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Intermittent compared to continuous real-time fMRI neurofeedback boosts control over amygdala activation

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ABSTRACT

Real-time fMRI neurofeedback is a feasible tool to learn the volitional regulation of brain activity. So far, most studies provide continuous feedback information that is presented upon every volume acquisition. Although this maximizes the temporal resolution of feedback information, it may be accompanied by some disadvantages. Participants can be distracted from the regulation task due to (1) the intrinsic delay of the hemodynamic response and associated feedback and (2) limited cognitive resources available to simultaneously evaluate feedback information and stay engaged with the task. Here, we systematically investigate differences between groups presented with different variants of feedback (continuous vs. intermittent) and a control group receiving no feedback on their ability to regulate amygdala activity using positive memories and feelings. In contrast to the feedback groups, no learning effect was observed in the group without any feedback presentation. The group receiving intermittent feedback exhibited better amygdala regulation performance when compared with the group receiving continuous feedback. Behavioural measurements show that these effects were reflected in differences in task engagement. Overall, we not only demonstrate that the presentation of feedback is a prerequisite to learn volitional control of amygdala activity but also that intermittent feedback is superior to continuous feedback presentation.

Introduction

Various studies have highlighted the usability of real-time fMRI (rt-fMRI) neurofeedback as a tool to enable participants or patients to dynamically self-regulate activation in several brain areas through the use of mental strategies, thereby affecting behavior specifically attributed to the function of the targeted brain region (e.g. Caria et al., 2007; Rota et al., 2009; Scharnowski et al., 2012). Rt-fMRI may therefore offer numerous possible applications, having the advantage of being both, non-invasive and allowing for whole brain coverage, which allows targeting of even subcortical structures. However, there are several technical challenges in developing rt-fMRI paradigms, discussed at the first conference on real-time fMRI neurofeedback in Zurich 2012 and summarized by Sulzer et al. (2013a). One issue, for example, relate to the superiority of implicit vs. explicit mental strategy use or the appropriate experimental control condition, with sham feedback (e.g. Caria et al., 2007; Linden et al., 2012; Rota et al., 2009; Yoo et al., 2008) or no feedback conditions typically applied (e.g. deCharms et al., 2005; Hartwell et al., 2016; Sulzer et al., 2013b). Another debated issue concerns the optimization of feedback presentation. In this respect deciding on the timing of neurofeedback delivery is a fundamental issue. Previous neurofeedback studies are mainly based on continuous rt-fMRI feedback presentation (e.g. Johnston et al., 2010; Lawrence et al., 2014; Rota et al., 2011; Weiskopf et al., 2004). As continuous feedback is updated after each acquired volume, it provides participants with feedback information at the highest possible temporal resolution. However, there might be

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some constraints that neutralize the beneficial effect of high temporal resolution: First, the cognitive load of continuous feedback paradigms is enormously high. Attention has to be divided between the application of a regulation strategy and monitoring of the feedback. Depending on the nature of the regulation task at hand, the focus of attention may have to be redirected between internal (regulation) and external (feedback). Further, the time lag of the hemodynamic response induces a temporal delay in feedback delivery. Consequently, participants have to associate feedback to mental events that occurred several seconds ago while simultaneously evaluating the feedback as well as still engaging in the experimental paradigm.

As an alternative to continuous feedback delivery, a few studies have averaged the BOLD signal over longer intervals, presenting feedback intermittently, i.e., at the end of a regulation block (Posse et al., 2003; Shibata et al., 2011; Yoo and Jolesz, 2002). It has to be noted that the term 'intermittent feedback' might be misleading and has to be differentiated from 'intermittent reinforcement'. For clarification, here 'intermittent' refers to the presentation of a delayed feedback at the end of an instructed task block. This is different from 'intermittent reinforcement' where rewards are given inconsistently and occasionally. The term 'delayed feedback' might be more precise, however, to keep the term in line with previous literature (Emmert et al., 2017; Johnson et al., 2012; Zilverstand et al., 2017), 'intermittent feedback' is used throughout. At least under some conditions, intermittent feedback seems to improve learning of self-regulation in comparison to continuous feedback, probably by reducing the aforementioned distraction factors (Johnson et al., 2012). In this pilot study, the authors compared continuous and intermittent feedback for improving self-regulation capability of cortical motor brain regions and could show that intermittent feedback outperformed the continuous feedback in this particular region. In a recent patient study intermittent feedback has been successfully applied to reduce anxiety in spider phobia patients (Zilverstand et al., 2015). Very recently, a study by Emmert et al. (2017) compared continuous and intermittent feedback in a small sample of tinnitus patients. The patients were supposed to learn to down-regulate primary auditory cortex. Importantly they were not instructed to use a specific strategy. The authors of this study conclude advantages of continuous feedback on long-term training.

In the current study, we systematically compared self-regulation efficacy induced by either continuous or intermittent feedback on brain activity in the amygdala with instructed mental imagery of positive memories and feelings. Additionally, we investigated the effect of neurofeedback on learning success by comparing neurofeedback in contrast to the usage of pure mental strategies without feedback delivery.

Given the less distracting nature of intermittent feedback we hypothesized that this variant of feedback would boost control over a predefined region of interest (ROI) when compared to continuous feedback. Further, we hypothesized that neurofeedback generally surpasses pure mental strategies by allowing volitional regulation of ROI-based brain activity. We selected the amygdala as a ROI, based on several studies demonstrating participants' ability to self-modulate its activity by means of neurofeedback (Brühl et al., 2014; Paret et al., 2014; Posse et al., 2003; Zotev et al., 2011). Also, the amygdala is an essential component of emotion regulation networks and mood regulation success (Kohn et al., 2014a,b) as well as salience processing (Kroemer et al., 2015) and has been related to several diseases such as depression, addiction, and obesity (Dietrich et al., 2016; García-García et al., 2014; Grabenhorst et al., 2013). Furthermore, the amygdala might play a role in sustained positive mood and autobiographic memory recall (Piefke et al., 2003; Vandekerckhove et al., 2005) and positive mood induction (Habel et al., 2005; Kohn et al., 2014a,b; Schneider et al., 1997). Although recent work hints at an extended network of brain regions involved in emotion regulation (Kohn et al., 2014a,b; Wager et al., 2008) that may be differentially involved in specific diseases, such as the subgenual anterior cingulate cortex in depression (Drevets et al., 2008), specifically the amygdala is an important brain hub that might be relevant for a variety of potential neurofeedback applications. Rt-fMRI regulation of amygdala thus represents a potential complement for therapeutic interventions of such diseases (Young et al., 2014). The results of this study contribute to the optimization of neurofeedback training of this subcortical structure. Maybe even more important, it proves the feasibility of time-delayed and sparse feedback in neurofeedback. This is of special interest for more complex analysis approaches, such as feedback based on functional and effective connectivity of brain networks as very recently presented by Koush et al. (2017), which require more computational time and, as a consequence, can be exclusively presented intermittently.

