Comparing Cognitive and Somatic Symptoms of Depression in Myocardial Infarction Patients and Depressed Patients in Primary and Mental Health Care

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Review

Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies

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ABSTRACT

Models describing the neural correlates of biased emotion processing in depression have focused on increased activation of anterior cingulate and amygdala and decreased activation of striatum and dorsolateral prefrontal cortex. However, neuroimaging studies investigating emotion processing in depression have reported inconsistent results. This meta-analysis integrates these findings and examines whether emotional valence modulates such abnormalities. A systematic literature search identified 26 whole-brain and 18 region-of-interest studies. Peak coordinates and effect sizes were combined in an innovative parametric meta-analysis. Opposing effects were observed in the amygdala, striatum, parahippocampal, cerebellar, fusiform and anterior cingulate cortex, with depressed subjects displaying hyperactivation for negative stimuli and hypoactivation for positive stimuli. Anterior cingulate activity was also modulated by facial versus non-facial stimuli, in addition to emotional valence. Depressed subjects also showed reduced activity in left dorsolateral prefrontal cortex for negative stimuli and increased activity in orbitofrontal cortex for positive stimuli. Emotional valence is a moderator of neural abnormalities in depression, and therefore a critical feature to consider in models of emotional dysfunction in depression.

Contents

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1. Introduction

Major depressive disorder is characterized by maladaptive and persistent emotional responses to stressors (Hammen, 2005). Such an emotional response has the potential to interfere with functioning in all aspects of daily life. Therefore, depression is likely to be associated with fundamental abnormalities in emotional processing, which continuously influence the processing of incoming sensory information (Harmer et al., 2009). Research has indeed demonstrated preferential processing of negative compared to positive information in depressed patients for multiple cognitive domains, such as perception, attention and memory (Disner et al., 2011; Roiser et al., 2012). Neuroimaging research provides a tool to visualize the core of the emotional dysfunction that occurs in the brain of depressed patients.

Several models of emotion processing in the depressed brain have been proposed, in which several brain regions are hypothesized to play a key role, with models differing in their emphases regarding the functions involved (for instance compare (Drevets et al., 2008; Krishnan and Nestler, 2008; Leppanen, 2006; Mayberg, 1997; Phillips et al., 2003). Emotion identification is generally attributed to subcortical structures such as the ventral striatum and amygdala, integration of somatic responses is subserved by the insula and anterior cingulate cortex (ACC) and affective state monitoring is related to medial and dorsolateral prefrontal cortex (DLPFC) function. However, the predictions arising from these models have not been systematically evaluated in the light of recent literature. Moreover, the models do not make clear predictions regarding interactions between activation abnormalities and emotional valence.

Emotional processing could be abnormal in depressed patients at different levels of processing. The initial appraisal of incoming information may be biased, leading to preferential processing of negative information and an amplified emotional response. In particular, it has been suggested that the amygdala may be highly sensitive to negative information (Murray et al., 2011), whereas the ventral striatum, an area predominantly involved in processing positive information, has been hypothesized to be less sensitive in depressed patients (Diekhof et al., 2008). Monitoring of the affective state may also be compromised by reduced cognitive control from the DLPFC and ACC, leading to insufficient capacity to downregulate the response of the amygdala (Beck, 2008; Pizzagalli, 2011). Although these general models of emotional dysfunction in depression lead to specific predictions, empirical studies investigating the neural correlates of emotional dysfunction in depressed patients have produced inconsistent results. It is still insufficiently known which levels are affected during the basic processing of emotional stimuli in emotion perception tasks and whether activation abnormalities are modulated by emotional valence at different levels of processing.

Meta-analysis of functional magnetic resonance imaging (fMRI) studies in depressed patients is critical to validate and advance models of emotional dysfunction in depression. To date, two such meta-analyses have been performed (Diekhof et al., 2008; Fitzgerald et al., 2008). Their findings however were not fully consistent. In particular, while Fitzgerald and colleagues found that processing negative stimuli resulted in *hypo*activation in depressed patients in pregenual anterior cingulate, Diekhoff and colleagues found that negative stimuli resulted in *hyper*activation of the same area. Similarly, the amygdala is identified as hyperactive during negative emotional processing in one of the meta-analyses (Fitzgerald et al., 2008), but not the other one. This variation in results is probably due to methodological limitations, as these previous meta-analyses included a limited sample of studies (6 in Fitzgerald et al., 2008; 10 in Diekhof et al., 2008), and employed a potentially biased fixed-effects meta-analytical approach that does not adequately incorporate between-study variance, and as a consequence has since been superseded (Eickhoff et al., 2009). Furthermore, these studies did not take into account negative findings or region-of-interest studies, and thereby introduced bias in their selection of study samples.

In the present work, the brain activation patterns of depressed patients were compared to healthy subjects in a meta-analysis on the processing of negative and positive emotion. An up-to-date systematic literature search was conducted to identify a larger number of studies relative to previous meta-analyses. In addition, an innovative analytical procedure for the pooling of results was employed. This approach employs not only the locations of significant effects, but also their effect size. Because statistical thresholds are taken into account during this analysis, this method allows for the combination of results from studies investigating the whole brain and specific regions of interest. It was hypothesized that depressed patients would show greater activation in amygdala and anterior cingulate cortex and less activation in ventral striatum and prefrontal areas. Furthermore, the consistency of results across emotional valence and stimulus type was explored.

2. Methods

2.1. Literature search

A literature search was performed to identify relevant fMRI studies investigating processing of emotional information in depressed patients. The search was conducted using standardized search strings capturing the key elements "(f)MRI AND depression OR MDD AND emotion(*) OR affect(*) OR reward". Articles were retrieved from the electronic databases PubMed, EMBASE and Web of Science until September 1, 2011. The search string was constructed to comprise the following Medical Subject Headings (MeSH terms): "magnetic resonance imaging", "depressive disorder", "emotions" and "affect". After completing the database search, reference lists from eligible articles and major reviews were examined for additional relevant articles.

2.2. Study selection

A two-step procedure was used to identify articles eligible for inclusion. First, articles were assessed by reviewing their titles and abstracts for matching the following inclusion criteria: written in English language; reported as an empirical article; making use of fMRI; including a patient group with a primary diagnosis of current major depressive disorder (MDD); including a healthy control group. Articles were excluded when a diagnosis of depression was secondary to a somatic condition such as temporal lobe epilepsy or multiple sclerosis. Articles were also excluded when depression was investigated solely as a comorbid psychiatric condition

or as post-partum depression. In case the abstract provided insufficient information to make a final decision, the study was selected for full-text review. The title/abstract review was conducted by two independent assessors (NG and EO) and inconsistencies were resolved by asking a third independent assessor (AA).

