NeuroImage 58 (2011) 275–285

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Fear is only as deep as the mind allows
A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect

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ARTICLE INFO

Article history:
Received 16 December 2010
Revised 4 May 2011
Accepted 25 May 2011
Available online 6 June 2011

Keywords:
GingerALE
Cognitive reappraisal
Placebo effect
Extinction recall
fMRI
PET

ABSTRACT

Humans have the ability to control negative affect and perceived fear. Nevertheless, it is still unclear whether this affect regulation capacity relies on a common neural mechanism in different experimental domains. Here, we sought to identify commonalities in regulatory brain activation in the domains of fear extinction, placebo, and cognitive emotion regulation. Using coordinate-based activation-likelihood estimation meta-analysis we intended to elucidate concordant hyperactivations and the associated deactivations in the three experimental domains, when human subjects successfully diminished negative affect. Our data show that only one region in the ventromedial prefrontal cortex (VMPFC) controlled negative affective responses and reduced the degree of subjectively perceived unpleasantness independent of the experimental domain. This down-regulation of negative affect was further accompanied by a concordant reduction of activation in the left amygdala. Finally, the soothing effect of placebo treatments and cognitive reappraisal strategies, but not extinction retrieval, was specifically accompanied by a coherent hyperactivation in the anterior cingulate and the insular cortex. Collectively, our data strongly imply that the human VMPFC may represent a domain-general controller of perceived fear and aversiveness that modulates negative affective responses in phylogenetically older structures of the emotion processing system. In addition, higher-level regulation strategies may further engage complementary neural resources to effectively deal with the emotion-eliciting events.

Introduction

During the last decade there have been a growing number of neuroimaging studies that dealt with the neural underpinnings of the regulation of negative affect in general and of experienced fear in particular. Using different experimental approaches researchers have thereby tried to reveal the neural mechanisms through which humans can modulate the perception of threatening and unpleasant events. It has been demonstrated that the degree of negative affect elicited by aversive stimuli and their predictors can be significantly reduced by misleading advance information (like in placebo experiments; e.g., de Jong et al., 1996; Diekhof et al., 2011; Wager et al., 2004b), by prior experience of significant changes in the original stimulus–outcome associations (like in fear extinction experiments; e.g., Kalisch et al., 2006a), or by a voluntary cognitive reappraisal of these events (like in experiments involving a cognitive down-regulation of negative emotion; e.g., Ochsner et al., 2004). This raises the question of whether these different experimental domains share a common neural mechanism for the control of perceived aversiveness and negative affect.

In fact, from a process-oriented perspective the three experimental domains of fear extinction, placebo control and voluntary cognitive emotion regulation are quite heterogeneous and show only partial overlap in the involved cognitive operations. During fear extinction conditioned fear responses are extinguished following non-reinforced exposure to the feared conditioned stimulus (CS). Thereafter, two memories exist in the brain: the original, weakened association between the CS and the unconditioned aversive stimulus (UCS), and a new CS/no-UCS association, which leads to a decline of conditioned responses like anticipatory anxiety and negative arousal (Myers and Davis, 2007; Quirk et al., 2006). Conversely, a reduction of the subjectively experienced aversiveness of painful or otherwise unpleasant stimuli through placebo interventions (i.e., a sham treatment or a misleading expectation) is commonly achieved through two processes that supposedly act in concert. On the one hand, placebo treatments produce a soothing effect because the recipient expects them to do so. This means that simply by expecting a less aversive stimulus than factually presented, stimulus perception is altered (e.g., pain is reduced), which ultimately changes the associated physiological responses and also reduces the degree of experienced negative affect (Kirsch, 1985). On the other hand, through repeated association

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doi:10.1016/j.neuroimage.2011.05.073

with an US (e.g., the effect of the active drug), objects, places, people, and procedures can become CSs, capable of eliciting an effect, which is similar or related to the real drug effect. Thus the placebo acts as a CS that leads to a placebo effect, which can be understood as a conditioned response (Steward-Williams and Podd, 2004). In that way, placebo interventions can alter the subjective experience of an aversive event through a combination of placebo expectancy and placebo conditioning (e.g., Nitschke et al., 2006; Wager et al., 2004b; Watson et al., 2009). Finally, voluntary cognitive emotion regulation operates on an event that – like in placebo studies – maintains its objective aversiveness (e.g., a photograph of a mutilated dead body). However, through cognitive reappraisal the meaning of the aversive event can be altered which over time significantly changes the associated physiological responses and reduces the degree of subjectively experienced negative affect. Common reappraisal strategies employ emotional detachment, reinterpretation, mental imagery or cognitive reexamination to control negative physiological responses like the degree of experienced fear (see Ochsner and Gross, 2005). The cognitive operations involved in these cognitive regulation strategies are by far more sophisticated than those underlying implicit placebo conditioning or extinction recall, and further need to be voluntary engaged to cope with the aversive event.

In line with the differences between the three experimental domains, neuroimaging studies have identified various brain regions implicated in the down-regulation of negative affective responses. Studies of fear extinction have put forward an important role for the ventromedial prefrontal cortex (VMPFC) and adjacent rostral anterior cingulate cortex (rACC) (Finger et al., 2008; Milad et al., 2007; Soliman et al., 2010) as well as for the hippocampus (Kalisch et al., 2006a; Milad et al., 2007) in extinction recall and for the basolateral nucleus of the amygdala in the early phases of extinction learning (Quirk and Beer, 2006; Quirk et al., 2006). Together these regions may control physiological fear responses in down-stream areas like the central nucleus of the amygdala (Milad et al., 2006). Moreover, placebo effects were found to be mediated by several prefrontal regions that reduced the threatening potential and the perceived aversiveness of the painful or otherwise aversive stimuli. Among these were the VMPFC with the adjacent rACC and the subgenual ACC (sgACC) (e.g., Bingel et al., 2006; Eippert et al., 2009; Diekhof et al., 2011; Petrovic et al., 2005; Sarinopoulos et al., 2006), the lateral orbitofrontal cortex (OFC) (e.g., Diekhof et al., 2011; Sarinopoulos et al., 2006; Wager et al., 2004b), and parts of the dorsolateral prefrontal cortex (e.g., Wager et al., 2004b). Increased activation in these brain regions was found to accompany reduced activation in the amygdala and sensory cortices (e.g., Petrovic et al., 2005; Sarinopoulos et al., 2006), which significantly changed the evaluation of the events. Other studies, which particularly tested placebo-induced responses in neurotransmission, found increased opioidergic and dopaminergic transmission in the same control regions during the experience of placebo analgesia (e.g., Scott et al., 2008; Zubieta et al., 2005). Finally, studies in the domain of cognitive emotion regulation put forward an important role for higher-order brain regions, mainly located in the dorsolateral and dorsomedial prefrontal cortex as well as in the lateral OFC (see Ochsner and Gross, 2005 for review). Increased activation in these prefrontal regions was accompanied by a significant reduction of the perceived aversiveness of the presented photographs and an (indirect) modulation of negative affective responses in the amygdala and associated brain regions (e.g., Banks et al., 2007; Delgado et al., 2008). A fraction of these affect regulation studies also found evidence for an involvement of the VMPFC in the voluntary regulation of negative affect (e.g., Delgado et al., 2008; Urry et al., 2006), although less consistently than in the other two experimental domains. Collectively, these diverse findings leave open the question whether there is a central regulation system that controls negative affective responses in the human brain.

