Effective amygdala-prefrontal connectivity predicts individual differences in successful emotion regulation

Carmen Morawetz,1,4 Stefan Bode,2 Juergen Baudewig,3 and Hauke R. Heekeren1,4

1Department of Education and Psychology, Freie Universität Berlin, Germany, 2Melbourne School of Psychological Sciences, The University of Melbourne, Australia, 3Functional Imaging Unit, German Primate Center, Germany, and 4Center for Cognitive Neuroscience Berlin, Freie Universität Berlin, Germany

Correspondence should be addressed to Carmen Morawetz, Department of Education and Psychology, Freie Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin, Germany. E-mail: Carmen.morawetz@fu-berlin.de

Abstract

The ability to voluntarily regulate our emotional response to threatening and highly arousing stimuli by using cognitive reappraisal strategies is essential for our mental and physical well-being. This might be achieved by prefrontal brain regions (e.g. inferior frontal gyrus, IFG) down-regulating activity in the amygdala. It is unknown, to which degree effective connectivity within the emotion-regulation network is linked to individual differences in reappraisal skills. Using psychophysiological interaction analyses of functional magnetic resonance imaging data, we examined changes in inter-regional connectivity between the amygdala and IFG with other brain regions during reappraisal of emotional responses and used emotion regulation success as an explicit regressor. During down-regulation of emotion, reappraisal success correlated with effective connectivity between IFG with dorsolateral, dorsomedial and ventromedial prefrontal cortex (PFC). During up-regulation of emotion, effective coupling between IFG with anterior cingulate cortex, dorsomedial and ventromedial prefrontal cortex as well as the amygdala correlated with reappraisal success. Activity in the amygdala covaried with activity in lateral and medial prefrontal regions during the up-regulation of emotion and correlated with reappraisal success. These results suggest that successful reappraisal is linked to changes in effective connectivity between two systems, prefrontal cognitive control regions and regions crucially involved in emotional evaluation.

Key words: PPI; fMRI; ventrolateral prefrontal cortex; reappraisal

Introduction

The ability to regulate our emotions is essential for our mental and physical well-being (Gross and Munoz, 1995; Gross et al., 2006; Efekhari et al., 2009; Berking and Wupperman, 2012). Impairment in self-regulating emotions plays a role in psychological disorders such as anxiety, major depression and several personality disorders (Davidson, 2000; Astadter, 2008; Cisler et al., 2010; Gruber et al., 2012; Krause-Utz et al., 2014). One well-studied emotion regulation strategy is reappraisal, which refers to the ability to cognitively change the appraisal of an emotional situation by altering its emotional impact (Gross and Thompson, 2007). Emotion regulation relies on basal cognitive functions such as working memory, attention, self-reflection, semantic memory and language (Ochsner and Gross, 2005; Zelazo and Cunningham, 2007; Phillips et al., 2008), which are represented in a widespread neural network (Kalisch, 2009; Ochsner et al., 2012; Buhle et al., 2014; Frank et al., 2014; Kohn et al., 2014; Morawetz et al., 2016b).

Previous research into emotion regulation has mainly used standard correlation analysis to investigate the association between activation in the cortical control network and the subcortical affective system and converged on a top-down model whereby neural responses to emotional stimuli in the amygdala and ventral striatum are down-regulated by prefrontal regions...
(Ochsner and Gross, 2005; Urry et al., 2006; Johnstone et al., 2007; Phillips et al., 2008; Wagner et al., 2008; Ochsner et al., 2012). For example, using functional magnetic resonance imaging (fMRI), an increase in activation in the ventrolateral (Ochsner et al., 2002), orbitofrontal (Ochsner et al., 2004) and ventromedial prefrontal cortex (VMPFC) (Urry et al., 2006) has been found to correlate with decreased amygdala activity during emotion regulation. Only few studies, however, have directly measured changes in effective connectivity during reappraisal. These further yielded inconsistent results regarding patterns of connectivity as well as proposed directions in connectivity changes (Banks et al., 2007; Kanske et al., 2011; Fayer et al., 2012; Sripada et al., 2014). One possible explanation for these inconsistencies is that connectivity patterns might directly relate to individuals’ reappraisal ability (i.e. regulation success), which has not been considered in most studies. Only two studies assessed emotion regulation success using behavioral self-report, but not in conjunction with effective connectivity. Using mediation analysis, one of these studies found that both ventrolateral prefrontal cortex (VLPFC) activity and reappraisal success were mediated by activity in the ventral striatum (Wager et al., 2008). The second study showed that activity in the left amygdala correlated with self-reported reappraisal success (Eippert et al., 2007).

We recently used dynamic causal modeling (DCM) to investigate effective connectivity during emotion regulation and demonstrated the importance of left IFG in emotion regulation (Morawetz et al., 2016c). In particular, bidirectional changes in connectivity strength between the IFG and dorsolateral prefrontal cortex (DLPFC) were found to be the neural substrate of a feedback mechanism mediating reappraisal. However, as amygdala activity could not be consistently observed in each participant—which is a prerequisite for regions to be included into the DCM model space (Friston et al., 2003; Lohmann et al., 2012)—the amygdala could not be included in the analysis (Morawetz et al., 2016c). Given that previous studies emphasized the importance of the amygdala, we aimed to expand on our findings by explicitly investigating how patterns of effective connectivity change during reappraisal in a broader network of brain regions involved in emotion regulation (including cortical and subcortical seed regions), and how these changes are linked to individuals’ reappraisal success. We hypothesized that the IFG is involved in linking the prefrontal control system to regions that are directly related to basal emotion processing (such as the amygdala) in order to orchestrate emotion regulatory processes. Specifically, this study examined within-subject effective connectivity (Friston et al., 1997; Friston, 2011) of the IFG and the amygdala and its association with reappraisal success using fMRI and psychophysiological interaction (PPI) analysis.

However, emotional responses not only involve changes in the brain, but also in autonomic physiology. Previous studies investigating spontaneous reactions to unpleasant pictures reported increased electrodermal activity (EDA) (Bradley et al., 2008). Furthermore, reappraisal processes have been demonstrated to modulate skin conductance responses (SCRs); i.e. EDA was higher when increasing and lower when decreasing compared with maintaining emotional responses thereby indicating a modulation of emotional arousal by reappraisal (Eippert et al., 2007; Urry et al., 2009; Morawetz et al., 2016b,c). Thus, we also recorded EDA to obtain a physiological control measure, which was expected to mirror self-reports of emotional state after emotion regulation.

Our participants were presented with highly arousing and aversive pictures while using cognitive reappraisal to increase, maintain, or decrease their emotional responses. Based on previous studies showing the involvement of the left amygdala and VLPFC in successful reappraisal (Eippert et al., 2007; Wagner et al., 2008; Morawetz et al., 2016b), we hypothesized task-dependent inter-regional covariance between the IFG and the amygdala with other brain regions that are crucially involved in emotion regulation. In addition, we were interested in how effective coupling might be dependent on reappraisal success. Since previous results were inconsistent, and no study has used cortical seed regions or included up-regulation of emotion in the experimental design, hypotheses regarding the interaction of effective coupling and regulation skills were rather unspecific. However, there are neuroanatomical studies, which demonstrated interconnections within the prefrontal cortices (Barbas and Pandya, 1989, 1991; Barbas, 2000, 2009; Goulas et al., 2012; Veteran et al., 2012) and reciprocal connections between the amygdala and PFC (Amaral and Price, 1984; Ghasshghaei and Barbas, 2002; Ghashghaei et al., 2007). Prior neuroimaging studies also demonstrated that VLPFC and DLPFC are intrinsically connected during resting state and effectively coupled during emotion regulation (e.g. Goulas et al., 2012; Morawetz et al., 2016c), and similar results have been obtained for amygdala and frontal regions (e.g. Banks et al., 2007; Kanske et al., 2011; Ray and Zald, 2011). Based on this, we expected that (i) enhanced connectivity within the prefrontal network including lateral (VLPFC, DLPFC) and medial PFC regions (ventromedial and dorsomedial PFC; VMPFC and DMPFC) would correlate with reappraisal success, and (ii) enhanced coupling between the amygdala and PFC would predict reappraisal success.

