A review of fMRI studies during visual emotive processing in major depressive disorder

NATALIA JAWORSKA1,2,3, XIAO-RU YANG1,3, VERNER KNOTT4 & GLENDA MACQUEEN1,2

1Mathison Centre for Mental Health Research & Education, Department of Psychiatry, University of Calgary, Calgary, AB, Canada, 2Hotchkiss Brain Institute (HBI), University of Calgary, AB, Canada, 3Alberta Children’s Hospital Research Institute (ACHRI), University of Calgary, AB, Canada, 4University of Ottawa Institute of Mental Health Research (IMHR), Ottawa, ON, Canada

Abstract
Objectives. This review synthesized literature on brain activity, indexed by functional magnetic resonance imaging (fMRI), during visual affective information processing in major depressive disorder (MDD). Activation was examined in regions consistently implicated in emotive processing, including the anterior cingulate cortex (ACC), prefrontal cortex (PFC), amygdala, thalamus/basal ganglia and hippocampus. We also reviewed the effects of antidepressant interventions on brain activity during emotive processing.

Methods. Sixty-four fMRI studies investigating neural activity during visual emotive information processing in MDD were included. Results. Evidence indicates increased ventro-rostral ACC activity to emotive stimuli and perhaps decreased dorsal ACC activity in MDD. Findings are inconsistent for the PFC, though medial PFC hyperactivity tends to emerge to emotive information processing in the disorder. Depressed patients display increased amygdala activation to negative and arousing stimuli. MDD may also be associated with increased activity to negative, and decreased activity to positive, stimuli in basal ganglia/thalamic structures. Finally, there may be increased hippocampus activation during negative information processing. Typically, antidepressant interventions normalize these activation patterns.

Conclusion. In general, depressed patients have increased activation to emotive, especially negative, visual stimuli in regions involved in affective processing, with the exception of certain PFC regions; this pattern tends to normalize with treatment.

Key words: depression, emotion, imaging, gender, antidepressant

Introduction
Major depressive disorder (MDD) can broadly be conceptualized as a disorder stemming from disturbances in the complex interplay between neural networks implicated in affective and cognitive processing as well as autonomic system activity, resulting in a heterogeneous array of emotive, cognitive and behavioural abnormalities. Although abnormalities in emotive circuits typically accompany depression, the nature of these disturbances varies.

The ability to identify and process the meaning of emotive visual information, such as facial expressions, is critical in communicating emotions and regulating social interactions (Gosselin et al. 1995). One dominant cognitive theory posits that depressed individuals are more likely to appraise their environment with negative schemas and exhibit cognitive biases toward negative stimuli (Kovacs and Beck 1978; Giesler et al. 1996; Gotlib and Joormann 2010). Indeed, depressed individuals, and even those at-risk for MDD, display enhanced memory and attention for sad faces and interpret neutral ones more negatively than non-depressed individuals (Gotlib et al. 2004; Leppänen et al. 2004; Surguladze et al. 2005; Le Masurier et al. 2007; Gollan et al. 2008). Others have extended this bias to all negative expressions, such as fear, anger and disgust (Bouhuys et al. 1999; Leyman et al. 2007). Similar findings exist to emotive scenes or words, with depressed individuals exhibiting preferential attention to negative stimuli (Kellough et al. 2008; Leung et al. 2009; Koster et al. 2010). A handful of behavioural studies also indicate that blunted emotive information processing, in general, may exist in MDD (Gur et al. 1992; Rubinow and Post 1992; Koschack et al. 2003; Leppänen et al. 2004). Other cognitive theories propose that depressed individuals display reduced perceptual sensitivity to positive
stimuli, but engage in more in-depth and sustained processing of negative ones (Gollan et al. 2008). However, few studies have demonstrated this double-dissociation in MDD (Goeleven et al. 2006). Despite the utility of behavioural data in informing cognitive theories of depression, assessments of brain activity can provide insight into the neural modulations associated with emotive information processing in MDD that may not be captured behaviourally.

Converging data have identified circuits involved in processing emotive stimuli and in emotive regulation (Davidson et al. 2002). Specifically, the prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala, hippocampus and several subcortical regions, including the thalamus and basal ganglia, are critically involved in these functions. As such, most functional magnetic resonance (fMRI)-indexed brain activity studies during emotive processing in MDD has focused on the circuits comprising these regions. This review focused on studies of brain activity to visual emotive information processing, indexed via blood oxygen level dependent (BOLD)-fMRI signals in individuals with MDD.

Methods

Search methods and study inclusion criteria

A literature search was conducted using PubMed to identify English language studies assessing visual emotive information processing in MDD up to and including August 2012. Search terms/search term combinations included: 1. “emotion” + “depression”; 2. “emotion processing” + “depression”; 3. “depression” + “fMRI”; 4. “major depressive disorder” + “fMRI”; 5. “depression” + “neuroimaging”; 6. “major depressive disorder” + “neuroimaging”; 7. “major depressive disorder” + “imaging”; 8. “depression” + “imaging”; 9. “emotion” + “depression” + “fMRI”; 10. “emotion” + “major depressive disorder” + “imaging.” Using these broad search terms, a total of 827 studies were initially surveyed. Studies were included in this review based on the following criteria: 1. Evaluation of individuals with a primary diagnosis of MDD (according to standardized criteria, such as Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Diseases [ICD] criteria, or equivalent); 2. fMRI was carried out during a visual emotive processing task (using emotive facial expressions, images or words); 3. Brain activity was assessed in one of the following regions: ACC/cingulate cortex, PFC/frontal cortex, hippocampus, basal ganglia (including any of the following: striatum, caudate, putamen, globus pallidus, nucleus accumbens), thalamus, amygdala. Exclusion criteria included: 1. Studies examining only remitted patients; 2. Studies that included patients with psychiatric co-morbidity other than anxiety.

A small number of studies were identified that consisted of an adolescent population (N = 3 studies) and were included in this review; the majority of the studies examined adult populations. In total, 64 studies were included. Tables I–V present sample characteristics, methodology and relevant fMRI findings across studies.

Defining regions of interest

We attempted to report cortical findings in terms of Brodmann areas (BA). If BAs were not specified, they were extracted from Talairach or MNI coordinates; occasionally, BAs were inferred from activation maps (consensus approach between NJ and X-RY). For the purposes of this review, BAs comprising the ventro-rostral ACC (“affective” ACC aspect) included BA24, BA32 and BA25 (subgenual ACC/sgACC). The dorsal ACC (“cognitive” ACC aspect) consisted of BA24 and BA32. When possible, we indicated whether activation in the dorsal or ventro-rostral ACC aspects was reported. The PFC tends to be subdivided into the medial and lateral aspects. In this review, the medial PFC (mPFC) included the frontopolar (BA10) and orbitofrontal cortices (OFC; BA11); together, they comprise the ventromedial PFC (vmPFC; BA10/11). The mPFC can also include dorsomedial PFC aspects (BA6/8/9). Lateral PFC areas include the dorsolateral PFC (DLPFC; BA9/46). The DLPFC may encompass the superior (BA9/8/6) and middle (BA9/46) frontal gyri. The lateral inferior frontal gyrus constitutes ~BA44/45, while the most inferior lateral PFC aspect includes BA47.

Results

Anterior cingulate cortex

The ACC is involved in modulating emotion-driven behaviours (Drevets et al. 2008), including conflict monitoring, error detection and in evaluating the emotional significance of stimuli (George et al. 1995; Pizzagalli et al. 2006). The dorsal ACC, referred to as the “cognitive” ACC aspect, is intimately connected with the DLPFC, a region highly implicated in cognitive control (Davidson et al. 2002). As such, dorsal ACC activation may represent a call for further processing and cognitive control of emotive stimuli. The ventro-rostral ACC, known as the “affective” aspect, has extensive connections with the amygdala and hippocampus. The sgACC projects to various nuclei of the basal ganglia and thalamus and
receives dense dopaminergic innervations; it is likely implicated in regulating reward contingencies (Gaspar et al. 1989; Wise and Rompre 1989). The ventro-rostral ACC also plays a role in modulating automatic aspects of emotional processing and in forming emotive associations (Drevets et al. 2008).

Depressed individuals tend to exhibit ACC hyperactivity within the ventro-rostral region, specifically the sgACC, to negative stimuli (Gotlib et al. 2005; Fales et al. 2008, 2009; Tao et al. 2012), although increased activation has also been found to positive stimuli (Kumari et al. 2003; Baeken et al. 2010). Depression severity has also been found to correlate with sg/ventro-rostral ACC activity to sad expressions (Keedwell et al. 2005b, 2010).

Hyperactivity to emotive and negative stimuli extending beyond the sgACC in MDD has also been observed (BA24/32; Bearegard et al. 1998; Elliott et al. 2002; Fu et al. 2004; Anand et al. 2005; Mitterschiffthaler et al. 2008; Dichter et al. 2009; Fales et al. 2009; Sheline et al. 2009; Yoshimura et al. 2010). Some investigators have found increased rostral ACC activity to processing happy and emotive facial expressions and pictures (Gotlib et al. 2005; Grimm et al. 2009a; Yang et al. 2010) or to cues signalling upcoming presentations of emotional pictures (BA32; Bermpohl et al. 2009) in MDD. In contrast, depressed individuals exhibited decreased left ACC activation (BA32) to targets presented after sad image distracters. This may reflect preferential capture by negative images, which may interfere with ACC-mediated attention switching (Wang et al. 2008b).

A few studies have reported decreased ACC activity to negative stimuli (Davidson et al. 2003; Kumari et al. 2003), implicit sad face processing (Fu et al. 2008) and positive pictures (Lee et al. 2007). This decreased ACC activity to emotive processing may be related to volumetric ACC decreases in MDD (Drevets et al. 1997; Wagner et al. 2008) or reflect ACC activity normalization following antidepressant treatment.