In view of the heterogeneity of the neuroimaging findings it is interesting to investigate whether a common neural mechanism underlies the human ability to alter the subjective perception of aversive stimuli regardless of the type of regulation strategy employed. To identify those regions in the human brain that are consistently implicated in the control of negative affective responses independent of paradigm-specific cognitive operations and sensory modality (most extinction and placebo studies used painful stimuli, while reappraisal studies predominantly presented aversive pictures to induce negative affective responses; see Tables A1–3), we performed a coordinate-based quantitative meta-analysis. Through an integration of the results of the entirety of relevant neuroimaging studies, coordinate-based quantitative meta-analysis offers a powerful tool to assess convergence of findings from different experimental domains (Eickhoff et al., 2009; Laird et al., 2005a; Turkeltaub et al., 2002). In that way, it further overcomes the drawbacks of study-specific characteristics like differences in experimental design, stimulus modality, data analysis technique or imprecise use of anatomical labels, which complicate the generalizability of the results from individual studies (Caspers et al., 2010). Our hypothesis was that brain regions, which are activated irrespective of the above described differences between the experimental domains of fear extinction, placebo control and cognitive emotion regulation, can be regarded as belonging to a universal affect regulatory brain system. The identification of the common neural substrate of diminishing negative affect is not only important for a procedural understanding of affect regulation, but also holds further implications for our understanding of how mental processes may drive physiological responses in general and how they can bias sensory perception.

Material and methods

We performed a coordinate-based quantitative meta-analysis using the activation likelihood estimation (ALE) method (Eickhoff et al., 2009; Laird et al., 2005a; Turkeltaub et al., 2002 available at http://brainmap.org/ale/index.html). This analysis assessed the voxelwise correspondence of neuroimaging results from three types of affect regulation experiments (i.e., (1.) fear extinction, (2.) placebo control, and (3.) cognitive emotion regulation). In particular, we wanted to examine the functional role of higher-order brain regions in the reduction of perceived aversiveness and of the accompanying negative affective responses by assessing the spatial concordance and regional overlap of activation under different experimental manipulations.

Pubmed search criteria

We pursued a systematic Pubmed search for the search terms (1.) “fear extinction” or “extinction learning”, (2.) “emotion regulation” or “reappraisal”, and (3.) “placebo effect”. These terms were each combined (“AND”) with “fMRI” or “PET” to identify relevant functional neuroimaging studies. The reference lists of the identified articles were further used in a snowball search to identify additional relevant research papers. We thereby restricted our search to relevant research articles published within the last decade (i.e., the publication date lay between January 2000 and January 2011). Studies were included if they reported functional brain imaging results from the population of healthy adult subjects. This means that neuroimaging studies dealing with pediatric cases, adolescent cases or with patients only as well as data from pharmacological studies were not included in the data base. In addition, we also did not include results from structural MRI studies and excluded functional MRI studies that did not report coordinates. Of the relevant articles, coordinates were included if they reflected hyperactivations during the down-regulation of negative affect during either the expectancy or perception of an aversive or fear-eliciting stimulus (e.g., a painful shock or a photograph showing a picture of a mutilated body) in comparison to activation elicited by the same event perceived without regulation (e.g., the contrast of “regulate fear response versus attend fear-eliciting stimulus”; see Tables A1–A3 for the relevant contrasts in individual studies that were included in the meta-analyses). If this contrast was not available we used the comparison against an

affectively neutral baseline (e.g., the comparison of "extinction versus control"). If both comparisons were available coordinates from the higher-order contrast (i.e., the comparison of "fear reduction versus fear") were preferred. Further, in case a study also reported contrasts that tested for complementary aspects of affect regulation (e.g., Milad et al., 2007, who reported data for both the contrasts of "early extinction" and "extinction recall", see Table A1) or presented additional results from brain–behavior correlations (e.g., the correlation of subjective reports of decreases in negative affect and activation in the contrast "reappraise fear-eliciting event versus look"; see McRae et al., 2009), then the respective coordinates were also included in the meta-analysis.

Further, the domain of "placebo control" was not only restricted to the modality of pain. Studies also fell in this experimental domain, if a misleading expectancy of reduced unpleasantness successfully reduced the subjectively experienced aversiveness and associated negative affective responses elicited by the factually identical stimuli (i.e., a "quasi placebo effect" induced by a "quasi placebo expectancy"). This criterion applied to three studies, which presented highly aversive pictures (Petrovic et al., 2005), a bitter taste (Sarinopoulos et al., 2006), or fearful facial expressions (Diekhof et al., 2011) under different expectancy manipulations.

In the domain of "cognitive emotion regulation" we restricted the database to studies that assessed the voluntary down-regulation of perceived fear through cognitive reappraisal or related typically human cognitive regulation strategies that comprised a reinterpretation of or a distancing from the experienced aversive, fear-eliciting events. Studies, in which regulation was restricted to a voluntary suppression of negative affect, were not included. This was done, because affect suppression typically leads to little or no change in the ongoing experience of the aversive event (Gross, 2002), and thus less effectively reduces negative physiological responses in comparison to other high-level cognitive strategies (Goldin et al., 2007). Further, we also did not include neuroimaging studies that assessed forms of the interaction between cognition and emotion that did not comprise a "real" regulatory component that led to a reinterpretation of the meaning of the sensory event. This means that studies, in which subjects performed attentionally demanding cognitive tasks (e.g. a high-load working memory task) that simply reduced attentional resources for the processing of emotion-eliciting distracters and thus attenuated negative affective responses (e.g. Kellermann et al., 2011), were not included.

Finally, all identified articles were also screened for coordinates from the reverse contrasts. This reexamination was intended to reveal those brain regions that were consistently down-regulated during diminished negative affect independent of experimental domain.

ALE meta-analysis of hyperactivations mediating the reduction of perceived aversiveness and negative affect

ALE maps were created according to the procedure described by Turkeltaub et al. (2002) and Laird et al. (2005a), using the algorithm revised by Eickhoff et al. (2009), which has been implemented in GingerALE. The revised algorithm assesses above-chance clustering between experiments and is used to model the spatial uncertainty of each coordinate by using an estimation of the intersubject and interlaboratory variability. It includes a weighting of each study by the number of included subjects. The identified coordinates can then be modeled with a three-dimensional Gaussian distribution and the concordance across experiments can be quantitatively assessed. By calculating the above-chance clustering between experiments the meta-analytic results can be generalized to the entire population of studies analyzed (i.e., random-effects inference; Eickhoff et al., 2009).