Methods

Participants

Forty-nine right-handed men participated in this study. They were randomly assigned to one of the two intervention groups (continuous feedback: CON; intermittent feedback: INT) or the control group (no feedback: NOF). Exclusion criteria were contraindications to MRI, abnormalities in structural scans and presence of mental or psychiatric disorders. The latter was established using an in-house questionnaire for fMRI that captures the participant's individual and family history of neurological and psychiatric disorders. All participants participated for the first time in rt-fMRI neurofeedback experiments. Due to head motion (scan-to-scan movements of more than 3 mm) 7 participants were excluded (1, 4 and 2 exclusions from groups CON, INT, NOF, respectively), leaving 42 usable datasets (CON: $n = 16$, mean age 25.8 ± 2.4 years; INT: $n = 18$, mean age 27.8 ± 3.8 years, NOF: $n = 8$, mean age 26.9 ± 3.9 years). The ethics committee of the Medical Faculty of the University of Leipzig approved the study in accordance with the Human Subjects Guidelines of the Declaration of Helsinki.

Experimental paradigm

All participants were instructed to generate a positive mood by remembering positive memories or creating general positive feelings. Prior to scanning every participant was given time to keep several positive memories in mind. The rt-fMRI neurofeedback experiment consisted of 5 runs (Baseline run, 3 Training runs, Transfer run) lasting 8 min 40 s each. A short Localizer run (20 s) at the beginning of the experiment was applied for amygdala mask positioning (see Fig. 1.).

Prior to training, a practice run (Baseline) was conducted in order to give participants the opportunity to test the effectiveness of certain strategies and get used to the rt-fMRI neurofeedback procedure. This Baseline consisted only of five REST (40 s each) and four HAPPY (80 s each) blocks arranged in alternating succession and feedback was already provided with respect to group. The three neurofeedback training runs (Training 1-3) therefore contained three conditions (HAPPY, COUNT, REST) changing block wise in alternating succession, with each block lasting 40 s. During the HAPPY condition participants were instructed to perform mental strategies, such as reminiscing about personal experiences of happy situations, being with friends and sexual memories (for a full list of strategies see Supplemental Information) to generate positive feelings. During COUNT the instruction was to count backwards from

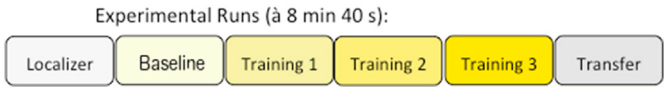

Fig. 1. Rt-fMRI neurofeedback protocol: The experiment consisted of 5 runs with a length of 8 min 40 s each. At the beginning of the experiment a localizer was conducted for amygdala mask positioning (participants were instructed to relax). In the subsequent Baseline run participants could familiarize with the neurofeedback procedure. During the three following training runs participants performed neurofeedback-based regulation of amygdala. For the final transfer run participants were instructed to perform the same procedure but no feedback was given.

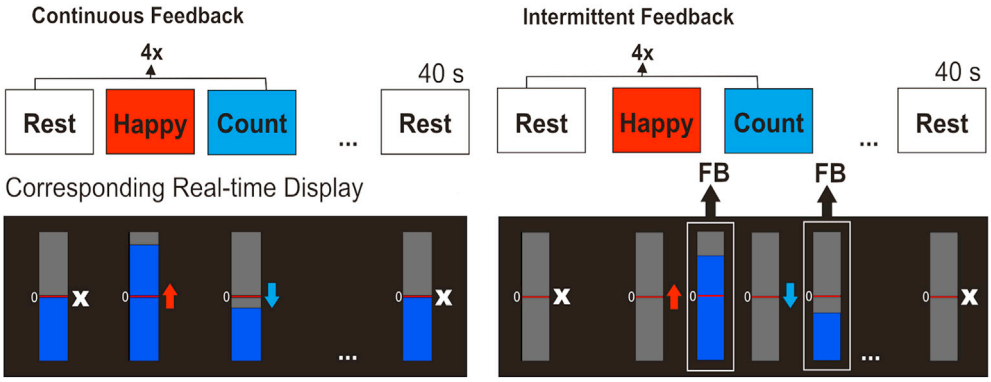

Fig. 2. Design of experimental runs: The three training runs as well as the transfer run consisted of alternating blocks of REST, HAPPY and COUNT conditions each lasting 40 s. The three conditions were indicated by different symbols next to the feedback bar: REST - white cross, HAPPY - red arrow, COUNT - blue arrow. a) Group given continuous feedback (CON): neurofeedback was presented continuously during the three training runs. b) Group given intermittent feedback (INT): neurofeedback was presented for 4 s after every HAPPY and COUNT block averaged for the preceding block. The control group (NOF) received no neurofeedback throughout the whole experiment. During Transfer no neurofeedback was presented in general.

100 by subtracting 3. During REST participants were instructed not to think about anything specific. To ensure effective disengagement from positive memories, a COUNT block followed every HAPPY block. A similar procedure was recommended by Zotev et al. to distract the participants' attention from the positive feelings and to attenuate activity of the emotion regulation network (Zotev et al., 2011).

Each condition was prompted by a different cue (HAPPY: red arrow upwards, COUNT: blue arrow downwards; REST: white cross). The cues were presented on a screen beside a grey bar, representing a thermometer, which was visible for all participants in every group (Fig. 2). However, with respect to group, the thermometer was updated in three different ways: (1) For the NOF groups the display remained constant. (2) For the CON group the thermometer (reflecting the current rt-fMRI neurofeedback signal) was continuously updated with every TR depending on the online BOLD activity during the conditions HAPPY and COUNT. Prior to scanning participants of this group were informed about the temporal character of the BOLD response resulting in a delayed neurofeedback presentation of 5–6 s after the actual neuronal activation. (3) Participants of the INT group received the averaged BOLD signal as updated thermometer value only at the end of HAPPY or COUNT blocks for 4 s (Fig. 2.). Participants of both feedback groups were instructed to attempt to maximally increase (HAPPY) or maximally decrease (COUNT) the thermometer display. During REST the thermometer remained still at the zero point. During the last run (Transfer), no neurofeedback was presented independent of the group. This run was conducted to evaluate transferability to situations without feedback.

