A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression

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A B S T R A C T

Major depressive disorder (MDD) is characterized by altered emotional and cognitive functioning. We performed a voxel-based whole-brain meta-analysis of functional neuroimaging data on altered emotion and cognition in MDD.

Forty peer-reviewed studies in English-language published between 1998 and 2010 were included, which used functional neuroimaging during cognitive-emotional challenge in adult individuals with MDD and healthy controls. All studies reported between-groups differences for whole-brain analyses in standardized neuroanatomical space and were subjected to Activation Likelihood Estimation (ALE) of brain cluster showing altered responsivity in MDD. ALE resulted in thresholded and false discovery rate corrected hypo- and hyperactive brain regions.

Against the background of a complex neural activation pattern, studies converged in predominantly hypoactive cluster in the anterior insular and rostral anterior cingulate cortex linked to affectively biased information processing and poor cognitive control. Frontal areas showed not only similar under- but also over-activation during cognitive-emotional challenge. On the subcortical level, we identified activation alterations in the thalamus and striatum which were involved in biased valence processing of emotional stimuli in MDD. These results for active conditions extend findings from ALE meta-analyses of resting state and antidepressant treatment studies and emphasize the key role of the anterior insular and rostral anterior cingulate cortex for altered emotion and cognition in MDD.

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Introduction

Major depressive disorder (MDD) is associated with emotional and cognitive impairments including negative affect or loss of pleasure, and reduced capabilities to concentrate or decide as hallmark features for the diagnosis (American Psychiatric Association, 2000).

Neuroimaging methods such as positron emission tomography and functional magnetic resonance imaging allow to gain a comprehensive understanding of neural mechanisms in MDD, emphasizing aberrant function and interaction of cortical, subcortical, and (para)limbic regions mediating mood, emotion, and cognition as well as autonomic and stress responses (Davidson et al., 2002; Drevets, 2001; Drevets et al., 2008; Mayberg, 1997, 2003; Phillips et al., 2003). Although there is growing consensus about key regions involved in altered brain processes in MDD, neuroimaging activation studies accumulate remarkable heterogeneity in the localization and direction of altered activity. This is well recognized for prefrontal areas by studies showing both frontal hypo- and hyperactivity in MDD (Fitzgerald et al., 2006).

Ambiguous neural responding has also been found in various other structures implicated in MDD such as the cingulate cortex (Matthews et al., 2009; Mitterschiffthaler et al., 2003), insula (Elliott et al., 2002; Mayberg et al., 1999), striatum (Knutson et al., 2008; Remijnse et al., 2009), thalamus (Fu et al., 2004; Kumari et al., 2003), (para)hippocampal areas (Bremner et al., 2004; Werner et al., 2009), amygdala (Fales et al., 2008; Lee et al., 2008), and additional subcortical and cortical regions (Fitzgerald et al., 2008a).

Differences in sample characteristics, medication status, and experimental paradigms may account for observed inconsistencies in the neural signature of MDD. In addition, foci of dysfunctional networks in MDD may show both adaptive and maladaptive activations (Mayberg, 2003) in accord with variations in illness characteristics. Moreover, heterogeneous neuroimaging findings may reflect the fundamental difficulty to define MDD as a homogeneous phenotype (Drevets, 2001).