ALE was performed in MNI reference space using GingerALE version 2.0.4. Coordinates originally published in Talairach space were converted to MNI reference space using the Lancaster transformation (tal2icbm; Lancaster et al., 2007). ALE maps were thresholded at a false discovery rate (FDR) of $p<0.05$, corrected (Laird et al., 2005b), with a minimal clustersize of 200 mm^3. Images were displayed on the Colin T1-template (http://brainmap.org/ale/index.html) in Mango (multi-image analysis GUI; Research Imaging Center San Antonio; http://ric.uthscsa.edu/mango/).

Meta-analyses were performed for each of the domains independently. In order to examine the regional overlap of ALE maps from different experimental domains, formal two-way and three-way conjunction analyses were performed by multiplying binarized versions of the thresholded ALE maps with imcalc as implemented in SPM5 (i.e., a test against the conjunction null at $p<0.05$, FDR-corrected). Additionally, we also performed a meta-analysis of the main effect of affect regulation that included coordinates from all studies independent of experimental domain. This meta-analysis comprised 382 coordinates from 49 studies.

Since we also wanted to rule out potential gender effects as driving source for the meta-analytic results in the cognitive emotion regulation experiments (10 of these studies assessed only female subjects), a confirmatory meta-analysis was performed that excluded all studies that were restricted to one gender. This meta-analysis consisted of 15 studies yielding a total of 107 foci.

Finally, we performed additional meta-analyses on coordinates from the reverse contrast that explored the pattern of concordant deactivations during affect regulation in the three experimental domains. Several previous animal and human studies found evidence for a reciprocal relationship between brain regions involved in regulatory processes (e.g., VMPFC, lateral PFC) and those representing the degree of subjectively experienced negative affect (e.g., amygdala, insula; e.g. Delgado et al., 2008). Finding a convergent hyperactivation of the VMPFC in the three experimental domains raised the question whether the domain-independent activation of this brain region was also accompanied by a concordant down-regulation in any of the brain regions mediating subjectively perceived aversiveness in general and fear in particular. Of the 49 studies in our database, 31 studies (i.e., 5 fear extinction studies, 10 placebo studies, and 16 cognitive reappraisal studies) reported hypoactivations during affect regulation. These studies were entered in a meta-analysis to assess the main effect of the down-regulation of negative affective responses. In addition, we also performed three independent meta-analysis for each of the three experimental domains. (Please note that the five fear extinction studies yielded only 6 relevant coordinates. This makes the meta-analytic result less reliable than those from the other two domains, although we identified a significant cluster in the left amygdala.) We also performed a formal conjunction analyses with imcalc (i.e., a test against the conjunction null at $p<0.05$, FDR-corrected) to examine the regional overlap between ALE maps from different domains.

Results

The Pubmed search and subsequent application of the inclusion criteria yielded a total of 49 relevant articles published within the last decade. Ten of these articles assessed hyperactivations underlying the process of fear extinction yielding 55 foci inside the brain mask used by GingerALE 2.0.4 (see Table A1). Another 14 studies assessed the neural mechanisms mediating placebo effects. These studies yielded 122 coordinates within the borders of the brain mask (see Table A2). Finally, 25 studies dealt with the neural (control) mechanisms underlying emotion regulation through cognitive reappraisal producing 204 foci within the brain mask (see Table A3).

Coordinates from these studies were entered into three separate ALE meta-analyses to test for regional concordance within each of the experimental domains. These analyses revealed several concordant regions of activation, most of which appeared to show a domain-specific distribution. The meta-analysis of coordinates from the fear extinction experiments revealed one concordant cluster in the VMPFC (Fig. 1) as well as two additional clusters located in the subgenual anterior cingulate cortex (sgACC) and in the ACC extending into

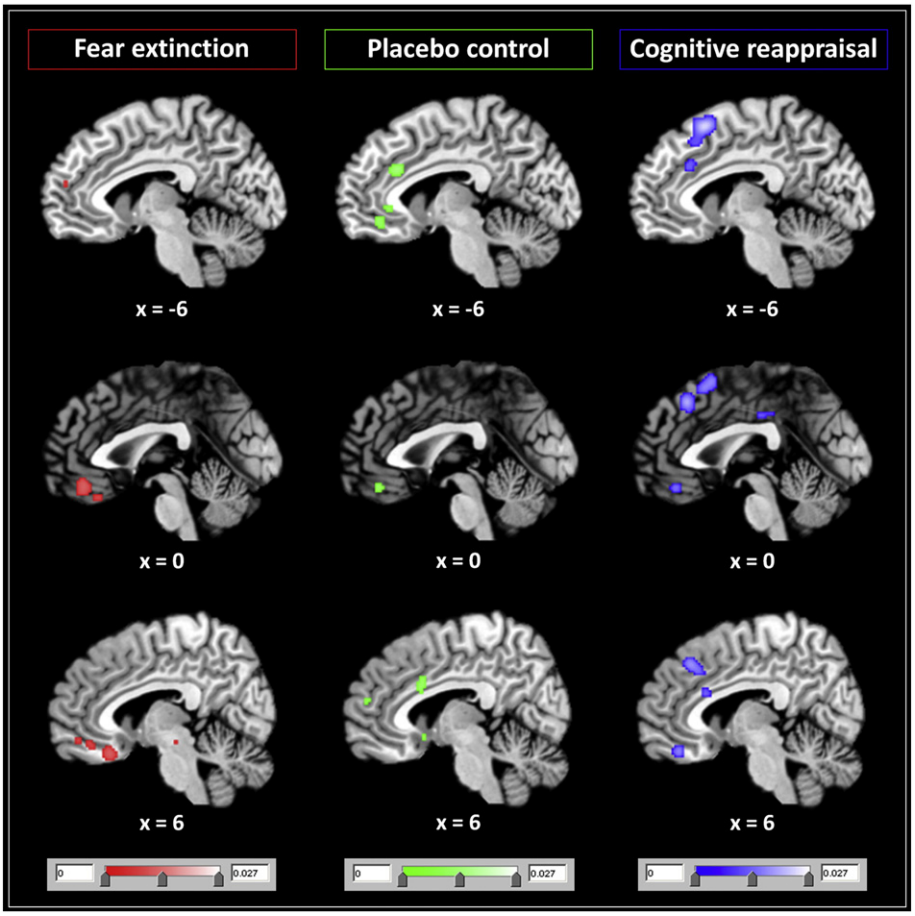

Fig. 1. Results of the ALE meta-analyses of studies reporting hyperactivations during diminishing negative affect in the three experimental domains (fear extinction, placebo control, and emotion regulation). Meta-analytic maps are displayed on axial slices of the VMPFC on the Colin T1-template in MNI reference space. Scales display ALE-values within significant clusters.

adjacent medial PFC (Table 1). Moreover, the ALE meta-analysis of experiments assessing the representation of placebo control in the human brain identified a similar cluster in the VMPFC (Fig. 1). Apart from that, we also found that eight additional brain regions of concordance that were located in the right frontomarginal sulcus, in the right inferior frontal junction (IFJ), in the left and right ACC extending into midcingulate cortex, in the right inferior frontal gyrus (IFG) and adjacent anterior insular cortex, in the left anterior IFG and in the right superior frontal sulcus (Table 2; see also Fig. A1). Finally, the ALE meta-analysis of cognitive emotion regulation experiments also revealed a region of convergence in the VMPFC (Fig. 1). Above that, this analysis identified 15 additional clusters located in the dorsomedial PFC and adjacent ACC, in the middle frontal gyrus (MFG) and the adjoining inferior frontal sulcus, in the inferior frontal cortex, in the intraparietal cortex with adjacent inferior parietal lobule (IPL), in the left inferior temporal sulcus, in the anterior insular cortex, in the left middle temporal cortex, in the right frontomarginal sulcus, and in the right inferior and superior frontal gyri (Table 3; see also Fig. A1). The confirmatory ALE meta-analysis of emotion regulation studies that assessed both female and male subjects confirmed most of these clusters including the cluster in the VMPFC (Table 4).

