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Training emotion regulation through real-time fMRI neurofeedback of amygdala activity

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ABSTRACT

Being in control of one's emotions is not only desirable in many everyday situations but is also a great challenge in a variety of mental disorders. Successful intentional emotion regulation is related to down-regulation of amygdala activity. Training mental interventions supported by neurofeedback of one's own amygdala activity using real-time (rt-)fMRI might be beneficial for mental health and well-being. Rt-fMRI guided amygdala-downregulation using cognitive interventions such as a "reality check", however, have not been well-investigated.

Fifteen healthy subjects underwent four rt-fMRI sessions with neurofeedback of their own amygdala activity while applying a reality check as an emotion regulation strategy in order to down-regulate their amygdala signal during a stimulation with emotional pictures. The Control group comprised of eleven subjects also trained emotion regulation but without obtaining feedback. We hypothesized more prominent down-regulation of amygdala activity at the end of the training in the Feedback group. We investigated effects over time and between groups and further task specific connectivity of the amygdala by using psychophysiological interaction analyses.

Four weekly amygdala-based feedback sessions resulted in significantly decreased amygdala activity ($p = 0.003$, $d = 0.93$), also compared to the Control group ($p = 0.014$, $d = 1.12$). Task specific connectivity of the amygdala with the anterior cingulate cortex, hippocampus and distinct prefrontal areas was increased in the Feedback group.

Training of emotion regulation supported by rt-fMRI neurofeedback resulted in a prominent amygdala down-regulation compared to training without feedback. The finding implicates successful emotion regulation, compliant with emotion control models, through an easily applicable reality check strategy. Rt-fMRI neurofeedback may support emotion regulation learning and bears clinical potential for psychotherapy.

1. Introduction

Guiding one's own mental state, and as such central nervous processes, is an evolutionarily highly developed capability. Strategies to voluntarily direct cognitive and emotional processes are old in human intellectual history. Marc Aurel stated around 2000 years ago that the own appraisal of external events is what disturbs us and that we have the power to change it (Meditations VIII. 47; Long, 1862). However, we regularly experience anxiety, sadness, anger, or even rage, and we are often not capable to overcome such negative emotions. We try to cope with and regulate emotions as well as accompanying thoughts by applying individual strategies; but strengthening emotion regulation is often desired. Emotion regulation is a crucial skill associated with well-being and mental health in general (Gross, 2002). In mental disorders, such as anxiety, depression, and emotional instability, emotion regulation is typically impaired, representing a characteristic of the disorder, and improving emotion regulation skills is a primary aim of psychotherapeutic interventions (Anthes, 2014).

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A well-established neurobiological model of emotion regulation associates cognitive control of emotions to prefrontal cortex areas which down-regulate emotion-generative areas including amygdala (LeDoux, 2000; Dolan, 2007; Buhle et al., 2014; Diekhof et al., 2011; Disner et al., 2011; Ochsner and Gross, 2005; Etkin et al., 2015). An adaptive emotion regulation strategy which is also an element of cognitive-behavioral psychotherapy is the *reappraisal* of an emotional situation (Gross and John, 2003). Faced with such a situation one may reinterpret the emotional meaning for oneself and adopt a describing perspective on the situation called a *reality check*, thereby intentionally activating cognitive resources (Herwig et al., 2007). In clinical populations, higher levels of reappraisal have been associated with lower levels of psychopathology (e.g. Visted et al., 2018). However, clinical experience shows that such strategies are sometimes difficult to learn and use, particularly in emotionally challenging situations, or in patients suffering from mood and anxiety disorders or in emotional instability. Accordingly, developing tools to improve training of emotion regulation strategies is desirable. A problem in this context is the difficulty to imminently measure the success or the effect of an applied strategy, which may lead to inefficient development of regulation skills. Providing such a measure to a training subject may enhance learning and help develop successful emotion regulation. A potential measure at the neurobiological level is the extent of amygdala down-regulation associated with the application of a regulation strategy. Recent evidence suggests real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback can enable such amygdala down-regulation (Brühl et al., 2014; Paret et al., 2014) for improving emotion regulation skills.

Rt-fMRI neurofeedback provides the possibility to guide mental activity based on immediate feedback of the activity in the brain region to be regulated. The feasibility of rt-fMRI to selectively modulate regional brain activity has been well demonstrated (for review, see Sulzer et al., 2013a). It has also been shown in clinical context, for instance, in depression with an up-regulation of reward related brain areas or amygdala by means of a task inducing positive emotions (Linden et al., 2012; Linden, 2014; Young et al., 2014, 2017a; b; 2018). On the other hand, current emotion regulation models implicate down-regulation of the amygdala as mechanism of controlling emotions in clinical contexts (Disner et al., 2011; Buhle et al., 2014; Etkin et al., 2015). As such, up-regulation of the amygdala may represent a rather indirect method of addressing the pathophysiology of disorders. Accordingly, mental strategies leading to down-regulation may also bear clinical potential. Sarkheil et al. (2015) demonstrated that feedback-guided up-regulation of the lateral prefrontal cortex consecutively improved down-regulation of amygdala activity. Paret et al. (2014) reported amygdala down-regulation in a single session feedback trial in healthy participants as well as training effects on effective connectivity (Paret et al., 2016a, b). Their psychophysiological interaction (PPI) analysis revealed that voluntary amygdala down regulation was associated with increased connectivity between the right amygdala and the vmPFC in a single session. Nicholson et al. (2017) demonstrated successful amygdala downregulation over three sessions in post-traumatic stress disorder (PTSD) patients. While these studies show a proof-of-concept of neurofeedback-guided amygdala down-regulation, there is a lack of studies with control conditions and training success (for review and recommendations see: Thibault et al., 2018).

The clinical potential of rt-fMRI neurofeedback as a treatment tool for psychotherapy of disorders of emotion regulation requires sustained amygdala down-regulation over multiple sessions in different indications and with distinct mental interventions to suggest that the emotion regulation is trainable. We hypothesized that four weekly feedback-supported cognitive emotion regulation training sessions would improve down-regulation of amygdala activity over sessions, and this effect is stronger than training without feedback. Compared to our earlier pilot study in six subjects (Brühl et al., 2014), we increased the sample size, included a control group as sham condition in a single-blind design, and used emotional pictures instead of faces and focused on a *reality check* as regulation strategy. Reality checking is an established mental strategy practiced in cognitive behavior therapy to cope with actual stressors, with stimuli or triggers inducing fear, anger or sadness and even with unwanted thoughts and unpleasant bodily feelings. Reality checking is an intentionally induced cognitive intervention that directs attention onto the 'real' features of a situation compared to anticipated or fear-exaggerated features by focusing on the description (but not the interpretation) of the situation. A classic example is observing and describing the social situation in a non-interpretative manner during exposure therapy in patients with social anxiety disorder. This intervention can generally be applied in emotion inducing situations if appropriate to cope with.