Both emotional and cognitive symptoms are present in MDD. Experimental studies focusing on emotional disruptions in MDD mainly applied stimuli (e.g., images, faces) differing in emotional valence to
evoke basic affective responses. Therefore, emotion induction studies inherently include the perception and recognition of emotional valence as an integral part of emotion processing. Some protocols additionally require explicit judgment and categorization of the emotional stimulus materials. Moreover, emotion modulation studies target the capability of depressed individuals to either increase or decrease their emotional responses. In the cognitive domain, mainly altered attention, memory, and executive function have been addressed in MDD. In addition to standard paradigms such as the n-back working memory task, studies investigated the impact of emotional valence of stimuli and feedback on task performance. For instance, attentional bias paradigms use modified versions of standard procedures (e.g., Stroop, go/no-go task) by presenting emotionally valenced stimuli. Incentive (delay) and reversal learning tasks were applied to assess altered sensitivity to negative and positive outcomes and feedback in MDD (cf. Elliott et al., 2011). Recent research has shown that emotion and cognition highly interact by accessing identical brain regions in broadly overlapping neural networks to guide behavior (Duncan and Barrett, 2007; Pessoa, 2008, 2010; Pessoa and Adolphs, 2010). Thus, we expected that core regions of altered responsivity in MDD would show stable alterations (hypo- or hyperactivity) across manifold cognitive–emotional conditions and might therefore be substantially linked to the pathopsychophysiology of MDD. In particular, we expected generalized hyperactivity both in the rostral anterior cingulate cortex (rACC) and the anterior insula (AI), which represent important relay stations for cognitive–emotional information flow (Bush et al., 2000; Menon and Uddin, 2010) and are highlighted in neurobiological models of MDD (Mayberg, 2003; Price and Drevets, 2010). Besides indirect and direct evidence from multiple neuroscientific findings for the involvement of specific brain regions (e.g., amygdala) in MDD, current depression models substantially refer to resting state and treatment studies to highlight the importance of some regions (e.g., subgenual ACC) for the disorder. Accordingly, these findings are predominantly deduced from either passive conditions (rest) or within-subjects designs (pre vs. post treatment). However, the analysis of alterations in activation in depressed compared to healthy subjects during active conditions is highly significant to determine the adaptive potential of brain regions involved in MDD. A brain region with increased activity during rest but decreased activity during active conditions (and vice versa) shows the potential for adaptive adjustment. However, activity changes may exaggerate the ‘normal’ level and thus be considered as inflated compensatory responses. In addition, consistent activity during rest and activation may indicate a generally limited potential for adaptive adjustment of a certain region. Antidepressant treatment is assumed to change malfunctional responsivity, which requires knowledge of effects during both rest and activation for the evaluation of findings. So far, the adaptive potential of brain regions involved in the pathopsychophysiology of MDD is ill-defined because results from activation paradigms were recognized mainly on the individual study level. Meta-analyses of neuroimaging data for resting state (Fitzgerald et al., 2008a; Sacher et al., 2011) as well as pharmacological treatment effects during active conditions (Delaveau et al., 2011) are already available. Here, we present a meta-analysis of between groups differences during active conditions of cognitive–emotional challenge.

To this aim and in concordance with previous meta-analyses (Delaveau et al., 2011; Fitzgerald et al., 2008a; Sacher et al., 2011), we integrated neuroimaging results using the Activation Likelihood Estimate (ALE) method (Turkeltaub et al., 2002), which provides a kernel-based approach for meta-analyses of neuroimaging data in BrainMap (Laird et al., 2005a). Compared to previous ALE studies, we examined a larger number (Delaveau et al., 2011; Fitzgerald et al., 2008a; Sacher et al., 2011) of studies on emotion and cognition in MDD and examined not only prefrontal areas (Fitzgerald et al., 2006) but also whole brain findings associated with aberrations in cognitive–emotional information processing in MDD. In addition, we analyzed study samples investigating medication-free depressed patients only to assess whether ALE results were driven by pharmacologically untreated depressed individuals.

Methods

Study selection

We identified peer-reviewed published English language studies between 1988 and 2010 in PubMed that reported functional neuroimaging in MDD. PubMed was searched for Medical Subject Headings Major Topics “functional magnetic resonance imaging” or “positron emission tomography” or “single photon emission computed tomography” and “depression” and “emotion” or “cognition”. Studies (n = 74) not investigating a cognitive or emotional paradigm in MDD subjects compared to healthy controls and those with an age range of participants of <18 or >65 years were excluded. Studies reporting incomplete neuroimaging statistics (e.g., missing neuroanatomical coordinates) or investigating merely a priori regions of interest (ROI) were also excluded, since BrainMap accepts only data based on whole-brain analyses. This resulted in a sample of 40 studies eligible for the meta-analysis (for full study characteristics see Table 1 in the data supplement). Studies not yet included in BrainMap were coded along with the corresponding design data via BrainMap Scribe (Version 1.2) (Fox and Lancaster, 2002; Laird et al., 2005b) and submitted for quality control and insertion into the BrainMap database (n = 22). Studies investigated a total of 558 depressed and 569 healthy individuals in an age range of 23 to 48 years and mean scores of depression severity in the patient samples of 26.7 on the Beck Depression Inventory (BDI) (Beck et al., 1996) and 22.8 on the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960).