As we were particularly interested in the common neural regulator of diminishing negative affect we performed a formal three-way conjunction analysis that tested for significant regional overlap between the three experimental domains. This analysis confirmed the finding of regional concordance in the VMPFC (see Fig. 2), but in none of the other regions identified by the three independent meta-analyses. An additional meta-analysis including the coordinates from all studies located the main effect of affect regulation in the VMPFC, namely in the gyrus rectus of the OFC (MNI-coordinates (x y z): 0 40–18; ALE-value = 0.037; clustersize = 2952 mm^3; see also Fig. A2 for distribution of individual coordinates in the VMPFC).

We also performed three additional exploratory two-way conjunction analyses that tested for significant regional overlap between domain

Table 1
ALE meta-analysis of hyperactivations in studies of fear extinction.

Region	MNI-coordinates	ALE-value	Clustersize (mm^3)	Number of foci inside cluster	Number of studies inside cluster
L/R VMPFC	**2 40 −16**	**0.013**	**856**	**4**	**3**[a]
	6 50 −12	**0.009**			
R sgACC/posterior VMPFC	8 26 −22	0.012	600	3	2
R ACC/medial PFC	12 36 22	0.016	560	2	1

This meta-analysis contained coordinates from 10 studies including 178 subjects with a total of 55 foci within the mask ($p<0.05$, corrected; clustersize>200 mm^3). Meta-analytic clusters that are located in the VMPFC are highlighted in bold.
[a] Kalisch et al. (2006a), Milad et al. (2007), Schiller et al. (2008).

Table 2
ALE meta-analysis of hyperactivations in studies of placebo control.

Region	MNI-coordinates	ALE-value	Clustersize (mm^3)	Number of foci inside cluster	Number studies inside cluster
R frontomarginal sulcus	28 50 −8	0.015	1352	6	5
	30 48 8	0.014			
	30 52 −2	0.013			
R IFJ/middle frontal gyrus	42 6 30	0.017	768	5	3
	36 18 38	0.011			
L/R VMPFC	**−8 40 −12**	**0.013**	**648**	**5**	**3**[a]
	0 40 −18	**0.012**			
	14 36 −12	**0.013**	**224**	**2**	**2**[b]
L ACC	−6 28 26	0.014	392	3	3
R ACC/midcingulate cortex	10 12 32	0.014	576	4	4
R anterior insula/inferior frontal gyrus	46 20 −2	0.015	368	2	1
L anterior inferior frontal gyrus	−40 52 6	0.013	296	3	2
L anterior OFC	−38 52 −18	0.015	272	2	1
R superior frontal sulcus	22 14 38	0.015	240	2	1

This meta-analysis contained coordinates from 14 studies including 271 subjects with a total of 122 foci within the mask ($p<0.05$, corrected; clustersize>200 mm^3).
Meta-analytic clusters that are located in the VMPFC are highlighted in bold.
[a] Bingel et al. (2006), Eippert et al. (2009), Watson et al. (2009).
[b] Eippert et al. (2009), Watson et al. (2009).

pairs (i.e., fear extinction AND placebo, placebo AND reappraisal, and reappraisal AND fear extinction). This was done, because one may also expect commonalities in regional brain activation between two, but not three of the domains that could have arisen from similarities in certain paradigmatic aspects or in the associated cognitive control operations, or simply from sharing the same sensory modality. The conjunctions of "fear extinction AND placebo" and "reappraisal AND fear extinction" did not yield regions of significant overlap outside of the VMPFC. Only when comparing "reappraisal and placebo" we identified two additional clusters that significantly overlapped between the domains. One of these clusters was thereby located in the ACC (BA 32), while the other one was situated in the anterior insula (Fig. 3). An exploratory meta-analysis of the pooled data from the two domains located the main effect of placebo control and cognitive emotion regulation in the left ACC proper (MNI-coordinates (x y z): −6 28 26; ALE-value = 0.026; clustersize = 1192 mm^3) and in the right anterior insula (MNI-coordinates (x y z): 46 18–2; ALE-value = 0.027; clustersize = 3504 mm^3).

Finally, we assessed the regional concordance of coordinates from different studies in the reverse contrast that tested for reductions in activation during affect regulation in the three experimental domains (i.e., the down-regulation of negative affective responses). This was done, because we sought to find out whether the domain-independent activation of the VMPFC was accompanied by a concordant down-regulation in any of the brain regions mediating subjectively perceived aversiveness in general and fear in particular. Thirty-one of the 49 studies reported relevant coordinates from the respective contrast that lay within the GingerALE brain mask. Of these, five studies were from the domain of fear extinction, 10 studies reported reduced activation during placebo interventions, and 15 studies listed coordinates of deactivations observed during the cognitive regulation of negative affect. Three independent coordinate-based meta-analyses revealed one cluster in the left amygdala that could be found in each of the experimental domains (Tables A4–A7; these Tables also contain additional regions that will not be discussed here). A formal three-

Table 3
ALE meta-analysis of hyperactivations in studies of cognitive emotion regulation (reappraisal).

Region	MNI-coordinates	ALE-value	Clustersize (mm^3)	Number of foci inside cluster	Number of studies inside cluster
L/R dorsomedial PFC/ACC	−6 16 58	0.024	5648	21	14
	2 32 44	0.020			
L middle frontal gyrus/inferior frontal sulcus/IFJ	−42 18 44	0.025	2808	12	11
	−42 4 48	0.013			
R middle frontal gyrus/inferior frontal sulcus	40 22 44	0.025	984	4	4
L inferior frontal gyrus/anterior insula	−50 30 −10	0.026	1808	9	8
	−54 22 −2	0.016			
	−52 42 −6	0.012			
R inferior frontal gyrus	50 30 −10	0.030	1248	5	5
L intraparietal cortex	−46 −66 36	0.020	1800	8	6
	−42 −56 38	0.014			
	−38 −60 30	0.012			
R intraparietal cortex	50 −58 42	0.016	352	2	2
L inferior temporal sulcus	−60 −36 −2	0.027	1800	6	5
L anterior insula/frontal operculum	−38 20 −4	0.013	272	2	2
R anterior insula/frontal operculum	46 14 0	0.017	1208	6	4
L/R VMPFC	**6 40 −22**	**0.016**	**624**	**4**	**3**[a]
	0 38 −18	**0.014**			
L middle temporal gyrus	−64 −4 −22	0.015	360	3	3
R frontomarginal sulcus	34 60 8	0.016	352	3	3
R inferior frontal gyrus	60 26 6	0.014	352	1	1
L ACC	−8 28 28	0.014	288	2	2
R superior frontal gyrus	18 24 58	0.013	224	2	2

This meta-analysis contained coordinates from 25 studies including 527 subjects with a total of 204 foci within the mask ($p<0.05$, corrected; clustersize>200 mm^3).
Meta-analytic clusters that are located in the VMPFC are highlighted in bold.
[a] Urry et al. (2006), Johnstone et al. (2007), Delgado et al. (2008).