Material and methods

Subjects

Twenty-three right-handed subjects (mean age = 25.70 years, s.d. = 5.95 years; 12 female) participated in the study. Handedness was assessed with Edinburgh-Handedness...
Inventory (Oldfield, 1971), and eligibility was assessed with a general health questionnaire and fMRI safety screening form. Subjects had normal or corrected to normal vision, gave written, informed consent to participate in the study and had no history of neurological or psychiatric disease. The study was approved by the ethics committee of the German Psychological Society and carried out in accordance to the Declaration of Helsinki.

**Stimuli**

Stimuli consisted of 126 aversive and 42 neutral pictures from the International Affective Picture System (IAPS) (Bradley and Lang, 2007). During the fMRI experiment, images were presented in the centre of the screen with an 800 x 600 pixel display subtending 32° × 24° visual angle on dual display goggles (VisuaStim, MR Research, USA) using the stimulation software Presentation (Version 14.1, Neurobehavioral Systems, USA). Pictures subtended a 24° × 18° visual angle, presented against a black background.

**Task**

The task design was adapted from previous studies (Kim and Hamann, 2007; Morawetz et al., 2016b). Four task conditions were implemented (Figure 1): two reappraisal conditions (‘Increase, Decrease’) and two control conditions (‘Look-Neutral, Look-Negative’). (i) In the ‘Increase’ condition, subjects were asked to engage themselves with the depicted situation and to increase their sense of subjective closeness to the displayed events by e.g. imaging a close friend/family member in the situation depicted in the picture (Ochsner et al., 2004; Eippert et al., 2007; Urry et al., 2009). (ii) Conversely, in the ‘Decrease’ condition subjects were instructed to reduce the intensity of the negative emotion by distancing themselves from the image by becoming a detached observer e.g. through thinking that the depicted situation is not real. (iii) In the ‘Look’ condition, subjects were asked to view the neutral (‘Look-Neutral’) or negative (‘Look-Negative’) stimuli attentively and allow themselves to experience/feel any emotional responses, which these might elicit without trying to manipulate them. Subjects received a training session to practice the emotion reappraisal strategies before scanning.

Pictures were presented in an event-related design (Figure 1). Each trial started with an instruction screen (2s) showing a symbol indicating one of the experimental conditions (camera symbol: ‘Look’, red arrow pointing upwards: ‘Increase’, green arrow pointing downwards: ‘Decrease’, green arrow pointing left: ‘Look-Neutral’, red arrow pointing left: ‘Look-Negative’).

![Fig. 2. (A) SCRs during scanning. Mean changes in EDA (μS) as a function of task conditions. (B) Emotional state ratings as a function of task conditions. After each emotion regulation phase subjects rated their current emotional state on a scale from 1 (not negative) to 4 (very negative). Error bars represent standard errors.](https://www.oup.com/scan/article-abstract/12/4/569/2739707)
pointing downwards: ‘Decrease’). Subsequently, a picture was presented (8 s), followed by a rating of the current emotional state (4 s) (four-point Likert scale from 1 to 4; less negative to very negative). Subjects indicated their affect by pressing a button on a button fiber optic response pad (Cambridge Research Systems Ltd., England). Finally, a fixation cross presented in the centre of the screen (4–8 s) concluded the trial. One experimental run consisted of 28 trials (7 trials per condition). Each experimental session consisted of six runs (168 trials in total). Experimental conditions were randomized within runs.

Electrodermal activity

Previous research demonstrated that EDA is modulated by emotional arousal and emotion regulation (Urry et al., 2009). We recorded EDA using two cup electrodes with an internal impedance of 15 kΩ (7 mm) filled with isotonic paste and attached to the proximal phalanges of the index and middle fingers on the left hand. EDA was acquired at a sampling rate of 5000 Hz using an MR-compatible amplifier system (BrainAmp GSR-module, Brain Products, Gilching, Germany) and constant voltage electrode excitation. During the analysis, the data was down-sampled offline to 10 Hz. We then decomposed skin-conductance data into continuous tonic and phasic activity (Benedek and Kaernbach, 2010a) and averaged across trials within each condition applying an 8 s time window using Ledalab Version 3.3.1 (Benedek and Kaernbach, 2010b). SCRs were defined as a deflection of at least 0.01 μS occurring 1–8 s after stimulus onset. Only runs including more than 10% SCRs exceeding the above criterion were used for analysis. Values for phasic SCRs were extracted as the difference between a local minimum and the succeeding local maximum within the response window. Due to technical problems at recording, data from seven subjects could not be analyzed, leaving a total of n = 16 EDA data sets.

Analysis of self-report data

As the main focus of our study was successful emotion regulation, we calculated reappraisal success scores based on the affect ratings acquired after each trial. Overall reappraisal success was defined as either the mean decrease or mean increase in reported emotion when applying a cognitive reappraisal strategy (‘Increase’ and ‘Decrease’) relative to the mean affect ratings of the control condition (‘Look-Negative’), the latter representing the ‘natural’ emotional response to the stimuli. The ‘Look-Neutral’ condition served mainly as a break in the task design in which no emotions were elicited. Thus, reappraisal success scores for ‘Increase’ (‘Increase’ minus ‘Look-Negative’) and ‘Decrease’ (‘Decrease’ minus ‘Look-Negative’) for each participant were used as a predictor in the PPI analysis.

fMRI data acquisition

Whole brain functional and anatomical images were acquired using a 3.0 T Magnetom TrioTim MRI scanner (Siemens, Erlangen, Germany) with a 12-channel head coil. A high-resolution 3D T1-weighted dataset was acquired for each subject (176 sagittal sections, 1 × 1 × 1 mm³; 256 × 256 data acquisition matrix). Functional images were acquired using a T2*-weighted, gradient-echo planar imaging pulse sequence recording 37 sections oriented parallel to the anterior and posterior commissure at an in-plane resolution of 3 × 3 × 3 mm³ (interslice gap = 0; TE = 30 ms; TR = 2 s; FA = 90°; FoV = 192 × 192 mm²; 64 × 64 data acquisition matrix). For each experimental run 285 whole brain volumes were recorded.

fMRI data analysis

Data were analyzed using a random effects general linear model (GLM) as implemented in BrainVoyager QX 2.3.1 (Brain Innovation, Maastricht, The Netherlands). Pre-processing of fMRI data included 3D-motion-correction, temporal high pass
Table 1. Effects of reappraisal