Activation Likelihood Estimation

BrainMap GingerALE (Version 2.0) was used in combination with BrainMap Slehut (Version 1.2) for the ALE meta-analysis (Laird et al., 2005a). When necessary, neuroanatomical coordinates were converted from the standard space of the Montreal Neurological Institute (Collins et al., 1994) to Talairach space (Talairach and Tournoux, 1988) using the icbm2tal transformation (Lancaster et al., 2007). The ALE procedure followed three steps: 1. ALE and significance testing: ALE values (indicating the probability that any foci are located within a given voxel) were computed for each voxel in the brain. In a random-effects analysis, ALE values were nested across contrasts and tested against a null hypothesis of random spatial distribution of foci by means of a permutation test (Eickhoff et al., 2009). In contrast to fixed-effects analyses, random-effects analyses allow generalization of results (Wager et al., 2007). The size of the modeled three-dimensional Gaussian distribution was empirically determined and included a weighting of each study by the number of included subjects (Eickhoff et al., 2009). The permutation test for significance testing was limited to regions of gray matter. 2. Thresholding: By setting the False Discovery Rate to P<.05 (corrected for multiple comparisons (Laird et al., 2005a)) with an extent threshold greater than 200 mm3, only statistically significant voxels were entered in the thresholded ALE map. 3. Finally, a cluster analysis was performed, based on the minimum volume defined for thresholding. Anatomical labels were drawn from the Talairach Daemon (Lancaster et al., 2000). For visualization (Fig. 1) a standardized anatomical template in Talairach space (Colin1.1.nii (Laird et al., 2005a)) was used.

Meta-analytic approaches and integration of ALE results

As shown in Table 2 in the data supplement in more detail, studies addressed emotional alterations by mainly presenting emotionally valenced materials in terms of affective pictures (Abler et al., 2007;
Davidson et al., 2003; Grimm et al., 2008; Johnstone et al., 2007; Mitterschiffthaler et al., 2003; Tremblay et al., 2005), picture–caption pairs (Kumari et al., 2003), words (Canli et al., 2004), emotional faces (Fu et al., 2004; Fu et al., 2007; Gotlib et al., 2005; Norbury et al., 2010; Surguladze et al., 2005; Victor et al., 2010), movie clips (Beauregard et al., 2006), personal comments (Hooley et al., 2009), and autobiographical scripts (Keedwell et al., 2005; Mayberg et al., 1999). Some studies explicitly combined stimulus presentation with a cognitive task (e.g., gender identification (Fu et al., 2004; Gotlib et al., 2005; Surguladze et al., 2005), face matching (Norbury et al., 2010; Victor et al., 2010), emotional judgment (Grimm et al., 2008), and lexical decision (Canli et al., 2004)) or emotion modulation (Beauregard et al., 2006; Johnstone et al., 2007; Keedwell et al., 2005).

Studies focusing on cognitive alterations used a variety of paradigms targeting executive function (Continuous Performance Test (Holmes et al., 2005; Hugdahl et al., 2004), Tower of London (Elliott et al., 1997, 1998), gambling (Smoski et al., 2009; Steele et al., 2004) and guessing tasks (Elliott et al., 1998), Stroop task (Mitterschiffthaler et al., 2008; Wagner et al., 2006), stop signal task (Matthews et al., 2009; Remijnse et al., 2009), oddball (Dichter et al., 2009; Wang et al., 2008) and go/no go tasks (Elliott et al., 2002), verbal fluency (Audenaert et al., 2002; Okada et al., 2003), incentive delay task (Knutson et al., 2008)), learning (associative learning (Werner et al., 2009), reversal learning (Taylor Tavares et al., 2008)), and memory (retrieval (Bremner et al., 2007), n-back working memory (Fitzgerald et al., 2008b; Harvey et al., 2005; Matsu et al., 2007)). Tasks in this domain also included emotional targets (Dichter et al., 2009; Elliott et al., 2002; Wang et al., 2008), words (Bremner et al., 2007; Mitterschiffthaler et al., 2008), motivational feedback (Elliott et al., 1998; Taylor Tavares et al., 2008), and gain/loss (Knutson et al., 2008; Remijnse et al., 2009; Smoski et al., 2009) conditions.
Based on an integrated perspective, which assumes constant interactions between emotional and cognitive aspects in all paradigms, a global ALE meta-analysis based on the total study sample was performed, which should result in clusters sensitive for generalized alterations in activation during cognitive–emotional challenge in MDD. To additionally assess the influence of sample characteristics (Supplementary Table 1) on ALE results, differences between studies which did vs. did not contribute to ALE clusters were tested by means of post hoc t-Tests for independent samples (with two-tailed levels of significance: \(P<.05\)) and \(\chi^2\)-Tests \(\left( P<.05 \right)\). Furthermore, we rerun the global analysis by including only those studies investigating medication-free depressed patients (Beauregard et al., 2006; Bremner et al., 2007; Davidson et al., 2003; Dichter et al., 2009; Epstein et al., 2006; Fu et al., 2004, 2007; Grimm et al., 2008; Johnstone et al., 2007; Knutson et al., 2008; Matsuo et al., 2007; Matthews et al., 2009; Mitterschiffthaler et al., 2008; Remijnse et al., 2009; Smolik et al., 2009; Taylor Tavares et al., 2008; Tremblay et al., 2005; Victor et al., 2010; Wagner et al., 2006) to assess global ALE results in respect of the medication status of depressed individuals. Here, we also tested for differences in sample characteristics between studies which included medication-free MDD subjects only and those which included medicated patients. In studies with medicated patients, the fraction of patients which received pharmacological treatment varied between 47 and 100\% (cf. Supplementary Table 1). Only 10 studies investigated a fully medicated sample of MDD patients. We did not perform a direct comparison between studies solely including medication-free (n=18) vs. fully medicated (n=10) samples of depressed individuals.

