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fMRI neurofeedback of amygdala response to aversive stimuli enhances prefrontal–limbic brain connectivity

Christian Paret [a,b,f,*], Matthias Ruf [a,f], Martin Fungisai Gerchen [c,d,f], Rosemarie Kluetsch [b,f], Traute Demirakca [a,f], Martin Jungkunz [b,f], Katja Bertsch [e], Christian Schmahl [b,f,1], Gabriele Ende [a,f,1]

[a] Department Neuroimaging, Germany
[b] Department of Psychosomatic Medicine and Psychotherapy, Germany
[c] Department of Clinical Psychology, Germany
[d] Bernstein Center for Computational Neuroscience Heidelberg/Mannheim, J5, D-68159 Mannheim, Germany
[e] Department of General Psychiatry, Center for Psychosocial Medicine, Heidelberg University, Voßstr. 2, D-69115 Heidelberg, Germany
[f] Central Institute of Mental Health Mannheim, Medical Faculty Mannheim, Heidelberg University, J5, D-68159 Mannheim, Germany

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ABSTRACT

Down-regulation of the amygdala with real-time fMRI neurofeedback (rtfMRI NF) potentially allows targeting brain circuits of emotion processing and may involve prefrontal–limbic networks underlying effective emotion regulation. Little research has been dedicated to the effect of rtfMRI NF on the functional connectivity of the amygdala and connectivity patterns in amygdala down-regulation with neurofeedback have not been addressed yet.

Using psychophysiological interaction analysis of fMRI data, we present evidence that voluntary amygdala down-regulation by rtfMRI NF while viewing aversive pictures was associated with increased connectivity of the right amygdala with the ventromedial prefrontal cortex (vmPFC) in healthy subjects ($N = 16$). In contrast, a control group ($N = 16$) receiving sham feedback did not alter amygdala connectivity (Group × Condition t-contrast: $p < .05$ at cluster-level). Task-dependent increases in amygdala–vmPFC connectivity were predicted by picture arousal ($\beta = .59$, $p < .05$). A dynamic causal modeling analysis with Bayesian model selection aimed at further characterizing the underlying causal structure and favored a bottom-up model assuming predominant information flow from the amygdala to the vmPFC ($xp = .90$). The results were complemented by the observation of task-dependent alterations in functional connectivity of the vmPFC with the visual cortex and the ventrolateral PFC in the experimental group (Condition t-contrast: $p < .05$ at cluster-level).

Taken together, the results underscore the potential of amygdala fMRI neurofeedback to influence functional connectivity in key networks of emotion processing and regulation. This may be beneficial for patients suffering from severe emotion dysregulation by improving neural self-regulation.

Introduction

Real-time functional magnetic resonance imaging neurofeedback (rtfMRI NF) has attracted increasing interest from basic and clinical scientists. With rtfMRI NF, information on brain activation is fed back to the participant via a brain–computer interface (Weiskopf, 2012). Cumulative evidence is reported for a potential effect of rtfMRI NF on brain self-regulation in domains of high relevance for clinical psychology and psychiatry, such as emotion regulation (e.g. Brühl et al., 2014; Caria et al., 2010; Scheinost et al., 2013; Veit et al., 2012; Zotev et al., 2011), and an improved regulation of disturbed brain circuits supported by neurofeedback training may yield therapeutic benefits (Linden, 2014; Stoeckel et al., 2014).

There is initial evidence for an alteration of amygdala–prefrontal connectivity via amygdala neurofeedback when giving the instruction to upregulate (Yuan et al., 2014; Zotev et al., 2011, 2013). Though, to date, it is unknown whether amygdala neurofeedback with the instruction to down-regulate involves similar neural mechanisms. This is of eminent interest for advancing rtfMRI NF towards the treatment of mental disorders involving limbic hyperactivation and aberrant prefrontal–limbic connectivity, that might become a therapeutic option in the future.

In a previous study, we recently demonstrated that blood oxygenation level dependent (BOLD) signal feedback from the amygdala can be used to improve amygdala down-regulation in healthy individuals (Paret et al., 2014). We adapted an established emotion regulation paradigm that involved viewing aversive and scrambled 'neutral' pictures

* Corresponding author at: Central Institute of Mental Health, J5, D-68159 Mannheim, Germany.
E-mail address: christian.paret@zi-mannheim.de (C. Paret).
[1] Authors contributed equally.

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in an fMRI environment. Participants were instructed to regulate a continuously updated biofeedback signal, obtained from the amygdala and displayed at both sides of the aversive picture (Fig. 1). They significantly decreased amygdala activation when instructed to regulate the feedback signal as compared to the instruction to respond naturally, i.e., to view the picture. In this recent report, however, changes in brain connectivity were not addressed. Hence, the major aim of the present paper is to delineate changes in functional amygdala connectivity with rtfMRI NF and the instruction to down-regulate the amygdala response to aversive pictures. This is not only necessary for advancing the development of the technique towards clinical application. It is also needed to scrutinize the present reports on connectivity with amygdala neurofeedback, which focused on amygdala up-regulation and interpret changes of prefrontal–limbic connectivity in terms of a top-down control model. Data from amygdala down-regulation are suited to test this model and deepen our understanding of the dialectic interplay of prefrontal cortex and amygdala in neurofeedback regulation. Addressing this point in this paper, it is expected, that amygdala neurofeedback compared to control region feedback would enhance functional connectivity of the amygdala with the prefrontal cortex. Functional connectivity is analyzed in the data set described above using psychophysiological interaction (PPI) analysis to identify prefrontal regions communicating with the amygdala in a task-dependent and (amygdala-feedback) specific manner. Connectivity with the ventromedial prefrontal cortex (vmPFC) region detected with this approach is further investigated for causal directionality using dynamic causal modeling (DCM) to inform the interpretation of connectivity changes in terms of top-down and bottom-up processes.

