity regulation in the experimental group, but not in the control group (either on average, or in the last block/session). The evaluation was complemented by "++" if the study directly evaluated the group differences (either in regression analysis, or by t-tests, criterion 1, 2, or 3 met), and by "+" if the study only provided separate results for experimental and control groups (criterion 4 met) to reflect the robustness of the results (see Table 1).
- *Training time effect* describes whether the subjects improved in ROI activity regulation across the NF training course in studies comprising multiple blocks or/and sessions, where ROI activity regulation is defined as a significant difference in regulation and control condition. Hence, the training effect was evaluated as positive if (1) there was a significant effect of training time (either across training blocks or across training sessions) on the ROI activity regulation if regression analysis of the training time effect was reported, or (2) if the ROI activity regulation significantly increased from the first block/session to the last block/session.
- *Transfer effect* was evaluated as positive if there was successful ROI activity regulation in a transfer block, i.e. in a block without NF presentation and following NF training. In studies with a control group, we also evaluated whether there was significant difference in ROI activity regulation in the transfer run between the experimental and control groups (see Table 1).
- Finally, *cognitive or clinical effects vs. baseline or/and control group* was rated positive if there was a significant effect on cognitive or clinical variables in the experimental group following the NF training. A positive result was recorded if there was a difference in cognitive or clinical variables from baseline (i.e., before NF training). If a study included a control group, we also recorded whether there was a significant difference in the effect between the experimental and control groups (see Table 1).

Table 2
Review of rt-fMRI-NF in emotion regulation study parameters.

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
Berman et al. (2013)	right anterior insula (functional: blink suppression task)	up	unspecified upregulation	healthy subjects	C	none	14	none	autobiographical mental imagery
Brühl et al. (2014)	right amygdala (functional: watching negative vs. neutral pictures)	down	negative downregulation	healthy subjects	C	none	6	fearful, sad and angry faces	cognitive reappraisal
Buyukturkoglu et al. (2015)	bilateral anterior insula (anatomical + functional: watching symptom-provoking vs. neutral pictures)	down	negative downregulation	patients with OCD	I	none	3	contamination-related pictures	find a cognitive strategy
Caria et al. (2007)	right anterior insula (anatomical)	up	unspecified upregulation	healthy subjects	C	multiple: 1) no NF, 2) alternate ROI NF (large background region)	9 (EG) +3 (CG1) +3 (CG2)	none	autobiographical mental imagery
Caria et al. (2010)	left anterior insula (anatomical)	up	unspecified upregulation	healthy subjects	C	multiple: 1) no NF, 2) alternate ROI NF (large background region)	9 (EG) +9 (CG1) +9 (CG2)	none	autobiographical mental imagery
Cohen Kadosh et al. (2016)	bilateral insula (functional: emotional Go/NoGo task)	up, down	positive upregulation, unspecified downregulation	healthy children and adolescents (age 7 to 16)	C	none	17	none	happy mental imagery/ relaxation
Gerin et al. (2016)	bilateral amygdala (functional: watching/hearing anxiety-provoking stimuli)	down	negative downregulation	patients with PTSD	C	none	3	personalized trauma scripts (audio recordings)	none (but information about ROI provided)
Greer et al. (2014)	bilateral nucleus accumbens (anatomical)	up, down	positive upregulation, unspecified downregulation	healthy women	C	none	25	none	mental imagery of exciting/boring events
Gröne et al. (2014a)	anterior ACC (anatomical)	up	unspecified upregulation	healthy subjects	C	comparing 3T and 7T scanners	24 (15 in 3T scanner group scanning + 9 in 7T scanner group))	none	mental imagery, concentration on bodily sensations
Hamilton et al. (2011)	subgenual ACC (functional: watching negative images vs. baseline)	down	positive upregulation	healthy subjects	C	yoked NF	8 (EG) +9 (CG)	none	increase positive mood
Hamilton et al. (2016)	individual (functional: watching negative pictures, resulting in AI, OFC, dorsal ACC, or IFG)	down	negative downregulation	women with major depressive disorder	I	yoked NF	10 (EG) +10 (CG)	aversive pictures	cognitive reappraisal, attentional redirection, mental imagery
Hellrung et al. (2018)	left amygdala (anatomical)	up	positive upregulation	healthy men	C, I	continuous NF vs. intermittent NF vs. no NF	16 (continuous) +18 (intermittent) + 8 (no NF)	none	positive autobiographical mental imagery
Herwig et al. (2019)	amygdala (functional: watching negative vs. neutral pictures)	down	negative downregulation	healthy subjects	C	random values	15 (EG) +11 (CG)	aversive pictures	cognitive reappraisal
Johnston et al. (2010)	individual (functional: watching negative vs. neutral pictures, resulting in VLPFC/insula, or MTL incl. amygdala)	up	unspecified upregulation	healthy subjects	C	none	13	none	emotional imagery
Johnston et al. (2011)	individual (functional: watching positive vs. neutral pictures, resulting in VLPFC, DLPFC, insula, or MTL)	up	unspecified upregulation	healthy subjects	C	no NF	17 (EG) +10 (CG)	none	none (but information about ROI selection procedure provided)
Koush et al. (2017)	connectivity from DMPFC onto bilateral amygdala	up	positive upregulation	healthy subjects	I	yoked NF	9 (EG) +6 (CG)	pictures of positive social situations/ nonsocial neutral objects	mental imagery (experiencing the social situation)
Lawrence et al. (2014)	right anterior insula (anatomical)	up	unspecified upregulation	healthy subjects	C	alternate ROI NF (middle parahippocampal region)	16 (EG) +8 (CG)	none	positive/negative autobiographical mental imagery or interceptive awareness

(*continued on next page*)

Table 2 (*continued*)