Results

Full account of results for the ALE analyses with Brodmann Areas (BA), ALE values, cluster volumes, and Talairach coordinates is given in Table 3 in the data supplement. The included studies reported 112 group comparisons (cf. Table 2 in the data supplement) which did not differ in the frequency of group comparisons addressing hypo- (n=54) or hyperresponsive (n=58) brain regions \(\left( \chi^2(1) = 0.14, \text{n.s.} \right)\). Accordingly, individual studies mainly reported both hypo- and hyperactive brain regions (both, n=21; only hypoactivity, n=7; only hyperactivity, n=12). In line with our hypothesis, we focused on regions which showed stable hypo- or hyperactivity. In addition, we report regions which predominantly showed hypo- or hyperactivity. These regions demonstrated consistent activation changes in one direction during multiple conditions while only few conditions (max. 2) were linked to reversed activation changes (e.g., right inferior frontal BA9, see Fig. 1). Consequently, regions characterized by coincidental hyper- and hyporesponsivity will not be addressed in the Results section (right precentral BA9/6, right middle frontal BA9, right inferior frontal BA47, left inferior frontal/precentral BA9, left inferior parietal BA40, right lateral globus pallidus, left putamen; see Supplementary Fig. 1).

Neocortical, cingulate, and insular activation changes in the total study sample

As shown in Fig. 1, altered activity on the neocortical level was present in several frontal regions, the ACC, and the AI as well as in temporal, parietal, and occipital areas.

Hypactive regions

A cluster in the frontal cortex and the right AI exclusively showed hypactivity. Frontal hypactivity (medial frontal gyrus, BA6; right paracentral lobule, BA31) was associated with mood-congruent processing toward negatively valenced emotional stimuli. The left rACC (BA32) showed hypactivity during most of the conditions associated with mechanisms of cognitive control (error processing, response selection for positive outcomes), appraisal of emotional stimuli, feedback processing, as well as memory encoding and retrieval. Hypactivity in the right AI (BA13) was associated with negative mood-congruent emotional processing as well as induced sadness and poor cognitive control. In parietal regions, left postcentral BA40 predominantly showed hypactivity linked to negative mood-congruent emotional processing and reduced responsivity to positive stimuli. An additional cluster in the left posterior parietal lobe consistently showed hypactivity during positive feedback and retrieval of emotional stimuli. Hypactivity in the left middle occipital gyrus/precuneus (BA19/31) was associated with poor cognitive control and negative mood-congruent processing.

Hyperactive regions

Increased activity was predominantly found in the right inferior frontal gyrus (BA9) during induced sadness, feedback processing, and working memory load. Likewise, right superior frontal BA6 predominantly showed hyperactivity during working memory load and negative mood-congruent emotional processing. Finally, hyperactivity in right superior temporal BA39 was predominantly associated with cognitive control (planning and working memory) as well as biased mood-congruent processing including positive outcomes.

Subcortical activation changes in the total study sample

On the subcortical level, hypo- and hyperactivity were found in basal ganglia structures (globus pallidus, putamen, and caudate) and the thalamus.

Hypactive regions

Hypactivity was preferentially present in the right caudate (body and head) linked to the processing of positive emotional stimuli and outcomes.

Hyperactive regions

A cluster including the left medial globus pallidus and the parahippocampal gyrus consistently showed hyperresponsivity when negative emotional stimuli were expected or presented. Likewise, the left thalamus showed enhanced activation during the presentation not only of sad faces but also of rewarding outcomes. For the amygdala and hippocampus, enhanced activity was reported mainly in the parahippocampal gyrus extending to the amygdala (Fu et al., 2004; Hooley et al., 2009; Surguladze et al., 2005) or in the sublenticular extended amygdala (Abler et al., 2007; Knutson et al., 2008) but this did not cluster directly in the amygdala or hippocampus in the global ALE analysis. Likewise, an additional exploratory analysis found only two studies converging in enhanced activity in subgenual cingulate BA25 (cluster volume: 480 mm\(^3\), center at: x = −6, y = 12, z = −8) in severely depressed suicidal (Audenaert et al., 2002) and treatment resistant (Kumari et al., 2003) patients.