| Region                             | BA | Side | x    | y    | z    | Voxels | t-value |
|------------------------------------|----|------|------|------|------|--------|---------|
| **‘Increase > Decrease’ > Look Negative’** |    |      |      |      |      |        |         |
| Superior Frontal Gyrus*            | 6  | LH   | −15  | 11   | 70   | 197    | 4.11    |
| SFG                               | 6  | LH   | −15  | 11   | 70   | LM     | 4.11    |
| medFG                             | 6  | LH   | −9   | 2    | 61   | LM     | 2.96    |
| STG                               | 39 | LH   | −45  | −52  | 28   | 234    | 3.96    |
| MFG                               | 6  | LH   | −39  | −1   | 64   | 162    | 3.93    |
| IFG                               | 13 | LH   | −45  | 26   | 7    | 186    | 3.75    |
| IFG                               | 13 | LH   | −45  | 26   | 7    | LM     | 3.75    |
| **‘Look Negative > Increase + Decrease’** |    |      |      |      |      |        |         |
| medFG                             | 10 | LH   | −6   | 65   | 16   | 11306  | 6.10    |
| Insula                            | 13 | LH   | −45  | −13  | 7    | LM     | 5.95    |
| Post-central gyrus                | 2  | LH   | −57  | −22  | 31   | LM     | 5.61    |
| Transverse temporal gyrus         | 41 | LH   | −42  | −31  | 13   | LM     | 5.29    |
| SFG                               | 9  | RH   | 42   | 35   | 25   | LM     | 5.27    |
| Posterior cingulate               | 30 | RH   | 12   | −61  | 10   | LM     | 5.25    |
| MFG                               | 8  | RH   | 24   | 11   | 40   | LM     | 5.25    |
| Insula                            | 13 | LH   | −27  | −28  | 16   | LM     | 5.19    |
| Insula                            | 13 | RH   | 33   | −22  | 19   | LM     | 5.06    |
| Precuneus                         | 7  | RH   | 24   | −61  | 34   | LM     | 4.98    |
| Post-central gyrus                | 2  | RH   | 51   | −28  | 40   | LM     | 4.96    |
| medFG                             | 8  | RH   | 18   | 29   | 43   | LM     | 4.95    |
| Pre-central gyrus                 | 6  | RH   | 48   | −10  | 22   | LM     | 4.84    |
| Inferior parietal lobule          | 40 | RH   | 36   | −34  | 46   | LM     | 4.79    |
| Inferior parietal lobule          | 40 | RH   | 54   | −28  | 22   | LM     | 4.51    |
| MFG                               | 6  | RH   | 27   | 14   | 61   | LM     | 4.32    |
| Lingual gyrus                    | 19 | LH   | −15  | −61  | 4    | LM     | 4.29    |
| Lentiform nucleus                 | 33 | RH   | −13  | 4    | LM    | 4.29    |
| medFG                             | 6  | RH   | 15   | −13  | 49   | LM     | 4.15    |
| Paracentral lobule                | 5  | RH   | 12   | −37  | 46   | LM     | 4.15    |
| SFG                               | 10 | RH   | 27   | 53   | 16   | LM     | 4.09    |
| Cingulate gyrus                   | 31 | RH   | 3    | −37  | 31   | LM     | 4.08    |
| Paracentral lobule                | 4  | RH   | 9    | −37  | 58   | LM     | 3.83    |
| SFG                               | 10 | RH   | 9    | 68   | 13   | LM     | 3.82    |
| Post-central gyrus                | 2  | LH   | −24  | −34  | 67   | LM     | 3.80    |
| Cingulate gyrus                   | 24 | LH   | −4   | 31   | LM    | 3.73    |
| Inferior temporal gyrus           | 20 | RH   | 54   | −46  | −11  | LM     | 3.68    |
| Caudate                           |    | LH   | −6   | 8    | −2   | LM     | 3.55    |
| Superior parietal lobule          | 7  | LH   | −27  | −52  | 43   | LM     | 3.53    |
| Precuneus                         | 31 | LH   | −24  | −67  | 22   | LM     | 3.50    |
| Lentiform nucleus                 | 24 | RH   | 24   | −1   | −2   | LM     | 3.46    |
| Post-central gyrus                | 3  | RH   | 30   | −31  | 61   | LM     | 3.37    |
| Inferior parietal lobule          | 40 | RH   | −42  | −37  | 40   | LM     | 3.36    |
| Post-central gyrus                | 43 | RH   | 66   | −13  | 16   | LM     | 3.31    |
| medFG                             | 9  | RH   | 15   | 41   | 19   | LM     | 3.29    |
| Parahippocampal gyrus             | 28 | RH   | 27   | −22  | −5   | LM     | 3.28    |
| Sub–gyral                         | 40 | RH   | −21  | −34  | 55   | LM     | 3.26    |
| Fusiform gyrus                    | 37 | LH   | −51  | −43  | −17  | LM     | 3.22    |
| Cingulate gyrus                   | 24 | RH   | 9    | −13  | 40   | LM     | 3.21    |
| Pre–central gyrus                 | 9  | RH   | 45   | 17   | 34   | LM     | 3.21    |
| Insula                            | 13 | LH   | −39  | −1   | −8   | LM     | 3.20    |
| Fusiform gyrus                    | 37 | LH   | −39  | −58  | −8   | LM     | 3.16    |
| Middle temporal gyrus             | 19 | RH   | 33   | −61  | 10   | LM     | 3.16    |
| Caudate                           | 21 | RH   | 66   | −7   | −2   | LM     | 3.01    |
| Middle temporal gyrus             | 21 | RH   | 66   | −7   | −2   | LM     | 3.01    |
| Caudate                           |    | RH   | 9    | 11   | −2   | LM     | 3.00    |
| STG                               | 22 | LH   | −66  | −19  | 1    | LM     | 2.96    |
| Cingulate gyrus                   | 31 | LH   | −15  | −25  | 34   | LM     | 2.91    |
| medFG                             | 6  | LH   | −9   | −16  | 46   | LM     | 2.89    |
| medFG                             | 9  | RH   | 6    | 50   | 25   | LM     | 2.87    |
| Cingulate gyrus                   | 24 | LH   | −12  | −7   | 46   | LM     | 2.61    |

(continued)
filtering (three cycles/run), linear trend removal, slice scan time correction, spatial smoothing (Gaussian smoothing kernel, 8 mm full width half maximum), and transformation into Talairach space (Talairach and Tournoux, 1988).

Data were visualized and statistically thresholded using NeuroElf Version 0.9c (neuroelf.net). We utilized height and cluster size thresholding after establishing family wise error (FWE) thresholds using the alphsim procedure (Forman et al., 1995) at an initial significance level of \( P < 0.001 \) and an FWE cluster level correction of \( P < 0.05 \) (implemented in NeuroElf, http://neuroelf.net). AlphaSim was computed for each map separately so as to accurately estimate the inherent smoothness of each contrast, rather than to rely on the size of the Gaussian kernel used during pre-processing which can lead to errors in thresholding (Bennett et al., 2009). Extent thresholds for the contrasts of the univariate analysis were thresholded at 95 voxels and PPI maps were thresholded at 91 voxels.

**Univariate analysis.** Separate regressors in the GLM were specified for the instruction cue, rating, and the conditions during stimulus viewing. The regressors-of-interest were the four task conditions ‘Increase, Decrease, Look-Negative and Look-Neutral’. The ‘Look-Negative’ condition constituted the natural response to all images and was used as a control condition. As described below, emotion regulation contrasts were defined as ‘differences’ to this control condition.

In line with our a priori hypotheses, we used the left IFG and amygdala as regions of interest (ROIs). The left IFG and the amygdala were chosen as ROIs and seed regions for the PPI analyses on the basis of the following three criteria: (i) Prior evidence of their functional involvement in emotion regulation tasks: Several meta-analyses have implicated both regions in evidence of their functional involvement in emotion regulation (Kohn et al., 2012). Furthermore, recent meta-analyses support the view that (‘Increase > Look-Negative’) and (‘Decrease > Look-Negative’) were used as psychological context, to create the PPI term. This interaction term was entered into a voxelwise regression, with the covariates of amygdala and IFG raw time-series and all original regressors of the GLM model (Instruction, Rating, ‘Increase, Decrease, Look-Negative, Look-Neutral’). The resulting PPI parameter estimates denoted the change in strength of effective coupling between the seed regions and the remainder of the brain during reappraisal relative to ‘Look-Negative’ trials (see Supplementary Tables S1 and S2). To examine the extent to which individual differences in reappraisal ability predicted this connectivity, reappraisal success scores were entered as a covariate into a voxelwise regression, serving as a predictor of the PPI map.

**Results**

**Behavioral results**

**Emotion induction.** Skin conductance data provided support for the success of the emotion induction (Figure 2A). We found a significant main effect of task \( F(1,15) = 3.80, P < 0.01 \). Post-hoc t-tests indicated that SCRs during ‘Increase’ were higher compared with ‘Decrease’ \( t(15) = 2.62, P < 0.05 \) and ‘Look-Neutral’ \( t(15) = 2.78, P < 0.05 \). The SCR amplitudes were significantly higher during the ‘Look-Negative’ compared with the ‘Look-Neutral’ condition \( t(15) = 2.35, P < 0.05 \).