Some work suggests that observations of decreased ACC activity during emotive processing in MDD may be mainly attributed to decreased dorsal ACC activity. For instance, MDD patients exhibited decreased activity in the dorsal ACC (BA24/32) extending to the superior frontal gyrus (BA8) to processing and judging negative stimuli (Fu et al. 2008; Grimm et al. 2009b). Additionally, during the processing of neutral and fearful faces, MDD patients exhibited decreased dorsal and superior-rostral ACC (BA24/32; Fales et al. 2009). Symptomatic patients also exhibited decreased dorsal ACC (BA24) activity to processing threatening expressions compared with controls and those in remission (van Wingen et al. 2011). However, increased dorsal ACC activity (BA24) was found to positive word encoding (van Tol et al. 2012) and during the viewing of a sad film clip (Beauregard et al. 2006) in MDD.

Higher rostral ACC activity during the processing of emotive, particularly negative, stimuli has been associated with an enhanced antidepressant response. Depressed individuals with greater baseline ACC activity to negative images showed a robust response to a serotonin norepinephrine reuptake inhibitor (SNRI; Davidson et al. 2003). Greater right sgACC (BA25) responses to sad facial expressions in the early stages of treatment were also associated with good clinical outcome to various antidepressants in melancholic depressed individuals (Keedwell et al. 2009, 2010); increased baseline activity to happy expressions was associated with a smaller response (Keedwell et al. 2010). Faster improvement following chronic treatment with a selective serotonin reuptake inhibitor (SSRI) was also predicted by higher baseline ACC activity (BA25/32) to sad faces (Chen et al. 2007); a similar finding predicted remission with cognitive behavioural therapy (CBT; Costafreda et al. 2009). Although exceptions exist (Siegle et al. 2006), this enhanced rostral ACC activation may represent greater emotive monitoring, which may be a precursor for a positive response. Successful treatment may normalize ACC activation to emotive information processing (Fu et al. 2004, 2008; Robertson et al. 2007), but further work is required to confirm this (Table I).

Prefrontal cortex

The PFC is important for the planning and execution of or restraining from actions, especially those guided by emotions (Fuster 2001; Davidson et al. 2002). The DLPFC receives input from sensory cortices and is densely connected with premotor areas, frontal eye fields and lateral parietal cortex. The mPFC receives hypothalamic and brainstem projections that mediate visceral autonomic activity associated with emotion elicitation/processing, as well as from the ventral striatum, which signals reward and motivational value. The DLPFC has been primarily associated with cognitive functions, whereas the mPFC is largely ascribed affective roles. In healthy individuals, the DLPFC tends to be active during negative emotion regulation (Herwig et al. 2007; Stein 2008; Domes et al. 2010); mPFC activity is evoked when generating and regulating emotions (Jung et al. 2006; Kensinger and Schacter 2006; Gillihan et al. 2011). The vmPFC is implicated in representing reward and punishment (Davidson et al. 2002).

Several groups have reported that depressed individuals exhibit enhanced right mid/superior DLPFC...
Table I. Pertinent characteristics and main findings of fMRI studies examining anterior cingulate cortex (ACC) activity during the processing of visual emotive information.

**Anterior cingulate cortex (ACC)**

| Study                   | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion | Brain region | Finding (MDD vs. HC) | TX |
|-------------------------|-----------------------|-------------------------------------------|--------------|------------------|--------|---------|-------------|---------------------|----|
| Anand et al. 2005       | MDD (15: 11/4) HC (15: 11/4) | DSM criteria; HAMD_{25}; 31 ± 8          | MDD: 28 ± 9 HC: 28 ± 7 | unmedicated    | passive viewing of pictures | positive, negative, neutral | dorsal ACC (BA24/32) | increased activity to negative |    |
| Backen et al. 2010      | MDD (12: 0/12) HC (12: 0/12) | MINI; BDI; 28.0 ± 9.7                    | MDD: 36.0 ± 10.9 HC: 30.2 ± 8.1 | unmedicated    | viewing baby faces | happy, sad, neutral | sgACC (BA25) | increased activity to emotive; decreased L vs R to sad |    |
| Beauregard et al. 1998  | MDD (7: 3/4) HC (7: 3/4) | DSM criteria; HAMD_{21} 25 ± 6           | MDD: 42 HC: 45 (SD N/A) | medicated & unmedicated | film clip viewing | sad, neutral | R ACC (BA32) | increased activity to sad |    |
| Beauregard et al. 2006  | MDD (12: 3/9) HC (12: 3/9) | SCID; HAMD_{21} 25 ± 6                   | MDD: 43 ± 11 HC: 45 ± 10 | unmedicated    | viewing film clips & emotion suppression | sad, neutral | R dorsal ACC (BA24) | increased activity to emotion suppression of sad clips |    |
| Bermphol et al. 2009    | MDD (15: 5/10) HC (21: 11/10) | SCID; HAMD_{21} 24.7 ± 3.6              | MDD: 43.4 ± 10.2 HC: 24.1 ± 2.5 | medicated & unmedicated | cued/ uncued picture viewing | positive, negative, neutral | L ACC (BA32) | increased activity to cues signalling emotional (vs. neutral) |    |
| Chen et al. 2007        | MDD (17: 5/12) | SCID; HAMD_{17} 20.9 ± 2.2               | MDD: 44.06 ± 8.36 | unmedicated at baseline | implicit facial emotion processing; gender ID | sad (varying intensities) | pregenual ACC (BA32), sgACC (BA25), dorsal ACC (BA24) | baseline pregenual/sg ACC activity predicted faster response; dorsal ACC activity inversely associated with MDD severity activity to mild & intense sadness predicted remission increased baseline activity to negative vs. neutral associated with greatest response | SSRI (8 wk) |
| Costafreda et al. 2009  | MDD (16: 3/13) | SCID; HAMD_{17} 20.9 ± 1.9               | MDD: 40.06 ± 9.4 | unmedicated    | implicit facial emotion processing; gender ID | sad (varying intensities) | dorsal ACC (BA24/32) | CBT (16 sessions) |    |
| Davidson et al. 2003    | MDD (12: 4/8) HC (5: 4/1) | SCID; HAMD_{17} ~25                     | MDD: 38.2 ± 9.3 HC: 27.8 ± 10.4 | unmedicated at baseline | viewing pictures | positive, negative, neutral | L ACC (~BA24/32) | increased baseline activity to negative vs. neutral associated with greatest response | SNRI (8 wk) |

(Continued)
### Table I. (Continued)

| Study            | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design                     | Emotion | Brain region | Finding (MDD vs. HC) |
|------------------|-----------------------|--------------------------------------------|--------------|-------------------|----------------------------|---------|--------------|---------------------|
| **Anterior cingulate cortex (ACC)** |                        |                                            |              |                   |                            |         |              |                     |
| **Dichter et al. 2009** | MDD (14: 7/7)          | SCID; BDI: 26.9 ± 4.9                      | MDD: 34.8 ± 14.3 | unmediated        | emotional oddball (images) | sad, neutral | pregenual ACC (~BA32) | increased activity to targets embedded in sad blocks |
|                  | HC (15: 6/9)          |                                            | HC: 30.8 ± 9.6 |                   |                            |         |              |                     |
| **Elliott et al. 2002** | MDD (10: 3/7)          | DSM criteria/ SADS-LA; HAMD$_{17}$: 23.1 ± 3.9; MADRS: 31.3 ± 5.2 | MDD: 42.2 ± 8.3 | medicated         | emotional go/no-go (words) | happy, sad, neutral | R ventral ACC (BA24/32) | increased activity to sad |
|                  | HC (11: 3/8)          |                                            | HC: 37.6 ± 9.7 |                   |                            |         |              |                     |
| **Fales et al. 2008** | MDD (27: 10/17)       | DSM criteria; HAMD$_{17}$: 20 ± 2.3        | MDD: 33.4 ± 8 | unmedicated       | emotional interference (attended/unattended faces) | fearful, neutral (houses) | sgACC (BA25) | increased activity to attended & unattended fearful |
|                  | HC (24: 12/12)        |                                            | HC: 36.4 ± 9 |                   |                            |         |              |                     |
| **Fales et al. 2009** | MDD (23: 10/13)       | SCID; HAMD$_{17}$: 20 ± 2.3                | MDD: 36.4 ± 9.4 | unmedicated at baseline | emotional interference (attended/unattended faces) | fearful, neutral (houses) | dorsal ACC (BA32) | increased activity to fearful vs. neutral |
|                  | HC (18: 9/9)          |                                            | HC: 33.4 ± 8.2 |                   |                            |         |              |                     |
| **Fu et al. 2004** | MDD (19: 6/13)        | SCID; HAMD$_{17}$: 21.1 ± 2.3              | MDD: 43.2 ± 8.8 | unmedicated       | implicit facial emotion processing; gender ID | sad (varying intensities) | L ACC (BA24/32) | increased activity (dynamic range); decreased dynamic range in ACC with tx |
|                  | HC (19: 8/11)         |                                            | HC: 42.8 ± 6.7 |                   |                            |         |              |                     |