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
Li et al. (2016a)	individual (MVPA of happy/sad mental imagery)	up	unspecified upregulation	healthy subjects	C	none	12	none	positive/negative autobiographical mental imagery
Li et al. (2016b)	individual (MVPA of happy/sad mental imagery)	up	positive upregulation	healthy subjects	C	no NF	12 (EG) +11 (CG)	none	positive autobiographical mental imagery
Linden et al. (2012)	individual (functional: watching positive vs. neutral pictures, resulting in VLPFC, insula or DLPFC)	up	positive upregulation	patients with current major depressive episode	C	outside the scanner	8 (EG) +8 (CG)	none	positive autobiographical mental imagery
Lorenzetti et al. (2018)	individual (tenderness vs. neutral and anguish vs. neutral contrast, 2 methods: ROI and SVM)[a]	up	positive and negative upregulation	healthy subjects	C	none	8	none	feel tenderness/anguish intensely
MacDuffie et al. (2018)	ACC (functional: negative upregulation vs. (negative downregulation + count) contrast)	up, down	negative upregulation and downregulation	patient with depression after CBT treatment	I	none	13	none	individual strategies training
Marxen et al. (2016)	bilateral amygdala (anatomical)	up, down	unspecified upregulation and downregulation	healthy subjects	C, I	none	33	none	none
Mehler et al. (2018)	individual (functional: watching positive vs. neutral pictures, resulting in limbic and frontal areas)	up	positive upregulation	patients with depression	C	alternate ROI NF (parahippo-campal area)	16 (EG) +16 (CG)	none	positive mental imagery
Misaki et al. (2018)[b]	left amygdala (anatomical)	up	positive upregulation	war veterans with and without PTSD	C	alternate ROI NF (hIPS)	non-PTSD veterans: 17 (EG) [+PTSD veterans: 21 (EG) +9 (CG)]	none	positive autobiographical mental imagery
Moll et al. (2014)	individual (SVM based patterns for tenderness/affection vs. pride-related autobiographical memories)	up	tenderness/ affection or pride upregulation	healthy subjects	C	no NF	12 (EG) +12 (CG)	none	tenderness/affection or pride-evoking autobiographical mental imagery
Nicholson et al. (2017)	bilateral amygdala (anatomical + functional BVS: watching trauma-related vs. neutral words)	down	negative downregulation	patients with PTSD	C	none	10	personalized trauma words	regulate the brain feeling center
Nicholson et al. (2018)[c]	bilateral amygdala (anatomical + functional BVS: watching trauma-related vs. neutral words)	down	negative downregulation	patients with PTSD	C	none	14	personalized trauma words	regulate the brain feeling center
Paret et al. (2014 + 2016b)	bilateral amygdala (anatomical + functional BVS: watching negative vs. neutral pictures)	down	negative downregulation	healthy women	C	alternate ROI NF (rostral caudate)	16 (EG) +16 (CG)	aversive pictures	regulate the brain feeling center
Paret et al. (2016a)	bilateral amygdala (anatomical + functional BVS: watching negative vs. neutral pictures)	down	negative downregulation	women with borderline personality disorder	C	none	8	aversive pictures	regulate the brain feeling center
Paret et al. (2018)	right amygdala (anatomical)	up, down	negative upregulation and downregulation	healthy women	C	none	20	aversive pictures	none
Posse et al. (2003)	bilateral amygdala (anatomical)	up	negative upregulation	healthy subjects	I	none	6	sad and neutral faces	sad autobiographical mental imagery
Rance et al. (2018)	individual (functional: watching neutral vs. symptom provoking	up, down	negative upregulation and downregulation	patients with OCD	C	yoked NF	10 (EG) +7 (CG)	OCD symptom-provoking pictures	none (but information about ROI provided)

(*continued on next page*)

Table 2 (*continued*)

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
	pictures, resulting in orbitofrontal/ ventral frontopolar cortex)								
Ruiz et al. (2013)	bilateral insula (functional: autobiographical mental imagery vs. rest)	up	unspecified upregulation	patients with paranoid schizophrenia	C	none	9	none	autobiographical mental imagery
Sarkheil et al. (2015)	left LPFC (functional: regulate vs. watch aversive pictures)	up	negative downregulation	healthy subjects	I	no NF	8 (EG) +6 (CG)	aversive pictures	cognitive reappraisal training
Scheinost et al. (2013)	orbitofrontal cortex (functional: watching neutral vs. contamination pictures)	up, down	negative upregulation and downregulation	subjects with sub-clinical contamination anxiety	C	yoked NF	10 (EG) +10 (CG)	contamination-related pictures	preparation of strategies with a clinical psychologist before the experiment
Scheinost et al. (2014) [d]	orbitofrontal cortex (functional: watching neutral vs. contamination pictures)	up, down	negative upregulation and downregulation	patients with OCD	C	none	5	contamination-related pictures	preparation of strategies with a clinical psychologist before the experiment
Sitaram et al. (2014)	left anterior insula (functional: autobiographical mental imagery vs. counting task)	up	negative upregulation	sexual offenders	C	none	4	none	negative autobiographical mental imagery
Sulzer et al. (2013)	substantia nigra/ventral tegmental area (anatomical)	up	positive upregulation	healthy subjects	C	inverted NF	15 (EG) +17 (CG)	none	rewarding mental imagery
Veit et al. (2012)	left anterior insula (functional: watching negative pictures vs. rest)	up, down	negative upregulation and downregulation	healthy subjects	C	none	11	threat-related pictures	imagery of being involved in/absent from the aversive pictures
Weiskopf et al. (2003)	rostral—ventral ACC + dorsal ACC (anatomical)	up, down	unspecified upregulation and downregulation	healthy subject	C	none	1	none	none
Yao et al. (2016)	left anterior insula (functional: watching painful vs. neutral pictures)	up	negative upregulation	healthy subjects	C	alternate ROI NF (background region)	18 (EG) +14 (CG)	none	negative autobiographical mental imagery
Young et al. (2014)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (hIPS)	14 (EG) +7 (CG)	none	positive autobiographical mental imagery
Young et al. (2017b + 2017a, 2018)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (hIPS)	19 (EG) +17 (CG)	none	positive autobiographical mental imagery
Yuan et al. (2014)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (hIPS)	27 (EG) +27 (CG)	none	positive autobiographical mental imagery
Zilverstand et al. (2015)	right anterior insula (functional: watching spider pictures vs. rest) + left DLPFC (functional: regulate spider pictures vs. rest)	down (insula) + up (DLPFC)	negative downregulation	women with spider phobia	I	no NF	9 (EG) +9 (CG)	spider pictures	cognitive reappraisal training
Zotev et al. (2011 + 2013)	left amygdala (anatomical)	up	positive upregulation	healthy subjects	C	alternate ROI NF (hIPS)	14 (EG) +14 (CG)	none	positive autobiographical mental imagery
Zotev et al. (2014) [e]	left amygdala (anatomical)	up	positive upregulation	healthy subjects	C	none	6	none	positive autobiographical mental imagery
Zotev et al. (2016)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (left hIPS)	13 (EG) +11 (CG)	none	positive autobiographical mental imagery
Zotev et al. (2018)	left amygdala (anatomical)	up	positive upregulation	patients with PTSD	C	alternate ROI NF (hIPS)	20 (EG) +11 (CG)	none	positive autobiographical mental imagery

(*continued on next page*)

Table 2 (*continued*)

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
Zweerings et al. (2018)	ACC (anatomical)	up	positive upregulation	patients with PTSD + healthy controls	C	none	9 (EG) +9 (CG: healthy controls)	none	positive mental imagery, concentration on bodily sensations

Note: ACC = anterior cingulate cortex, AI = anterior insula, BVS = best voxel selection, CBT = cognitive behavioral therapy, CG = control group, ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, EG = experimental group, hIPS = horizontal intraparietal sulcus, I/C = intermittent/continuous, IFG = inferior frontal gyrus, LPFC = lateral prefrontal cortex, MTL = medial temporal lobe, MVPA = multivariate voxel pattern analysis, NF = neurofeedback, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, ROI = region of interest, SVM = support vector machine, VLPFC = ventrolateral prefrontal cortex.

[a] ROI method resulted in septohypothalamic area for tenderness vs. neutral contrast and right amygdala for anguish vs. neutral contrast.

[b] Study includes original data from 17 war veterans without PTSD and additional analyses of data from 30 war veterans with PTSD (21: EG, 9: CG) previously published in Zotev et al. (2018).

[c] 10 out of 14 subjects are the same subjects whose data was already presented in Nicholson et al. (2017).

[d] Only originally obtained data are reported for this study; however, the study also presents a secondary analysis of data from 10 subjects with sub-clinical contamination anxiety (only experimental group) from a study by Scheinost et al. (2013).

[e] This study used simultaneous fMRI and EEG neurofeedback presentation.

3. Results

Study characteristics are described in Table 2.

3.1. Target brain areas and target populations

Fig. 1 shows a representation of target brain regions and target populations.