**Emotion regulation.** A significant main effect of task was found \( F(1,22) = 50.92, P < 0.001 \) (Figure 2B). Post-hoc t-tests...
Table 2. Effects of down-regulation of emotion

| Region                           | BA | Side | x    | y    | z    | Voxels | t-value |
|----------------------------------|----|------|------|------|------|--------|---------|
| **‘Decrease>Look Negative’**     |    |      |      |      |      |        |         |
| IFG                              | 45 | LH   | −45  | 23   | 10   | 164    | 3.94    |
| IFG                              | 45 | LH   | −45  | 38   | 1    | LM     | 2.71    |
| SFG                              | 6  | LH   | −12  | 11   | 67   | 145    | 3.79    |
| SFG                              | 6  | LH   | −9   | −1   | 73   | LM     | 2.65    |
| STG                              | 22 | LH   | −51  | −55  | 19   | 161    | 3.61    |
| **‘Look Negative>Decrease’**     |    |      |      |      |      |        |         |
| medFG                            | 10 | LH   | −6   | 65   | 16   | 12716  | 7.35    |
| Inferior occipital gyrus         | 18 | LH   | −33  | −97  | −11  | LM     | 6.13    |
| Insula                           | 13 | RH   | 33   | −25  | 19   | LM     | 6.03    |
| Pre-central gyrus                | 6  | RH   | 48   | −10  | 25   | LM     | 5.82    |
| Post-central gyrus               | 40 | LH   | −63  | −22  | 19   | LM     | 5.70    |
| Inferior parietal lobe           | 40 | RH   | 57   | −28  | 22   | LM     | 5.48    |
| Caudate                          |    |      | −9   | 20   | 13   | LM     | 5.46    |
| Insula                           | 2  | LH   | −57  | −22  | 31   | LM     | 5.23    |
| Insula                           | 13 | LH   | −30  | −31  | 16   | LM     | 5.19    |
| Post-central gyrus               | 2  | RH   | 36   | −25  | 31   | LM     | 5.11    |
| Insula                           | 41 | LH   | −45  | −25  | 16   | LM     | 4.86    |
| Post-central gyrus               | 2  | LH   | −24  | −37  | 67   | LM     | 4.71    |
| Cuneus                           | 23 | RH   | 15   | −70  | 10   | LM     | 4.57    |
| Posterior cingulate              | 30 | LH   | −12  | −61  | 13   | LM     | 4.56    |
| Cingulate gyrus                  | 31 | LH   | −21  | −40  | 37   | LM     | 4.51    |
| Caudate                          |    |      | −3   | 11   | 7    | LM     | 4.50    |
| Cingulate gyrus                  | 32 | RH   | 18   | 20   | 31   | LM     | 4.47    |
| Caudate                          |    |      | 36   | −34  | −5   | LM     | 4.40    |
| Cingulate gyrus                  | 24 | RH   | 18   | 8    | 28   | LM     | 4.29    |
| Posterior cingulated             | 30 | LH   | −21  | −52  | 10   | LM     | 4.29    |
| medFG                            | 6  | LH   | −12  | −7   | 49   | LM     | 4.19    |
| Posterior cingulate              | 30 | RH   | 30   | −61  | 10   | LM     | 4.16    |
| Caudate                          |    |      | 15   | 26   | 7    | LM     | 4.15    |
| Parahippocampal gyrus            | 27 | RH   | 9    | −37  | 4    | LM     | 4.12    |
| Precuneus                        | 7  | RH   | 24   | −61  | 34   | LM     | 4.09    |
| MFG                              | 8  | RH   | 24   | −20  | 43   | LM     | 4.07    |
| Insula                           | 13 | LH   | −45  | −7   | 10   | LM     | 4.05    |
| Paracentral lobule               | 5  | LH   | −6   | −37  | 49   | LM     | 4.02    |
| Cingulate gyrus                  | 31 | LH   | −15  | −25  | 37   | LM     | 4.01    |
| Inferior parietal lobe           | 40 | RH   | 36   | −34  | 46   | LM     | 3.97    |
| SFG                              | 9  | RH   | 39   | 35   | 25   | LM     | 3.97    |
| medFG                            | 6  | RH   | 12   | −13  | 49   | LM     | 3.89    |
| Post-central gyrus               | 2  | RH   | 51   | −25  | 40   | LM     | 3.88    |
| Parahippocampal gyrus            | 36 | LH   | −36  | −28  | −17  | LM     | 3.88    |
| Post-central gyrus               | 5  | RH   | 27   | −40  | 64   | LM     | 3.88    |
| Cingulate gyrus                  | 31 | RH   | 15   | −22  | 37   | LM     | 3.88    |
| Parahippocampal gyrus            | 35 | LH   | −24  | −25  | −23  | LM     | 3.84    |
| Insula                           | 13 | LH   | −39  | −1   | −8   | LM     | 3.81    |
| Cingulate gyrus                  | 31 | LH   | 0    | −43  | 34   | LM     | 3.79    |
| Post-central gyrus               | 3  | LH   | −9   | −34  | 64   | LM     | 3.74    |
| Paracentral lobule               | 4  | RH   | 9    | −37  | 58   | LM     | 3.72    |
| Anterior cingulate               | 32 | LH   | −3   | 47   | 1    | LM     | 3.71    |
| Precuneus                        | 7  | RH   | 9    | −34  | 43   | LM     | 3.71    |
| Post-central gyrus               | 7  | RH   | 6    | −52  | 67   | LM     | 3.66    |
| Pre-central gyrus                | 4  | RH   | 18   | −28  | 64   | LM     | 3.66    |
| Parahippocampal gyrus            | 30 | RH   | 21   | −49  | 10   | LM     | 3.66    |
| medFG                            | 10 | RH   | 15   | 47   | 13   | LM     | 3.55    |
| Cuneus                           | 18 | RH   | 15   | −100 | −2   | LM     | 3.51    |
| Inferior Parietal Lobule         | 40 | LH   | −45  | −34  | 37   | LM     | 3.48    |
| Precuneus                        | 19 | LH   | −30  | −67  | 31   | LM     | 3.46    |
| Cingulate Gyrus                  | 32 | RH   | 24   | 8    | 43   | LM     | 3.46    |
| Cingulate Gyrus                  | 31 | RH   | 27   | −49  | 25   | LM     | 3.43    |
| Middle Occipital Gyrus           | 18 | LH   | −27  | −79  | 1    | LM     | 3.41    |
| Caudate                          |    |      | 33   | −43  | 10   | LM     | 3.39    |

(continued)
revealed significantly more negative emotional state ratings for ‘Increase’ compared with ‘Decrease’ \((t(22) = 9.25, P < 0.001)\), as well as for ‘Increase’ compared with ‘Look-Negative’ \((t(22) = 6.13, P < 0.001)\) and ‘Look-Neutral’ \((t(22) = 16.24, P < 0.001)\’. ‘Look-Negative’ also resulted in more negative emotional state ratings compared with ‘Decrease’ \((t(22) = 3.98, P < 0.01)\) and compared with ‘Look-Neutral’ \((t(22) = 12.20, P < 0.001)\’. ‘Decrease’ was associated with higher emotional state ratings as ‘Look-Look’ \((t(22) = 9.88, P < 0.001)\). These results confirm that emotion regulation was successful.

**fMRI data**

**General effects of reappraisal.** First, we tested for reappraisal effects independent of reappraisal goals by contrasting ‘[Increase + Decrease > Look-Negative]’ (Figure 3, Table 1). Reappraisal was associated with increased responses in prefrontal regions including superior frontal (SFG), medial frontal (medFG), middle frontal (MFG) and IFG as well as superior temporal gyrus (STG).

