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ORIGINAL ARTICLE

Changes in Effective Connectivity Between Dorsal and Ventral Prefrontal Regions Moderate Emotion Regulation

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Abstract

Reappraisal, the cognitive reevaluation of a potentially emotionally arousing event, has been proposed to be based upon top-down appraisal systems within the prefrontal cortex (PFC). It still remains unclear, however, how different prefrontal regions interact to control and regulate emotional responses. We used fMRI and dynamic causal modeling (DCM) to characterize the functional interrelationships among dorsal and ventral PFC regions involved in reappraisal. Specifically, we examined the effective connectivity between the inferior frontal gyrus (IFG), dorsolateral PFC (DLPFC), and other reappraisal-related regions (supplementary motor area, supramarginal gyrus) during the up- and downregulation of emotions in response to highly arousing extreme sports film clips. We found DLPFC to be the central node of the prefrontal emotion regulation network, strongly interconnected with the IFG. The DCM analysis further revealed excitatory changes of connection strength from the DLPFC to the IFG and strong inhibitory changes of connection strength between the IFG and DLPFC during reappraisal. These bidirectional changes in connectivity strength indicate a feedback mechanism by which the IFG may select one out of several possible goal-appropriate reappraisals held active in working memory (represented in the DLPFC) and inhibits the DLPFC once the selection process is completed.

Key words: dynamic causal modeling, fMRI, inferior frontal gyrus, reappraisal

Introduction

The cognitive modulation of emotional experience is highly relevant for adaptive social behavior as well as mental and physical health (Gross and Muñoz 1995; Gross and John 2003; Eftekhari et al. 2009). Reappraisal is the most commonly used and studied emotion regulation strategy (Gross and John 2003; Ochsner and Gross 2005; Kalisch 2009; Ochsner et al. 2012; Buhle et al. 2014). It refers to the cognitive reevaluation of a potentially emotionally arousing event, aimed at altering its emotional impact (Gross and Thompson 2007) and is based on different cognitive processes such as working memory, selective attention as well as response selection and inhibition (Ochsner and Gross 2008).

The most prominent model of emotion regulation proposes 2 top-down appraisal systems, both located in prefrontal cortex (PFC) (Ochsner and Gross 2005, 2007, 2008; Ochsner et al. 2012). The first system is thought to comprise dorsomedial and

dorsolateral prefrontal cortex (DMPFC, DLPFC), which are implicated in selective attention and working memory, thereby promoting the generation of mental representations of affective states and reappraisal to regulate emotion (Miller 2000; Miller and Cohen 2001; Curtis and D'Esposito 2003; Wager and Smith 2003; Wager et al. 2004; Gazzaley and D'Esposito 2007; Ochsner et al. 2012). The second system is discussed to play a role in top-down outcome-based appraisal and includes ventromedial and ventrolateral prefrontal cortex (VMPFC, VLPFC), which are involved in response selection and inhibition, as well as cognitive control of choice (Aron et al. 2004; Thompson-Schill et al. 2005; Badre and Wagner 2007; Hare et al. 2009; Ochsner et al. 2012).

In support of the top-down appraisal systems, several studies demonstrate amygdala-frontal coupling during emotion regulation (Ochsner et al. 2002; Urry et al. 2006; Banks et al. 2007; Delgado et al. 2008; Kanske et al. 2011). Emotion regulation processes might, however, not necessarily be related to changes in amygdala activity as previous studies directly contrasting reappraisal strategies with different goal-specificity (Increase and Decrease) report no modulation of the amygdala (Ochsner, Ray et al. 2004; Urry et al. 2006; Eippert et al. 2007; Kim and Hamann 2007). Furthermore, meta-analyses demonstrated that the comparison between reappraisal (Increase and Decrease) and an emotional baseline condition does not yield differences in amygdala activity (Kalisch 2009; Buhle et al. 2014; Kohn et al. 2014). Thus, emotion regulation processes might be better understood as a result of the interplay of lateral PFC regions, in line with models which suggest that strategy initiation and application are promoted by these regions (Phillips et al. 2008; Ochsner et al. 2012), but no study to date has examined changes in effective connectivity between dorsal and ventral prefrontal regions during reappraisal.

In the present study, participants were asked to up- and downregulate their emotions while viewing highly arousing extreme sports film clips in an MRI scanner. We assessed the functional interrelationships among dorsal and ventral PFC regions involved in reappraisal by combining conventional statistical parametric mapping (SPM) with dynamic causal modeling (DCM) of functional magnetic resonance imaging (fMRI) data (Friston et al. 2003). Previous studies showed that both DLPFC and VLPFC, including inferior frontal gyrus (IFG), are connected to temporal and parietal regions (Petrides and Pandya 1999; Catani et al. 2005; Petrides 2005; Frey et al. 2008; Keller et al. 2009; Geva et al. 2011). Furthermore, DLPFC and VLPFC have been shown to be interconnected in nonhuman primates (Barbas and Pandya 1989, 1991; Barbas 2000, 2009; Yeterian et al. 2012) and in humans (Goulas et al. 2012). Therefore, we hypothesized that reappraisal, specifically the up- and downregulation of emotion, would be driven by the interplay between ventral and dorsal prefrontal systems, leading to increased reciprocal connectivity between them.

Experimental Procedures

Subjects

Twenty-three right-handed subjects (mean age = 22.95 years, SD = 3.57 years; 15 females) participated in the study. Handedness was assessed using the Edinburgh-Handedness Inventory (Oldfield 1971), and eligibility was assessed using a general health questionnaire and fMRI safety screening form. Subjects had normal or corrected-to-normal vision and gave written, informed consent to participate in the study, which was approved by the ethics committee of the German Psychological Society (DGPs). None of the subjects had ever done skydiving before or reported fear of heights or acrophobia. The study was carried out in accordance to the Declaration of Helsinki.

Stimuli and Task

Stimuli originally consisted of a set of 180 film clips, comprising 120 highly arousing extreme sports film clips (Skydiving, BASE jumping, Downhill-Skateboarding, Freeride Snowboarding, Big Wave Surfing, Kite Surfing, Whitewater Kayaking, Snow Paragliding) and 60 neutral control film clips (Landscape, Airplane Flights, Helicopter Flights). The skydiving/BASE-jumping film clips were obtained from a skydiving school (www.gojump.de), and all other film clips were obtained from a professional videographer (www.danny-strasser.de) and Red Bull Media House GmbH (www.redbull.com). To note, no participant had previously seen any of the film clips due to them not being published or used for any commercial purposes. The film clips were rated on valence and arousal by a different group of 17 subjects (mean age = 26.82 years, SD = 6.91 years; 13 females) using a nine-point Likert scale (1: very negative/calm to 9: very positive/high arousing). On the basis of these ratings, 60 high-arousing film clips of skydiving and BASE jumping and 42 neutral film clips were selected for the fMRI study. In extreme sports, skydiving and BASE jumping are considered to carry a high risk of severe physical injury or even death (Brymer 2005). Both parachute sports involve willfully jumping through the open door of an airplane or jumping off a rock or a building, respectively. BASE jumping has been ranked as being among the most dangerous sports (Pedersen 1997). Only extreme sports film clips from the first-person perspective (helmet camera) were used (i.e., depicting the actual jump of an airplane or off a rock) to induce strong feelings of anxiety and high arousal. Emotionally neutral film clips were matched to the sports clips with respect to the perspective (i.e., bird's eye view of landscapes taken from an airplane or helicopter). The final selection of film clips was rated significantly higher on negative emotion experience (sports: mean = 4.81 ± 1.83, neutral: mean = 6.55 ± 1.10, $t_{(17)} = 3.84$; $P < 0.001$) and higher on arousal (sports: mean = 6.81 ± 1.07, neutral: mean = 3.57 ± 1.61, $t_{(17)} = 7.91$, $P < 0.001$) for sports versus neutral film clips with 1 indicating "very negative/calm" and 9 indicating "very positive/high arousing." Note that, for the sports film clips, the mean of the valence ratings was close to the mean of the scale, while the arousal was high. Thus, while not being negative per se, sports film clips were nevertheless emotionally engaging and could be used to actively modulate (increase or decrease) potential negative emotions in both directions. After scanning, the fMRI sample rated all stimuli again on valence and arousal on a nine-point Likert scale.

The task design was adapted from previous studies on emotion regulation (Ochsner, Ray et al. 2004; Kim and Hamann 2007; McRae et al. 2008; Wager et al. 2008). An explicit emotion regulation task was used that implemented 4 conditions. In the *Look* condition, subjects were asked to view the film clips attentively and allow themselves to experience/feel any emotional responses, which these might elicit without trying to influence or change them, for both the neutral film clips (*Look-Neutral*) and the extreme sport clips (*Look-Sports*). In the other conditions (*Increase*, *Decrease*), subjects were asked to reappraise the negative emotional value of the extreme sport clips. In the *Increase* condition, subjects were instructed to amplify the intensity of their *negative* emotion. For this, subjects were trained before the scanning session to actively engage themselves with the depicted situation in order to increase their sense of subjective closeness to the pictured events (e.g., imagining themselves as the skydiver

or BASE jumper, jumping out of an airplane, etc.) and to amplify their subjective experience as the actions unfolded in the film clip. They were further required to imagine a *negative* outcome of the depicted situation (e.g., accident; parachute not opening). Conversely, in the *Decrease* condition, subjects were asked to reduce the intensity of the *negative* emotion, for which they were trained to imagine a positive outcome of the depicted situation (e.g., safe landing; joy of the jump). After each trial, subjects were asked to indicate the extent of their negative emotions on a Likert-scale from 1 = "not at all negative" to 4 = "extremely negative."

During the fMRI experiment, film clips were presented against a black background in the middle of the screen with an 800 × 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). Film clips subtended a 32° × 21° visual angle.

fMRI and Procedure

Before the scanning session, subjects received an introduction to BASE jumping and skydiving by a written description of both extreme sports followed by 2 short film clips illustrating the sports (BASE jumping clip: 5 min, skydiving clip: 1 min). Afterward, the experimental conditions were explained in detail (*Increase, Decrease, Look*) and reappraisal strategies were introduced. The exact trial sequence was described to the subjects. This instruction phase was followed by a sequence of 10 practice reappraisal trials for each reappraisal goal (*Increase, Decrease*) and 10 practice control trials (*Look-Neutral, Look-Sports*). The training procedure lasted approximately 10 min.

Film clips were presented using an event-related design (Fig. 1). Each trial started with an instruction screen (2 s) indicating the experimental condition using a symbol as a cue (camera symbol: *Look*; red arrow pointing upwards: *Increase*; green arrow pointing downwards: *Decrease*). A film clip was presented subsequently for 8 s, followed by the words "How negative do you feel?" for 4 s during which subjects had to rate their emotional state from 1 (not at all negative) to 4 (extremely negative). Subjects rated their affect by pressing a button on a 4-button fiber-optic response pad (fORP, Cambridge Research Systems Ltd, England). Finally, a central fixation-cross presented for a jittered duration of 4–8 s concluded the trial. One run consisted of 28 trials (7 trials per condition). Each sports clip was shown twice and each neutral clip once during the experiment. Each experimental session consisted of 6 runs.