3.2. Emotion regulation protocols

Fig. 2 shows the distribution of emotion regulation protocols (downregulation vs. upregulation and use of additional emotion-evoking stimuli). If a study used more than one regulation condition (e.g., negative downregulation and negative upregulation), it is included in all respective categories in Fig. 2. Studies that instructed the subjects to increase the intensity of emotions without specifying the emotional valence, and studies that instructed the subjects to regulate the NF scale directly without further specification are referred to as "unspecified upregulation" in Table 2 and Fig. 2. Studies that instructed the subjects to downregulate emotions without specifying the emotional valence (i.e., to generally detach from emotional experiences or simply "calm down emotionally") and studies that instructed the subjects to downregulate the NF scale directly without further specification are referred to as "unspecified downregulation" in Table 2 and Fig. 2.

3.3. Continuous vs. intermittent NF presentation

Most studies (k = 42) presented NF as a continuous scale, updated with every newly acquired brain scan. K = 7 studies presented intermittent NF. Hellrung et al. (2018) directly compared the use of continuous and intermittent NF, and Marxen et al. (2016) presented continuous NF to the subjects in the first two blocks followed by a third block with intermittent NF.

3.4. Control groups

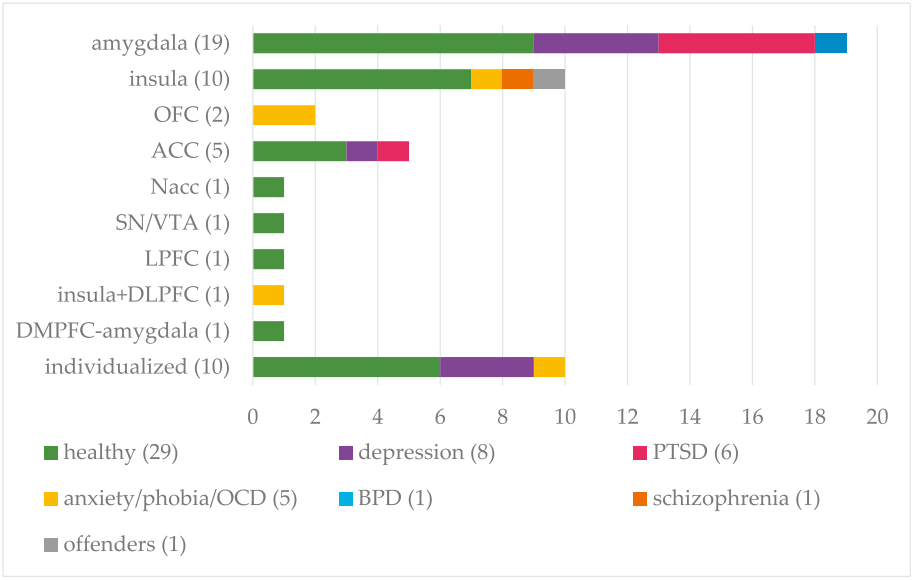
Fig. 3 shows the distribution of control groups.

3.5. Instructions for emotion regulation

Fig. 4 shows the distribution of instructions provided to subjects. If multiple instruction options were given in one study, the study is included in all relevant categories in Fig. 4.

3.6. Evaluation of study results

Table 3 presents the evaluation of the results of studies with a predefined target brain area, structured according to the target brain areas, target populations, and emotion regulation protocols (i.e., direction of ROI regulation, direction and valence of emotions to regulate, presentation of emotion-evoking stimuli, and number of fMRI sessions including NF training). Table 4 presents the evaluation of the results of studies with individually navigated brain targets. Pilot studies with six or fewer subjects were not included in Tables 3 and 4 because the small sample size prevented statistical evaluation (Buyukturkoglu et al., 2015; Gerin et al., 2016; Scheinost et al., 2014; Sitaram et al., 2014; Weiskopf et al., 2003; Zotev et al., 2014). Moreover, Rance et al. (2018) was not included as the results are not presented separately for the group performing emotion regulation NF training.



Note: ACC = anterior cingulate cortex, BPD = borderline personality disorder, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, LPFC = lateral prefrontal cortex, Nacc = nucleus accumbens, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, SN/VTA = substantia nigra/ventral tegmental area

Fig. 1. Target brain regions and populations.
Note: ACC = anterior cingulate cortex, BPD = borderline personality disorder, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, LPFC = lateral prefrontal cortex, Nacc = nucleus accumbens, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, SN/VTA = substantia nigra/ventral tegmental area.

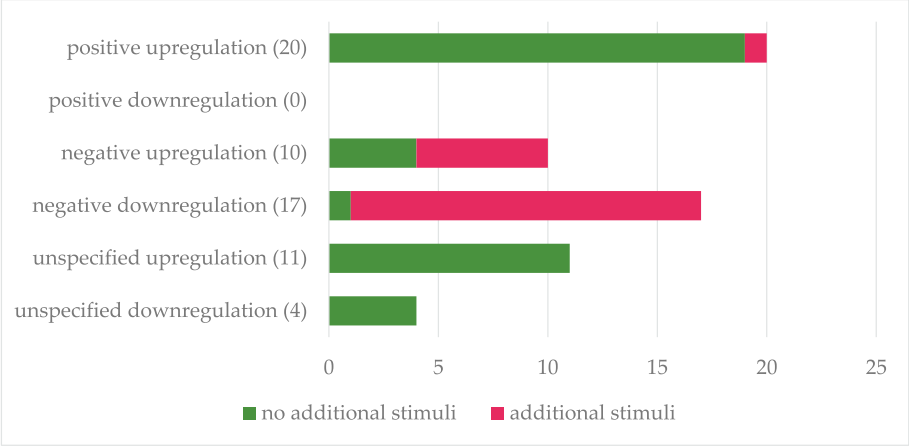


Fig. 2. Emotion regulation tasks and emotional stimuli presentation.

4. Discussion

4.1. Brain targets and populations

4.1.1. Amygdala

Healthy people as well as patients with depression have been found to upregulate activity in the amygdala by increasing positive emotions at rates higher than control groups in all studies that reported an intergroup comparison (see Table 3). In all of these studies, training and transfer effects were also positive (if assessed). Moreover, three out of four studies in patients with depression found significant improvement in depression, anxiety, or happiness over the control groups. PTSD patients upregulated amygdala activity by increasing positive emotions only in the first out of three sessions in a study by Zotev et al. (2018), but a decrease in PTSD symptoms was found after the training, although this was not different from the control group. Amygdala upregulation by increasing negative emotions was explored in two studies (see Table 3); only the subjects in the study by Posse et al. (2003) achieved ROI upregulation. Subjects in this study may have been successful in regulation due to the choice of baseline condition, which consisted of watching neutral pictures (in comparison to watching negative pictures in the experimental condition), as opposed to the study by Paret et al. (2018), in which negative amygdala upregulation was not successful in comparison to the baseline consisting of watching negative pictures. Moreover, the subjects in the study by Paret et al. (2018) performed both upregulation and downregulation tasks within one session, which might be more challenging, and it could require more time than a single session to learn amygdala regulation.