The contrast ‘Decrease’ compared with ‘Look-Negative’ revealed increased activity in left IFG, SFG, and STG (Table 2). The contrast between ‘Increase’ and ‘Look-Negative’ revealed enhanced responses in left MFG, SFG, IFG, STG and pre-central gyrus (Table 3).

**Univariate ROI analyses.** Based on our *a priori* hypotheses, we performed ROI analyses on bilateral amygdala by calculating the mean signal change across all voxels within the ROI (Supplementary Figure S1). This analysis was conducted to provide evidence of activity related to emotion regulation i.e. either differential activity between ‘Increase’ and ‘Decrease’, or between ‘Decrease’ and ‘Look-Negative/Look-Neutral’, or ‘Increase’ and ‘Look-Negative/Look-Neutral’, supporting the applicability of the following PPI analysis in these regions.

A main task effect was observed in the left amygdala \(F(1,22) = 3.08, P < 0.05\), but not within the right amygdala. Post-hoc tests revealed that responses in the left amygdala significantly differed between the ‘Increase’ and ‘Decrease’ condition \((t(22) = 2.72, P < 0.05)\). Thus, the left amygdala was used as seed region in the subsequent PPI analyses.

**Effective connectivity analysis.** We applied a seed-based connectivity analysis to examine changes in effective connectivity during emotion regulation relative to the ‘Look-Negative’ condition with respect to reappraisal skills (ability to successfully regulate emotions, as measured by the reappraisal success scores). PPI analyses were performed on two seed regions, left IFG and left amygdala. For this, we determined task-dependent effective interaction based on the contrast ‘Increase’ or ‘Decrease’ vs control condition (‘Increase > Look-Negative’ and ‘Decrease > Look-Negative’) using the individual mean reappraisal success scores as predictor of the PPI map, meaning that the better subjects could regulate their emotions, the stronger was the effective coupling between the seed regions and the remainder of the brain. A positive correlation means that the greater the task-dependent change in effective connectivity between these regions and the seed region, the more effectively participants regulated their emotions during the ‘Increase’ or ‘Decrease’ condition. Contrarily, a negative correlation means that a greater task-dependent change in effective connectivity between these regions and the seed region was associated with less effective emotion regulation during the ‘Increase’ or ‘Decrease’ condition.

**Left IFG seed region.** During the up-regulation of emotion we found a positive correlation between ‘Increase’ success and the effective coupling of the left IFG (seed region) and left STG, VMPFC and bilateral amygdalae (Table 4; Figure 4A illustrates one of these positive correlations, using the success-dependent connectivity between IFG as seed region and the left amygdala). We also observed a negative correlation between ‘Increase’ success and activity of the left IFG that was coupled with pregenual anterior cingulate cortex (pgACC), DMPFC, caudate, right insula,
Table 3. Effect of up-regulation of emotion

| Region                   | BA | Side | Coordinates     | Voxels | t-value |
|--------------------------|----|------|-----------------|--------|---------|
| **‘Increase>Look Negative’** |    |      | x   y   z      |        |         |
| STG                      | 13 | LH   | -42 -46 25     | 234    | 4.66    |
| MFG                      | 6  | LH   | -36 -1 61     | 351    | 4.15    |
| SFG                      | 6  | LH   | -6 11 73 48   | LM     | 3.74    |
| SFG                      | 6  | LH   | -6 -4 64      | LM     | 3.09    |
| IFG                      | 45 | LH   | -47 37 4     | 175    | 3.41    |
| IFG                      | 45 | LH   | -49 22 11    | LM     | 2.85    |
| IFG                      | 44 | LH   | -47 4 14     | LM     | 2.46    |
| Insula                   | 13 | LH   | -35 0 14     | LM     | 2.36    |
| **‘Look Negative>Increase’** |    |      | x   y   z      |        |         |
| Post-central gyrus       | 1  | RH   | 66-16 28 614  | 6174   | 7.02    |
| medFG                    | 8  | RH   | 15 29 43     | LM     | 5.98    |
| Cingulate gyrus          | 32 | RH   | 24 8 40      | LM     | 5.01    |
| Precuneus                | 19 | RH   | 30 -61 40    | LM     | 4.94    |
| Post-central gyrus       | 3  | RH   | 33 -34 46    | LM     | 4.61    |
| MFG                      | 6  | RH   | 24 11 61     | LM     | 4.59    |
| Lentiform nucleus        |    | RH   | 33 -13 4     | LM     | 4.48    |
| Posterior cingulate      | 30 | RH   | 12 -61 10    | LM     | 4.48    |
| Post-central gyrus       | 2  | RH   | 51 -25 40    | LM     | 4.36    |
| MFG                      | 46 | RH   | 42 35 22     | LM     | 4.24    |
| Pre-central gyrus        | 9  | RH   | 45 17 34     | LM     | 4.23    |
| Insula                   | 13 | RH   | 30 -22 19    | LM     | 4.02    |
| Lingual gyrus            | 19 | RH   | -15 -58 2    | LM     | 4.01    |
| Insula                   | 13 | RH   | 39 -28 13    | LM     | 3.96    |
| Cingulate gyrus          | 31 | RH   | 3 -37 31     | LM     | 3.83    |
| Inferior temporal gyrus  | 20 | RH   | 51 -49 11    | LM     | 3.78    |
| Paracentral lobule       | 5  | RH   | 9 -37 46     | LM     | 3.61    |
| Cingulate gyrus          | 24 | RH   | 3 -1 31      | LM     | 3.56    |
| Lingual gyrus            | 19 | RH   | 15 -46 2     | LM     | 3.52    |
| STG                      | 41 | RH   | 54 -19 10    | LM     | 3.50    |
| Parahippocampal gyrus    | 36 | RH   | 33 -28 23    | LM     | 3.43    |
| Paracentral lobule       | 5  | LH   | 0 -43 61     | LM     | 3.36    |
| Post-central gyrus       | 3  | RH   | 33 -31 61    | LM     | 3.15    |
| Inferior parietal lobule | 40 | RH   | 57 -46 49    | LM     | 2.79    |
| medFG                    | 6  | LH   | 6 -19 49     | LM     | 2.73    |
| Middle occipital gyrus   | 37 | RH   | 39 -61 4     | LM     | 2.26    |
| STG                      | 22 | LH   | -48 -13 7    | 1253   | 5.26    |
| Post-central gyrus       | 2  | LH   | -60 -22 34   | LM     | 4.70    |
| Post-central gyrus       | 40 | LH   | -63 -19 19   | LM     | 4.43    |
| STG                      | 41 | LH   | -42 -34 13   | LM     | 4.20    |
| Insula                   | 13 | LH   | -33 -19 19   | LM     | 3.85    |
| Inferior parietal lobule | 40 | LH   | -48 -28 46   | LM     | 3.59    |
| STG                      | 22 | LH   | -66 -19 1    | LM     | 3.33    |
| Superior parietal lobule | 7  | LH   | -27 -55 46   | LM     | 3.32    |
| IFG                      | 9  | LH   | -63 8 31     | LM     | 2.84    |
| Post-central gyrus       | 5  | LH   | -30 -40 58   | LM     | 2.66    |
| Post-central gyrus       | 2  | LH   | -24 -34 67   | LM     | 2.64    |
| MFG                      | 10 | RH   | 27 62 22     | LM     | 4.04    |
| MFG                      | 10 | RH   | 27 62 22     | LM     | 4.04    |
| SFG                      | 10 | RH   | 9 68 13      | LM     | 3.61    |
| SFG                      | 10 | LH   | -9 65 16     | LM     | 3.37    |
| SFG                      | 10 | RH   | 3 65 28      | LM     | 2.52    |
| medFG                    | 9  | RH   | 6 50 28      | LM     | 2.48    |
| Parahippocampal gyrus    | 36 | LH   | -33 -28 17   | 303    | 4.02    |
| Fusiform gyrus           | 37 | LH   | -42 -58 -8    | LM     | 3.61    |
| Fusiform gyrus           | 37 | LH   | -48 -46 -14   | LM     | 3.08    |
| Middle occipital gyrus   | 19 | LH   | -57 -67 5     | LM     | 2.99    |
| Middle temporal gyrus    | 21 | LH   | -66 -55 4    | LM     | 2.77    |
| STG                      | 22 | LH   | -63 -61 16    | LM     | 2.75    |
| Middle occipital gyrus   | 19 | LH   | -51 -82 10   | 250    | 3.72    |
| Fusiform gyrus           | 18 | LH   | -27 -97 -17   | LM     | 3.61    |
| STG                      | 38 | RH   | 48 17 20     | 102    | 3.31    |
| IFG                      | 47 | RH   | 36 20 -14    | LM     | 3.23    |