Questionnaires

Before and after the fMRI experiment, subjects rated their state anxiety using the State Trait Anxiety Inventory (STAI) (Spielberger et al. 1970; Laux et al. 1981) to assure that our sample did not differ from the population average. After the fMRI session, subjects completed several questionnaires. As the personality construct of alexithymia encompasses a cluster of characteristics reflecting impaired emotion processing and regulation, we assessed alexithymia with the Toronto Alexithymia Scale (TAS-20) (Bach et al. 1996). The Sensation Seeking Scale (SSS-V) (Beauducel et al. 2003) was used to exclude any potential extremely high sensation seekers (not found in our sample).

After the fMRI experiment, we assessed individual differences in emotion regulation strategies (suppression and reappraisal) by obtaining self-ratings of emotion experience and expression using the Emotion Regulation Questionnaire (ERQ) (Gross and John 2003; Abler 2009). Additionally, subjects rated their ability to regulate their negative emotions for *Increase* and *Decrease* trials during the fMRI experiment in a separate general questionnaire on a 7-point scale (1: "not successful at all" to 7: "very successful"). Subjects were also asked to rate whether they succeeded in imagining themselves in the depicted situations in general. In 2 open questions, subjects were given the opportunity to provide additional feedback regarding the emotion regulation strategies.

Electrodermal Activity

It has been demonstrated that electrodermal activity (EDA) is modulated by emotional arousal and emotion regulation (Urry et al. 2009). We recorded EDA as a measure of affective value of stimuli using 2 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, Gliching, Germany) and constant voltage electrode excitation. During the analysis, the data were down-sampled offline to 10 Hz. We applied continuous decomposition analysis to decompose skin-conductance data into continuous tonic and phasic activity (Benedek and Kaernbach 2010) and averaged across trials within each condition applying an 8-s time window using Ledalab Version 3.3.1 (Benedek and Kaernbach 2010). Skin-conductance responses (SCRs) were defined as a deflection of at least 0.01 μS occurring 1–8 s after stimulus onset. Only runs

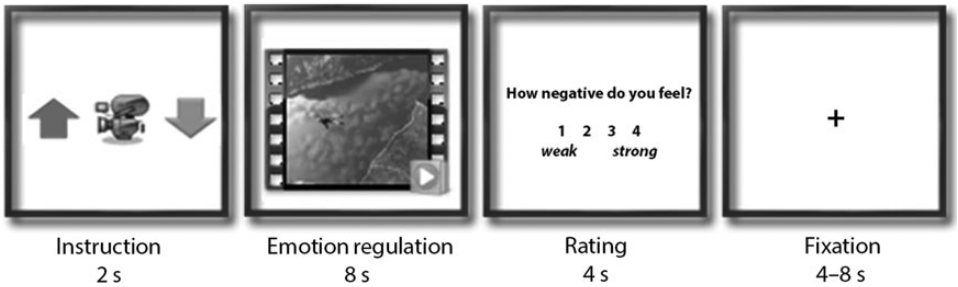

Figure 1. Task Design. Each trial started with an instruction screen of 2 s, displaying a cue for each experimental condition: Red arrow pointing upward symbolized *Increase*, video camera indicated *Look* and green arrow pointing downward indicated *Decrease*. After the instruction, participants performed the instructed emotion regulation goal for 8 s while either a neutral or negative film clip was presented. Subsequently subjects were asked to rate their current emotional state (How negative do you feel?) on a scale from 1 (weak) to 4 (strong), followed by a fixation phase of 4–8 s.

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. Based on this criterion, one subject had to be excluded from the EDA analysis.

Statistical Analysis of Self-Report Data

Mean negative affect ratings were calculated for all 4 conditions. We performed repeated-measures ANOVA using SPSS 20 (SPSS, Inc.) to analyze the effect of the different task conditions on emotional state ratings, followed by post hoc paired *t*-tests (two-tailed).

To assess successful emotion regulation, we calculated reappraisal success scores based on the negative affect ratings acquired after each trial. Reappraisal success was defined as either the decrease or increase in reported negative emotion when applying a cognitive reappraisal strategy to the sports clips (*Increase* and *Decrease*) relative to the mean affect ratings of the *Look-Sports* condition representing the "natural" emotional response to the stimuli. On this basis, each reappraisal trial (*Increase* or *Decrease*) was categorized as either successful or unsuccessful by subtracting the affect rating from the mean baseline (*Look-Sports*). Hence, positive values during *Decrease* represent successful trials (subject reported stronger negative affect) while negative values represent unsuccessful trials (subject reported weaker negative affect) and vice versa for *Increase*. Accordingly, reappraisal success scores were calculated as the percentage of successful reappraisal trials for each subject for both reappraisal conditions separately.

Imaging Data Acquisition

Whole-brain functional and anatomical images were acquired using a 3.0-T Magnetom TIM Trio scanner (Siemens, Erlangen, Germany) and a 12-channel head coil. Additionally, a high-resolution 3D T_1-weighted dataset was acquired for each subject (176 sagittal sections, $1 \times 1 \times 1$ mm^3; 256×256 data acquisition matrix). Functional images were acquired using a T_2*-weighted, gradient-echo echo planar imaging (EPI) pulse sequence recording 37 sections oriented roughly parallel to the anterior and posterior commissure at an in-plane resolution of $3 \times 3 \times 3$ mm^3 (interslice gap = 0; TE = 30 ms; TR = 2 s; FA = 90°; FoV = 192×192 mm^2; 64×64 data acquisition matrix). Slices were acquired in an interleaved ascending order. As the amygdala is a region that can be affected by susceptibility-induced magnetic field inhomogeneities (Merboldt et al. 2001), we used an standard MR sequence, which has been demonstrated to be suitable for the investigation of changes in amygdala activation (Morawetz et al. 2008) (see Supplementary Fig. 1 for image quality in the amygdala). For each experimental run, 285 whole-brain volumes were recorded.

fMRI Data Analysis

Preprocessing

Functional imaging data analysis was performed using SPM8 (Statistical Parametric Mapping, Wellcome Institute for Cognitive Neurology, London, UK) and Matlab 8.0.0 (MathWorks, Natick, MA, USA). As interleaved slice acquisition was used, we included slice time correction during the preprocessing of the fMRI data (Sladky et al. 2011). In addition, preprocessing of fMRI data included realignment to the mean image, spatial normalization to the standard EPI template (Montreal Neurological Institute, MNI template, as implemented in SPM8) and spatial smoothing with an 8-mm full-width at half-maximum isotopic Gaussian kernel.

First-Level (Within-Subject) Analysis

For each subject, the data from the 6 experimental runs were modeled with a general linear (convolution) model. Stimulus onset vectors representing the task conditions (*Increase, Decrease, Look-Sports, Look-Neutral*) (8 s), instruction (2 s), and rating (4 s) were convolved with a canonical hemodynamic response function. Six movement parameters were also entered as nuisance covariates. Contrast images of brain activations associated with emotion regulation (*Increase* + *Decrease*) compared with *Look-Sports* were produced for each participant.

We also performed an additional region of interest (ROI) analysis on the amygdala using MarsBaR v0.43 (Brett et al. 2002). The anatomical ROIs were created using the WFU Pick Atlas toolbox (version 3.0) (Maldjian et al. 2003) (left amygdala: $x = -24$, $y = -2$, $z = -18$; right amygdala: $x = 27$, $y = -1$, $z = -19$). As it has previously been demonstrated that amygdala activity decreases upon repeated presentation of negative stimuli (Breiter et al. 1996; Fischer et al. 2000, 2003; Wright et al. 2001; Phan et al. 2003; Ishai et al. 2004; Britton et al. 2008), we tested for habituation effects. To do this, we divided the trials within each run into early (1–3) and late (4–7) trials and performed another ROI analysis within the amygdala.

Regions-of-Interest Selection

Prior to the DCM analyses, a conventional second-level fMRI analysis was conducted to determine the ROIs for the DCM analyses. These group-level analyses were based on random-effects analyses of the single-subject contrast images using the summary statistic approach. We identified regions, which were involved in either reappraisal goal (*Increase* + *Decrease*) relative to the control condition (*Look-Sports*) [0.5 0.5 –1]) (using a relatively liberal threshold of $P < 0.001$ uncorrected and a minimum cluster size of 50 voxels) in order to obtain regions, which are involved in reappraisal in general. We specifically aimed to identify regions independent of the emotion regulation strategy used (strategy-unspecific). This contrast identified left dorsolateral prefrontal cortex (DLPFC), left IFG, left supramarginal gyrus (SMG), precentral gyrus, and pre-supplementary motor area (pre-SMA) (Fig. 2 and Table 3) as ROIs, in line with previous studies describing the emotion regulation network (Ochsner et al. 2012; Ray and Zald 2012; Buhle et al. 2014).

To reduce the complexity and size of the model space (Lohmann et al. 2012), we selected the 4 ROIs based on the above contrast (DLPFC, IFG, pre-SMA, and SMG). Previous studies suggested that precentral gyrus is not crucial for emotion regulation processes but implicated in goal-directed action observation (Grèzes and Decety 2001; Perani et al. 2001; Morin and Grèzes 2008); thus, this region was excluded for the following analyses. The remaining functional ROIs were masked with anatomical ROIs taken from the WFU Pick Atlas toolbox (version 3.0) (Maldjian et al. 2003) to assure their belonging to a given anatomical region (DLPFC: $x = -53$, $y = 20$, $z = 24$; IFG: $x = -44$, $y = 25$, $z = -7$; pre-SMA: $x = -6$, $y = 9$, $z = 60$; SMG: $x = -57$, $y = -45$, $z = 29$). Using this approach, we aimed to optimize the selection of regions for the ROIs included in the DCM analysis. Given its general role in visual stimulus processing, an additional anatomical ROI was determined within the primary visual cortex (BA 17, V1), using a sphere of 10 mm around the central coordinates of V1 according to the WFU Pick Atlas ($x = -8$, $y = -85$, $z = 3$).

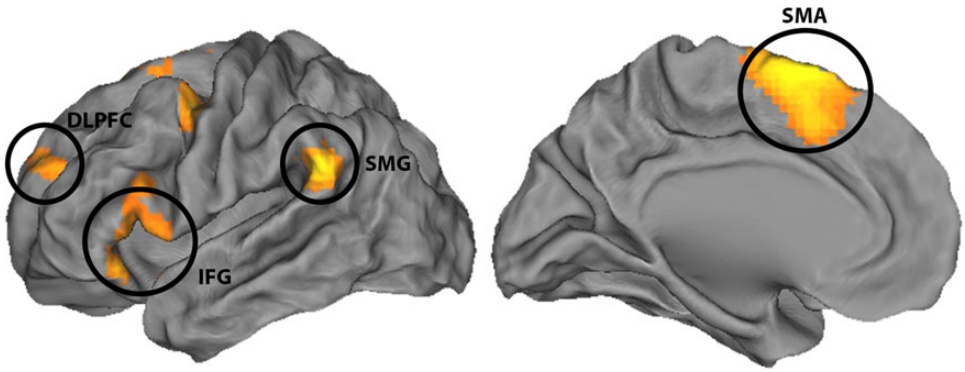

Figure 2. Emotion regulation-related activation. Emotion Regulation (*Increase* + *Decrease*) versus *Look* ($P < 0.001$ uncorrected, $k = 50$). Left dorsolateral prefrontal cortex (DLPFC), left inferior frontal gyrus (IFG), left supramarginal gyrus (SMG), and left supplementary motor area (SMA) were used as regions of interest for the subsequent DCM analysis (highlighted).