The primary outcome measures were the beta weights of the fMRI signal in the emotion regulation condition (*regulate*) as compared to the viewing condition (*view*). We hypothesized that the beta weights in the *regulate* condition would decrease from the first to the fourth session as compared to the *view* condition and that this effect would be more pronounced in the Feedback group than in the Control group. Additional control assessments consisted of the analysis of a sensorimotor cortex region, which is supposedly unaffected by emotion regulation, and in a task which should demonstrate the transfer of the training effect to another emotion regulation condition. Furthermore, we assessed task-specific functional connectivity of the amygdala with emotion regulation relevant areas by conducting an amygdala-seeded psychophysiological interaction (PPI) analysis.

2. Methods

2.1. Subjects

In all, we recruited 40 healthy participants for two groups: the Feedback group (initially 24 subjects, new sample compared to Brühl et al., 2014) and the Control group (initially 16 subjects). The sample size had been estimated based on a power analysis based on the results of the pilot study (Brühl et al., 2014). Out of 24 subjects of the Feedback group, 15 subjects (mean age 26.7 years, SD 4.8, range 21–38, 8 male, 7 female) completed the four training sessions and had technically suitable data. Nine subjects had to be excluded due to: non-completion of the training sessions (n = 2), movement artefacts of more than 3 mm in any direction (n = 1), insufficient amygdala activation onto emotional stimulation in the first session (n = 3), technical problems (n = 3). Out of 16 subjects in the Control group, 11 subjects completed the experiment and had suitable data (mean age 27.3 years, SD 7.3, range 19–42, 5 male, 6 female). Five subjects had to be excluded for the following reasons: movement artefacts n = 1, non-completion of the training sessions n = 1, technical problems n = 3. The resulting 26 subjects with a total of 104 fMRI scanning sessions provided the basis for our analysis.

All participants were healthy, as assessed with semi-structured interviews and checklists (abbreviated version of the Mini Neuropsychiatric Interview (MINI (Sheehan et al., 1998),). Exclusion criteria were prior and current neurological and psychiatric diagnoses; pregnancy; intake of any medication (except for oral contraceptives) or psychotropic drugs including excessive consumption of alcohol (regular intake of >7 units/week), cigarettes (>1 pack/day) and caffeine (>5 cups/day) and general contraindications against MRI examinations. All participants were right-handed, assessed with the Annett handedness questionnaire (Annett, 1970). To characterize emotional, emotion regulation and impulsivity traits at baseline, the participants completed questionnaires on depression (Self-rating depression scale, SDS, Zung, 1965), impulsivity (Barret impulsiveness scale, BIS-11, Patton et al., 1995), alexithymia (Toronto alexithymia scale, TAS, Bach et al., 1996), emotion regulation (emotion regulation questionnaire, ERQ, Abler and Kessler, 2009), and mindfulness (Mindful Attention Awareness Scale, MAAS, Brown and Ryan, 2004), and Freiburg Mindfulness Inventory (FMI, Walach et al., 2006). After each session, subjects were asked in a structured interview on tiredness, general feelings, specific experiences and

the strategies used for regulation (Table S1). The mean period between sessions was 7.46 days (SD = 1.39, range = 3–17). The study was approved by the ethics committee of the canton of Zürich and conducted in compliance with the Declaration of Helsinki. All subjects gave written informed consent and received modest financial compensation. The study was funded by the Swiss National Science Foundation, which was not involved in performing and publishing.

2.2. Experimental task and scanning procedure

Prior to the first session, all subjects were given written instructions. The Feedback group was informed about the feedback delay of about 5–6 s due to the hemodynamic response of the brain. The amygdala was first localized functionally for each participant in each session. In the localizer task, participants were presented negative and neutral pictures from the International Affective Pictures System (IAPS, Lang, 2005). Pictures were presented in a blocked design with 8 pictures in each block, each shown for 3 s (total block time 24 s). After each block a baseline period (fixation cross) of 26 s allowed the blood oxygen level dependent (BOLD)-signal to reach steady state before the next condition. Subjects were instructed to passively look at the pictures. In total, four negative and four neutral blocks were presented (total duration of the localizer: 6 min). Based on the contrast negative versus neutral, we localized the area, responding to negative emotional stimulation in the anatomical area of the right amygdala.

The feedback task (Fig. 1) was constructed similar to the localizer task in a blocked design, but only containing negative IAPS stimuli. A run consisted of 14 blocks of 24 s, comprising 8 pictures shown for 3 s each. Prior to each block, the instruction to *view* or *regulate* was given on the screen for 1 s. For the *regulate* condition, the participants were instructed to apply cognitive reappraisal by using reality checking and were provided examples such as “these are only pictures”, “I am lying in the scanner”, “I am participating in an experiment” (Herwig et al., 2007). In the *view* condition they were instructed to just regard the pictures.

The experimental task consisted of a passive viewing (*view*) and an emotion regulation (*regulate*) condition. The visual representation of feedback was presented as bilaterally positioned squares changing colours. (a) Instructions were presented for one second, followed by eight different pictures, each presented for 3 s and baseline periods of 25 s. (b) Feedback color spectrum coding amygdala activation.

Stimulation blocks were separated by a baseline period (fixation cross) of 25 s (baseline + instruction = 26 s). Each run consisted of 6 *view* conditions and 10 *regulate* conditions. Participants performed two feedback runs in sessions 1 and 4 and three runs in sessions 2 and 3. In some cases, participants completed only 2 runs per session due to high self-reported drowsiness (mean number of feedback runs per session: 2.42). Picture sequences were randomized and in each session 50% of the pictures were new, prior unseen pictures to prevent habituation and effects of familiarity. Amygdala activity was recorded from the region identified in the localizer task and was given as real-time feedback to the participant in form of color-changing blocks laterally on both sides of the pictures (Fig. 1). Color-blocks were positioned bilaterally and in the middle of the vertical axis to avoid distraction to either side or away from the center of the negative pictures.

The Control group completed the same task, except that the color-blocks changed in the same color range but in a random fashion, not associated with the individual's amygdala activation. Participants in the Control group received the same instructions to regulate as the Feedback group. Subjects were told that these changing color blocks were meaningless.

Finally, in order to detect a possible transfer effect of the training to another emotion regulation task and without amygdala feedback, participants performed a “transfer” task prior the first session and after the last session an emotion regulation task. The transfer task consisted of video stimuli displaying negative emotional facial expressions including anger, fear, sadness, disgust, and embarrassment (van der Schalk et al., 2011). The task consisted of 5 *view* and 5 *regulate* blocks, displaying 5 short videos (length between 3 and 6 s) within a total time of 24 s. Total duration for the transfer task was 6 min, 54 s.