Behavioral measurements

In addition to MR data, we assessed individual chronic stress level by means of The Trierer Inventory for the Assessment of Chronic Stress (TICS) (Schulz et al., 2004). The TICS asked for stress experience and particular stress situations over the past 3 months. The TICS consists of 57 items yielding several stress dimensions. Twelve of these 57 items constitute the Screening Subscale of Chronic Stress (TICS-SCSS) measuring overall chronic stress which was included as a covariate for the analyses of this study. The stress parameter has been acquired since it has been shown that stress influences the capability of emotion regulation (see e.g. Sapolsky, 2007). Moreover, participants completed Visual Analogue Scales (VAS) about experiences during the experiment, and indicated strategy use on a questionnaire (see Supplement for detailed information). VAS scales comprised the following questions (answers from "not at all" to "maximal"): "Have you been able to concentrate on the task?", "Have you been able to clear your mind during REST blocks?", "Have you been able to emotionally disengage during COUNT blocks", "To what extent the presented feedback and your internally perceived feeling of control corresponded?", "If you could do the experiment again, could you believe to further improve your regulation ability" (answers from "not at all" to "definitely"). Several group comparisons were conducted on these behavioral measures using SPSS. Determined by one-way ANOVA and Bonferroni-corrected post-hoc analysis, we tested for group differences in chronic stress level (TICS-SCSS) and individual task experiences (VAS scales). For questions assessable in the feedback groups only, we performed independent t-tests. To compare strategies between the groups, we used a $\chi 2$-test to test for differences in the distribution of strategy usage. For all tests we determined statistical significance at $p < 0.05$.

Region of interest placement

Following Zotev et al. this study is based on a region-of-interest (ROI) approach choosing left amygdala as ROI. In contrast to the previous study, a neurologist individually defined the ROI by creating a mask for the area of the left amygdala based on participants' T1-weighted MR images using the software package FSL[1] (see Fig. 3). At the beginning of each of the five experimental runs this mask has been co-registered with the functional MR images to minimize displacement artifacts due to slow head movements. The feedback signal presented to the feedback groups (CON, INT) represented mean BOLD activity in this predefined region. Although the control group (NOF) received no neurofeedback, participant's individual ROIs were defined for offline data analysis. As amygdala is located near the sphenoid sinus, the difference in the magnetic susceptibilities of brain tissue and air leads to unwanted gradients in the local magnetic field, which results in signal losses and geometric distortions (Chen et al., 2003; Robinson et al., 2004). To reduce these effects and avoid contamination of the fMRI signal by activation of neighbouring brain regions (especially hippocampus), individually defined amygdala masks were eroded using an ellipsoid with radius and height of 5 elements (Matlab unit).

MR data acquisition

Functional images were acquired on a 3T whole body scanner with standard 12-channel head coil (Siemens MAGNETOM Trio, Tim System, Siemens, Erlangen, Germany). Based on the recommendation for echo-planar-imaging (EPI)-protocols by Robinson et al. (2004), allowing more reliable acquisition of signals from limbic regions (especially the amygdala) of the brain, we used an EPI-sequence with the following parameters: TR = 2 s, TE = 25 ms, matrix size = 64 × 64 voxel,

[1] http://fsl.fmrib.ox.ac.uk/.

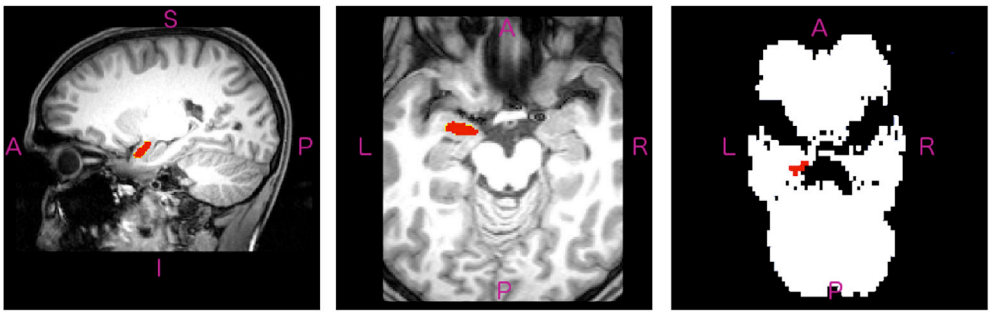

Fig. 3. Amygdala ROI: Example of ROI placement in the left amygdala after mask erosion and individual registration during the experiment.

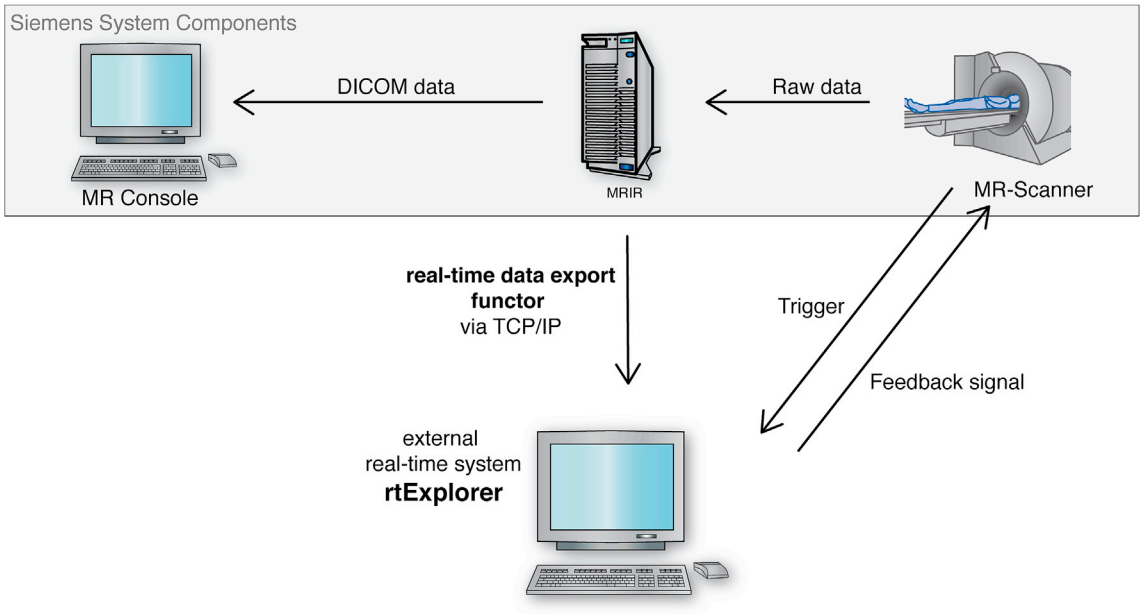

Fig. 4. MR Setup: The setup of the real-time fMRI system consisted of a custom made export functor that sent functional MR data directly from the reconstruction computer to an external analysis computer equipped with the analysis software rtExplorer.

bandwidth = 1953 Hz, flip angle = 90°. Thirty-two axial slices (voxel size = 3 × 3 × 2.6 mm^3, gap = 0.26 mm) AC/PC-aligned were acquired. In order to minimize head movements an additional foam cushion and patch stripe on participant's nose was used to fixate the head.