Comparison of sample characteristics of contributing and non-contributing studies to global ALE results

Thirty studies of the total study sample (n=40) contributed to the global ALE results. Studies not contributing to ALE findings did not differ in sample characteristics (see Supplementary Table 1) from contributing studies, except for age of the healthy control subjects \(\left( t(38) = 2.65, \text{P}=.01 \right)\), which was slightly higher in non-contributing studies \(\left( \text{Mean} = 38.9, \text{SD} = 5.4; \text{contributing studies: Mean} = 33.3, \text{SD} = 5.9 \right)\).
Hypo- and hyperactive neocortical regions including the cingulate and insular cortex in studies with medication-free depressed patients only

Medication-free depressed subjects consistently showed frontal hypoactivity in the cluster spanning left medial frontal BA6 and right paracentral BA31 linked to negative mood-congruent processing. Negative mood-congruent processing in addition to affective switching was also associated with hypoactivity in left inferior frontal/precentral BA9 (see Supplementary Fig. 1). The left rACC (BA23) consistently showed hypoactivity linked to cognitive control demands (error processing, affective switching) and appraisal of emotional stimuli. Likewise, the right AI consistently showed hypoactivity during affective switching and cognitive control demands. An additional cluster was found in the left occipital cortex (lingual gyrus, BA18) showing constantly reduced activity linked to positive affective load and negative feedback.

Consistent hyperactivity was solely evident in left middle frontal BA9 associated with cognitive control demands (working memory load and response selection for rewarding outcomes; see Supplementary Fig. 1).

Hypo- and hyperactive subcortical regions in studies with medication-free depressed patients only

In medication-free depressed subjects emotional appraisal and especially the confrontation with positive stimuli were robustly associated with hypoactivity in the right lateral globus pallidus. Stable hypoactivity was also found in the right thalamus associated with positive emotional load, affective switching, and feedback processing. Constant hyperactivity was solely found in the left medial globus pallidus/parahippocampal gyrus during the processing (expectation and perception) of negative emotional stimuli.

Comparison of sample characteristics of studies with medicated vs. medication-free MDD subjects

We compared the sample characteristics of studies which included medicated MDD subjects (n = 19; M-MDD studies) vs. studies which included medication-free (MF) MDD subjects only (n = 18; MF-MDD studies; for 3 studies information about medication status was not reported). No significant differences were found in measures of depression severity (BDI, HDRS) both within the MDD and the healthy control groups (all Ps > .3; cf. Supplementary Table 1). In addition, age of subjects and gender distribution did not differ. However, studies investigating solely MF-MDD subjects were published more recently than studies, which also included medicated (M) patients (Mean publication year M-MDD studies = 2004, range: 1998–2004; Mean publication year MF-MDD studies = 2007, range: 2003–2010; t(35) = 2.79, P = .009). Since 90% of the studies used fMRI and a more recent date of publication may indicate the use of more refined imaging techniques, we tested post-hoc for differences in magnetic field strengths (Tesla) between M-MDD and MF-MDD studies. We found nearly identical field strengths in both study samples (T; M-MDD studies Mean = 1.99, SD = .81, MF-MDD studies Mean = 2.12, SD = .84; t(31) = .52, P = .61). Finally, the number of participants both for MDD subjects and HC differed significantly between studies with larger sample sizes in studies investigating MF-MDD subjects (Number MDD subjects_M-MDD studies Mean = 12.16, SD = 4.15, MDD subjects_MF-MDD studies Mean = 16.00, SD = 3.53, t(35) = 3.02, P = .005; Number HC_M-MDD studies Mean = 12.53, SD = 4.58, HC_MF-MDD studies Mean = 16.28, SD = 6.09, t(35) = 2.13, P = .04).

Discussion

ALE meta-analyses of 40 functional imaging studies examining cognitive–emotional challenge in MDD subjects and healthy controls identified a set of brain regions showing altered responsivity in MDD. We were particularly interested in whether these regions showed stable activity changes, taking into account that both emotional and cognitive demands, sample characteristics and medication status may affect neural responding linked to the pathopsychophysiology of MDD.

At first glance, activation studies converged in a complex activation pattern in MDD. This, however, was generally not due to general sample characteristics since whole-brain studies contributing to this finding did not differ from non-contributing studies regarding sample characteristics with the exception that the mean age of contributing healthy control samples was lower than that of non-contributing healthy control samples. Altered function in multiple brain regions with increasing age both in terms of under- and overrecruitment during cognitive and emotional tasks is well documented (Grady, 2008). Thus, the finding that the age of healthy controls differed between contributing and non-contributing studies may reflect the fact that increasing age enhances heterogeneity in neural activity in healthy subjects, obliterating homogeneity in activation contrasts with depressed subjects. In addition, medication status influenced ALE results. However, studies investigating MF-MDD subjects only did not differ from studies that involved medicated MDD subjects in depression severity, age, and gender of patients and controls. Thus, we assume that indeed medication status rather than other subjects’ characteristics have driven the respective ALE results. In addition, there seems to be a recent tendency in neuroimaging research on MDD to investigate medication-free patients and larger sample sizes.