2.3. Image acquisition

Imaging was performed with a 3.0 T Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands, equipped with an 8-channel receive head-coil array). Echo-planar imaging was performed for fMRI (repetition-time (TR)/echo-time (TE) 2000/25 ms, 30 sequential axial slices, whole brain, slice thickness: 3.0 mm, field of view: 240 × 240 mm, resulting voxel size: 3 × 3 × 3 mm, axial orientation, SENSE-factor: 2.0). The localizer run consisted of 190 vol, the feedback runs of 330 vol, the “transfer” run of 207 volumes. At each session, high-resolution T1 weighted anatomical data were acquired via a 3D magnetization-prepared rapid gradient-echo sequence (MP-RAGE; T1w: voxel size = 1.1 × 1.1 × 1.2 mm, time between two inversion pulses = 2302 ms, inversion time = 900 ms, inter-echo delay = 6.7 ms, flip angle = 9°, field of view = 230 × 226 mm, 2, 145 sagittal slices) for coregistration with the functional data. Stimuli were presented via digital

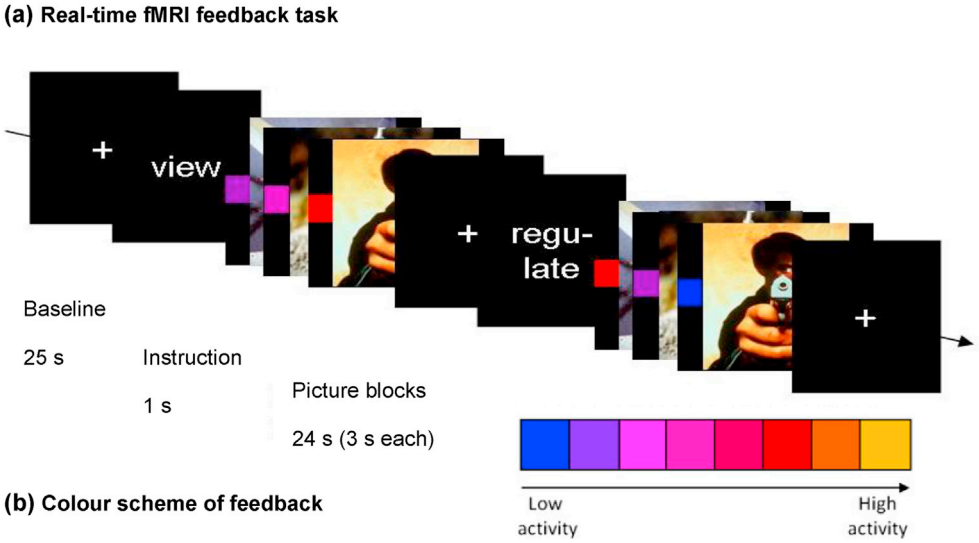

Fig. 1. Experimental task.

goggles (Resonance Technologies, Northridge, CA).

2.4. FMRI online real-time analysis

Functional data were analyzed online during fMRI with Turbo-BrainVoyager™ (TBV) Version 3.2 (Brain Innovation, Maastricht, NL). The processing has been described previously (Caria et al., 2010; Goebel, 2001). Real-time data analysis comprised incremental 3D motion detection and correction and drift removal and resulted in incrementally computed statistical maps based on the general linear model (GLM) and event-related averages. After the localizer scan, a region of interest (ROI) was individually placed within the right amygdala extending over 3 slices (= 9 mm) using a t-value threshold of 2.0. The size and centers of these individual localizer ROIs are given in Table S3.

Compared to studies aiming at up-regulating brain regions, the down-regulation of a brain region is particularly sensitive to individual differences in the total reactivity of the BOLD signal. Therefore, we computed the individual reactivity of the amygdala from the localizer using the average percent signal change from baseline in the individual amygdala ROI. This was entered as the maximum value (i.e. bright orange) for the range of colours during *regulate* blocks. The signal changes during *regulate* were computed as percent of the individual maximum change. The feedback was first normalized based on the percent signal increase from the previous baseline condition (last 5 vol), then three-point averaged (averaging the current value with the previous two) to reduce noise and strong fluctuations of the feedback (in parallel to (Sulzer et al., 2013b)). This feedback signal was computed and presented by custom made software running on VisualStudio™ 2008 (Microsoft, Redmond, WA, USA).

2.5. Offline analysis and statistics

2.5.1. Preprocessing

After scanning, the acquired images were processed offline using BrainVoyagerQX™ 2.8 (Brain Innovation, Maastricht, NL (Goebel et al., 2006),). Standard preprocessing with BrainVoyagerQX included motion correction, slice scan-time correction, high-frequency temporal filtering and removal of linear trends. All individual functional datasets were checked for excessive head movements. We excluded runs with >3 mm head movement in at least one direction. In cases where there was one single spike >3 mm in an otherwise steady run, we discarded the part of the run (containing the spike) from analysis (resulting in half runs of 155 vol). In cases where we had less than 1 run (or 2 half runs) for a session, we excluded the subject from our analysis. Functional data were co-registered with the individual T1-weighted 3D-structural data. Structural and functional data were transformed into Talairach space and spatially smoothed with a 4 mm full-width half-maximum Gaussian kernel for subsequent within- and between-subject analysis.

Since we were interested in feedback-guided emotion regulation we modelled the *regulate* condition as a box car function starting 10 s after feedback-onset to account for both the delay in the feedback signal and the estimated time for applying emotion regulation based on the feedback. The instruction period and first 10 s of the feedback were modelled as a separate predictor but were not analyzed further. We modelled the *view* condition correspondingly, with the same phase of the block (11–24 s) as the basis for comparison with the *regulate* condition.

Further, our model contained boxcar functions for the baseline periods between blocks. Boxcars were convolved with the standard hemodynamic response function provided by BrainVoyager adapted to the duration of the blocks. Boxcars were convolved with the standard hemodynamic response function provided by BrainVoyager adapted to the duration of the blocks. Three-dimensional statistical parametric maps were calculated for the conditions *regulate* and *view* for all four sessions. We included six head movement regressors representing translation and orientation as confounds. These datasets were combined into group wise random effects general linear models (GLMs) and random effects group GLM (both groups).

2.5.2. ROI analysis

2.5.2.1. Analysis feedback group. We extracted the mean beta-weights of the right individual amygdala ROI, identified in this session's localizer of each subject, condition and session. Subsequent analyses were performed in SPSS 22 (IBM, Armonk, NY, USA). In order to investigate training effects in the Feedback group, we computed repeated measures ANOVA with the within-subject factor *session* (2 levels: session 1, session 4) and *condition* (2 levels: *regulate*, *view*) including confirmation of sphericity (Mauchly's test of sphericity). Further, we computed paired two-sampled t-tests on the conditions *regulate* and *view* as well as on the main contrast *regulate* > *view* to test our directed hypothesis of decreased amygdala activity in the *regulate* condition as compared to the *view* condition in session 4 compared to session 1.