Online data analysis (ROI)

For the online data analysis, we used the in-house software packages rtExplorer (Hollmann et al., 2011, 2008) for real-time data analysis and the preprocessing module of BART (Hellrung et al., 2015) for real-time motion correction. For the processing we transferred the data from the Siemens internal reconstruction computer to our external computer using a custom made functor directly integrated into the Siemens functor pipeline (see Fig. 4). The data were sent volume-wise to a network port and stored into the random access memory of the analysis computer. Each volume was first motion-corrected before generating a feedback signal. For the CON group, the feedback signal was generated as the mean average of the ROI signal over the last three volumes and presented with each volume. For the INT group, the feedback signal was averaged over the whole preceding block (40 s, HAPPY or COUNT) and presented at the end of the block on the thermometer display for 4 s.

Offline data analysis (ROI and whole brain)

In each experimental run 260 vol were acquired resulting in 1300 scans in total excluding 20 scans for the localizer block at the beginning of the experiment. Data were analysed using SPM 8 (Wellcome Department of Imaging Neuroscience, London, UK) and Matlab 2010b.[2] Preprocessing of the data comprised correction for slice acquisition time within each volume, motion correction, spatial normalization to the standard MNI template brain using individual high-resolution, T1-weighted structural images resulting in a voxel size of 3 × 3 × 3 mm^3, smoothing using a Gaussian kernel with a full width at half maximum of 8 mm, and high-pass filtering (filter size 240 s, since each of the three condition block has a length of 40s, resulting in a length of 120 s, which was doubled with regard to Nyquist theorem). Further, individually eroded amygdala masks were normalized to the standard MNI template using the participants' T1-weighted structural images.

On single-subject level, a general linear model (GLM) was defined including six regressors for the three training runs and two regressors for the transfer runs modelling HAPPY and COUNT conditions respectively. The REST condition has not been modelled explicitly but has been included as baseline in this model. Six motion parameters (translation and rotation) were added as nuisance regressors. The localizer run (only relevant for mask positioning) has not been modelled. The Baseline run has been modelled separately since it only comprises HAPPY and REST conditions.

BOLD signal changes (% signal change) for the particular regressors were extracted from SPM analysis results (contrast images) within the

[2] http://www.mathworks.com.

individual ROIs and mean averaged across ROI. Values of the HAPPY and COUNT conditions were transferred to SPSS (IBM SPSS Statistics 19.0) and R (R-project R3.3.0) as variables for the following group analysis based on the contrast HAPPY – COUNT (HAPPY – REST for Baseline respectively).

First, we quantified whether the groups were able to up-regulate amygdala activity (i.e., showed a linear increase). To this end, we first checked for a positive increase in % signal change separately within each group by fitting a linear regression along the training runs and compared slopes (m). To quantify learning effects, we inspected solely Transfer and compared each feedback group with the control group using t-tests. Second, we assessed participants' ability to follow the HAPPY, COUNT or REST instructions group-wise during the whole experiment. To this end we used a correlational approach to compare the fit of the predicted and observed signal within each run. We calculated Pearson correlation coefficients between feedback block design model and measured BOLD signal using Matlab 2010b, i.e., we calculated the correlation between predicted and observed time courses. We compared these correlations between groups with Fishers' r-to-z transformation. Lastly, we quantified the performance over all runs and between groups with the help of a mixed effect model in R using REML with random slopes and random intercepts for both group and run (accounting for individual variability). Here, the focus was specifically on group differences in performance along the runs (3 Training + 1 Transfer x 2 groups). The model was adjusted for the level of chronic stress to account for variance associated with this variable. We modelled the main effects of the between-subjects factor group and the within-subject factor run, as well as the interaction of both. For a better understanding of performance differences between the regulation conditions, we also analysed HAPPY and COUNT conditions separately (results are presented in the inline Supplement).

To assess the validity of the overall experiment and training-induced differences between feedback groups beyond the ROI, we additionally conducted whole brain analyses for the third training and the transfer runs using full factorial GLM analysis modelling the factors group (CON, INT, NOF) and condition (HAPPY, COUNT), including TICS-SCSS as a covariate.

Results

Behavioral measurements

The level of chronic stress (TICS-SCSS) was included as covariate in all analysis since stress influences emotion regulation capabilities. Importantly, it did not differ significantly between the groups (means CON: 4.9 ± 6.9, INT: 8.4 ± 3.7, NOF: 9.0 ± 5.1, $F(2,39) = 2.370$, $p = 0.107$; it has to be noted that excluding this covariate would not change the interpretation of the results). We found no group differences regarding "overall concentration to the experiment" ($F(2,32) = 1.610$, $p = 0.216$) and "emotional disengagement during COUNT" ($F(2,32) = 2.215$, $p = 0.126$), but a significant group difference for "clearing the mind during REST" ($F(2, 32) = 7.82$, $p = 0.002$). A Bonferroni-corrected post-hoc test revealed that the group receiving continuous feedback was less effective in distancing from the emotional thoughts during the REST phases in comparison to the intermittent feedback group ($p = 0.002$) and the no neurofeedback group ($p = 0.045$). "Feedback/feeling of control correspondence" and "beliefs about possible improvement" ($t(25) = -0.970$, $p = 0.314$) did not differ between the feedback groups determined by independent t-tests, although we observed a trend regarding correspondence between feedback and self-perceived feeling of control ($t(25) = -1.8$, $p = 0.083$). Please see Table 1 of Supplemental Material for details on VAS measures per group. With regard to the strategies used for the up-regulation of amygdala, we descriptively compared the strategies used within the groups. Participants of the three groups have used all our proposed strategies. We found no differences in the distribution of strategy usage between the three groups (χ^2-test: χ^2 $(3,28) = 14.37$, $p = 0.98$). For detailed information about strategy usage see Table 2 of Supplemental Material.