After defining the 5 ROIs, the principal eigenvariate time series was extracted from each ROI within a 6-mm radius sphere of the local maxima on a single-subject level and adjusted to the *F*-contrast (*Increase, Decrease, Look-Sports, Look-Neutral*) of each subject. Based on these time courses, DCM, as implemented in DCM10 (SPM8), was used to model the effective connectivity between these regions. For the DCM analysis, we recombined the regressors of the univariate analysis to extract the time courses: 1) Film Clips (all experimental conditions: Increase, Decrease, Look-Sports, Look-Neutral), 2) Sports Film Clips (all sports film clips: Increase, Decrease, Look-Sports), and 3) Emotion Regulation (reappraisal conditions: Increase, Decrease).

Dynamic Causal Modeling Analysis

DCM employs a Bayesian framework to infer effective connectivity between interacting cortical regions or nodes of interest (Friston et al. 2003). Effective connectivity describes the causal influences that one region exerts over another (Friston 1994). The basic idea of DCM is to construct a reasonably realistic neuronal model, which specifies the endogenous connections between the nodes, the locations of a stimulus input that drives specific areas directly, and the modulation of the strengths of functional coupling within the system induced by some experimental condition. Briefly, DCM characterizes those task-dependent neuronal interactions between regions and estimates of 3 different sets of parameters: 1) direct influences of driving inputs (extrinsic parameters) on the neuronal states (in this case, all visual input presented irrespective of the task), 2) strengths of intrinsic connections (endogenous parameters) reflecting the context-independent coupling between neuronal states in different regions, and 3) modulatory or bilinear inputs (modulatory parameters) representing context-dependent changes in coupling between regions induced by a particular task condition (in this case, emotion regulation). The different parameters are expressed in Hertz (Hz) within the DCM framework. The endogenous and modulatory parameters of the DCM model and their posterior probabilities are assessed with Bayesian inversion by means of an expectation-maximization algorithm (for more details see Friston et al. 2003).

Each hypothesis about a system of interest can be represented by a specific model. Thus, the estimated model is context-dependent, which means that interactions and coupling among regions are constrained by the user-specified connections, inputs, and modulations. Inferences made from DCM are always relative to the model space one tests. The different models can be compared with all other models to determine which model best predicts the data using a Bayesian Model Selection (BMS) scheme (Penny et al. 2004). Multiple models can further be grouped into families, which share a common element of interest and can be compared (Penny et al. 2010).

DCM Model Space

According to our hypotheses and some basic assumptions (see below), we used our 5 ROIs within the left hemisphere as sources and systematically constructed a model space, divided into 2 model families with 2 different central nodes (Fig. 3*A* and *B* respectively): family #01 was characterized by the DLPFC representing the central node (red), while, in family #02, the IFG was the central node (blue). All competing models within one family had the same architecture with 6 endogenous connections that modeled the forward and backward connections between regions. One basic premise was that the driving input always enters the models through V1. By conflating all experimental conditions into a single regressor, we specified the driving input to our models, which as such contained all visual stimuli (*Increase, Decrease, Look-Neutral, Look-Sports*). Within each of the 2 families (central node IFG or DLPFC), the modulatory effects of emotion regulation were modeled using 9 variants (with models 09 and 18 representing the most complex models; see Fig. 3 for a complete overview). The modulatory effects consisted of both *Increase* and *Decrease* conditions to investigate emotion regulation independent of reappraisal goal. The intrinsic connections between the ROIs of both model families were directly derived from previous work: Based on anatomical and diffusion tensor imaging studies, we integrated a direct intrinsic connection between the SMG and DLPFC (Petrides and Pandya 1999; Petrides 2005) in the first model family as well as between SMG and IFG (Catani et al. 2005; Frey et al. 2008; Keller et al. 2009; Geva et al. 2011) in the second model family. Previous studies further established direct connections between the DLPFC and pre-SMA (Luppino et al. 1993; Lu et al. 1994; Nachev et al. 2008) and between the IFG and pre-SMA (Keller et al. 2009), which we integrated as intrinsic connections in our model space. Direct visual input from V1 has been shown to spread dorsally to the parietal lobe (Ungerleider and Mishkin 1982; Goodale and Milner 1992; Ungerleider and Haxby 1994), which was implemented in our model space as an endogenous connection between V1 and the SMG.

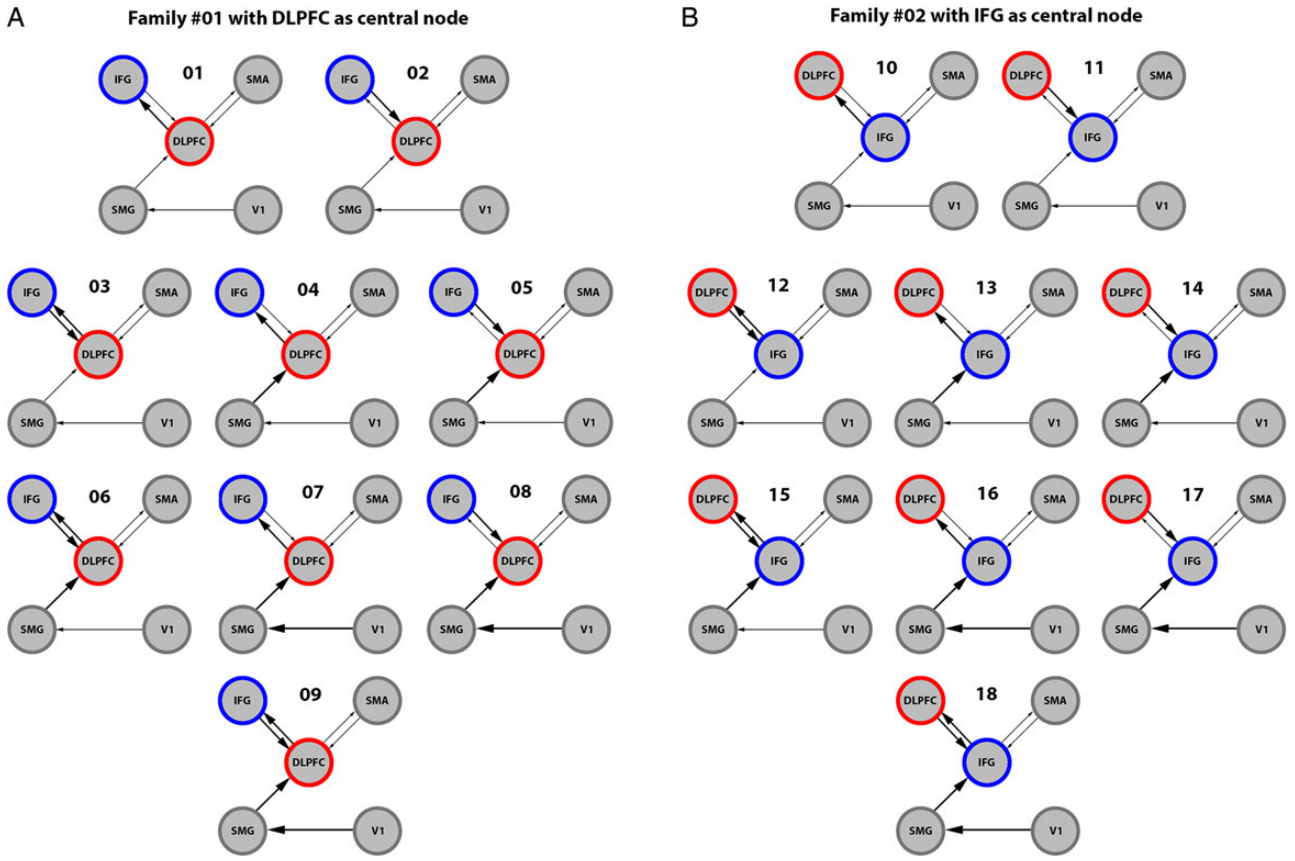

Figure 3. Model specification. Illustration of the 18 different models estimated and compared here. The sources comprising the models were V1, supramarginal gyrus (SMG), dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), and inferior frontal gyrus (IFG) only in the left hemisphere. All models within one family have the same endogenous connections. Modulated changes in connectivity by emotion regulation are shown with thicker arrows. Models are arranged in respect to their complexity: Models of the first row (01, 02, 10, 11) include one modulatory effect; models of the second and third row (03–08, 12–17) include 2 and 3 modulatory effects, respectively; models of the last row (09 and 18) represent the most complex models with 4 modulatory effects. Driving input of "all conditions" (Increase, Decrease, Look-Sports, Look-Neutral) enters V1 in all models. A The 9 models that constitute the first family with DLPFC (red) as central node. B The 9 models that constitute the second family with IFG (blue) as central node.

Table 1 Questionnaires

Questionnaire	Female ($n = 15$)				Male ($n = 7$)				Total ($n = 22$)			
	M	SD	PA	PA SD	M	SD	PA	PA SD	M	SD	PA	PA SD
STAI (pre-experiment)	36.73	6.48	32.57	8.01	35.40	7.09	36	10				
STAI (postexperiment)	38.23	9.63	33.85	13.04	36.70	10.81						
TAS-20	41.93	10.09	43.45	9.8	41.00	12.20	47.19	10.3	41.63	10.52		
Reappraisal (ERQ)	2.95	0.76	4.24	0.9	2.61	1.51	4.07	1.2	2.84	1.03		
SSS	22.00	4.91	16.9	5.5	22.71	5.58	19.9	6.6	22.22	5.01		

STAI, State Trait Anxiety Inventory; TAS-20, Toronto Alexithymia Scale-20; ERQ, Emotion Regulation Questionnaire; SSS, Sensation Seeking Questionnaire; M, mean; SD, standard deviation; PA, population average; PA SD, standard deviation of population average.
PA for STAI: Spielberger et al. (1970); PA for TAS-20: Parker et al. (1993); PA for ERQ: Abler (2009); PA for SSS: Beauducel et al. (2003).

Random-Effects BMS

For each subject, all 18 models had the same endogenous connections and driving input within one family but differed in respect to the modulatory effects (Fig. 3, bold arrows). In a first step, we tested which family of models has the higher likelihood using random-effect BMS at the family level as implemented in SPM8. We computed the evidence of each family of models, represented by the exceedance probability (xp), to determine which family is more likely than the other, given the data from all subjects. Next, we used the random-effects BMS procedure to determine the most plausible model within the winning family. We computed the group evidence of the winning model represented by the "exceedance" probability (xp) that one model is more likely than any other model, given the group data.