In addition, to control for unspecific effects, we selected a control region that was assumed to not be involved in brain activation associated with emotion regulation (Buhle et al., 2014) for the Feedback group, the right primary sensorimotor cortex (x/y/z = ±33/-24/62; 10 mm diameter). We then performed the same analysis previously mentioned with the amygdala ROIs.

2.5.2.2. Feedback group vs. Control group. For the comparison of the *Feedback group* with the *Control group* we conducted the analysis within a ROI in the amygdala based on a previous study (sphere centered on Talairach coordinates x = 19, y = −8, z = −15, radius 4.5 mm, Brühl et al., 2014). We computed a mixed effects ANOVA on the beta-weights of the main contrast (*regulate* > *view*) with the within-subject factor *session* and the between-subject factor "group". Further, we conducted post-hoc independent two-sampled t-tests to test our directed hypothesis of decreased amygdala activity in the Feedback group compared to the Control group in session 4 and of equal activity in session 1. Even though we were mainly interested in the main contrast (*regulate* > *view*) we considered it as relevant to disentangle the contribution of the two single conditions (*regulate* > *baseline*, *view* > *baseline*) to changes in contrast and presented results of the single contrasts against baseline as additional information.

We additionally computed an exploratory whole brain group comparison on the contrast *regulate* > *view* in session 1 and session 4 (voxel-wise threshold $p < 0.05$, Monte-Carlo simulations, 1000 iterations, corrected cluster threshold $p < 0.01$).

2.5.3. Psychophysiological interaction (PPI) analysis

The aim of PPI analysis is to identify task specific changes in connectivity between two brain areas, which is measured in terms of the strength of regression of activity in one brain area to the other. We employed a generalized PPI approach (McLaren et al., 2012) which allows for including more than two task conditions in the same PPI model by encompassing the entire experimental model. We used the respective plugin for BrainVoyager and conducted separate PPI analyses for each group (Feedback, Control). First, task-related regressors (*regulate/view/instruction*) were convolved with the standard hemodynamic response function (HRF). Then BOLD signal time course from the right amygdala ROI were extracted and entered into a model comprising the task-related regressors, the physiological regressor of the amygdala ROI time course and the interaction terms for each subject and the sessions 1 and 4 as well as 6 motion parameters as confounds. The PPI regressor was deconvolved before modelling. These datasets were then combined into group wise random effects GLMs.

For first-level analysis, we calculated the contrasts between the interaction terms of the two conditions *regulate* > *view* by conducting separate t-statistics for each session (1, 4). Effects were considered significant on a whole brain false discovery rate of $p < 0.01$ (liberal: $p < 0.05$). The minimum cluster size for significance was estimated with

Monte-Carlo simulations (1000 iterations, corrected cluster threshold $p < 0.01$). For second-level analysis, we conducted further t-statistics for the differences between the interaction terms (*regulate* > *view*) in order to determine changes in task-specific connectivity between sessions (4 > 1). Effects were also considered significant on a whole brain false discovery rate of $p < 0.01$ (liberal: $p < 0.05$) and the minimum cluster size for significance was estimated with Monte-Carlo simulations (1000 iterations, corrected cluster threshold $p < 0.01$). Finally, we determined differences between groups on a qualitative level. We analyzed differences in amygdala effective connectivity with the rest of the brain between the two conditions (*regulate* > *view*) for both groups (i.e. Feedback and Control groups) individually by conducting separate t-statistics within each session (1, 4) and between sessions (4 > 1, *regulate* > *view* as dependent variable).

2.5.4. Transfer task

When analyzing the transfer task, we also analyzed each individual's amygdala ROI activation during *regulate* and *view* and compared the difference between sessions in a repeated measures ANOVA, with the within-subject factor *session* (2 levels, session 1 and 4) and *condition* (3 levels: *regulate*, *view*, *regulate-view*) in the Feedback and the Control group.

3. Results

3.1. Demography, psychometric and behavioral data

The groups did not differ with respect to gender, age, state depression (SDS), impulsivity (BIS), trait emotion regulation (ERQ), trait mindfulness (MAAS, FMI) and alexithymia (TAS-20 ($p = 0.19$, all other $p > 0.3$; Table 1). After each session, we assessed the extent of tiredness, pain as well as the affective states that subjects had experienced during the scan. The two groups did not differ with regards to tiredness, pain and affective state, neither in the 1st nor in the 4th session (Supplementary Table S1a). Furthermore, participants were asked about the strategies they had applied for emotion regulation and about their perceived regulation success. The values of application frequency of the strategies (cognitive, attention, mindfulness and suppression) and perceived regulation success are specified in Supplementary Table S1b.

Table 1
Demographic and psychometric data of subjects.

Measures	Mean/SD (range)		Group comparison
	Feedback group	Control group	Statistics
N	15	11	
Age	26.67/4.8 (21–38)	27.6/7.3 (19–42)	n.s. ($t = 0.36$, $p = 0.72$)
Gender	8 m/7 f	5 m/6 f	n.s. (chi2 = 0.16, $p = 0.69$)
TAS	37.62/6.61 (27–49)	33.8/6.70 (24–47)	n.s. ($t = 1.37$, $p = 0.187$)
BIS	24.31/4.00 (18–29)	24.40/7.00 (14–37)	n.s. ($t = 0.04$, $p = 0.97$)
SDS	42.12/6.80 (35–59)	39.90/4.06 (31–48)	n.s. ($t = 0.91$, $p = 0.37$)
ERQ_rea	28.92/4.25 (22–36)	29.40/7.78 (14-40	n.s. ($t = 0.19$, $p = 0.85$)
ERQ_sup	11.85/3.80 (8–22)	13.00/5.10 (4–20)	n.s. ($t = 0.62$, $p = 0.54$)
MAAS	39.77/7.33 (31–54)	34.40/8.45 (24–51)	n.s. ($t = 1.63$, $p = 0.12$)
FMI	38.15/6.71 (28–46)	41.1/6.15 (32–48)	n.s. ($t = 1.08$, $p = 0.29$)

Given are the mean/SD (range) of the assessed demographic data. Abbreviations: N number of subjects, m male, f female, TAS Toronto Alexithymia Scale, BIS Barratt Impulsiveness Scale, SDS Sheehan Disability Scale, ERQ Emotion Regulation Questionnaire, rea reappraisal sub score, sup suppression sub score, MAAS Mindfulness Attention Awareness Scale, FMI Freiburg Mindfulness Inventory, n.s. not significant, *t*-test two-tailed.