ROI analysis: learning by feedback and time course correlations

Exercise of self-control on amygdala activity, assessed by the contrast HAPPY-COUNT, progressively increased across the Training for the feedback groups, but not for the control group (see Fig. 5 left). The respective slope parameters of the linear regression describing the linear increases of all groups were calculated (CON: $m = 0.12$, INT: $m = 0.22$, NOF: $m = -0.05$). We found no significant differences between the slopes of the two feedback groups but a trend between INT and NOF groups (INT vs. NOF: $p = 0.1$, CON vs. NOF: $p = 0.3$). We also tested for differences during Baseline as a kind of pre-training regulation capability of all groups. In comparison to the CON and NOF group % signal change during this run was significantly lower in the INT group (average % signal change CON: 0.18, INT: −0.06, NOF: 0.16, $p = 0.04$). It has to be noted that during Baseline, participants already received feedback and performed HAPPY and REST condition only. However, if this run would be added to the analysis, the slopes would change as follows: CON: $m = 0.09$, INT: $m = 0.22$, NOF: $m = 0.02$ and a significant difference in

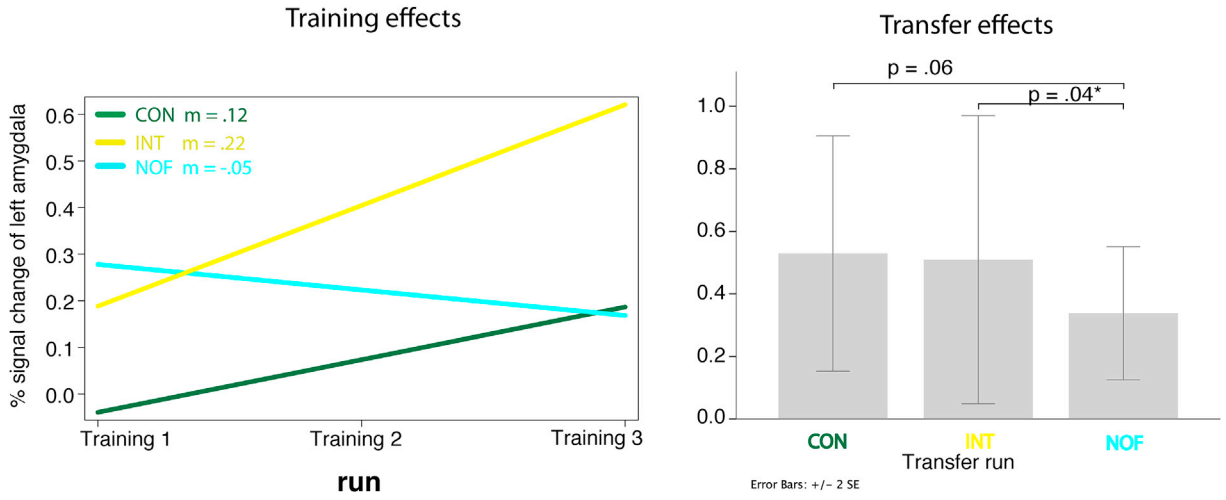

Fig. 5. Learning effect induced by feedback: Throughout the Training, both feedback groups show a positive slope (m) in the linear regression fit over their self-regulation capability while the control group remains almost constant (left). In comparison to the control group (NOF), the regulation capability in the amygdala during Transfer was higher in both feedback groups (right).

slope between INT and NOF ($p = 0.01$) could be observed. Due to the different conditions in Baseline, we refer in our discussion to the results for Training and Transfer effects only.

To quantify learning effects, we analysed Transfer separately and compared the feedback groups with the control group (see Fig. 5 right). We found a significant increase in amygdala self-regulation capability in the INT over the NOF group and a strong trend of the CON over the NOF group (mean activity CON: 0.52, INT: 0.51, NOF: 0.33; INT vs. NOF: $F(2,24) = 4.53$, $p = 0.04$; CON vs. NOF: $F(2,22) = 3.9$, $p = 0.06$). Only the feedback groups did show an increase in self-regulation capability throughout Training and both feedback groups showed an improved regulation capability during Transfer.

The differences in % signal change of the left amygdala (effect sizes) between the first and last Training run were CON: $\Delta = 0.22$, INT: $\Delta = 0.43$ and NOF $\Delta = 0.13$ and respectively between Transfer and Baseline CON: $\Delta = 0.34$, INT: $\Delta = 0.57$ and NOF: $\Delta = 0.32$.

As a qualitative measure of performance, assessing participants' ability to follow the instructions, we calculated Pearson correlation coefficients between the modelled experimental design and the measured BOLD signal of the left amygdala for all runs (see Table 1 and Fig. 6). The results indicate that participants receiving intermittent feedback could follow the regulation most precisely at the end of the training and improved throughout Training. In comparison, the observed signal from the CON group is less correlated with the predicted model during Training. We observed no differences at all of these correlations during Transfer.

Table 1
Correlation coefficients between predicted and observed signal over all runs and between groups.

Correlation coefficients	Run 1		Run 2		Run 3		Transfer	
INT	0.23*		0.38*		0.41*		0.39*	
CON	0.05		0.19*		0.17*		0.40*	
NOF	0.23*		0.33*		0.09		0.39*	
Fishers' r-to-z								
	z=	p=	z=	p=	z=	p=	z=	p=
INT vs. CON	0.49	0.3	0.55	0.29	0.7	0.24	-0.03	0.48
INT vs. NOF	0.0	0.5	0.11	0.46	0.67	0.25	0.0	0.5
CON vs. NOF	0.6	0.27	-0.29	0.39	0.15	0.4	0.02	0.49

*$p < 0.05$.

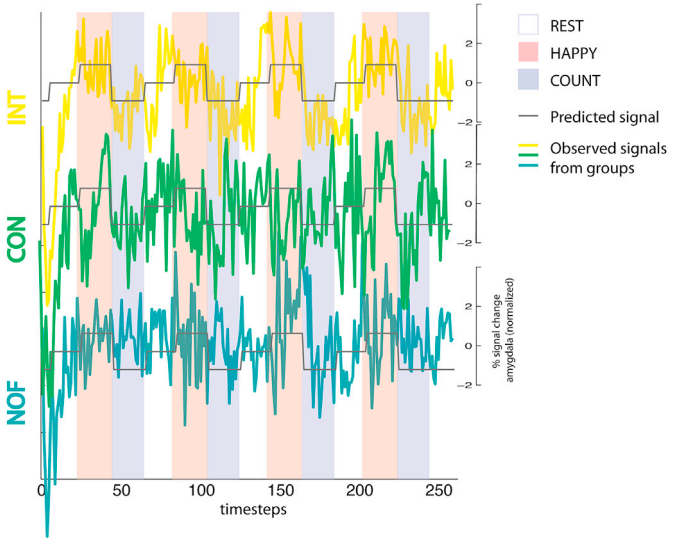

Fig. 6. Time courses of left amygdala (last training run): The averaged time courses of all participants per group show that participants who received intermittent feedback could follow the experimental instructions most precisely.

ROI analysis: comparison of feedback groups

To compare the feedback groups, we extracted the BOLD signal difference of HAPPY and COUNT blocks (HAPPY-COUNT) based on the individual amygdala masks and compared them over the three training runs and the transfer run (see Fig. 7). We formally tested the influence of feedback group and time on the contrast HAPPY-COUNT by fitting a repeated-measures linear mixed-effect model, which was adjusted for the level of chronic stress to account for variance associated with this variable. We modelled the main effects of the between-subjects factor group and the within-subject factor run as well as the interaction of both. Results indicate significant effects of both group ($\chi^2(1) = 5.04$, $p = 0.025$) and run ($\chi^2(3) = 11.63$, $p < 0.001$), but no interaction effect of group and run ($\chi^2(3) = 2.90$, $p = 0.407$). The calculated % signal changes over the runs were for CON: -0.06 ± 0.44; 0.11 ± 0.26; 0.16 ± 0.47; 0.52 ± 0.75 and INT: 0.15 ± 0.52; 0.47 ± 0.6; 0.58 ± 0.8, 0.51 ± 0.9.