Neuroimaging studies included in the ALE meta-analyses mainly addressed alterations in negative and positive affect (mood-congruent processing bias) as well as cognition (attention, executive function) as core domains (Sanislow et al., 2010) of the pathopsychophysiology of MDD. From an integrated perspective (Pessoa, 2008), affect and cognition strongly interact on the neural level (Gray, 2002) and therefore we expected that MDD should be associated with stable and generalized functional alterations during diverse cognitive–emotional conditions.

Neocortical, cingulate, and insular activation changes

In line with previous ALE meta-analyses (Fitzgerald et al., 2006, 2008a), frontal regions showed both hypo- and hyperactivity during various tasks. Frontal hyperactivity was evident in medicated (right inferior frontal BA9, right superior frontal BA6) as well as MF-MDD patients (left middle frontal BA9) not only during executive control demands but also during induced sadness and negative mood-congruent processing. In contrast, frontal hypoactivity was especially found in MF-MDD patients during conditions capturing mood-congruent processing toward negatively valenced emotional stimuli (left medial frontal BA6, right paracentral BA31, left inferior frontal/precentral BA9) and during affective switching (left inferior frontal/precentral BA9). This activation pattern is consistent with the hypothesis that preferentially left-hemispheric prefrontal regions (especially BA9) are linked to reduced approach-related behavior in MDD (Davidson et al., 2002). Our data suggest that hypersensitivity to negative emotional stimuli and feedback is associated with a lack of prefrontal control in the left hemisphere that impairs approach-related processing toward appetitive stimuli and enhances attention to negative information. Since resting-state findings showed enhanced activity in left inferior and medial parts of the prefrontal cortex (Fitzgerald et al., 2008a), we assume that these regions are down-regulated below the level of healthy subjects during task-related conditions in MDD, suggesting an overreaching compensatory response. Antidepressant treatment seems effective in antagonizing this effect, since stable activity increases in these regions were found in pharmacological pre/post studies during task-related conditions within depressed subjects (Delaveau et al., 2011). However, the
present ALE data suggest that hypoactivity in comparison to healthy controls still persists.

Altered frontal control mechanisms were also found for hyperactivity. Especially MF-MDD subjects over-activate left middle frontal BA9 during executive processes (working memory, response selection). Since resting state activity was found to be reduced in left middle frontal BA9 (Fitzgerald et al., 2008a) in MDD, this region might show increased activation to achieve adequate performance during (experimentally induced) goal-oriented behavior. Antidepressant treatment was found to reduce this enhanced left middle frontal activity in MDD (Delaveau et al., 2011), potentially to the level of healthy individuals as our results were driven by MF-MDD subjects only. Moreover, the ALE results point to hyperactive inferior (BA9) and superior (BA6) prefrontal regions in the right hemisphere linked to executive function and emotion processing even in medicated patients. However, ALE meta-analyses of both resting state and treatment studies have not identified these regions as showing altered activation patterns (Delaveau et al., 2011; Fitzgerald et al., 2008a).

Therefore, the functional significance of right inferior BA9 and superior BA6 hyperactivity remains to be determined, although the present ALE results point to their involvement in negative emotional states and impeded flexible mental adaptation during cognitive–emotional challenge in MDD. The same may hold true for the observed hyperactivity in right superior temporal areas (BA39) for which resting-state activity was found to be predominantly increased in the left hemisphere (Fitzgerald et al., 2008a) and clear medication effects are missing (Delaveau et al., 2011). Left inferior parietal (BA40) activity changes are similarly equivocal.