LM, local maxima.
### Table 4. Task-related PPI analysis with success scores as covariate for left IFG seed region

| Region                                      | BA | Side  | x   | y   | z   | Voxels | t-value |
|---------------------------------------------|----|-------|-----|-----|-----|--------|---------|
| **‘Decrease > Look Negative with Decrease success as covariate’** |    |       |     |     |     |        |         |
| Middle temporal gyrus                       | 21 | RH    | 39  | –4  | –23 | 173    | 0.70    |
| Middle temporal gyrus                       | 21 | RH    | 39  | –4  | –23 | LM     | 0.70    |
| STG                                         | 22 | RH    | 51  | –16 | –8  | LM     | 0.61    |
| STG                                         | 38 | RH    | 42  | 5   | –11 | LM     | 0.59    |
| STG                                         | 38 | RH    | 57  | 14  | –11 | LM     | 0.54    |
| SFG/DMPFC                                   | 10 | LH    | –27 | 44  | 16  | 148    | 0.63    |
| SFG                                         | 10 | LH    | –27 | 44  | 16  | LM     | 0.63    |
| medFG                                       | 11 | RH    | 18  | 35  | –17 | 155    | –0.69   |
| IFG                                         | 11 | RH    | 18  | 35  | –17 | LM     | –0.69   |
| IFG                                         | 47 | RH    | 21  | 23  | –17 | LM     | –0.62   |
| SFG                                         | 11 | LH    | –12 | 44  | –14 | 100    | –0.62   |
| **‘Increase > Look Negative with Increase success as covariate’** |    |       |     |     |     |        |         |
| Uncus                                       | 20 | LH    | –24 | –7  | –41 | 184    | 0.66    |
| Parahippocampal gyrus (amygdala)            | 38 | LH    | –30 | 8   | –20 | LM     | 0.59    |
| Parahippocampal gyrus (amygdala)            | 34 | RH    | 27  | 5   | –14 | LM     | 0.52    |
| IFG/VMPFC                                   | 47 | RH    | 26  | 17  | –11 | LM     | 0.57    |
| Anterior cingulate                          | 32 | LH    | –12 | 38  | 10  | 1146   | –0.83   |
| Cingulate gyrus                             | 24 | LH    | –9  | 14  | 25  | LM     | –0.72   |
| Cingulate gyrus                             | 24 | LH    | –6  | 5   | 25  | LM     | –0.67   |
| medFG/DMPFC                                 | 10 | RH    | 15  | 53  | 13  | LM     | –0.70   |
| medFG/DMPFC                                 | 10 | LH    | 0   | 56  | 16  | LM     | –0.54   |
| Anterior cingulate/DMPFC                    | 32 | RH    | 12  | 35  | 16  | LM     | –0.62   |
| Cingulate gyrus/DMPFC                       | 32 | RH    | 9   | 20  | 34  | LM     | –0.54   |
| Caudate                                     | 32 | RH    | 9   | 20  | 34  | LM     | –0.70   |
| Insula                                      | 13 | RH    | 33  | 29  | 10  | LM     | –0.52   |
| Caudate                                     | 32 | RH    | 12  | 38  | 10  | LM     | –0.52   |
| Fusiform gyrus                              | 18 | LH    | –24 | –100| –14 | 151    | –0.69   |
| Cingulate gyrus                             | 24 | LH    | –9  | –7  | 37  | 679    | –0.69   |
| Cingulate gyrus                             | 31 | RH    | 34  | 34  | 34  | LM     | –0.66   |
| Cingulate gyrus                             | 31 | RH    | 9   | –22 | 40  | LM     | –0.62   |
| Cingulate gyrus                             | 24 | RH    | 9   | –4  | 37  | LM     | –0.60   |
| Cingulate gyrus                             | 31 | LH    | –18 | –46 | 25  | LM     | –0.60   |
| Cingulate gyrus                             | 31 | RH    | 24  | –22 | 40  | LM     | –0.59   |
| medFG                                       | 6  | RH    | 9   | –16 | 58  | LM     | –0.58   |
| Cingulate gyrus                             | 31 | LH    | –18 | –28 | 37  | LM     | –0.57   |
| Inferior parietal lobe                      | 40 | LH    | –30 | –37 | 37  | LM     | –0.56   |
| Precuneus                                   | 31 | RH    | 9   | –46 | 34  | LM     | –0.54   |
| Paracentral lobule                          | 6  | LH    | –6  | –25 | 52  | LM     | –0.53   |
| Paracentral lobule                          | 5  | RH    | –21 | –34 | 49  | LM     | –0.50   |
| MFG                                         | 47 | RH    | 51  | 41  | 14  | LM     | –0.67   |
| STG                                         | 38 | RH    | 54  | 20  | –14 | LM     | –0.67   |
| IFG                                         | 46 | RH    | 51  | 41  | 13  | LM     | –0.59   |
| Cuneus                                      | 19 | RH    | 30  | –88 | 28  | 239    | –0.65   |
| Cuneus                                      | 19 | RH    | 12  | –91 | 25  | LM     | –0.59   |
| Pre-central gyrus                           | 6  | RH    | 57  | 2   | 37  | 177    | –0.65   |
| Middle temporal gyrus                       | 21 | RH    | 66  | –4  | –5  | LM     | –0.62   |
| STG                                         | 22 | RH    | 60  | 2   | 4   | LM     | –0.53   |
| STG                                         | 22 | RH    | 48  | –10 | –2  | LM     | –0.54   |

LM, local maxima.
left IPL, right MFG, right STG and right IFG (Table 4). Figure 4B illustrates the negative correlation between ‘Increase’ success and connectivity between left IFG and ACC.

The results further indicated significant positive effective coupling between the left IFG (seed region) and DLPFC, DMPFC, right MTG and STG during down-regulation of emotion depending on reappraisal success (Table 4). Figure 4C illustrates the positive correlation between effective connectivity beta estimates for the left IFG and SFG and ‘Decrease’ success. In contrast, a negative correlation between effective connectivity and ‘Decrease’ success was found between left IFG (seed region) and right IFG, left SFG/VMPFC and left orbital gyrus (Table 4). Figure 4D illustrates the negative correlation between effective connectivity beta estimates for the left IFG (and left SFG/VMPFC) and ‘Decrease’ success.

Left amygdala seed region. The PPI analysis based on the left amygdala as seed region demonstrated a positive correlation between ‘Increase’ success and the coupling with a number of regions such as left IFG, left MFG, left SFG, subgenual ACC (sgACC), left STG, left insula, left IPL, left MTG and left parahippocampal gyrus (Table 5). Figure 5A illustrates the positive correlation between successful up-regulation of emotion and effective coupling of the left amygdala (seed region) with left IFG. Effective connectivity between the left amygdala (seed region) and the right SFG/OFC was negatively correlated with ‘Increase’ success, illustrated in Figure 5B and reported in Table 5.

The activity in the left amygdala was positively correlated with activity in the bilateral fusiform gyri, right parahippocampal gyrus and occipital cortex and ‘Decrease’ success (Table 5). We also found a negative correlation between ‘Decrease’ success and the effective coupling between the left amygdala and the right precuneus.