Downregulation of the amygdala by decreasing negative emotions has been found successful in healthy people (except in the 2018 study by Paret et al., see above) and in patients with BPD and PTSD (see Table 3). However, only two of these studies employed a control group and they show a different pattern of intergroup comparison. While healthy people in the study by Herwig et al. (2019) did downregulate amygdala activity significantly better than the control group, there was no difference in amygdala downregulation between the groups of healthy people in the

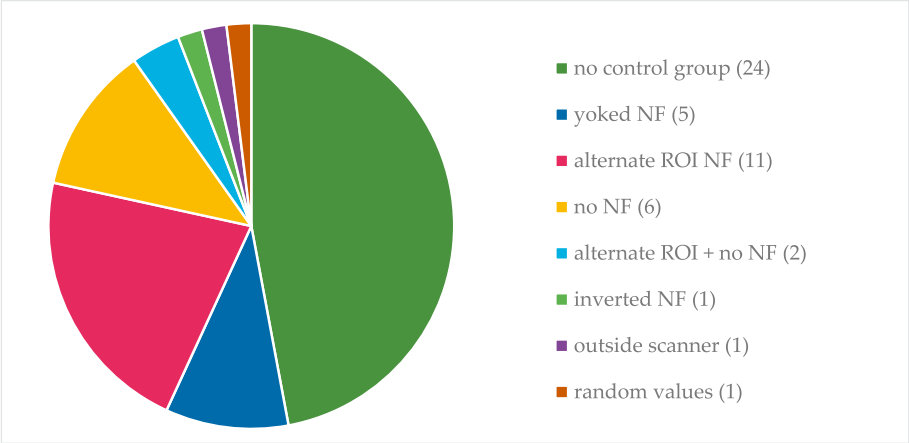


Fig. 3. Control groups.

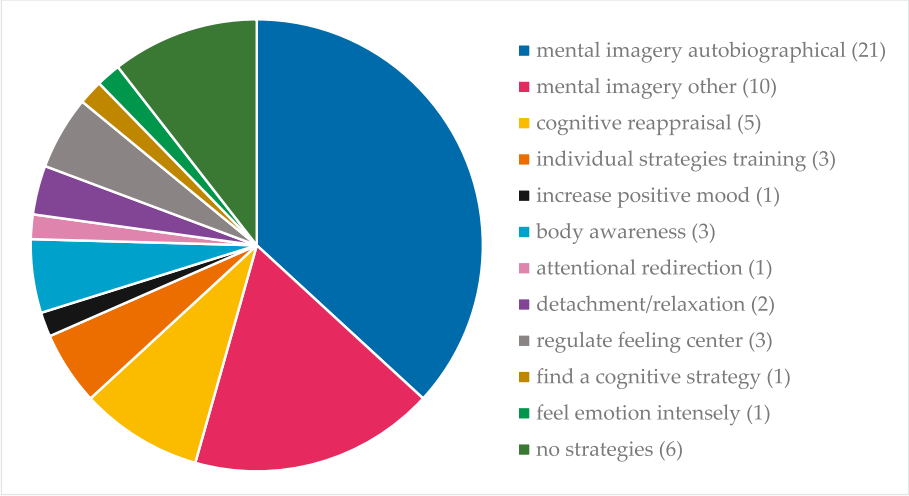


Fig. 4. Instructions for emotion regulation strategies.

study by Paret et al. (2014). However, the experimental group in this study was successful in amygdala downregulation in transfer run, unlike the control group. Also note that the subjects in this study only underwent a single NF session, while the subjects in the study by Herwig et al. (2019) were training for four sessions. Thus, a longer time provided for NF training can naturally lead to stronger ROI regulation in experimental groups. Moreover, the clinical effects of NF training were evaluated by Paret et al. (2016a). A decrease in dissociation and an increase in emotional awareness was found following the NF training in patients with BPD, but comparison with a control group is lacking.

In sum, NF has been shown to promote amygdala upregulation by increasing positive emotions in both healthy people and patients with depression. NF training has also shown amygdala upregulation improvement lasting after the removal of NF and clinical symptom improvement in the patients with depression. Successful amygdala downregulation by decreasing negative emotions while using NF has been observed in healthy people and patients with BPD and PTSD, though control groups are lacking in most of these studies.

4.1.2. Anterior insula

Most studies of AI upregulation do not distinguish between positive and negative emotional upregulation strategies (i.e., unspecified upregulation). All of these studies found successful AI upregulation in healthy people in comparison to control conditions as well as to control groups (where available). Successful AI upregulation was also found in patients with schizophrenia (Ruiz et al., 2013) where the training led to improvement in emotion recognition (without control group involvement). AI upregulation by direct instruction to upregulate negative emotions has been found to be successful in healthy people in two studies. One of these studies involved a control group and found the NF in the experimental group led to more successful AI upregulation as compared to control group (Yao et al., 2016). AI upregulation by increasing negative emotions was also explored in sexual offenders (Sitaram et al., 2014). Only four subjects participated in this study and only one of them upregulated AI. The sample size in this study was too low to draw definite conclusions; however, NF training can be possibly more challenging and require more training time and motivation in this clinical group.

On the other hand, AI downregulation seems to be more challenging, with only one study demonstrating successful AI downregulation by decreasing negative emotions in subjects with spider phobia (Zilverstand et al., 2015). NF in the experimental group in this study led to more successful AI downregulation in comparison to the control group as well as to a larger long-term decrease in spider phobia-related anxiety. Unlike the other studies of AI downregulation, Zilverstand et al. (2015) presented the subjects with AI NF and also with PFC NF, which may have influenced the regulation success. Moreover, the studies that either did not find or did not report the AI downregulation as compared to the control condition used both downregulation and upregulation within one study. The results of the study by Cohen Kadosh et al. (2016) are difficult

Table 3
Evaluation of the results of studies with predefined brain targets in relation to target brain area, target population, and emotion regulation protocols.

Region	Task	Emotions	Population	Studies	Emotional stimuli	NF sessions	ROI regulation (vs. CG)	Training time effect	Transfer effect	Cogn./clin. effects vs. baseline (and CG)
amygdala	up	positive up	healthy	Hellrung et al. (2018)	N	1	NR	NR	Y (CG ++)	NA
				Zotev et al. (2011)	N	1	Y (CG++)	Y	Y (CG ++)	NA
			depression	Young et al. (2014)	N	1	Y (CG ++)	Y	Y (CG ++)	Y (CG ++)
				Young et al. (2017b)	N	2	Y (CG ++)	NR	Y (CG ++)	Y (CG ++)
				Yuan et al. (2014)	N	1	NR	NR	NR	Y (CG -)
				Zotev et al. (2016)[a]	N	1	N (CG ++)	Y	Y (CG +)	Y (CG, ++)
			PTSD	Misaki et al. (2018)	N	3	NR	NR	NR	Y (CG +)
				Zotev et al. (2018)	N	3	N[b] (CG -)	N	N	Y (CG +)
		negative up	healthy	Paret et al. (2018)	Y	1	N[c] (no CG)	NR	NA	NA
				Posse et al. (2003)	Y	1 to 5	Y (no CG)	NA	NA	NA
		unspec. up	healthy	Marxen et al. (2016)	N	3	N (no CG)	N	N[d]	NA
	down	negative down	healthy	Brühl et al. (2014)	Y	4	Y (no CG)	Y	NA	NA
				Herwig et al. (2019)	Y	4	Y (CG ++)	Y	N[e]	NA
				Paret et al. (2014)	Y	1	Y (CG -)	NR	Y (CG +)	NA
				Paret et al. (2018)	Y	1	N[f] (no CG)	NR	NA	NA
			BPD	Paret et al. (2016a)	Y	4	Y (no CG)	NR	N	Y (no CG)
			PTSD	Nicholson et al. (2017)	Y	1	Y (no CG)	N	Y	NA
				Nicholson et al. (2018)	Y	1	Y (no CG)	N	Y	NA
		unspec. down	healthy	Marxen et al. (2016)	N	3	N (no CG)	N	Y	NA
anterior insula	up	positive up	healthy	Cohen Kadosh et al. (2016)	N	4	NA[g] (no CG)	N	NA	NA
		negative up	healthy	Veit et al. (2012)	Y	1	Y (no CG)	N	NA	NA
				Yao et al. (2016)	N	1	Y (CG ++)	Y	Y (CG ++)	Y (CG ++)
		unspec. up	healthy	Berman et al. (2013)	N	1	Y (no CG)	N	N	NA
				Caria et al. (2007)	N	1	Y (CG +)	Y	Y (CG NA)	NA
				Caria et al. (2010)	N	1	Y (CG ++)	Y	NA	Y (CG ++)
				Lawrence et al. (2014)	N	1	Y (CG ++)	Y	NA	N
			schizophrenia	Ruiz et al. (2013)	N	4	Y (no CG)	Y	N	Y (no CG)
	down	negative down	healthy	Veit et al. (2012)	Y	1	N[h] (no CG)	N	NA	NA
		negative down	spider phobia	Zilverstand et al. (2015)	Y	1	Y (CG ++)	Y	NA	Y (CG ++)
		unspec. down	healthy	Cohen Kadosh et al. (2016)	N	4	NA[f] (no CG)	N	NA	NA
ACC	up	positive up	PTSD	Zweerings et al. (2018)[i]	N	3	Y (no CG)	Y	Y (no CG)	Y (no CG)
		unspec. up	healthy	Gröne et al. (2014a)	N	1	Y (no CG)	Y	NA	Y
	down	positive up	healthy	Hamilton et al. (2011)	N	1	Y (CG ++)	N	N	NA
		negative down	depression	MacDuffie et al. (2018)	N	1	NR (no CG)	NR	NA	Y
OFC	up + down	negative up + down	contam. anxiety	Scheinost et al. (2013)	Y	2	NR	NR	NR	Y (CG ++)
NAcc	up	positive up	healthy	Greer et al. (2014)	N	1	Y (no CG)	N	N	NA
	down	unspec. down	healthy	Greer et al. (2014)	N	1	N (no CG)	N	N	NA
SN/VTA	up	positive up	healthy	Sulzer et al. (2013)	N	1	Y/N[j] (CG +)	N	Y	NA