(Continued)
Table I. (Continued)

| Study | Participants | MDD diagnosis criteria & severity | Age (M ± SD) | Medication status | Design | Emotion | Brain region | Finding (MDD vs. HC) | TX |
|-------|--------------|-----------------------------------|--------------|-------------------|--------|---------|--------------|----------------------|----|
| Fu et al. 2008 | MDD (16: 3/13) | SCID; HAMD; 20.9 ± 1.9 | MDD: 40.0 ± 9.4 | unmedicated | implicit facial emotion processing; gender ID | ACC (BA24/32) | decreased activity; CBT normalized activity; baseline activity in MDD inversely correlated to clinical response | | |
| HC (16: 3/13) | | | HC: 39.2 ± 9.3 | | | | |
| Gotlib et al. 2005 | MDD (18: 5/13) | SCID; BDI: 24.6 ± 8.3 | MDD: 35.2 | medicated | implicit facial emotion processing; gender ID | happy, sad, fearful, angry, neutral, scrambled | L sgACC (BA25) | increased activity to sad (vs. neutral) | |
| HC (18: 5/13) | | | HC: 30.8 (SD N/A) | | | | |
| Grimm et al. 2009b | MDD (19: 8/11) | DSM criteria; HAMD; 33.1 ± 7.1; BDE 29.9 ± 4.9 | MDD: 40.0 | unmedicated | picture judgements & passive viewing | positive, negative | perigenual/rostral ACC (~BA24/32) | increased activity to happy (vs. neutral) | |
| HC (29: 8/21) | | | HC: 35.2 (SD N/A) | | | | |
| Grimm et al. 2009a | MDD (25: 16/9) | DSM criteria; HAMD; 26.8 ± 7.1; BDE 26.6 ± 9.1 | MDD: 37.0 | medicated | picture judgement (self-relatedness) & passive viewing | positive, negative | supragenual cingulate (BA24/32) | decreased activity to judging negative | |
| HC (25: 13/12) | | | HC: 32.4 (SD N/A) | | | | |
| Hsu et al. 2010 | MDD (23: 8/15) | SCID; HAMD; 19.4 ± 2.6 | MDD: 41.3 ± 11.7 | unmedicated | viewing words | positive, negative, neutral | sgACC (BA25) | no group differences on negative (vs. neutral) | |
| HC (20: 7/13) | | | 40.6 ± 10.4 | | | | | |

(Continued)
| Study                  | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design                     | Emotion                          | Brain region | Finding (MDD vs. HC)<sup>b</sup>                                                                 |
|-----------------------|-----------------------|--------------------------------------------|--------------|-------------------|----------------------------|---------------------------------|--------------|-----------------------------------------------------------------------------------------------|
| Keedwell et al. 2005b | MDD (12: 4/8)         | ICD-10; BDIF: 33.5 ± 11.2; Fawcett-Clarke Pleasure scale (FCPS) | MDD: 43 ± 9.8 | medicated         | memory prompts & mood-congruent faces | sad, happy, neutral            | ACC (BA24/32) | activity to happy correlated positively withanhedonia                                            |
| Keedwell et al. 2009  | MDD (12: 6/6)         | ICD-10 criteria; HAMD<sub>21</sub>: 25 ± 7; BDIF: 31.8 (SD N/A) | MDD: 49 (SD N/A) | medicated         | implicit facial emotion processing; gender ID | happy, sad, neutral (moderate/intense) | R sgACC (BA25) | activity to sad correlated positively with depression scores; greatest activity reductions to sad associated with greatest response |
| Keedwell et al. 2010  | MDD (12: 6/6)         | ICD-10 criteria; HAMD<sub>21</sub>: 25 ± 7 | MDD: 49 (SD N/A) | medicated         | implicit facial emotion processing; gender ID | happy, sad, neutral (moderate/intense) | R sgACC (BA25) | baseline activity to sad correlated positively with response to sad baseline activity to happy correlated inversely with response |

(Continued)
| Study                  | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design                      | Emotion          | Brain region       | Finding (MDD vs. HC) |
|------------------------|-----------------------|---------------------------------------------|--------------|-------------------|---------------------------|------------------|-------------------|-------------------|
| Kumari et al. 2003     | MDD: 6: 0/6 HC: 6: 0/6 | SCID; HAMD<sub>17</sub>; BDI: 19.3 ± 1.0; BDI: 34.0 ± 2.5 | MDD: 47 ± 3.6 HC: 44 ± 2.4 | medicated pictures-captions (congruent/ incongruent) | positive, negative | ACC (BA24) | decreased activity to negative & positive increased activity to positive |
| Lee et al. 2007        | MDD: 15: 3/12 HC: 15: 1/14 | SCID; HAMD<sub>17</sub>; 19.8 ± 4.5 | MDD: 48.4 ± 6.4 HC: 45.5 ± 4.4 | medicated & unmedicated viewing pictures | positive, negative, neutral sad, neutral | R dorsal ACC (~BA24) | decreased activity to positive |
| Mitterschiffthaler et al. 2008 | MDD: 17: 3/14 HC: 17: 3/14 | DSM criteria; HAMD<sub>17</sub>; 19.4 ± 1.0; BDI: 33.6 ± 2.5 | MDD: 39.3 ± 9.4 HC: 39.4 ± 9.2 | unmediated emotional word Stroop | positive, negative, neutral | L rostral ACC (BA32) | increased activity to sad |
| Robertson et al. 2007  | MDD: 10: 3/7 | DSM criteria; HAMD<sub>17</sub>; 21 ± 1.4 | MDD: 41.4 ± 7 | unmediated at baseline (images) | shapes as standards & targets, negative & neutral distractors negative, neutral | R ACC (~BA24/32) | tx reduced baseline activity to negative distractors |
| Sheline et al. 2009    | MDD: 24: 12/12 HC: 21: 6/15 | DSM criteria; HAMD<sub>17</sub>; 21 ± 3.5 | MDD: 34 ± 9.4 HC: 35 ± 7.3 | unmediated picture viewing & emotion regulation | negative, neutral | dorsal ACC (BA32) & rostral ACC (BA24) | increased activity to negative viewing & emotion regulation to negative |
| Siegle et al. 2006     | MDD: 14: 7/7 HC: 21: 9/12 | SCID; BDI: 24 ± 11.7 | MDD: 45.2 ± 9.3 HC: 31.3 ± 8.6 | unmediated word judgement (personal relevance) | positive, negative, neutral | sgACC (BA25) | low sustained sgACC activity to negative associated with greatest response increased activity to fearful; normalized with tx SSRI (8 wk) |
| Tao et al. 2012        | MDD: 19: 8/11 HC: 21: 12/9 | DSM criteria; CDRS-R: 51.9 ± 7.6 | MDD: 14.2 ± 1.9 HC: 14.9 ± 2.5 | unmedicated implicit facial emotion processing; gender ID | fearful, neutral | sgACC (BA25) | increased activity to fearful; normalized with tx SSRI (8 wk) |
| van Tol et al. 2012    | MDD: 51: 20/31 HC: 49: 19/30 | CIDI; MADRS: 12.6 ± 8.9 (remitted+ non-remitted) | MDD: 36.4 ± 10.1 HC: 38.8 ± 10.0 | medicated & unmedicated word encoding & recognition | positive, negative, neutral | L dorsal ACC (BA24) | increased activity to positive |
Table I. (Continued)

| Study                        | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion | Brain region | Finding (MDD vs. HC) | TX |
|------------------------------|-----------------------|---------------------------------------------|--------------|-------------------|--------|----------|--------------|----------------------|----|
| van Wingen et al. 2011       | MDD (18: 7/11) HC (30: 13/17) | SCID; HAMD<sub>17</sub>; BDI 21.8 ± 4.2; BDE 27.4 ± 8.9 | MDD: 33.3 ± 11.7 HC: 35 ± 12 | unmedicated | facial emotion labelling & matching | angry, fearful, control (vertical bars) target shapes, sad & neutral distractors | dorsal ACC (BA24/33) | decreased activity to emotive faces |
| Wang et al. 2008a            | MDD (19: 7/12) HC (20: 7/13) | DIS; HAMD<sub>17</sub>; 19.9 ± 5.3 | MDD: 39.3 ± 9 HC: 36.5 ± 10.5 | medicated & unmedicated | emotional oddball (images) | | L ACC (BA32) | decreased activity to targets after sad distractors |
| Yang et al. 2010             | MDD (12: 7/5) HC (12: 7/5) | DSM criteria/K-SADS-PL; CDRS-R: 76 ± 9 | MDD: 15.9 ± 1.4 HC: 15.4 ± 1.7 | unmedicated | facial emotion matching | angry, fearful, happy, control (shapes) | ACC (~BA24/32) | increased activity to emotive faces |
| Yoshimura et al. 2010        | MDD (13: 9/4) HC (13: 9/4) | SCID; BDI: 26.5 ± 6.9 | MDD: 37.6 ± 6.2 HC: 38.2 ± 6.6 | medicated | word judgement (self- or other-relatedness) | positive, negative | rostral ACC (BA32) | increased activity to self-referential negative & other-referential positive |

*Ultimately included 15/group; †Unless specified otherwise, results represent MDD vs. HC comparisons; TX refers to systematically explored effects of a specific antidepressant intervention on brain activity in the study (e.g., comparison of activity pre-/post-intervention); ACC, anterior cingulate cortex; BA, Broadmann area; BDI, Beck Depression Inventory; BOLD, blood oxygen level dependent; CBT, cognitive behavioural therapy; CDRS-R, Children’s Depression Rating Scale – Revised; CIDI, Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders (usually DSM-IV); HAMD, Hamilton Depression Scale (17, 21 or 24 item versions); HC, healthy control; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10); K-SADS-PL, Kiddie-Sads-Present and Lifetime Version; L, left; M, mean; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; MINI, Mini-International Neuropsychiatric Interview; R, right; SADS-LA, Schedule for Affective Disorders and Schizophrenia - Lifetime version (modified version); SCID, Structured Clinical Interview for DSM Disorders (usually DSM-IV); SD, standard deviation; sgACC, subgenual anterior cingulate cortex (ACC); SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TX, treatment.
Activity relative to controls while processing positive stimuli (Elliott et al. 2002; Grimm et al. 2008; Bermpohl et al. 2009; Demenescu et al. 2011; Liao et al. 2012). In general, however, mid/superior DLPFC hyperactivity occurs in anticipation of and during the processing of negative stimuli (Canli et al. 2004; Keedwell et al. 2005a,b; Anand et al. 2005; Friedel et al. 2009; Herwig et al. 2010; Scheuerecker et al. 2010; Ritchey et al. 2011; Samson et al. 2011; Mintjian et al. 2012). A similar finding was noted in the inferior DLPFC (BA45; van Wingen et al. 2011).