The insular cortex is viewed as an interface of cognitive, affective, and homeostatic mechanisms and is suggested to represent an integral structure for stimulus-driven processing and monitoring of the internal milieu (Craig, 2009). Menon and Uddin (2010) proposed a network model of insular function in higher-level cognitive control, attentional, and emotional processes. In this model especially the right AI is assumed to play a critical role in cortical networks providing the generation of appropriate behavioral responses to salient external or internal stimuli. In line with this assumption and our hypothesis, the present ALE results point to consistently reduced activity in the right AI related to reduced attention to target stimuli, restricted switching to new stimulus–response contingencies (especially in MF-MDD subjects), and negative mood-congruent processing. Hypoactivity during almost identical conditions was found in prefrontal (see above), parietal (left postcentral BA40, left posterior lobe) as well as occipital (left middle occipital gyrus/precuneus; BA19/31, left lingual gyrus; BA18) regions. In addition, especially MF-MDD patients showed reduced occipital (BA18) activation during both positive and negative emotional conditions. Functional alterations in occipital regions were frequently reported but have rarely been related to the pathophysiology of MDD (for an exception, see Sanacora et al., 1999). Our ALE results suggest that reduced activity in both parietal and occipital association areas is linked to altered valence processing of emotional stimuli and outcomes in MDD and may be associated with reduced AI activity. In particular the lingual gyrus was found to be hyperactive during rest (Fitzgerald et al., 2008a) and we observed hypoactivity in MF-MDD patients, whereas pre/post pharmacological treatment studies (Delaveau et al., 2011) again found hyperactivity. Thus, in depressed subjects the lingual gyrus seems to show compensatory deactivation during task-related conditions and this is most likely positively influenced by antidepressant medication. An analogous response pattern was found in the insular cortex: In MDD the insular cortex was found to be hyperactive in the resting state (Fitzgerald et al., 2008a, predominantly left-sided) and antidepressant medication was shown to bilaterally increase insular (BA13) activity during task-related conditions (Delaveau et al., 2011). We found generalized hypoactivity in the right insula (AI; BA13) during active conditions linked to negatively biased information processing, attention, and cognitive control. Given the assumed integral position of the right AI in the integration of cognition and emotion, reduced activity may therefore be related to altered salience processing of emotional stimuli, mirroring anhedonic aspects of MDD. Hypoactivity in the right AI was present both in medicated and MF-MDD patients and thus seems to be not fully responsive to antidepressant medication.

The AI and the ACC have been found to coactivate during multiple cognitive–emotional demands (Torta and Cauda, 2011) and were proposed to represent the two major cortical nodes in the salience network (Menon and Uddin, 2010). In addition, hyper- and hypoactivity in distinct subregions of the ACC are assumed to bias the regular integration of cognition and emotion for adaptive behavior (Davidson et al., 2002; Drevets, 2001) with high relevance for treatment response (Mayberg, 1997, 2003; Pizzagalli, 2011) in depressed individuals. In line with the importance of the ACC in MDD, numerous tasks were linked to reduced rACC function in the present ALE meta-analysis both in medicated and MF-MDD patients. Consistent with reduced insular activity, we therefore suggest that hypoactivity in the rACC during active conditions is critically linked to MDD. However, the pattern of ACC findings in the depression literature is complex and reflects that ACC function is highly heterogeneous. Previous ALE meta-analyses showed that resting-state activity is reduced in the pregenual (i.e., rostral ACC; BA32, inferior BA24) (Fitzgerald et al., 2008a) but enhanced in the subgenual (BA25, caudal BA32/24) part (Sacher et al., 2011). In line with resting-state findings, we found predominant hypoactivity in the pregenual ACC across many studies and hyperactivity in the subgenual ACC in two studies that investigated severely depressed suicidal and treatment-resistant patients. Therefore, it is reasonable to speculate that illness severity differentially impacts these anterior cingulate regions in MDD. This also corresponds to results from treatment studies which showed that increased activity during rest and active conditions in the pregenual ACC (Pizzagalli, 2011) but reduced activity in the subgenual part during active conditions (Siegle et al., 2006) predicts better treatment response (cf. Ressler and Mayberg, 2007). However, meta-analytic results for treatment-related antidepressant effects during active conditions are so far missing for subgenual BA25 and are equivocal for pregenual BA32 (Delaveau et al., 2011). In addition, we have to mention that two out of eight studies contributing to the finding of altered pregenual ACC responsivity in MDD found hyperactivity in this region; one study with medicated patients (Steele et al., 2004) and the other study (Fu et al., 2004) with medication-free patients. Likewise, studies showing hypoactivity in the pregenual ACC investigated both medicated (Hooley et al., 2009; Werner et al., 2009) and medication-free patients (Matthews et al., 2009; Remijnse et al., 2009; Tremblay et al., 2005). Studies showing the pregenual ACC hypoactive vs. hyperactive did descriptively not differ in illness severity (HDRS) of MDD subjects (cf. Supplementary Tables 1 and 3). Thus, future research might particularly focus on the impact of both antidepressant treatment and illness severity on altered rACC function in MDD. As we observed that pregenual regions of the ACC are predominantly hypoactive, in close correspondence with resting state findings, the potential for compensatory adjustment in these regions during active conditions seems important, with antidepressant treatment obviously not necessarily resulting in stable adaptive activity changes. This is of special importance, since the central positions of both AI and ACC regions significantly contribute to the engagement of task-relevant and disengagement of task-irrelevant brain regions for effective information processing (Menon and Uddin, 2010; Pizzagalli, 2011).