Table 4
Confirmatory ALE meta-analysis of hyperactivations observed in studies of cognitive emotion regulation (reappraisal) that assessed both female and male subjects.

Region	MNI-coordinates	ALE-value	Clustersize (mm^3)	Number of foci inside cluster	Number of studies inside cluster
L intraparietal cortex	−46 −66 36	0.020	2192	8	6
	−42 −56 38	0.014			
R intraparietal cortex	50 −58 42	0.016	536	3	3
L middle frontal gyrus/inferior frontal sulcus/IFJ	−42 18 44	0.015	1336	6	6
	−42 4 48	0.013			
L/R dorsomedial PFC/ACC	−6 16 58	0.015	1192	6	6
	−10 22 60	0.015			
	−24 20 56	0.010			
L inferior frontal gyrus/anterior insula	−50 28 −10	0.016	1176	5	5
	−54 20 0	0.015			
R inferior frontal gyrus/anterior insula	50 30 −8	0.026	1096	4	4
	46 16 4	0.014	896	5	3
	42 20 −4	0.011			
L inferior temporal sulcus	−62 −36 −4	0.018	968	4	4
L/R VMPFC	**6 40 −22**	**0.016**	**848**	**4**	**3**[a]
	0 38 −18	**0.014**			
L/R mid-cingulate cortex/posterior cingulate cortex	0 −24 34	0.012	384	3	3
	0 −30 36	0.011			
R angular gyrus/posterior superior temporal gyrus	56 −56 28	0.012	224	2	2

This meta-analysis contained coordinates from 15 studies with a total of 107 foci within the mask ($p<0.05$, corrected; clustersize>200 mm^3).
Meta-analytic clusters that are located in the VMPFC are highlighted in bold.
[a] Urry et al. (2006), Johnstone et al. (2007), Delgado et al. (2008).

way conjunction analysis confirmed this finding of regional concordance in the left amygdala (see Fig. 4).

Moreover, we also examined the probability of a co-occurrence of increased activation in the VMPFC and of reduced activation in the left amygdala. This was done, because a high probability of co-occurrence may suggest a functional association of these brain regions during the down-regulation of negative affect. Since the GingerALE algorithm cannot determine conditional probabilities, we tried to approximate the probability by doing the following: We first counted the total number of studies that reported hypoactivations during emotion regulation (N = 31). Of these, 17 studies reported reduced activation in the left amygdala (i.e., Knight et al., 2004; Ochsner et al., 2004; Bingel et al., 2006; Petrovic et al., 2005; Eippert et al., 2007, 2009; Goldin et al., 2007; Herwig et al., 2007; Johnstone et al., 2007; Urry et al., 2006; Delgado et al., 2008; McRae et al., 2009; Walter et al., 2009; Hayes et al., 2010; Soliman et al., 2010; Spoormaker et al., 2010; Winecoff et al., 2010). Further, 11 of the 31 studies reported a hyperactivation of the VMPFC (i.e., Bingel et al., 2006; Petrovic et al., 2005; Eippert et al., 2009; Johnstone et al., 2007; Urry et al., 2006; Delgado et al., 2008; Finger et al., 2008; Mak et al., 2009; Watson et al., 2009; Soliman et al., 2010; Diekhof et al., 2011). Finally, 7 studies reported both decreased activation in the left amygdala AND hyperactivation of the VMPFC (i.e., Bingel et al., 2006; Petrovic et al., 2005; Eippert et al., 2009; Johnstone et al., 2007; Urry et al., 2006; Delgado et al., 2008; Soliman et al., 2010). From this it follows that the conditional probability to find "VMPFC hyperactivation AND amygdala hypoactivation" was about 64% in our database.

Discussion

In the present study, we used coordinate-based ALE meta-analysis to determine brain areas central to the (voluntary) down-regulation of negative affect and to the control of perceived aversiveness. We were particularly interested in control regions and therefore only coordinates from studies reporting hyperactivations related to diminishing negative affect were included in three independent meta-analyses. The three independent meta-analyses of hyperactivations revealed that a region in the VMPFC (i.e., gyrus rectus and adjacent medial frontal cortex) concordantly mediated diminished negative affect in the domains of (1.) fear extinction, (2.) placebo control, and (3.) cognitive emotion regulation (see Tables 1–3; Figs. 1and2).This was also confirmed by the results of a three-way conjunction analysis and a pooled meta-analysis of all studies. Apart from that, we also identified two regions of significant overlap in the left ACC and right anterior insula in the two-way conjunction of placebo control and cognitive emotion regulation (Fig. 3). Finally, the meta-analyses of hypoactivations during diminishing negative affect further identified a domain-independent cluster in the left amygdala (see Tables A4–A7; Fig. 4). Reduced activation in this brain region thereby accompanied increased activation of the VMPFC with a conditional probability of approximately 64%. In sum, these data strongly

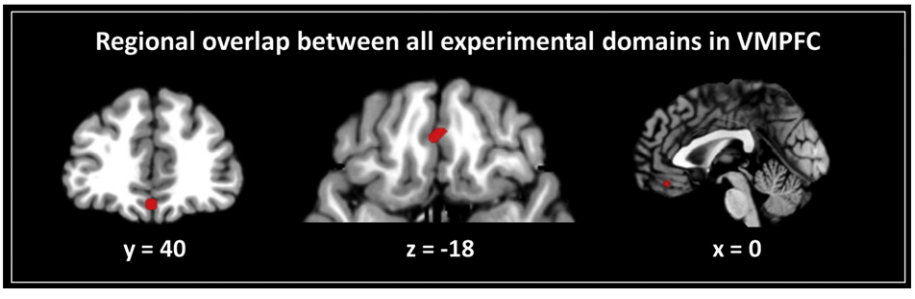

Fig. 2. The three-way conjunction of meta-analytic results from the three experimental domains confirms concordant hyperactivation of the VMPFC during reduction of negative affect ($p<0.05$, corrected, displayed on the Colin T1-template in MNI reference space).