Other studies, however, have reported decreased DLPFC and inferior lateral PFC activity in MDD during emotive processing (BA9/46/44; Davidson et al. 2003; Mitterschiffthaler et al. 2003; Canli et al. 2004; Lawrence et al. 2004; Schaefer et al. 2006; Siegle et al. 2007; Fales et al. 2008, 2009; Lee et al. 2008; Wang et al. 2008b; Ritchey et al. 2011). Fu et al. (2004) also noted a decreased dynamic range for activation (i.e., affective load response) to processing varying intensities of sadness in MDD in the inferior lateral PFC and DLPFC (BA9/44). In an earlier meta-analysis by Fitzgerald et al. (2006), no consistent pattern of results could be extracted from studies examining DLPFC activity to presentations of positive and negative stimuli.

Results of studies examining mPFC activity during emotive information are also inconsistent, with some (Beauregard et al. 1998; Anand et al. 2005; Sheline et al. 2009; Herwig et al. 2010; Yoshimura et al. 2010; Mintjian et al. 2012) studies reporting increased activity to negative stimuli and others (Fu et al. 2008; Bermpohl et al. 2009; Grimm et al. 2009b) reporting decreased activity. Activity in the vmPFC (BA10/11/47), encompassing the OFC and frontopolar cortices, appears to be increased to negative stimuli (Elliott et al. 2002; Gotlib et al. 2005; Dichter et al. 2009; Sheline et al. 2009; Surguladze et al. 2010; Tao et al. 2012), and may even correlated with depression severity (Lee et al. 2007), though not everyone has found this (Lawrence et al. 2004; Lee et al. 2008; Friedel et al. 2009; Hsu et al. 2010). vmPFC activation has also been reported in response to positive images in MDD (Kumari et al. 2003; Mitterschiffthaler et al. 2003) and for cues signaling upcoming presentations of emotional (vs. neutral) pictures (Bermpohl et al. 2009). Finally, vmPFC hyperactivity to emotive stimuli correlated with depression severity and feelings of hopelessness (Grimm et al. 2009a).

A few studies have examined PFC activity to emotive information processing following antidepressant treatment. SSRIs enhanced initially blunted DLPFC (BA9) activity to unattended fearful stimuli in MDD (Fales et al. 2009) and increased the dynamic range for activation (i.e., affective load response) to processing sad facial expressions of varying intensities in DLPFC regions (BA9/44; Fu et al. 2004). Chronic treatment with the non-SSRI antidepressant bupropion, however, reduced activation to sad pictures in mPFC regions (~BA10/11, ~BA9/8) pre- to post-treatment, though increased activation in the left inferior frontal cortex persisted (~BA47; Robertson et al. 2007). Greater bilateral DLPFC (BA9/47) activity to emotive faces at baseline may predict a poor antidepressant response (Keedwell et al. 2009, 2010) although another group noted that increased baseline activity to sad faces in the dorsomedial PFC (~BA6/9/32) and superior frontal gyrus (BA6/8/9) was associated with a greater response to antidepressant pharmacotherapy (Samson et al. 2011; Table II).

Amygdala

The amygdala is implicated in recruiting and coordinating cortical resources to novel or ambiguous stimuli or those that elicit action tendencies (e.g., fear-eliciting cues; Davis and Whalen 2001). It is also implicated in the rapid processing of emotive stimuli (Zald 2003), emotional learning and memory formation (Barbas 2000; Phelps and LeDoux 2005). Amygdala projections are widespread – reciprocal connections exist with the forebrain, midbrain and brainstem regions; amygdalar nuclei receive information from all sensory modalities, though visual projections are most plentiful. The basolateral amygdalar nucleus has strong reciprocal connections with the PFC and hippocampus (Sah et al. 2003). The centromedial amygdalar nucleus projects primarily to the hypothalamus where it can influence hormonal release. Its tracts also terminate in other brainstem structures where they can modulate visceral autonomic functions in relation to the emotional significance of stimuli (Knapka et al. 2003).

Amygdalar hyperactivity to negative stimuli is typically evident in MDD (Sheline et al. 2001; Siegle et al. 2002, 2007; Fu et al. 2004; Anand et al. 2005; Surguladze et al. 2005; Wang et al. 2008a; Beesdo et al. 2009; Peluso et al. 2009; Suslow et al. 2010; van Wingen et al. 2011; Tao et al. 2012). Depression severity and lifetime psychiatric hospitalizations have been found to correlate with amygdala activity to negative stimuli (Lee et al. 2007; Dannlofski et al. 2008; Peluso et al. 2009; Mintjian et al. 2012), while inverse correlations exist with activity to positive stimuli (Keedwell et al. 2005a,b; Suslow et al. 2010). Finally, increased amygdala activation to stimuli of varied valences, including positive, has also been noted in patients with MDD (Matthews et al. 2008;
Table II. Pertinent characteristics and main findings of fMRI studies examining prefrontal cortex (PFC) activity during the processing of visual emotive information.

| Study            | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design          | Emotion       | Brain region          | Finding (MDD vs. HC) | TX |
|------------------|-----------------------|---------------------------------------------|--------------|-------------------|-----------------|---------------|----------------------|---------------------|----|
| Anand et al. 2005 | MDD (15: 11/4); HC (15: 11/4) | DSM criteria; HAMD25: 31 ± 8               | MDD: 28 ± 9  | unmedicated       | viewing pictures | positive, negative, neutral | DLPFC (BA9); mPFC (BA8/9) | increased activity to negative |     |
| Beauregard et al. 1998 | MDD (7: 3/4); HC (7: 3/4) | DSM criteria; HAMD24≥25                    | MDD: 42      | medicated & unmedicated | film clip viewing | sad, neutral | L mPFC (BA8) | increased activity to sad |     |
| Bermohl et al. 2009 | MDD (15: 5/10); HC (21: 11/10) | SCID; HAMD21: 24.7 ± 3.6                  | MDD: 43.4 ± 10.2 | medicated & unmedicated | cued/uncued picture viewing | positive, negative, neutral | L dmPFC/superior frontal gyrus (BA8/9) | decreased activity to cued emotive, particularly positive |     |
| Canli et al. 2004 | MDD (15: 3/12); HC (15: 3/12) | SCID; BDI: 25.1 ± 11.3                    | MDD: 35.1    | medicated         | lexical decision (word/ non-word) | happy, sad, threatening (socially & physically), neutral | R lateral superior/ mid frontal gyrus (BA6/9) | increased activity to cued emotive, particularly positive |     |
| Davidson et al. 2003 | MDD (12: 4/8); HC (5: 4/1) | SCID; HAMD17: ~25                          | MDD: 38.2 ± 9.3 | unmedicated       | viewing pictures | affective, neutral | L inferior frontal gyrus (BA4/10) | decreased activity to physically threatening | venlafaxine (SNRI) |
| Demenescu et al. 2011 | MDD (59: 23/26); HC (56: 19/37) | DSM criteria; MADRS: 11.2 ± 8.7 (MDD: 19.6 (8.4; MDD + Anxiety)) | MDD: 36.2 ± 10.8 | medicated         | implicit facial emotion processing; gender ID | angry, fearful, sad, happy, neutral | R superior frontal gyrus (BA9/10) | increased activity to happy |     |
| Ditcher et al. 2009 | MDD (14: 7/7); HC (15: 6/9) | SCID; BDI: 26.9 ± 4.9                      | MDD: 34.8 ± 14.3 | unmedicated       | emotional oddball | targets; sad/neutral distractors | mid (BA9/46), inferior (BA45) & orbital (BA10/11) frontal gyri | increased activity to targets embedded in sad blocks |     |

(Continued)
| Study           | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion | Brain region | Finding (MDD vs. HC) | TX  |
|----------------|----------------------|-------------------------------------------|--------------|-------------------|--------|---------|-------------|---------------------|-----|
| Elliott et al. 2002 | MDD (10: 3/7)       | SADS-LA/DSM criteria; HAMD17: 23.1 ± 3.9; MADRS: 31.3 ± 5.2 | MDD: 42.2 ± 8.3 MDD: 37.6 ± 9.7 | medicated | emotional go/no-go | happy, sad, neutral | R DLPFC (BA9/46) | increased activity to sad |
| Fales et al. 2008 | MDD (27: 10/17)     | DSM criteria; HAMD17: 20 ± 2.3             | MDD: 33.4 ± 8 HC: 36.4 ± 9 | unmedicated | emotional interference (attended/unattended faces) | fearful, neutral (houses) | R lateral PFC (BA11/47) | increased activity to sad (vs. neutral) |
| Fales et al. 2009 | MDD (23: 10/13)     | SCID; HAMD17: 20 ± 2.3                     | MDD: 36.4 ± 9.4 HC: 33.4 ± 8.2 | unmedicated | emotional interference (attended/unattended faces) | fearful, neutral (houses) | R DLPFC (BA9) | decreased activity to unattended fearful faces |
| Friedel et al. 2009 | MDD (21: 16/5)        | ICD-10; HAMD21: 20.2 ± 4.3; BDI: 26.9 ± 8.1 | MDD: 40 ± 10 HC: 38 ± 12 | unmedicated | cued/uncued picture viewing | unpleasant/ negative | mid PFC (BA10) | decreased activity to negative uncued pictures - correlated with depression severity; increased activity to negative cued pictures |
| Frodl et al. 2009 | MDD (12: 5/7)       | DSM criteria; HAMD21: 17.5 ± 4.4           | MDD: 43.3 ± 11.2 HC: 41.3 ± 11.7 | medicated & unmedicated | emotion matching (explicit & gender ID) (implicit facial emotion processing) | angry, sad | L mid PFC/ DLPFC (~BA9) | increased activity to sad/ angry (collapsed across implicit/ explicit) |
| Fu et al. 2004   | MDD (19: 6/13)      | SCID; HAMD17: 21.1 ± 2.3                   | MDD: 43.2 ± 8.8 HC: 42.8 ± 6.7 | unmedicated | implicit facial emotion processing; gender ID | sad (varying intensities) | L mPFC/mid frontal gyrus (BA8/9); inferior frontal gyrus (BA44) | decreased dynamic range (affective load response); increased with tx | SSRI (8 wk) |
Table II. (Continued)