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Table 3 (*continued*)

Region	Task	Emotions	Population	Studies	Emotional stimuli	NF sessions	ROI regulation (vs. CG)	Training time effect	Transfer effect	Cogn./clin. effects vs. baseline (and CG)
PFC	up	negative down	healthy	Sarkheil et al. (2015)	Y	1	NR (CG -)	NR	NA	N
			spider phobia	Zilverstand et al. (2015)	Y	1	Y (CG -)	N	NA	Y (CG ++)
PFC-limbic connectivity	up	positive up	healthy	Koush et al. (2017)	Y	3	Y (CG ++)	Y	Y (CG ++)	Y (CG ++)

Y = yes, N = no, NA = not assessed, NR = not reportedACC = anterior cingulate cortex, AI = anterior insula, BPD = borderline personality disorder, CG = control group, clin. = clinical, cogn. = cognitive, contam. = contamination, NAcc = nucleus accumbens, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PFC = prefrontal cortex, PTSD = posttraumatic stress disorder, ROI = region of interest, SN/VTA = substantia nigra/ventral tegmental area, unspec. = unspecified.

[a] Results FDR corrected.

[b] ROI regulation significant only in the first out of three sessions.

[c] Refers to comparison with control "view" condition; ROI upregulation was significant in comparison with "down" condition.

[d] Refers to comparison with "rest" condition; ROI upregulation was significant in comparison with "down" condition in transfer run.

[e] As compared to baseline task performed before NF training.

[f] Refers to comparison with control "view" condition; ROI downregulation was significant in comparison with "up" condition.

[g] Only comparison of downregulation vs. upregulation conditions available.

[h] Refers to comparison with "no-regulation" condition, comparison with "up-regulation" condition was significant.

[i] No relevant CG for evaluation of the NF effect, CG included healthy participants who underwent the same procedure as participants in the EG.

[j] Yes based on average results per three runs; No based on the results from the last run.

to interpret because no neutral control condition was used. However, the subjects in the study by Veit et al. (2012) demonstrated successful AI upregulation, but not downregulation, suggesting that downregulating AI could be more challenging than upregulating it.

In sum, NF has been found to promote AI upregulation in healthy people. AI upregulation with the use of NF has also been found successful in patients with schizophrenia, but comparison with a control group is needed. AI downregulation, in contrast, seems to be more challenging, but still possible, as demonstrated by successful AI downregulation in phobia patients, associated with long-term anxiety decreases, as compared to a control group (Zilverstand et al., 2015).

4.1.3. Other regions related to emotional arousal

ACC has been successfully upregulated with the use of NF in healthy people (Gröne et al., 2014b) and in patients with PTSD (Zweerings et al., 2018) in which the NF training also led to decreased PTSD symptoms. Moreover, NF led to more successful ACC downregulation in an experimental group as compared to a control group in healthy people (Hamilton et al., 2011). Note that ACC upregulation (Zweerings et al., 2018) and downregulation (Hamilton et al., 2011; subgenual ACC) was achieved by the same strategy, specifically by increasing positive emotions. This fact probably relates to functional differentiation of ACC subparts (Stevens et al., 2011) which should be addressed in rt-fMRI-NF studies using ACC.

OFC has been selected as a suitable region for rt-fMRI-NF training in patients with OCD because of its hyperactivity associated with OCD symptoms (Mataix-Cols et al., 2004, 2003). The respective studies (Scheinost et al., 2014, 2013) used a design in which the subjects were trained to both downregulate and upregulate the OFC to achieve better general control over it (Hampson et al., 2012). Regulation success for OFC downregulation and upregulation in comparison to control conditions was not presented in these studies; however, the training led to significant long-term decreases in anxiety in subjects with contamination anxiety as compared to the control group (Scheinost et al., 2013), and to some decrease in anxiety in patients with OCD which was not statistically evaluated because of the small sample size (Scheinost et al., 2014).

Finally, upregulation of dopaminergic reward-related areas was found to be successful with positive emotion upregulation in healthy people in two studies (Greer et al., 2014; Sulzer et al., 2013). Downregulation of these regions seems to be more challenging, as demonstrated by unsuccessful downregulation as compared to control conditions in Greer et al. (2014).

4.1.4. Prefrontal cortex

NF did not yield augmented PFC-regulation in two studies that explored this issue (see Table 3). The results suggest that the PFC can be regulated with or without NF, but that subjects do not regulate the PFC better with PFC NF presentation. However, although subjects with spider phobia did not regulate the PFC more than the control group in Zilverstand et al. (2015), the presence of the PFC NF signal may have influenced the successful AI and anxiety downregulation observed in this study. Similarly, in Sarkheil et al. (2015), the subjects did not regulate the PFC more than the control group, but amygdala activity was significantly lower in the experimental group who trained emotion regulation with PFC NF as compared to the control group. Koush et al. (2017) presented NF not separately from the PFC, but directly from prefrontal-limbic connectivity, which was found to represent cognitive emotion regulation ability (Ochsner et al., 2012). The authors found that healthy people were able to upregulate connectivity between DMPFC and the amygdala more successfully than the control group. In sum, it seems that the PFC regulation is not improved by NF, but that presentation of NF from the PFC might improve regulation of other regions, such as the amygdala or insula.