Results

Behavioral Results

Confound Control

A battery of questionnaires (see Materials and Methods) was administered. Our sample did not differ from the reported population averages (PA), that is, differed less than 1 standard deviation (SD) from the mean on state anxiety (using the STAI, Laux et al. 1981), alexithymia (using TAS-20, Parker et al. 2003), sensation seeking (using the SSS, Beauducel et al. 2003), and individual differences in general emotion regulation strategies (reappraisal and suppression) (using the ERQ, Abler 2009) (Table 1).

After scanning, subjects rated their ability to regulate their emotions during the study (1 = very bad to 7 = very good) as above average for *Increase* ($M = 4.65$, $SD = 0.27$, $t_{(18)} = 3.92$, $P < 0.01$) and *Decrease* ($M = 4.75$, $SD = 0.29$, $t_{(18)} = 3.86$, $P < 0.01$), and for their ability to vividly put themselves into the depicted situation ($M = 5.05$, $SD = 0.99$, $t_{(18)} = 6.53$, $P < 0.001$). When asked about their emotion regulation strategies after the fMRI session, more than half of all subjects explicitly stated that they used inner speech to regulate their emotions ($n = 13$).

Emotion Induction

To assess whether the stimuli induced the desired emotion, subjects rated all previously seen film clips on valence and arousal in a postscan session. Subjects rated the extreme sport film clips as more arousing (arousal: sport film clips: $M = 5.07$, $SE = 0.25$; neutral clips: $M = 2.40 \pm 0.29$; $t_{(22)} = 8.55$, $P < 0.001$; 1 = calm to 9 = highly arousing) and less positive (valence: sports film clips: $M = 6.04 \pm 0.23$; neutral clips: $M = 7.30 \pm 0.26$; $t_{(22)} = -4.70$, $P < 0.001$; 1 = negative to 9 = positive) than the neutral film clips.

Skin-conductance data provided additional support for the success of the emotion induction by indicating an increase or decrease in arousal (Fig. 4A): In both *Increase* ($t_{(22)} = 3.87$, $P < 0.001$) and *Decrease* ($t_{(22)} = 3.00$, $P < 0.01$) conditions, SCR amplitudes were higher compared with the control condition (*Look-Neutral*). Increasing ($t_{(22)} = 1.68$, $P = 0.10$) and decreasing ($t_{(22)} = 0.76$, $P = 0.45$) emotion was not significantly different from the *Look-Sports* condition. The difference of SCR amplitudes during the emotion regulation phase bordered significance and were higher for the *Increase* than for the *Decrease* condition ($t_{(22)} = 2.08$, $P = 0.05$). SCRs in *Look-Sports* were significantly increased compared with *Look-Neutral* ($t_{(22)} = 3.85$, $P = 0.001$).

Emotion Regulation

Analysis of the emotional state ratings (ranging from 1 = not at all negative to 4 = extremely negative) after each trial in the scanner revealed a significant main effect of task condition ($F_{1,22} = 70.95$, $P < 0.001$) (Fig. 4B). Significantly greater negative affect was reported for the sports clips ($M = 1.81 \pm 0.45$) compared with the neutral film clips ($M = 1.25 \pm 0.22$) in the Look condition ($t_{(22)} = 7.36$, $P < 0.001$), confirming that sports clips induced relatively more negative affective responses. Comparisons between task conditions showed that the reappraisal tasks significantly differed from Look conditions, confirming that the reappraisal instruction resulted in successful increase ($M = 2.50 \pm 0.52$) and decrease ($M = 1.71 \pm 0.54$) of negative affect, respectively (Increase > Look-Sports: $t_{(22)} = 8.64$, $P < 0.001$; Increase > Look-Neutral: $t_{(22)} = 11.65$, $P < 0.001$; Decrease > Look-Sports: $t_{(22)} = -1.98$, $P = 0.06$; Decrease > Look-Neutral: $t_{(22)} = 4.95$, $P < 0.001$).

Furthermore, we tested for effectiveness of emotion regulation (percent effective trials), which was above average for *Increase* ($M = 75\%$, $SD = 21.99$, $t_{(22)} = 5.54$, $P < 0.001$) and *Decrease* ($M = 72\%$, $SD = 20.97$, $t_{(22)} = 5.12$, $P < 0.001$). There was no significant difference in effectiveness between the 2 regulation conditions ($t_{(22)} = 0.425$, $P = 0.68$).

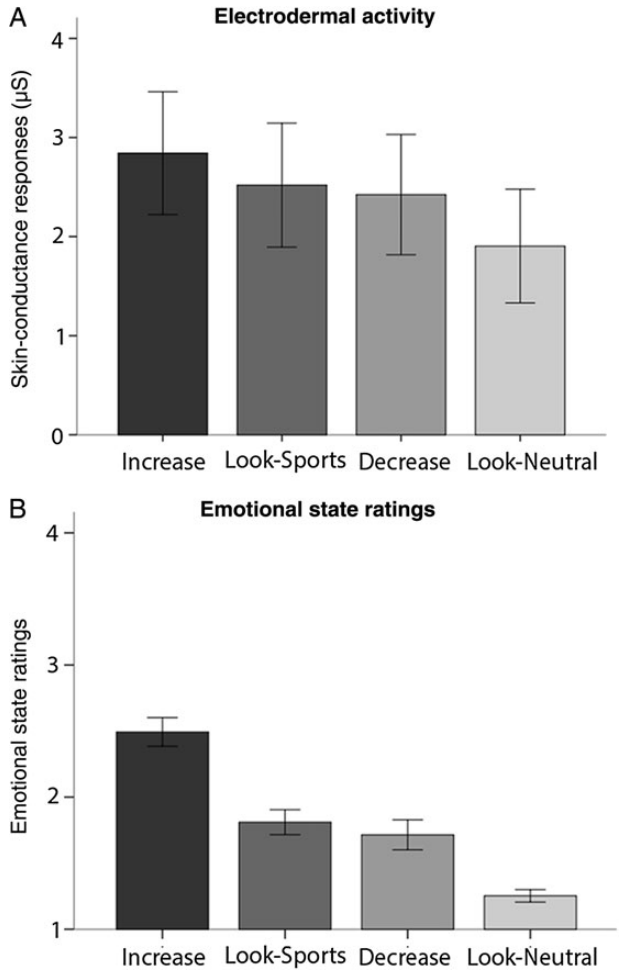

Figure 4. (*A*) Mean amplitude of skin-conductance responses as function of task condition. (*B*) Emotional state ratings during scanning as a function of task condition. Error bars represent standard error of the mean. Refer to text for statistics.

fMRI Results

Emotion Induction

First, we contrasted activation during exposure to all extreme sport clips (*Increase, Decrease, Look-Sports*) with the neutral film clips to search for neural correlates of the emotional effects. Increased activity was observed in a widespread network of regions including middle temporal gyrus, SMG, IFG, cingulate cortex, and fusiform gyrus (Table 2).

Emotion Regulation

Next, we investigated activity changes due to emotion regulation. For this, we contrasted both emotion regulation goals (*Increase, Decrease*) to the control condition (*Look-Sports*). This analysis revealed that the SMA, SMG, IFG, DLPFC, and precentral gyrus were activated during reappraisal regardless of the reappraisal goal (Fig. 2 and Table 3). Based on our a priori hypotheses and previous findings that some of these regions will not be directly involved in emotion regulation but rather have supportive

functions, we selected 4 regions as ROIs for the following DCM analyses: left DLPFC, left IFG, left SMG, and left SMA (see Materials and Methods, highlighted in Fig. 2). To ascertain that the activity in the selected ROIs was related to both reappraisal goals, we performed an additional ROI analysis as control. The results revealed that both reappraisal goals were associated with increased activity in the DLPFC, IFG, SMG, and SMA (Fig. 5).

Using the same contrast, we did not observe any signal changes in the amygdala on the whole-brain level. Therefore, we performed a ROI analysis of the amygdala (Fig. 6). An ANOVA revealed no significant main effect for task ($F_{1,22} = 2.39$, $P = 0.07$) and the change in BOLD signal in the amygdala during *Increase* was not significantly greater compared with *Decrease* ($t_{(22)} = 1.86$, $P = 0.07$). To test for habituation effects, *t*-tests between early and late trials were computed. This analysis revealed no significant habituation effects in the amygdala for any experimental condition (*Look-Sports*: $t_{(22)} = -1.66$, $P = 0.11$; *Look-Neutral*: $t_{(22)} = 0.38$, $P = 0.70$; *Increase*: $t_{(22)} = 1.80$, $P = 0.08$; *Decrease*: $t_{(22)} = 0.64$, $P = 0.52$). Consequently, the amygdala was not included into the DCM analyses.

DCM Results

We constructed 18 models, separated in 2 families, each of which assumed either the DLPFC or the IFG as the central node (see Materials and Methods). First, the winning family across all subjects was identified using random-effects BMS at the family level to determine the optimal intrinsic connections and modulations of emotion regulation. The results revealed that family #01, with DLPFC as central node, represented the best explanation of the data with a total exceedance probability of 0.997 as opposed to family #02 (exceedance probability = 0.003).

Next, we compared the exceedance probability between all models within family #01 to identify a winning model using random-effects BMS (Fig. 7). Model 6 (Table 4) outperformed all other models (including the most complex model 9 which came second) with an exceedance probability of 0.557 (the difference between model 6 and 9 consists of an additional modulatory effect between V1 and SMG in model 9, adding complexity to this model) (for an example time course and model fit see Supplementary Fig. 2).

The analysis of the intrinsic connection strength of the winning model 6 showed that, except for one connection (SMA to DLPFC), all the endogenous/intrinsic connectivity parameters were significant and most of them positive with values ranging from 0.04 to 0.87 Hz (Table 4). One intrinsic connection (IFG to DLPFC) was found to be negative. These connectivity parameters reflect the context-independent coupling between the selected brain regions in our DCM model; in other words, the effective connectivity between regions irrespective of the task modulations. Positive effective connectivity indicates that changes in activity in one region increased with changes in activity in other regions, while negative effective connectivity represents an inhibitory influence.

The subsequent analysis of the modulatory effects of emotion regulation was based on the winning model. It revealed significant modulations of connectivity from the DLPFC to the IFG and from the IFG to the DLPFC. These modulations of connectivity

Table 2 Regions activated by extreme sports film clips (Increase, Decrease, Look-Sports) relative to neutral film clips (Look-Neutral)

Region	Side	x	y	z	Size	Z-score
Middle temporal gyrus	R	48	−61	13	471	6.90
Supramarginal gyrus	R	57	−37	25	198	6.77
	L	−60	−40	25	629	6.74
Cingulate cortex	R	6	−19	43	3138	6.50
Inferior frontal gyrus	R	42	23	10	224	5.57
	L	−48	20	−8	165	4.98
Fusiform gyrus	R	45	−46	−20	20	4.87
Thalamus	L	−6	−28	−5	182	5.16
Cuneus	R	12	−76	40	76	5.46
	L	−15	−76	37	34	4.70
Cerebellum	R	18	−49	−50	80	4.90
	L	−30	−40	−38	30	4.80
	R	27	−64	−29	14	4.61

L, left; R, right.
$P < 0.05$; FWE corrected, $k = 10$.