| Study         | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion | Brain region | Finding (MDD vs. HC) | TX \(^c\) |
|---------------|-----------------------|--------------------------------------------|--------------|-------------------|--------|----------|--------------|----------------------|---------|
| Fu et al. 2008 | MDD (16: 3/13)        | SCID; HAMD17: 20.9 ± 1.9                   | MDD: 40.0 ± 9.4 | unmedicated       | implicit facial emotion processing; gender ID | sad (varying intensities) | superior frontal gyrus (BA8) | decreased activity; increased with CBT | CBT (16 sessions) |
|               | HC (16: 3/13)         |                                            | MDD: 39.2 ± 9.3 |                   | HC: 35.2 |                      |                           |                      |         |
|               |                       |                                            | MDD: 30.8      |                   | HC: 30.6      |                      |                           |                      |         |
|               |                       |                                            | (SD N/A)       |                   | (SD N/A)    |                      |                           |                      |         |
| Gotlib et al. 2005 | MDD (18: 5/13)       | SCID; BDI: 24.6 ± 8.3                      | MDD: 40.0 ± 9.9 | medicated         | implicit facial emotion processing; gender ID | fearful, angry, sad, happy, neutral, scrambled faces | L inferior frontal gyrus (BA47) | increased activity to sad (vs. neutral) |         |
|               | HC (18: 5/13)         |                                            | MDD: 35.2      |                   | HC: 35.6      |                      |                           |                      |         |
|               |                       |                                            | (SD N/A)       |                   | (SD N/A)    |                      |                           |                      |         |
| Grimm et al. 2008 | MDD (19: 8/11)       | DSM criteria; BDI: 29.9 ± 4.9               | MDD: 40.0 ± 9.9 | unmedicated       | picture viewing & emotion judgement | positive, negative | L DLPPC (BA9) | activity positively related to ratings of positive pictures; HCs had a negative correlation |         |
|               | HC (29: 8/21)         |                                            | MDD: 35.2 ± 7.5 |                   | HC: 35.5      |                      |                           |                      |         |
|               |                       |                                            | (SD N/A)       |                   | (SD N/A)    |                      |                           |                      |         |
| Grimm et al. 2009b | MDD (19: 8/11)       | DSM criteria; BDI: 33.1 ± 7.1               | MDD: 40.0 ± 9.9 | unmedicated       | picture viewing & emotion judgement | positive, negative | vmPFC (~BA10) | increased activity (decreased negative BOLD response); increased relative activity (decreased negative BOLD response) correlated with depression severity & hopelessness |         |
|               | HC (29: 8/21)         |                                            | MDD: 35.2 ± 7.2 |                   | HC: 35.5      |                      |                           |                      |         |
|               |                       |                                            | (SD N/A)       |                   | (SD N/A)    |                      |                           |                      |         |
| Grimm et al. 2009a | MDD (25: 16/9)       | DSM criteria; BDI: 26.8 ± 7.1               | MDD: 37.0 ± 8.5 | medicated         | picture viewing & judgement (self-relatedness) | positive, negative | dmPFC (~BA6/8) | decreased activity to judging negative |         |
|               | HC (25: 13/12)        |                                            | MDD: 26.8 ± 9.1 |                   | HC: 26.6      |                      |                           |                      |         |
|               |                       |                                            | (SD N/A)       |                   | (SD N/A)    |                      |                           |                      |         |
| Herwig et al. 2010 | MDD (14: 8/6)        | ICD-10; HAMD21: 24.4 ± 7.2                 | MDD: 40.4 ± 10.7 | medicated         | anticipation of known/unknown pictures | pleasant, unpleasant, neutral | mPFC (BA8); L DLPPC (BA9/46) | decreased activity to judging negative |         |
|               | HC (14: 8/6)          |                                            | MDD: 24.8 ± 9.9 |                   | HC: 24.8      |                      |                           |                      |         |
|               |                       |                                            | (MADRS) 26.9 ± 8.1 |                   | (MADRS) 24.8 ± 9.9 |                      |                           |                      |         |

(Continued)
## Table II. (Continued)

| Study                  | Participants | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design                      | Emotion         | Brain region                             | Finding (MDD vs. HC) |
|------------------------|--------------|--------------------------------------------|--------------|-------------------|---------------------------|-----------------|------------------------------------------|----------------------|
| Hsu et al. 2010        | MDD (23: 8/15) | SCID; HAMD17: 19.4 ± 2.6                 | MDD: 41.3 ± 11.7 | unmedicated       | viewing words             | positive, negative, neutral | inferior frontal gyrus (BA45) | activity when anticipating unknown similar to known unpleasant no difference |
|                        | HC (20: 7/13) |                                          | HC: 40.6 ± 10.4                        |                  |                           |                 |                                          |                      |
| Keedwell et al. 2005b  | MDD (12: 4/8) | ICD-10; BDI: 33.5 ± 11.2; Fawcett-Clarke Pleasure scale (FCPS) | MDD: 43 ± 9.8 | medicated         | memory prompts & mood-congruent faces | sad, happy, neutral | bilateral mid & superior frontal gyri (BA9/10); L OFC (BA11) | activity to happy correlated positively with anhedonia scores |
|                        | HC (12: 4/8) |                                          | HC: 36 ± 14.6                            |                  |                           |                 | L DLPFC (BA9); R vlPFC/inferior frontal gyrus (BA47) | activity to happy correlated positively with subjective happy ratings |
|                        |              |                                          |                                          |                  |                           |                 | R lateral sulcus (BA38/47)              | activity to happy correlated inversely with anhedonia scores |
|                        |              |                                          |                                          |                  |                           |                 | R OFC & vmPFC (~BA10/11)              | activity to happy correlated inversely with subjective happy ratings |
|                        |              |                                          |                                          |                  |                           |                 | R vlPFC/inferior frontal gyrus (BA47); R DLPFC (BA45/4) | activity to sad correlated positively with BDI scores |
|                        |              |                                          |                                          |                  |                           |                 | R DLPFC (BA40/44/45); R vlPFC (BA47) | activity to sad correlated negatively with sad subjective mood ratings |
| Keedwell et al. 2005a  | MDD (12: 4/8) | ICD-10; BDI: 33.5 ± 11.2                 | MDD: 43 ± 9.8 | medicated         | memory prompts (auditory) & mood-congruent faces | sad, happy, neutral | R DLPFC (BA9) | increased activity for sad |

(Continued)
| Study                      | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion | Brain region | Finding (MDD vs. HC) | TX |
|---------------------------|-----------------------|--------------------------------------------|--------------|-------------------|--------|---------|--------------|---------------------|-----|
| Keedwell et al. 2009      | MDD (12: 6/6)         | ICD-10; HAMD21: 25 ± 7; BDI: 31.8 (SD N/A) | MDD: 49 (SD N/A) | start of TX | viewing faces | happy, sad, neutral | L vlPFC (BA47) & DLPFC (BA9/46) | increased activity to sad post-tx (vs. pre-) | various drugs (mean 12 wk) |
| Keedwell et al. 2010      | MDD (12: 6/6)         | ICD-10 criteria; HAMD21: 25 ± 7 (SD N/A)   | MDD: 49 (SD N/A) | medicated    | implicit facial emotion processing; gender ID | happy, sad, neutral (moderate/intense) | bilateral dmPFC (~BA9/10); R OFC (BA11) | negative correlation between baseline activity to sad and happy and tx. response | various drugs (mean 12 wk) |
| Kumari et al. 2003        | MDD (6: 0/6)          | SCID; HAMD21: 19.3 ± 1.0; BDI: 34.0 ± 2.5 | MDD: 47 ± 3.6 (SD N/A) | medicated | pictures-captions (congruent/incorncuent) | positive, negative | L mid frontal gyrus (BA10/32) | decreased activity to positive | |
| Lawrence et al. 2004      | MDD (9)               | DSM criteria; BDI: 31.8 ± 11.8 (SD N/A)    | MDD: 41 ± 11 (grps. collapsed) | medicated | implicit facial emotion processing; gender ID | happy, sad, fearful (mild/intense) | R DLPFC (BA44) & OFC (BA11) | increased activity to positive decreased activity to mild fear | |

(Continued)
| Study               | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion          | Brain region                  | Finding (MDD vs. HC) | TX |
|--------------------|-----------------------|--------------------------------------------|--------------|-------------------|--------|-----------------|-------------------------------|---------------------|----|
| Lee et al. 2007    | MDD (15: 3/12)        | SCID; HAMD17: 19.8 ± 4.5                   | MDD: 48.4 ± 6.4 | meditated & unmedicated | viewing pictures | positive, negative, neutral | OFC (BA10/11)            | activity to negative correlated positively with depression severity |    |
|                    | HC (15: 1/14)         |                                            | HC: 45.5 ± 4.4 |                                 |                    |                               |                               |                     |    |
| Lee et al. 2008    | MDD (21: 3/18)        | SCID; HAMD17: 22.2 ± 4.1                   | MDD: 46.8 ± 9.1 | meditated & unmedicated | viewing faces    | sad, angry, neutral           | DLPFC (~BA9)             | decreased activity to sad |    |
|                    | HC (15: 2/13)         |                                            | HC: 48.7 ± 3.5 |                                 |                    |                               |                               |                     |    |
| Liao et al. 2012   | MDD (16: 5/11)        | CCMD-2; HAMD24: 33.6 ± 7.0; BDI: 24.9 ± 7.9 | MDD: 28.9 ± 7.2 | unmedicated        | emotional interference (attended/unattended faces) | happy, neutral | inferior/mid OFC (~BA10/11) | decreased activity to sad & angry |     |
|                    | HC (16: 7/9)          |                                            | HC: 30.1 ± 7.4 |                                 |                    |                               | R DLPFC (BA9/46)          | increased activity to attended happy |    |
| Mingtian et al. 2012 | MDD (27: 11/16) | SCID; CES-D: 25.1 ± 5.4                     | MDD: 20.4 ± 1.9 | unmedicated        | face matching     | fearful, angry                | L mid frontal gyrus (BA46) | increased activity |    |
|                    | HC (25: 11/16)        |                                            | HC: 21.0 ± 1.5 |                                 |                    |                               |                               |                     |    |
| Mitterschiffthaler et al. 2003 | MDD (7: 0/7) | DSM criteria; HAMD17: 19.4 ± 1.0; BDI: 33.6 ± 2.5 | MDD: 46.3 ± 8.1 | medicated          | viewing pictures   | positive, neutral            | R superior frontal gyrus (~BA6/8/9) | decreased activity |     |
|                     | HC (7: 0/7)           |                                            | HC: 48.3 ± 10.1 |                                 |                    |                               | inferior frontal gyrus (BA10/47) | increased activity to positive |    |
| Ritchey et al. 2011 | MDD (22: 9/13)        | DSM criteria; HAMD17: 26.7 ± 6.7; BDI: 25.1 ± 8.8 | MDD: 36.1 ± 10.1 | unmedicated        | picture rating ("pleasantness") | positive, negative, neutral | mid frontal gyrus (BA6/8) | decreased activity to positive |     |
|                     | HC (14: 5/9)          |                                            | HC: 34.6 ± 6.9 |                                 |                    |                               | vmPFC (BA11)               | decreased activity to picture processing; increased activity predicted CBT response; increased activity with CBT to emotive (positive/negative) |     |
|                     |                       |                                            |               |                                 |                    |                               | superior frontal gyrus (BA6) | decreased activity to emotive (positive/negative) |     |
|                     |                       |                                            |               |                                 |                    |                               | DLPFC (~BA6)               |                           |     |