Next, the methodology of the selected articles was critically examined in a full-text review. Only data from adult participants (age >18) were included, to ensure a homogeneous sample. The minimal sample size for inclusion was 5 participants in each group. Experimental paradigms had to contain a visual emotional element, such as displaying emotional faces or words. This criterion was adopted to promote homogeneity in the included data, as auditory emotional tasks have been shown to recruit different neural systems than primary visual emotional tasks (Phan et al., 2002). Moreover, visual emotional paradigms are commonly employed. The contrasts of interest were positive or negative emotion versus non-emotional control condition. This had to be an active experimental condition, in order to adequately control for task effects. The full-text review was conducted by two assessors (NG and EO). Studies making a whole-brain or a region-of-interest comparison between depressed patients and healthy controls in at least one of the contrasts of interest were included in the first stage of the meta-analysis. It was ensured that the same study sample was not included twice after repeated analysis in separate articles. In the next step, studies using a Region-Of-Interest (ROI) approach were omitted from the analysis to investigate the robustness of the results. Finally, the analyses were repeated separately for studies presenting facial and non-facial task paradigms, to examine whether the activation differences between depressed and controls were similar across tasks.

2.3. Statistical analysis

A modified version of parametric voxel-based meta-analysis (PVM; Costafreda et al., 2009a) was employed allowing the pooling of both ROI-based and coordinate-based findings from individual studies. These modifications are summarized in the following paragraphs, and further details on the original method can be found in the original publications (Costafreda et al., 2009a; Costafreda, 2012). From the studies included in the functional meta-analysis, the coordinates of activation, their associated effect size, the statistical threshold below which findings were considered non-significant in that study (e.g. $p < 0.001$ uncorrected) and the anatomical labels as provided in the paper were extracted, for both whole-brain and ROI contrasts. When appropriate, coordinates were transformed from Talairach to the Montreal Neurological Institute coordinate system by using a non-linear transformation (Brett et al., 2001). Effect sizes were also converted from *Z*, *T* or *P* values to *Z*-scores, using as appropriate the cumulative probability function for the *T* distribution and the cumulative distribution function for the standard normal distribution. Both the total sample size as well as the number of subjects in each diagnostic group were used to compute the degrees of freedom, resulting in exact transformations.

Summary maps for each study were then created by convolving the effect sizes for each focus with a uniform kernel (radius 20 mm). This radius size was selected on the basis of previous empirical evidence suggesting that kernels of 15–25 mm offer optimal sensitivity without loss of specificity, when evaluated against a gold standard of image-based meta-analysis. Optimizing sensitivity is of particular importance when using a conservative analytical approach (Radua and Mataix-Cols, 2009; Salimi-Khorshidi et al., 2009). The effect of this convolution was that for brain locations located within radial distance of a focus, the effect size was estimated to be the same *Z*-value as at the focus (referred as "exact observations"). For areas located outside radial distance of a focus in whole-brain contrasts, the effect size estimate was an interval, determined by the statistical threshold (e.g. a nonsignificant finding with threshold $p < 0.001$ implies $|Z| < 3.09$; these are further referred as "interval observations"). ROI contrasts contributed effect size estimates only for the relevant region of interest, as determined after conversion of anatomical labels as described by the study's authors to the standard labelling system of the automated anatomical labelling (AAL) scheme described by Tzourio-Mazoyer et al. (2002). When a study reported whole brain and ROI contrasts, the most precise measurement available (i.e. either an exact measurement for a significant finding or the most conservative threshold for a null result) was used in the summary map for that study. Significant findings from contrasts of greater brain activity in depressed patients than in healthy controls were represented by positive *Z*-values, while findings from greater activity in controls than depressed patients resulted in negative *Z*-values.

In the estimating procedure, it was assumed that the voxelwise exact and interval *Z*-values were independently and identically distributed across studies, and generated by a Normal overarching distribution. The hypothesis to be tested was whether the mean of this distribution is significantly different from zero. Statistical inference therefore required integration of exact and interval data, precluding standard methods of model fitting such as least squares which require exact inputs. Therefore, maximum likelihood estimates of the population mean and standard deviation under normality distributional assumptions were obtained by direct (numerical) optimisation of the likelihood function (Nelder and Mead, 1965). In the likelihood function, the contributions from exact observations were represented by their exact (point) probability value according to the probability density function of the normal distribution, while interval observations contributions were represented by the corresponding integral under the same normal probability density function. This procedure allowed valid inference on the parameters that maximise the likelihood of obtaining the observed results (both exact and interval values) given the data and our assumption of a normal distribution of the *Z*-values. That is, this procedure resulted in the value of a mean effect most compatible with the available data.

Statistical tests on the estimated mean of this distribution of *Z*-values across studies for each voxel were then conducted based on normality assumptions, with a voxelwise null hypothesis H0: $|\mu| = 0$. The assumption of normality is common in neuroimaging, and underpins many analytical approaches, such as Gaussian random field theory as implemented in SPM. As a correction for multiple comparisons, we employed the false discovery rate (Benjamini and Hochberg, 1995). Voxels with a *p*-value in this test below the FDR threshold were deemed to show significant evidence for the alternative hypothesis $|\mu| > 0$, i.e. evidence of differential brain activation between depressed patients and healthy controls. The template employed was the Montreal Neurological Institute (MNI) atlas, with dimensions $2\,\text{mm} \times 2\,\text{mm} \times 2\,\text{mm}$. The software was implemented using the R statistical software (http://www.r-project.org) and is available upon request.