4.1.5. Individualized target areas

Some studies did not use a predefined region from which to present NF, but instead located target regions individually by functional navigation. This approach may result in NF more closely corresponding with a specific function/emotion and may overcome individual differences in functional localization. On the other hand, interpretation of the results is more difficult, because subjects regulate different neural patterns within one study, not necessarily confined to a particular brain region (see Table 4). Brain targets in these studies are navigated either by the BOLD signal contrast between watching emotional vs. neutral pictures, or by the BOLD signal corresponding to emotional imagery. The resulting brain targets are usually located within areas such as the insula, amygdala, ACC, or various PFC regions (see Table 4). In some studies, a corresponding brain network pattern rather than a single target region has been found by computational methods and used for NF (Li et al., 2016a, 2016b; Lorenzetti et al., 2018; Moll et al., 2014). In all of these studies with available respective analyses, the successful regulation of brain targets in comparison to control conditions and control groups has been observed with one exception (Mehler et al., 2018; see Table 4). Thus, individual navigation of brain targets for NF generally leads to successful ROI regulation in healthy people which seems to be augmented by NF.

Table 4
Evaluation of the results of studies with individually navigated brain targets in relation to functional navigation type, target population, and emotion regulation protocols.

Study	Functional navigation (target areas)	Task	Emotions	Population	Emotional stimuli	NF sessions	ROI regulation	Training time effect	Transfer effect	Cogn./clin. effects vs. baseline (and CG)
Hamilton et al. (2016)	watching negative pictures (AI, OFC, dACC, IFG)	down	negative down	healthy subjects	Y	1	NR	NR	Y (CG ++)	Y (CG ++)
Johnston et al. (2010)	watching negative vs. neutral pictures (VLPFC, insula, MTL incl. amygdala)	up	unspec. up	healthy subjects	N	1	Y (no CG)	Y	NA	NR
Johnston et al. (2011)	watching positive vs. neutral pictures (VLPFC, insula, amygdala)	up	unspec. up	healthy subjects	N	1	Y (CG ++)	Y	NA	N
Li et al. (2016a)	MVPA of happy/sad mental imagery	up	unspec. up	healthy subjects	N	1	NR (no CG)	NR	NA	NA
Li et al. (2016b) [b]	MVPA of happy/sad mental imagery	up	positive up	healthy subjects	N	1	Y (CG ++)	Y	NA	N
Linden et al. (2012)	watching positive vs. neutral pictures (VLPFC, insula, DLPFC)	up	positive up	patients with depression	N	4	Y (CG outside scanner)	Y	NA	Y (CG ++)
Lorenzetti et al. (2018)	tenderness/anguish vs. neutral, 2 methods: 1. ROI: septo-hypothalamic area (tenderness), right amygdala (anguish); 2. SVM)	up	positive and negative up	healthy subjects	N	2	Y[c] (no CG)	NR	NA	Y
Mehler et al. (2018) [d]	watching positive vs. neutral pictures (limbic and frontal regions)	up	positive up	patients with depression	N	4	N (CG -)	N	N	Y (CG -)
Moll et al. (2014) [a]	SVM of tenderness and pride	up	positive up	healthy subjects	N	1	Y (CG ++)	Y	NA	N

Y = yes, N = no, NA = not assessed, NR = not reportedAI = anterior insula, CG = control group, clin. = clinical, cogn. = cognitive, contam. = contamination, dACC = dorsal anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, MTL = middle temporal lobe, MVPA = multivoxel pattern analysis, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, ROI = region of interest, SVM = support vector machine, unspec. = unspecific, VLPFC = ventrolateral prefrontal cortex.

[a] Yes based on average results per three runs; No based on the results from the last run.

[b] ROI regulation results are based on percentage of trials correctly classified by SVM classifier, taken as an indicator of successful engagement of ROI reflecting predefined emotional state.

[c] Results FWE corrected.

[d] Results FDR corrected.

One study also demonstrated successful ROI regulation in patients with depression with improvement in depression scores as compared to a control group.

4.1.6. Summary of brain targets and populations

In sum, the amygdala and AI were shown to be suitable targets for rt-fMRI-NF in healthy people and in several patient groups. Amygdala activity turned out to be a feasible target for upregulation by increasing positive emotions and for downregulation by decreasing negative emotions. In contrast, the feasibility of AI upregulation gained more empirical support than downregulation in healthy people, though one study showed positive outcomes for phobic patients (Zilverstand et al., 2015). Other regions related to emotional processing, such as the ACC, OFC, and dopaminergic reward-related regions, appear to be suitable for NF in emotion regulation as well. On the other hand, PFC regulation does not seem to be augmented by NF, at least in studies that presented NF from a predefined region. The presence of PFC NF can be associated with decreased activity in limbic regions and reduction in clinical symptoms. The feasibility of prefrontal regulation is more consistent in studies that used individual functional navigation of ROIs. Connectivity-based NF seems to be a promising path to NF emotion regulation training. Although the individual selection of target regions based on functional navigation has been shown to produce successful NF regulation in healthy people and patients with depression, this approach may have limitations for patient populations in general. It is possible that regions could not be detected by functional localizer tasks because these regions are not activated in the contrast due to functional impairment. In terms of patient populations suitable for NF, patients with depression, PTSD, OCD, contamination anxiety, spider phobia, BPD, and schizophrenia have been shown to be able to regulate the activity of various brain regions using NF presentation, though more studies with control groups are needed. Some studies have also shown improvement in clinical symptoms and potential for long-term clinical effect sustainability following NF training. Since many studies lack control groups and/or cognitive/clinical effect evaluation, the conclusions are rather preliminary and require further empirical testing and more conservative elaboration in the future (e.g., by a meta-analysis when enough data is generated).

4.2. Emotion regulation protocols

4.2.1. Upregulation tasks

All but one study instructing subjects to upregulate positive emotions presented no additional stimuli (Fig. 2). Another group of studies similarly did not present any additional stimuli but instructed the subjects to use either positive or negative mental strategies for upregulation (referred to as “unspecified upregulation”). The majority of these studies show positive results irrespective of brain targets and populations (see Table 3), although comparisons with control groups are absent in some studies. The relative lack of studies presenting additional stimuli and instructing subjects to upregulate emotions may stem from the task characteristic itself: if we want the subjects to learn to increase the intensity of their emotional experiences, it could be counterproductive to evoke emotions by presenting additional stimuli at the beginning of the

trial. In such designs, a possible ceiling effect could prevent subjects from further increasing their emotions. Another reason could be that most upregulation studies instruct subjects to use mental imagery for upregulation, which can potentially interfere with other visual stimuli.

On the other hand, Koush et al. (2017) showed that positive emotion upregulation using additional stimuli is possible. In this study, NF led to more successful PFC-limbic connectivity upregulation in subjects who were watching positive social situation pictures and their task was to imagine experiencing the scene. This study shows the potential for enhancing positive emotions associated with specific, e.g. socially desirable stimuli. In contrast, several studies used the upregulation of negative emotions with the presentation of additional stimuli. In contrast to the study by Paret et al. (2018), subjects in the study by Veit et al. (2012) were able to upregulate AI while watching threat pictures by imagining themselves being involved in the situation. The discrepancy in the results of the two studies is likely related to the different target regions. While upregulation of amygdala activity by increasing negative emotions during simultaneous presentation of negative stimuli is difficult because of the ceiling effect, upregulation of AI activity in the same situation could be more feasible because AI is involved not only in the processing of negative emotions, but also in the general NF control network (Emmert et al., 2016; Paret et al., 2018).