(Continued)
## Prefrontal cortex (PFC)

| Study                  | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion | Brain region | Finding (MDD vs. HC) | TX |
|------------------------|-----------------------|----------------------------------------------|--------------|-------------------|--------|---------|--------------|----------------------|----|
| Robertson et al. 2007  | MDD (10: 3/7)         | DSM criteria; HAMD17: 21 ± 1.4               | MDD: 41.4 ± 7 | unmedicated at baseline | emotional oddball (images) | R DLPFC (BA6); L vlPFC (BA47) | increased activity to negative (vs. positive); predicted CBT response | CBT (mean 20.7 sessions) |    |
| Samson et al. 2011     | MDD (21: 14/7)        | SCID; HAMD17: 21.3 ± 5.4                    | MDD: 35.8 ± 11.4 | unmedicated | viewing faces & images | sad, neutral (houses) | R OFC/vmPFC (BA10/11), R inferior PFC (~BA47), L dmPFC (~BA8/9) | decreased activity to sad distractors with tx | bupropion (8 wk) |
| Schaefer et al. 2006   | MDD (9: 3/6)          | SCID; HAMD17: 23.4 ± 7.2                    | MDD: 36.5 ± 9.9 | unmedicated | viewing pictures | positive (social, facial, erotic), negative, neutral | dmPFC (BA6/9/32), superior frontal gyrus (BA8/9) | increased activity to negative associated with tx response | SNRI or mirtazapine (4 wk) |
| Scheuerecker et al. 2010 | MDD (13: 10/3)      | SCID; HAMD17: 20.5 ± 4.7                    | MDD: 37.9 ± 10.1 | unmedicated | emotion matching (explicit & gender ID (implicit facial emotion processing)) | sad, angry | L mid frontal gyrus (~BA46) | decreased activity to positive; normalized with tx | SNRI (mean 22 wk) |
| Sheline et al. 2009    | MDD (24: 12/12)       | DSM criteria; HAMD17: 21 ± 3.5               | MDD: 34 ± 9.4  | unmedicated | picture viewing & emotion regulation | neutral, negative | vmPFC (BA10) | increased activity to negative; increased activity to emotion regulation of negative |    |
|                        | HC (21: 6/15)         |                                              | HC: 35 ± 7.3  |                    |                              |                              | L mPFC (BA8) | increased activity to emotion regulation of negative |    |
| Study                    | Participants (N: M/F) | MDD diagnosis criteria & severity (M ± SD) | Age (M ± SD) | Medication status | Design | Emotion                  | Brain region                              | Finding (MDD vs. HC)                      | TX          |
|-------------------------|-----------------------|--------------------------------------------|--------------|-------------------|--------|-------------------------|-------------------------------------------|------------------------------------------|-------------|
| Siegle et al. 2007      | MDD (20: 9/11)        | SCID; BDI: 27.3 (SD N/A)                   | MDD: 38.8    | unmedicated       | word judgement (personal relevance) | positive, negative, neutral               | DLPFC (~BA9)                             | decreased activity to emotive vs. DLPFC-activating task | TX          |
|                         | HC (21: 9/12)         |                                            | HC: 36 (SD N/A) | meditated         | implicit facial emotion processing; gender ID | fear, disgust (mild/intense)               | L orbitofrontal gyrus (BA47)              | increased activity to intense disgust     |             |
| Surguladze et al. 2010  | MDD (9: 5/4)          | DSM criteria; HAMD17; 17.7 ± 5.5; BDI: 31.8 ± 11.8 | MDD: 42.8 ± 7.2 | HC: 39.7 ± 14.6  | implicit facial emotion processing; gender ID | fearful, neutral                          | OFC (BA11)                               | increased activity to fearful; normalized with tx | SSRI (8 wk) |
|                         | HC (9: 5/4)           |                                            |              |                   |                             |                                            |                                          |                           |             |
| Tao et al. 2012         | adolescent MDD (19: 8/11) | DSM criteria; CDRS-R: 51.9 ± 7.6                | MDD: 14.2 ± 1.9 | HC: 14.9 ± 2.5    | facial emotion labelling & matching | angry, fearful, control (vertical bars)   | L inferior frontal gyrus (BA45)           | increased activity to labelling fearful/angry |             |
|                         | HC (21: 12/9)         |                                            |              |                   |                             |                                            |                                          |                           |             |
| van Wingen et al. 2011  | MDD (18: 7/11)        | SCID; HAMD17: 21.8 ± 4.2; BDI: 27.4 ± 8.9 | MDD: 33.3 ± 11.7 | HC: 35 ± 12       |                             |                                            |                                          |                           |             |
|                         | HC (30: 13/17)        |                                            |              |                   |                             |                                            |                                          |                           |             |
| Wang et al. 2008a       | MDD (19: 7/12)        | DIS; HAMD17: 19.9 ± 5.3                     | MDD: 39.3 ± 9 | HC: 36.5 ± 10.5   | emotional oddball (images) | target shapes, sad & neutral distractors  | L mid frontal gyrus (BA9)                | decreased activity to sad distractors (i.e., increased deactivation to non-task dependent distractors) |             |
|                         | HC (20: 7/13)         |                                            |              |                   |                             |                                            |                                          |                           |             |
| Yoshimura et al. 2010   | MDD (13: 9/4)         | SCID; BDI: 26.5 ± 6.9                      | MDD: 37.6 ± 6.2 | HC: 38.2 ± 6.6    | word judgement (self- or other-relatedness) | positive, negative                       | R mPFC (BA8)                             | increased activity to self-referential negative & other-referential positive |             |
|                         | HC (13: 9/4)          |                                            |              |                   |                             |                                            |                                          |                           |             |

*Ultimately included 15/group; †Unless specified otherwise, results represent MDD vs. HC comparisons; TX refers to systematically explored effects of a specific antidepressant intervention on brain activity in the study (e.g., comparison of activity pre-/post-intervention); BA, Broadman area; BDI, Beck Depression Inventory; BOLD, blood oxygen level dependent; CBT, cognitive behavioural therapy; CDRS-R, Children's Depression Rating Scale - Revised; CES-D, Center for Epidemiologic Studies Depression Scale; DIS, Diagnostic Interview Schedule; DLPFC, dorsolateral prefrontal cortex (PFC); dmPFC, dorsomedial prefrontal cortex (PFC); DSM, Diagnostic and Statistical Manual of Mental Disorders (usually DSM-IV); HAMD, Hamilton Depression Scale (17, 21 or 24 item versions); HC, healthy control; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10); K-SADS-PL, Kiddie-Sads-Present and Lifetime Version; L, left; M, mean; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, Major Depressive Disorder; mPFC, medial prefrontal cortex (PFC); OFC, orbitofrontal cortex; R, right; SADS-LA, Schedule for Affective Disorders and Schizophrenia – Lifetime version (modified version); SCID, Structured Clinical Interview for DSM Disorders (usually DSM-IV); SD, standard deviation; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TX, treatment VMpFC, ventromedial prefrontal cortex (PFC); vPFC, ventrolateral prefrontal cortex (PFC).
Several studies have examined the effects of antidepressant treatment on amygdala activity during emotive processing. Chronic SSRI treatment diminishes amygdala hyperactivity to negative/emotive stimuli (Sheline et al. 2001; Fu et al. 2004; Canli et al. 2005; Tao et al. 2012), normalizes pretreatment amygdala hypoactivity to fearful faces (Fales et al. 2009) and normalizes decreased activity to happy and increased activity to sad faces (Victor et al. 2012). Comparable normalization of hyperactivity to negative expressions was found with chronic bupropion treatment (Robertson et al. 2007), although, SNRI treatment did not alter amygdala activity to emotive processing in an earlier study (Davidson et al. 2003).

Psychotherapy may also influence amygdala dysregulation in MDD. In one study, initially diminished discriminant amygdala activity to emotive (vs. neutral) pictures increased with CBT (Ritchey et al. 2011). Successful CBT in MDD also attenuated initially elevated amygdala activity to sad expressions (Fu et al. 2008). Stronger recovery with CBT was also associated with increased pretreatment amygdala activity to negative words (Siegle et al. 2006). Work is required to elucidate the predictive nature of amygdala activity to antidepressant outcome – particularly to specific types of antidepressant interventions (Supplementary Table I, available online only at http://informahealthcare.com/doi/abs/10.3109/15622975.2014.885659).