3. Results

3.1. Study selection

The initial database search elicited 2896 results (search strategy depicted in Fig. 1). In the title-abstract review 197 articles were selected that fulfilled the inclusion criteria. The inter-rater reliability of the two independent observers was good (Cohens $\kappa = 0.90$). In total, 44 studies met our inclusion criteria (described in Table 1), including data from a total of 795 depressed patients and 792 healthy controls (HC). A variety of emotional tasks were

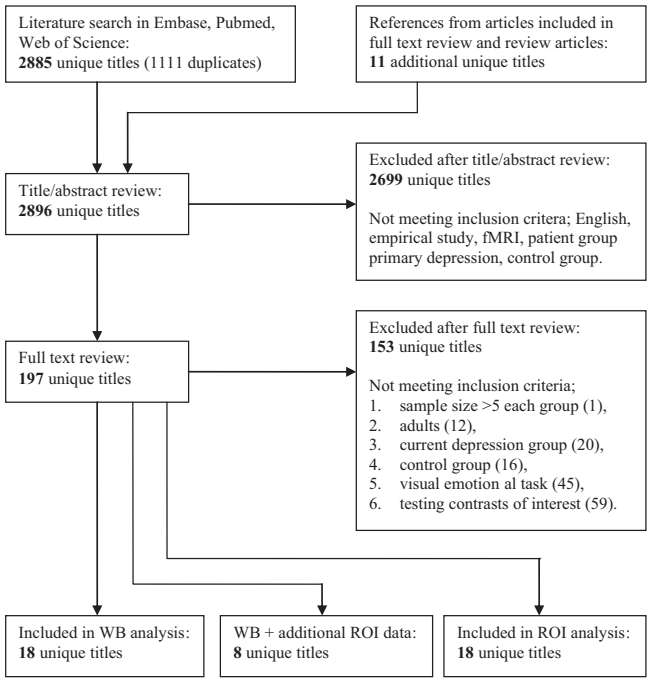

Fig. 1. Schematic representation of the selection procedure for articles to be included in the final analyses on whole-brain (WB) comparisons and region of interest (ROI) comparisons.

represented in every contrast. The tasks consisted of paradigms involving reward or loss feedback and the presentation of emotional faces, words or pictures. Most studies presented a neutral stimulus well-matched to the active stimuli except for emotional valence (e.g., faces with neutral expressions compared to faces with negative expressions), however some studies used low-level baseline tasks, such as comparing emotional faces to geometrical shapes or a scrambled face. The reported smoothing parameters ranged from 4 mm to 10 mm. Some studies did not report the smoothing procedure. There were 18 studies that examined the contrasts in a region-of-interest (ROI) analysis. Seven studies performed a ROI analysis next to a whole-brain analysis.

3.2. Meta-analysis on both whole-brain and region-of-interest studies

Meta-analysis including both studies using a whole-brain method and studies using a region-of-interest method showed differences between patients and HC in several areas (Fig. 2). Full results for the contrasts of interest including coordinates, Brodmann areas (BA) and *Z*-scores are presented in Table 2.

In response to negative emotions versus a neutral baseline, there was more activity in patients than in HC in bilateral basal temporal areas (including parahippocampal gyrus and amygdala), cingulate gyrus (dorsal anterior BA24/32 and middle BA24), right cerebellum, left putamen and left fusiform gyrus. In addition, patients showed less activity in the left dorsolateral prefrontal cortex (superior frontal gyrus).

Processing of positive emotions compared to a neutral baseline resulted in more activity in patients than in HC in the lingual gyrus and orbitofrontal cortex. Patients had less activity in the left cerebellum, a cluster in left temporal/parietal area (including superior temporal gyrus, supramarginal gyrus and insula), cingulate gyrus (dorsal anterior BA24 and pregenual BA25), fusiform gyrus, and a cluster including right insula, striatum, amygdala and hippocampus, bilateral parahippocampal gyrus.

3.3. Meta-analysis on whole-brain studies only

To investigate the robustness of results after excluding region-of-interest studies, the meta-analysis was repeated on whole-brain studies only. This analysis showed a comparable pattern of findings as the meta-analysis on both whole-brain and region-of-interest studies (supplementary Table 1), but the amount of significant differences between patients and HC was less in this second analysis. This may be due to a loss of power especially in basal temporal regions, as the amygdala in particular was investigated by a number of ROI studies.

In response to negative emotional stimuli compared to a neutral baseline, patients had more activity than HC in left basal temporal/occipital clusters, the left putamen and insula. These clusters included the middle occipital and middle temporal gyrus. A third cluster showing more activity in patients than in HC was seen in the right cerebellum. Patients showed less activity in the left dorsolateral prefrontal cortex (DLPFC).

In addition, during processing of positive stimuli compared to a neutral baseline, patients showed more activity in regions of the right lingual gyrus, left hippocampus and bilateral orbitofrontal cortex. Less activity was seen in patients than in HC in bilateral cerebellum, the anterior cingulate cortex (ACC; BA 24), a cluster including the regions left insula, superior temporal gyrus and supramarginal gyrus and in a cluster including the right amygdala, insula, putamen and caudate nucleus.

3.4. Meta-analysis on tasks presenting facial stimuli and non-facial stimuli separately

To investigate potential task-specific effects, the analyses were repeated separately on data from studies using facial stimuli (23 studies included for the negative emotion contrast and 11 studies for the positive emotion contrast) and on combined data from the tasks using non-facial stimuli (19 studies included for the negative emotion contrast and 13 studies for the positive emotion contrast). Both analyses showed a comparable pattern of findings to the previous meta-analyses, particularly for negative facial stimuli (supplementary Table 2). For positive facial stimuli some previously significant clusters did not reach significance after correction for multiple comparisons, possibly due to reduced power as relatively few studies investigated these contrasts. Noteworthy, task-specific differential activation between groups was found in the pregenual ACC (BA24/25). In this area, patients demonstrated increased activation relative to controls during processing of facial stimuli and reduced activation during processing of non-facial stimuli. This effect was found for both the negative and positive emotion contrasts, although for positive facial stimuli the effect did not survive multiple comparison correction (Fig. 3). There was no further evidence for task-specific effects.

4. Discussion

A meta-analysis of neuroimaging studies on emotion processing in major depression was conducted to test predictions from models about the brain areas involved in dysfunctional emotion processing and to examine whether emotional valence modulates activation abnormalities. We were able to include 44 studies that contrasted MDD patients to healthy controls performing tasks with emotional stimuli during fMRI measurements. For the processing of negative emotion, depressed patients showed more activation in the right amygdala, left striatum, dorsal anterior cingulate and parahippocampal areas than healthy controls. In contrast, during processing of positive emotion these same areas (including right instead of left striatum) showed less activation

Table 1
(a) Study characteristics extracted from articles reporting whole-brain results included in the combined meta-analyses for the four contrasts of interest. (b) Study characteristics extracted from articles reporting region-of-interest results included in the combined meta-analyses for the four contrasts of interest.