4.2.2. Downregulation tasks

All but one study focused on downregulating negative emotions presented emotion-evoking stimuli (see Fig. 2). The suitability of this approach, i.e. arousing emotions by external stimuli and the subsequent downregulation of the evoked emotions, is supported by successful brain target regulation in the majority of respective studies, irrespective of the target population and the nature of the emotional stimuli (see Table 3). The two studies that did not find regulation success compared to control conditions were from Veit et al. (2012) and Paret et al. (2018). As mentioned earlier, mixing downregulation and upregulation in these studies could have made the negative downregulation more difficult. However, the absence of control groups in most of these studies prevented the evaluation of NF-added value. The only study involving negative emotion downregulation without emotional stimuli used an approach in which the subjects were first instructed to upregulate negative emotions themselves using mental imagery and, subsequently, to downregulate those negative emotions (MacDuffie et al., 2018), but the results of the ROI downregulation were not reported in this study.

Downregulation of positive emotions has not been studied. Two out of four studies referred to in Fig. 2 and Table 2 as “unspecified downregulation” instructed subjects to decrease overall emotional experiences without presenting any additional stimuli; subjects were instructed specifically to relax or “turn off the engine” (Cohen Kadosh et al., 2016) or to imagine boring events (Greer et al., 2014). This approach could serve for more general, situation-unspecific training of relaxation or meditation that could be aided by fMRI-NF. However, existing studies do not provide sufficient support for the success of this approach due to a lack of control conditions and control groups. To be successful, this kind of neural regulation may require more training time, since the number of sessions in the current studies was limited. Another two studies exploring unspecified downregulation (Marxen et al., 2016; Weiskopf et al., 2003) did not provide the subjects with any instructions for regulation. Weiskopf et al. (2003) presented only single-subject data; the subjects in Marxen et al. (2016) did not downregulate ROI during the NF training as compared to the control condition, but they were successful in transfer runs.

In sum, the use of NF to upregulate either positive or negative emotions seems to be possible without presenting additional stimuli, though success depends on the target region. A few studies show the feasibility of upregulating emotions with a parallel presentation of emotion-evoking stimuli, though this task seems prone to failure. On the other hand, downregulation training seems to be more suitable with the use of stimuli to evoke emotions that can be consequently downregulated.

4.2.3. Ethical issues in emotion upregulation and downregulation

While upregulating positive emotions and downregulating negative emotions represent clearly desirable tasks from a clinical point of view, the upregulation of negative emotions and downregulation of positive emotions bring some ethical concerns. How could it be useful to promote negative emotions? In total, 10 studies included negative upregulation. The studies can be divided into three categories based on the purpose of the negative upregulation. Lorenzetti et al. (2018), Paret et al. (2018), Posse et al. (2003), and Veit et al. (2012) used negative upregulation training in healthy people from a basic science perspective, i.e. to examine the neural correlates of the negative emotion upregulation process. These studies contributed to the understanding of brain mechanisms of emotion regulation, NF control, and NF monitoring.

Two other studies used negative upregulation with the aim of promoting emotional awareness or empathy, specifically Sitaram et al. (2014) in sexual offenders and Yao et al. (2016) in healthy people. Emotional awareness, including awareness of both positive and negative emotions, is an important condition for adaptive emotion regulation (Gross and Jazaieri, 2014) and it is decreased in many psychiatric patient populations, such as patients with eating disorders (Westwood et al., 2017), schizophrenia (O'Driscoll et al., 2014), addiction (Morie et al., 2017), and somatization disorders (De Gucht and Heiser, 2003). Thus, negative upregulation as part of emotional awareness training could be theoretically beneficial in patient groups with reduced emotional awareness, but careful debriefing and clinical monitoring is needed to prevent any adverse effects on emotional wellbeing.

Finally, MacDuffie et al. (2018), Rance et al. (2018), Scheinost et al. (2013), and Scheinost et al. (2014) used negative upregulation together with negative downregulation as part of training to generally control the target brain area. Since all four studies demonstrated improvements in some cognitive or clinical outcomes in the experimental groups, such an approach could constitute a promising method of brain activity regulation learning, possibly by teaching the patients flexible neural control or by making the patients aware of the mental processes that promote symptom intensity.

Overall, using negative upregulation might be useful in some cases, but could be harmful in others. It is necessary to point out that rt-fMRI-NF has the potential to induce long-term changes that should be considered when implementing negative upregulation in NF designs. The question remains whether positive emotion downregulation, which has not yet been used in rt-fMRI-NF studies, could be also beneficial in some way. Although intentional reduction of positive emotions may sound clinically irrelevant or even inappropriate, it could theoretically be useful in patients who show exaggerated reactions to positive stimuli with possibly adverse consequences, such as patients with bipolar disorder (Keener et al., 2012) or with high positive urgency (Cyders and Smith, 2007).

4.3. Continuous vs. intermittent NF

Hellrung et al. (2018) directly compared success in amygdala upregulation between continuous and intermittent NF with a no NF control group. The authors conclude that intermittent presentation is superior to continuous presentation because continuous NF is more cognitively demanding. However, this factor did not lead to a difference in regulation success between the groups, suggesting that both methods of NF presentation (i.e., continuous and intermittent) may have their specific characteristics, but can be similarly effective. Regarding the hypothesis that intermittent NF may be more useful in studies with additional stimuli presentation due to the reduction of visual distractors, all studies that presented NF in the intermittent form also presented emotional stimuli (Buyukturkoglu et al., 2015; Hamilton et al., 2016; Koush et al., 2017; Posse et al., 2003; Sarkheil et al., 2015; Zilverstand et al., 2015). However, ROI regulation success seems to follow from different parameters than the choice of continuous or intermittent NF presentation in these studies. Specifically, ROI regulation was successful for all ROIs in these studies except the PFC regulation in Sarkheil et al. (2015) and

Zilverstand et al. (2015) and the results of Buyukturkoglu et al. (2015) are influenced by low statistical power. On the other hand, another group of studies that presented emotion-evoking stimuli used continuous NF (Brühl et al., 2014; Herwig et al., 2019; Nicholson et al., 2017; Paret et al., 2018, 2016a; 2014; Rance et al., 2018; Scheinost et al., 2014, 2013; Veit et al., 2012), but most of these studies did not use a control group or do not report regulation success or found differences only in down-regulation vs. upregulation blocks, not in comparison to a baseline control condition.

In sum, successful ROI regulation in studies with emotion evoking stimuli were reported in studies with both intermittent (Hamilton et al., 2016; Koush et al., 2013; Zilverstand et al., 2015) and continuous (Brühl et al., 2014; Herwig et al., 2019; Paret et al., 2016a, 2014) NF. However, there is currently not enough evidence to state whether the use of continuous or intermittent NF is superior in emotion regulation. More studies comparing both continuous and intermittent NF presentation are needed, especially studies with simultaneous emotional stimuli presentation.

4.4. Control groups

Some changes following the presentation of alternate ROI NF in control groups were found; however, the observed effects were more pronounced in the experimental groups. Specifically, healthy subjects in both the experimental and control groups in the study by Paret et al. (2014) were able to downregulate the amygdala, but the effect persisted in the transfer run only in the experimental group, and connectivity with the VMPFC only increased with amygdala NF (Paret et al., 2016b). Yuan et al. (2014) found altered amygdala connectivity in both the experimental and control groups in patients with depression; however, it was related to decreased depression symptoms only in the experimental group. Other studies found successful regulation and behavioral effects only in experimental groups (Hamilton et al., 2016; Lawrence et al., 2014; Misaki et al., 2018; Yao et al., 2016; Young et al., 2017b, 2014, Zotev et al., 2018, 2011). The only study with alternate ROI NF control group which found the same pattern of results in experimental and control groups is the study by Mehler et al. (2018); however, the study presents results only with FDR correction which probably makes the results underestimated in comparison to the majority of studies presenting uncorrected results.