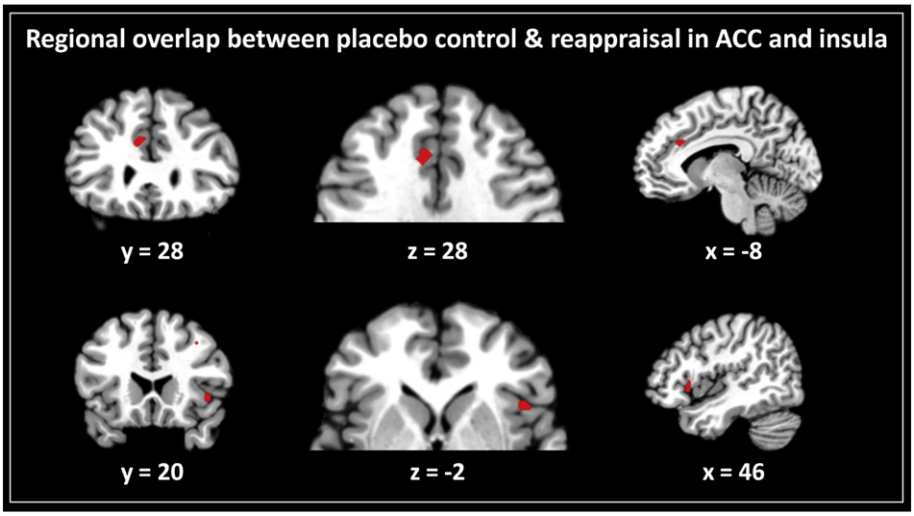

Fig. 3. The two-way conjunction of meta-analytic results from the domains of "placebo control" and "cognitive reappraisal" reveals concordant hyperactivation of the left ACC and right anterior insula during reduction of negative affect ($p<0.05$, corrected, displayed on the Colin T1-template in MNI reference space).

imply that the human VMPFC may function as a domain-general controller of negative affect, which may also control stimulus-driven activation in down-stream areas of the emotion processing circuitry.

Hyperactivation of the VMPFC during diminishing negative affect is domain-general

The present observation of a concordant hyperactivation of the VMPFC during successful reduction of negative affect and perceived aversiveness is consistent with previous theories on the functional role of this brain region in diminishing fear and in the control of negative affect (Delgado et al., 2008; Milad et al., 2007; see also Quirk and Beer, 2006; Quirk et al., 2006). In fact, a striking convergence exists between the rodent and human literature on retrieval of fear extinction, which implies that the prefrontal fear extinction mechanism is highly conserved across species. It has been demonstrated that after extinction the VMPFC controls perceived fear by activating GABAergic intercalated cells in the amygdala, which inhibit the central nucleus of the amygdala and thus effectively cancel amygdala-generated affective responses (Milad et al., 2006; Quirk and Beer, 2006; Quirk et al., 2006).Our meta-analytic data extend these findings by showing that the human VMPFC may universally control negative affective responses even beyond the context of fear extinction and can thus modulate the subjectively perceived aversiveness of unpleasant or fear-eliciting events.

The central role of the human VMPFC in the reduction of negative affect and perceived aversiveness regardless of domain-specific differences is thereby further underscored by (1.) the present observation of a concurrent domain-general down-regulation of the left amygdala in more than half of the studies that identified activation in the VMPFC, (2.) the observation that the VMPFC was activated independent of stimulus modality (e.g., pain or vision) and domain-specific cognitive demands and operations (Tables 1–3), and (3.) the fact that hyperactivations in the remaining prefrontal control regions (e.g. the lateral PFC) showed no concordance across domains. In particular, our data suggest that domain-specific processes involved in the regulation of fear and negative affective responses may in part exert their influence on emotional processing through a common mechanism, in which the VMPFC appears to be the central node. In that way, the meta-analytic findings may also agree with the view that the VMPFC functions as a mediator between phylogenetically newer parts of the well developed human lateral prefrontal regulation system and phylogenetically older structures of the emotion processing system (e.g. the amygdala) as well as extero- and interoceptive sensory cortices (Banks et al., 2007; Delgado et al., 2008; Diekhof et al., 2011; Ochsner and Gross, 2005; Wager et al., 2008, 2009a,b; Watson et al., 2009). This assumption also seems plausible when considering the nature of the anatomical connections between the VMPFC and both lateral prefrontal regions and the respective subcortical brain areas (Barbas, 2000; Barbas and Zikopoulos, 2007; Carmichael and Price, 1996; Johansen-Berg et al., 2008; Öngür and Price, 2000; Price, 1999; Rolls, 2000a,b). In non-human primates connections between the VMPFC and the amygdala have been found to be robust and bidirectional, while connections

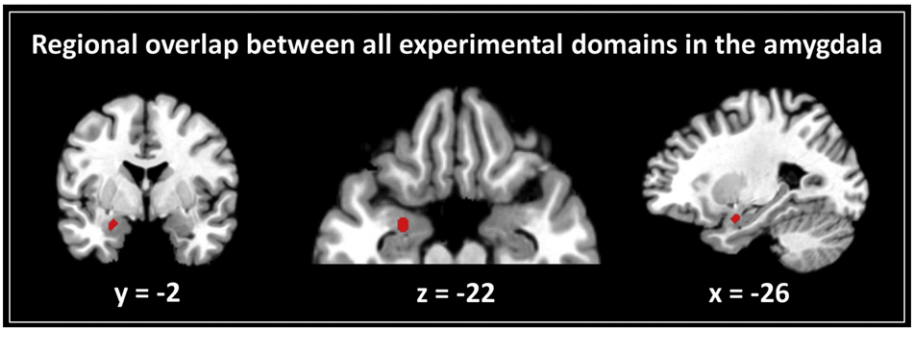

Fig. 4. The three-way conjunction of meta-analytic results from the three experimental domains confirms concordant hypoactivation of the left amygdala during reduction of negative affect ($p<0.05$, corrected, displayed on the Colin T1-template in MNI reference space).

between the amygdala and the lateral PFC appeared to be sparse, unidirectional and ascending (Ghashghaei and Barbas, 2002). This suggests, that particularly in the highly sophisticated emotion regulation tasks the VMPFC may provide one possible route through which higher-order cognitive operations can be translated into an actual soothing effect that reduces fear-related arousal in lower-level brain regions (see also Delgado et al., 2008).