3.2. ROI analysis

3.2.1. Effect on amygdala activation in the Feedback group

The primary study question addressed the effect of repeated training sessions on amygdala regulation in the Feedback group (Fig. 2): in this group, the repeated measures ANOVA on the beta weights of the contrast *regulate* > *view* in the right amygdala revealed a significant main effect of *session* ($F(3,14) = 3.29$, $p = 0.030$, partial $\eta^2 = 0.190$). The effect of *session* on amygdala activity during *regulate* (vs. *baseline*) was highly significant ($F(3,14) = 5.44$, $p = 0.003$, partial $\eta^2 = 0.280$), while it was not significant during *view* (against *baseline*) ($F(3,14) = 0.507$, $p = 0.679$, partial $\eta^2 = 0.035$).

Post-hoc paired two sample t-tests directly compared amygdala activation between sessions 4 and 1 for the conditions *regulate* > baseline, *regulate* > *view* and *view* > *baseline*. Amygdala activation during *regulate* (against *baseline*) was significantly lower in session 4 compared to session 1: $t(14) = -3.56$, $p = 0.003$, Cohen's d: 0.93. Amygdala activation during the contrast *regulate* > *view* was also significantly lower in session 4 compared to session 1: $t(14) = -2.45$, $p = 0.028$, Cohen's d: 0.70. There was no difference between Session 1 and 4 during *view* > *baseline* ($p = 0.679$). The individual localizer ROIs in the Feedback group did not differ in size between sessions. The results over sessions for the Control group are provided in the Supplementary Fig. S2.

The control ROI in the Feedback group within the sensorimotor cortex ((Brühl et al., 2014): x/y/z = ± 30/-24/62; 10 mm diameter) did not show differences between sessions 1 and 4 in the '*regulate* versus *view*' condition ($t = -0.58$, $p = 0.57$).

3.2.2. Comparison of feedback vs. Control group

When computing a mixed effects ANOVA on the beta-weights in the spherical ROI on the contrasts *regulate* > *view* with the within-subject factor *session* and the between-subject factor *group*, we found a significant effect of *group* ($(F1, 24) = 5.448$, $p = 0.028$, partial $\eta^2 = 0.185$), a trend-level effect of *session* ($(F1, 24) = 3.142$, $p = 0.089$, partial $\eta^2 = 0.116$) and a trend-level interaction between *session* and *group* ($(F1, 24) = 2.748$, $p = 0.110$, partial $\eta^2 = 0.103$). Post-hoc independent two-sampled t-tests, revealed a significant group difference of the contrast *regulate* > *view* in session 4 ($t(24) = -2.643$, $p = 0.014$, Cohen's d: 1.12)), but no difference in session 1 ($p = 0.648$).

Additional t-statistics on the group differences in the single conditions (*regulate* against baseline, *view* against baseline) revealed no significant difference between groups in the *view* condition at session 1 and 4 ($p = 0.620$ and $p = 0.496$). There was no significant difference between the groups in the *regulate* condition in the first session ($p = 0.895$), but a trend level difference in the fourth session ($p = 0.055$). To sum up, these results show significantly enhanced amygdala down regulation in the feedback but not in the Control group (Fig. 3).

In the Control group, we found no differences between sessions neither in the main contrast *regulate* > *view* nor in the contrasts *view* > *baseline* and *regulate* > *baseline* (*regulate* > *view*: $p = 0.524$, *view*: $p = 0.940$, *regulate*: $p = 0.791$). When using a larger ROI (5.9 mm radius) centered on the center of gravity of all the feedback ROIs from the Feedback group, the results were not different, showing no effect of session on any of the conditions.

At the whole-brain level, the group comparison on the contrast *regulate* > *view* showed a lower activation in the inferior frontal gyrus/insula in session 1 and lower activation in the right amygdala, the posterior temporal cortex, the bilateral cerebellum and the bilateral hippocampus in session 4 (Voxel-wise threshold $p < 0.05$, Monte-Carlo simulations, 1000 iterations, corrected cluster threshold $p < 0.01$) (Table 2). For the whole brain analysis of the Feedback group, we performed contrasts against baseline in order to characterize the effects of the individual conditions. In the contrast *regulate* > baseline we found significantly lower activation in the left pre-SMA and the right superior frontal gyrus in session 4 as compared to session 1 (Supplementary Fig. S1).

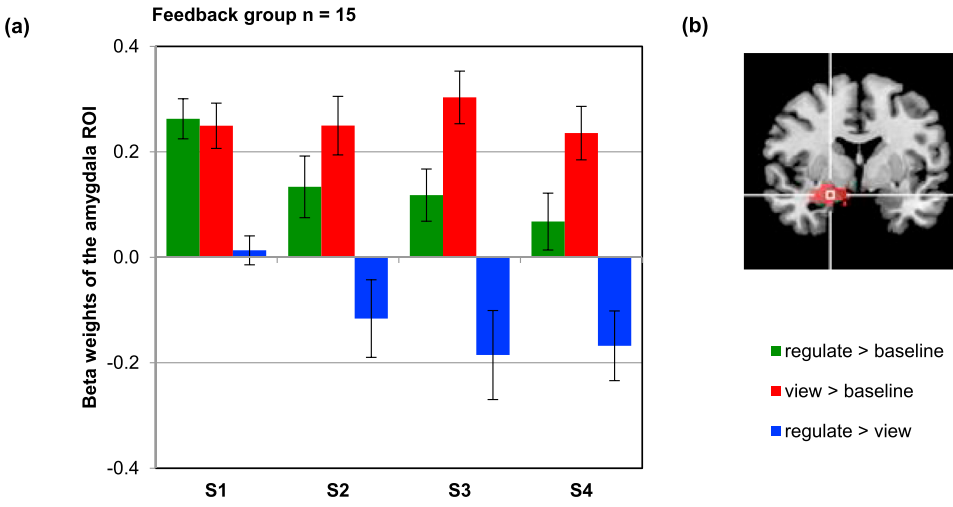

Fig. 2. Results of the amygdala ROI analysis in the Feedback group
(a) Mean beta weights of the subjects' individual localizer amygdala regions of interest (ROI). Conditions *regulate* (green), *view* (red) and *regulate* > *view* (blue) are presented over the four sessions (S1-4). Error bars represent standard errors. (b) The mask of area in the amygdala region is covered by all individual ROIs of the Feedback group.