(a)

Study	Reference	*N* patients	*N* controls	Task paradigm	Control stimuli	Smoothing	ROI-selection	Positive > Neutral		Negative > Neutral	
								HC > DP	DP > HC	HC > DP	DP > HC
1	Wang et al. (2008a)	19	20	Emotional distraction	Neutral distractor	8.0 mm				x	
2	Wang et al. (2008b)	12	20	Emotional distraction	Neutral distractor	8.0 mm				ns	x
3	Fu et al. (2004)	21	19	Emotional faces	Low sad face	–				ns	x
4	Gotlib et al. (2005)	18	18	Emotional faces	Neutral face	8.0 mm		x	x	x	x
5	Surguladze et al. (2005)	16	14	Emotional faces	Neutral face	–	ACC + AMG	x	ns	ns	x
6	Frodl et al. (2009)	12	12	Emotional faces	Geometric shapes	8.0 mm					x
7	Scheuerecker et al. (2010)	13	15	Emotional faces	Geometric shapes	8.0 mm				ns	x
8	Surguladze et al. (2010)	9	9	Emotional faces	Neutral face	7.2 mm				x	x
9	Townsend et al. (2010)	15	15	Emotional faces	Geometric shapes	5.0 mm	Marsbar AMG + IFG			x	ns
10	Frodl et al. (2011)	24	15	Emotional faces	Geometric shapes	8.0 mm				ns	ns
11	Zhong et al. (2011)	29	31	Emotional faces	Geometric shapes	6.0 mm	SVC AMG			x	x
12	Demenescu et al. (2011)	59	56	Emotional faces	Scrambled face	8.0 mm		ns	x	ns	ns
13	Derntl et al. (2011)	15	15	Emotional faces	Neutral face	8.0 mm		x	x	x	ns
14	Canli et al. (2004)	15	15	Emotional words	Neutral word	8.0 mm		x	ns	x	x
15	Epstein et al. (2006)	10	12	Emotional words	Neutral word	7.5 mm	SVC striatum	x		x	x
16	Mitterschiffthaler et al. (2008)	17	17	Emotional words	Neutral word	8.0 mm	Marsbar ACC				x
17	Hsu et al. (2010)	15	15	Emotional words	Neutral word	8.0 mm				ns	ns
18	Keedwell et al. (2005)	12	12	Faces and stories	Neutral face	–		x	x	x	x
19	Mitterschiffthaler et al. (2003)	7	7	IAPS pictures	Neutral picture	7.0 mm		x	x		
20	Abler et al. (2007)	13	12	IAPS pictures	Neutral picture	8.0 mm	SVC AMG	ns	x	ns	x
21	Erk et al. (2010)	17	17	IAPS pictures	Neutral picture	8.0 mm	AMG + dorsolateral PFC			ns	ns
22	Knutson et al. (2008)	14	12	Monetary reward	Nongain outcome	4.0 mm	Medial PFC	x	ns	ns	x
23	Pizzagalli et al. (2009)	30	31	Monetary reward	Nongain outcome	6.0 mm		x	x	x	x
24	Remijnse et al. (2009)	20	27	Monetary reward	Nongain outcome	6.0 mm		ns	x	x	x
25	Smoski et al. (2009)	16	15	Monetary reward	Nongain outcome	5.0 mm		x	x		
26	Kumari et al. (2003)	6	6	Picture-caption pairs	Incongruent pairs	–		x	x	x	x
Total WBR		*N* = 454	*N* = 457				8 additional ROI	14	13	22	23

(b)

Study	Reference	*N* patients	*N* controls	Task paradigm	Control stimuli	Smoothing	ROI-selection	Positive > Neutral		Negative > Neutral	
								AMG	ACC	AMG	ACC
1	Sheline et al. (2001)	11	11	Emotional faces	Neutral face	8.0 mm	Manual	HC > DP		DP > HC	
2	Matthews et al. (2008)	15	16	Emotional faces	Geometric shapes	4.0 mm	Talairach Daemon			DP > HC	
3	Lee et al. (2008)	21	15	Emotional faces	Neutral face	–	Marsbar			ns	ns
4	Fales et al. (2008)	27	24	Emotional faces	Neutral face	9.0 mm	Manual			ns	DP > HC
5	Dannlowski et al. (2008)	28	28	Emotional faces	Neutral face	6.0 mm	Marsbar	ns		ns	
6	Peluso et al. (2009)	14	15	Emotional faces	Geometric shapes	5.0 mm	Coordinates 8 mm			DP > HC	
7	Victor et al. (2010)	22	25	Emotional faces	Neutral face	8.0 mm	SVC	HC > DP		DP > HC	
8	Almeida et al. (2010)	15	15	Emotional faces	Neutral face	8.0 mm	Pickatlas	ns		ns	
9	Suslow et al. (2010)	30	30	Emotional faces	Neutral face	8.0 mm	Pickatlas	HC > DP		DP > HC	
10	Baeken et al. (2010)	12	12	Emotional faces	Scrambled face	8.0 mm	Marsbar		DP > HC		DP > HC
11	Aizenstein et al. (2011)	33	27	Emotional faces	Geometric shapes	10.0 mm	SVC			ns	DP > HC
12	Siegle et al. (2006)	14	21	Emotional words	Neutral words	6.0 mm	SVC	ns		DP > HC	
13	Brassen et al. (2008)	13	13	Emotional words	Neutral words	8.0 mm	Coordinates 10 mm		ns		HC > DP
14	Irwin et al. (2004)	12	14	IAPS pictures	Neutral picture	–	Manual			ns	
15	Lee et al. (2007)	15	15	IAPS pictures	Neutral picture	–	Marsbar	ns	ns	ns	ns
16	Hamilton and Gotlib (2008)	14	12	IAPS pictures	Neutral picture	4.0 mm	SVC	ns		DP > HC	
17	Friedel et al. (2009)	21	21	IAPS pictures	Neutral picture	8.0 mm	Pickatlas			ns	
18	Sheline et al. (2009)	24	21	IAPS pictures	Neutral picture	9.0 mm	Functional			DP > HC	DP > HC
Total ROI		*N* = 341	*N* = 335					8	3	16	7

Note: For clarity purposes, the amygdala and anterior cingulate cortex are shown as regions of interest. Other regions were included in the meta-analysis as well. *Abbreviations*: ROI: region of interest; HC: healthy control group; DP: depressed group; ACC: amygdala; ACC: anterior cingulate cortex; IFG: inferior frontal gyrus; PFC: prefrontal cortex; SVC: small volume correction.