In summary, we found that the down-regulation of emotion was associated with increased effective connectivity in a prefrontal network, including the left VLPFC, DLPFC and DMPFC, depending on reappraisal success (Figure 6A). Furthermore, decreased coupling between left IFG and VMPFC during the down-regulation of emotion was correlated with greater reappraisal success. Up-regulation of emotion was based on
Table 5. Task-related PPI analysis with success scores as covariate for left amygdala seed region

| Region                                      | BA | Side | Coordinates | Voxels | t-value |
|---------------------------------------------|----|------|-------------|--------|---------|
| 'Decrease: Look Negative with Decrease success as covariate' |    |      |             |        |         |
| Lingual Gyrus                               | 18 | RH   | 6          | −88    | −11     | 447    | 0.71 |
| Middle occipital gyrus                      | 19 | RH   | 30         | −91    | 16      | LM     | 0.67 |
| Inferior occipital gyrus                    | 17 | RH   | 18         | −91    | −5      | LM     | 0.61 |
| Fusiform gyrus                              | 19 | RH   | 24         | −82    | −14     | LM     | 0.60 |
| Inferior occipital gyrus                    | 18 | LH   | −30        | −91    | −2      | 293    | 0.63 |
| Fusiform gyrus                              | 19 | LH   | −39        | −76    | −11     | LM     | 0.63 |
| Lingual gyrus                               | 18 | LH   | −18        | −97    | −11     | LM     | 0.62 |
| Fusiform gyrus                              | 37 | RH   | 36         | −43    | −11     | 99     | 0.63 |
| Parahippocampal gyrus                       | 36 | RH   | 36         | −34    | −14     | LM     | 0.56 |
| Precuneus                                   | 7  | RH   | 30         | −46    | 52      | 98     | −0.60 |
| Precuneus                                   | 7  | RH   | 15         | −61    | 49      | LM     | −0.54 |
| 'Increase: Look Negative with Increase success as covariate' |    |      |             |        |         |
| IFG/VLPFC                                   | 47 | LH   | −33        | 17     | −11     | 1542   | 0.71 |
| STG                                         | 22 | LH   | −45        | −10    | −5      | LM     | 0.67 |
| Insula                                      | 13 | LH   | −39        | −25    | 16      | LM     | 0.64 |
| IFG                                         | 47 | LH   | −30        | 32     | −2      | LM     | 0.64 |
| Inferior parietal lobule                    | 40 | LH   | −48        | −31    | 22      | LM     | 0.63 |
| Pre-central gyrus                           | 4  | LH   | −51        | −10    | 25      | LM     | 0.62 |
| Middle temporal gyrus                       | 19 | LH   | −39        | −61    | 13      | LM     | 0.62 |
| Insula                                      | 13 | LH   | −33        | 26     | 13      | LM     | 0.60 |
| Post-central gyrus                          | 2  | LH   | −36        | −25    | 28      | LM     | 0.60 |
| Inferior temporal gyrus                     | 21 | LH   | −60        | −13    | −17     | LM     | 0.59 |
| Post-central gyrus                          | 43 | LH   | −63        | −10    | 16      | LM     | 0.55 |
| Caudate                                     |    |      |             |        |         |
| Parahippocampal gyrus                       | 36 | LH   | −24        | −37    | −8      | LM     | 0.52 |
| Lentiform nucleus                            |    |      |             |        |         |
| STG                                         | 22 | LH   | −57        | −43    | 13      | LM     | 0.50 |
| STG                                         | 39 | LH   | −39        | −58    | 31      | LM     | 0.45 |
| MFG/DLPFC                                   | 9  | LH   | −42        | 11     | 34      | 498    | 0.71 |
| MFG                                         | 6  | LH   | −24        | 8      | 43      | LM     | 0.65 |
| medFG                                       | 8  | RH   | 12         | 38     | 40      | LM     | 0.64 |
| SFG                                         | 8  | LH   | −9         | 41     | 43      | LM     | 0.63 |
| medFG                                       | 8  | LH   | −12        | 26     | 46      | LM     | 0.60 |
| medFG                                       | 6  | LH   | −15        | 29     | 37      | LM     | 0.60 |
| Anterior cingulate                          | 32 | RH   | 12         | 38     | 25      | LM     | 0.58 |
| Anterior cingulate                          | 32 | LH   | −3         | 38     | 19      | LM     | 0.52 |
| Middle temporal gyrus                       | 21 | LH   | 63         | −40    | −14     | 1255   | 0.67 |
| Lentiform nucleus                            | 33 | RH   | 33         | −16    | 1       | LM     | 0.65 |
| Middle temporal gyrus                       | 21 | RH   | 60         | −22    | −8      | LM     | 0.63 |
| Insula                                      | 13 | RH   | 45         | −16    | 22      | LM     | 0.61 |
| Middle temporal gyrus                       | 21 | RH   | 57         | −40    | 1       | LM     | 0.61 |
| Thalamus                                    | 21 | RH   | 21         | −34    | 1       | LM     | 0.59 |
| Midbrainred nucleus                         |    |      |             |        |         |
| STG                                         | 22 | RH   | 48         | −1     | 1       | LM     | 0.57 |
| STG                                         | 42 | RH   | 66         | −25    | 1       | LM     | 0.57 |
| STG                                         | 39 | RH   | 45         | −52    | 19      | LM     | 0.51 |
| Anterior cingulate                          | 24 | RH   | 3          | 35     | 7       | 133    | 0.66 |
| medFG/DMPFC                                 | 10 | LH   | −12        | 50     | 7       | LM     | 0.63 |
| MFG/DMPFC                                   | 10 | LH   | −24        | 50     | 4       | LM     | 0.58 |
| Post-central gyrus                          | 3  | LH   | −18        | −37    | 70      | 165    | 0.65 |
| Post-central gyrus                          | 1  | LH   | −33        | −34    | 64      | LM     | 0.62 |
| Post-central gyrus                          | 2  | LH   | −42        | −28    | 52      | LM     | 0.52 |
| Posterior cingulate                         | 23 | RH   | 3          | −34    | 16      | 244    | 0.56 |
| Cingulate gyrus                             | 31 | LH   | −15        | −49    | 19      | LM     | 0.56 |
| Posterior cingulate                         | 30 | LH   | −6         | −52    | 13      | LM     | 0.55 |
| SFG/OFC                                      | 11 | RH   | 27         | −53    | −20     | 117    | −0.67 |
| SFG/OFC                                      | 11 | RH   | 18         | −53    | −17     | LM     | −0.63 |

LM, local maxima.
increased effective connectivity between the left IFG and VMPFC and correlated positively with reappraisal success (Figure 6B). A negative correlation between reappraisal success and connectivity of the left IFG with the DMPFC and pgACC during the up-regulation of emotion was observed. Moreover, increased effective coupling between the IFG with the amygdala correlating positively with reappraisal success was found for the 'Increase' condition. The amygdala was further coactivated with the sgACC, DLPFC and DMPC and this coupling was predicted by higher reappraisal success when up-regulating emotions. In contrast, there was a negative relationship between reappraisal success during the up-regulation of emotional responses and the coupling between the amygdala with the OFC. These results indicate that emotion regulation was based on amygdala-prefrontal interactions that were tightly linked to the ability to successfully regulate emotions.

Discussion

Previous studies on reappraisal indicated that VLPFC, in particular the IFG, and the amygdala serve different key functional roles in the reappraisal process (Eippert et al., 2007; Wager et al., 2008). However, the effective coupling between VLPFC and amygdala with other regions of the brain during reappraisal and their association with reappraisal success is unclear. The present work constitutes the first investigation into this question by explicitly including reappraisal success as a regressor in the connectivity model.