Studies which used yoked NF in control groups generally did not find regulation success or cognitive/clinical effects in the control groups in healthy people (Hamilton et al., 2011; Koush et al., 2017), patients with depression (Hamilton et al., 2016), or patients with anxiety (Rance et al., 2018; Scheinost et al., 2013). From the studies with no NF control group, Zilverstand et al. (2015) found reduced anxiety after AI downregulation training in both the experimental and the control group, supporting the learning potential of the emotion regulation protocol itself; however, the effect was again more pronounced in the experimental group (regarding both AI downregulation and anxiety decrease). Other studies found successful NF regulation or cognitive/clinical effects only in experimental groups (Hellrung et al., 2018; Johnston et al., 2011; Li et al., 2016b; Moll et al., 2014; Sarkheil et al., 2015). Two studies provided a direct comparison of multiple control groups (Caria et al., 2010, 2007). In both studies, healthy people were instructed to upregulate AI and the regulation was successful only in the experimental group as compared to the no NF and alternate ROI NF control groups. However, samples in both studies are too small to draw further conclusions about the control group types.

In sum, regardless of control group type, most studies show some effects in experimental groups exclusively. Although some studies demonstrated either successful ROI regulation or cognitive/clinical effects in control groups, the results were usually more pronounced in experimental groups, demonstrating an additional effect of NF. First, it should be noted that at least some of the findings likely result from unplanned exploratory analyses. Therefore, the risk of false positives is increased and findings that have not yet been replicated should be interpreted with caution. Second, there is no evidence that yoked or alternate ROI NF would lead to worse performance or negative cognitive/clinical effects, with the exception of the study by Caria et al. (2010) in which the control group decreased activity in AI while their task was AI upregulation. Third, yoked NF could undermine learning emotion regulation by confusing the subjects, leading to an absence of changes in control groups. Compared to yoked NF, more effects in both regulation success and cognitive/clinical effects have been observed in control groups with alternate ROI NF of the subject's own brain. It is theoretically possible that subjects can partially profit from seeing this form of NF that still results from activity in their own brains. Fourth, only one study in which the control group used no NF found partial effects in the control group. However, learning can be undermined in such no NF groups because of the absence of blinding and the different motivational aspects between the experimental and control groups. More studies with sufficiently large samples and appropriate blinding are needed to directly compare outcomes with different control group types.

4.5. Emotion regulation instructions

Studies differ in the type of emotion regulation instructions (e.g., mental imagery or cognitive reappraisal; see Fig. 4), as well as in the level of instruction detail or previous training in emotion regulation strategies. For example, in studies instructing subjects to use emotional imagery, some authors performed interviews with the subjects before the experiment to facilitate emotion retrieval (Young et al., 2014; Yuan et al., 2014; Zotev et al., 2016, 2013, 2011) or instructed subjects to write down several specific memories before the experiment (Li et al., 2016b, 2016a; Zotev et al., 2014). Brühl et al. (2014) provided simple instructions for cognitive reappraisal; Sarkheil et al. (2015) and Zilverstand et al. (2015) provided subjects with previous training of cognitive reappraisal. Some studies provided only more general instructions (see in Fig. 4).

Based on the current literature, it is not possible to say whether it is more advantageous to provide subjects with specific strategies or even training, or rather to let the subjects to find their own strategies during the task. However, providing subjects with no information about the regulation task at all seems to create more difficult conditions, as demonstrated by the overall unsuccessful results in ROI regulation during three fMRI sessions in the study by Marxen et al. (2016). In some cases, providing specific instructions might be necessary to prevent the use of undesirable strategies. This is especially a concern for upregulation studies providing NF from brain targets such as the amygdala or AI, since their activity increases with emotional intensity irrespective of emotional valence. If no strategies or strategies for unspecific emotional imagination are provided, the subjects can increase ROI activity with both positive and negative emotions, which might not be desirable in some cases. For example, in patients with depression, it might be necessary to specify the need for employing positive emotion-evoking strategies; the undesirable use of negative emotion-evoking strategies for ROI upregulation might even be harmful.

4.6. Suggestions for results presentation in rt-fMRI-NF studies

As can be seen in Tables 3 and 4, studies differ in the parameters according to which they evaluate the success of NF training. Most studies present the results of several analyses; however, only a few take into account correction for multiple comparisons. Thus, there is an increased risk of false positives. On the other hand, some studies do not present the evaluation of ROI regulation results at all, making it impossible to evaluate the study in this respect based on the published information. Another problem is the frequent absence of control groups, which makes it impossible to conclude firmly whether NF led to the improvement of ROI regulation. In addition, as previously raised by Thibault et al. (2018),

experiment results are often overstated. For instance, significant ROI regulation found only in a small part of the NF training can be presented as overall successful ROI regulation. Some studies also describe statistical trends as positive results.

We believe that the quality of rt-fMRI-NF in emotion regulation can be significantly improved by establishing a consensus on which results should be reported and by preplanning the analysis accordingly. Based on this literature review, we have several recommendations for result presentation for forthcoming NF studies.

First, ROI activity regulation as compared to control conditions is one of the most fundamental results of such studies, and therefore it should be reported. Control conditions should be designed so that they are as close as possible to the experimental condition. For example, when comparing upregulation while watching emotional pictures with upregulation while watching neutral pictures or with resting, it is more likely to find successful ROI regulation with the emotional pictures. A more appropriate control condition could be watching similar emotional pictures without attempting regulation.

Second, if we suppose that NF induces learning of ROI regulation, the analyses of linear trends in ROI regulation should be presented. Furthermore, results should be reported for time blocks separately, or in addition to the average per session.

Third, if possible, control groups should be implemented in studies and the results of comparisons between experimental and control groups in all analyzed parameters should be reported.

Fourth, the consequences of NF training should be evaluated. This can be done in multiple ways. One way is implementing and analyzing transfer runs. Additionally, studies with patient samples should evaluate the clinical effects of NF training. If possible, it is appropriate to assess long-term clinical effects since some existing studies suggest that the NF training effects could be delayed.

It is worth noting that some studies demonstrate clinical benefits of NF training, although they did not find significant ROI regulation (e.g., Zotev et al., 2018) or they did not report relevant results (Hamilton et al., 2016; MacDuffie et al., 2018; Scheinost et al., 2013). It is possible that NF training can induce beneficial effects even though ROI regulation during NF training was not successful. This could be explained by short NF training (typically one session), low statistical power of the study (e.g., small sample), or correction for multiple comparisons (if it was applied). The consistent presentation of ROI regulation in the literature can aid future meta-analyses in resolving this issue.

5. Conclusion

Real-time fMRI neurofeedback (rt-fMRI-NF) is a promising tool for emotion regulation enhancement in some groups of patients with mental disorders associated with emotion regulation impairment. The strongest support for the beneficial effect of rt-fMRI-NF has been shown in increasing positive emotion experiencing in patients with depression and in decreasing anxiety in patients with anxiety disorders. Symptom reduction following NF training has been reported in patients with PTSD, BPD, and schizophrenia, but the absence of direct comparisons with control groups in these studies makes it impossible to evaluate the added value of NF.

The ability to aggregate results is limited because of the lack of standards for evaluating results. Future studies are well advised to adhere to widely accepted guidelines in reporting results, such as the guidelines outlined in the consensus paper preprint by Ros et al. (2019). The field will benefit from explicit differentiation of a priori and exploratory hypotheses, and of reporting of ROI regulation success. The use of control groups and assessments of clinical symptom changes following NF training in patient groups is also recommended.

Declaration of interests

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