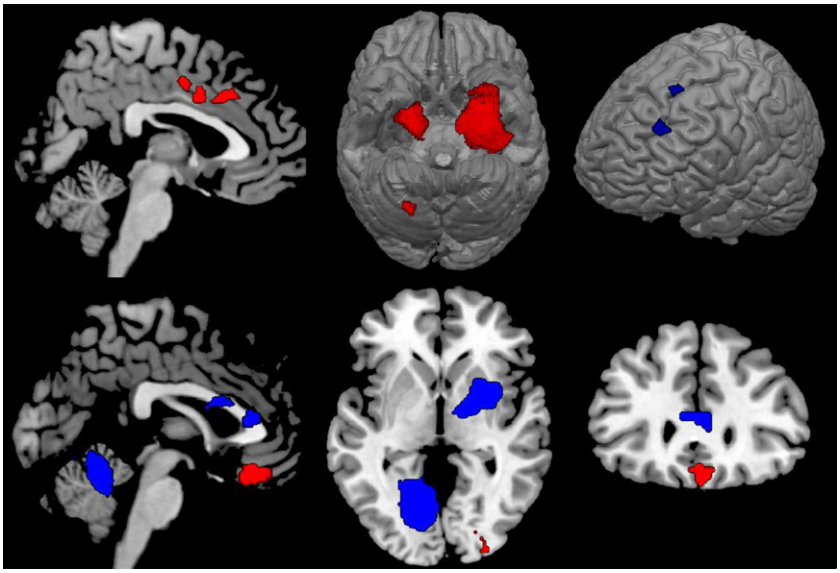

Fig. 2. Group differences in activation from the combined meta-analyses on whole-brain and region-of interest-studies; presented separately for negative and positive emotion. Top row: Negative emotions (MDD > HC in red, HC > MDD in blue). *From left to right*: Sagittal section at $X = +3$ mm showing increased activation in patients during negative emotional processing in mid and anterior cingulate cortex; Rendering of the basal brain showing increased activation in patients in basal temporal lobes and limbic areas; Rendering of increased left dorsal prefrontal activations in controls relative to patients during negative emotional processing. Bottom row: Positive emotions (MDD > HC in red, HC > MDD in blue). *From left to right*: Sagittal section at $X = +1$ mm showing increased activation in patients in orbitofrontal cortex, with relatively reduced activation in patients relative to controls in dorsal cingulate and cerebellum; Axial section at $Z = 0$ mm showing increased activation in controls relative to patients in right insula, striatum and thalamus, and left lingual gyrus; Coronal section at $Y = +30$ mm showing increased activation in orbitofrontal cortex and decreased activation in anterior cingulate cortex. MNI space. Results corrected at FDR $p < 0.05$.

in depressed patients compared to healthy controls. Moreover, depressed patients demonstrated less activity in the left dorsolateral prefrontal cortex (DLPFC) during processing of negative emotion and more activity in the medial orbitofrontal cortex (OFC) during processing of positive emotion. In summary, opposing effects of emotional valence were found in limbic and visual brain areas, accompanied by valence-specific effects in the prefrontal cortex.

4.1. Opposing effects of emotional valence in limbic brain areas: negativity bias

The current meta-analysis showed abnormal activation in the amygdala and striatum, subcortical structures which have been implicated in emotion identification by models describing the neural correlates of emotional dysfunction in depression (e.g. Leppanen, 2006; Phillips et al., 2003). The amygdala is involved in directing attention at emotional information, facilitating emotional memory and generating an autonomic emotional response (Pessoa, 2010). Amygdala activation has been associated with the processing of both negative and positive emotions (Costafreda et al., 2008; Murray, 2007), and is involved in relevance detection in the brain, i.e. responding to stimulus features relevant for the subject's interests (e.g. survival), and prioritizing processing in other brain areas (Jacobs et al., 2012; Sander et al., 2003). According to a review by Haber and Knutson (2010), the ventral striatum receives input from and interacts with the amygdala, but is more often associated with the processing of positive emotion. As a central part of the reward circuit it is sensitive to the anticipation and receipt of reinforcers, and in this way contributes to emotional learning. Stronger activation for negative emotional stimuli and less activation for positive emotional stimuli in amygdala and striatum might contribute to the negativity bias often reported in depression (Harmer et al., 2009; Roiser et al., 2012), by stimulating negative information and inhibiting positive information for further processing.

The evidence for negativity bias given by the opposing effects of emotional valence in limbic brain areas was complemented by similar mirroring effects in the fusiform region, a secondary visual area linked to face processing. Facial stimuli depicting specific emotions were used by over half of the studies in this meta-analysis, and the activation in the fusiform areas was substantially more extensive for the studies presenting facial stimuli than for the studies presenting non-facial stimuli. Patients with depression showed increased activation relative to healthy controls in left fusiform cortex during the processing of negative emotional stimuli, and, conversely, decreased activation during positive emotional processing. This finding suggests that the negativity bias may be initiated as a perceptual bias towards negative, and away from positive stimuli, early in the perceptual processing stream as has been proposed before (Fales et al., 2008; Leppanen, 2006; Poulsen et al., 2009). This modulation of fusiform activity may be understood as part of a visual-limbic feedback loop that is biased in depression, given a strong bidirectional interaction between amygdala and fusiform gyrus during emotional facial processing (Herrington et al., 2011; Morris et al., 1998).

A similar modulating effect of emotional valence was observed in the anterior cingulate cortex (ACC). During processing of negative emotion, depressed patients showed stronger activation than HC in a cluster in the dorsal ACC (with the peak located at the intersection of BA24 and BA32), extending to the dorsomedial prefrontal cortex. In contrast, the dorsal perigenual ACC (BA24/25), a cluster located slightly more rostral than the cluster for negative emotion, was less active during processing of positive emotion. The dorsal ACC has been associated with attention and learning from negative feedback (Shackman et al., 2011). Furthermore, the dorsal ACC is thought to work in concert with the amygdala to generate the bodily response to emotion (Etkin et al., 2011). It has been suggested that the ACC, as part of the default-mode network, plays an important role in rumination and self-associations (Pizzagalli, 2011). Hence, abnormal dorsal ACC functioning could contribute to a multitude of depressive symptoms, ranging from biased

Table 2
Peak coordinates of significant group differences in activation for negative and positive emotional stimuli from the combined meta-analysis on whole-brain and region-of-interest studies.