However, although the meta-analyses revealed concordant activation of the VMPFC across domains, the majority of the studies in our database did not report increased activation in this brain region. In fact, only 17 of the 49 studies reported a hyperactivation of the brain area that covers part of the medial OFC, the subgenual and rostral ACC as well as the anterior MPFC (see Fig. 1A). These comprised five of the ten fear extinction studies (i.e., Finger et al., 2008; Kalisch et al., 2006a; Milad et al., 2007; Schiller et al., 2008; Soliman et al., 2010), seven of the 14 studies that assessed the neural correlates of placebo control (i.e., Bingel et al., 2006; Diekhof et al., 2011; Kong et al., 2006; Petrovic et al., 2005; Scott et al., 2008; Watson et al., 2009), and only five of the 25 studies that dealt with the neural (control) mechanisms underlying emotion regulation through cognitive strategies (i.e., Banks et al., 2007; Delgado et al., 2008; Johnstone et al., 2007; Mak et al., 2009; Urry et al., 2006). Thus, particularly in the domain of cognitive reappraisal it became obvious that only a minority of studies reported activation in the VMPFC. This raises the question whether there was another common characteristic besides the reduction of negative affect that may have driven the present results. For one thing, differences in discriminatory power due to signal loss in basal parts of the VMPFC or because of variation in experimental designs (e.g., blocked vs. event-related design) could in part account for discrepancies between studies and domains. However, we would like to put forward another line of evidence that has implicated the VMPFC in the basic process of using internal states to deal with environmental stimuli (see Buckner and Carroll, 2007). Accordingly, several previous neuroimaging studies already suggested that the value signal in the VMPFC may be significantly driven by internal biases derived from cognitive frames or other types of preconceptions, which can ultimately override objective sensory input (e.g., Diekhof et al., 2011; Grabenhorst et al., 2007). For example, Plassmann et al. (2008) found increased activation in the medial OFC when subjects believed to taste a wine with a higher price, which was also evaluated as being more delicious, than when tasting the identical wine in association with a lower price. Apart from that, it has recently been suggested that the VMPFC may be part of a brain system that proactively deals with environmental stimuli by linking internal representations derived from associative memory, mental imagery, or introspection with incoming sensory information (Bar, 2007; Bar, 2009; Moulton and Kosslyn, 2009; for empirical evidence on the role of the VMPFC in internal processing see also Bar, 2007; Mason et al., 2007; Mechelli et al., 2004; Northoff et al., 2006; Schacter et al., 2007; Schneider et al., 2008; Summerfield et al., 2009). It is noteworthy that three of the cognitive reappraisal studies that identified increased activation in the VMPFC employed a mental simulation strategy to achieve a significant down-regulation of negative affect (see Table A3). Similarly, in the placebo study by Diekhof et al. (2011) subjects performed anticipatory mental imagery to produce the "illusion" of reduced fearfulness when viewing facial expressions. Moreover, in the studies by Bingel et al. (2006), Petrovic et al. (2005), Eippert et al. (2009), and Watson et al. (2009) subjects underwent placebo conditioning, during which they built up the preconception of a real treatment effect, before they underwent MR-scanning with the fake treatment. Similarly, during fear extinction subjects learned the new association between the CS and the absent aversive UCS before they were tested again during extinction recall (e.g., Kalisch et al., 2006a). It has previously been demonstrated that the mere expectancy of an upcoming event has the power to trigger crude forms of mental simulation that mimic the expected perceptual experience (Holland, 1990; Rescorla, 1988; Rilling and Neiworth, 1987) and pre-activate the associated sensory-perceptual (and affective) systems (Bermpohl et al., 2006; Boly et al., 2007; Carlsson et al., 2000; Nitschke et al., 2006; Onoda et al., 2008; Ploghaus et al., 1999; Ploner et al., 2010; Porro et al., 2002). One would therefore imagine that a similar substitution of the expected event may have ultimately biased perception and affective evaluation during placebo treatments and extinction retrieval. This assumption is further supported by the recent observation that the number of conditioning trials before a placebo treatment influenced the persistence and strength of subsequent placebo effects, and thus supposedly reflected the learning-related strengthening of internal CS-UCS associations (Colloca et al., 2010). Diminishing negative affect may thus be in part a product of an internally predicated resolution on the subjectively perceived affective value of the (expected) sensory event, which influences perceptual-affective processing in lower-level cortices (see also Summerfield et al., 2006). In the present experimental domains, associations between the (expected) reduction of unpleasantness and the related perceptual and affective representations may have been either created implicitly through prior experience (like in extinction recall and placebo conditioning) or may have relied on a voluntary top-down mental simulation strategy (like in the respective cognitive reappraisal studies). This would also conform with the idea of the VMPFC as a polymodal convergence zone that integrates internal representations with external inputs, further linking extero- or interoceptive sensations to derive a conclusive, but rather subjective evaluation of environmental stimuli (see Bouret and Richmond, 2010).

Do additional hyperactivations during diminishing negative affect reflect complementary regulation mechanisms?

Important to note, the remaining brain regions that were identified in the independent meta-analysis showed no regional concordance across experimental domains, but rather appeared to have quite different regional distributions (see Tables 1–4). Although this may in part be attributable to differences in discriminatory power between domains (e.g., the domain of fear extinction included only 55 coordinates, while the domain of cognitive reappraisal yielded a total of 204 foci), one may also assume that differences in cognitive operations and in the predominant stimulus modality may have driven the specific patterns of regional distribution. We can only speculate that most of these clusters may have originated from "real" differences between domains, which would conform with the previously proposed functions of the respective brain regions.

Accordingly, we observed that the lateral and dorsomedial PFC were preferentially activated by cognitive emotion regulation studies (Table 3), which is consistent with the role of these brain areas in cognitive control processes, goal representations and high-level appraisal of affective stimuli (Kalisch et al., 2006b; Miller and Cohen, 2001). In addition, the cognitive down-regulation of negative affect was accompanied by concordant hyperactivations in the intraparietal and temporal cortices, which have been implicated in visual attention (Corbetta and Shulman, 2002; Corbetta et al., 2008; Gruber et al., 2009). This suggests that these brain regions may have been involved in the voluntary redirection of attention to affectively neutral aspects of the emotionally salient stimuli (most of the time aversive photographs), while subjects performed high-level cognitive reappraisal.

Moreover, placebo studies led to convergent activation in somewhat different parts of the lateral prefrontal cortex and in the anterior OFC (Table 2). Consistent with previous observations, hyperactivations in these brain regions supposedly represented specific aspects of placebo studies like for example "placebo expectancy", which may have recruited additional modulatory brain regions during the anticipatory period (Petrovic et al., 2005; Sarinopoulos et al., 2006; Wager et al., 2004b; see also Atlas et al., 2010). Alternatively, these brain regions may have in part also

reflected placebo-induced activation of opioidergic neurotransmission (Scott et al., 2008; Zubieta et al., 2005).

Finally, during fear extinction we also found two domain specific clusters that were concordant between extinction studies (Table 1). Both regions were located in cortices along the midline of the human brain that are closely anatomically linked with both the VMPFC and the amygdala (Johansen-Berg et al., 2008; Öngür and Price, 2000). For this reason, one may assume a complementary role for the sgACC and the ACC/medial PFC during fear extinction, particularly in the early phases of extinction learning (Lang et al., 2009).

It is further noteworthy that the two-way conjunction analysis of "placebo control AND cognitive reappraisal" revealed a significant overlap between domains that was located in the left ACC and in the right anterior insula (see Fig. 3). This regional commonality was probably related to the fact that in both domains the aversive stimulus was still present during affect regulation. This was in contrast to the domain of fear extinction, in which the CS was presented without the aversive UCS. Given this paradigmatic difference, one may assume that in the presence of an aversive stimulus the regulatory effort had to be increased to cope with this event. This would also conform with previous findings that suggested a role for the ACC in the effortful rather than the automatic down-regulation of fear and negative affect (Eippert et al., 2007; Kim and Hamann, 2007; Modinos et al., 2010; see also Phillips et al., 2003), which is promoted by (mainly unidirectional) projections to various nuclei of the amygdala (Amaral and Price, 1984; Ghashghai et al., 2007). The anterior insula has further been implicated in processing of stimulus salience (Corbetta and Shulman, 2002; Corbetta et al., 2009), but also in the representation of subjective interoceptive awareness (Craig, 2009; Critchley et al., 2004; Wiech et al. 2010). In addition, there is converging evidence that the anterior insula may contribute to the mediation of fear-related arousal and negative affective states through its extensive reciprocal connections with the amygdala (Anders et al., 2004; Augustine, 1996). Finally, also outside of the context of affect regulation these two brain regions have been implicated in several executive control operations (e.g., the allocation of attention towards currently relevant stimulus dimensions or tasks; Wager et al., 2004a). It is therefore possible that increased activation of the anterior insula during placebo control and cognitive reappraisal could have complemented the function of the VMPFC by supporting internal processes that determined the subjectively perceived affective value of the aversive stimulus. Alternatively, increased activation of the anterior insula may have originated from the (residual) bottom-up arousal elicited by the still present aversive stimulus.