Table 4 Parameters of the model with the best fit (model 6), including intrinsic connections, modulation of intrinsic connections, and driving inputs (family #01)

	Mean (Hz)	SD (Hz)	t	P (corr.)
Intrinsic connectivity [A]				
V1 to SMG	0.04	0.03	6.19	<0.001
SMG to DLPFC	0.49	0.56	4.25	<0.001
DLPFC to SMA	0.81	0.95	4.08	<0.001
DLPFC to IFG	0.87	0.73	5.73	<0.001
SMA to DLPFC	0.32	0.67	2.33	n.s.
IFG to DLPFC	−0.60	0.65	−4.45	<0.001
Modulation by emotion regulation [B]				
SMG to DLPFC	−0.23	1.05	−1.07	n.s.
DLPFC to IFG	−0.52	0.81	−3.06	0.005
IFG to DLPFC	−0.56	0.73	−3.67	0.001
Driving input [C]				
to V1 (all conditions)	0.62	0.41	7.33	<0.001

Significant parameters are Bonferroni-corrected for multiple comparisons.

Table 3 Regions activated by emotion regulation (Increase and Decrease) relative to Look-Sports

Region	Side	x	y	z	Size	Z-score
Supplementary motor area (SMA)	R	3	8	67	628	5.83
Supramarginal gyrus (SMG)	L	−60	−46	28	114	4.93
Inferior frontal gyrus (IFG)	L	−48	23	−8	297	4.80
Precentral gyrus	L	−42	2	52	115	4.15
Dorsolateral prefrontal cortex (DLPFC)	L	−18	59	31	56	3.79

L, left; R, right.
$P < 0.001$; uncorrected, $k = 50$.

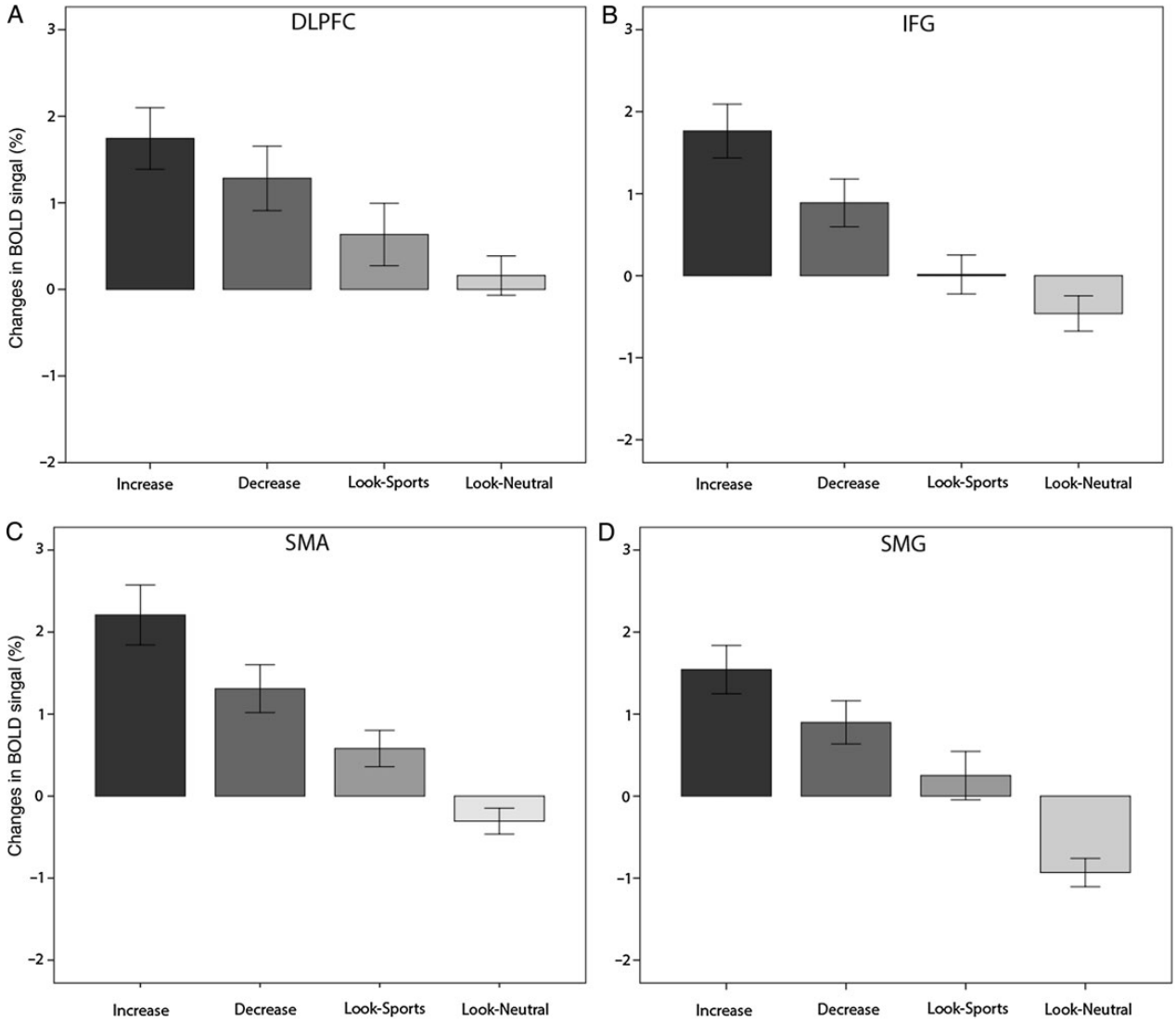

Figure 5. ROI analysis of the (*A*) left dorsolateral prefrontal cortex (DLPFC), (*B*) left inferior frontal gyrus (IFG), (*C*) left supplementary motor area (SMA), and (*D*) left supramarginal gyrus (SMG). Responses as function of task conditions. Error bars represent standard error of the mean.

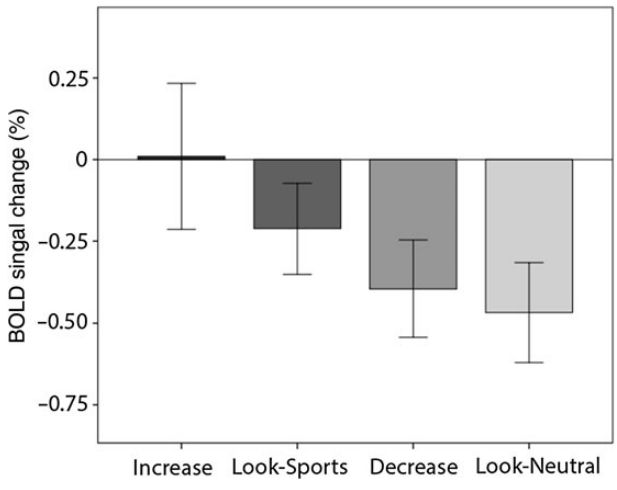

Figure 6. ROI analysis of the left and right amygdala. Amygdala responses as function of task conditions. Error bars represent standard error of the mean.

represent context-dependent changes in coupling between regions induced by emotion regulation. A graphic illustration of these connectivity changes for model 6 due to emotion regulation processes is shown in Figure 8. Reappraisal reduced the effective connectivity between the DLPFC and IFG in both directions. However, given the initial positive intrinsic coupling between the DLPFC and IFG, the negative modulatory influence was not sufficient to reverse the sign of DLPFC-IFG coupling, as evident from the persisting positive total connectivity. On the other hand, the IFG effectively inhibited the DLPFC during emotion regulation, as reflected by the sum of the posterior intrinsic parameters and modulation parameters yielding a net modulation that became more negative.

Discussion

Previous studies on reappraisal indicate the engagement of PFC regions in the top-down control of emotion regulation (Ochsner and Gross 2005; Quirk and Beer 2006; Urry et al. 2006; Johnstone et al. 2007; Phillips et al. 2008; Wager et al. 2008; Kober et al.

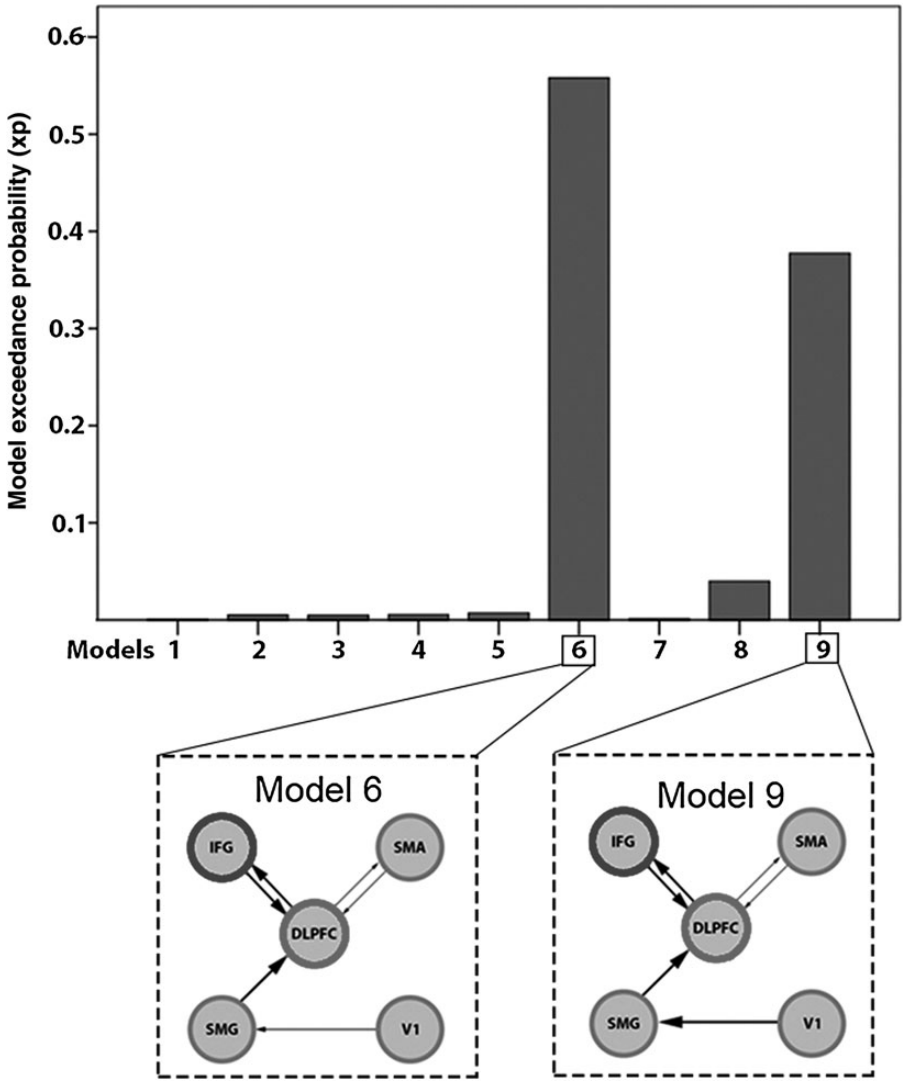

Figure 7. BMS results. Exceedance probability for all models of family #01. Notably, the winning model 6 outperformed the more complex model 9. Both are illustrated in the lower panel.