Anatomical label	BA	Volume	MNI coordinates			Mean *Z*-score
		# voxels	*x*.max	*y*.max	*z*.max	
Negative emotion versus neutral baseline						
Areas of increased activity in patients						
Left basal temporal						
Fusiform gyrus	20	263	−36	−26	−28	2.44
Superior temporal pole	38	82	−36	10	−20	2.43
Cerebellum	–	10	−24	−24	−30	2.31
Middle temporal pole	35	71	−22	−2	−36	2.34
Parahippocampal gyrus	36	86	−20	−10	−34	2.30
Inferior temporal gyrus	20	172	−38	−24	−28	2.33
Middle temporal gyrus	20	13	−48	−16	−20	2.29
Insula	48	9	−36	8	−12	2.25
Right basal temporal						
Parahippocampal gyrus	35	212	26	0	−32	2.18
Olfactory cortex	48	31	26	12	−18	2.04
Superior temporal pole	34	17	26	6	−22	2.09
Fusiform gyrus	20	14	28	−4	−38	2.12
Insula	48	1	28	12	−18	1.90
Hippocampus	28	9	24	−2	−22	2.06
Amygdala	28	41	24	0	−22	2.07
Medial cingulate gyrus						
Middle cingulate cortex	24	115	−6	24	34	2.32
Middle cingulate cortex	24	173	2	28	34	2.29
Dorsal anterior cingulate	24	47	−8	4	32	2.11
Superior medial frontal gyrus	32	4	0	30	36	2.15
Right cerebellum	–	29	22	−70	−38	2.15
Left occipital/temporal						
Middle occipital gyrus	39	46	−34	−62	24	2.23
Middle temporal gyrus	37	3	−36	−62	14	2.28
Left putamen	48	68	−30	6	6	2.18
Left fusiform gyrus	37	39	−30	−42	−18	2.05
Areas of decreased activity in patients						
Left superior frontal gyrus	8	24	−22	26	58	−2.54
Left superior/middle frontal gyrus	9	47	−22	38	32	−2.52
Positive emotion versus neutral baseline						
Areas of increased activity in patients						
Right occipital/temporal						
Lingual gyrus	18	135	26	−92	−14	2.54
Calcarine sulcus	18	7	22	−96	−6	2.36
Inferior occipital gyrus	18	38	28	−92	−8	2.36
Medial orbitofrontal cortex						
Olfactorius cortex	11	4	4	22	−14	2.55
Rectus	11	78	2	30	−24	2.55
Rectus	11	58	0	24	−24	2.55
Areas of decreased activity in patients						
Left cerebellum and occipital						
Cerebellum	–	2837	−22	−76	−28	−2.93
Lingual gyrus	18	988	−18	−62	−6	−2.91
Fusiform gyrus	18	184	−22	−74	−14	−2.79
Calcarine sulcus	19	106	−20	−54	4	−2.71
Left temporal/parietal						
Rolandic opperculum	48	141	−40	−24	20	−2.74
Superior temporal gyrus	41	8	−40	−36	12	−2.74
Heschl gyrus	48	1	−46	−16	12	−2.72
Postcentral gyrus	48	55	−50	−18	18	−2.69
Supramarginal gyrus	48	26	−50	−22	18	−2.66
Insula	48	37	−34	−30	22	−2.18
Medial cingulate gyrus						
Anterior cingulate cortex	24	60	−6	32	12	−2.83
Anterior cingulate cortex	25	15	4	30	12	−2.81
Right subcortical/basal temporal						
Putamen	48	517	28	−4	8	−2.55
Pallidum	48	170	18	0	−4	−2.58
Thalamus	–	37	14	−12	0	−2.52
Insula	48	84	38	10	−12	−2.07
Hippocampus	35	16	16	−6	−14	−1.96
Left parahippocampal gyrus	28	21	−14	−2	−26	−2.42
Left angular gyrus	39	24	−38	−56	26	−2.41
Right parahippocampal areas						
Parahippocampal gyrus	36	124	24	−14	−30	−2.20
Fusiform gyrus	36	22	28	−10	−34	−2.20
Right fusiform gyrus	37	31	44	−62	−20	−2.17

Abbreviations: BA: Brodmann Area; MNI: Montreal Neurological Institute (MNI) atlas.

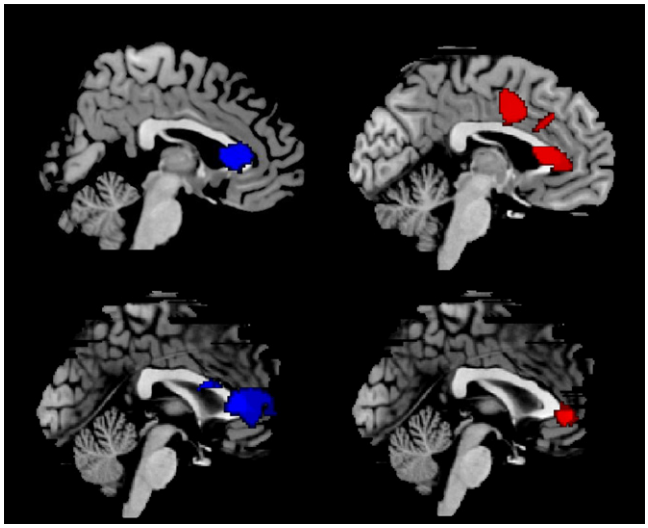

Fig. 3. Group differences in anterior cingulate cortex activation from the combined meta-analyses on facial and non-facial stimuli; presented separately for negative and positive emotion. Top row: Negative emotions (MDD > HC in red, HC > MDD in blue). *Left side*: Decreased activation for non-facial stimuli in patients compared to controls in anterior cingulate cortex (BA25). *Right side*: Increased activation for facial stimuli in patients compared to controls in anterior cingulate cortex (BA25), accompanied by increased dorsal anterior cingulate activation (BA24/32). Bottom row: Positive emotions (MDD > HC in red, HC > MDD in blue). *Left side*: Decreased activation for non-facial stimuli in patients compared to controls in anterior cingulate cortex (BA24/25). *Right side*: Increased activation for facial stimuli in patients compared to controls in pregenual anterior cingulate cortex (BA25). All maps corrected at FDR $p < 0.05$, except for positive facial stimuli, which is $p < 0.001$ uncorrected.

attention to negative stimuli and rumination to increased sensitivity to stress.

Interestingly, when investigating whether the activation differences between depressed patients and controls were related to the type of stimulus used, an effect of stimulus type was found in the pregenual ACC (BA25). This area showed increased activation to facial stimuli and decreased activation to non-facial stimuli in depressed patients, irrespective of emotional valence. It is noteworthy that the large majority of studies included a neutral stimulus as control condition, so the activation differences could be associated with hyperresponsivity to emotional faces and hyposensitivity to non-facial emotional stimuli. It would be interesting to examine the effects of other social cues for emotional states such as body language, to investigate whether the hyperresponsivity applies to social stimuli in general. Moreover, it is interesting that this area has been proposed to play a central role in integrating cognitive and emotional processes (Mayberg, 1997). The presentation of facial stimuli depicting emotional states might elicit more integration of cognitive and emotional processes than the presentation of non-facial stimuli in depressed patients.