Basal ganglia and thalamus

The basal ganglia refer to a collection of subcortical nuclei surrounding the thalamus. Core basal ganglia structures typically include the caudate, putamen, globus pallidus (GP) and nucleus accumbens (NAc). The basal ganglia subserve aspects of cognition and emotive processing, including guiding actions towards motivationally salient stimuli, evaluating stimuli and regulating motoric expressions associated with emotive states (e.g., facial expressions; Ring and Serra-Mestres 2002; Camara et al. 2008). The basal ganglia and thalamus are richly interconnected with the DLPFC, OFC and ACC; the caudate also receives extensive amygdalar projections. Similarly, the dorsomedial nucleus of the thalamus is densely connected with medial cortical and limbic regions (Taber et al. 2004) and may thus be important in affective processing and regulation (Drevets et al. 2008).

The relatively sparse literature on basal ganglia activity during emotive visual information processing suggests increased activation to negative stimuli and decreased activation to positive stimuli in MDD. For instance, depressed individuals exhibited increased left putamen activity to sad faces while controls showed increased right putamen activity to happy ones (Surguladze et al. 2005). Patients also had greater putamen, caudate and thalamus activity when processing negative pictures and expressions (Scheuerecker et al. 2010; Mingtian et al. 2012). Similarly, when expecting unknown pictures, depressed patients showed medial thalamus activity similar to when expecting negative ones (Herwig et al. 2010). Conversely, they demonstrated decreased ventral striatum and overall basal ganglia activity to positive stimuli (Epstein et al. 2006; Schaefer et al. 2006), which correlated negatively with depression and anhedonia scores (Keedwell et al. 2005a, b, 2009). Though exceptions exist (Kumari et al. 2003; Mitterschiffthaler et al. 2003; Lee et al. 2008), extant evidence suggests increased activation to negative and decreased activation to positive visual stimuli in the basal ganglia/thalamus in MDD.

Fu et al. (2004) found that depressed subjects treated with SSRIs had reduced ventral striatum activation to sad expressions; symptom improvement was also associated with a reduced dynamic range of activation to varying intensities of sadness. The same group also reported that greatest clinical improvement with CBT was associated with low activity in the left putamen and GP during implicit sad expression processing (Fu et al. 2008). Similarly, right caudate activity decreased to emotional distracters in patients treated with bupropion (Robertson et al. 2007). Furthermore, depressed patients with initially decreased basal ganglia activity to positive images exhibited increased activity following SNRI treatment (Schaefer et al. 2006). Finally, patients who had diminished discriminant caudate activity to neutral versus emotive pictures prior to treatment showed increased discriminant activity following CBT (Ritchey et al. 2011). Preliminary data therefore suggests that antidepressant therapies may decrease basal ganglia activity during emotive, particularly negative, information processing (Supplementary Table II, available online only at http://informahealthcare.com/doi/abs/10.3109/15622975.2014.885659).

Hippocampus

The hippocampus is a primary structure comprising the limbic system; it has a central role in episodic memory formation and spatial navigation (Duvernoy...
1988). It is intimately connected with the amygdala and its efferents project to the NAc and ventral striatum as well as prefrontal and temporal cortices (Campbell and MacQueen 2004). Anterior hippocampal regions are strongly connected with the mPFC, whereas posterior regions are primarily connected with the DLPFC (Witter et al. 2000).

Studies examining hippocampus activation during visual emotive information processing in MDD are sparse, but suggest hippocampal hyperactivity to processing negative stimuli (Lee et al. 2007; Fu et al. 2008) and reduced activation to positive stimuli (Schaefer et al. 2006; van Tol et al. 2012; but see also Lee et al. 2008). Symptom severity may correlate with hippocampal activity to sad expressions (Keedwell et al. 2005b, 2009).

Data on fMRI-indexed hippocampal activity during emotive processing following antidepressant therapy are also limited. One group reported that low baseline activity in the hippocampus and other limbic regions normalized with chronic SNRI treatment (Schaefer et al. 2006). Increased activation to emotive pictures was also noted following CBT in MDD (Ritchey et al. 2011). In a study examining the potential antidepressant effects of erythropoietin (vs. placebo), patients exhibited reduced hippocampal activity to fearful versus happy faces after treatment (Miskowiak et al. 2009; Supplementary Table III, available online only at http://informahealthcare.com/doi/abs/10.3109/15622975.2014.885659).

Discussion

This review aimed to synthesize research on neural activity during visual emotive information processing in MDD. Overall, evidence suggests increased ventro-rostral/sgACC activation to emotive, particularly negative, stimuli and perhaps decreased dorsal ACC activity during emotive processing. Findings are inconsistent for the PFC. There appears to be increased amygdalar activation in MDD to negative visual stimuli, but also to emotive/arousing stimuli in general. The degree of amygdalar activation may correlate with depression severity. In the basal ganglia and thalamus, patients seem to have increased activation to negative stimuli and decreased activation to positive stimuli compared to healthy controls. Finally, some evidence suggests that depressed individuals also demonstrate increased hippocampal activation during negative emotion processing.

There are few, if any, regions that have not had divergent reports with respect to activation in response to emotive stimuli. Such inconsistency may be partially accounted for by variability in regional labels (i.e., reporting BAs, Talairach or MNI coordinates) and in the tasks utilized (e.g. passive or active). Other sources of variability may be related to heterogeneity of the clinical populations studied, including factors such as depressive symptom severity, co-morbidity, age and methodological issues such as not controlling for total brain volume or volume loss. Gender and medication status are other aspects that may influence brain activity to emotive information processing (Stevens and Hamann 2012). Both were investigated in this review, though the scarcity of research directly assessing the contributions of these factors (especially gender) on brain activity prevents us from drawing conclusions. Generally, studies examining antidepressant pharmacotherapy or psychotherapy have reported that treatment normalizes brain activity abnormalities during emotive information processing.

Certain limitations must be acknowledged with respect to our review. First, unlike a meta-analytic approach, our review cannot comment on the degree of activation reliability in specific spatial coordinates implicated in emotive processing. Second, neuroimaging meta-analyses and reviews, including ours, are affected by publication biases, which favor the increased probability of published studies reporting significant (versus null) results (Wager et al. 2007). Third, we did not include non-English studies in the current review and may have thus missed pertinent research in the field.

Networks consisting of a number of brain areas comprise the brain’s emotion circuitry. Evidence points toward dysregulation of these circuits in patients with MDD. Future studies may focus more on exploring the connectivity/dysconnectivity in these emotive networks rather than activation of isolated regions. Ideally, such studies will control for clinical sources of variation (or whole-brain assessments to increase statistical rigour) and use rigorous definitions of regions of interest, such that variation in results across studies can be better understood.

Ultimately, greater understanding into the dominant brain activity anomalies during emotive processing in MDD may facilitate in characterizing individuals at-risk for developing the disorder. This, in turn, may help with the development and employment of targeted prevention/intervention strategies. Further, greater insight into the functional correlates of depression may aid in predicting treatment response in different MDD subtypes. Finally, better understanding of the putative mediating effects of gender on brain function in depression may help us to better integrate gender-focused treatment strategies in the future.
Acknowledgements
We would like to thank Dr Anda Smith and Dr Vanessa Taler for their initial assistance and feedback on this work.

Statement of Interest
None to declare.