In our reappraisal task, subjects had to either up- or down-regulate their emotions in response to aversive pictures. The effect of emotion regulation was demonstrated on the behavioral, psychophysiological and neural level. First, during emotion regulation subjects rated their emotional state as either increased or decreased compared with the control condition. Second, SCRs were increased during the up-regulation compared with the down-regulation of emotion (Eippert et al., 2007; Urry et al., 2009; Morawetz et al., 2016b,c). Third, in accord with previous findings, reappraisal compared with the control condition was associated with enhanced responses in VLPFC, temporal and parietal regions as well as the amygdala (Urry et al., 2006; Eippert et al., 2007; Kim and Hamann, 2007; Buhle et al., 2014; Frank et al., 2014; Kohn et al., 2014; Morawetz et al., 2016c). We therefore conclude that our paradigm was suited to investigate the effect of emotion regulation on connectivity and its relation to reappraisal success.

Prefrontal network underlying the down-regulation of emotion

No study to date has used the IFG as seed region for a connectivity analysis in the context of emotion regulation. This is surprising since the left IFG has been implicated in response selection and inhibition, language, social cognition and inner speech during the emotion regulation process (Ochsner et al., 2012; Kohn et al., 2014; Messina et al., 2015). Here we found that increased effective coupling between the left IFG and dorsal prefrontal regions (DMPFC and DLPC) was associated with reappraisal success during the down-regulation of emotional responses. In a previous study, we found that emotion regulation was mediated by directional changes of connection strength between the IFG and DLPC (Morawetz et al., 2016c). We now demonstrate that the ability to successfully regulate ones emotions was predicted by an enhanced effective connectivity between those two prefrontal regions. This indicates that the suggested feedback mechanism between DLPC and IFG during emotion regulation (Morawetz et al., 2016c) might be more prominent in individuals possessing higher reappraisal skills. Within this frontal network, DMPFC appears to play a critical role in emotion regulation as it has repeatedly been shown to be involved in various aspects of reflective emotional processing (Phan et al., 2002). This region has been suggested to be implicated in the control of emotional behaviors and to relay internal state information to the DLPC and VLPFC via a feed-forward mechanism (Phillips et al., 2008).

Interestingly, we found a negative correlation between IFG-VMPFC coupling and down-regulation success, while the reverse pattern was found for the up-regulation of emotion. These findings are closely aligned with the view that VMPFC plays a key role in conceptually driven affect (Roy et al., 2012). Reappraisal as a conceptually-driven form of emotion regulation, i.e. with the goal to generate positive ('Decrease') or negative ('Increase') conceptual frames, has previously been linked to VMPFC activity (Diekhof et al., 2011). Previous imaging studies also implicated the VMPFC in the positive and negative...
valuation of stimuli in a context- and goal-dependent manner (Hare et al., 2009; Hutcherson et al., 2012). Our results show that the successful reframing of negative stimuli in a positive direction (i.e. decreasing emotions to feel less negative affect) was related to less effective coupling between IFG and VMPFC. In contrast, the successful reframing of aversive pictures in a negative direction (i.e. increasing emotions to feel more negative affect) was associated with enhanced effective connectivity between IFG and VMPFC. These findings indicate that the up-regulation of emotion might be more cognitively demanding which could lead to the stronger subsequent recruitment of the VMPFC. In the opposite scenario, it might be easier to develop appropriate positive concepts to down-regulate emotions, and this process might therefore be associated with less effective coupling between IFG and VMPFC.

Of note, the observed network is based on the IFG as seed region because this prefrontal region has been directly linked to reappraisal success in previous studies (see ‘Materials and methods’ section). However, it might be worthwhile to use other prefrontal regions as seed regions if there is an indication that this region is related to successful emotion regulation. In the present study we used a hypothesis-driven analysis approach and only considered brain regions for which clear evidence for a direct link to emotion regulation success was given.

**Amygdala-prefrontal network underlying the up-regulation of emotion**

Consistent with previous findings (Banks et al., 2007) we found that increased connectivity between the left amygdala and OFC was associated with the experience of less negative affect. In addition, we extended previous studies (Banks et al., 2007; Kanske et al., 2011; Sripada et al., 2014) by showing that several other prefrontal regions (VLPFC, DLPFC, DMPFC and sgACC) demonstrated increased coupling with the amygdala with increasing success in up-regulating emotions.

The reappraisal-modulated coactivation of amygdala and IFG with ACC with respect to regulating negative affect is in line with prior neuroimaging results that implicate the ACC in emotion assessment, emotion related learning, and active, voluntary emotion regulation (Ochsner and Gross, 2005; Phillips et al., 2009).
Our findings suggest that the successful down-regulation of emotions predicted increased coupling of prefrontal regions, while the successful up-regulation of emotional experience was related to increased coupling of amygdala-prefrontal interactions. The discrepancy to previous studies (Urry et al., 2006; Banks et al., 2007; Kanake et al., 2011) reporting amygdala-frontal coupling during the down-regulation of emotion might be explained by individual differences in reappraisal success. To test this hypothesis, we performed the same PPI analysis with the left amygdala as seed region ‘without’ using reappraisal success as covariate. Consistent with the notion that frontal cortex exerts a top-down inhibitory effect on the amygdala (Ochsner et al., 2002; Quirk and Beer, 2006; Urry et al., 2006; Johnstone et al., 2007; Phillips et al., 2008; Wager et al., 2008), we found that increased activity in bilateral VL/VPFC was associated with decreased activity in the left amygdala during the down-regulation of negative affect. In contrast, an increase in response in the left VL/VPFC was associated with an increase in signal change in the amygdala during the up-regulation of emotions (see Supplementary Table S1). This supports the idea that individual differences in reappraisal success might affect amygdala-frontal coupling during the down-regulation of emotion.

Furthermore, amygdala-frontal coupling might also be affected by reappraisal training. Recent findings indicate that reappraisal training, i.e. increasing reappraisal success, not only results in reductions in self-reported negative affect over time (Denny and Ochsnner, 2014), but also leads to long-lasting effects on the amygdala response (Denny et al., 2015). In line with these findings, previous studies demonstrated that neurofeedback training leads to an increase in top-down connectivity from the DMPFC onto the amygdala (Koush et al., 2015) as well as in bottom-up connectivity from the amygdala to the VMPFC (Paret et al., 2016). These findings indicate that the amygdala-frontal coupling underlying successful emotion regulation can be modulated in a self-organized, endogenous fashion. Furthermore, the coupling within cortico-limbic circuits can also be influenced pharmacologically by targeting the serotonergic system, which has been implicated in a wide range of psychiatric diseases, in particular in anxiety disorders and depression. Serotonin has been linked to several aspects of emotional information processing (Merens et al., 2007) and thus might be implicated in amygdala-frontal coupling. Indeed, a recent study demonstrated that effective connectivity within the prefrontal-amygdala network can be modulated by (S)-citalopram, a selective serotonin reuptake inhibitor, during emotional face processing (Sladky et al., 2015). Hence, the proposed emotion regulation network could not only be modulated on a behavioral, but also on a neuropharmacological level.

Conclusions

Our findings have several implications, first by providing further evidence for the importance of frontal brain regions to regulate emotions. Furthermore, these findings add to prior neuroimaging studies by showing that up- and down-regulation of emotions are based on different coupling between prefrontal regions and the amygdala. Increased coupling within a prefrontal network was related to success in down-regulation of emotions, and increased coupling between the amygdala and the prefrontal network was related to success in the up-regulation of emotions. They additionally suggest that there is a direct link between effective connectivity underlying emotion regulation and the success in controlling emotions thereby highlighting the role of individual differences. In relation to conceptual models of emotion regulation (Ochsner et al., 2012), the findings demonstrate that successful reappraisal might rely on a more direct interaction between a system involved in the control of emotions based on frontal regions and a system implicated in generating emotions involving emotion-related regions such as the amygdala. Finally, given that psychiatric disorders have been found to be associated with affective instability and emotion dysregulation (Phillips et al., 2003), our findings might inform future studies investigating whether specific connectivity deficits could underlie emotion regulation deficits in mental disorders, such as anxiety, mood and personality disorders.

Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest. None declared.

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