In addition, we explicitly analysed the HAPPY and COUNT blocks separately to differentiate between the regulation effects of conditions. As illustrated in inline Supplement Fig. 1 the results show that differences are based on up-regulation of the amygdala during HAPPY blocks ($F(1,31) = 4.007$, $p = 0.054$), while down-regulation during COUNT blocks does not differ between the groups ($F(1,31) = 1.17$, $p = 0.288$).

Whole brain analysis

To assess conceptual validity of the experiment, we tested for the main effect of regulation (HAPPY-COUNT, transfer run) over all groups (see Fig. 8). We found increased activity of the left amygdala as instructed by the feedback task contrasting HAPPY vs. COUNT. Additionally, other emotion-related brain regions, such as ventromedial prefrontal cortex (vmPFC), precuneus and orbitofrontal cortex showed significantly increased activation. Furthermore, memory-related parahippocampal areas were significantly activated. Moreover, we observed significantly decreased activation in calculation-related regions of the superior and medial frontal gyrus contrasting HAPPY vs. COUNT (see Table 2).

Additionally, we compared the last Training between the feedback groups on a whole brain level (see Fig. 9 and Table 3). For the contrast 'CON > INT', we observed significantly higher activations in the anterior insula and the inferior frontal gyrus (IFG). The inverse contrast did not show significant differences.

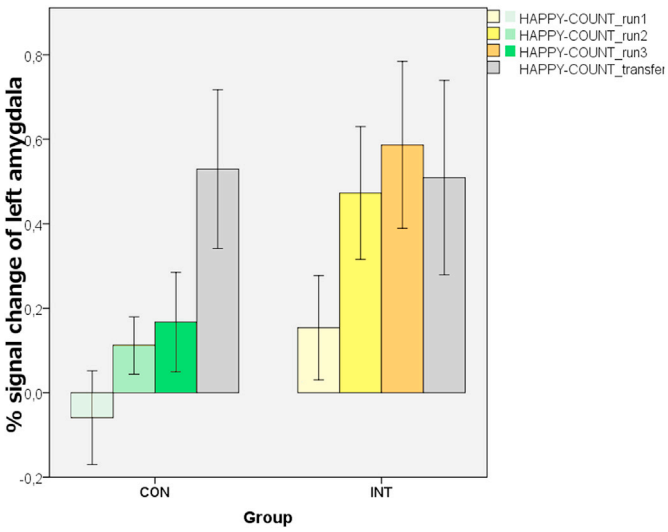

Fig. 7. Comparison of feedback groups (Training and Transfer): % signal change of the left amygdala (mean ± s.e.) over all runs.

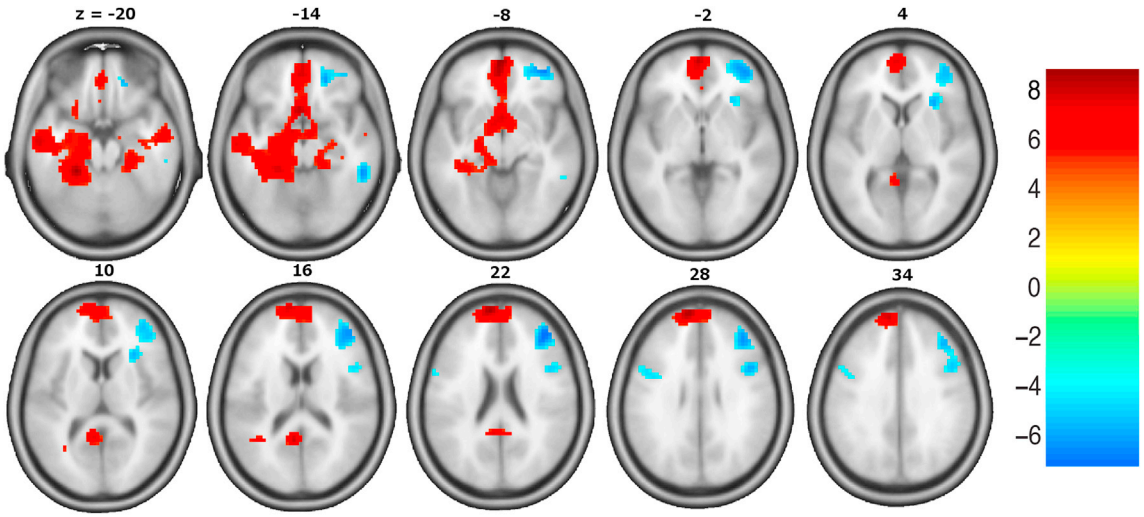

Fig. 8. Main effect regulation: The positive (red color map) and negative (blue color map) contrasts of HAPPY-COUNT (transfer run) show brain areas involved in emotion-regulation and mental calculation. This is in congruence with participants' instruction and proves the feasibility of the regulation.

Discussion

In this study, we systematically compared different types of rt-fMRI neurofeedback presentations, used as tool to learn the volitional regulation of amygdala activity. Feedback was either presented continuously (after every TR), intermittently (averaged over the preceding regulation block) or not at all. First, we demonstrated that neurofeedback was necessary to learn volitional up-regulation of amygdala activity during Training, as constant improvement in the ability to regulate amygdala activity was not present in the no feedback group. Furthermore, compared to the control group we demonstrated strongly improved regulation capabilities after the training (i.e., during Transfer) in the feedback groups. This indicates that pure mental strategy use without any feedback about its effectiveness on the brain level may not be sufficient to successfully learn to regulate brain activity. Moreover, our finding of feedback-induced learning of amygdala activity is in line with a previous study showing participants' capability of amygdala up-regulation by means of continuous neurofeedback presentation in comparison to sham feedback (Zotev et al., 2011). In addition to this study we demonstrated that intermittent feedback presentation might even boost regulation performance in comparison to continuous feedback, since the group presented with intermittent feedback outperformed those participants receiving the feedback continuously during Training. Interestingly, we found that participants' ability to follow the regulation conditions during Training was specifically prominent in the intermittent feedback group (highest correlation and improvement over runs). This ability remained almost constant in the control group and was less pronounced in the continuous feedback group. There might be several reasons for these effects. As continuous feedback is updated after each acquired volume, it provides participants with a maximum of information. An advantage of continuous feedback presentation may be that it induces greater interest or engagement in the task to ensure high attention as mentioned in a pilot study by Johnson et al. (2012). However, there might be some constraints of continuous feedback inhibiting participants' performance. Participants have to (1) associate feedback to mental events that occurred several seconds prior (temporal delay due to HRF delay) while (2) simultaneously evaluating the feedback and (3) staying engaged in the experimental paradigm. Taken together, these multiple processes might distract from the regulation training. Johnson and colleagues intra-individually compared the effects of continuous neurofeedback vs. intermittent feedback and sham vs. real neurofeedback to no feedback for pre-motor cortex. They have shown that both feedback variants lead to increased brain activity in comparison to no feedback blocks. However, possibly due to their relatively small sample size of n = 13 and the intra-individual design, they did not find any significant differences between the two feedback variants. To the individual participant, experiencing different feedback modes in addition to either receiving sham or real feedback within the same experiment might have introduced some amount of uncertainty and therefore hampered optimal usage of neurofeedback. Further, the mixture of conditions might have blurred differences between conditions. Our results, the increased amplitudes of neural activity in amygdala over Training and improved self-regulation capability during Transfer, are very well in line with this study and even significantly underpin the varying performance between the feedback variants during Training. Emmert et al. (2017) recently compared the effectiveness of continuous and intermittent feedback presentation in a clinical sample of tinnitus patients. Fourteen patients, seven in each group, were instructed to down-regulate activity in primary