References
Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al. 2005. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol Psychiatry 57:1079–1088.
Baeken C, Van Schuerbeek P, De Raedt R, Ramsey NF, Bossuyt A, De Mey J, et al. 2010. Reduced left subgenual anterior cingulate cortical activity during withdrawal-related emotions in melancholic depressed female patients. J Affect Disord 127:326–331.
Barbas H. 2000. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull 52:319–330.
Beauregard M, Leroux JM, Bergman S, Arzoumanian Y, Beaudoin G, Bourgouin P, et al. 1998. The functional neuro-anatomy of major depression: an fMRI study using an emotional activation paradigm. Neuroreport 9:3253–3258.
Beauregard M, Paquette V, Lévesque J. 2006. Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. Neuroreport 17:843–846.
Beeds K, Lau JY, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, et al. 2009. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry 66:275–285.
Bermopli F, Walter M, Sajonz B, Lücke C, Hägele C, Sterzer P, et al. 2009. Attentional modulation of emotional stimulus processing in patients with major depression – alterations in prefrontal cortical regions. Neurosci Lett 463:108–113.
Bouhuys AL, Geerts E, Gordijn MC. 1999. Depressed patients’ perceptions of facial emotions in depressed and remitted states are associated with relapse: a longitudinal study. J Nerv Mental Dis 187:595–602.
Canli T, Sivers H, Thomason ME, Whiffin-Gabrieli S, Gabrieli JD, Gotlib IH. 2004. Brain activation to emotional words in depressed vs healthy subjects. Neuroreport 15:2585–2588.
Canli T, Cooney RE, Goldberg P, Shah M, Sivers H, Thomason ME, et al. 2005. Amygdala reactivity to emotional faces predicts improvement in major depression. Neuroreport 16:1267–1270.
Camara E, Rodríguez-Fornells A, Münte TF. 2008. Functional connectivity of reward processing in the brain. Front Hum Neurosci 2:19.
Campbell S, MacQueen G. 2004. The role of the hippocampus in the pathophysiology of major depression. J Psychiatry Neurosci 29:417–426.
Chen CH, Ridler K, Sukkling J, Williams S, Fu CH, Merlo-Pich E, et al. 2007. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. Biol Psychiatry 62:407–414.
Costafreda SG, Khanna A, Mourao-Miranda J, Fu CH. 2009. Neural correlates of sad faces predict clinical remission to cognitive behavioural therapy in depression. Neuroreport 20:637–641.
Dannlowski U, Ohrmann P, Bauer J, Deckert J, Hohoff C, Kugel H, et al. 2008. 5-HTTLPR biases amygdala activity in response to masked facial expressions in major depression. Neuropsychopharmacology 2:418–424.
Davis M, Whalen PJ. 2001. The amygdala: vigilance and emotion. Molec Psychiatry 6:13–34.
Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. 2002. Depression: perspectives from affective neuroscience. Ann Rev Psychol 53:545–574.
Davidson RJ, Irwin W, Anderle MJ, Kalin NH. 2003. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 160:64–75.
Demenescu LR, Renken R, Kortekaas R, van Tol MJ, Marsman JB, van Buchem MA, et al. 2011. Neural correlates of perception of emotional facial expressions in out-patients with mild-to-moderate depression and anxiety. A multicenter fMRI study. Psychol Med 41:2253–2264.
Dichter GS, Felder JN, Smoski MJ. 2009. Affective context interferes with cognitive control in unipolar depression: an fMRI investigation. J Affect Disord 114:131–142.
Domes G, Schulze L, Böttger M, Grossmann A, Haußenkemper K, Wirtz PH, et al. 2010. The neural correlates of sex differences in emotional reactivity and emotion regulation. Hum Brain Mapp 31:758–769.
Dreven WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386:824–827.
Dreven WC, Savitz J, Trimble M. 2008. The subgenual anterior cingulate cortex in mood disorders. CNS Spectrums 13:663–681.
Duvernoy HM. 1988. The human hippocampus: An atlas of applied anatomy. Munich: Springer Verlag.
Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. 2002. The neural basis of mood-congruent processing biases in depression. Arch Gen Psychiatry 59:597–604.
Epstein J, Pan H, Kocsis JH, Yang Y, Butler T, Chusid J, et al. 2006. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. Am J Psychiatry 163:1784–1790.
Etkin A, Schatzberg AF. 2011. Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. Am J Psychiatry 168:968–978.
Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, Cohen JD, et al. 2008. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. Biol Psychiatry 63:377–384.
Fales CL, Barch DM, Rundle MM, Mintun MA, Mathews J, Snyder AZ, et al. 2009. Antidepressant treatment normalizes hypovacuity in dorsolateral prefrontal cortex during emotional interference processing in major depression. J Affect Disord 112:206–211.
Fitzgerald PB, Oxlcy TJ, Laird AR, Kulkarni J, Egan GF, Daskalakis ZJ. 2006. An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression Psychiatry Res 148:33–45.
Friedel E, Schlagenauf F, Sterzer P, Park SQ, Bermpohl F, Ströhle A, et al. 2009. 5-HTT genotype effect on prefrontal-amygdala coupling differs between major depression and controls. Psychopharmacology (Berlin) 205:261–271.
Frodl T, Scheuerzecker J, Albrecht J, Kleemann AM, Müller-Schunk S, Koutsouleris N, et al. 2009. Neuronal correlates of emotional processing in patients with major depression. World J Biol Psychiatry 10:202–208.
Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, et al. 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a pro-
spective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry 61:877–889.

Fu CH, Williams SC, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. 2008. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatry 64:505–512.

Fuster JM. 2001. The prefrontal cortex – an update: time is of the essence. Neuron 30:319–333.

Gaspar P, Berger B, Febvret A, Vigny A, Henry JP. 1989. Catecholamine innervation of the human cerebral cortex as revealed by comparative immunohistochemistry of tyrosine hydroxylase and dopamine-beta-hydroxylase. J Comp Neurol 279:249–271.

George MS, Ketter TA, Parche PI, Horwitz B, Herscovitch P, Post RM. 1995. Brain activity during transient sadness and happiness in healthy women. Am J Psychiatry 152:341–351.

Giesler RB, Josephs RA, Swann WB Jr. 1996. Self-verification in clinical depression: the desire for negative evaluation. J Abnorm Psychol 105:358–368.

Gillihan SJ, Xia C, Padon AA, Heberlein AS, Farah MJ, Fellows LK. 2011. Contrasting roles for lateral and ventromedial prefrontal cortex in transient and dispositional affective experience. Soc Cogn Affect Neurosci 6:128–137.

Goeleven E, De Raedt R, Baert S, Koster EH. 2006. Deficient inhibition of emotional information in depression. J Affect Disord 93:149–57.

Gollan JB, Pane HT, McCluskey MS, Coccaro EF. 2008. Identifying differences in biased affective information processing in major depression. Psychiatry Res 159:18–24.

Gosselin P, Kirouac G, Doré FY. 1995. Components and recognition of facial expression in the communication of emotion by actors. J Person Soc Psychol 68:83–96.

Gotlib IH, Krasnoperova E, Yue DN, Joormann J. 2004. Attentional biases for negative interpersonal stimuli in clinical depression. J Abnorm Psychol 113:121–135.

Gotlib IH, Sivers H, Gabrieli JD, Whitfield-Gabrieli S, Goldin P, Minor KL, et al. 2005. Subgenual anterior cingulate activation to valenced emotional stimuli in major depression Neuroreport 16:1731–1734.

Gotlib IH, Joormann J. 2010. Cognition and depression: current status and future directions. Annu Rev Clin Psychol 6:285–312.

Grimm S, Boesiger P, Beck J, Schuepbach D, Bermpohl F, Walter M, et al. 2009a. Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. Neuropsychopharmacology 34:932–943.

Grimm S, Ernst J, Boesiger P, Schuepbach D, Hell D, Boeker H, et al. 2009b. Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. Hum Brain Mapp 30:2617–2627.

Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. 2008. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry 63:369–376.

Gur RC, Erwin RJ, Gur RE, Zwil AS, Heimberg G, Kraemer HC. 1992. Facial emotion discrimination: II. Behavioral findings in depression. Psychiatry Res 42:241–251.

Herwig U, Baumgartner T, Kaffenberger T, Brühl A, Kottlow M, Schreiter-Gasser U, et al. 2007. Modulation of anticipatory emotion and perception processing by cognitive control. NeuroImage 37:652–662.

Herwig U, Brühl AB, Kaffenberger T, Baumgartner T, Boeker H, Jänecke L. 2010. Neural correlates of “pessimistic” attitude in depression. Psychol Med 40:789–800.

Hsu DT, Langenecker SA, Kennedy SE, Zubieta JK, Heitzeg MM. 2010. fMRI BOLD responses to negative stimuli in the prefrontal cortex are dependent on levels of recent negative life stress in major depressive disorder. Psychiatry Res 183:202–208.

Jung YC, An SK, Seok JH, Kim JS, Oh SJ, Moon DH, et al. 2006. Neural substrates associated with evaluative processing during co-activation of positivity and negativity: a PET investigation. Biol Psychol 73:253–261.

Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. 2005a. A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. Biol Psychiatry 58:495–503.

Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. 2005b. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry 58:843–853.

Keedwell P, Draper D, Surguladze S, Giampietro V, Brammer M, Phillips M. 2009. Neural markers of symptomatic improvement during antidepressant therapy in severe depression: subgenual cingulate and visual cortical responses to sad, but not happy, facial stimuli are correlated with changes in symptom score. J Psychopharmacol 23:775–788.

Keedwell PA, Draper D, Surguladze S, Giampietro V, Brammer M, Phillips M. 2010. Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. J Affect Disord 120:120–125.

Kellough JL, Beeser CG, Ellis AJ, Wells TT. 2008. Time course of selective attention in clinically depressed young adults: an eye tracking study. Behav Res Ther 46:1238–1243.

Kensinger EA, Schacter DL. 2006. Processing emotional pictures and words: effects of valence and arousal. Cogn Affect Behav Neurosci 6:110–126.

Knapska E, Radwanska K, Werka T, Kaczmarek L. 2003. Functional internal complexity of amygdala: focus on gene activity mapping after behavioral training and drugs of abuse. Physiol Rev 87:1113–1173.

Koschack J, Hoschel K, Irel E. 2003. Differential impairments of facial affect priming in subjects with acute or partially remitted major depressive episodes. J Nerv Mental Dis 191:175–181.

Koster EH, De Raedt R, Leyman L, De Lissnyder E. 2010. Mood-congruent attention and memory bias in dysphoria: exploring the coherence among information-processing biases. Behav Res Ther 48:219–225.

Kovacs M, Beck AT. 1978. Maladaptive cognitive structures in depression. Am J Psychiatry 135:525–533.

Kumari V, Mitterschiffthaler MT, Teasdale JD, Malhi GS, Brown RG, Giampietro V, et al. 2003. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. Biol Psychiatry 54:777–791.

Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, et al. 2004. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biol Psychiatry 55:578–587.

Le Masurier M, Cowen PJ, Harmer CJ. 2007. Emotional bias and waking salivary cortisol in relatives of patients with major depression. Psychol Med 37:403–410.

Lee BT, Seong WC, Hyung SK, Lee BC, Choi IG, Lyoo IK, et al. 2007. The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. Progr Neuropsychopharmacol Biol Psychiatry 31:1487–1492.

Lee BT, Seok JH, Lee BC, Cho SW, Yoon BJ, Lee KU, et al. 2008. Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorder. Progr Neuropsychopharmacol Biol Psychiatry 32:778–785.

Visual emotive processing in MDD 469
Wagner G, Koch K, Schachtzabel C, Reichenbach JR, Sauer H, Schlösser RG. 2008. Enhanced rostral anterior cingulate cortex activation during cognitive control is related to orbitofrontal volume reduction in unipolar depression. J Psychiatry Neurosci 33:199–208.

Wager TD, Lindquist M, Kaplan L. 2007. Meta-analysis of functional neuroimaging data: current and future directions. Soc Cogn Affect Neurosci 2:150–158.

Wang L, Krishnan KK, Steffens DC, Potter GG, Dolcos F, McCarthy G. 2008a. Depressive state- and disease-related alterations in neural responses to affective and executive challenges in geriatric depression. Am J Psychiatry 165:863–871.

Wang L, LaBar KS, Smoski M, Rosenthal MZ, Dolcos F, Lynch TR, et al. 2008b. Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. Psychiatry Res 163:143–155.

Supplementary material available online
Supplementary Tables I-III.