Subcortical activation changes

On the subcortical level, cognitive–emotional challenge was more often associated with hypo- than hyperactive regions especially in
MF-MDD subjects. The processing of emotional and particularly positive stimuli was predominantly linked to reduced right-sided activation in the caudate, lateral pallidum, and thalamus. The right thalamus additionally showed hypoactivity during affective switching and feedback processing but left-sided hyperactivity during both positive and negative emotional conditions. In addition, hyperactivity was found in the left medial pallidum and the parahippocampal gyrus for negative emotional stimuli. This response pattern, especially in structures forming the striatum [caudate, putamen (where we found equivocal results), and pallidum], may point to a hemispheric differentiation between right-sided structures being more strongly related to the processing of positive and left-sided structures to the processing of negative emotional stimuli. In addition, the bilateral involvement of the thalamus may underscore its role in relaying sensory information by interacting with subcortical and cortical areas (Guillery, 1995). Although striatal structures display an inconclusive resting state activation pattern (Fitzgerald et al., 2008a), antidepressant treatment was shown to reduce task-related activity especially in the right caudate and right thalamus (Delaveau et al., 2011). In addition, resting state activity in the right thalamus was found to be increased. Thus, at least for the right thalamus treatment of inflated hypoactivity during active conditions seems possible, as we found hypoactivity in the right thalamus in MF-MDD patients but not in medicated patients. Data for striatal structures are inconclusive. Altered striatal (and anterior cingulate) activity has been discussed to be sensitively linked to impaired reward and punishment learning in MDD (Knutson et al., 2008; Pizzagalli et al., 2009). Our ALE results suggest that striatal structures in general are closely linked to altered affective valence processing in MDD with right-sided hyperactivity related to positive and left-sided hyperactivity related to negative stimuli and outcomes.

Conclusions

Our findings emphasize that MDD is predominantly characterized by activity constraints in the anterior insular and rostral anterior cingulate cortex linked to biased salience processing of emotional and cognitive stimuli. Hypoactivity in these regions may hamper the regular formation of signals for cortical control, which normally results in adaptive engagement of task-relevant and disengagement of task-irrelevant brain regions for the detection and processing of significant stimuli. Remarkably, hypoactivity in the anterior insular and cingulate cortex may be specific for major depressive episodes as a recent ALE meta-analysis found no evidence for stable activity alterations in these regions during active conditions in patients with bipolar disorder neither in the manic nor euthymic state (Houenou et al., 2011). Restricted responsivity in anterior insula, rostral ACC and additionally biased thalamic activity may thus result in an overall heterogeneous frontal, temporal, and parietal activation pattern in MDD as typically seen on the individual study level. Hypersensitivity to negative information and reduced executive functioning seem to be critically linked to a lack of prefrontal control as mirrored by both exaggerated hypo- and hyperactivity during cognitive-emotional challenge. Left-sided prefrontal regions predominantly showed hypoactivity and right-sided prefrontal regions hyperactivity. On the subcortical level, the reversed hemispheric activation pattern was found, with striatal structures proposed to be predominantly involved in valence processing of positive (right) and negative (left) information. The regions detected in the ALE meta-analysis are in line with evidence from structural, neuropathological and lesion studies, suggesting that medial prefrontal, limbic and striato-pallido-thalamic regions are critically involved in the pathophysiology of MDD (Drevets et al., 2008; Price and Drevets, 2010). These neurocircuitry models of MDD also highlight hyperactivation in the amygdala and hippocampus, which were not identified in the present ALE meta-analysis. In addition, the subgenual cingulate cortex received much attention, especially linked to treatment responsivity. However, the prominent view of altered amygdala, hippocampal and subgenual cingulate activity in MDD is mainly driven by resting-state studies and treatment studies using within-subjects designs (besides evidence for their importance in cognition–emotion interaction in the neuroscientific literature). Both study types are in clear contrast to studies investigating MDD subjects under active conditions in between-subjects designs, which were the focus of this meta-analysis. Furthermore, stable alterations across studies during cognitive–emotional challenge should reflect a reliable picture of altered neural activation patterns in MDD. Due to their higher power, meta-analyses are more likely to reveal consistent activations than individual studies (Wager et al., 2007). Moreover, individual studies are more prone to type I error due to small sample sizes. Since meta-analyses try to rule out false positive findings, direct activation changes in the hippocampus, amygdala, and subgenual ACC seem not consistent enough to become significant across studies or related to specific subject characteristics, as suggested for the subgenual ACC.

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Appendix A. Supplementary data

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References