Almost all the differences identified in medial frontal regions concerned pregenual and dorsal ACC. While precise location of findings is arduous in meta-analysis, it is striking that we did not find differences in the subgenual part of the ACC, because this structure is thought to play a prominent role in depression (Drevets and Savitz, 2008; Hamani et al., 2011; Mayberg, 1997). One possible explanation for this negative finding is that most tasks did not target processes that are deviant in the subgenual ACC of depressed patients. For instance, the subgenual ACC has been associated more with the experience rather than perception of emotion, and may be targeted by explicit mood induction (Berna et al., 2010) or self-referential instructions (Lemogne et al., 2009). On the other hand, the differences may be more pronounced in resting state activity rather than reactivity to emotional stimuli (Drevets and Savitz, 2008; Mayberg, 1997). It should be noted that considering the conservative analytical procedure, it remains possible that there are modest effects of emotional processing that went undetected. Future research should investigate the conditions under which there are abnormalities in subgenual ACC functioning in depression.

4.2. Valence-specific effects in prefrontal areas: impaired affective state monitoring

The left DLPFC was less active in depressed patients than in HC during processing of negative emotion. This is consistent with the hypothesis of impaired affective state monitoring in depression (e.g. Beck, 2008; Phillips et al., 2003). This finding also supports the rationale for use of transcranial magnetic stimulation over the left DLPFC to enhance cortical activation of this region in patients with MDD (George and Post, 2011). The left DLPFC is thought to inhibit amygdala activity during voluntary emotion regulation using suppression, attention redirection or reappraisal strategies. These voluntary strategies have been contrasted with automatic emotion regulation by medial prefrontal structures (Phillips et al., 2008). Accordingly, depressed patients might make limited use of emotion regulation strategies during emotional perception. The studies included in the present meta-analysis did not instruct the participants to regulate their emotions. However, active emotion regulation might be part of typical emotional functioning.

During processing of positive emotion, the medial OFC was more active in depressed patients than in HC. The OFC is thought to code an abstract representation of value that is sensitive to change. Therefore, it acts as a complex dynamic system that is involved in different stages of affective state monitoring (Rolls and Grabenhorst, 2008). Neurons in the OFC have been shown to compute and compare values between stimuli before decision making occurs, compute the actual outcomes after stimulus presentation, compare the outcome to the prediction and adjust the value of the stimulus accordingly (Peters and Buechel, 2010). Therefore the temporal pattern of activation is crucial for the interpretation of activation differences. Higher activation in depressed patients might represent the drive that projects a correct value representation to the striatum and other limbic areas. Decreased feedback from the striatum might induce prediction errors in the OFC.

4.3. Comparing results to predictions from models on emotion processing in depression

Previous models describing the neural basis of emotion processing in depression have hypothesized three processes to be critical to depression; namely emotional appraisal, integration of the somatic response and affective state monitoring. The models have mapped these processes to neural systems. The results from our meta-analysis are mostly supportive of abnormalities in structures thought to be involved in appraisal and affective state monitoring, but less supportive of abnormalities in the integration of the somatic response. At the appraisal level, the fusiform areas is suggested to project to the amygdala and striatum, and these areas are thought to work in concert to generate a negative bias in emotion recognition (Leppanen, 2006). This bias might be operational for the processing of both negative and positive emotional information.

Decreases in activity in the left DLPFC in response to negative stimuli and increases in the OFC in response to positive stimuli might both reflect impaired affective state monitoring (Johnstone et al., 2007; Murray et al., 2011; Phillips et al., 2008). Some authors have described the OFC as part of the somatic response network together with the subgenual ACC (Leppanen, 2006; Phillips et al., 2003). Indeed, an increase in OFC activity during processing of positive emotional stimuli could be associated with lower somatic

responsivity through inhibitory pathways. On the other hand, the findings are also in line with the hypothesis that OFC activity reflects affective state monitoring, as has been suggested by other authors (Beer et al., 2003; Krishnan and Nestler, 2008; Rolls and Grabenhorst, 2008) and in a later publication by Phillips et al. (2008). In summary, the role of the OFC appears to be broader than somatic integration alone, as it has also been associated with more complex functions such as decision-making and motivated behavior. Unfortunately, there is a paucity of research on the monitoring of positive affective states in depressed patients.

The dorsal ACC was hypothesized to be less active in depression as a part of the affective state monitoring network. Instead, we found increased dorsal ACC activity for processing negative emotion and decreased activity in dorsal pregenual ACC for processing positive emotion. This may be associated with decreased input from the DLPFC and increased output to the amygdala, providing a link between the dorsal and ventral networks as proposed by Mayberg (1997) for the pregenual ACC. Future research should test this hypothesis. On the other hand, the dorsal ACC may be involved in appraisal or generating an emotional response.

The results of the meta-analysis are not fully consistent with the predictions from the models. Some important areas were not consistently found, most notably the subgenual ACC implicated in generating the emotional response (Drevets et al., 2008; Krishnan and Nestler, 2008; Mayberg, 1997; Phillips et al., 2003). However, the outcomes do grossly resemble the model by Leppanen (2006) that was specifically developed to reflect biased processing of emotional information in depressed patients and takes emotional valence into account. Our results suggest two potential modifications to the network proposed by Leppanen. The first is related to the frontal areas involved in emotion regulation. The involvement of OFC and DLPFC might be valence-specific, the OFC mostly involved in positive and DLPFC in negative emotion. The dorsal ACC and dorsomedial PFC might provide a link between the frontal and subcortical areas. The second potential modification concerns the evidence for a role of the cerebellum and parahippocampal areas. Both areas have been consistently implicated in typical emotion processing (Lindquist et al., 2012; Phan et al., 2002; Schutter and Van Honk, 2005). The hypothesized role of the parahippocampal areas is to establish contextual information (Bar and Aminoff, 2003), and the cerebellum might play an integrative and regulatory role in emotion processing (Schmahmann, 2000), comparable to the ACC. These areas deserve more investigation to determine which processes are altered in depression and how this translates to the Leppanen (2006) model.