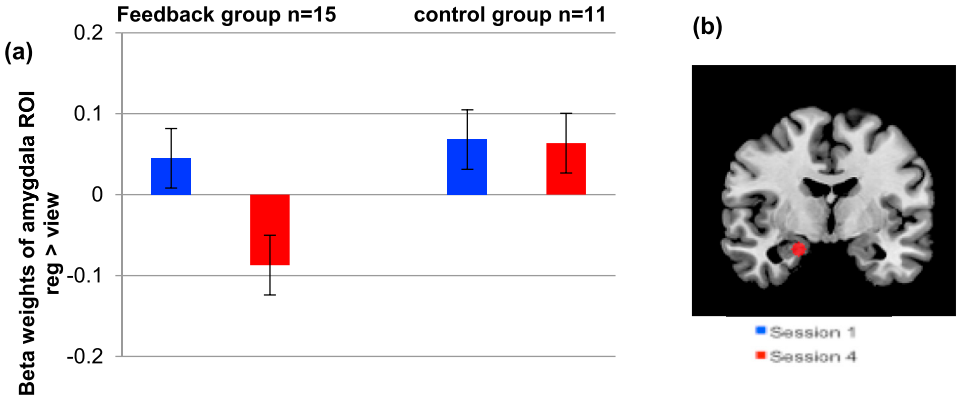

Fig. 3. Results of the amygdala ROI analysis of the main contrast (regulate > view) in the group comparison
(a) The Feedback group, as compared to the Control group showed significantly decreased amygdala activity in the main contrast (*regulate* > *view*) ($t(24) = -2.643$, $p = 0.014$, partial $\eta^2 = 0.225$) in the 4th session but not in the first session (*regulate* > *view*: $p = 0.648$). Bars indicate standard errors. (b) Spherical ROI in the right amygdala.

Table 2
Results of the whole-brain group comparison of the contrast regulate > view in Session 1 and 4.

Region	BA	Voxels	Talairach coordinates			t-value	p-value
		mm^3	Peak voxels			max	max
			x	y	z		
Session 1							
IFG/insula (vlPFC) L	13	1645	−42	−4	16	−4.33	0.00021
Session 4							
Posterior temporal cortex L	37	6765	−39	−61	10	−3.54	0.0017
Cerebellum R	–	3965	24	−26	−20	−4.53	0.00014
Cerebellum L	–	3995	−21	−25	−27	−4.53	0.00014
Amygdala R*	–	565	21	−10	−20	−2.64	0.014
Hippocampus R	35	954	24	−25	−20	−5.08	0.000034
Hippocampus L	35	1101	−21	−25	−27	−4.53	0.00014

Voxel-wise threshold $p < 0.05$ (Monte-Carlo simulations, 1000 iterations, corrected cluster threshold $p < 0.01$, * uncorrected only). Negative t-values reflect decreased activation in the specified regions in the Feedback group as compared to the Control group in the main contrast (*regulate* > *view*). L left, R right, BA Brodmann area, IFG inferior frontal gyrus, vlPFC ventrolateral prefrontal cortex.

3.3. Functional connectivity analysis

In the Feedback group, the PPI analysis of our main contrast *regulate* > *view* revealed no clusters exhibiting significant task related connectivity with the amygdala in session 1. In session 4, however, the following clusters showed significantly increased connectivity (*regulate* > *view*) with the amygdala: ACC, DLPFC, DMPFC, pre-SMA and VLPFC. A direct comparison between session 1 and session 4 (4 > 1) with the main contrast (*regulate* > *view*) as dependent variable revealed a significant increase in task related connectivity of the amygdala with the following clusters: Right/left inferior frontal gyrus (BA 47), left midbrain, left anterior cingulate gyrus (BA 32) and right/left superior frontal gyrus (BA 9/10). The PPI parameter estimates of clusters that were discovered on a whole brain discovery rate of $p < 0.01$ (Monte-Carlo simulations, 1000 iterations, corrected cluster threshold $p < 0.01$) are displayed in Fig. 4.

The PPI parameter estimates of the contrast *regulate* > *view* (a) reflect (b) a significant increase in connectivity between the right amygdala and the left ACC from the first to the fourth session. Further, in the fourth session connectivity from the amygdala (c) to the left MidFG (dlPFC) and (d) to the right pre-SMA (dmPFC) was significantly stronger in the *regulate* condition compared to the *view* condition. (*$p < 0.01$, minimum cluster size for significance estimated with Monte-Carlo simulations (1000 iterations, corrected cluster threshold $p < 0.01$). Bars indicate standard errors. Abbreviation: PPI psychophysiological interaction analysis, ACC anterior cingulate cortex, MidFG middle frontal gyrus, dlPFC dorsolateral prefrontal cortex, SMA supplementary motor area, dm dorsomedial.

In the Control group, the PPI analysis revealed significantly enhanced connectivity in the contrast *regulate* > *view* between the amygdala and the bilateral insula (BA 13) in session 1. In session 4 the amygdala showed enhanced connectivity with the cerebellum (culmen bilateral). A comparison between sessions (session 4 > session 1) with the main contrast

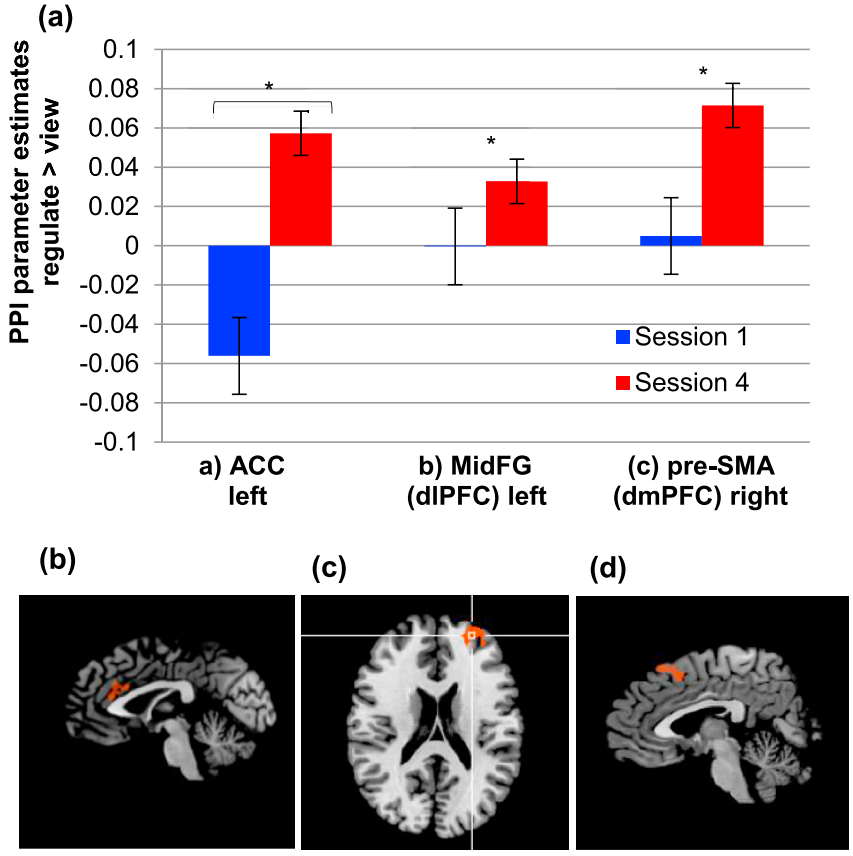

Fig. 4. Results of amygdala seeded PPI analysis in the Feedback group.

regulate > *view* as dependent variable revealed no significant clusters that exhibited increased connectivity with the amygdala. Detailed properties of all clusters are illustrated in Table 3.