Table 2
Activation network corresponding to neural activity shown in Fig. 8.

Region (Cluster and peaks)		MNI coordinates			Statistics	
C	Peak activation	x	y	z	t-value	p-value (FWE-corrected)
HAPPY-COUNT (red color map)						
1	Superior Frontal Gyrus	−9	62	25	8.24	<0.001
	Middle Temporal Gyrus	−60	−13	−17	7.16	<0.001
	Medial Frontal Gyrus	−3	50	−8	7.72	<0.001
	Parahippocampal Gyrus	−18	−25	−17	6.16	<0.001
	Left Hippocampus	−21	−19	−14	6.20	<0.001
	Left Amygdala	−21	−4	−20	4.73	<0.05
	Left Fusiform Gyrus	−24	−40	−27	7.78	<0.001
2	Precuneus	−6	−55	16	7.22	<0.001
3	Cerebellum	6	−52	−44	7.05	<0.001
4	Cerebellum	27	−76	−35	6.82	<0.001
5	Inferior Temporal Gyrus	57	−7	−20	6.02	<0.001
	Right Fusiform Gyrus	24	−31	−20	5.57	=0.002
6	Superior Temporal Gyrus	−36	−55	16	5.87	=0.001
COUNT-HAPPY (blue color map)						
7	Middle Frontal Gyrus (Brodman area 10)	42	41	22	7.64	<0.001
	Superior Frontal Gyrus	21	41	−17	6.71	<0.001
8	Inferior Temporal Gyrus	54	−40	−14	6.94	<0.001
	Right Brodman area 9	48	11	31	6.46	<0.001
9	Left Brodman area 9	−45	5	31	5.25	=0.005
	Brodman area 44 (Broca areal)	−60	5	19	5.02	=0.010

FWE-corrected p-values ($p < 0.05$), cluster size > 20, C – cluster.

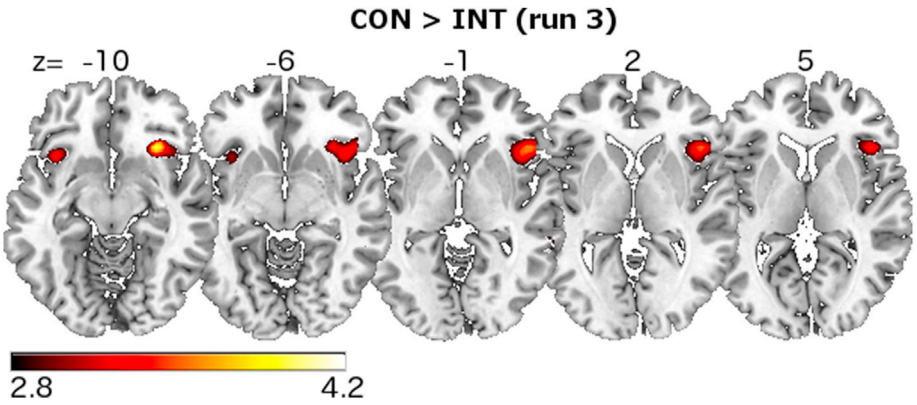

Fig. 9. Feedback differences during training run 3: This contrast shows the differences between the feedback groups during the third training run. For CON > INT feedback, insula and IFG are more active, which indicates a higher cognitive load of feedback processing during continuous feedback presentation.

Table 3
Activation network corresponding to neural activity shown in Fig. 9.

Region (Cluster and peaks)		MNI coordinates			Statistics	
C	Peak activation	x	y	z	t-value	p-value (uncorrected)
1	Inferior Frontal Gyrus	30	23	−11	4.08	<0.001
	Frontal Operculum	48	23	−2	3.42	<0.001
	Insula	30	23	10	2.79	=0.003
2	Inferior Frontal Gyrus	−36	17	−14	3.35	=0.001
3	Medial Frontal Gyrus	3	38	40	3.03	=0.002
	Superior Frontal Gyrus	−3	38	55	2.74	=0.003

P < 0.005 (uncorrected), cluster size > 20, C - cluster.

auditory cortex with the help of receiving either continuous or intermittent neurofeedback during three training sessions on each of three consecutive days. It is important to note here that patients were not explicitly instructed to use a specific strategy. The authors found a significant down-regulation effect in the continuous group only, but did not find significant group differences for the two types of feedback. Importantly, several methodological differences exist between our present study and the study of Emmert and colleagues: targeting a subcortical rather than a primary sensory ROI for feedback generation, differences in sample size, duration of neurofeedback training (three training sessions on one day vs. nine training sessions over three days), explicit instruction of strategy vs. no instruction, inclusion of a control group vs. patients only, different regulation conditions, i.e. up- and down-regulation vs. down-regulation only. Here, mainly the aspect of strategy instruction seems to be important to explain the different results. For a non-instructed regulation, the maximum amount of information about the current brain activity is required to figure out efficient regulation strategies. Contrary, as in our study, when a set of given strategies is instructed an intermittently presented feedback combines two advantages, lower cognitive load during training and learning success. The effects on feedback training using a patient sample, a down-regulation only and different training period cannot be compared explicitly between these studies and requires further investigation. Possibly, different feedback types might be beneficial in different settings, especially with regard to strategy instruction. Future studies should carefully consider the influence of these factors on regulation success.