Overall, the present meta-analysis identified additional control regions that could have served specific functions during emotion regulation in each of the three experimental domains. Therefore, one cannot rule out that apart from a phylogenetically older ventromedial prefrontal affect regulation mechanism that can also be found in rodents (Quirk and Beer, 2006; Milad et al., 2006), alternative higher-order cognitive control mechanisms may exist in the human brain (see for example Delgado et al., 2008). These mechanisms may be complementary to the one executed by the VMPFC and could underlie more sophisticated ways to deal with distressing stimuli. For instance, one may speculate that cognitive regulation strategies, which involve a voluntary change of the interpretation of a certain situation, may indirectly attenuate reflexive fear-related responses in the amygdala and associated sensory cortices. This could in turn reduce the need for direct intervention by the ventromedial prefrontal cortex. Since the present meta-analyses cannot answer these open questions, it will be necessary for future neuroimaging studies to further concern themselves with the domain-specific mechanisms.

Limitations

Several limitations need to be taken into account when interpreting the present meta-analytic findings. Firstly, the majority of the studies included in the meta-analyses used both a region-of-interest (ROI) approach (i.e., in most cases a statistical correction for small volume; Worsley et al., 1996) and a whole-brain analysis to reveal the neural circuitry involved in affect regulation. This means that the effects in ROIs that were defined a priori are to some extent overrated. In particular, this has to be kept in mind when it comes to the reported deactivations located in the left amygdala, since only five of the 17 studies did not use a ROI approach (i.e., Goldin et al., 2007; Herwig et al. 2007; Knight et al. 2004; Petrovic et al., 2005; Walter et al. 2009; Winecoff et al. 2010). Conversely, of the studies that identified the VMPFC seven of 11 studies did not use preselected ROIs (i.e., Diekhof et al., 2011; Finger et al., 2008; Johnstone et al., 2007; Mak et al., 2009; Petrovic et al., 2005; Urry et al., 2007; Watson et al., 2009).

Secondly, one also has to bear in mind that the domain-general reciprocal relationship between the VMPFC and left amygdala did not apply to all studies that identified either of these regions. Even though a conditional probability of 64% for coactivations in VMPFC and amygdala may suggest a functional relationship, the absence of VMPFC activation in most of the cognitive reappraisal studies, despite significant deactivations in the amygdala, leaves open the possibility that there may be other brain mechanisms that either directly or indirectly modulate negative affective responses. Most of the functional neuroimaging studies included in the present meta-analyses focused on activity changes that occurred when subjects experienced the reduction of negative affective responses. Only a minority of these studies further assessed the functional connectivity or specific interactions between brain regions involved in emotion regulation (e.g., Delgado et al., 2008; Diekhof et al., 2011). To be able to draw a more conclusive picture of the brain mechanisms underlying emotion regulation, it is certainly necessary to further assess process-specific interactions between the associated brain regions. In addition, in the cognitive domain it has already been demonstrated that the functional importance of a certain brain region (also in terms of its efficiency) does not merely depend on activation strength. Instead, other factors like a focusing of regional processing, which results in reduced activation due to an involvement of a limited number of relevant neuronal populations, or an increased neural synchrony between task-relevant brain regions may rather determine behavioral success (e.g., Ghuman et al., 2008). Therefore, one cannot rule out that the VMPFC could have acted as a mediator of negative affect also in those studies that found no significant hyperactivation in this region, since the above described phenomena could have concealed its involvement. A more thorough assessment of network relations in the emotion circuitry could certainly help to resolve the question whether the human VMPFC may indeed be a mediator between higher-level control regions and lower-level cortices involved in affect representation (e.g., like suggested by the results of the study by Delgado et al., 2008), and whether this brain region may be primarily confined to those regulation tasks that involve a crude simulatory component (i.e., mainly fear extinction and placebo studies).

Thirdly, another limitation of the interpretability of the present results was that most studies failed to dissociate between anticipatory and perceptual processing. This dissociation is particularly important for the interpretation of ventromedial prefrontal function in placebo and cognitive emotion regulation studies. If the VMPFC in fact acted as a mental simulator that predisposes the perceptual system for a certain percept or even a misperception, one may assume that this brain region would be specifically recruited during anticipation (e.g., Sarinopoulos et al., 2006).If the VMPFC rather functioned as an evaluative brain region, one would presume that it should rather participate in the evaluation of the present stimulus during the perception phase (e.g., Grabenhorst et al., 2007). One may even assume that different subregions of the VMPFC may participate in either anticipatory or perceptual-evaluative processing (e.g., Diekhof et al., 2011). Future studies have to further concern themselves with these questions.

Finally, the lack of a formal meta-analytic contrast analysis precludes the inference that any of the brain regions that showed a domain-specific distribution were indeed selective for a certain domain (see Do additional hyperactivations during diminishing negative affect reflect complementary regulation mechanisms?). The interpretation of the role of domain-specific regions is even more difficult than that of domain-general regions, since our study lacked a clear a priori hypotheses regarding their specific functions. Although one can infer that the function of a certain brain region is domain specific and characteristic for the specific requirements of the paradigm (e.g., higher cognitive demands during reappraisal), it is also possible that this brain region was simply involved because of differences in the predominant task modality (e.g., vision). This makes the interpretation of the functional role of domain-specific regions to some extent speculative. Further, the lower number of coordinates in the fear extinction domain, which probably decreased discriminatory power, may have concealed some additional, functionally important regions of concordance (e.g., the hippocampus). Future studies therefore have to more carefully assess the differences between domains as well as the relation between the specific high-level mental processing capacity of the human brain and a domain-specific involvement of certain brain regions (e.g., areas in the lateral PFC).

Conclusion

Taken together, the present meta-analytic findings underscore the important role of the human VMPFC in the control of perceived aversiveness and negative affect. By demonstrating a domain-general response in the VMPFC that was accompanied by a significant down-regulation of activation in the amygdala, our data suggest that this prefrontal brain region may be an important controller of subjectively perceived aversiveness that modulates affective responses in the human brain regardless of task demands. However, our data also imply that humans can make use of more sophisticated cognitive emotion regulation mechanisms that engage additional brain regions to control perceived aversiveness.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.05.073.

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