2010). However, to date, no study has explicitly investigated the connectivity between different PFC regions during emotion regulation. We investigated effective connectivity between the IFG, DLPFC, SMA, and SMG during the up- and downregulation of emotion using fMRI and DCM. In our study, reappraisal was based on effective connectivity between the DLPFC and IFG. Our data were best explained by a model in which reappraisal attenuated the excitatory connectivity between DLPFC and IFG and increased the inhibitory connectivity between the IFG and DLPFC. Our findings clearly highlight the functional role of the IFG in emotion regulatory processes.

During scanning, subjects performed a reappraisal task in which they had to either up- or downregulate their negative emotions. Emotion regulation was successful, as evidenced on the subjective, behavioral, psychophysiological, and neural level: 1) when regulating their emotions, subjects rated their emotional state as more negative during the upregulation and as less negative during the downregulation of emotional responses. Significant success scores demonstrated a high ability for reappraisal in our sample; 2) SCRs were increased during emotion regulation when compared with the control condition (Eippert et al. 2007), with significantly higher responses for increasing compared with decreasing emotions; 3) in line with previous research, we found greater activation in frontal, parietal, and cingulate cortex in response to the generally more emotionally arousing sports film clips compared with neutral film clips (Straube et al. 2010); and 4) in accord with previous studies (Ochsner et al. 2012; Ray and Zald 2012; Buhle et al. 2014), activity in several frontal (DLPFC, IFG, MFG), parietal (SMG), and medial (SMA) regions was enhanced during both reappraisal conditions.

It is important to note that the sports film clips were not only associated with negative emotions. Our first behavioral study showed that extreme sports film clips were more arousing than neutral film clips, providing support for the notion that, in general, participants could easily emotionally engage with the stimuli. The mean of valence ratings, however, corresponded closely to the mean of the scale, which gave sufficient scope for the up- and the downregulation of negative emotions. We also found that postexperiment valence ratings for the sports film clips were more positive than in the initial behavioral experiment. This might be explained by the repeated exposure to these stimuli during the fMRI study that would have caused adaptation

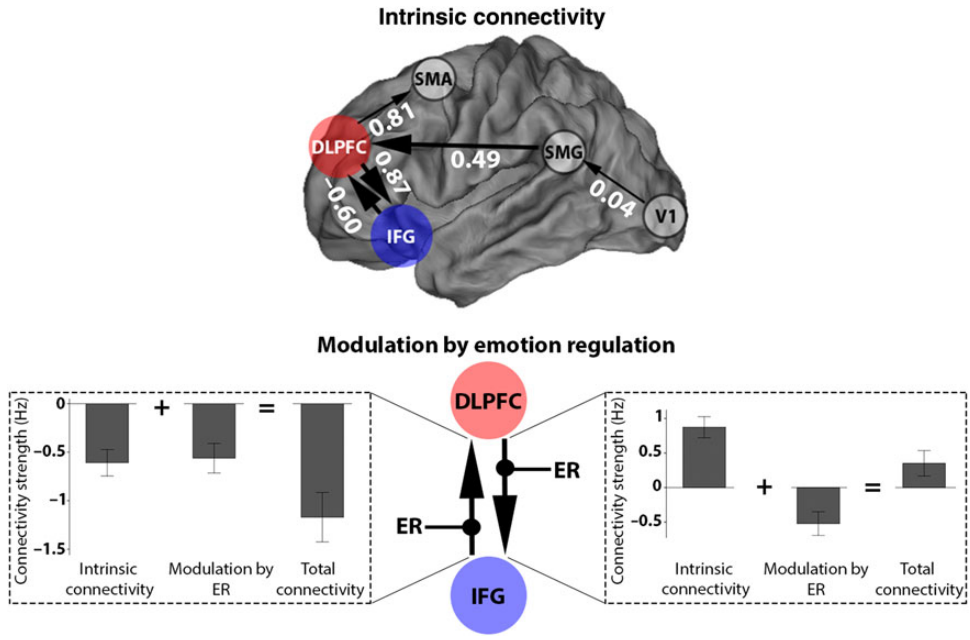

Figure 8. Graphic illustration of model 6, which was found to have the best fit (Table 3). Driving input (not shown graphically) enters through V1. The values under the arrows represent connectivity strength in Hz (only significant results are depicted). (*A*) Intrinsic connectivity (black arrows). (*B*) Modulation of connectivity by emotion regulation (ER). BMS results and SD are shown.

effects, in particular considering that active emotion regulation took place for an hour. Building up familiarity with these stimuli would most likely have reduced the threatening aspect of these scenes over time, at least to some extent. Note, however, that the postexperimental valence ratings did not reach ceiling (i.e., were below the highest rating of 9), indicating that, during the entire fMRI experiment, there was sufficient scope for emotion regulation in both directions. Further, the observed shift was in the positive direction (compared with the behavioral study). This makes it likely that the neutral baseline (*Look-Sports* condition) slightly shifted toward eliciting more positive emotions over the course of the experiment. This natural reduction of negative emotions due to repeated exposure might in turn be one reason for why the *additional* effect for actively decreasing one's negative emotions were relatively smaller compared with increasing negative emotions. With stimuli becoming slightly more positive over time, the scope for regulation toward the positive direction becomes smaller and the scope for regulation toward the negative direction becomes larger. This shift appears to be unavoidable in an emotion regulation experiment using repeated stimulation, but it most likely did not impact on our results: It has been demonstrated before that up- and downregulation of emotions in response to positive and negative pictures activate highly similar and overlapping brain regions (Kim and Hamann 2007; Ochsner et al. 2012).

The model family comparison and random-effects BMS results provide evidence that the DLPFC plays a central role in emotion regulation processes as significant connectivity was observed between the DLPFC, IFG, SMA, and SMG. We found bidirectional intrinsic changes of connection strength between the DLPFC and IFG, with a strong excitatory effect of the DLPFC on the IFG (reflected in positive intrinsic connectivity parameters) and a strong inhibitory effect of the IFG on the DLPFC (reflected in negative intrinsic connectivity parameters). These results are plausible as direct connections have been demonstrated between the DLPFC and IFG in nonhuman primates (Barbas and Pandya 1989, 1991; Barbas 2000, 2009; Yeterian et al. 2012). A recent fMRI resting-state study corroborated these findings in humans (Goulas et al. 2012). Importantly, reappraisal attenuated the effective connectivity between the DLPFC and IFG in our study. The endogenous coupling from the DLPFC to the IFG was reduced during emotion regulation, although it is important to note that the total connectivity still remained positive. In contrast, the endogenous coupling from the IFG to the DLPFC became even more negative during reappraisal. This means that reappraisal may be achieved by a combination of excitatory (DLPFC to IFG) and inhibitory (IFG to DLPFC) effects on connection strength between lateral prefrontal regions.

Our findings align well with the process-specific model of the PFC and the proposed dorsal–ventral axis of organization (Petrides 1994, 1996, 2005; Petrides and Pandya 2002). According to this model, the IFG represents the primary interface of the PFC, with posterior sensory association cortices, and is important for first-order executive processes including the selection, retrieval, and strategic regulation of information in posterior regions. In addition, this model proposes that the DLPFC orchestrates superordinate higher control processes including the monitoring and manipulation of representations in working memory related to basic first-order executive activities of the IFG.

Our results suggest that during the emotion regulation process, first the DLPFC together with the SMG might be involved in directing attention to the emotional stimulus, and the DLPFC might then play a role in actively maintaining the content and the goals of one's reappraisal in working memory (Ochsner and Gross 2005, 2008; Phillips et al. 2008; Ochsner et al. 2012; Buhle et al. 2014). In support of this interpretation, both regions have been implicated in verbal working memory and selective attention (Miller 2000; Miller and Cohen 2001; Curtis and D'Esposito 2003; Wager and Smith 2003; Wager et al. 2004; Gazzaley and D'Esposito 2007). During emotion regulation, top-down regulatory processes might then facilitate the

selection of goal-appropriate reappraisals and further the active reinterpretation of the meaning, consequence, and personal significance of the emotion-inducing stimulus (Ochsner and Gross 2005; Ochsner et al. 2012; Buhle et al. 2014), represented in positive connectivity between the DLPFC and the IFG. This step could be achieved by using verbal labeling, categorizing, or separation of affect (Burns and Engdahl 1998; Ochsner and Gross 2008), cognitive functions that are likely to involve the IFG (Thompson-Schill et al. 1997, 2005; Ochsner, Knierim et al. 2004; Badre and Wagner 2007; Binder and Desai 2011). Importantly, when multiple representations of stimulus-appropriate reinterpretations are activated, a selection is needed to resolve competition among the various representations to drive goal-directed behavior (Fletcher et al. 2000; Moss et al. 2005; Badre and Wagner 2007). This selection process has been associated with IFG activity (Badre et al. 2005; Gold et al. 2006; Badre and Wagner 2007). The final selection of a stimulus-appropriate reappraisal could then trigger the inhibition of the DLPFC because this region is no longer required to support the monitoring and manipulation of representations in working memory for response modulation (Jonides et al. 1998; Egner 2011). This would explain why the inhibitory effect of the IFG on the DLPFC becomes stronger during emotion regulation, that is, shows an increase in connectivity into the negative direction. In contrast to a recently introduced heuristic model of neural processing of emotion regulation (Kohn et al. 2014), which proposes that the IFG is not involved in emotion regulatory processes per se but rather in emotion evaluation and perception, our results strongly point toward a key role for the IFG in emotion regulation.