In our study, the assumption that continuous feedback might induce distraction is supported by our behavioural findings. Participants in the continuous group reported significantly more problems to clear their mind in the REST phases as compared to participants of the intermittent group. On-going rumination about previous regulation blocks in the group presented with continuous feedback may have caused this difference. Moreover, this effect might have been intensified by a more pronounced incongruence between presented feedback and participants' self-perceived performance (trend significance in comparison to intermittent group), supposedly due to the temporal delay between mental events and the hemodynamic response associated with the feedback. Apart from the temporal delay, spontaneous fluctuations in the BOLD signal that are not systematically associated with the regulation effort of participants might induce additional noise to the continuous feedback signal. Taken together, our results show that although intermittent feedback is averaged over longer periods and hence has a lower temporal resolution, a reduction of the mentioned distracting factors supposedly outweighs this loss of information.

Main effects of conditions in the whole brain analysis showed that participants performed the regulation tasks as instructed, i.e. HAPPY condition with positive memories and COUNT with mental calculations. Within the group analysis of both conditions we indeed found neural activity related specifically to the instruction. HAPPY condition led to emotion-related brain activation within amygdala, precuneus, parahippocampal and medial frontal gyrus, which is functionally labelled as ventromedial prefrontal cortex (vmPFC). These brain structures have been associated with emotional states (Sabatinelli et al., 2011) and emotion regulation (Ochsner et al., 2004). Down-regulation (i.e. counting), on the other hand, was related to activation in superior and medial frontal gyri. These brain areas have been functionally associated with mental calculation (Rickard et al., 2000) as instructed in the COUNT condition. These results clearly show that the regulation was achieved by strategy-specific regulation and cannot only be attributed to a general physiological increase of brain activity. Critically, we did not acquire additional physiological data and therefore cannot quantify such effects on amygdala regulation. Here, we carefully evaluated motion parameters and interestingly, we found that motion, described as median framewise displacement values (Jenkinson et al., 2002), was increased for both feedback groups compared to the NOF group (see Supplement for details). This is in contrast to previously described reduced motion while continuous feedback is given (Zilverstand et al., 2017). But in addition, we observed that motion did not change over the runs within each group. If the amygdala regulation would only be motion-related, motion should be increased over the runs, which it is not. Furthermore, both feedback groups would have had to apply the same “physiological” strategy, which is unlikely. However, the highly interesting question about the physiological noise influence cannot be answered within this study and differences between feedback and control groups requires further investigations.

To assess whole brain differences between the feedback groups, we compared the last training run between the feedback groups. Participants in the continuous feedback group showed significantly higher activation in the anterior insula and the IFG. The insula has recently been described in a neurofeedback meta-analysis as region generally associated with

continuous feedback (Emmert et al., 2016). This finding is underpinned by previous studies describing anterior insula as a part of a network involved in task-control signals, which comprises feedback processing (Dosenbach et al., 2008, 2007). In a meta-analysis, Cauda et al. (2012) have shown that the anterior insula is mostly activated by cognition and belongs to a network, which is related to saliency detection. In a study by Menon and Uddin (2010) the anterior insula has been described as an integral hub in mediating dynamic interactions between large-scale brain networks involved in externally oriented attention and internally oriented or self-related cognition. Furthermore, the IFG is widely known as an area involved in self-awareness, self-perception and in the theory of mind (Saxe et al., 2006; Young et al., 2010). All these results may support the assumption of a higher cognitive load and corresponding neural resource allocation in the continuous feedback group in insula and IFG.

Further limitations of our study have to be noted. First, we did not include an additional sham feedback group. However, the systematic comparison of amygdala regulation performance induced by either valid neurofeedback or sham feedback has been done in a previous study of Zotev et al. (2011). Therefore, we decided to assess the direct influence of feedback in comparison to pure mental strategy use by inclusion of a no feedback control group. Second, we did not acquire a pre-training transfer (without feedback) run to test for baseline participants' regulation capabilities. This is also the case in many other neurofeedback studies, but this could unify and simplify the comparison of neurofeedback learning effects based on the differences between pre- and post-training.

As a very general aspect, we claim that learning via neurofeedback in our study fits very well with the theory of cognitive skill learning as described in the review papers of Birbaumer et al. (2013) and Sitaram et al. (2016). As it is still under debate, which learning theory may underlie learning from neurofeedback, we avoid any speculative interpretations on this matter. Our results show that neurofeedback regardless of the type of presentation helps to learn self-regulation of the amygdala. If the neurofeedback helps in distinguishing efficient from inefficient regulation strategies, it is really interesting to differentiate between the continuous and intermittent feedback. We assume that it is less demanding for participants to integrate the feedback intermittently. But this is only true if a set of strategies has been instructed previously; otherwise a maximum amount of feedback information is required for learning. However, here overall performance during training runs differs between feedback groups, potentially due to reduced distraction and less cognitive load with regard to dual-task processing in the CON group. This leads to another important issue in neurofeedback learning being currently under debate, which is the use of mental strategies. It has been shown that it is not necessary to provide mental strategies for learning (e.g. Marxen et al., 2016; Shibata et al., 2011). This is especially supported by animal literature. However, it also has been shown that a strategy can be advantageous and may increase the effects of learning. Scharnowski and Weiskopf (2015) investigated the effect of instructions and compared learning without instructed strategy at the beginning of a neurofeedback experiment to learning after providing instructions in the same participants. The authors could demonstrate a significant increase in regulation success after suggesting a mental strategy. Furthermore, a recent study by Sorger et al. (2016) has demonstrated that using mental approaches was sufficient for gradual changes in self-regulation. These general aspects should be carefully considered for individual questions of further neurofeedback studies.

Conclusions

Overall, our study has shown that intermittent rt-fMRI neurofeedback is superior to continuous neurofeedback during training with given strategies as a means to train participants to volitionally self-regulate brain activity. Moreover, we conclude that intermittent feedback is valid for learning brain self-regulation when a set of regulation strategies is pre-defined. This may be due to distraction and cognitive overload associated with continuous neurofeedback presentation. Thus, the usage of less distracting intermittent feedback might potentially help to reduce cognitive load of rt-fMRI experiments - that are per se rather exhausting - thereby improving performance in future tasks. Moreover, this leads to the conclusion that neurofeedback trainings based on more complex analysis approaches of large data quantities, such as the integration of several ROIs or network connectivity analysis (Koush et al., 2013; Monti et al., 2014), are feasible using intermittent approaches. Thus, these results help to pave the way for new possibilities of rt-fMRI neurofeedback trainings. Apart from that, neurofeedback targeting the amygdala yields a promising approach in therapeutic applications, as it has already been shown for depression (Young et al., 2014), anxiety disorders (Brühl et al., 2014; Paret et al., 2014), phobia (Zilverstand et al., 2015), and post-traumatic stress disorder (Nicholson et al., 2016).

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The authors declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.10.031.

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