3.4. Transfer task

We analyzed the 'transfer' task before and after the training in both groups in parallel to the analysis of the feedback data. We found regulation success already in the task prior training, but no difference before to after the training in right amygdala activity during the conditions *regulate* [$F(3,14) = 0.40$, $p = 0.54$, partial $\eta^2 = 0.03$], *view* [$F(3,14) = 0.95$, $p = 0.35$, partial $\eta^2 = 0.07$], or the contrast *regulate* > *view* [$F(3,14) = 0.87$, $p = 0.37$, partial $\eta^2 = 0.06$], shown in Supplementary Fig. S3. Furthermore, there was no difference between the Feedback and the Control group in the transfer task after the training.

4. Discussion

4.1. Amygdala down-regulation

The aim of this study was to examine the effect of rt-fMRI based neurofeedback of individual amygdala activity in four training sessions applying a 'reality check', a cognitive intervention established for emotion regulation, on amygdala down-regulation. The experimental group showed significantly decreased amygdala activation in the fourth as compared to the first session when being asked to down-regulate their feedback signal. This effect was superior to the one in the Control group which also trained emotion regulation but without amygdala feedback. In the control region, the sensorimotor cortex, we did not find training-associated activity changes, supporting the assumption training specificity on the amygdala but not on brain areas that are not involved in emotion regulation. The data further confirm and extend earlier findings from a pilot study with a comparable design on six subjects (Brühl et al., 2014) and shows a higher effect size, which is usually not the case in bigger sample sizes if the initial statistical power was low (Button et al., 2013). The applied technique could support training of emotion regulation strategies in the context of psychotherapy of affective, anxiety and personality disorders, which should be a further subject of investigation.

An important advance of this approach is the application of a cognitive strategy based on emotion processing resulting in amygdala down-regulation compliant with the basic model of emotion regulation (Etkin et al., 2015). In the field of emotional disturbances it is particularly relevant to control negative emotions such as fear, anger or sadness. These emotions are associated with increased amygdala activation, the control of which is the main target of cognitive emotion regulation (Buhle et al., 2014). Earlier studies on rt-fMRI mostly demonstrated the up-regulation of the activity within a certain brain regions that may also impact emotions. For example, Greer et al. (2014) reported an increase of nucleus accumbens activation through rt-fMRI neurofeedback as an indicator of reward related brain activation; Linden et al. (2012) and Young et al. (2014; 2017a; b) found an increase of amygdala activity through induced positive emotions in depression; Veit et al. (2012) demonstrated coping with threatening stimuli due to up-regulation of the anterior insula.

Down-regulation of brain activity through rt-fMRI has also been demonstrated in the anterior cingulate cortex for regulating craving in smokers (Li et al., 2013), in the insula for three patients with obsessive-compulsive disorder (Buyukturkoglu et al., 2015) or in borderline patients (Paret et al., 2016a). Amygdala down-regulation represents directly the neurobiological correlate of emotion regulation (Etkin et al., 2015). Neurofeedback-guided amygdala down-regulation in healthy subjects was demonstrated in an early feasibility study (Brühl et al., 2014). This effect was also shown after a single neurofeedback session in a 'transfer' task (Paret et al., 2014). A sample of PTSD patients

Table 3
Results of the PPI analyses showing regions with increased right amygdala connectivity (regulate > view) in the Feedback- and Control group.

Region	BA	Voxels	Talairach coordinates			t-value	p-value
		mm^3	Peak voxels				
			x	y	z		
a) Feedback group							
Session 4							
Pre-SMA (dmPFC) R (Fig. 4)*	6	856	3	14	49	5.18	0.00014
MidFG (dlPFC) L (Fig. 4)*	10	500	−27	50	19	4.4	0.00061
ACC L/R	32	1193	3	26	28	3.48	0.0037
SFG (dlPFC) R	6	1954	24	5	55	5.32	0.00011
MidFG (dlPFC) R	9	1678	39	29	28	4.36	0.00065
Session 4 > Session 1							
ACC L (Fig. 4)*	24	620	0	29	16	4.33	0.0007
IFG/Insula (vlPFC) R	47	3103	39	20	−11	4.36	0.00066
MidFG (dlPFC) R	9	2664	36	32	28	4.54	0.00047
Midbrain	–	904	6	−22	−8	4.89	0.00024
Hippocampus L	28	1086	−24	−22	−8	4.17	0.00095
SFG (frontal pole) L	10	1715	−21	50	19	4.35	0.00066
IFG (vlPFC) L	47	1133	−37	23	−11	4.34	0.00067
b) Control group							
Session 1							
Insula R	13	1650	51	−10	4	4.039	0.0024
Posterior insula L	13	1693	−36	−13	4	4.33	0.0015
Session 4							
Cerebellum R	–	3101	21	−46	−29	4.51	0.0011
Cerebellum L	–	2056	−24	−58	−29	4.9	0.00062

Whole brain discovery rate: $p < 0.05/p < 0.01$* (Monte-Carlo simulations, 1000 iterations, corrected cluster threshold $p < 0.01$). L left, R right, BA Brodmann area, ACC anterior cingulate cortex, MidFG middle frontal gyrus, dlPFC dorsolateral prefrontal cortex, SMA supplementary motor area, dm dorsomedial, IFG inferior frontal gyrus, vlPFC ventrolateral prefrontal cortex, SFG superior frontal gyrus.

achieved to down-regulate amygdala over three rt-fMRI sessions, however, without a control group (Nicholson et al., 2017). Here we have demonstrated for the first time that healthy individuals can down-regulate amygdala activity using neurofeedback compared to a control group. This was achieved by using the easily applicable basic mental intervention of a 'reality check'.

Our additional aim, to show the transfer of the training effect into another related function, did not result in an improvement over training nor reveal any differences between the groups. This may have been the result of multiple causes. First, the ability of healthy participants to regulate prior to training may have resulted in a ceiling effect of neurofeedback training. The emotional reaction due to the short video clips might have been easier to down-regulate compared to the series of negative emotional pictures, possibly because it was much shorter than the feedback sessions. Further, the initial 'transfer' task was performed *prior* the first scanning session and the final one was performed immediately *after* the last scanning session. Yet, after the last scanning session, the subjects were fatigued and could have been less capable and motivated to concentrate on the task, therefore corroborating the effect. Thus, despite this lack of a transfer into the other task, this does not exclude a relevant effect when performing the rt-fMRI training, for instance, in patients where the improvement might rather be stronger than in healthy, well-regulated volunteers.