Of note, we found no significant changes in activation in the amygdala in response to emotion regulation and therefore did not include the amygdala as a seed region into our DCM analysis. Our result is in accordance with all those neuroimaging studies that have examined effects of reappraisal implementing both reappraisal goals, Increase and Decrease, in the same study by contrasting emotion regulation in general with a control condition (Urry et al. 2006; Eippert et al. 2007; Kim and Hamann 2007; Opitz et al. 2012). This finding is also in line with 2 recent meta-analyses (including mostly studies with decreasing as reappraisal goal) reporting no amygdala activity when contrasting general reappraisal versus baseline (Buhle et al. 2014; Kohn et al. 2014). Most likely, increasing and decreasing emotional responses are 2 opposing reappraisal goals, which would lead to modulation of activation into opposite directions in regions involved in emotion processing, such as the amygdala. Thus, activation changes would cancel each other out across conditions, with the net effect that the amygdala appears not to be responsive. Previous studies implementing both reappraisal goals and directly contrasting the up- and downregulation of emotion on a whole-brain level seem to support this idea and do not report changes in amygdala activity (Urry et al. 2006; Kim and Hamann 2007; Opitz et al. 2012). Only one study demonstrated differences in amygdala activity in response to both reappraisal goals, however, using a masking analysis instead of a whole-brain analysis (Eippert et al. 2007). The results of our ROI analysis of the amygdala support this hypothesis partially as there was a tendency of a greater change in BOLD signal in response to Increase compared with Decrease, however not reaching statistical significance. Another potential explanation for the lack of a change in amygdala activity might be the use and content of film clips. Other studies using film clips as stimulus material also did not find a modulation of amygdala activity in the whole-brain analyses (Beauregard et al. 2001; Lévesque et al. 2003; Goldin et al. 2008; Shimamura et al. 2013). It is also important to note that those studies using different stimulus types such as videos (Beauregard et al. 2001; Lévesque et al. 2003; Goldin et al. 2008; Shimamura et al. 2013), positive photos (Hollmann et al. 2012), task errors (Ichikawa et al. 2011), memories (Kross et al. 2009), scripts (Lang et al. 2012), and reward (Staudinger et al. 2009, 2011) did not report changes in amygdala responses during reappraisal (Ochsner et al. 2012). This indicates that the amygdala might be more responsive to emotional pictures in contrast to other emotional material during reappraisal. Our film clips were all very similar in content depicting a skydiver or BASE jumper jumping off a cliff or out of an airplane. Thus, the lack of amygdala activity in response to those film clips could likely result from learning related to experimental task and stimuli, for example, habituation (Breiter et al. 1996; Phillips et al. 2001; Wright et al. 2001; Fischer et al. 2003; Swartz et al. 2013). It has consistently been demonstrated that amygdala activity decreases upon repeated presentation of negative stimuli (Breiter et al. 1996; Fischer et al. 2000, 2003; Wright et al. 2001; Phan et al. 2003; Ishai et al. 2004; Britton et al. 2008), which may reflect the diminishment of an initial orienting response to salient affective stimuli (Holland and Gallagher 1999; Fischer et al. 2003; Britton et al. 2008). However, our findings demonstrate that habituation effects seem to be a rather unlikely explanation for the absence of significant effects in the amygdala. Another reason could be that the stimuli were not rated entirely negative on valence, which might also result in less involvement of the amygdala. We acknowledge that our model therefore does not account for emotion regulation effects reflected in differential amygdala responses. This drawback, however, was deliberately tolerated here to set necessary limits for the complexity of the model space.

Note that most of our conclusions are based on DCM analyses, which are built on a priori hypotheses about brain regions used to define the model space, and thus limited with respect to the predefined regions. These regions, however, were derived from our unbiased whole-brain BOLD analysis and were all well-established reappraisal-related regions according to state-of-the-art models of emotion regulation (Ochsner and Gross 2005; Phillips et al. 2008; Ochsner et al. 2012; Buhle et al. 2014), providing strong support for our model. Future studies will need to validate and extend our model by considering different reappraisal scenarios that might involve different strategies (e.g., distancing) and possibly different, more specifically associated brain regions. Our results further do not differentiate between the up- and downregulation of emotion as the primary focus of the present study was to investigate the effective connectivity between prefrontal regions independently of the goal-specificity of the reappraisal strategy, but also to reduce complexity and allow for meaningful inference.

In summary, the results of our DCM analyses support the hypothesis that emotion regulation is mediated by bidirectional changes of connection strength between the IFG and DLPFC. Our model of effective connectivity indicates a feedback mechanism between the DLPFC and IFG during emotion regulation, in which the selection process of a reappraisal, most likely involving the IFG, modulates the connectivity between IFG and DLPFC. Thus, our findings provide strong evidence for the neural correlates of the reappraisal selection process, a key processing stage in the deliberate regulation of human emotions.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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References

Abler B. 2009. Emotion Regulation Questionnaire—Eine deutschsprachige Fassung des ERQ von Gross und John. Diagnostica. 55:144–152.

Aron AR, Robbins TW, Poldrack RA. 2004. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 8:170–177.

Bach M, Bach D, De Zwaan M, Serim M, Bohmer F. 1996. Validierung der deutschen Version der 20-Item Toronto Alxithymie Skala bei Normalpersonen und psychiatrischen Patienten. Psychother Psychosom Medizinische Psychol. 46:23–28.

Badre D, Poldrack RA, Paré-Blagoev EJ, Insler RZ, Wagner AD. 2005. Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. Neuron. 47:907–918.

Badre D, Wagner AD. 2007. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia. 45:2883–2901.

Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL. 2007. Amygdala-frontal connectivity during emotion regulation. Soc Cogn Affect Neurosci. 2:303–312.

Barbas H. 2000. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull. 52:319–330.

Barbas H. 2009. Prefrontal cortex: structure and anatomy. In: Squire LR, editor. Encyclopedia of neuroscience. Vol. 7. Oxford: Academic Press. pp. 909–918.

Barbas H, Pandya DN. 1989. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol. 286:353–375.

Barbas H, Pandya N. 1991. Patterns of connections of the prefrontal cortex in the rhesus monkey associated with cortical architecture. In: Levin H, Eisenberg H, Benton A, editors. In: Frontal lobe function and dysfunction. New York: Oxford Univ. Press. p. 35–58.

Beauducel A, Strobel A, Brocke B. 2003. Psychometrische Eigenschaften und Normen einer deutschsprachigen Fassung der Sensation Seeking-Skalen, Form V. Diagnostica. 49: 61–72.

Beauregard M, Lévesque J, Bourgouin P. 2001. Neural correlates of conscious self-regulation of emotion. J Neurosci. 21:1–6.

Benedek M, Kaernbach C. 2010b. A continuous measure of phasic electrodermal activity. J Neurosci Methods. 190:80–91.

Benedek M, Kaernbach C. 2010a. Decomposition of skin conductance data by means of nonnegative deconvolution. Psychophysiology. 47:647–658.

Binder JR, Desai RH. 2011. The neurobiology of semantic memory. Trends Cogn Sci. 15:527–536.

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE, Rosen BR. 1996. Response and habituation of the human amygdala during visual processing of facial expression. Neuron. 17:875–887.

Brett M, Anton J, Valabregue R, Poline J. 2002. Region of interest analysis using an SPM toolbox. NeuroImage. 16(2): Abstract 497.

Britton JC, Shin LM, Barrett LF, Rauch SL, Wright CI. 2008. Amygdala and fusiform gyrus temporal dynamics: responses to negative facial expressions. BMC Neurosci. 9:44.

Brymer GE. 2005. Extreme dude! A phenomenological perspective on the extreme sport experience. [Doctoral Dissertation]. University of Wollongong, Retrieved 24 October 2007 from http://www.library.uow.edu.au/adtNWU/uploads/approved/adt NWU20060508.145406/public/02Whole.pdf.

Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, Weber J, Ochsner KN. 2014. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb Cortex. 24(11):2981–2990.

Burns TR, Engdahl E. 1998. The social construction of consciousness. Part 2: individual selves, self-awareness, and reflectivity. J Conscious Stud. 2:166–184.

Catani M, Jones DK, Ffytche DH. 2005. Perisylvian language networks of the human brain. Ann Neurol. 57:8–16.

Curtis CE, D'Esposito M. 2003. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci. 7(9):415–423.

Delgado MR, Nearing KI, Ledoux JE, Phelps Ea. 2008. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron. 59:829–838.

Eftekhari A, Zoellner LA, Vigil SA. 2009. Patterns of emotion regulation and psychopathology. Anxiety Stress Coping. 22:571–586.

Egner T. 2011. Right ventrolateral prefrontal cortex mediates individual differences in conflict-driven cognitive control. J Cogn Neurosci. 23:3903–3913.

Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S. 2007. Regulation of emotional responses elicited by threat-related stimuli. Hum Brain Mapp. 28:409–423.

Fischer H, Furmark T, Wik G, Fredrikson M. 2000. Brain representation of habituation to repeated complex visual stimulation studied with PET. Neuroreport. 11(1):123–126.

Fischer H, Wright CI, Whalen PJ, McInerney SC, Shin LM, Rauch SL. 2003. Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. Brain Res Bull. 59:387–392.

Fletcher PC, Shallice T, Dolan RJ. 2000. "Sculpting the response space"—an account of left prefrontal activation at encoding. Neuroimage. 12:404–417.

Frey S, Campbell JSW, Pike GB, Petrides M. 2008. Dissociating the human language pathways with high angular resolution diffusion fiber tractography. J Neurosci. 28:11435–11444.

Friston KJ. 1994. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp. 2:56–78.

Friston KJ, Harrison L, Penny W. 2003. Dynamic causal modelling. Neuroimage. 19:1273–1302.

Gazzaley A, D'Esposito M. 2007. Unifying prefrontal cortex function: Executive control, neural networks and top-down modulation. In: Miller B, Cummings J, editors. The human fontal lobes. New York: Guildford Publications.

Geva S, Correia M, Warburton Ea. 2011. Diffusion tensor imaging in the study of language and aphasia. Aphasiology. 25: 543–558.

Gold BT, Balota DA, Jones SJ, Powell DK, Smith CD, Andersen AH. 2006. Dissociation of automatic and strategic lexical-semantics: functional magnetic resonance imaging evidence for differing roles of multiple frontotemporal regions. J Neurosci. 26:6523–6532.

Goldin PR, Mcrae K, Ramel W, Gross JJ. 2008. The neural bases of emotion regulation : reappraisal and suppression of negative emotion. Biol Psychiatry. 63:577–586.