Materials and methods

Participants

Thirty-two females aged 24.56 ± 3.91 (M ± SD) who did not report any current or lifetime psychiatric diagnosis participated in the study. Group assignment to the experimental and control group was randomized and blinded. Groups were matched for age, highest educational attainment and sample size (N = 16 per group). Results from the same sample had been published earlier (Paret et al., 2014); more details on sample characteristics can be obtained there. For the purpose of this article, the data were re-analyzed using a different analysis approach.

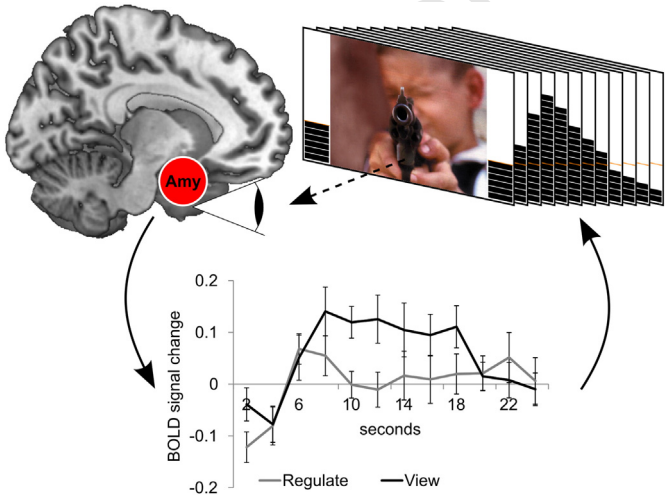

Fig. 1. Schematic visualizing the neurofeedback loop. The BOLD signal change of the amygdala is recorded by fMRI and analyzed in real-time. With each new volume, information on the current activation level of the brain is available. Via a thermometer displayed to both sides of the picture, neurofeedback is returned to the participant, resulting in a closed loop.

The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg. All participants provided written informed consent before participation and received financial compensation.

Procedure

Participants were instructed to regulate a continuously updated biofeedback signal, obtained either from the amygdala (experimental group) or from a control region (control group). The signal was displayed at both sides of the aversive picture via a thermometer display. In the 'regulate'-condition, participants were instructed to down-regulate the thermometer while they were asked to respond naturally to the picture in the 'view'-condition. In the 'neutral'-condition, scrambled pictures were presented. The experiment comprised one neurofeedback session consisting of 3 runs. In each run, the conditions were presented 5 times each in semi-randomized order and a 10 s rest period between subsequent conditions. The last neurofeedback run was followed by a transfer run, which had the same design as a neurofeedback run but without thermometer presentation. The BOLD signal from a bilateral amygdala region-of-interest (ROI experimental group) or a control region located in the basal ganglia (control group) was obtained with TurboBrainVoyager (TBV) software (version 3.0, Brain Innovations, Maastricht, Netherlands), applying motion correction and spatial smoothing (full width at half maximum [FWHM] = 4 mm). 33% of voxels in the ROI were dynamically selected for signal extraction, depending on the 'view vs. neutral' condition contrast and applying the 'best voxel selection' tool implemented in TBV. For feedback presentation, the BOLD signal value was temporally smoothed by taking the average of the 4 most recent data points and a baseline was subtracted (mean from the late 4 data points from the preceding rest period). The thermometer covered 4 percent signal change. An orange line divided the thermometer in an upper part displaying activation and a lower part indicating deactivation from baseline.

Ratings

Subjective ratings of picture valence and arousal were assessed after each training session outside the scanner suite (1 = relaxed/very positive, 5 = highly aroused/very negative). The average of all picture ratings provided by the participant in a session was used for further analysis.

Image acquisition

Brain images were acquired on a 3 Tesla MRI Scanner (Trio, Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-channel head coil. Functional images were acquired with a gradient echo T2*-weighted echo-planar-imaging sequence (TE = 30 ms, TR = 2 s, FOV = 192 × 192 mm, matrix size = 64 × 64, flip angle = 80°). One volume comprised 36 slices tilted −20° from AC-PC orientation with a thickness of 3 mm and slice gap of 1 mm. Participants' heads were lightly restrained using soft pads. The experimental runs comprised 284 volumes each. The T1-weighted anatomical image recording parameters were as follows: TE = 3.03 ms, TR = 2.3 s, 192 slices, FOV = 256 × 256 mm and matrix size = 256 × 256.

FMRI analysis

Preprocessing

FMRI data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The standard preprocessing pipeline included slice time correction, realignment, unwarping, coregistration to anatomy, segmentation and normalization to the Montreal Neurological Institute (MNI) standard template, and smoothing with an