4.2. Connectivity

We analyzed differences in amygdala effective connectivity with the rest of the brain for each group (i.e. Feedback, Control) individually. In the Feedback group, the PPI analysis revealed increased effective connectivity between the amygdala and brain regions such as the DMPFC, V/DLPFC and ACC. While no task specific connectivity between the amygdala and these areas was present in the first session, it significantly increased over sessions and revealed significant connectivity in the fourth session. In the Control group, however, we did not observe such an effect. We detected task-specific connectivity between the amygdala and the bilateral insula in the first session; however, neither the insula nor any other brain area increased its connectivity with the amygdala over sessions. The PPI results are interesting referring to our whole brain results that exhibited extensively enhanced activity in the DMPFC and DLPFC in the first session and a decrease in activity over time (Supplementary Fig. S1). Whereas neurofeedback training resulted in decreased activation in emotion regulation areas, task specific connectivity between the amygdala and these areas increased. The strengthened connectivity that was found over the course of the sessions supports the notion of more efficient emotion regulation resulting through training. Thus, it is possible that higher cognitive resources were no longer required and emotion regulation became more implicit as result of training. This observation was exclusively made for the Feedback group, which indicates that the observed increase in task specific connectivity between the amygdala and the above specified emotion regulation areas might be particularly attributed to the provided amygdala feedback.

Studies targeting feedback-supported amygdala regulation already investigated corresponding alterations in connectivity between the amygdala and regulation specific brain areas in healthy subjects. (Zotev et al., 2011, 2013), for example, showed that successful up-regulation of the left amygdala was associated with an increase in functional connectivity between the amygdala, the DMPFC and the ACC. Sarkheil et al. (2015) demonstrated that feedback supported DLPFC up-regulation resulted in decreased amygdala activation. Paret et al. (2014; 2016b) used a similar study design to ours. A PPI analysis revealed that successful amygdala down-regulation was associated with increased connectivity between the amygdala and the VMPFC (Paret et al., 2016b), which was also shown in PTSD patients (Nicholson et al., 2017, 2018). Our data support and extend these findings, indicating neurofeedback-driven enhanced connectivity between amygdala and prefrontal brain regions, which may be subsumed as being a correlate of strengthened emotion regulation capacities. Here, we investigated connectivity changes post-hoc. Other studies directly used connectivity analyses as the basis for neurofeedback (Koush et al., 2017; Scharnowski et al., 2013). In order to particularly strengthen cognitive reappraisal skills, it might be desirable to develop connectivity-based feedback paradigms that more precisely reflect neural correlates of cognitive reappraisal. This is especially important with respect to the future scope to implement rt-fMRI neurofeedback in clinical routine. Addressing connectivity features may generally bear a potential field of application in rt-fMRI.

4.3. Limitations

With respect to the limitations of this study, a lack of direct behavioral control may be considered. However, being guided to external stimuli in the frame of a behavioural control condition, for instance by an evaluation with a consecutive motor task was not considered to provide essential additional information, but rather would interfere with cognitive control. Thus, we intentionally went without using a behavioral control in order to avoid distraction or influence from external stimuli. Another issue refers to control conditions in rt-fMRI investigations. Whenever the major aim was to assess a training effect in the Feedback group, the comparison with a control group is important (Thibault et al., 2016). We decided for a control group that should also train emotion regulation in a similar design but without obtaining feedback. However, since we did not use a sham-controlled approach we could not control for potential effects of experience gained self-efficacy. We analyzed fifteen subjects in the Feedback group and eleven in the Control group. A bigger sample size might have been desirable in order to increase the statistical

power of our results. Furthermore, we had relatively high dropout rates due to technical problems, movement artefacts and subjects who did not complete the four sessions. And finally, we did not assess whether the Control group would have been able to accomplish down-regulation when provided with real feedback, for instance in a cross-over design. However, the data are based on 104 fMRI scanning sessions, providing a substantial database.

The PPI analysis was able to detect effects of task specific connectivity, which were only over and above what could be explained by task- or seed region specific activity alterations. However, PPI analyses reveal no information about whether connectivity between two brain regions is inverse or positive, in contrast to simple correlation analyses. In order to investigate this information flow, methods such as dynamic causal modelling are required, which was performed separately based on the data as presented elsewhere (Sladky et al., 2017, congress report).

4.4. Clinical implications

In general, providing feedback of one's own neurobiological or psychophysiological parameters has a relatively long history in the field of neuropsychiatry and psychotherapy (Lehrer, 2017; Sitaram et al., 2017). However, until now no neurofeedback application has been broadly established in clinical psychiatry. This may be due to often low anatomical specificity of the feedback signal in relation to the function to modify which might be better addressed by providing direct feedback of brain activity more closely associated with a mental act or a psychological function. Rt-fMRI can provide direct feedback information from the activity of selected brain regions, networks (Sitaram et al., 2011) or from connectivity measures (Koush et al., 2013; Lee et al., 2012). Subjects can use this information to acquire better control over the underlying neural activity (Cox et al., 1995; Sulzer et al., 2013b) and to change related behavior. This may have particular impact for disorders of mental functions that might be consciously modified in a health promoting way.

We consider the results meaningful also for certain clinical populations which are susceptible for cognitive behavioral psychotherapy interventions, as reality checking is a simple and established intervention in this frame. The instructions are typically such that patients are supposed to attend to and describe in a neutral (non-interpretative) way their reality, i.e. objectively observable features of the environment. The instructions given here are therefore adapted to and specified for the experimental environment, but are not categorically distinct from the therapeutically trained instructions in patients with mental disorders. Therefore, we consider our “reality check” a relevant paradigm for experimental and therapeutic purposes.

The principal goal of this study was to support treatments of emotional and affective disorders in psychiatry. Scientific applications of rt-fMRI in the field of psychiatry have addressed some disorders, particularly depression (Johnston et al., 2011; Linden et al., 2012;; Young et al., 2014, 2017a; 2017b, 2018), but also schizophrenia (Ruiz et al., 2013), addiction (Hartwell et al., 2016), and PTSD (Nicholson et al., 2017). Modified applications of realtime fMRI, such as intermittent training, may even boost its effects (Hellrung et al., 2018). A practical application for further investigations is the training of emotion regulation in disorders with primary emotional disturbances or mood alterations such as anxiety disorders, borderline personality disorder with emotional instability and depression.

5. Conclusion

Training of emotion regulation particularly through down-regulation of amygdala activity consistent with emotion regulation models (Etkin et al., 2015), supported and improved by rt-fMRI, may help to cope with emotionally challenging situations. Potential practical applications may involve cognitive behavioral psychotherapy (Disner et al., 2011; Holmes et al., 2014) as an augmentation method for learned cognitive techniques of emotion regulation.

Our results indicate that a training of emotion regulation by using the cognitive intervention of a reality check supported be amygdala-feedback is more efficient than training without this feedback. The finding has basic implications for learning emotion regulation strategies with potential relevance for mental disorders, where better emotion regulation represents a key capability for symptom improvement. Neuroimaging-feedback has translational potential for clinical application, by providing an integrative link of psychotherapy and neurobiology in the sense if an ‘augmented psychotherapy’.

Declaration of interests

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.09.068.

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