4.4. Comparison to the previous meta-analyses on emotion processing in depression

The results of the current meta-analysis corroborate and extend the results from two previous meta-analyses on emotion processing in depression (Diekhof et al., 2008; Fitzgerald et al., 2008) in demonstrating lower activation in prefrontal and higher activation in limbic areas for the processing of negative emotion. We demonstrated higher activity in the dorsal ACC (BA32) in accordance with Diekhof et al. (2008), whereas Fitzgerald et al. (2008) found lower activity. However, we found stronger activity in the left amygdala, whereas Fitzgerald et al. (2008) found higher activity in the right amygdala and Diekhof et al. (2008) did not report any differences in the amygdala. It is noteworthy that the 16 region-of-interest studies investigating the amygdalae did report stronger activation for depressed patients fairly consistently. Therefore, the results remain inconclusive with respect to amygdala activation. For positive emotion, the main results were consistent as well (Fitzgerald et al., 2008). However, the other meta-analyses did report a large number of additional activation differences that could not be replicated even though 41 studies were included in the current meta-analysis compared to 6 (Fitzgerald et al., 2008) and 10 (Diekhof et al., 2008) in the others. Therefore, the current meta-analysis is higher in power and has less sensitivity to outliers. Moreover, both previous meta-analyses employed an approach designed to test for above-chance clustering of individual foci rather than consistency of results across studies. This may result in summaries biased towards those studies artificially reporting more activations, for example by employing a more lenient statistical threshold. This source of bias has been corrected in later versions of the method (Eickhoff et al., 2009).

4.5. Robustness of results when including only whole-brain studies in the meta-analyses

To examine the robustness of the results, the meta-analyses were repeated including only the 26 studies using a whole-brain rather than a region-of-interest (ROI) approach. The results were comparable to the main analyses, although for processing of negative emotions three important clusters of stronger activation in depressed patients did not reach significance. The clusters were located in the bilateral temporal areas surrounding hippocampus and amygdala and ACC. These areas were repeatedly investigated in ROI-studies, where for the left amygdala 9 additional peaks and for the ACC 5 additional peaks were recorded. Similarly, two clusters in the parahippocampal areas disappeared for the positive emotion contrast, although the pre-existent limbic cluster came to include a peak in the amygdala. Presumably, this is also due to the large number of ROI studies examining the amygdala.

The discrepant findings between whole-brain and ROI approaches may be explained by the smaller search volume and therefore higher sensitivity to small effect sizes in ROI studies. The consistency in results from whole brain studies was remarkably low. This could indicate that the true effect sizes are relatively small and need more power and thus larger sample sizes to be detected. Relatively weak but widespread functional abnormalities during negative emotional processing have been shown to have diagnostic value when classifying patients with depression versus healthy controls, further suggesting that small but real effects exist in areas beyond those usually associated with depression (Costafreda et al., 2009b; Fu et al., 2008; Nouretdinov et al., 2011). Increased power for meta-analysis would be achieved through the integration of the full measurements (i.e. before statistical thresholding), as provided in statistical parametric images (Salimi-Khorshidi et al., 2009).

4.6. Strengths and limitations

This meta-analysis is characterized by substantial methodological strengths. First, a major strength is the combination of ROI and whole-brain studies. Since most ROI studies targeted the amygdala, this approach generated a lot of additional power to investigate the limbic areas. Furthermore, the sensitivity analysis demonstrated that the ROI studies provided valuable information that was not revealed in whole-brain studies. Second, the parametric testing provided information about effect sizes that is lacking in classic neuroimaging meta-analysis approaches. Testing was performed conservatively by treating study as a random factor and applying a false-discovery rate correction. The systematic search strategy was standardized and the independent assessment of eligibility showed good inter-rater reliability. Finally, heterogeneity according to facial versus non-facial stimuli was investigated through separate analyses, which suggested that the presence of faces in the visual stimuli was a substantial moderator of activation, particularly in anterior cingulate cortex.

Even after taking this factor into consideration, substantial sources of heterogeneity are likely to remain that we did not test for. There was for instance substantial task heterogeneity, however unfortunately there was not enough power to investigate all the tasks separately. The activation abnormalities might not be generalizable to all the different tasks. A potential influential factor that we did not take into account is differences in the control condition. However, only faces tasks showed a plurality of control conditions. Most of the results were replicated in the non-faces tasks, suggesting that the influence of control condition was limited. Furthermore, the contrasts were structured by valence of emotion. While this stratification allowed for data pooling across a sufficiently large number of studies, it may obscure differences associated to specific emotions, such as anger or disgust. Similarly, it would be informative to investigate the effects of arousal irrespective of valence, however arousal scores are rarely reported. The analysis could be biased by underrepresentation of unpublished negative results, although the innovative method presented here allows for the integration of null results in the meta-analytical summary. Smoothing may have influenced the results as well, although the smoothing parameter of 20 mm applied to the data before meta-analysis has been reported to give accurate results for the range of smoothing kernels that were used in the included studies (Salimi-Khorshidi et al., 2009). The studies that did not report smoothing may have resulted in an underestimation of the effect.

To examine a homogeneous depressed state, studies investigating depressed children, remitted depressives and groups at risk for depression were excluded. It would be very interesting to see if the activation abnormalities that were identified are generalizable to these groups. Moreover, several studies were identified that did collect data in which the contrasts of interest could be investigated, yet opted for a different analysis such as testing for functional connectivity, interaction effects and combinations of negative and positive emotion. From the perspective of facilitating future meta-analyses, we would recommend the analysis of basic contrasts including full reports of statistical thresholds, effect sizes and coordinates, as these data would allow the application of more advanced meta-analysis techniques, as well as ensuring potential replication of findings.

4.7. Conclusions

In conclusion, this extensive meta-analysis showed that depressed patients display activation abnormalities in brain areas implicated in emotion identification, affective state monitoring and generation of autonomic emotional responses. These brain areas were generally consistent with predictions from models on emotional dysfunction in the depressed brain. The processing of incoming emotional information appears to be strongly altered in depressed patients at multiple levels of processing. This includes multiple emotional networks, with nodes at the amygdala and striatum at the early stages of processing, and cognitive control networks in prefrontal areas subserving affect monitoring and regulation. The direction of effects in limbic areas was opposite across emotional valence, demonstrating the pertinence of taking emotional valence into account when investigating emotion processing. Considering the large body of work on emotion perception tasks in depression, further research should be aimed at explicating functional mechanisms by innovative experimental manipulation. Advanced connectivity analyses and longitudinal designs which allow for investigation of the temporal dynamics of activation abnormalities will further advance our understanding of emotional dysfunction in depression.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2012.11.015.

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