Goodale MA, Milner AD. 1992. Separate visual pathways for perception and action. Trends Neurosci. 15:20–25.
Goulas A, Uylings HB, Stiers P. 2012. Unravelling the intrinsic functional organization of the human lateral frontal cortex: a parcellation scheme based on resting state fMRI. J Neurosci. 32(30):10238–10252.
Grèzes J, Decety J. 2001. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum Brain Mapp. 12:1–19.
Gross JJ, John OP. 2003. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol. 85:348–362.
Gross JJ, Muñoz RF. 1995. Emotion regulation and mental health. Clin Psychol Sci Pract. 2:151–164.
Gross JJ, Thompson RA. 2007. Emotion regulation: Conceptual foundations. In: Gross JJ, editor. Handbook of emotion regulation. New York: Guilford Press. p. 3–26 .
Hare TA, Camerer CF, Rangel A. 2009. Self-control in decision-making involves modulation of the vmPFC valuation system. Science. 324:646–648.
Holland PC, Gallagher M. 1999. Amygdala circuitry in attentional and representational processes. Trends Cogn Sci. 3(2):65–73.
Hollmann M, Hellrung L, Pleger B, Schlögl H, Kabisch S, Stumvoll M, Villringer A, Horstmann A. 2012. Neural correlates of the volitional regulation of the desire for food. Int J Obes. 36(5):648–655.
Ichikawa N, Siegle GJ, Jones NP, Kamishima K, Thompson WK, Gross JJ, Ohira H. 2011. Feeling bad about screwing up: emotion regulation and action monitoring in the anterior cingulate cortex. Cogn Affect Behav Neurosci. 11(3):354–371.
Ishai A, Pessoa L, Bikle PC, Ungerleider LG. 2004. Repetition suppression of faces is modulated by emotion. Proc Natl Acad Sci USA. 101:9827–9832.
Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J Neurosci. 27:8877–8884.
Jonides J, Smith EE, Marshuetz C, Koeppe RA, Reuter-Lorenz PA. 1998. Inhibition in verbal working memory revealed by brain activation. Proc Natl Acad Sci USA. 95:8410–8413.
Kalisch R. 2009. The functional neuroanatomy of reappraisal: time matters. Neurosci Biobehav Rev. 33:1215–1226.
Kanske P, Heissler J, Schönfelder S, Bongers A, Wessa M. 2011. How to regulate emotion? Neural networks for reappraisal and distraction. Cereb Cortex. 21:1379–1388.
Keller SS, Crow T, Foundas A, Amunts K, Roberts N. 2009. Broca's area: nomenclature, anatomy, typology and asymmetry. Brain Lang. 109:29–48.
Kim SH, Hamann S. 2007. Neural correlates of positive and negative emotion regulation. J Cogn Neurosci. 19:776–798.
Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN. 2010. Prefrontal-striatal pathway underlies cognitive regulation of craving. Proc Natl Acad Sci USA. 107:14811–14816.
Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. 2014. Neural network of cognitive emotion regulation—an ALE meta-analysis and MACM analysis. Neuroimage. 87:345–355.
Kross E, Davidson M, Weber J, Ochsner K. 2009. Coping with emotions past: the neural bases of regulating affect associated with negative autobiographical memories. Biol Psychiatry. 65:361–366.
Lang S, Kotchoubey B, Frick C, Spitzer C, Grabe HJ, Barnow S. 2012. Cognitive reappraisal in trauma-exposed women with borderline personality disorder. Neuroimage. 59:1727–1734.
Laux L, Glanzmann P, Schaffner P, Spielberger CD. 1981. Das State-Trait-Angstinventar (STAI), Weinheim Beltz. Weinheim, Germany: Beltz.
Lévesque J, Eugène F, Joanette Y, Paquette V, Mensour B, Beaudoin G, Leroux J-M, Bourgouin P, Beauregard M. 2003. Neural circuitry underlying voluntary suppression of sadness. Biol Psychiatry. 53:502–510.
Lohmann G, Erfurth K, Müller K, Turner R. 2012. Critical comments on dynamic causal modelling. Neuroimage. 59:2322–2329.
Lu M, Preston JB, Strick PL. 1994. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. J Comp Neurol. 341:375–392.
Luppino G, Matelli M, Camarda R, Rizzolatti G. 1993. Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. J Comp Neurol. 338(1):114–140.
Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 19:1233–1239.
McRae K, Ochsner KN, Mauss IB, Gabrieli JJD, Gross JJ. 2008. Gender differences in emotion regulation: an fMRI study of cognitive reappraisal. Gr Process Intergr Relations. 11:143–162.
Merboldt KD, Fransson P, Bruhn H, Frahm J. 2001. Functional MRI of the human amygdala? Neuroimage. 14:253–257.
Miller EK. 2000. The prefrontal cortex and cognitive control. Nat Rev Neurosci. 1:59–65.
Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 24:167–202.
Morawetz C, Holz P, Lange C, Baudewig J, Weniger G, Irle E, Dechent P. 2008. Improved functional mapping of the human amygdala using a standard functional magnetic resonance imaging sequence with simple modifications. Magn Reson Imaging. 26:45–53.
Morin O, Grèzes J. 2008. What is "mirror" in the premotor cortex? A review. Neurophysiol Clin. 38:189–195.
Moss HE, Abdallah S, Fletcher P, Bright P, Pilgrim L, Acres K, Tyler LK. 2005. Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. Cereb Cortex. 15:1723–1735.
Nachev P, Kennard C, Husain M. 2008. Functional role of the supplementary and pre-supplementary motor areas. Nat Rev Neurosci. 9:856–869.
Ochsner KN, Bunge SA, Gross JJ, Gabrieli JDE. 2002. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 14:1215–1229.
Ochsner KN, Gross JJ. 2005. The cognitive control of emotion. Trends Cogn Sci. 9:242–249.
Ochsner KN, Gross JJ. 2008. Cognitive emotion regulation: insights from social cognitive and affective neuroscience. Curr Dir Psychol Sci. 17:153–158.
Ochsner KN, Gross JJ. 2007. The neural architecture of emotion regulation. In: Gross JJ, editor. Handbook of emotion regulation. New York: Guilford Press. p. 87–109.
Ochsner KN, Knierim K, Ludlow DH, Hanelin J, Ramachandran T, Glover G, Mackey SC. 2004. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. J Cogn Neurosci. 16:1746–1772.
Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ. 2004. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage. 23:483–499.
Ochsner KN, Silvers J, Buhle JT. 2012. Functional imaging studies of emotion regulation: a synthetic review and evolving model

of the cognitive control of emotion. Ann N Y Acad Sci. 1251: E1–24.
Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 9:97–113.
Opitz PC, Rauch LC, Terry DP, Urry HL. 2012. Prefrontal mediation of age differences in cognitive reappraisal. Neurobiol Aging. 33:645–655.
Parker JDA, Taylor GJ, Bagby RM. 2003. The 20-Item Toronto Alexithymia Scale III. Reliability and factorial validity in a community population. J Psychosom Res. 55:269–275.
Parker JDA, Bagby RM, Taylor GJ, Endler NS, Schmitz P. 1993. Factorial validity of the 20-item Toronto Alexithymia Scale. Eur J Pers. 7(4):221–232.
Pedersen DM. 1997. Perceptions of high risk sports. Percept Mot Skills. 85:756–758.
Penny WD, Stephan KE, Daunizeau J, Rosa MJ, Friston KJ, Schofield TM, Leff AP. 2010. Comparing families of dynamic causal models. PLoS Comput Biol. 6:e1000709.
Penny WD, Stephan KE, Mechelli A, Friston KJ. 2004. Comparing dynamic causal models. Neuroimage. 22:1157–1172.
Perani D, Fazio F, Borghese NA, Tettamanti M, Ferrari S, Decety J, Gilardi MC. 2001. Different brain correlates for watching real and virtual hand actions. Neuroimage. 14:749–758.
Petrides M. 1994. Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In: Boller F, Grafman J, editors. Handbook of neuropsychology. Amsterdam: Elsevier Science. p. 59–82.
Petrides M. 2005. Lateral prefrontal cortex: architectonic and functional organization. Philos Trans R Soc Lond B Biol Sci. 360:781–795.
Petrides M. 1996. Specialized systems for the processing of mnemonic information within the primate frontal cortex. Philos Trans R Soc Lond B Biol Sci. 351:1455–1461; discussion 1461–1462.
Petrides M, Pandya DN. 2002. Association pathways of the prefrontal cortex and functional observations. In: Stuss DT, Knight RT, editors. Principles of frontal lobe function. New York: Oxford University Press. p. 31–50.
Petrides M, Pandya DN. 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur J Neurosci. 11:1011–1036.
Phan KL, Liberzon I, Welsh RC, Britton JC, Taylor SF. 2003. Habituation of rostral anterior cingulate cortex to repeated emotionally salient pictures. Neuropsychopharmacology. 28:1344–1350.
Phillips ML, Ladouceur CD, Drevets WC. 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry. 13:829–857.
Phillips ML, Medford N, Young AW, Williams L, Williams SC, Bullmore ET, Gray JA, Brammer MJ. 2001. Time courses of left and right amygdalar responses to fearful facial expressions. Hum Brain Mapp. 12:193–202.
Quirk GJ, Beer JS. 2006. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr Opin Neurobiol. 16:723–727.
Ray RD, Zald DH. 2012. Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. Neurosci Biobehav Rev. 36:479–501.
Shimamura AP, Marian DE, Haskins AL. 2013. Neural correlates of emotional regulation while viewing films. Brain Imaging Behav. 7:77–84.
Sladky R, Friston KJ, Tröstl J, Cunnington R, Moser E, Windischberger C. 2011. Slice-timing effects and their correction in functional MRI. Neuroimage. 58:588–594.
Spielberger CD, Gorsuch RL, Lushene RE. 1970. Manual for the State-Trait Anxiety Inventory. Palo Alto (CA): Consulting Psychologists Press.
Staudinger MR, Erk S, Abler B, Walter H. 2009. Cognitive reappraisal modulates expected value and prediction error encoding in the ventral striatum. Neuroimage. 47:713–721.
Staudinger MR, Erk S, Walter H. 2011. Dorsolateral prefrontal cortex modulates striatal reward encoding during reappraisal of reward anticipation. Cereb Cortex. 21:2578–2588.
Straube T, Preissler S, Lipka J, Hewig J, Mentzel H-J, Miltner WHR. 2010. Neural representation of anxiety and personality during exposure to anxiety-provoking and neutral scenes from scary movies. Hum Brain Mapp. 31:36–47.
Swartz JR, Wiggins JL, Carrasco M, Lord C, Monk CS. 2013. Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. J Am Acad Child Adolesc Psychiatry. 52:84–93.
Thompson-Schill SL, Bedny M, Goldberg RF. 2005. The frontal lobes and the regulation of mental activity. Curr Opin Neurobiol. 15:219–224.
Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. 1997. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci USA. 94:14792–14797.
Ungerleider LG, Haxby JV. 1994. "What" and "where" in the human brain. Curr Opin Neurobiol. 4:157–165.
Ungerleider LG, Mishkin M. 1982. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. Analysis of visual behavior. Cambridge (MA): MIT Press. p. 549–586.
Urry HL, Reekum V, Marije C, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, Jackson CA, Frye CJ, Greischar LL, et al. 2006. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J Neurosci. 26:4415–4425.
Urry HL, van Reekum CM, Johnstone T, Davidson RJ. 2009. Individual differences in some (but not all) medial prefrontal regions reflect cognitive demand while regulating unpleasant emotion. Neuroimage. 47:852–863.
Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. 2008. Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron. 59:1037–1050.
Wager TD, Jonides J, Reading S. 2004. Neuroimaging studies of shifting attention: a meta-analysis. Neuroimage. 22:1679–1693.
Wager TD, Smith EE. 2003. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. 3:255–274.
Wright CI, Fischer H, Whalen PJ, McInerney SC, Shin LM, Rauch SL. 2001. Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. Neuroreport. 12:379–383.
Yeterian EH, Pandya DN, Tomaiuolo F, Petrides M. 2012. The cortical connectivity of the prefrontal cortex in the monkey brain. Cortex. 48:58–81.